

**Final evaluation of Australia's investment in Product
Development Partnerships (2013-2018):
Evaluation findings and options for future DFAT investment**

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**Specialist
Health
Service**

Strategic input on health to the Australian Government

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Executive summary

The objective of the current engagement was to conduct an end-of-term evaluation of DFAT's AUD 40 million investment in Product Development Partnerships (PDPs) (2013/4 – 2017/18): the Foundation for Innovative Diagnostics (FIND), the Medicines for Malaria Venture (MMV) and the TB Alliance. These PDPs are the leading therapeutic and diagnostic PDPs in the tuberculosis (TB) and malaria space. The evaluation findings will be used to guide and design DFAT's future PDP investment strategy.

Evaluation methodology involved triangulation of data from 1) literature review, 2) document review, 3) PDP website review, and 4) key informant interviews. Fourteen semi-structured interviews were conducted with 21 key informants identified across four stakeholder groups: donors (N=5, including DFAT), Australian research organisations (N=4), industry (N=3), and PDP representatives (N=9).

The key criteria for the evaluation were the PDPs' performance in meeting DFAT's investment outcome and output. Also assessed were the investment's achievements according to the Australian Aid Policy's four investment tests: 1) pursuing national interest and extending Australia's influence; 2) impact on promoting growth and reducing poverty; 3) Australia's value-add and leverage (including working with Australian research institutions); and 4) making performance count¹. These tests include the goals of the Health for Development Strategy (2015-2020) that sit under the Australian Aid Policy and align with DFAT's new Regional Health Security Initiative. Standard OECD Development Assistance Committee (DAC) evaluation criteria including relevance, effectiveness, efficiency and sustainability were also assessed, in addition to governance.

Top level findings

Outputs and outcomes – DFAT's investment in the three PDPs resulted in five products meeting the outcome criteria of a successfully trialled new or modified product registered for patients' use in the Asia Pacific. The five products include two TB diagnostics, one TB medicine, and two malaria medicines. At least 17 products met the output criteria of completing a late stage clinical trial or demonstration study for new and adapted products.

Definitions - While it is clear that the investment was successful in progressing products that meet identified diagnostic and treatment needs along the innovation lifecycle, a key challenge in quantifying the outcome and outputs was that there was no mutual understanding or standard definition for the outcome criteria. Difficulties in operationalising the output and outcome may be due to differing pathways for different products (including types of approvals, research stages, etc.), and the many nuances associated with specific product pathways. Also, information on specific dates related to trial completion or other milestones was not immediately available from PDPs. For example, PDPs do not tend to have direct knowledge of the dates of country registrations (or the in-country authorities), which is the manufacturers' responsibility. Thus, the evaluation had to develop a working definition of the outcome criteria.

¹ Australian aid: promoting prosperity, reducing poverty, enhancing stability (2014). Accessed at: <https://dfat.gov.au/about-us/publications/Documents/australian-aid-development-policy.pdf>

Focus on access for impact - Many of the products within the three PDPs' portfolios have only recently begun to reach the market readiness stage. True impact will rely on effective delivery, access to and uptake of these products by end-users. As PDPs primarily focused on the research and development of new products, access-related activities have not been a core focus during this investment period. Some exceptions include MMV's Lihir and Odisha programs and FIND's lab strengthening activities in Myanmar, Vietnam, India and Indonesia including improved use of diagnostics). However, as products get to market, issues of access and incentivising building partnerships to achieve access, are of increasing priority and should receive attention from DFAT and other donors in any future PDP investment.

Partnerships in the Asia Pacific - The PDPs are effectively engaging with stakeholders throughout the Asia Pacific through a significant number of partnerships, particularly with leading Australian researchers. Strengthening partnerships with the private sector, regulatory bodies and national health authorities at the country level, and regional alliances such as the Asia Pacific Leaders Malaria Alliance (APLMA) and the Asia Pacific Malaria Elimination Network (APMEN) offers opportunities for PDPs to improve research and development (R&D) and access capabilities in the Asia Pacific, thus enabling and accelerating delivery of both diagnostics and therapeutic products to population in need.

DFAT-PDP relationships - DFAT management of the investment improved significantly over time, transitioning from a more traditional grants management relationship with PDPs to a more active and collaborative one. The general consensus amongst those interviewed was that DFAT was in a strong and unique position to play a greater leadership role in the PDP space, not only as a strategically important funder, but also an enabler and/or convener of collaborations between PDPs to maximise synergies between diagnostics and treatments, collaborations among donors and other partnerships (e.g. with regulatory agencies or the private sector), particularly with regard to the Asia Pacific and health security.

Governance and risk management - The three PDPs have strong processes in place to ensure good governance, ethics, and risk management.

Value-for-money - Considering the progression of products along the innovation lifecycle, DFAT's investment in all three PDPs, through core funding, represented good value for money. PDPs have been able to leverage other sources of funding, pool risk, and pursue strict portfolio management strategies.

BMGF Medical Research Institute - The development of the Bill and Melinda Gates Foundation (BMGF) Medical Research Institute (MRI) has the potential to influence the PDP landscape significantly. As the largest/primary funder of PDPs, BMGF have already shaped the landscape, and this new initiative is likely to do the same. Plans for the MRI should be closely monitored through bilateral discussions as well as through the PDP Funders Group (PFG) over the coming months, and consideration given to how their decisions will influence options being considered by DFAT. There may be particular implications for the TB Alliance given the MRI's planned areas of focus.

PDP-specific findings

The performance of the three PDPs has been strong. All three PDPs continue to innovate products, processes/approaches, partnership models, commercialisation and scale-up strategies. This has resulted in effective R&D for diseases of global health significance.

For DFAT, TB and malaria focused PDPs continue to be a priority, with FIND, MMV and TB Alliance being sound investment decisions with the potential for continued impact through product introduction. The table below summarises the overall assessment of each PDP against the four aid policy tests. Based on the analysis of all data, each PDP was qualitatively assessed as either low, medium or high performing. It is important to take into account differences when assessing PDPs focused on pharmaceutical products (TB Alliance and MMV) and PDP focused on diagnostics (FIND).

Qualitative assessment of PDPs against Australia's aid policy tests

TEST	FIND	MMV	TB Alliance
Test 1 - Pursuing national interest	High	High	High
Test 2 - Promoting growth and reducing poverty	Medium	Medium	Medium
Test 3 - Australia's value-add and leverage	High	High	High
Test 4 - Making performance count	High	High	High

Test 1: TB and malaria focused PDPs are addressing a critical global health security threat to Australia and the Asia Pacific region as a whole, particularly when it comes to combatting drug resistant forms of the diseases. FIND, MMV and TB Alliance are engaged in the region (e.g. Indonesia and Papua New Guinea) and there has been good leadership coming from Australia.

Test 2: TB and malaria are two of the major diseases of poverty, with strong linkages to economic instability and hindered economic growth. By developing critical diagnostic tools and therapies targeted at various facets of these diseases, the three PDP investments are promoting growth and reducing poverty.

Products that have progressed along the product pipeline with DFAT support are only beginning to enter markets, with additional promising new products/regimens in the pipeline. These products are poised to deliver additional impact over the coming years but have yet to do so in any significant way, hence the medium rating for this test. There is a strong potential for continued alignment with Australia's development goals and justification for continued support of these PDPs.

Test 3: Regarding Australia's value add, the role that Australian researchers have played in PDP-related research deserves special attention. The PDPs and Australian researchers have mutually benefited from collaborating in globally significant, multi-sectoral partnerships. The collaboration has raised Australia's reputation on the international stage.

Test 4: The PDP investment lacked a strong monitoring and evaluation (M&E) framework and DFAT and the PDPs did not have a shared definition of the expected outcome and output. The sustainability of PDPs' achievements is bolstered by the pipeline of new product developments but threatened by the adverse funding climate.

Future investment options

Australia has done well to invest in diagnostics and medicines for TB and malaria. As Australia considers its future R&D investment under the Regional Health Security Initiative, PDPs represent a sensible investment. A diversified portfolio and supporting projects across the prevention-to-access

value-chain (including vaccines, vector control strategies, diagnostics, and medicines) are critical for future regional public health security. This evaluation report presents five options for future Australian investment in PDPs.

Key recommendations

1. From the range of five options developed, Australia's commitment to addressing health security issues in the Asia Pacific would be best addressed through a PDP investment which included a combination of:
 - Option 1 - Maintain current investments continuing to focus on TB and malaria diagnostics and medicines,
 - Option 2 - Investment in vector control in addition to continuing to focus on TB and malaria diagnostics and medicines, and
 - Option 5 – Develop a cross cutting supplemental program with a focus on enabling access and uptake for PDP products.
2. For any future investment in PDPs, DFAT should ensure a strong M&E framework is developed. This should include clearly defined outputs and outcomes, agreed to and developed in collaboration with PDPs. In particular, definitions of “successfully trialed” (e.g. successful at moving a product through the pipeline or successful at answering an important research question), “completion of late stage clinical trial” (i.e. with reference to diagnostics), “new or modified product”, and “registration in the Asia Pacific” should be operationalised for each PDP. This M&E framework should take a systems perspective, incorporating outcome indicators along the path from product development to uptake and effective use. Harmonising M&E efforts through the PFG is advisable.
3. Take a full innovation lifecycle approach and integrate support of product R&D with support for ensuring uptake and optimal use. With more products in the PDP pipelines reaching market readiness, greater attention should be placed on access, uptake, and preparing health systems to absorb PDP innovations most effectively.
4. Link DFAT research portfolios better to achieve a stronger end-to-end approach and greater coordination between R&D and access. Of DFAT's entire portfolio of health and medical research, thirty percent (30%) of the AUD30 million per annum currently goes toward PDPs, while 70% is for policy and systems research across a range of other health issues. While linkages do exist, use of formal mechanisms to link research activities with each other and with other aid investments will help maximise Australia's influence.
5. To provide greater transparency and alignment of investments to achieve product development results, it is recommended that DFAT further leverage the PFG to develop a more integrated monitoring and evaluation framework that reflects DFAT priorities. More generally, DFAT may wish to consider a greater leadership role on the PFG, particularly to help drive progress in the Asia Pacific.

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Acronyms and abbreviations

ACT	Artemisinin-based combination therapy
APLMA	Asia Pacific Leaders Malaria Alliance
AS	Artesunate
BMGF	Bill and Melinda Gates Foundation
CE Mark	European compliant mark
CPTR	Critical path to TB drug regimens
CRO	Contract research organisation
DALY	Disability-adjusted life year
DFAT	Department of Foreign Affairs and Trade (Australia)
DfID	Department for International Development (UK)
DNDi	Drugs for Neglected Diseases initiative
DR-TB	Drug resistant Tuberculosis
DS-TB	Drug sensitive Tuberculosis
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDC	Fixed dose combination
FIND	Foundation for Innovative New Diagnostics
GMP	Good manufacturing practices
IPTp	Intermittent preventive treatment in pregnancy
LMIC	Low-and-middle income countries
LPA	Line probe assay
MDA	Mass drug administration
MDR-TB	Multi-drug resistant Tuberculosis
MMV	Medicines for Malaria Venture
MRI	Medical Research Institute (Gates Foundation)
MTB	Mycobacterium Tuberculosis
NTD	Neglected tropical disease
PDP	Product development partnership
PNG	Papua New Guinea
PRND	Poverty related and neglected disease
R&D	Research & development
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TBA	TB Alliance (Global Alliance for TB Drug Development)
TBVI	Tuberculosis Vaccine Initiative
UK	United Kingdom
US	United States of America
WB	World Bank
WHO	World Health Organization
XDR-TB	Extensively drug-resistant Tuberculosis

REQUEST:

Evaluate the existing DFAT PDP investments and provide options and recommendations for the next round of funding grants for PDPs.

Final evaluation of DFAT Australia's investment in Product Development Partnerships (2013-2018): Evaluation findings and options for future DFAT investment

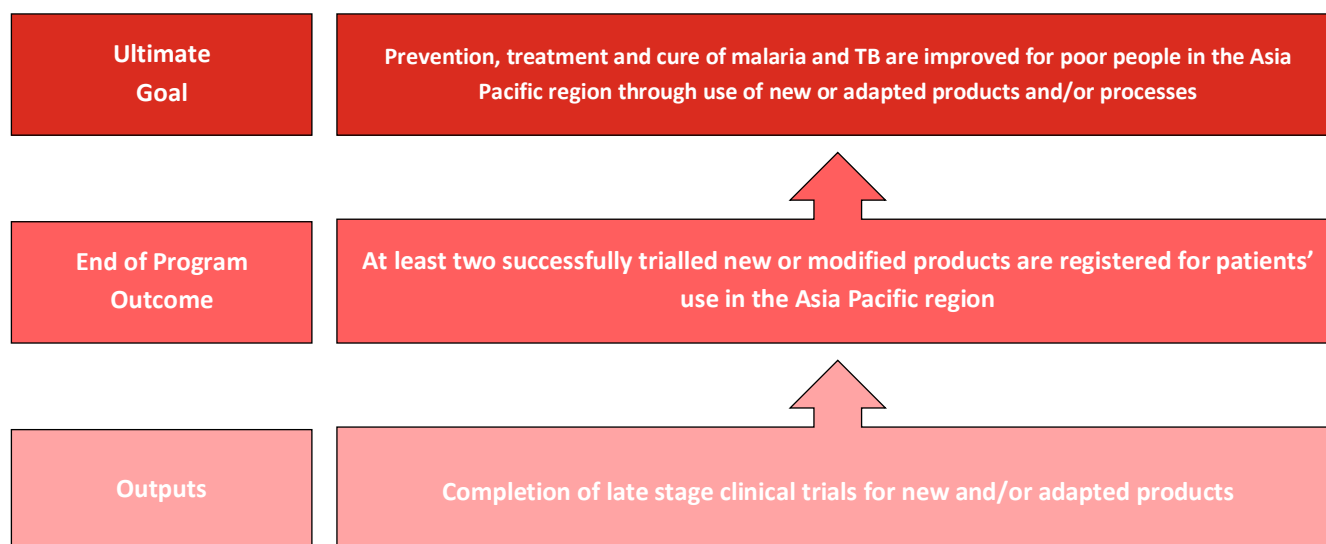
1. Introduction and methodology

1.1. Description of investment

Under the Australian Government's aid policy, *Australian aid: promoting prosperity, reducing poverty, enhancing stability* (2014), DFAT has invested AUD 40 million since 2013 in research for health and development through Product Development Partnerships (PDPs). These PDP investments were for the development and trial of new drugs, vaccines and diagnostic tests to respond to high burden diseases in the Asia Pacific region, specifically malaria and tuberculosis (TB).

The ultimate goal of the investment was to improve the prevention, treatment and cure of malaria and TB for the poor within the Asia Pacific region through the development of new or adapted products and processes. Figure 1 summarises the logic model for the investment. The investment's output was "completion of late stage clinical trials for new and/or adapted products". This output was to lead to an end-of-program outcome of "at least two successfully trialled new or modified products" being registered for patients' use in the Asia Pacific region by June 2017 across all of the PDPs. That is, the combined investment was to result in the registration of two new or modified products in the Asia Pacific region.

Figure 1. Simplified results framework for PDP investment PDPs were selected through a competitive bidding process that took advantage of a call for proposals process led by The Department for



International Development (DfID) in the United Kingdom (UK) opened in March 2012. In June of 2013, four PDPs received initial, one-year, core funding investments of AUD 2.5 million each (total = AUD 10 million) from DFAT. Funding to Aeras [PDP for TB vaccine research and development (R&D)] was suspended following an independent midterm evaluation².

A medium-term (three-year) investment continued for the three remaining PDPs that make up the current portfolio. This constituted AUD \$10 million each in core funding for:

- **Foundation for Innovative New Diagnostics (FIND)** for the development of better diagnostic tools and tests for TB and malaria;
- **Medicines for Malaria Venture (MMV)** for the development of antimalarial medicines; and
- **Global Alliance for TB Drug Development (TB Alliance)** for the development of new TB drugs and regimens, including for drug-resistant TB.

These three PDP investments are due to end in mid-2018 and are the focus of the current evaluation.

Assignment objectives

The work consisted of three objectives:

1. To evaluate the three PDPs supported by the investment (2013-present)
2. To draw lessons from the evaluation and develop a set of recommendations and options for the next round of PDP investments, targeting regional health security priorities; and
3. Development of the strategic design for DFAT's future PDP investment under the regional health security research pillar following DFAT review of proposed options.

This report covers the first two objectives. Section 2 includes the evaluation of the overall DFAT investment in PDPs for medical research. Section 3 is the evaluation of each of the three PDP investments (FIND, MMV and TB Alliance). Section 4 provides five options for DFAT's consideration for the next round of PDP investments with some recommendations.

1.2. Rationale for Investing in Product Development Partnerships

Prioritising TB and malaria

Despite tremendous progress over the past decade, poverty-related diseases such as HIV/AIDS, TB, malaria, and neglected tropical diseases still cause 6.7 million deaths and the loss of 354 million years of healthy and productive life in developing countries every year³. As with most of the poverty-related and neglected diseases, current drugs, vaccines and diagnostic and vector control technologies for TB and malaria are imperfect and

² In the evaluation, each of the PDPs were rated against the four investment tests in the Australian Aid policy. The lowest scoring PDP was Aeras, reflecting that vaccine development is a higher risk, longer term and more costly process compared to R&D for drugs and diagnostics. Developing TB vaccines is complex with a high risk of failure. Aeras had no late stage products in the pipeline and thus had low potential impact on disease burden over the next 5 years. (Meredith, S. Product Development Partnerships Assessment. Health Resource Facility for Australian Aid Program, 2014.)

³ Institute for Health Metrics and Evaluation (IHME). Global Burden of Disease Study 2015 (GBD 2015) Location Hierarchies. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017. Available from: <http://www.healthdata.org/data-visualization/gbd-compare>

have limited use because of their toxicities, durations, inadequate efficacies, or because they do not prevent reinfection⁴. Addressing TB and malaria require new approaches for scaling up existing strategies for treatment and prevention, novel tools to counter the growing threat of drug and insecticide resistance, and better surveillance mechanisms to more efficiently target interventions to populations and areas of high risk. Investing in new technologies for TB and malaria has been found to be comparable or more cost effective than scaling up existing technologies for the same diseases⁵.

Tuberculosis

Current approaches to preventing, diagnosing, and treating TB are inadequate. The World Health Organization (WHO) End TB Strategy urges the development of point-of-care TB diagnostic tests, a regimen to treat all forms of TB, research on detecting and treating latent TB infection, and the development of an effective vaccine⁶. Today's TB vaccine (BCG) is more than 85 years old; it provides limited protection for newborns and children (i.e. it is effective against disseminated TB in children, but not against primary infection or reactivation) and no protection against pulmonary TB in adults, which accounts for most of the worldwide disease burden. Today's most commonly used TB diagnostic, sputum microscopy, is more than 100 years old, is labour intensive for health providers, requires special skills, and lacks sensitivity, detecting only half of all cases. Delay in proper diagnosis costs patients valuable time and money in receiving treatment. Finally, today's TB drug regimen is more than 40 years old, must be taken for 6-9 months, assumes that a healthcare worker will supervise the full duration of treatment, and has significant side effects. The result is that many patients end treatment prematurely. Erratic or inconsistent treatment breeds drug resistant strains. Treatment for rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) is long, and requires more expensive and more toxic drugs⁷, although WHO guidance in 2016 has reduced the duration and cost of treatment. The cure rate for MDR-TB is approximately 50 percent and around 16 percent for XDR-TB⁸.

Malaria

New malaria drugs and insecticides are needed in response to the emergence of resistance to artemisinin-based combination therapies (ACTs) and pyrethroids. The plasticity of the mosquito and the *Plasmodium* parasite has led to increasing resistance to medicines and insecticides. Resistance to ACTs has been detected in five countries⁹ in the Asia Pacific region. In Cambodia, high failure rates after treatment with an ACT have been detected for four different ACTs. Resistance to dihydroartemisinin-piperaquine, first detected in Cambodia in 2008, has spread eastwards and was detected in Viet Nam in 2015¹⁰. The spread of these strains to Africa or the

⁴ Hotez PJ, Pecoul B (2010) "Manifesto" for advancing the control and elimination of neglected tropical diseases. PLoS Negl Trop Dis 4: e718. PMID:20520793

⁵ Gardner C., based on Disease Control Priorities Project www.dcp2.org and unpublished research by the Office of Health Economics, London UK (later commissioned by The Rockefeller Foundation) in Grace C. External Review of Product Development Partnership Grant Framework, 2009)

⁶ WHO, (2014) End TB Strategy, Global strategy and targets for tuberculosis prevention, care and control after 2015 http://www.who.int/tb/post2015_strategy/en/

⁷ Global TB Report 2016. Available at: <http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf>

⁸ Access and Delivery Partnership (2016). A Pipeline Analysis of New Products for Malaria, TB and NTDs – Working Paper. Available at: https://www.finddx.org/wp-content/uploads/2016/08/AccessDeliveryPartnership_Pipeline_Analysis_Report-2016.pdf

⁹ Cambodia, Vietnam, Lao, Thailand, Myanmar, +China (Yunnan Province)

¹⁰ Global Malaria Report 2016. Available at: <http://apps.who.int/iris/bitstream/10665/252038/1/9789241511711-eng.pdf>

Indian subcontinent could be catastrophic. In Africa, resistance has been detected against two or more insecticides in two-thirds of countries where malaria is endemic.

A focus on malaria eradication requires prioritisation of different types of medicines. Emphasis needs to be on breaking the cycle of disease transmission, rather than curing individual patients¹¹. Ideally, there will be a safe and sufficiently tolerated single-dose regimen which can be given to the widest range of recipients, including infants, pregnant women and those with no detectable infection. The key role of new medicines for the medium term including their minimum and ideal requirements under the eradication strategy for malaria is highlighted in a recent paper summarising the Technical Product Profiles for required malaria medicines¹².

Current field tests are not sensitive enough to pick up the low density of parasites in low-transmission areas. New diagnostics are particularly needed for non-falciparum species, to distinguish between malaria and other febrile illnesses, and to detect asymptomatic infections.¹⁵ As transmission decreases, it is increasingly clustered in at-risk populations such as forest workers, who often migrate between job sites, taking the disease with them; or geographically resistant areas or “hotspots” such as swamps and other sources of stagnant water that serve as breeding sites¹³.

Benefits of PDPs

The development problem to be addressed through DFAT’s investment was a market failure for the development of new drugs and diagnostics for TB and malaria. Because these diseases primarily affect people in some of the world’s poorest places, and due to the high costs and risks of such R&D, there is little commercial incentive for the private sector to develop these tools. Both the private and public sectors acknowledge that “a pure market mechanism generally does not work”¹⁴ where such tools are involved, and new approaches are needed.

To redress the imbalance in the availability of these tools in developing countries, PDPs use public and philanthropic funds to incentivise and engage industry and research institutions to develop much needed tools (e.g. medicines, diagnostics, vector control tools, vaccines, microbicides, etc.)¹⁵. Each PDP is focused on a specific technical goal. Some PDPs limit themselves to a particular disease area, while others focus on a small

¹¹ Burrows et al. New developments in anti-malarial target candidate and product profiles. *Malar J* (2017) 16:26

¹² Burrows et al. 2017

¹³ Hemingway J, Shretta R, Wells TNC, Bell D, Djimdé AA, Achee N, et al. (2016) Tools and Strategies for Malaria Control and Elimination: What Do We Need to Achieve a Grand Convergence in Malaria? *PLoS Biol* 14(3)

¹⁴ Buse K, Walt G. Global public–private partnerships: part 1 – a new development in health? *Bulletin of the World Health Organization*, 2000, 78(4):549–561.

¹⁵ Incentives for the development of poverty related and neglected disease technologies can be categorised into “push” and “pull” categories. “Push” funding policies aim to incentivise industry via reduced costs during the R&D stages, whereas “pull” mechanisms create incentives for private sector engagement by creating viable market demand. Push mechanisms pay for “effort” on the part of researchers, by underwriting the cost of that effort, while pull mechanisms pay for “results”. Donors supporting PDPs with direct grants would fall under the “push” category, while on the “pull” side, there have been increases in development assistance for health (e.g. USD \$70B in 2000 to USD \$142B in 2016). Much of this has been routed through global health institutions such as the Global Alliance for Vaccines and Immunisation (GAVI), the Global Fund for AIDS, TB and Malaria, and UNITAID. It is estimated that about 40% of Global Fund grants are used for health commodity purchase and a much higher percentage of GAVI and UNITAID funds are directed towards commodity purchase. These funds send “pull” signals to industry that a credible market exists, though the strength of these signals is limited because the financial amount is not pre-defined well in advance, donors are not legally obligated to honour their funding commitments, and the products, volumes and purchase price are not committed in advance. (Source: Grace C. & Kyle M. Comparative advantages of push and pull incentives for technology development. *Global Forum Update on Research*; 6: 147-151).

sub-set of diseases. PDPs tend not to undertake R&D in-house, but rather allocate resources to the most promising projects, provide technical insight, facilitate partner R&D activities and manage project portfolios to fulfil objectives. The majority of PDPs tend to work as virtual non-profit R&D organisations. By actively managing a portfolio of projects, PDPs pursue multiple innovation avenues to distribute risk and increase chances of success.

1.3. Methodology

Evaluation methodology

The evaluation team comprised Dr Rohit Ramchandani of Antara Global Health Advisors¹⁶ and Barbara Bulc of Global Development (GD)¹⁷. The engagement (evaluation and design of next investment) ran from July 21 – September 13, 2017. See Annex 1 for Terms of Reference (TORs).

The evaluation methodology for this end-of-investment assessment consisted of 1) a published and peer reviewed grey literature review, 2) additional document review (as provided by DFAT and individual PDPs), 3) PDP website review, and 4) key informant interviews. Key documents and peer-reviewed literature are cited throughout this report. Data gathered from all of these sources were analysed and triangulated to inform this assessment including the related design options and recommendations.

Fourteen semi-structured interviews were conducted with 21 key informants identified across four stakeholder groups – donors (N=5) (including DFAT representatives), Australian researchers (N=4), industry (N=3), and PDP representatives (N=9). Respondents were chosen using purposive sampling based on seniority within their organisations and relevance of their role. All of the individuals who received an interview request agreed to participate. A list of individuals and organisations interviewed is in Annex 2. All interviews were conducted by phone/Skype, with Barbara Bulc also attending the Geneva-based PDP interviews in person. Interview protocols (see Annex 3) were developed for each stakeholder group covering the core evaluation criteria identified by DFAT. Respondents were sent the questions before the interview and asked to provide written answers. This allowed the interview to focus on clarifying the written responses and discuss broader themes. The purpose of the interview and the use of the information collected was explained. Interviews were audio-recorded to assist in analysis.

Methodological limitations

The evaluation encountered the usual limitations of desk reviews. Available documentation did not always provide the most comprehensive or up to date information, answers to specific evaluation questions, or address biases (i.e. PDP materials may sometimes be biased towards the positive). Information provided by the PDP or previous reviewers was not validated or cross-checked.

The final assessment was conducted over a very short period relative to the scope of the evaluation. Having to manage calls across multiple time-zones during a peak holiday season resulted in delayed interviews, some identified potential respondents not being available during the data collection period, and a smaller sample size of key informants (e.g. donors). The short turnaround times meant that findings were shared with PDPs for

¹⁶ <https://www.antaraglobal.com> based in Toronto, Canada

¹⁷ <http://www.gd-impact.org/> based in Geneva, Switzerland

validation purposes after the first draft was completed. There was limited opportunity to conduct comparative assessments with other investment strategies. Validation was limited to the triangulation of findings with secondary sources during the analysis, which helped mitigate some of the challenges.

Key findings were clarified with PDPs during the revision stage, with a focus on product progression timelines (i.e. how/when DFAT-supported products moved through the pipelines of individual PDPs).

2. Overall PDP evaluation

2.1. Assessment against design outcomes and outputs

The objective of DFAT's investment in PDPs, as described in the Investment Design, was to address the need for new and adapted products for diseases of the poor. Specifically, the investment aimed to improve the diagnosis and treatment of such diseases prevalent in the Asia Pacific. With TB and malaria accounting for much of the disease burden amongst the poor, developing products for these diseases was (and remains) a priority, and the three PDPs that comprise this investment were selected to meet these objectives.

"We have products coming out the other side and have been pleased with our portfolio so far.... Over the next five year period we would expect to see five new products between now and 2021 across all of the PDPs [we invest in].... We should be very pleased. This is unheard of productivity. Let's celebrate that success."

- Donor

A key challenge in establishing what the investment achieved was that DFAT and the PDPs did not have a clear mutual understanding of the definitions of the expected output and end-of-program outcome. Specifically, there was ambiguity around the definitions of "registration for patients' use in the Asia Pacific" and "a successfully trialled new or modified product".

One cause of the ambiguity was that the three funded PDPs have different modes of operation, types of products, and the types of milestones their products must achieve as they move through the pipeline. To address this challenge, PDPs were asked to specify the progression timelines for products in their pipelines and to clarify how they defined the outcome and output for the investment. The definitions used by some of the PDPs are broader than what the original DFAT design intended. Thus, for this evaluation, more stringent criteria were used.

To meet the investment outcome, products had to be registered in at least one high burden (TB/malaria) Asia Pacific country (which is the first key step towards impact in the Asia Pacific) and have received a stringent regulatory authority approval. However, in most cases, the specific timing around when products were registered in individual countries and by what specific regulatory authority is unknown to the PDPs because registration is the manufacturer's responsibility. In these cases, the evaluators considered the outcome to be met if the product had gained WHO pre-qualification or approval by the US Food and Drug Administration (FDA) or a European agency during the investment period and was known to be registered in an Asia Pacific country at some time.

PDP products that progressed through key trial milestones with support from the DFAT investment were considered to have met the output objective. A range of products meet these criteria, reflecting that the trials of “new or modified” products may have multiple stages or associated studies and test different aspects/functions of a product, with some trial components being years apart. Diagnostic tests do not go through clinical trials, but efficacy tests under field conditions are conducted.

Using these clarified definitions (to the extent possible retrospectively) the evaluation concludes that the PDPs have collectively registered five new or modified products in the Asia Pacific during the period of the DFAT investment to date (2013-17):

- An initial test for multi-drug resistant TB (MDR-TB) targeting first line drugs
- An existing testing system, shown during the reporting period to be highly sensitive for TB *and* MDR-TB and suitable for district level labs in low and middle income countries, gained expanded WHO and FDA endorsements in this period
- Affordable, child-friendly fixed dose combination treatment to treat paediatric patients with drug sensitive TB
- The first artemisinin-based combination therapy (ACT) approved to treat acute, uncomplicated malaria caused by either *P. falciparum* or *P. vivax* in children and adults
- A treatment for uncomplicated *P. falciparum* that also protects against new infections, for use in countries using mass drug administration to accelerate malaria elimination.

Details on the newly registered or approved products for use in the Asia Pacific are in Annex 4.

The PDPs also reported at least 17 drugs and diagnostic tools that were in some form of late stage trials regarding aspects of their efficacy or formulation. These are described briefly here and in detail in Annex 5.

- Nine diagnostic tests for malaria and TB and a set of reference material for the testing of the quality of malaria rapid diagnostic tests
- Five phase 2 and phase 3 trials for various combination treatments for TB
- Trials in Asian countries of a single dose treatment for relapsing *P. vivax*, the first potential new medicine to treat this in more than 60 years
- Trials of a dispersible form of registered drugs already available in a different form to treat and protect against malaria caused by *P. falciparum*.

The PDPs also provided examples of several products of note which do not technically meet the definition used for assessing successful completion of the investment output but indicate progression of products through the product pipeline. These are included in Annex 5.

- Various studies to enable the commercial production of a formulation of paediatric MDR-TB treatments (not strictly a clinical trial, but work necessary for product development following new WHO guidelines). This involved the three drugs used in combination to treat paediatric patients.
- A diagnostic test for TB that completed trials in 2010 but was given approval by a stringent regulatory agency and WHO endorsement in the investment period.

- A number of malaria compounds including, but not limited to, an inhibitor of a key enzyme required for the plasmodium parasite's survival, a potential single-exposure cure potent against malaria's blood stage, and a potential replacement for artemisinin.

2.2. Assessment against aid policy tests

DFAT's PDP investment was designed to meet the four Australian aid policy tests which determine if the program will meet Australian policy objectives. The evaluation examined the evidence that the PDPs' efforts during the investment period contributed to the policy objectives. The analysis incorporates capacity building (Test 2), governance/management of the PDPs (Test 4), and sustainability (Test 4).

Three of the five key investment priorities under the Health for Development Strategy (2015-2020) were addressed by the PDP investment, and are assessed under the relevant Aid Policy Tests. These include:

- Investments to combat health threats that cross borders – TB and Malaria
- Investment in a more effective global health response in the Asia Pacific region
- Investments to promote health innovation

Test 1: Pursuing national interest & extending Australia's influence

Test 1

Australia's aid policy notes that considerations under the first aid investment test will include "an assessment of the costs of regional instability and insecurity, including financial, humanitarian, political and health-related risks, prospects to strengthen trade and investment, and the potential to extend Australia's influence."

Assessment of this aid policy test has been broken down into two subsections: 1) health security and prosperity in the national interest, and 2) extending Australia's influence.

Health security & prosperity in the national interest

Australia's aid policy recognises the centrality of health-related risks to regional stability and economic prosperity. DFAT's Health for Development Strategy¹⁸ specifically includes strengthening regional preparedness and capacity to respond to emerging health threats as one of two strategic outcomes. Combatting health threats that cross national borders and development of new approaches and solutions that benefit the region are seen as two of the key investment priorities to achieve this outcome. While increased regional connectivity provides opportunities for stronger collective action, it also presents new challenges in containing the spread of communicable diseases, of which TB and malaria are recognised priorities.

FIND and TB Alliance focus on TB, one of the top ten causes of death worldwide, and the leading cause of death from an infectious disease in the Asia Pacific region¹⁹. FIND and MMV focus on malaria. Nearly half of the world's population is at risk of malaria; in the Asia Pacific 15.6 million people had malaria in 2015²⁰. PDP research and development of products focused on both of these diseases has begun to improve health security

¹⁸ <http://dfat.gov.au/about-us/publications/Documents/health-for-development-strategy-2015-2020.PDF>

¹⁹ OECD/WHO. Health at a Glance: Asia/Pacific 2016: Measuring Progress towards Universal Health Coverage. Accessed at: http://dx.doi.org/10.1787/health_glance_ap-2016-en

²⁰ WHO. World Malaria Report 2016.

and prosperity in Australia, and will increasingly do so as developed and developing products move towards scale in the region. PDP contributions under this investment are examined based on how they could increase regional health security.

Tuberculosis

TB Alliance progressed optimised **paediatric fixed-dose combinations (FDCs)** through their pipeline during the investment period, with support from DFAT. Their STEP-TB project was launched in 2013 (with WHO as co-implementer). Under this program, TB Alliance developed and launched the first correctly dosed, appropriately formulated, child-friendly FDCs of standard line paediatric therapy. The new FDCs adhere to current WHO guidance and were launched by two manufacturers in 2015 and 2016. Since the FDCs were launched, they have been introduced in 36 countries (including countries in the Asia Pacific region – see Annex 5 for details). The six month course is being provided at an affordable price of USD15.54.

These new drug formulations offer significant advantages over previous drugs such as ease of administration due to quick dispersability into liquid and palatable fruit flavours. Based on such advantages, the new products are expected to improve treatment adherence and outcomes, including in the Asia Pacific. Before this, there was no standard TB treatment for children and treatment was estimated based on standard adult measure, which required crushing pills and often inaccurate dosing.

Inadequate diagnosis and therapy have led to the emergence of multi-drug resistant MDR-TB (MDR-TB). The Asia Pacific region has been recognised as an epicentre for emerging infectious diseases, including drug resistant TB (DR-TB). In 2015 an estimated 580,000 TB patients in the Asia Pacific were resistant to rifampicin²¹. However, less than 70% of new TB cases and only 25% of new drug-resistant cases were diagnosed or treated. FIND has developed new TB diagnostic products to meet this challenge and two of them met the outcome criteria during the investment period, with others being close behind.

The first product that met the outcome criteria is the **GeneXpert® MTB/RIF (Xpert)**. The development of the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA) was a major step forward for improving the point-of-care or decentralised diagnosis of TB and rifampicin resistance detection globally.

Xpert MTB/ RIF assay is used for rapid, simultaneous detection/diagnosis of *Mycobacterium tuberculosis* (MTB) and rifampicin resistance in less than two hours. In comparison, standard liquid cultures can take two to six weeks for MTBC to grow and conventional drug resistance tests can add three more weeks. The information provided by the Xpert MTB/RIF assay aids in selecting treatment regimens and reaching infection control decisions quickly. Minimal technical training is required to run the test.

Additionally, the Xpert MTB/RIF assay can quickly identify possible MDR-TB, because rifampicin resistance is a predictor of MDR-TB as rifampicin resistance typically co-exists with Isoniazid (INH) resistance. Rapid diagnosis of rifampicin resistance potentially allows TB patients to start on effective treatment much sooner. Although it received CE Mark in 2009 and was endorsed by the WHO in December of 2010²² following 18 months of rigorous field assessments, it was granted marketing authorisation by the FDA in 2013 and also received WHO endorsement for use in paediatric patients, and to detect extra-pulmonary TB (related trials ended in 2014). In

²¹ WHO Global Tuberculosis Report 2016. Available at: http://www.who.int/tb/publications/factsheet_global.pdf

²² WHO endorses new rapid tuberculosis test" 8 December 2010

February of 2015, the FDA cleared the assay for expanded use to help practitioners determine if patients with suspected TB can be removed from airborne infection isolation²³. This Ultra cartridge (compatible with the GeneXpert) and developed by Cepheid (Sunnyvale, USA), has shown significantly better performance (increased sensitivity leading to 10-20% more cases diagnosed and treated rapidly) compared to the current Xpert MTB/RIF cartridge in specimens with low numbers of bacilli, especially in smear-negative, culture-positive specimens (e.g. persons with HIV co-infection), in paediatric specimens and in extra-pulmonary specimens (notably cerebrospinal fluid). The accuracy in detection of rifampicin resistance was also better although not enough data were available to confirm this conclusively. Ultra performance approaches that of liquid culture but is faster and easier to use at the point of care²⁴. Countries with access to concessional pricing will pay USD 9.98 for the test. Registration and uptake in countries recently kicked off and will be ongoing through 2018. A list of specific countries within the Asia Pacific should be available shortly.

The second FIND product meeting the outcome criteria was a **line probe assay (LPA) for 1st line TB drugs** (version 2.0), with commercial producers including HAIN, Germany (Geno Type MTBDRplus) and NIPRO, Japan (NTM+MDR-TB Detection kit 2). Growing concerns regarding the spread of MDR-TB and alarm over the emergence of XDR-TB have sparked a great deal of interest in the development and application of rapid diagnostic tests for the detection of DR-TB. Early detection of MDR-TB and extensively drug resistant TB (XDR-TB) is critical to initiate appropriate treatment, reduce morbidity and mortality, and prevent further transmission of drug-resistant strains of TB. Molecular assays to detect gene mutations that signal drug resistance are widely recognised as being most suited for rapid diagnosis. LPAs, are a family of novel DNA strip-based tests that use Polymerase chain reaction (PCR) and reverse hybridisation methods for the rapid detection of mutations associated with drug resistance. A major advantage of LPAs is that these assays can be directly used on clinical specimens like sputum.

Other TB products that did not quite meet the outcome criteria, but have pending submitted dossiers or are in the late stages of the pipeline and therefore poised for potential impact include (See Annex 5 for details):

- **TB Alliance:** Correct dose dispersible INH (Isoniazid), E (Ethambutol), and Z (Pyrazinamide) single formulations, BPaL, BPaMZ
- **FIND:** TB LAM RDT, TB LAMP, LPA for 2nd line drugs, TrueNat/TruLab

Malaria

Malaria is endemic in 17 countries within the Asia Pacific²⁵, associated with poverty and hindering progress towards economic well-being among affected communities. Leaders in the region have recognised malaria as a key issue during discussions on regional security and stability, territorial disputes and economic partnership²⁶.

²³ <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434226.htm>

²⁴ Quote from Alland D. Professor of Medicine and Director of the Center of Emerging Pathogens, Rutgers New Jersey Medical School. Available at: <http://www.cephheid.com/us/about-us/news-events/press-releases/216-2017-launch-of-new-tb-test-ultra-backed-by-who-recommendation>

²⁵ Papua New Guinea, Solomon Islands, Pakistan, India, Nepal, Philippines, Indonesia, Myanmar, the Lao PDR, Cambodia, Thailand, DPR Korea, China, Viet Nam, Bangladesh, Republic of Korea and Malaysia.

²⁶ <http://news.trust.org//item/20151204051403-2sqh4/>

Early diagnosis and treatment of malaria reduces morbidity and prevents death. It also contributes to reducing malaria transmission. Pregnant women, young children, and non-immune travellers from malaria-free areas are particularly vulnerable. While the proportion of women who receive intermittent preventive treatment in pregnancy (IPTp) for malaria has been increasing over time, coverage levels remain below national targets.

In many countries, progress in malaria control is threatened by the rapid development and spread of antimalarial drug resistance. To date, parasite resistance to artemisinin – the core compound in WHO-recommended combination treatments for uncomplicated malaria, has been detected in five countries of the Greater Mekong sub-region – Cambodia, Laos, Myanmar, Thailand and Viet Nam. Resistance to chloroquine and other commonly available antimalarial drugs is also a major issue in the region, as it is worldwide²⁷. The emergence of chloroquine (and pyrimethamine) resistance in South East Asia and subsequent spread to Africa is thought to have contributed to the death of millions of African children²⁸.

The problem is aggravated by the increasing proliferation of low-quality and counterfeit drugs, and widespread irrational drug use in the private sector. Drug-resistant malaria emerging in the Greater Mekong sub-region threatens to undermine a decade of progress globally, potentially costing billions²⁹.

Rapid diagnostic testing (RDTs), introduced widely over the past decade, has made it easier to swiftly distinguish between malarial and non-malarial fevers, enabling timely and appropriate treatment, helping to prevent resistance.

Under this PDP investment, both MMV and FIND focused on products for malaria. The MMV products that met the outcome criteria included **FDC products of pyronaridine and artesunate**. Combination therapy of two or more drugs with different modes of action, particularly using artemisinin-based compounds, is highly effective and may help delay drug resistance. The products are being used to counter resistance to artemisinin and partner drugs in Asia and as an alternative first-line treatment in sub-Saharan Africa, to delay the emergence of resistance. This new product is also expected to contribute to improvement in adherence to treatment due to the patient-friendly, once-daily dosing regimen and availability of the child-friendly granule formulation.

Produced by Shin Poong Pharmaceuticals in South Korea under the brand **Pyramax®**, this is the first ACT to be granted positive scientific opinion under EMA Article 58 procedure (2015 – including approval for paediatric granules and a newly expanded label for adult tablets). The product is the first and only ACT approved for blood-stage treatment of *P. falciparum* and *P. vivax*, as well as the first Korean product included in WHO's list of prequalified medicines for malaria. The product received WHO prequalification in 2016 and expanded European Medical Authority (EMA) approval in 2015. The latter removed all restrictions on repeat-dosing, use only in areas of high resistance and low transmission, and requirements for liver function monitoring.

Eurartesim® (dihydroartemisinin-piperaquine, DHA-PQP) was the second MMV product that met the outcome criteria for the investment. While EMA approval (marketing authority) was granted in 2011, WHO prequalification was received in 2015³⁰. WHO prequalification represents the second critical milestone on the

²⁷http://www.wpro.who.int/southpacific/programmes/communicable_diseases/malaria/page/en/index2.html

²⁸ Eline L. Korenromp et al. 2003. Measurement of Trends in Childhood Malaria Mortality in Africa: An Assessment of Progress toward Targets Based on Verbal Autopsy. *The Lancet Infectious Diseases* 3: 349–357.

²⁹ <http://www.cdc.gov/globalhealth/security/actionpackages/default.htm?>

³⁰ <https://www.mmv.org/newsroom/news/eurartesim-dihydroartemisinin-piperaquine-receives-who-prequalification>

path to make this highly efficacious medicine available to as many malaria patients as possible. It was registered in Cambodia in 2012 (the first country in the world to register), and in Thailand during the investment period. DHA-PQP is one of the ACTs recommended by WHO for the treatment of uncomplicated *P. falciparum* malaria. It has been adopted as first-line treatment in several South East Asian countries and is increasingly considered for second-line and in some cases first-line treatment in African countries. It is taken once a day for three days and is therefore expected to contribute to improvement in adherence to treatment due to the patient-friendly, once-daily dosing regimen and availability of the child-friendly granule formulation. Given its relatively long half-life, it affords patients with a useful period of protection from the risk of new malaria infections. Eurartesim is also under evaluation in various mass drug administration trials and is being tested as an IPTp, this with support from DFAT. MMV also expects submission of a dispersible paediatric formulation to EMA before the end of 2017.

One FIND diagnostic focused on malaria that did not quite meet the outcome criteria, but achieved relevant milestones, was the **Malaria Molecular LAMP (Loop-mediated Isothermal Amplification)**. WHO has recommended the use of molecular tests like this as an elimination tool for the detection of sub-microscopic infections. The test received CE Mark in 2012 and WHO endorsement for use in asymptomatics in 2014. While the trials focused on registration requirements ended in December 2012, demonstration studies for detection in asymptomatic patients are ongoing (including in Philippines and Indonesia). The dual testing kit is used for *P. falciparum* as well as *P. spp.* It has a role in identifying hidden infections in screening programmes for elimination, as is being done in six low-transmission countries in the Asia Pacific, including Indonesia. It is intended 1) to serve as a reference standard against which RDTs and other malaria diagnostics can be evaluated, 2) to confirm the presence or absence of malaria parasites in complex cases, and 3) to support clinical trials. It is designed for use with the LAMP platform and is intended as a field tool to detect very low-density malaria infections given its high sensitivity and is an important tool for malaria elimination. Globally, approximately 35,000 kits are being sold by Eiken per year. In-country registration in Asia Pacific countries is in progress.

Other malaria products that also did not quite meet the outcome criteria, but have pending submitted dossiers or are in the late stages of the pipeline and therefore poised for potential impact include:

- **MMV:** Tafenoquine, Rectal Artesunate, Dispersible Eurartesim,
- **FIND:** Malaria Highly Sensitive RDT (e.g. Alere Malaria Ag P.f - Ultra Sensitive)

Limitations of current investment on health security: access and uptake

All the products described address a gap in previous testing and treatment options. However, developing the products to the point of being market ready is only one step towards making Asia Pacific more resilient to TB and malaria. Getting products to market readiness does not necessarily equate to the treatment of large numbers of patients and therefore will not on its own stop transmission. Furthermore, many products have still not been introduced and taken to scale in Asia Pacific countries. A couple of examples illustrate the point:

- According to the latest figures obtained by the evaluators, paediatric FDCs have not been distributed in the numbers required to treat all children with TB (seems to be a gap between total courses delivered by manufacturer vs annual need) nor malaria.
- While still crucial, it should be noted that, even if all children with TB were treated appropriately, the burden of TB in children in the Asia Pacific is limited and would not halt transmission. Incidence in

children (0-14) accounts for approximately 11.6% of all incident cases, while notifications in children are only around four per cent of all notified cases in WHO's Western Pacific Region³¹ (pointing to the need for improved diagnostics and health system strengthening). In WHO's South-East Asia Region, incidence in children accounts for approximately eight per cent of all incident cases, and notifications in children for approximately six per cent of all notified cases³².

- Sputum smear microscopy—which misses over half of TB cases³³ and gives no indication of drug susceptibility to guide appropriate treatment—is still the diagnostic standard in most of the world, despite the availability of the far more sensitive original GeneXpert MTB/RIF for more than six years³⁴.

Extending Australia's influence

Australia has played an important role as a funder of the three PDPs being evaluated. It has been able to maximise its investment in each PDP as a result of the core/portfolio funding approach, common across all three PDPs. This funding approach allows the PDPs to maintain a dynamic portfolio, thereby increasing chances of success, reducing the risk of failure, and ensuring efficiency and good value for money. The flexibility conferred by core/portfolio funding provides increased resilience when project-specific funding comes to an end (e.g. DFAT funding has been effectively used as bridge financing). Also, the agility to capitalise on new opportunities is also crucial in ensuring optimisation of the PDP model. These opinions were shared by the PDPs and other funders such as DFID, who noted, "It is unrealistic to only fund small parts of the portfolio. We are better off using our funding to support a portfolio of different products. ...This way the PDPs can be nimble and push the most useful ones [products] forward quickly as possible... [This funding approach] makes sure the PDPs can manage things most effectively."

While participation in the PDP Funders Group (PFG) also had the potential to be an avenue for extending Australia's influence, other donors expressed that Australia's involvement could have been more consistent. A lack of continuity in the staffing arrangements (i.e. program officers changed throughout investment period), hindered DFAT's contribution, although DFAT's engagement improved towards the end of the investment.

Interviewees felt that DFAT could play a stronger role going forward, particularly with regard to increasing attention and activities, as well as using its influence to help improve regulatory processes, within the Asia Pacific region. This has started happening to some extent. MMV, for example, noted that Australia was helping with the operational steps needed for finalising the development process and launch for Tafenoquine through cooperation with regulatory authorities across the Asia Pacific via Australia's Therapeutic Goods Administration (TGA). Australia's leadership in APLMA and APMEN and the Australian Parliamentary Commitment to PDPs (Senate, House of Representatives and relevant Committees) were seen to perform important advocacy roles.

The involvement of Australian researchers in the three PDPs, which has been critical to expanding Australia's influence, is discussed under Test 3.

³¹ Global TB Report, 2017. Accessed at: http://www.who.int/tb/publications/global_report/gtbr2017_annex3.pdf?ua=1, pg. 223

³² Global TB Report, 2017. Accessed at: http://www.who.int/tb/publications/global_report/gtbr2017_annex3.pdf?ua=1, pg. 222

³³ Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* [Internet]. 2006 Oct;6(10):664–74.

³⁴ World Health Organization. WHO endorses new rapid tuberculosis test. Geneva: World Health Organization; 2010 December 8. Available from: http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/

Test 2

Australia's aid policy notes that it will "direct aid where it will best tackle constraints to growth and poverty reduction. The poverty situation in a country will continue to be a major determinant of need. A country's capacity to mobilise domestic resources and self-finance its own efforts to accelerate and sustain growth and poverty reduction programs will inform future levels of aid as well as the types of aid provided."

Similar to Test 1, evaluation of the PDP investment against Test 2 is best examined from a target disease lens. It is well established that the economic welfare returns and impact on poverty alleviation associated with investments in health are exceptional and positive – with previously unrecognised implications for public sector resource allocation (substantiated by the WHO Commission on Macroeconomics and Health). These returns go well beyond the impact better health has on per capita income, which itself appears substantial^{35,36}.

While products from the three PDPs, focusing on malaria and TB, have only recently begun to penetrate markets and get uptake at the population level, including those that have received support from the DFAT investment, the groundwork is now laid for population level impact.

Tuberculosis

TB and poverty remain inextricably linked. Over 95% of TB deaths occur in low- and middle-income countries (LMICs), among communities where people live in absolute poverty. In these countries, TB heavily impacts the most marginalised groups including people living with HIV, women and children. Poverty facilitates the transmission of *Mycobacterium tuberculosis*, primarily through 1) its influence on living conditions, such as people living in overcrowded and poorly ventilated homes, 2) prolonged diagnostic delay and 3) increased vulnerability due to malnutrition and HIV infection^{37,38}.

Through the development and delivery of products to improve diagnosis and treatment of TB and DR-TB, both FIND and TB Alliance are making a potential contribution to economic growth and reduction of poverty. Specifically, three products, **LPA for 1st line TB drugs, the GeneXpert MTB/RIF, and Paediatric FDCs**, are addressing TB challenges related to resistance and vulnerable groups such as children.

The FIND technologies have and will continue to contribute to improved MDR-TB case notification rates in the Asia Pacific, which has significantly increased (>5x between 2009 and 2013, and >4x between 2010 and 2015³⁹)

³⁵ Bloom D. E., Canning D., Jamison D. T. Health, Wealth and Welfare. Finance and Development. 2004;41(1):10–15

³⁶ Lopez-Casasnovas, G., B. Rivera, and L. Currais, eds. 2005. Health and Economic Growth: Findings and Policy Implications. Cambridge, MA: MIT Press

³⁷ Marais BJ, Obihara CC, Warren RW, Schaaf HS, Gie RP, Donald PR. The burden of childhood tuberculosis: a public health perspective. Int J Tuberc Lung Dis 2005; 9:1305–1313.

³⁸ Marais BJ, Esser M, Godwin S, Rabie H, Cotton MF. Poverty and HIV in children a view from the Western Cape, South Africa. Ann N Y Acad Sci 2008; 1136:21–27.

³⁹ Islam T et al. Drug-resistant tuberculosis in the WHO Western Pacific Region. Western Pac Surveill Response J. 2014 Dec 18;5(4):34-46 + comparison of Global TB Report 2013 to 2016.

since the Xpert MTB/RIF received CE Mark approval⁴⁰. Countries like Indonesia and those in the Mekong are in the midst of scaling FIND technologies.

Malaria

Like TB, malaria and poverty are intimately connected. As both a cause and a consequence of poverty, malaria is most intractable for the poorest countries and communities in the world⁴¹. The impact of malaria takes its toll on the poorest – those least able to access preventive measures and medical treatment. Countries with high malaria transmission have historically had lower economic growth than in countries without malaria and countries that have been able to reduce malaria have shown substantial growth and improved prosperity⁴².

Investment in diagnostics and new treatments have been shown to reverse the negative economic impacts of malaria. FIND told the evaluators about a study in Senegal that showed correct diagnosis through RDT use has halved the use of ACT regimens, saving the country and the Global Fund (GFATM) €1.2 million.

The malaria products meeting the outcome criteria under this investment (Pyramax and Eurartesim) are helping treat cases of uncomplicated malaria in children (both *P. vivax* and *P. falciparum*). The products are being used as a preventative in mass drug administration campaigns in support of national elimination efforts where *P. falciparum* is the main cause of malaria. Eurartesim's potential use for IPTp may also help address a key vulnerable group (i.e. pregnant women) in the future.

Capacity building

The contribution of the three PDPs in capacity building plays a critical role in promoting growth and reducing poverty in the long run. All of the PDPs supported under this investment had capacity building activities, including building capacity to conduct trials, strengthen laboratories, train health workers and other health systems strengthening interventions (see individual evaluations for specific examples).

To illustrate, FIND has helped strengthen laboratory capacity in Indonesia. Indonesia is the second largest high burden country for TB after India and laboratories have been poorly staffed with no mechanism in place for referring samples. Laboratory strengthening activities have also taken place in Myanmar since 2007, resulting in an increase in DR-TB cases detected. In Vietnam, FIND helped establish an external quality assurance (EQA) program that will serve other countries in the region. Over 80% of India's diagnostic capacity to diagnose drug resistance has been established by FIND.

⁴⁰ Van Gemert, W. 2010-2015: uptake and impact of Xpert MTB/RIF. Available at: <http://www.stoptb.org/wg/gli/assets/documents/M7/1.%20VAN%20GEMERT%20Xpert%20update.pdf>

⁴¹ The Earth Institute, University of Columbia

⁴² The Economic Burden of Malaria, Jeffrey Sachs & John Luke Gallup, Center for International Development, Harvard, February 2001

Test 3

With regard to its third investment test, Australia's Aid Policy notes the importance of assessing "Australia's value-add and our realistic capability to shape partner countries' efforts to pursue economic reform, growth and poverty reduction."

As a result of Australia's investment, PDPs have been able to progress the goal of furthering the prevention, treatment and cure of TB and malaria in the Asia Pacific. Leveraging funding to accelerate product development is the core purpose of PDPs. PDPs act as facilitators, bringing dedicated sources of funding and know-how to committed researchers so they can collaborate on the right projects to fulfil the objectives of the PDP's mission. PDPs rely on partners for financing and other in-kind contributions (such as laboratories and expertise) and allocate resources to the most promising projects, coordinate partner activities for various stages of the R&D process, and manage project portfolios. They have been able to engage the private sector in development and manufacturing of priority health interventions. The PDPs' private partners include but are not limited to Newcrest Mining, Atomo, Cellabs, Omega Diagnostics (Dx) and PepsiCo.

All three PDPs have been successful in leveraging funding with significant non-cash contributions from their partners including those in the private sector. According to the TB Alliance, partners' contributions enabled them to leverage at least USD 0.68 for every dollar of donor funds invested. In-kind contributions in the form of facilities, staff and supplies represented on average 11.3% of FIND's total spend. For MMV, every USD 1 of donor funding leverages on average an additional USD 2.50 of matched and in-kind contributions from partners.

Furthermore, the PDP model is a more efficient process for drug development. According to estimates from the Tufts Center for the Study of Drug Development, the total cost of bringing a new drug to market surpasses USD 1.3 billion. The 12 largest pharmaceutical companies spent \$809 billion between 1997 and 2011 to gain approval for 139 drugs. That equates to an average cost of USD 5.8 billion per drug.⁴³ TB Alliance estimated that their projected cost for a registration trial, which accounts for the vast majority of their development expense is USD 70 million. But these values should be used with caution, particularly, the total cost of bringing a drug to market versus the cost for a clinical trial in which the early research has already been done (often by pharma) and with the costs of failure factored in. PDPs leverage the expertise of industry, including failures of early stage R&D and in-kind funding in general.

All of the PDPs evaluated remarked on the importance of DFAT funding. FIND specifically noted that DFAT funding helped them through a very difficult period after BMGF significantly reduced funding a few years ago. Today the organisation is back on track, has a strong pipeline, processes and partnerships in place to ensure the most effective R&D, and, relative to other PDPs, are doing innovative work on the access and uptake of their products. FIND noted that without DFAT portfolio funding, they may not have been able to continue.

By providing core or flexible funding to PDPs, Australia has been able to contribute to more outcomes than could have been achieved through direct funding of research activities or a single public-private partnership

⁴³ http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014.pdf

initiative. However, the investment in PDPs has enabled Australia to add value to the broader goal through mechanisms other than direct PDP investments. This has occurred in a number of ways, including:

- As a condition of funding, DFAT's contribution has directed greater attention to the needs of Asia Pacific populations in the selection of product development priorities.
- Greater coherence and consolidations with other Australian investments related to TB, malaria and health security, such as partnerships between PDPs and the Australian supported APLMA and separate funding to introduce or scale-up use of products originally developed or modified through PDPs.
- Supporting a platform that has assisted Australian researchers to have a higher profile in international TB and malaria related fields.

PDP collaboration with Australian research institutions

Of particular interest within the current evaluation was a deeper exploration of how this investment has leveraged Australian research.

"In my opinion, the PDP interactions are probably the most effective mechanism by which Australian research can have global impact." - Australian Researcher

The DFAT investment in PDPs is not tied to funding research by Australian institutions and scientists. However, the Australian scientists told the evaluators that the PDPs brought them many benefits which, in turn, strengthened Australia's international profile and brought additional opportunities to Australian science. These benefits include funding but also the greater exposure to other researchers and industry.

PDPs have been actively engaging Australian research expertise for over ten years. A summary of selected Australian research institutes' engagement with DFAT-supported PDPs is included in Annex 6. Australian researchers do not exclusively work with DFAT-supported PDPs. The evaluators were told of Australian researchers working with PATH and DNDi, and there may be researchers working with other PDPs as well.

The PDPs under review have benefited greatly from working with Australian researchers and vice-versa. The benefits accruing to each include:

- A partial tally of funding to Australian research institutions from the three PDPs (based on data from the Australian researchers interviewed alone) over the DFAT funding period totals about AUD 3 million. A specific example of total funding over the 2012-2017 period for one of the PDPs includes MMV funding to Australian researchers of USD 19 million, inclusive of MMV funding from BMGF.
- One Australian researcher noted that PDPs were a unique funding source for diagnostic development for neglected diseases. This is an underfunded area that does not receive the same level of funding as therapeutics. The researcher said, "we tend not to get (US) National Institutes of Health (NIH) grants for this type of research, so PDPs are filling an important void."
- The PDPs also provide the networks to translate Australian discoveries into new medicines that will contribute to improvements in global health, such as the use of the Australian developed 'human challenge model' which PDPs have further invested in as a method of testing the efficacy of anti-malarials.

- Australia does not have a well-developed pharmaceuticals industry, so access to networks and testing platforms not available in Australia greatly benefits Australian science.
- PDP partners have benefited from the advantages of the Australian regulatory system, which has allowed researchers/PDPs to do things more quickly than in the US for example. This lends an international competitive advantage, particularly for clinical trials (e.g. “I can scale up and test 2 or 3 drugs simultaneously” – Australian Researcher).
- Australian researchers stated they benefited from access to thought leaders and experienced industry scientists through the PDP review and mentoring process. One researcher noted that MMV’s annual review process, which occurs for all projects via MMV and their Expert Scientific Advisory Committee, has also become much more rigorous over time and involves many more industry-experienced drug discovery scientists than it did previously. This exposure is particularly important for academic discovery teams that do not have this first-hand industry experience.
- Opportunities to train junior scientists and provide networks for them to establish their own collaborations.

Test 4: Making performance count

Test 4

Australia’s aid policy fourth investment test is based on “a new performance framework *Making Performance Count: Enhancing the Accountability and Effectiveness of Australian Aid*⁴⁴ ensuring a stronger focus on results and value for money. “

In this context, we applied the criteria of Test 4 for DFAT’s health investments as per the Health for Development Strategy for all three PDPs. Specifically, we assessed Test 4 by investigating the ability of DFAT to demonstrate results through monitoring and evaluation systems, the value for money of the investments, the presence of appropriate governance arrangements and the sustainability of the investment.

Monitoring and evaluation (M&E) of performance and results

So far, DFAT’s PDP investment has not had a strong M&E framework (e.g. no baseline comparison, no aligned monitoring frameworks for different phases of product R&D, no over-arching logic model, no mutually agreed definitions for outputs/outcomes). The 2013 Investment Design document mentioned a plan to develop an overall results-based M&E framework for the Medical Research Program (including PDPs), and relevant processes to utilise this results-based framework. This M&E framework was not developed.

The PFG is an informal network of public and private organisations providing financial support to one or more PDPs developing new health technologies, established in 2010. The PFG provides a forum where those responsible for managing an institution’s PDP investments can share information and experiences to make better informed funding decisions and identify areas where it would be beneficial for funders to work together in a coordinated manner. The PFG also works to increase the overall resource base for R&D funding for neglected diseases, and more specifically to increase the funding available for PDPs.

⁴⁴ <http://dfat.gov.au/about-us/publications/Documents/framework-making-performance-count.pdf>

The PFG meets by phone or in person approximately ten times per year. A membership list from 2014 included eight national funding organisations in Europe, two European funding initiatives, USAID and the NIH in the United States, Wellcome Trust and BMGF⁴⁵. The PFG has a website but, aside from newsfeeds, it does not appear to have been up-dated since 2013⁴⁶.

To some extent monitoring and evaluation of activities and results have been addressed through the PFG reports. Through the PFG, PDPs have established a shared annual reporting format which includes the PDPs' performance frameworks. Some donors, such as DFID have used the PDPs' performance frameworks to populate their own logic models. DFAT receives the harmonised report from the PDPs they fund.

Value-for-Money

As addressed elsewhere, the PDP investment offered value-for-money by:

- Providing core funding that enabled PDPs to make efficient allocation of resources and pool risk
- Leveraging the investments and other contributions by other donors and private sector partners
- Contributing to synergies and consolidation of DFAT investments in malaria, TB and health security
- Accelerating the number of priority product outputs

Specific examples are provided in the annexed individual PDP evaluations in Annexes 7-9

Sustainability of the PDP investment

The PDP investment exceeded the outputs and outcomes specified in the original design. However, the sustainability of this achievement and the other products in the PDP pipeline must be considered to determine its overall performance. This evaluation investigated sustainability from three perspectives: the relevance of products and their access in the Asia Pacific; the pipeline of product developments; and the funding climate for the future financial sustainability of PDPs.

Product relevance and access in the region

From a health security lens, the burden of TB and malaria are currently the leading health challenges in the region, posing the greatest threat to resistance and account for a large burden of illness. Therefore, the products developed by the three PDPs, and those in their pipelines, are relevant to the Asia Pacific, although some products potentially have a greater impact on TB and malaria prevention, treatment and elimination than others.

In addition to product development, the focus of PDPs is expanding to the challenges of access and uptake of products. They are all increasingly engaging in the access space and grappling with the best ways to do so. There is broad agreement between stakeholders interviewed, for example, that attention is needed on facilitating affordability, registration, regulatory approval and procurement decisions. PDPs are also increasingly working on or considering, to varying degrees, access-related activities such as advocacy and communications, supply chain strengthening, demand creation, market-shaping, product acceptability and rational use, social behavioural

⁴⁵ Technopolis Group. Review of the PDP Fund (2011-2014). The evaluators requested an updated list, but the Chair of the PFG did not respond prior to submission.

⁴⁶ <http://www.pdpfundersgroup.org/>

change, and health worker training. As with product R&D, this will require collaboration with different partners and building capacity within regional bodies and national health systems.

Previously, there appears to have been an over-reliance on the Clinton Health Access Initiative (CHAI) for facilitating market access. All three PDPs identified CHAI as a principal access partner. Through partnerships with organisations like UNITAID, Global Fund, Malaria Consortium, London School of Hygiene and Tropical Medicine (LSHTM), this trend seems to be improving. MMV, over the last 12 months in particular, has begun using request for proposal processes that have resulted in a new range of access partners. Key to access efforts focused on impact in the future will also be development of partnerships with local non-government organisations and civil society organisations.

Among the three PDPs, FIND seems to be the most engaged in increasing access to their products (see Box 1). This may be the result of the unique health systems strengthening requirements for diagnostics, as well as having had more products and opportunities to focus on uptake. Approximately 24% of FIND's total budget is focused on accelerating access. MMV too, has increased investment in access and product management tenfold from 1.5% in 2006 to just under 15% in 2015. By pursuing catalytic work, MMV noted that their industry partners can often pursue large-scale implementation. For example, in their partnership with Guilin MMV pursued early market uptake while Guilin built a pan-African medical education and marketing function.

Box 1. FIND – an example of access and capacity building

Merging diagnostics with communications technology offers huge opportunities to maximise the health impact of diagnostic tests by enabling efficient collection, storage and transmission of test and patient data. Connected diagnostic tests can provide real-time results to clinicians and mobile alerts to patients, facilitating prompt treatment and reduce loss to follow-up. Likewise, connected diagnostics can improve supply chain management and forecasting, contribute to disease surveillance, and track the functioning of lab equipment. Currently, FIND is:

- Assisting manufacturers and solutions providers with the design, development and implementation of connectivity solutions;
- Demonstrating the impact of connectivity solutions for health systems through data utilisation frameworks and best practices;
- Guiding the development of connectivity solutions that meet priority needs with target product profiles developed in collaboration with global partners;
- Establishing a framework for data use and sharing agreements;
- Working with countries to build the capacity to use diagnostic data for decision-making; and
- Establishing pre-negotiated, discounted contracts for global SIM cards and data bundles.

Pipeline

To sustain the achievements of the DFAT investment the PDPs need pipelines of products in all stages of development. All three PDPs have extensive pipelines (Annex 10). Examples include:

- MMV is working to develop treatments to be combined with new highly sensitive RDTs to detect *P. vivax* better and meet the need of patients with glucose-6-phosphate dehydrogenase (G6PD deficiency). The goal is for a diagnostic test to be deployed with tafenoquine at the time of its potential approval in 2018-2019. MMV is closely aligning its projects with the development of the diagnostic
- Currently in the planning stages between TB Alliance and FIND is a collaboration to enable decentralised MDR- and XDR-TB care (BPaL and BPaMZ)
- FIND recently established a mini “arm” under the auspices of CEPI called CEPIdx. FIND will develop diagnostics for pathogens that are vaccine targets for CEPI as well as other WHO R&D Blueprint pathogens

Funding climate

The PDP model was intended to be a mechanism for donors to fund projects that address market barriers for health products for the poor. This model would be difficult to sustain without donor support despite improved paying capacity among LMICs.

Continued PDP financing represents one of the most critical risks to sustainability. Overall, funding to PDPs fell in 2015 by 13%, according to G-Finder’s 2016 Report⁴⁷. While the individual PDP budgets during the investment period were sufficient to meet the activities, outputs and outcomes achieved, all three PDPs under the DFAT investment claim to face funding shortfalls over the coming years (see individual evaluation Annexes 7-9). Lack of sustainable funding complicates strategic planning for PDPs. Inability to forecast future revenues puts the organisations in an unfavourable position in negotiations with partners, as the partner can see the uncertainty of the PDP’s funding as a risk^{48, 49}.

The PDPs have succeeded to some degree in diversifying funding. FIND, for example, started with one donor in 2003 and had 15 public and private funders in 2016. PDPs benefit from having a small set of dependable funders from an administrative and fundraising perspective, but having a few large funders makes organisations “more susceptible to the vagaries of external political, economic, and other forces”⁵⁰.

A report for the BMGF on sources of investment for PDPs concluded that there is scope for some PDPs to attract private sector impact investment and gave some examples of PDPs identifying revenue-generating activities, but noted that developing these approaches will require significant effort⁵¹.

In 2015, nearly half of all individual PDPs received a majority of their funding from the BMGF. The creation of the new Medical Research Institute (MRI), funded by the BMGF will have a significant, but unknown, impact on the future sustainability of some PDPs. See Box 2.

⁴⁷ Policy Cures Research, 2016, G-Finder Report, Neglected Disease Research and Development: a Pivotal Moment for Global Health, <http://www.policycuresresearch.org/downloads/Y9%20GFINDER%20full%20report%20web.pdf>

⁴⁸ Mahoney. “Product Development Partnerships: Case studies of a new mechanism for health technology innovation.”(2011)

⁴⁹ Technopolis Group. “Review of the Product Development Partnerships Fund 2011-2014: Final report to the Dutch Ministry of Foreign Affairs.” (2014)

⁵⁰ Policy Cures Research, 2016, G-Finder Report, Neglected Disease Research and Development: a Pivotal Moment for Global Health,

⁵¹ Investing for Global Health Impact in Product Development Partnerships. A Tideline Working Paper, June 2017.

Box 2. Bill and Melinda Gates Medical Research Institute (MRI)

The Bill & Melinda Gates Medical Research Institute (the institute) will focus on efforts to accelerate translational research in three areas: (1) therapeutics and vaccines for tuberculosis; (2) vaccines for malaria; and (3) vaccines for enteric and diarrheal diseases.

The institute will be a wholly owned subsidiary of the Bill & Melinda Gates Foundation. Its CEO will be Penny Heaton, who currently serves as Director of Vaccine Development & Surveillance. Penny will likely report to a board of directors represented by senior foundation executives. The MRI will also operate with the advice of a scientific advisory committee of independent experts. At this time, the BMGF anticipate that the MRI will be wholly funded by the BMGF. Over the next few years, they expect the total annual budget will increase to about USD \$100 million, and it will employ about 80-120 total staff.

BMGF anticipate that the institute will launch operations in early 2018, though the exact timing of its ability to accept preclinical candidates is contingent on progress in hiring staff and on developing agreements with collaborating partners. More specifics likely will be available till later this year.

The development of the BMGF MRI will have implications for the PDP landscape which should be closely monitored. Potential impacts noted include:

- Aeras likely to fold as a result
- FIND likely to be shielded, as diagnostics are not a focus of MRI, and BMGF has already pulled majority of their funding. They have weathered that storm
- Given that the MRI will target therapeutics for TB, this will be something for TB Alliance to monitor closely, focusing on partnership and leverage vs. competition
- As MMV is focusing on novel medicines for malaria, and not vaccines, they should be unaffected in the immediate term.

3. Individual PDP evaluations

In addition to assessing the overall DFAT investment in PDPs, the evaluation includes an assessment of each of the three PDPs supported by DFAT funding. Each PDP was rated as either high or medium for DFAT's aid policy tests. The PDPs' achievements in meeting the investment outcome and output targets is also described. A summary of the evaluation against the aid policy tests is provided in Table 2 below. Table 3 includes a summary of each PDP's contributions to meeting the outcome and output targets. Completed evaluations of each PDP are presented in Annexes 7, 8 and 9 for FIND, MMV and TB Alliance respectively.

Table 2: Qualitative assessment of PDPs against Australia's Aid Policy Tests

TEST	FIND	MMV	TB Alliance
Test 1 - Pursuing national interest	High	High	High
Test 2 - Promoting growth and reducing poverty	Medium	Medium	Medium
Test 3 - Australia's value-add and leverage	High	High	High
Test 4 - Making performance count	High	High	High

Table 3: Summary of PDPs' contribution to achievement of DFAT investment outcomes and outputs

	Outcome: number of products registered in at least one high burden Asia Pacific country	Output: number of products successfully completing late stage trials
FIND	2 (LPA for 1 st Line Drugs, Xpert MTB/RIF)	10 (LPA for 1 st Line Drugs, Xpert MTB/RIF, LPA for 2 nd line drugs, TB LAMP, Malaria LAMP (asymptomatic studies), Malaria High Sensitivity RDT, TrueLab/TrueNat, Xpert MTB/Rif Ultra, Positive Control Well for Malaria (and Reference Materials))
MMV	2 (Pyramax (tablets and granules), Eurartesim)	2 (Tafenoquine, Dispersible Paediatric Eurartesim)
TB Alliance	1 (Paediatric Fixed-Dose Combination (FDC))	5 (BPAL, BPAMZ, Linezolid, BPAZ, PaMZ)

All three PDPs continue to deliver results and good value for money. TB and malaria focused PDPs are addressing a critical global health security threat to Australia and the Asia Pacific region as a whole, particularly when it comes to combatting drug resistant forms of the diseases. FIND, MMV and TB Alliance are all well engaged in the region (for example, Indonesia and PNG).

By their very nature, as organisations created to address the specific development problem of lack of diagnostic tools and medicines for diseases of poverty, PDPs have clear commitments to reducing poverty and improving growth through reducing disease burden, but the link is indirect. Each PDP also undertakes a range of capacity building activities in DFAT partner countries including laboratory capacity and education. All PDPs engage with the private sector and have rigid engagement processes. They use these relationships to leverage in-kind support for product development, including access to staff, laboratories and funding.

DFAT investments in the PDPs is one way that Australia influences global medical research. The PDPs have strong relationships with Australian research institutions. Each PDP shows sufficient potential in their pipelines to expect continued successes through the product lifecycle if they can address some challenges, including access to market ready products.

The partnership approach is successful, with PDPs able to leverage relationships with the research community as well as industry. However, these partners do not routinely report against PDPs' internal M&E frameworks. The evaluation encountered problems when attempting to determine the access of PDP-supported products. PDPs did not routinely collect information on registration or distribution of products as these are the responsibility of manufacturers.

All the PDPs have well-defined internal frameworks and processes for M&E of product R&D, with both internal and external expert reviews and oversight. Each PDP relies on its own risk assessment criteria and has processes to identify and monitor financing and other risks. Individual donors regularly assess/evaluate PDPs but do not use aligned approaches. Multiple reporting requirements are a burden for PDPs and are often not an effective use of human resources in managing relationships with various donors.

Each PDP provided summaries of the product pipeline. Review of these found all three PDPs have a number of products at various stages of development, from initial research through translational investigations to final product development and clinical trials to market approval for access. These pipelines are available in Annex 10 for FIND, MMV and TB Alliance respectively.

While each PDP was rated as either high or medium for all aid policy tests, each has different strengths and opportunities for improvement.

3.1. FIND

Strengths:

FIND seems to be most advanced regarding their work on access. This is partially due to the nature of R&D costs associated with diagnostics, which require a different level of health systems integration earlier on in the process, thus they seem to be investing in this space more than others. The R&D process for diagnostics is very different from medicines, including shorter timeframes, a greater degree of accompanying health system strengthening activities, as well as different regulatory and R&D pathways.

Quality control/lot-testing systems for malaria RDTs developed by FIND have contributed significantly to their acceptability by health authorities and practitioners in many Asia Pacific countries. The introduction of RDTs has revolutionised malaria diagnosis and treatment by moving from syndromic to parasitologically confirmed treatment strategies.

FIND's support for TB diagnostics, and the GeneXpert platform in particular, is a recognised game-changer in the TB space.

FIND has many strong relationships with Australian research institutions and is building new relationships with private sector partners, generating funding from other donors and in-kind contributions.

FIND has been responsive to previous evaluation feedback, particularly regarding improvements in risk management, adding a formal risk register and regularly scheduled risk assessments. FIND is a lean organisation in the process of change and organisation growth, operating strong financial controls and practices to improve efficiency and productivity to ensure that limited resources are focused on program delivery.

Opportunities for Improvement:

Overall, FIND is able to demonstrate good value for money. However, there are areas for improvement including measuring the selected cost-effectiveness metrics, clearly defining impact, as well as related opportunities to streamline processes, projects and products both internally as well as externally with various partners. Stronger prioritisation and effective partnerships including with diverse private sector partners may help accelerate bringing key products to end-users at scale.

Its new strategy includes anti-microbial resistance (AMR) and outbreaks through a new focus on non-malarial fevers and cross-cutting identification of pathogens to identify outbreaks and provide targeted treatments. DFAT will need to determine if this still aligns closely enough with its own strategic priorities under the Regional Health Security Initiative.

FIND shows room for improvement in some areas of its partnerships with other PDPs, especially those in pharmaceutical development. Stronger synergies between diagnostics and treatments would ensure better

alignment of projects from health systems viewpoint, including joint definition and alignment of impact and M&E frameworks, advocacy, communication and capacity building.

3.2. MMV

Strengths:

MMV has a strong and varied pipeline with good potential for success in the short- to mid-term. Product development is a long-term goal, so many of the products from MMV have yet to hit the market, but this investment is crucial to reduce the threat of artemisinin resistance (ozonide drugs). Tafenoquine is due to be launched in 2018 and could transform the landscape for *P. vivax* treatment. Tafenoquine has important implications for Asia Pacific given that it will be the first malaria medicine in over 60 years to address relapsing malaria from *P. vivax*. Dispersible Eurartesim will also be important for elimination efforts in the Asia Pacific. MMV is also working on multiple single dose, potent treatments and an artemisinin replacement which works on different blood stages of parasitemia.

Of DFAT's PDP investments, MMV performs the strongest on research collaboration with Australian institutions. MMV has entered into agreements with some 20 Australia-based entities on R&D and access, has contributed almost AUD 33 million to Australian-based malaria research and has significantly increased research capacity in the region. MMV has also established contractual relationships with more than 100 private entities in Asia and the Pacific.

Regarding DFAT's key policy issues, MMV is prioritising the development of medicines for women, including pregnant women, and has several projects that aim to ensure equal access to gender-responsive services and health education. Also, the majority of MMV's product recipients have been children. Customisation of products for children remains a priority for MMV.

MMV now has a track record of facilitating access and uptake and has a dedicated team for access activities. Coartem, which MMV co-developed, and DHPA-piperaquine are now the main-stay of antimalarial therapy in all malaria endemic Asia Pacific countries and their rollout has contributed to the massive reduction in malaria burden across the regions.

Opportunities for Improvement:

Sustainability and diversity of funding are extremely important with anticipated funding gaps to 2021 expanding. Engagement with the private sector broadly will play an increasingly important role. MMV, along with other malaria focused organisations face the major challenge of antimalarial resistance, which will be exacerbated by very mobile populations.

MMV would benefit from closer collaborations with PDPs in the diagnostics space. Tying access to antimalarials with the appropriate diagnosis will be critical.

As with other assessed PDPs, joint definition and alignment of impact and M&E frameworks would be useful.

3.3. TB Alliance

Strengths:

TB Alliance shows potential for future success with their upcoming regimens BPamZ and BPaL.

TB Alliance has several strong contractual relationships with Australian research institutions and private sector partners. Relationships with research institutions are expected to expand as the rollout of further treatment regimens progress.

The organisation has a pool of dedicated funders that have made long term commitments. Their virtual model limits costs and allows them to focus funding on R&D activities. Strong processes and practices are in place to manage governance, including for trials, internal operations and engagement with partners.

TB Alliance has also undertaken important work to anticipate the regulatory introduction of products in 30 countries to improve the likelihood of achieving wide market access. In addition, they have pursued a unique commercialisation strategy based on in-depth market assessments.

Opportunities for Improvement:

The potential impact of the BMGF MRI could be greatest on TB Alliance as the MRI is also planning to focus on TB medicines. The potential impact on TB Alliance's operations and pipeline will have to be monitored closely. Based on their current portfolio, they have about three years to shift to a more independent position and DFAT, with its aligned goals of responding to the DR-TB threat and dealing with (regional) health security could be a key partner in that effort.

TB Alliance would benefit from closer collaborations with PDPs in the diagnostics space. Planning and strengthening cross-sectoral access activities for new regimens based on appropriate diagnosis will be critical.

Even though TB Alliance has a dedicated pool of committed funders, they note a shortfall of approximately AUD 30 million over the next three years which could lead to some delays in market access.

TB Alliance is currently evaluating processes relating to their procurement policy and practices to strengthen these. These processes were identified as weaknesses in other evaluations.

As with other assessed PDPs, joint definition and alignment of impact and M&E frameworks would be useful.

4. Options and recommendations

4.1. Considerations for future DFAT investment in PDPs for R&D

Based on the evaluation findings, the current investment in PDPs is effective, efficient and appropriate and should be continued. Specifically:

- Malaria and TB, including drug resistant strains, should still constitute the priority disease areas with regard to health security.
- Each PDP under review has had a strong track record, as measured by exceeding the key outcome of this DFAT investment. Also, products developed before DFAT's investment, have now hit markets and are having a significant impact.
- The prospects for all three PDPs are strong in the coming years. A number of highly relevant products will be coming to fruition (currently in Stage 3 and 4) and ready for market introduction and others in earlier stages of development.

- There are opportunities to create better linkages between the diagnostics and therapeutics being developed. The PDPs are actively working with partners to develop new products, such as integrated testing and treatment approaches to detect drug resistance for malaria and TB at the point of care.
- Australia has a comparative advantage in medical research that should continue to be exploited, particularly in relation to the development of diagnostic tests, treatments and vaccines. Involvement of Australian researchers is in Australia's broader national interest.
- An overall decline in funding for PDPs, reliance on a handful of donors with shifting priorities and the new MIR funded by the BMGF means that a continuing financial contribution by DFAT to PDPs is particularly valuable.

Other models for product development

While this evaluation recommends the continuation of the PDP model, PDPs are not the sole means by which to incentivise product discovery and development. There are initiatives which make the market more credible, so-called “pull” mechanisms such as the first Advanced Market Commitment and increased funding for health technology purchases through The Global Fund to fight AIDS, TB and Malaria, PEPFAR, UNITAID and GAVI. There are other initiatives, so-called “push” mechanisms, which, like the PDP model, are focused on reducing the costs and risks of R&D. These include the United States Food and Drug Administration (FDA) priority review voucher, Article 58 of the European Medicines Agency (EMA), and “Enterprise” type initiatives to promote greater scientific collaboration in HIV and AIDS research. The WHO Expert Working Group on R&D Financing reviewed an even wider list of possible incentive mechanisms, e.g. Prizes, platform technologies, and direct support to small and medium size enterprises in emerging markets.

The following list includes other models of public-private partnerships that are proving effective and could be considered by DFAT as other investment options other than PDPs:

- The OECD proposes a comprehensive approach with the following elements:
 1. A global collaborative research platform
 2. Push levers such as milestone prizes and grants
 3. Patent buyouts for successfully developed products
 4. Funding of clinical trials and a harmonised global approval process
- Grand Challenges model – based on the Grand Challenges Canada model
- The TB community has proposed the 3P Project. This is a new funding mechanism to incentivise collaborative research, reward investment in TB R&D and develop shorter pan-TB regimens by:
 - Awarding prize money for promising new TB drugs at an early stage (\$50 million)
 - Facilitating the early sharing of clinical data and intellectual property so that promising candidates can easily be combined
 - Offering grant-based funding to pay for clinical trials in new treatment regimens
- Tadataka Yamada, a venture partner at Frazier Healthcare Partners and previously Chief Medical and Scientific Officer and a Board Member of Takeda Pharmaceuticals and a global health leader at BMGF, has proposed “a full-fledged, global, not-for-profit pharmaceutical company with a research budget

equal to that of the world's top five for-profit companies, and with the singular objective of creating a pipeline of products to address the challenge of infectious threats"⁵².

The consensus of donors interviewed for this evaluation, however, was that the PDP model remained effective. There was no appetite for changing the basic structure or investing in a new approach. One donor representative said "Everyone wants to come up with a new idea – but we have something that is working... It's not about coming up with new ways. It's more about how to make better what we are doing." Another representative said, "I don't think trying to create lots of new models is the key thing, but rather we should continue to improve the PDP model."

Options for the forms and conditions of funding

Core funding should continue to be the basis of DFAT's PDP investment. Funding without restriction on its use, and with limited administrative processes, has allowed for longer-term planning and sustainability of the PDPs' programs.

From all three of the PDPs' perspectives, earmarked funding is relatively heavy administratively and risks creating both duplication and gaps in the business plans of each PDP. For example, if the development process of a prospective medicine with earmarked funding has to be discontinued because of negative results of clinical trials, a labour intensive paperwork exchange is often required between PDPs and the donor to agree on the reprogramming of funds for different compounds targeting the same public health outcomes.

PDPs also noted that donors sometimes believe that tightly earmarked funding allows for greater control over priorities. However, in the inherently risky arena of drug development—where PDPs are naturally going to have to stop development of products for a variety of reasons—and in the inherently opportunistic area of access to medicine—where there is a need to rapidly respond to the barriers to uptake that can vary tremendously from region to region—earmarked funding actually provides little benefit to donors at a relatively high administrative cost. Investing in the overall portfolio of R&D and access provides donors with the greatest value for money.

Keeping regular contact with the organisation, having an understanding of the business model and reasonable expectations, sharing knowledge of the organisation with other donors on a regular basis, having external reviews such as this one (and collaborating with other donors on external reviews), are all effective ways to gain the necessary confidence to provide unrestricted funds.

Although earmarked funding is not recommended, DFAT's core funding can be designated for specific disease areas, as in the current investments. The investment under review followed this strategy and worked very effectively. Given the positive evaluation findings, it is recommended that this strategy of directing core funding be continued.

Some respondents noted that a premise of the PDP model is partnering with the best experts from around the world. DFAT should avoid requiring PDPs to partner with Australian researchers. However, synergy between the PDP agendas and Australian expertise is an appropriate and strategic criteria for choosing PDP partners.

⁵² <https://mareeg.com/the-global-security-threat-of-antimicrobial-resistance/>

4.2. Five options for future DFAT investment in PDPs for R&D

Based on the positive evaluation findings, continuing to fund PDPs focusing on new products for TB and malaria is recommended. Other options involve a change to the current portfolio to include an explicit focus on end-to-end planning for new products and the addition of new health priorities relevant to health security in the Asia Pacific. The options are not mutually exclusive, and all options assume that future PDP investment will sit under health security.

Option 1	Considerations
<p>Maintain current investments continuing to focus on TB and malaria diagnostics and medicines</p> <p>Status quo/maintain and incentivise end-to-end approaches</p> <p>FIND, MMV, TB Alliance likely to be suitable investment options in this space</p>	<ul style="list-style-type: none"> • Increase funding, but maintain focus on TB and malaria with an open call to PDPs with a track record in this area • Select PDPs based on their diagnostic and therapeutic prospects at all stages of the pipeline and on their holistic, end-to-end approach to address health priorities
Option 2	Considerations
<p>In addition to continuing to focus on TB and malaria diagnostics and medicines, also invest in vector control</p> <p>Maintain and incentivise end-to-end approaches, and add one priority (shorter term wins)</p> <p>FIND, MMV, TB Alliance + IVCC likely to be suitable investment options in this space</p>	<ul style="list-style-type: none"> • Vector control is the main way to prevent and reduce transition of malaria and other vector borne diseases such as dengue, chikungunya and Zika. Insecticide-treated mosquito nets and indoor residual spraying are the principal vector control strategies, but mosquito resistance to insecticides is increasing. Since 2010, 60 of the 73 countries that monitor insecticide resistance have reported mosquito resistance to at least one insecticide. • This option is most complementary to Option 1 as it maintains the focus on malaria. • Like diagnostics, development of vector control products has a shorter timeline, so progress is more likely during the investment period.
Option 3	Considerations
<p>In addition to continuing to focus on TB and malaria diagnostics and medicines, re-enter the vaccine development space</p> <p>Maintain and incentivise end to end approaches, add two priorities (longer term wins)</p> <p>FIND, MMV, TB Alliance + CEPI are likely to be suitable investment options in this space</p>	<ul style="list-style-type: none"> • This would be a long-term investment as outcomes may not result as quickly • Means getting back into vaccines (after moving away from Aeras during the current investment) • Investing in vaccines offers a more balanced, holistic, value-chain portfolio (i.e. toolbox, not tool) approach • The BMGF MRI will change the vaccine development landscape
Option 4	Considerations

<p>In addition to continuing to focus on TB and malaria diagnostics and medicines, explore opportunities in AMR space.</p> <p>Maintain and incentivise end-to-end approaches, and add AMR focus (to be explored as part of health security pillar)</p> <p>FIND, MMV, TB Alliance + Global Antibiotic Research and Development Partnership (GARD-P) incubated by the Drugs for Neglected Diseases initiative (DNDi) in collaboration with the WHO, FIND, PATH likely to be suitable investment options in this space</p>	<ul style="list-style-type: none"> • AMR is a particular concern in the Asia Pacific, where, according to the Study for Monitoring Antimicrobial Resistance Trends (SMART), the levels of resistance are the highest worldwide.⁵³ • In addition to drug resistant TB and malaria - resistance to community-acquired infections including gonorrhoea, diarrhoeal diseases, and streptococcus pneumonia is now widespread across the region. • A remarkable increase in the prevalence of highly resistant bacteria such as methicillin-resistant <i>S. aureus</i> (MRSA) in health facility-acquired infections has been observed in the region. • Addressing AMR is aligned with the Health Security Initiative; Australia is committed to the “Asia Pacific One Health Initiative on AMR” to jointly identify and tackle challenges posed by AMR in the Asia Pacific region, including accelerated R&D in AMR (i.e. development of new antimicrobials, diagnostics and vaccines)⁵⁴ • No clear AMR focused PDP with a clear investment win yet, although GARD-P is quickly developing.
Option 5	Considerations
<p>Access and uptake for PDP products by end-users</p> <p>Ensure integrated investments that support access-related activities such as advocacy and communications, supply/value-chain strengthening, demand creation, market-shaping, product acceptability and rational use, social behavioural change, etc.</p>	<ul style="list-style-type: none"> • A cross-cutting, supplementary initiatives program with a focus on enabling access would help to address the barriers to uptake by end-users and increase the strategic lens on end-to-end product innovation • This program would provide funding for implementation science focused on product uptake and be explicitly tied to the products developed through supported PDPs • Incentivise more work focused on access to products (directly and through relevant partnerships) and create stronger linkages with other DFAT supported work, across the innovation lifecycle • In addition to core funding, funds under this complementary program could also be earmarked for specific priority projects • There has tended to be insufficient funding to PDPs for access-related activities in general, limiting the scale of impact for end-users

⁵³ Po-Ren Hsueh. 2012. Study for Monitoring Antimicrobial Resistance Trends (SMART) in the Asia Pacific Region, 2002–2010. International Journal of Antimicrobial Agents 40(S1)

⁵⁴ http://www.searo.who.int/entity/antimicrobial_resistance/tokyo-meeting-of-health-ministers-on-amr-2016/en/

4.3. Recommendations for DFAT

Prioritising options

TB and malaria should remain at the heart of DFAT's PDP investments because of the health burden of the diseases in the region and globally, the shortfall of R&D funding, and the strong linkages with the health security platform (i.e. risk to Australia and the Asia Pacific). Option 1 is therefore put forward as the highest priority recommendation.

Vector control, currently the main way to prevent and reduce malaria transmission, presents a strong complementary option for expanding the purview of DFAT PDP investments. Supporting vector control is a PDP investment option that would allow for maintenance of a disease specific strategy, which may also align well with Australia's strategic level target of increasing consolidation.

All of the options need to be supported by increased evidence and incentivised by an end-to end approach – from R&D to access and scale-up. Thinking about market uptake and scale-up was identified by industry respondents as an area requiring more attention by PDPs. It is perhaps the most commonly recognised gap within the PDP space. Option 5 is meant to support this need.

Therefore, based on the range of options developed, this evaluation recommends a combination of Options 1, 2, and 5. If there is scope for additional investment beyond this set of options, we would recommend the addition of option 3. This option could be added after an initial 3-year investment. Option 4 is not recommended at this time for reasons given in the table, but it is noted that by addressing drug resistant malaria and TB, DFAT is already supporting product development for AMR.

These recommendations should be considered within the context of a developing BMGF MRI, which has the potential to significantly influence the PDP landscape (see Box 2). Plans for the MRI should be closely monitored through bilateral discussions as well as the PFG over the coming months, and consideration given to how their decisions will influence the options being considered by DFAT. For the time being, BMGF are not planning to seek external funds and will be limiting their focus to 1) therapeutics and vaccines for TB; 2) vaccines for malaria; and 3) vaccines for enteric and diarrheal diseases.

Additional recommendations

A new DFAT investment in PDPs provides an opportunity to address limitations of the current investment. Therefore, the following points are also recommended to complement the primary recommendations above:

- **Take a full innovation lifecycle approach and integrate support of product R&D with support for ensuring uptake and optimal use.** With many products only recently becoming market-ready, the need to focus greater attention on delivery, access and adoption is only now beginning to receive greater attention. Australia's potential to facilitate uptake of market-ready, or soon to be ready, products and build country capacities within country health systems in the Asia Pacific was seen to be a critical opportunity for extending Australia's influence in the region. This perspective should be incorporated into the design of future PDP funding and be an overarching lens for viewing the range of health security

investments such as support for technical assistance in regulatory approval processes and garnering support from regional leaders on health security.

- **Link DFAT research portfolios better in order to achieve a stronger end-to-end approach and greater coordination between R&D and access.** Of DFAT's entire portfolio of health and medical research, thirty percent (30%) of the \$30 million per annum currently spent goes toward PDPs, while 70% is for policy and systems research across a range of other health issues. While linkages do exist, generating formal mechanisms to ensure sensible connections will be important and help maximise Australia's influence. While this concept applies to linkages within the DFAT research portfolio, it should extend to linkages between research funding and actual programmatic/implementation funding as well. This will likely require greater coordination between different groups within DFAT.
- **Work with future selected PDPs to define expected outputs and outcomes.** These should have clear definitions and be based on mutual understanding between DFAT and the PDPs. Given the complexities involved in the product lifecycle, and the different approval, registration and regulatory processes for different types of products (medicines, diagnostics, etc.), M&E frameworks should be adapted to each PDP, feeding up into a broader framework for the overall investment.
- To provide greater transparency and alignment of investments to achieve product development results it is recommended that DFAT further **leverage the PFG to develop a more integrated M&E framework that reflects DFAT priorities.** More generally, DFAT may wish to consider a greater leadership role on the PFG, particularly to drive progress in the Asia Pacific region.

Annex 1: Terms of Reference

Position Title:	Product Development Partnerships Specialists - Evaluation and Design of DFAT investment
ARF Professional Discipline Category:	D
ARF Job Level:	4
ARF Daily Rate:	-
Program:	Product Development Partnerships, Health security
Location/s:	Home base
Term:	Up to 38 days for both advisers
Reporting to:	DFAT representative: Cheryl Wong, Senior Policy & Program Officer, Health Strategies Section SHS representative: Zoe Croker, International Health Specialist
Background:	<p>The Specialist Health Service (SHS) provides strategic input on health to the Australian Government Department of Foreign Affairs and Trade (DFAT). The SHS allows DFAT to source high quality technical advice to support health policy, strategic planning and health programming across the aid management cycle.</p> <p>Under the Australian Government's aid policy, <i>Australian aid: promoting prosperity, reducing poverty, enhancing stability</i> (2014), DFAT has invested \$40 million since 2013 in research for health development through Product Development Partnerships (PDPs) for the development and trial of new drugs, vaccines and diagnostic tests to respond to high burden diseases in the Indo-Pacific region, such as malaria and tuberculosis (TB).</p> <p>The current PDP investments are:</p> <ul style="list-style-type: none"> • Foundation for Innovative New Diagnostics (FIND) – to develop diagnostic tools for the control of malaria and TB • Medicines for Malaria Venture (MMV) – to develop drugs to treat malaria • Global Alliance for TB Drug Development (TB Alliance) – to develop TB drugs. <p>These investments are due to end in mid-2018. Two independent evaluations have already been undertaken for PDPs. This evaluation would be the final evaluation for the current investments.</p> <p>PDPs are organisations which use an innovative public-private partnership model for co-investing in the development of new drugs, vaccines and diagnostic tests for use in developing countries. This is a pooled funding mechanism which allows Australia to co-invest with other donors, global health organisations and private</p>

	<p>philanthropic organisations such as the UK Department for International Development (DFID), the Bill and Melinda Gates Foundation, USAID and the EU. Several Australian research institutions and developers collaborate with PDPs, such as Monash University, Queensland Institute of Medical Research and the University of Sydney.</p> <p>The PDP climate is ever-changing. A number of actors in the PDP space are adjusting their investments and new PDPs have formed. The Bill and Melinda Gates Foundation has announced US\$100m per year to establish a research institute, and other PDP donors may review their priorities too.</p> <p>DFAT is in the process of designing investments in regional health security, of which PDPs is expected to be a major component of research and partnerships.</p>
Purpose and objectives:	<p>This assignment will guide DFAT’s next round of PDP investments.</p> <p>There are three objectives of this assignment.</p> <p>The first is to undertake an evaluation of the three PDPs. The second objective is to draw lessons from the evaluation to give options for the implementation of the next round of PDP investments, targeting regional health security priorities. The third is to design DFAT’s future PDP investment under regional health security research pillar.</p> <p>PDP Evaluation</p> <p>1) The evaluation should answer the following questions, from 2013 to now:</p> <p>a) Has the broader PDP investment achieved its intended outputs and outcomes?</p> <p>The assessment should focus on whether the investment achieved its intended outputs and outcomes as specified in the investment design and outcome statement. The assessment should also include whether the PDP investment met the Australian Aid Policy’s four investment tests of Pursuing national interest and extending Australia’s influence; Impact on promoting growth and reducing poverty; Australia’s value-add and leverage (including working with Australian research institutions); and Making performance count; and the goals of the Health for Development Strategy.</p> <p>b) Are the three PDP investments aligned with Australian development goals?</p> <p>The three PDPs should be assessed individually, according to the Australian aid policy’s four investment tests of Pursuing national interest and extending Australia’s influence; Impact on promoting growth and reducing poverty; Australia’s value-add and leverage (including working with Australian research institutions); and Making performance count; and DFAT’s Health for Development Strategy. Relevant outcomes and outputs in the investment design and outcome statement should also be assessed.</p> <p>c) How are the PDPs collaborating with Australian research institutions and the benefits of such collaborations? What other PDPs are working with Australian researchers?</p>

	<p>d) Were the monitoring and evaluation of clinical trials/projects adequate and managed appropriately by the PDPs?</p> <p>e) How effective were the governance arrangements, including risks and ethics management? How could they be improved?</p> <p>f) How sustainable is the work of the PDPs, taking into account:</p> <ul style="list-style-type: none"> i) Product relevance and access in the region ii) Funding climate iii) Views of major PDP donors, i.e. DFID, Gates Foundation, Germany iv) Views of Australian research institutions v) Challenges faced in developing the products and then product uptake, including but not limited to lack of funding, product access through regulatory issues, lack of manufacturing ability, R&D capabilities <p>2) The evaluation should provide a range of options and recommendations for the design of future investments in PDPs based on the findings.</p> <ul style="list-style-type: none"> a) Is the current portfolio of PDPs relevant and appropriate based on Australian development goals, including upcoming regional health security investments? Is the current mix of diagnostic and therapeutic products sufficient to meet strategic goals or should other areas be investigated? b) Are there any public-private partnerships, other than the PDPs, working on product R&D that are effective? c) What is the most appropriate funding option, e.g. core funding or earmarking; PDPs collaborating with an Australian research institute? <p>Design document of the investment/Calls for proposals</p> <p>The objective of the design document is to guide DFAT's call for proposals for the next round of investments. The design document should:</p> <ul style="list-style-type: none"> a) outline the parameters for DFAT's future investments; b) describe outcomes sought, intended activities, implementation arrangements and M&E requirements; c) recommend an assessment process, including criteria; and d) develop strategy for the call for proposals.
Duty Statement:	<p>The consultants will evaluate the existing DFAT PDP investments and provide recommendations, including options, for the next round of funding grants for PDPs. Following discussions with DFAT of the proposed options, the consultants will design the parameters around the call for proposals for the next round of PDP funding.</p>
Specific Duties:	<p>The consultants will:</p> <ul style="list-style-type: none"> • Develop an evaluation plan and methodology • Undertake consultations with a range of stakeholders including other PDP donors and PDP staff, Australian research partners and DFAT staff • Research and review available documents including annual PDP reports and websites, publicly available documents, the investment design and outcome statement, previous reviews, relevant DFAT strategies and policies etc.

	<ul style="list-style-type: none"> • Prepare an evaluation report that includes: <ul style="list-style-type: none"> ◦ An overall assessment of the performance of the PDP investment based on Australian development goals & value for money, effectiveness, efficiency and sustainability; ◦ An individual assessment of the three PDPs against the four aid policy tests in the Government's aid policy, as well as the Health for Development Strategy ◦ A list of any challenges or issues arising from the reports reviewed, including those relating to risk and ethics, monitoring and evaluation, product access, regulatory issues, etc. ◦ Recommendations on options for future investment in PDPs that will maximise value for money and impact, including mechanism for managing the call, target areas, risk management, governance and reporting/M&E. • Prepare the design of the next round of calls for grants: <ul style="list-style-type: none"> ◦ Using the findings of the evaluation and discussions with DFAT on the options for future investment, prepare a design document that outline the parameters for DFAT's future PDP investments, including the strategy for the 'Call for Proposal'. ◦ The design document will set out the clear logic between the outcomes sought, intended activities and implementation arrangements, and how progress will be measured, including M&E framework, performance indicators, & risk assessment. ◦ The design should also recommend an assessment process including criteria to assess applications for the new PDP investment and the recommended set-up of a grant review panel. <p>DFAT will prepare the guidelines for the call for proposals using the information in the design document.</p>																
Performance Outcomes and Deliverables, with dates:	<ul style="list-style-type: none"> • Evaluation report and recommendations, including options, for the next call for proposals (mid-August 2017) • Design for next round of grant proposals (late-August 2017) <p>Proposed number of days required for each activity:</p> <table border="1" data-bbox="432 1514 1436 1980"> <tr> <th colspan="2">Evaluation and recommendations</th></tr> <tr> <td>Develop evaluation plan including assessment criteria</td><td>2 days</td></tr> <tr> <td>Assessment of PDPs (x3)</td><td>8 days</td></tr> <tr> <td>Interviews and looking for other PDP activities in Australia</td><td>2 days</td></tr> <tr> <td>Writing including recommendations</td><td>9 days</td></tr> <tr> <td>Revisions</td><td>3 days</td></tr> <tr> <th colspan="2">Design</th></tr> <tr> <td>Writing</td><td>5 days</td></tr> </table>	Evaluation and recommendations		Develop evaluation plan including assessment criteria	2 days	Assessment of PDPs (x3)	8 days	Interviews and looking for other PDP activities in Australia	2 days	Writing including recommendations	9 days	Revisions	3 days	Design		Writing	5 days
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Revisions	3 days																
Design																	
Writing	5 days																

	Revisions	2 days
	TOTAL	31 days
	<p>Rohit Ramchandani of Antara Global Health Advisors will be the team leader. The team leader will complete up to 25 days' work and will be responsible for the overall evaluation and design. Barbara Bulc of Global Development will be a team member. The team member will complete up to 6 days' work and will contribute to the assessment of PDPs, analysis and writing, contribute to the design and will provide a strategic review.</p>	
Reporting:	<ul style="list-style-type: none"> Provide an activity report at end of assignment / when submitting invoices to SHS 	
Conditions:	<p>Conditions of engagement may include completing and signing the following documents:</p> <ul style="list-style-type: none"> The Deed of Confidentiality The Declaration of adviser status The Child Safe Code of Conduct <p>As per the requirements an Adviser Performance Assessment will be undertaken at the completion of the assignment.</p>	

Key Selection Criteria

Required Experience	<ol style="list-style-type: none"> At least 15 years of experience in public-private partnerships, ideally with expertise in PDPs for health. Demonstrated knowledge and experience in access to medicines, including specific knowledge of R&D for medical products and pharmaceutical manufacturing, particularly as it relates to low and middle-income countries. Experience in conducting evaluations and design work for bilateral or other international donors or multilateral organisations.
Required Skills and Qualifications	<ol style="list-style-type: none"> Strong analytical skills to assess a range of information and translate it into useful recommendations.
Cultural/Language Requirements	<ol style="list-style-type: none"> Fluency in English and demonstrated ability to express verbally and in writing complex ideas in clear and simple language for the DFAT audience.
Desirable Experience	<ol style="list-style-type: none"> Understanding of the Asia Pacific development context. Knowledge of the PDPs in which DFAT currently invests. Experience in reviews or evaluations of PDPs.

Annex 2: List of stakeholders interviewed

Key Informants Interviewed	Organisation
PDP Representatives	
Willo Brock, Senior Vice President for External Affairs	TB Alliance
Mel Spigelman, CEO	TB Alliance
David Reddy, CEO	MMV
Andrea Lucard, Executive Vice President, External Relations	MMV
Silvia Ferazzi, External Relations Officer	MMV
Catharina Boehme, CEO	FIND
Jerome St. Denis, Senior Resource Mobilization Officer	FIND
Sharon Saacks, Operations Director	FIND
Zachary Katz, Chief Access Officer	FIND
Donor representative	
Samia Saad, Senior Program Officer, Global Health R&D and Epidemic Preparedness Policy & Advocacy	Bill and Melinda Gates Foundation
Sue Kinn, Team Leader & Research Manager, Health & Education + Chair, PDP Funders Group	Department for International Development, UK
Australian Research Representative	
Dr Sue Charman, Professor and Director at Centre for Drug Candidate Optimisation	Monash University
Dr James McCarthy, Senior Scientist	QIMR Berghofer Medical Research Institute
Dr Ric Price, Professor of Global Health	Menzies School of Health Research and Centre for Tropical Medicine, University of Oxford
Dr Ivo Mueller, Professor and Joint Division Head, Population Health & Immunity	Walter & Eliza Hall Institute of Medical Research
Industry Representative	
Renuka Gadde, Vice President, Global Health	Becton Dickinson (BD)
Gary Cohen, Executive Vice President	Becton Dickinson (BD)
Adrian Thomas, Market Access and Commercial Operations	Johnson & Johnson Global Health
DFAT Representatives	
Lara Andrews	Department of Foreign Affairs & Trade, Australia
Renee Deschamps	Department of Foreign Affairs & Trade, Australia
Irene Whettenhall	Department of Foreign Affairs & Trade, Australia
Alex Stephens	Department of Foreign Affairs & Trade, Australia

Annex 3: Interview protocols

Interview protocol for DFAT

1. Please briefly describe your role at DFAT, specifically with regards your involvement with the PDP investment (2013-present)
2. Outside of the current evaluation process, what are DFAT's current thoughts on the direction of its PDP support strategy? Are there specific PDPs DFAT expects to fund going forward?
3. What are other PDPs, aside from FIND, TB Alliance and MMV that DFAT has explored/considered internally, if any? What is DFAT's outlook on these PDPs?
4. To what degree has DFAT been involved in engaging Australian researchers working in product R&D for global health? Can you please describe the nature of the involvement and provide any specific examples you may have?
5. What are DFAT's current thoughts on supporting PDPs through core funding vs project-directive funding?
6. In your opinion, what are the top 5 disease priorities for DFAT within the Asia Pacific region? What would you say are the key product development priorities and emerging priorities/opportunities, particularly with regard to the Asia Pacific region?
7. From DFAT's perspective has the PDP landscape changed over time? How and why? How have these changes influenced DFAT's strategic thinking with regard to PDP investment?
8. From DFAT's perspective, what was the quality of the relationship with the PDPs that were supported? How did the relationship change over time? What do you consider to have been the key strengths and weaknesses and how can the quality of such partnerships be improved going forward?
 - a. With regard to FIND?
 - b. With regard to MMV?
 - c. With regard to TB Alliance?
 - d. With regard to governance?
9. The original PDP investment Design notes that DFAT's contribution to Medical Research would represent thirty percent of the health research budget, with 70% of the portfolio remaining focused on policy and systems research to support and improve delivery of proven interventions. Are these research streams/programs linked in any way? How could they be better coordinated with a view towards supporting the entire continuum from product development to access and uptake?
10. The original PDP investment was done under the Heath [Medical] Research strategy. The new investment will take place under the Health Security strategy. Why the shift? What are the implications?
11. What are the potential alternative innovative mechanisms or new collaborative platforms to accelerate product development that DFAT has explored, if any? How do they compare to PDPs from DFAT's perspective?
12. The original PDP investment design noted that, given the scientific, financial and ethical considerations in investing in medical research, and the depth of expertise and resourcing necessary to assess PDPs, that it made sense to use the competition for PDPs which was opened by the DFID. This seems to have been an efficient use of resources, good example of collaboration/partnership between donors, and an effective way of meeting DFAT objectives. Were there any challenges with this process? Was a similar approach considered for the upcoming investment? Why or why not?
13. Is there anything we haven't covered that you would suggest be given consideration? Final comments?

DFAT Product Development Partnerships (PDPs) Investment

Final Evaluation & Future Design

INTERVIEW PROTOCOL

Date _____ **Location** ☐ Remote Interview (TC/Skype)
☐ Geneva (In-person)

Stakeholder Group: Australian Research

Name/Title:

Project Leads: Dr. Rohit Ramchandani, CEO, Antara Global Health Advisors in collaboration w/ Barbara Bulc, President, Global Development Impact

We have been engaged by DFAT Australia to conduct a final evaluation of their current PDP investments (FIND, MMV, TB Alliance) and recommend potential future directions. As one of the key donors and drivers of PDPs, your insights will be central to informing this process. The following questionnaire covers key areas of interest for DFAT with regard to their Aid Policy and Health for Development Strategy. Your responses to this evaluation protocol will help inform the final assessment of their investment and inform potential future PDP investment priorities.

The results of this evaluation will remain internal, and all responses can be considered confidential with attribution at the organizational level only. We ask that you please fill in responses to the questions and return to Dr. Rohit Ramchandani (rohit@antaraglobal.com) and Barbara Bulc (bbulc@gd-impact.org) at least 24 hours prior to your scheduled interview so that we may optimize our discussion. If you feel that any of the questions are not relevant, or you do not wish to answer a particular question, please feel free to respond “N/A” or “can’t comment”.

Thanking you in advance for your time and consideration. We look forward to speaking with you.

GENERAL

1. Can you please start off by briefly telling us about your role at [Research Institution] and what aspect of PDPs your research is focused on?
2. What PDPs have you been engaged with? What was the disease focus? What specifically was your role?
 - Can you briefly address the public health significance of the problem your research was trying to address, particularly with regard to the Asia Pacific Region?
 - If you were directly involved with research relating to PDPs, can you please contextualize and provide a summary of your key findings? Please provide references where available.
 - Can you provide examples of how your PDP-associated research has been disseminated; taken up; its degree of influence; or how it has influenced policy? Please provide quantitative examples where possible (e.g. # related publications, # conference presentations, impact factor, # citations, new policies, etc.)
3. If any of your research was funded through PDPs, can you please provide the amount of funding received and the associated time period?
4. From your/your institution's perspective, has the PDP landscape changed over time? How and why? How has this impacted your strategy for working with PDPs?
5. From your/your institution's perspective, and considering a changing development, health, and economic landscape, what are the key challenges you see with the PDP model (including the quality/processes related to your engagement with the PDP), and how would you propose to address them?
 - With regard to the product development stage?
 - With regard to the market introduction phase?
 - With regard to the scale-up phase?
6. What are potential alternative innovative mechanisms or new collaborative platforms to accelerate product development, and how do they compare to PDPs? Have you been involved in any of these other models?
 - Are there any public-private or other cross-sector partnerships (including with or between academic/research institutions), other than the PDPs, working on **product R&D** that are effective?
 - Has there been any consideration of or support for platforms that encourage information sharing (i.e. open source) to speed up development, introduction and uptake of products at scale? Any examples that stand out?
 - What other stakeholders, including other researchers, did you collaborate with? Through what mechanism? Why was this important? What other stakeholders would you have liked to engage with that you did not?

DFAT Test 1: Pursuing National Interest & Extending Australia's influence

7. Other than TB and Malaria, and applying a health security lens, what would you say are currently the key disease and product priorities for the Asia Pacific Region? What are emerging priorities/opportunities?
8. Considering Australia's regional interests in the Asia Pacific, its focus on stability, security and prosperity within the region, and prospects for strengthening its own trade and investment, in your opinion, how has investment in MMV, FIND, and TB Alliance helped it pursue its national interests and extend its influence?

Test 2: Impact on promoting growth and reducing poverty in the Asia Pacific

9. Can you provide any specific examples of how Australia's investment in [FIND, MMV, TB Alliance] has had an impact on growth and poverty reduction in the Asia Pacific Region? Can you direct us to any published evidence of this impact?
10. We know that often, a key challenge is not a lack of products or technologies, but effective delivery to people in need. This involves a range of activities. What specific strategies would you say have been used effectively by PDPs like FIND, MMV and TB Alliance, to ensure **reach to the poorest and most vulnerable populations at scale and sooner**?
 - What kinds of partnerships have been established to achieve this? How successful would you say they have been?
 - What were key challenges, and how do you suggest overcoming them?
 - What are specific factors that enhanced uptake at the national level? Provider level? User level? Please provide existing types of activities, partnerships, and results; and how do you see this changing in the future?

Test 3: Australia's value-add and leverage

11. Who are other Australian researchers you know of (including their institution) who work with PDPs for global health? Which ones? Are there potential partnerships with Australian researchers that should be further explored with regard to future PDP investments? Please also provide their contact information, if available.
12. Are you familiar with any specific PDP related activities in countries within the Asia Pacific region that DFAT may not currently be paying attention to, but should? Which countries? What are the activities and related outcomes?
13. What are future areas of research, with regard to product R&D for global health, where you see particular value-add potential by Australian researchers? Do you see particular core competencies within the Australian research community? If so, what are they?
14. Can you please specify any private sector stakeholders from the Asia Pacific region that your organization has worked with in reference to PDPs – and those you see potential in collaborating with? What was/is their role and [potential] value-add?
 - What specific Australian partners do you know of - whether from industry, academia, government, civil society, private foundations or otherwise – that could help accelerate Australia's influence with regard to PDPs for global health?
15. In your/your institution's view, what, if any, funding gaps exist that could be usefully funded by Australia moving forward? How would this make transformational change, and how would this support DFAT's pursuit of national interests and extending Australia's influence, as well as promoting growth and reducing poverty in the Asia Pacific region?
 - Is the current mix of TB and Malaria diagnostic and therapeutic products sufficient to meet DFAT's strategic goals (e.g. Tests 1 – 4) or should other areas be investigated?

Test 4: Making performance count

16. Given your research involvement in one of the PDPs supported by DFAT, how would you rate [FIND, MMV, TB Alliance]'s governance arrangements on a scale of one to five (with one being poor and five being excellent/thorough) in the following areas:

Please note which PDP you are scoring:

- Ethics Management:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 Poor Somewhat Poor Avg Good Excellent

Please comment, and include any suggestions for how governance in this area might be improved:

– Risk Management:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 Poor Somewhat Poor Avg Good Excellent

Please comment, and include any suggestions for how governance in this area might be improved:

– Clinical Trials Management:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐
 Poor Somewhat Poor Avg Good Excellent N/A

Please comment, and include any suggestions for how governance in this area might be improved:

– Overall Management:

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 Poor Somewhat Poor Avg Good Excellent

Please comment, and include any suggestions for how governance in this area might be improved:

17. From an Australian perspective, what, in your opinion, are the key benefits of your collaboration with [FIND, MMV, TB Alliance]? What are the benefits of such collaborations with Australian researchers more generally?

18. Is there anything we haven't covered that you would suggest be given consideration?

- ***If others within your organization were consulted during the course of developing responses to these questions, please provide information on who was consulted.**

DFAT Product Development Partnerships (PDPs) Investment

Final Evaluation & Future Design

INTERVIEW PROTOCOL

Date _____ **Location** ☐ Remote Interview (Skype)
☐ Geneva (In-person)

Stakeholder Group: Industry - _____

Name/Title: _____

Project Leads: Dr. Rohit Ramchandani, CEO, Antara Global Health Advisors in collaboration
w/ Barbara Bulc, President, Global Development Impact

Good afternoon. We have been engaged as advisors by DFAT Australia to conduct a final evaluation of their current PDP investments and recommend potential future directions. As a vital stakeholder within the PDP landscape, your insights as an industry representative will be central to informing this evaluation. Your responses to this evaluation protocol will help inform the final assessment of their investment and inform potential future PDP investment priorities/strategies.

The results of this evaluation will remain internal, and all responses can be considered confidential with attribution at the organizational level only. We ask that you please fill in responses to the questions and return to Dr. Rohit Ramchandani (rohit@antaraglobal.com) and Barbara Bulc (bbulc@gd-impact.org) at least 24 hours prior to your scheduled interview so that we may optimize our discussion. If you feel that any of the questions are not relevant, or you do not wish to answer a particular question, please feel free to respond “N/A” or “can’t comment”.

Thanking you in advance for your time and consideration. We look forward to speaking with you.

1. Can you please describe which PDPs your company works with and how? What specific role does your company play?
2. Can you identify specific examples of terms/conditions/arrangements that have facilitated your company’s involvement with PDPs? What are examples of some of the most successful partnerships and why?
 - a. Please share examples for (a) R&D, (b) product introductions and (b) scaling up/ market access activities.

- b. What could improve/enhance/facilitate industry involvement in PDPs going forward?
3. What kinds of governance arrangements exist between your company and the PDPs you work with? Can you provide specific examples?
 - a. With regards to clinical trials?
 - b. With regards to ethics management?
 - c. With regards to risk management?
4. One of DFAT's strategic interests is global health security. From your perspective, what would you say are the top 3 PDP priorities with regard to global health security that will result in transformational change?
5. What are your company's key priorities and prospects with regard to existing PDPs over the next 5-7 years?
6. From your/your company's perspective, and considering a changing development, health, and economic landscape, what are the key challenges you see with the PDP model across the innovation cycle, and how would you propose to address them?
 - a. With regard to the product development stage?
 - b. With regard to the market introduction phase?
 - c. With regard to the scale-up phase?
 - d. Are there specific challenges with regard to partnering with PDPs? Can you provide specific examples?
7. How can cross-industry collaborations be improved, within the context of PDPs across all phases of innovation, development, and launch (product development, introduction, market access). Please provide some examples:
 - a. e.g. between diagnostics, pharmaceutical (R&D, biotech, generics) and IT technology companies;
 - b. and beyond e.g. with financial sector, media/communication and companies with large operations/employee base in LMICs
8. Are there any public-private or other cross-sector partnerships, or emerging platforms other than PDPs, working on **product R&D** that are effective? What are potential alternative innovative mechanisms or new collaborative platforms to accelerate product development, and how do they compare to PDPs?
 - a. Have you been involved in any of these other models? What was your experience?
9. Access to available affordable products and services remains a challenge. Are there any public-private or other cross-sector partnerships, or emerging platforms working on **accelerating market access** that are effective?
 - a. Have you been involved in any of these other models? What was your experience?
10. Can you specify any specific Australian partners that your organization has worked with in reference to PDPs - whether from industry, academia, government, civil society, private foundations or otherwise? What was their value-add?
 - a. Are there any you see potential, or have interest, in collaborating with going forward that could help accelerate Australia's influence with regard to PDPs for global health?

DFAT Product Development Partnerships (PDPs) Investment

Final Evaluation

INTERVIEW PROTOCOL

Date _____ Location ☐ Remote Interview (Skype)
☐ Geneva (In-person)

Stakeholder Group: PDP representatives

Name/Title:

Project Leads: Dr. Rohit Ramchandani, CEO, Antara Global in collaboration with

Barbara Bulc, President, Global Development Impact

Good afternoon. We have been engaged by DFAT Australia to conduct a final evaluation of their current PDP investments and recommend potential future directions. As one of the PDPs that make up this investment, your insights will be central to informing this evaluation. The following questionnaire covers key areas of interest for DFAT with regard to their Aid Policy and Health for Development Strategy. Your responses to this evaluation protocol will help inform the final assessment of their investment and inform potential future PDP investment priorities.

The results of this evaluation will remain internal, and all responses can be considered confidential with attribution at the organizational level only. We ask that you please fill in responses to the questions and return to Dr. Rohit Ramchandani (rohit@antaraglobal.com) and Barbara Bulc (bbulc@gd-impact.org) at least 24 hours prior to your scheduled interview so that we may optimize our discussion. If you feel that any of the questions are not relevant, please feel free to respond "N/A".

Thanking you in advance for your time and consideration. We look forward to speaking with you.

GENERAL

1. Can you please start off by telling me a bit about your role at [Organization Name] and what your role is in relation to the [FIND, MMV, TB Alliance] PDP supported by DFAT, in context of how your PDP manages DFAT and other donor investments?
2. What are the key results that have been achieved by [FIND, MMV, TB Alliance] as a result of Australia's investment?
3. Can you please summarize the specific products DFAT investments have supported and their current status [e.g. stage of clinical trials, level of market uptake, specific challenges, etc.]?
4. What is % of DFAT investment in terms of your total donor investment, how has this changed and how do you anticipate changes in the future?

EFFECTIVENESS

Test 1: Pursuing National Interest & Extending Australia's influence

5. Considering Australia's regional interests in the Asia Pacific, their focus on stability, security and prosperity within the region, prospects for strengthening their own trade and investment, in your opinion, how has this investment helped them pursue their national interests and extend their influence?

Test 2: Impact on promoting growth and reducing poverty

6. Can you provide any specific examples of how Australia's investment in [FIND, MMV, and TB Alliance] has had an impact on growth and poverty reduction in the Asia Pacific Region? Can you direct us to any published evidence of this impact?
7. Can you provide insight into the specific countries in the Asia Pacific Region where [FIND, MMV, TB Alliance] have undertaken any specific activities? Where, and what were the activities?
8. To what extent has [FIND, MMV, TB Alliance] focused on targeting the poorest and most vulnerable populations in the Asia Pacific? What specific strategies have been used, and what kind of partnerships have been established? How successful have they been? What were key challenges, and how do you suggest overcoming them?
9. To what extent has [FIND, MMV, TB Alliance] engaged with the private sector? With whom (e.g. healthcare providers, pharmaceutical/ biotech companies, diagnostic/medical device companies, IT technology sector, financial sector, media/communication, others)? What was their role and value add? Please specify any private sector stakeholders from the Asia Pacific region you have worked with – and those you see potential in collaborating with.
10. Can you explain (by assigning percentages - %) how a \$1M investment in [FIND, MMV, TB Alliance] would be allocated with regard to flow of funds? (E.g. 15% overhead, 30% to research institution partner to conduct R&D, 40% to industry partner to manufacture and distribute, 10% for access and delivery interventions implemented by XX, etc.)?
 - a. What product-specific profits were achieved in 2016 and how were the profits shared?
11. What are [FIND, MMV, TB Alliance]'s key [product] prospects over the next 5-7 years? Please identify products, etc. completion of development phase, envisioned market introduction and uptake/scale up (geographies, est quantities).

Test 3: Australia's value-add and leverage

12. What, and with whom, are the key Australian partnerships you know of, that are involved with [FIND, MMV, TB Alliance], whether from industry, academia, government, civil society/advocates, private foundations or otherwise? And what has been their value-add?
13. What other funding (public, private, and other streams of development finance) has been leveraged by Australia's investment, and how?
14. What is the status of the total financial and technical resourcing available to [FIND, MMV, TB Alliance] from all sources as of the end of 2016, and projections going forward? Is it adequate to achieve targeted impact going forward?
15. What, if any, funding gaps exist that could be usefully funded by Australia moving forward? How would this make transformational change and how would this support DFAT Test 1 and test 2 criteria?

Test 4: Making performance count

16. Broadly speaking, how does [FIND, MMV, TB Alliance]'s monitor and evaluate of their performance and results?
 - a. With regard to the product development phase and clinical trials more specifically?
 - b. With regard to the market introduction phase?
 - c. With regard to the scale up phase?
 - d. How does the PDPs ensure adequacy and effective management of such M&E, for all phases – development, introduction and scale up?
17. Can you please outline the key strengths and weaknesses of [FIND, MMV, TB Alliance]'s governance arrangements? Were they implemented as planned?
 - a. How were the specific risks under this investment managed?
 - b. How were the ethical aspects related to this investment managed?
 - c. Do you see any opportunities for how your PDP's governance might be improved? How?
18. Can you tell me about some of the key strategies [FIND, MMV, TB Alliance] is using to ensure donors of value-for-money? Please provide specific examples for each strategy.
19. What, in your opinion, are the pros and cons of donors providing earmarked funds vs. core funding? What would be [FIND, MMV, TB Alliance]'s preference if funding from Australia were to continue, and why? Please provide specific examples.
20. How did/does [FIND, MMV, TB Alliance] avoid duplication of its efforts? And furthermore, how did/does you encourage synergies? Please provide specific examples.
21. How did/does [FIND, MMV, TB Alliance] collaborate for maximum alignment of development activities for of pharmaceutical products with development activities for diagnostic products for specific disease? (Including, for example WHO processes, external partners, awareness raising etc.)
22. How can DFAT potential investment further accelerate development, introduction and scale up of products? (E.g. supporting targeted communication/ advocacy, development of targeted cross-sectoral collaborative platforms etc.)

SUSTAINABILITY & HEALTH FOR DEVELOPMENT STRATEGY

23. What, if any, **capacity building** has taken place in LMICs as a result of the [FIND, MMV, TB Alliance] PDP? Please provide specific examples (type of capacity building, partners, funding model, results)
 - a. How has Australia's investment in the [FIND, MMV, TB Alliance] PDP help build **country-level systems and services** that are responsive to people's health needs?
 - b. How has it strengthened **regional preparedness** and capacity to respond to emerging health threats?

24. Beyond research and development, how is [FIND, MMV, TB Alliance] working to ensure uptake of ready-for-market products at the country level within the Asia Pacific? At the national level? Provider level? User level? Please provide existing types of activities, partnerships, and results; and how do you see this change in the future?
25. How do you see DFAT and other donor investments can incentivize sustainability of your PDP model? Please provide specific examples.
26. How do you envision opportunities for private or blended investments in your products and activities going forward? Please provide specific examples of products and potential partners you have explored where this would apply.
27. For the products produced with support of Australian funding, please provide information to complete the availability and affordability related table below (filled out example in row 1):

Partners	Drug Formulation (Disease)	Why relevant for PDP portfolio	Trial Locations in LMICs/ expected completion	Countries of Registration/ expected & time	Manufacturing Company	Distribution /expected time	Cost	Listed in National Treatment Guidelines in/ expected time:	Estimated health impact
MMV, Shin Poong Pharma	Pyramax (malaria)		Asia Pacific: Cambodia, Thailand, India, Indonesia + 18 countries in sub-Saharan Africa	Approved by European Medicines Agency and Korea FDA; WHO has granted Pyramax prequalified status. Product (Dossiers for registration submitted to Myanmar and Vietnam; Cambodia and Thailand to follow)	Shin Poong Pharmaceutical Company (South Korea)	Product not distributed yet. vs. for example - Distributed only to Cambodia thus far; 160 000 treatments delivered in July 2012)	Price/full treatment < US \$1 for adults and US \$0.50 for children ²⁵	Country X, Y, Z	

28. For the products above, why and how are they relevant to the Asia Pacific region? When will they be available to the populations in need, and will be expected social-economic impact?
29. Does [FIND, MMV, TB Alliance] have any kind of forecasting process to determine the amount of product needed at the country level based on population need/demand? Who do you partner with for forecasting?
30. What are the key challenges currently being faced by [FIND, MMV, TB Alliance]?
- With reference to product development?
 - With reference to product introduction?
 - With reference to uptake and scale up?
31. With reference to long-term sustainability, has any consideration been given to the potential local production of any of the products being pursued through PDPs? If so, please provide specific examples.
32. Other than TB and Malaria, and applying a health security lens, what would you say are the key disease and product priorities and emerging priorities/opportunities for the Asia Pacific region?
- *If others within your organization were consulted during the course of developing responses to these questions please provide information on who was consulted.

Annex 4: Outcome - Summary of successfully trialled new/modified PDP products registered in the Asia Pacific with support from DFAT (2013-2017)

PDP	Successfully Registered in 2013-2017 Product Name (Manufacturer)	Successfully Registered in 2013-2017 Product Brand Name (Manufacturer)	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]	Prequalification (Prequalified by/year)	Countries of Registration/Year [Asia Pacific]	Registration Authorities	Uptake/Market Access Information ⁵⁵ [Overall & in Asia Pacific; By country]
FIND	Line Probe Assay 1 st line drugs <ul style="list-style-type: none"> Geno Type MTBDR_{plus} (Hain) NTM+MDRTB Detection kit 2 (Nipro) 	Same as previous column	<p>What does it treat/disease targeted: TB and MDR-TB</p> <p>Intended for use in? In high prevalence areas of MDR-TB as well as for diagnosing patients in high-prevalence TB countries and high-burden MDR-TB regions.</p> <p>What gaps does it fill? The test can be applied for screening for MDR purposes to develop country-specific TB action plans. It is not typically used for case management</p> <p>Expected marginal benefit? Enables a result in <24h (solid culture ~4m) from a pulmonary patient specimen and from culture material. Also used for diagnosing patients after treatment failure and relapse.</p> <p>Partnership Info Hain Lifesciences GmbH (Germany), privately owned SME [IVD only] with distribution network Nipro (Japan), publically traded global company on Tokyo stock exchange [medical plastics and dialysis specialists]</p>	WHO endorsement 2016	Product registered in Fiji, PNG, Solomon Islands, Vanuatu, Indonesia, Cambodia, Lao PDR, Myanmar, Thailand, Vietnam Year of country registrations unknown to PDP	CE Mark Year of compliance mark not known by the PDP	750,000 per year; PDP does not have county specific information
FIND	Xpert MTB/RIF	Same as previous column	<p>What does it treat/disease targeted: TB and MDR TB</p> <p>Intended for use in? In LMICs for TB and MDR-TB (the testing platform the GeneXpert can be used for multiple diseases)</p> <p>What gaps does it fill? Sensitivity is significantly higher than microscopy, particularly in patients with HIV infection. The test can be run in district-level microscopy labs on the Cepheid GeneXpert® system and gives results in ~90 minutes. The closed system ensures no risk of contamination and no requirement for biosafety facilities apart from a hood for sample treatment. Training for use takes 1-2 days.</p> <p>Expected marginal benefit? This system (GeneXpert plus the Xpert MTB/RIF) is the technology that has most radically changed the diagnostic landscape in LMICs, first for TB and increasingly now in other diseases (notably HIV VL and Ebola in our markets).</p>	WHO endorsement on use in paediatrics and to detect extra-pulmonary TB (2013)	Product registered in Fiji, PNG, Solomon Islands, Vanuatu, Indonesia, Cambodia, Lao PDR, Myanmar, Thailand, Vietnam Year of country registrations unknown to PDP	CE Mark 2009, Expanded product claim FDA Approval 2015; FDA marketing authorisation 2013	7 million per year globally; PDP does not have county specific information

⁵⁵ Note on quantities for specific countries – please note that all the numbers are aggregated and therefore cannot be presented country-by-country. These figures are provided to PDPs by the manufacturer.

PDP	Successfully Registered in 2013-2017 Product Name (Manufacturer)	Successfully Registered in 2013-2017 Product Brand Name (Manufacturer)	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]	Prequalification (Prequalified by/year)	Countries of Registration/Year [Asia Pacific]	Registration Authorities	Uptake/Market Access Information ⁵⁵ [Overall & in Asia Pacific; By country]
			Partnership Info? Cepheid (US) at the time a publically traded (NASDAQ), now part of Danaher Inc. (US)				
TB Alliance	Paediatric Fixed-Dose Combinations (FDCs) • HRZ (rifampicin + isoniazid + pyrazinamide) • HR (rifampicin + isoniazid) (Macleods, Lupin)	3-FDC/RHZ-75/50/150-(B)-84 (28x3) 2-FDC/RH-75/50-(B)-84 (28x3) *Note: While these two FDCs are listed together, they are in fact two separate products. From a product development standpoint, they need separate development, testing, and prequalification.	Fixed dose, disbursable, optimised treatment for drug-sensitive TB in children Commercial Partners: Macleods, Lupin; part of STEP-TB Project, launched in 2013, led by TB Alliance and WHO as co-implementers, successfully developed and launched the first correctly dosed, appropriately formulated, child-friendly fixed dose combinations of standard first line pediatric therapy; launched eight months early by Macleods at affordable price through the Global Drug Facility in December 2015; Quickly dispersible improved medicines for children with drug-sensitive TB means dispersible tablets in the correct fixed dose combinations of the commonly used anti-TB drugs; Combination of rifampicin + isoniazid + pyrazinamide is used for first two months ("intensive phase"); Combination of rifampicin + Isoniazid is used for final four months ("continuation phase"); Significant advantages over previous drugs including: easy to administer due to quick dispersability into liquid, palatable fruit flavours, expected to improve treatment adherence and outcomes; Prior to this, there was no standard TB treatment for children and treatment was estimated based on standard adult measure, which required crushing pills and often inaccurate dosage; Affordable pricing of USD 15.54 for a six-month course.	WHO/2017 ERP/2014	Afghanistan, Laos, India, Lebanon, Bangladesh, Maldives, Bhutan, Papua New Guinea, Cambodia, Kiribati, Jordan, North Korea (DPKR), Tuvalu, Myanmar, Samoa, Pakistan, Solomon Islands, Sri Lanka, Timor Leste, Taiwan, Papua New Guinea, Philippines, Kiribati	Details not immediately available to PDPs	Global figures: Introduced in 65 countries with orders exceeding volume of ~400,000 (as of October 2017) treatment courses to date (40,000 courses delivered in 2016). Specific Asia Pacific orders/delivery not immediately available through PDPs 2010-2015
MMV	Pyronaridine artesunate (Shin Poong)	Pyramax® and Pyramax® granule	Pyramax tablets: Treatment of acute, uncomplicated malaria caused by <i>P. falciparum</i> or by <i>P. vivax</i> in adults (>20kg) and children (between 5 and 20kg). This is the only artemisinin combination therapy (ACT) approved for both <i>P. falciparum</i> and <i>P. vivax</i> (blood stage). No food restrictions. It can be used both to counter resistance to artemisinin and partner drugs in Asia and as an alternative first-line treatment in sub-Saharan Africa to delay the emergence of resistance. Pyramax is also expected to contribute to improvement in adherence to treatment thanks to patient-friendly, once-daily dosing regimen and availability of a child-friendly granule formulation.	2015: Positive opinion from EMA (Article 58) for new label (tablets) and approval (granules). 2016: WHO prequalification (granules). 2012: WHO prequalification (tablets)	Tablets formulation registered in Cambodia (Jun 2012), Myanmar (Sept 2004), the Philippines (Apr 2016), Thailand (Feb 2017), Vietnam (Dec 2013). During the reporting period, dossiers for the registration of Pyramax granules submitted to Cambodia, Laos,	Assumed national regulatory authority	The product has been distributed for WHO-led therapeutic efficacy studies in SE Asia (Greater Mekong Subregion). No broad distribution in Africa yet, as commercial partnerships are under development in key high-burden African countries.

PDP	Successfully Registered in 2013-2017 Product Name (Manufacturer)	Successfully Registered in 2013-2017 Product Brand Name (Manufacturer)	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]	Prequalification (Prequalified by/year)	Countries of Registration/Year [Asia Pacific]	Registration Authorities	Uptake/Market Access Information ⁵⁵ [Overall & in Asia Pacific; By country]
					Myanmar, Pakistan, Thailand, the Philippines, Vietnam.		
MMV	Dihydroartemisinin-piperaquine	Eurartesim® (Sigma-Tau/ Pierre Fabre)	Treatment of uncomplicated <i>P. falciparum</i> malaria in adults, children and infants >5kg. Eurartesim's long half-life offers excellent protection against new infections. This medicine is a treatment of choice in countries implementing mass drug administration to accelerate elimination.	2015: WHO prequalification	Cambodia, Thailand	2011: EMA approval End 2017: Expected submission of dispersible paediatric formulation to EMA	Approved in 19 countries. More than four million treatments have been distributed since its launch. Registered in 19 countries. Eurartesim has been widely used in parts of the Asia Pacific region as a first-line antimalarial and has also been distributed widely in private sector outlets in the Greater Mekong sub-region.

**For these products, FIND has negotiated preferential pricing with diagnostics suppliers for the public sector in low- and middle-income countries (LMICs). Listed countries are eligible for these prices. For more information see: <https://www.finddx.org/find-negotiated-product-pricing/>

Annex 5: Output - Summary of new/adapted products successfully completing late stage clinical trials with DFAT support (2013-2017)

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]
FIND	Line Probe Assay 1 st line drugs • Geno Type MTBDR _{plus} (Hain) • NTM+MDRTB Detection kit 2 (Nipro)	Ended Nov 2013	<u>Trial countries:</u> Germany; Uganda; South Africa; Azerbaijan	See Annex 4
FIND	Line Probe Assay 2 nd line drugs • Geno Type MTBDRs/ (Hain)	End date Dec 2015	<u>Trial countries:</u> Georgia; Moldova	WHO endorsement 2016, CE Mark (~2012); not yet registered in Asia Pacific countries What does it treat/disease targeted: TB and MDR-TB Intended for use in? In high prevalence areas of MDR-TB as well as for diagnosing patients in high-prevalence TB countries and high-burden MDR-TB regions. What gaps does it fill? On the same format as the LPA for 1st line drugs, this test can detect resistance to some fluoroquinolones (ofloxacin and levofloxacin) and all second-line injectables (kanamycin, amikacin, and capreomycin), and ethambutol. Expected marginal benefit? Given that it produces results quickly, it is very important for guiding who can take the newly-recommended shortened regimen. Partnership Info? As above for Hain
FIND	Xpert MTB/RIF	Ended Sept 2014	<u>Trial countries:</u> South Africa (specifically for extra data for paucibacillary patients – original evaluation in 6 countries, 11 sites – year unknown)	WHO endorsement on use in paediatrics and to detect extra-pulmonary TB 2013 ; CE Mark 2009, FDA Approved; 7M/Yr global delivery Registered in: Fiji, PNG, Solomon Islands, Vanuatu, Indonesia, Cambodia, Lao PDR, Myanmar, Thailand, Vietnam What does it treat/disease targeted: TB and MDR TB Intended for use in? In LMICs for TB and MDR-TB (the testing platform the GeneXpert can be used for multiple diseases) What gaps does it fill? Sensitivity is significantly higher than microscopy, particularly in patients with HIV infection. The test can be run in district-level microscopy labs on the Cepheid GeneXpert® system and gives results in ~90 minutes. The closed system ensures no risk of contamination and no requirement for biosafety facilities apart from a hood for sample treatment. Training for use takes 1-2 days. Expected marginal benefit? This system (GeneXpert plus the Xpert MTB/RIF) is the technology that has most radically changed the diagnostic landscape in LMICs, first for TB and increasingly now in other diseases (notably HIV VL and Ebola in our markets). See also later in this document under Xpert MTB7RIF Ultra and Omni. Partnership Info? Cepheid (US) at the time a publically traded (NASDAQ), now part of Danaher Inc. (US)
FIND	TB Loop-mediated isothermal	Ended Dec 2014	<u>Trial countries:</u>	WHO endorsement 2016 ; CE Mark, Japanese MoH regulatory approval 2011; not yet registered in any high burden Asia Pacific countries

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]
	amplification (LAMP) Detection Kit		Brazil; Peru; South Africa; Malawi; Uganda; Ivory Coast; India; Vietnam; Haiti; Madagascar; Tanzania	What does it treat/disease targeted? TB Intended for use in? LAMP has several features that make it attractive as a diagnostics platform for resource-poor settings that do not have access to Xpert. What gaps does it fill? It generates a result that can be detected with the naked eye and so does not need an imaging system. Expected marginal benefit? It is fast (15- 40 min), isothermal (requiring only a heat block and not a thermocycler), robust to inhibitors and reaction conditions that usually adversely affect PCR methods. Partnership Info? Eiken Chemical Company Ltd. (Japan), on the Tokyo stock market, mid-size IVD company
FIND	MALARIA Pan/Pf (LAMP) Detection Kit	End date (trials for registration data) Dec 2012 Ongoing demonstration for detection in asymptomatics	Trial countries: Cambodia; Uganda; UK; Sweden; Colombia (for registration data) Peru; Tanzania; Senegal; Philippines; Indonesia; Core d'Ivoire; Colombia	WHO recommendation on the use of molecular tests for asymptomatics in elimination programmes received 2014 ; CE Mark 2012; 35k/y global delivery; not a new or modified product, but late stage research for product application for asymptomatics so included here, but not above. In-country registration in the Asian Pacific region is in progress in India, Indonesia, Philippines, Vietnam, Cambodia, Lao PDR, Myanmar, and Papua New Guinea. What does it treat/disease targeted? Dual testing kit for <i>P. falciparum</i> specifically as well as <i>P.spp</i> malaria Intended for use in? The malaria LAMP kit is designed for use with the LAMP platform and is intended as a field tool to detect very low density malaria infections as it is very sensitive. What gaps does it fill? Has a role in identifying hidden infections in screening programmes for elimination. Expected marginal benefit? Intended i) to serve as a reference standard against which RDTs and other malaria diagnostics could be evaluated; ii) to confirm the presence or absence of malaria parasites in complex cases, and iii) to support clinical trials. Partnership Info? Eiken – see above
FIND	Malaria Highly Sensitive RDT Alere Malaria Ag P.f (Ultra Sensitive)	2015-2016 (Testing)	Trial countries: Evaluation was through Round 7 of the WHO FIND Malaria RDT Evaluation Program	WHO recommendation in 2016; CE Mark 2016; Not yet registered in any high burden Asia Pacific countries, may be too early. What does it treat/targeted disease Falciparum malaria Intended for use in? Malaria endemic LMICs. What gaps does it fill? The high-sensitivity RDT has an analytical sensitivity one order of magnitude better than the best RDTs currently available in the market. Expected marginal benefit? Useful in screen and treat programmes to accelerate elimination as it can detect low parasitemia (asymptomatics). FIND is particularly interested in its benefits for pregnant women and newborn health and is currently demonstrating impact in those population groups. Partnership Info? Standard Diagnostics (SD) Inc. (South Korea), part of Alere Inc. (see above)
FIND	TrueLab System (TruePrep plus TrueLab and TrueNat) for MTB detection	2 sites finished Apr 2017; 1 still going	Trial countries: South Africa; India	Currently (2017) being trialled in India for local registration; data will also likely go to WHO 2018; Other country registrations in progress; Not yet registered in high burden Asia Pacific country so not included in table above; CE Mark 2016 (system and TB assay) What does it treat/targeted disease TB Intended for use in? Lower levels of the health system in LMICs currently for TB detection only. A reflex Rif assay is currently RUO and still needs evaluation.

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function
				<p>[What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]</p>
				<p>What gaps does it fill? The significance of this system and its assays is that they are competitor products to Xpert, developed in a BRICS country (India) that has been successful largely due to the work that FIND has done with them through our S4S programme. Market diversification is expected to ultimately reduce assay pricing to the market.</p> <p>Expected marginal benefit? The system will be deployable at the lower levels of the healthcare system.</p> <p>Partnership Info? MolBio, (India) a joint venture with Bigtec that is a privately owned Indian SME</p>
FIND	Xpert MTB/Rif Ultra	Ended Dec 2016	<u>Trial countries:</u> India; South Africa; Georgia; Belarus	<p>WHO endorsement 2017; CE Mark, 2017; Not yet registered in high burden Asia Pacific countries</p> <p>What does it treat/targeted disease TB and MDR-TB</p> <p>Intended for use in? In LMICs for TB and MDR-TB. The testing platform the GeneXpert can be used for multiple diseases. The Ultra assay will be the first Xpert assay to be used in the new GeneXpert model, the Omni, which is a battery-operated, hand-held device that can be used at the point of care, allowing for full decentralisation of TB and DR TB detection (expected 2018)</p> <p>What gaps does it fill? Difficult to detect paucibacillary patients who are currently missed by microscopy and Xpert MTB/Rif, e.g. those in early stages of infection; children; HIV co-infection etc. Use on the Omni will bring additional benefits as we expect an eventual impact on TB transmission (due to early detection)</p> <p>Expected marginal benefit? Sensitivity is 10-fold higher than Xpert MTB/Rif which means that it will detect more smear negativeve, culture positive; and will be particularly useful in paucibacillary samples (i.e. when few TB organisms are present in sputum). FIND is working on a stool kit with Rutgers University that will make the use of this assay even easier in small children and will be validated in early 2018.</p> <p>Partnership Info? Cepheid – see above Rutgers State University of New Jersey (previously UMDNJ), specifically David Alland's lab.</p>
FIND	Positive Control Well (PCW) for Malaria RDTs (MicroCoat, Germany)	Evaluation/July/2016	Kenya, Tanzania	<p>What does it treat/targeted disease? Malaria</p> <p>Intended for use in? To ensure quality of malaria RDTs.</p> <p>What gaps does it fill? At present, users have no field-adapted method of ensuring that rapid diagnostic tests (RDTs) are still functioning properly after exposure to variable transport and storage conditions. FIND and its partner MicroCoat GmbH developed well-calibrated positive control wells containing recombinant malaria antigens (the main targets of malaria RDTs) and designed them to allow testing of malaria RDTs at clinic or village levels.</p> <p>Expected marginal benefit? These positive control wells will enable rapid direct evaluation of RDTs performance in remote locations without the need for cross-checking against expert microscopy. Such testing has the potential to increase the confidence of health providers in the quality of RDTs after transport to remote areas or prolonged storage, allowing them to confidently manage symptoms according to the RDT result. Manufacturers who wish to include these PCWs with their RDT kits can access them through MicroCoat.</p> <p>Partnership Info? Microcoat GmbH is a privately held German company which specialises in IVD Development Projects and manufactures IVD products as an OEM supplier to third parties.</p>
FIND	Reference material (MicroCoat, Germany): 1. HRP2 recombinant panel for	Evaluation/May/2016 Non-IVD ancillary products that are for use with registered	Nigeria	<p>What does it treat/targeted disease? Malaria</p> <p>Intended for use in? FIND and Microcoat developed calibrated recombinant panels for evaluation, optimisation and development of HRP2 tests. Also, 3 different panels (based on 3 different HRP2 types) were developed and are available for centralised lot testing (large-scale QA) by CDC and reference laboratories currently in 12 endemic countries.</p> <p>What gaps does it fill? Recombinant panels are designed to assess the limit of detection and monitor the lot-to-lot quality variation and degradation of malaria RDTs over time. Variation in RDT performance is well documented; in general, FIND and WHO's malaria lot-testing programme is intended to address poor-performing RDTs. The recombinant panels are products</p>

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]
	malaria diagnostic tests 2. GST-Pf-HRP2- FCQ79 (type A) 3. GST-Pf-HRP2- W2 (type B) 4. GST-Pf-HRP2- PH1 (type C)	IVDs. By definition, there will have been no <i>clinical</i> trials for these products, but rather analytical lab testing to demonstrate expected performance.		that have been developed to replace the original methods that were based on sourcing actual patient samples, which is expensive and logistically challenging. Expected marginal benefit? To ensure that only high-quality malaria RDTs are procured, FIND and the WHO have established quality control programs that are being conducted by national reference laboratories. These reference laboratories assess the limit of detection and monitor lot to lot quality variation or degradation of malaria RDTs. For these studies, the new standardised HRP2 recombinant panels will be used to evaluate the quality of malaria RDTs before they are purchased and used in malaria-endemic countries. Currently, only a HRP2 recombinant panel is commercially available but panels of recombinant <i>P. falciparum</i> and <i>P. vivax</i> lactate dehydrogenase (Pf LDH and Pv LDH) will be available soon. Partnership info Microcoat – see above. Centers for Disease Control Atlanta (US), which is part of the US NIH, has been a partner to FIND and WHO from the start of this project and still does centralised lot testing for this programme.
TB Alliance	Evaluating the efficacy of combination of bedaquiline, pretomanid and linezolid for XDR-TB (BPAL)	Phase 3 study (Nix / NC-007)/ 2017	South Africa	This treatment regimen can treat patient with XDR-TB, pre-XDR-TB and MDR-TB patients who are non-responsive or treatment intolerant to current MDR-TB treatment. This is a true breakthrough. Follow-up trial will include Georgia, Belarus and possibly Russia
TB Alliance	Evaluating the efficacy of combination of bedaquiline, pretomanid, moxifloxacin and pyrazinamide (BPAMZ)	Phase 2b study (NC-005)/ 2016	South Africa, Tanzania, Uganda	This treatment regimen can treat all DS and MDR-TB patient with TB between 3 and 6 months, complementing the BPAL regimen, to provide a breakthrough new treatment paradigm for all patients with TB.
TB Alliance	Linezolid dose-ranging study	Phase 2 (LIN) study / 2016	South Africa	The study evaluated the mycobactericidal activity, safety, tolerability, and pharmacokinetics of 5 doses of linezolid. It showed the use of linezolid, e.g. for the BPAL regimen
TB Alliance	Evaluating the efficacy of combination of bedaquiline and pretomanid (PA-824) and pyrazinamide (BPaz)	Phase 2B study (NC-003)/ 2013	South Africa, Tanzania	The NC-003 clinical trial tested the BPaz regimen. The two-week study found that the BPaz regimen killed more than 99% of TB bacteria over the course of 14 days and that the treatment was safe.
TB Alliance	PaMZ - Combination	Phase 2B study (NC-002)/ 2013	South Africa, Tanzania	NC-002 built on the TB Alliance's two-week NC-001 trial, initiated in 2010, which was the first study to test novel TB drugs in combination. In NC-001, PaMZ was found to kill more than 99 percent of patients' TB bacteria within two weeks, adding to

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function
				[What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]
	treatment for DS-TB and MDR-TB			the growing evidence that it could be more effective than existing treatments. NC-002 treated patients for two months and took place at 8 sites in South Africa and Tanzania. The trial was the first to enrol both drug-sensitive TB and MDR-TB patients and treat them with the same regimen.
MMV	Tafenoquine GlaxoSmithKline	Patient confirmatory	Part 1 trials completed in 2013 in Cambodia, India, the Philippines, Thailand (Nov); Thailand (Dec); Part 2 trials completed in Cambodia, Philippines, Thailand (close out: trial ended Nov 2016); Philippines, Thailand, Vietnam (close out: trial ended Nov 2016). Ongoing trials: Thailand, Vietnam (not yet indication of planned end); Indonesia: end planned Feb 2019.	Single dose treatment for relapsing <i>P. vivax</i> malaria. This is the first potential new medicine in more than 60 years to address relapsing malaria due to <i>P. vivax</i> .
MMV	Dihydroartemisinin - piperaquine dispersible Alfasigma/Pierre Fabre	Patient confirmatory	Papua New Guinea: December 2015; India: completed Q1 2017.	Dispersible formulation of Eurartesimin. Submission to EMA expected in 2017.
Products of note which don't technically meet the definition used for assessing successful completion of the investment output but indicate progression of products through the product pipeline				
FIND	TB lipoarabinomannan Antigen Detection Test (LAM RDT)	Only a systematic review during the investment period (2013-2017) FIND trials ended 2010	Tanzania; South Africa; and Zimbabwe	WHO endorsement 2015 (limited use in HIV infected); CE Mark 2014; No data on registrations in the region yet so not included above, may be too early; est >20k/y global delivery What does it treat/disease targeted? TB in HIV patients Intended for use in? This is first ever urine-based rapid diagnostic test for TB recommended for use in HIV-positive patients. What gaps does it fill? TB testing in vulnerable patients. Expected marginal benefit? Data show that the use of this test is already saving lives in this particularly vulnerable patient group. Future TB RDTs will aim at use for a wider patient group.

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function
				[What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]
	Alere Determine™ TB LAM Ag			Partnership Info? Alere Inc. (US) publically traded mature fully-integrated IVD company focussed on POC. Acquisition by Abbot Labs Inc. (US) expected to be finalised Q4 2017.
TB Alliance	INH disbursable (Isoniazid)	WHO changed guidelines for dosing in children in 2010. These were widely accepted recommendations, but no one was willing to develop products needed to implement them. Thus TB Alliance work involved working with WHO, generic pharma companies, and countries to ensure product formulations and CMC work was done. Also did update prevalence studies, market assessments, procurement chain analysis, helping to provide evidence for certainty that investments into production/CMC/regulatory work would be deemed secure enough for companies to invest. Thus included here. Evidence studies for the drugs were completed separately and done years ago.	Unknown	ERP approval , 2017; Not yet registered in Asia Pacific countries but dossiers are submitted. Given the uncertainties of the review timelines, final approval is not guaranteed but is expected any moment. Disbursable, optimised tablet for treatment of latent TB in children
TB Alliance	E disbursable (Ethambutol)		Unknown	ERP approval, 2017; Not yet registered in Asia Pacific countries but dossiers are submitted. Given the uncertainties of the review timelines, final approval is not guaranteed but is expected any moment. Disbursable, optimised tablet for drug-sensitive TB treatment in children (for countries prescribing HRZE to children)
TB Alliance	Z disbursable (Pyrazinamide)		Unknown	ERP approval, 2017; Not yet registered in Asia Pacific countries but dossiers are submitted. Given the uncertainties of the review timelines, final approval is not guaranteed but is expected any moment. Disbursable, optimised tablet for drug-sensitive TB treatment in children (for high-dose Z in certain patient groups)

PDP	Product Name Successfully Completing Late Stage Clinical Trial (2013-2017)	Trial Stage Completed [stage/month/year]	Trial Locations	Description of Product/Function [What does it treat? Intended for use in? What gaps does it fill? Expected marginal benefit? Partnership Info?]
Products progressing through earlier stages				
MMV	DSM265	Product development.	Four trials in Australia (June 2016; Feb 2017; May 2017; July 2017)	Triazolopyrimidine-based highly selective inhibitor of Plasmodium's dihydroorotate dehydrogenase (DHODH), a key enzyme for the parasite's survival.
MMV	MMV048	Product development.	Australia (completed: March 2016; October 2016)	This is a novel antimalarial compound from the aminopyridine class, and the first new medicine to be discovered by an African-led team. MMV048 is highly potent against the blood-stage of malaria, and as such it could be an important part of a single-exposure cure. The compound also has activity against other stages of the parasite lifecycle and all known resistant strains of the parasite.
MMV	OZ439	Product development.	Australia (March 2013; June 2014; July 2016; September 2016; May 2017), Thailand (march 2016). Ongoing: Vietnam (end planned May 2019)	This compound is on track to potentially replace artemisinin and become a part of the much-needed one-dose cure for malaria. Next step is to get the efficacy data in children.
MMV	MMV253	Translational (preclinical).		This compound has a novel mechanism of action, rapidly kills parasites across all intra-erythrocytic stages and has a long half-life, thus with the potential to develop into a single-dose cure for <i>P. falciparum</i> malaria.
MMV	UCT943	Translational (preclinical).		This is a new potent antimalarial development candidate with potential for both treatment and prevention of malaria. It has potent activity against all stages of the malaria parasite lifecycle and has the potential to block transmission of the parasite from person to person

Annex 6: Australian research institutes engaged with DFAT supported PDPs

To gain insight into the value-add of Australian researchers, the evaluators interviewed four leading researchers from QIMR Berghofer, Monash, the Walter and Eliza Hall Institute of Medical Research, and Menzies. Their research spans multiple areas including:

- Working with FIND to improve malaria diagnostics, including research to understand the biologic basis of malaria RDTs and the causes for false positive and false negative tests, as well as MMV to develop the human challenge model (CHMI – Controlled Human Malaria Infection) and then use it to test investigational drugs. [USD 2.6 million in funding from MMV since 2013 across 24 different projects; \$174,000 in funding from FIND since 2014 across two projects];
- Working with FIND to develop a completely novel type of diagnostic test – the first to detect carriers of dormant infections with *P. vivax* – that, if successful, would greatly help accelerate the elimination of malaria from *P. vivax* endemic areas in the Asia Pacific, the Americas and the Horn of Africa;
- Working closely with MMV to lead drug metabolism and pharmacokinetic (DMPK) activities for a range of candidates, working closely with drug discovery chemists and biologists to identify physicochemical, metabolic, and pharmacokinetic liabilities in their investigational compounds that would likely limit downstream development. Optimising physicochemical and DMPK properties is critical to ensure convenient dosing regimens and drug concentrations that are both efficacious and safe; and
- Working with MMV to test novel compounds in an ex vivo assay in PNG and Indonesia. One of the only places to assess activity against both *P. falciparum* and *P. vivax*, having tested over 65 compounds over the last ten years, some of which are now in phase 3 clinical trials. Results from this work have helped focus clinical development on the best compounds, most likely to succeed in clinical trials. [~ USD180,000 from MMV over six years] This is in addition to testing new diagnostics with FIND, the main focus of which is diagnostics for G6PD deficiency. Existing diagnostics for G6PD deficiency are not sufficient to support scaling up of treatment of *P. vivax*. A point-of-care diagnostic tool for G6PD deficiency is therefore desperately needed.

Annex 7. Evaluation of FIND

Investment outcomes
<p>Definition of outcomes used by PDP</p> <p><u>Registered product in the Asia Pacific:</u> Once a technology is CE marked, it is commercially available and can be exported with the appropriate registration in the receiving country. FIND does not track registrations beyond the initial stringent regulatory authority (SRA) clearance, which is generally in the country of origin. However, with all of the partner companies listed in the tables, FIND's assumption is that if the product is available in a country, it has received local registration. This information is acquired from the manufacturing companies.</p> <p><u>Successfully trialled new or modified product:</u> Trials where data are used for primary registration dossiers are essentially late stage trials. This means that all the 9 products included in Annex 5 table completed late stage trials, as they have received SRA and/or WHO clearance within the period of this assessment. 5 non-IVD ancillary products that are for use with registered IVDs are nonetheless included. By definition, there will have been no <u>clinical</u> trials for these product, but rather analytical lab testing to demonstrate expected performance.</p>
<p>Outcome: New/modified PDP products registered in Asia Pacific with DFAT support: 2</p> <p>Line Probe Assay 1st line drugs (Geno Type MTBDR_{plus} (Hain)) and NTM+MDRTB Detection kit 2 (Nipro); Xpert MTB/Rif</p> <p>Output: New/adapted products successfully completing late stage clinical trials with DFAT support: 10</p> <p>Line Probe Assay 1st line drugs (Geno Type MTBDR_{plus} (Hain)) and NTM+MDRTB Detection kit 2 (Nipro)); Line Probe Assay 2nd line drugs (Geno Type MTBDR_{sl} (Hain)); Xpert MTB/RIF; TB Loop-mediated isothermal amplification (LAMP) Detection Kit; MALARIA Pan/Pf (LAMP) Detection Kit; Malaria Highly Sensitive RDT (Alere Malaria Ag P.f (Ultra Sensitive); TrueLab System (TruePrep plus TrueLab and TrueNat) for MTB detection; Xpert MTB/Rif Ultra; Positive Control Well (PCW) for Malaria RDTs (MicroCoat, Germany); Reference material (MicroCoat, Germany): 1) HRP2 recombinant panel for malaria diagnostic tests, 2) GST-Pf-HRP2-FCQ79 (type A), 3) GST-Pf-HRP2-W2 (type B), 4) GST-Pf-HRP2-PH1 (type C)</p> <p>Information on these products is in Annexes 4 and 5</p>
<p>Test 1: Pursuing national interest and extending Australia's influence</p> <p>i. <i>Advance Australia's national and regional interests in terms of addressing risks to health security, stability and prosperity?</i></p> <p>FIND's focus on improved diagnosis of TB and Malaria has been crucial to address health security issues. Early diagnosis has made it easier to swiftly distinguish between malarial and non-malarial fevers, between resistant on non-resistant TB, enabling timely and appropriate treatment, helping to prevent resistance.</p>

In the instance of *P. vivax*, a form of the disease that is particularly endemic to the Asia Pacific region - over 80% of all attacks globally occur in the Asia Pacific, making this principally a regional problem. *P. vivax* is the most difficult form of malaria to eliminate because it causes recurring illness, which perpetuates the cycle of infection. All malaria parasites in the body must be killed to stop this cycle. This is known as radical cure. Currently, radical cure for *P. vivax* malaria can only be achieved with primaquine, an 8-aminoquinoline-based drug. But this class of drug can cause potentially lethal side effects in people with a common deficiency of an enzyme known as glucose-6-phosphate dehydrogenase (G6PD), which affects 400 million people worldwide. Therefore, it is critical for all patients to be tested for G6PD deficiency before they are treated with primaquine and tafenoquine.

Specifically, FIND focused on funding projects that fit with DFAT's Health for Development Strategy 2015-2020 as follows i) core public health capacities in partner countries; ii) combatting health threats that cross national borders; and iii) health innovations and solutions that benefit the region (3 of the listed 5 priorities)

ii. **Extending Australia's Influence**

"[Australia] is now more associated with international changes in health ecosystems (e.g. Essential Diagnostics List) and as a funder of game-changing innovation. Australia can also claim to fund all the way from innovation to implementation, and enables a seamless integration of products coming out of our R&D pipeline into funding mechanisms such as the Global Fund. Having its name on publications (in the funding acknowledgements) as a result of activities that affect the world's poorest and global health security helps increase this visibility – in our eyes Australia is starting to be seen as one of the forces that help shape the global health agenda."

-FIND

In addition to the product-specific outcomes achieved due to FIND innovations, and the influencers stated in the overall investment assessment to spur R&D (see Outputs and Outcomes Tables in annexes 4 and 5), through FIND, Australia has had tremendous influence in the region.

FIND is also engaging with three promising Australian diagnostics companies – Atomo, Cellabs, and soon to start Omega Diagnostics (Dx), all of which hope to see greater sales in the global health market, thereby extending Australia's influence. Sydney-based Cellabs produces a commercial ELISA kit that is globally accepted as the reference assay to compare with malaria RDTs. FIND has been working closely with Cellabs on development of standard protocols and on the establishment of an international biological standard for malaria RDTs. Products from Cellabs provide an important contribution towards ensuring distribution of high quality RDTs within countries in the region.

FIND also has partnerships in 6 of the countries that fall into DFAT's top ten bilateral trading partners list⁵⁶, with a formal presence in two of them. FIND executives noted that they see significant potential for more partnerships (with industry, academia, etc.) in Australia and the Asia Pacific region going forward. FIND would welcome developing a more in-depth relationship with DFAT to one that goes beyond donor-grantee relationship e.g. more in the implementation/ access work of new tests, given DFAT's investments in health system strengthening and in operational research. This includes working with DFAT and other branches of the Australian government to act as convener of Australian researchers and

⁵⁶ China, Japan, USA, DPR Korea, UK, India

Australian industry to further involve them and leverage their expertise for the benefit of global health and specifically in the Asia Pacific region. Also, in engaging with regulatory authorities in the region.

Test 2: Impact on promoting growth and reducing poverty

i. ***Based on past reporting and current work plans, what is the potential of FIND to have an impact on growth and poverty reduction?***

For TB, FIND implements capacity building and laboratory strengthening activities in partnership with national programs and as the Global Fund recipient. FIND trained approximately 2000 laboratory technicians per year since 2013 and supported countries in establishing connectivity and supply chain software solutions that enable strong diagnostic data management and therefore enhance diagnostic impact (linkage to care after diagnosis). Over 80% of India's diagnostic capacity to diagnose drug resistance has been established by FIND.

FIND conducts large clinical trials in the region. To ensure access, FIND carries out demonstration projects to help translate global policy recommendations for FIND-supported products or strategies into national policy. E.g. the use of Xpert for children in India doubled the case detection rate in this vulnerable group. The national policy was developed based on evidence from the FIND demonstration project working with over 10,000 private practitioners and the government. In parts, FIND conducts the work itself, or works through strategic partners, e.g. Burnet Institute for PNG. Country focus in the region covers India, Vietnam, Myanmar and PNG.

For malaria, other than the conduct of clinical evaluation studies to assess the performance of new tests (e.g. LAMP, highly sensitive RDT, new markers for *P. vivax* elimination), FIND activities include rolling out the global RDT quality assurance program in the region, co-leading a large fever mapping project to understand the distribution of fever pathogens in the region, working on and evaluating diagnostic strategies to reduce the harm of Malaria in pregnancy. FIND activities have now been expanded to include non-malarial fever, and a recent demonstration project shows how the use of simple diagnostics in Thailand and Laos can reduce the overuse of antibiotics in the region. Country focus in the region: Cambodia, Laos, Myanmar and PNG.

Country specific examples

PNG:

- Due to concerning rises in TB incidence over time and unprecedented rates of MDR-TB in PNG (Burnet report), along with the fact that many residents live in remote areas, the ability to provide decentralised testing with robust battery operated devices is especially critical.
- FIND, along with the Burnet Institute, is conducting a randomised trial to assess the impact of "Omni and Ultra" on patient outcomes, for improved TB and resistance detection.
- For malaria, *P. vivax* should be considered as a priority as this species is endemic in PNG and the required tools for diagnosis and treatment are sub-optimal; there is also a need to accelerate elimination in the region to avoid the spread of antimalarial resistance.
- FIND is working on the evaluation of LAMP and HS-RDT for the detection of malaria infections, particularly during pregnancy.

Indonesia:

- Indonesia is the second largest high burden country for TB next to India and laboratories have been poorly staffed, with no mechanism in place for referring samples
- FIND has engaged in crucial lab strengthening activities in Indonesia, and there remains a great need for improved diagnostic and treatment services for TB, TB/HIV and MDR-TB HBC.

Myanmar:

- FIND has participated in TB laboratory strengthening activities in Myanmar from 2007, resulting in an increase of drug resistant TB cases detected, though treatment gaps remain
- FIND has built strong relationships and trust with the Ministry of Health and the national disease programs
- FIND has implemented malaria projects, as well as controlled trials to understand anti-microbial resistance in Myanmar; HCV projects are in the in planning stages

Vietnam:

- FIND has been doing controlled trials with the Regional Lab at Ho Chi Minh City for several years, and established a formal presence there in 2016
- FIND helped establish an EQA program that will serve other countries in the region
- FIND is conducting an evaluation of LAMP for the detection and treatment of sub-microscopic infections to stop transmission and accelerate elimination of malaria

Bangladesh:

- Regulatory requirements make the importation of equipment and supplies into the country very challenging. Xpert when it was introduced into the country although the use of other technologies (liquid culture and LPA) was sub-standard
- FIND established TB containment facility, getting the Ministry of Health to take an ownership role
- FIND plans to work on outbreaks (i.e. Nipha) in the country

India:

- Partnership with RNTCP enabled the scale-up of diagnostics program with several thousands of MDR-TB cases detected
- Scale up of pediatric diagnostics, with 9 sites and continuing medical education (CME) sessions for managing pediatric TB
- Laboratory capacity strengthening and upgrades, including on-site training sessions
- Large-scale HCV project planned

ii. ***Based on past reporting and current work plans, to what extent is FIND focused on targeting the poorest and most vulnerable populations?***

FIND's core mission is to turn complex diagnostic challenges into simple solutions to overcome diseases of poverty and transform lives. FIND's activities are focused on developing and providing affordable quality diagnostics solutions, through partners and global partnerships, targeting low- and middle-income countries and as such including the poorest and most vulnerable populations.

Target populations of FIND's work include the most vulnerable populations at risk of contracting deadly poverty-related and neglected diseases, including in the Asia Pacific region. In addition, the diseases that

FIND works on predominately affect rural people and those who live in urban slums, whose income puts them in the two lowest quintiles (the poorest 40%).

FIND states a commitment to ensuring global access for all the products it supports to ensure the new tests are available, accessible and affordable to patients and countries, removing barriers that restrict access to improved diagnosis and treatment for the world's poor. The following points highlight FIND's strategies to serve the poorest and most vulnerable groups:

- FIND aims to develop tools that will be more accurate, easier to use by health professionals, and less expensive for the patient and the health system
- FIND aims to ensure that the tools can be used by local health agents (public and private) and include a connectivity feature to improve information sharing with patients and peripheral health authorities, which will help address the challenges faced by geographically hard-to-reach populations
- FIND collaborates closely with the WHO and the Global Fund to ensure access in the public sector in resource poor settings
- FIND works closely with Ministries of Health in the countries to ensure local policy around good quality and improved diagnostics; including providing them with the tools and know-how to plan and implement the most impactful algorithms and scale-up pathways; and how to get the most out of the connectivity features of diagnostics, which can lead to more lives saved, better forward planning and significant health cost savings.
- With regard to specific vulnerable groups (e.g. addressing access for children; sexual discrimination etc.), FIND is mindful of particularly vulnerable groups and has policies in place to ensure that no harm comes to children; FIND collects and analyses data appropriately (disaggregated) and if significant, the results are shared with programs and partners, and published to help guide planning and other interventions. Also, by aiming to decentralise care (i.e. focusing on POC), FIND aims to ensure that patients are diagnosed and treated where they first present rather than having to be referred to secondary or tertiary facilities. Quicker diagnostics can significantly benefit patients in LMICs, particularly those presenting at lower levels of the health system, and can help address equity and stigma issues where they exist.
- For malaria, and of relevance to the region, FIND is part of APMEN and APLMA advocating for implementation of improved diagnostics to support malaria elimination.

iii. ***Based on past reporting and current work plans, to what extent is FIND engaging effectively with the private sector to achieve better population health?***

FIND works with its partners to develop new diagnostic approaches, then evaluates them in laboratory and field trials to generate evidence for global adopters. All FIND's contracts with its commercial partners have clear Global Access terms and conditions (product availability and affordability, and knowledge accessibility) for FIND target markets (LMICs).

In 2016 FIND had 166 active partnerships across multiple categories: 68 partnerships were with universities, research institutes and clinical trial sites; 32 with industry; 35 with governments or multi-lateral agencies; 2 with advocacy agencies (plus numerous un-contracted, semi- or informal collaborations); 2 biorepositories; and 27 implementing partners.

Private sector partners in the Asia Pacific region: FIND partnerships are mostly restricted to in-vitro diagnostics (IVD) developers in India (MolBio/Bigtec); Japan (Fujifilm, Nipro, Otsuka, Eiken, Sysmex); S. Korea (SD/Alere, SD Biosensor, YD).

Private sector partners in Australia specifically: FIND has more research and advocacy partners in Australia than it has commercial companies that are product-focused. Examples include:

- Cellabs is a partner and produces ELISA test currently used as reference to evaluate performance of malaria RDTs. FIND has been working closely with Cellabs on development of standard protocols and on the establishment of an international biological standard for malaria RDTs. Products from Cellabs contribute to ensure that quality RDTs are distributed in the countries in the region.
- Cellestis, the original developers for the Quantiferon GIT assay for LTBI detection (they have since been acquired by Qiagen).
- AdAlta, biotech company with an interesting library of shark antibodies; FIND explored potential use of them as reagents in malaria diagnostics, but could not get specific-enough binding.

FIND sees significant untapped potential for more private sector partnerships in Australia and in the Asia Pacific region. The roles and the value of each type of partner includes 1) regional regulatory know-how; 2) sources of funding and local stock/capital markets and investors (e.g. Japan and S. Korea) that encourages innovation in small companies that FIND can tap into countries; and 3) each has a unique technology platform.

iv. ***Based on past reporting and current work plans, to what extent is FIND effectively addressing gender equality and empowerment of women and girls, and if so, how?***

FIND recognises that gender norms and roles influence unequal access to diagnosis and treatment and may differently expose men and women to higher risks of disease, for example, in South-east Asia, there is a higher risk of malaria for men who work in forested areas.

FIND's gender policy notes, in addition to staff representation and workplace issues, gendered approaches to its programmatic activities including identifying gender dynamics that influence the disease and its control; inclusion of gender perspectives in clinical trials indicating if/how sex impacts outcomes; an aim to ensure all capacity building activities include balanced target groups; linkages with groups that work to address gender disparities in FIND's target populations; and striving for equal participation of men and women.

v. ***Capacity building in support of country-level systems and services***

DFAT funding is used as co-funding toward capacity building in the region, country. FIND has conducted capacity building exercises in 28 countries in Asia, Central America, Eastern Europe and sub-Saharan Africa. Most of FIND's interventions are in response to the needs assessment and request by the country. FIND works closely with the MOH/national or state programmes, therefore focusing on local health needs. These activities include:

- Lab strengthening activities in Indonesia, Myanmar and Vietnam. Indonesia is the second largest high burden country for TB (after India) and laboratories have been poorly staffed with no mechanism in place for referring samples. Lab strengthening activities have also taken place in Myanmar since 2007, resulting in an increase in DR-TB cases detected. In Vietnam, FIND helped establish an external quality assurance (EQA) program that will serve other countries in the region.

- clinical trials aligned with global/ national policy and regulatory needs in the most efficient way
- Provision of evidence from clinical trials to: i) manufacturers to facilitate their product registration applications; ii) WHO to facilitate policy decisions and to support the development of detailed guidelines on, for example, quality assurance processes and operating procedures for new tools.
- Provision of evidence from early implementation studies and network mapping to national programs to help inform their national policy decisions and local registration
- Working with programs to build their capacity to select and manage improved diagnostic technologies (national programs must use their scarce resources to select products that are appropriate for their own contexts and disease burdens, and establish systems to monitor an ever-growing regime of equipment with the same level of human resources)
- Work with programs and users to ensure more effective use of diagnostic tools to drive scale-up of care programs (here mostly to help countries make better use of data from connected diagnostics - countries struggle to manage and optimise use of connected diagnostics technologies, limiting patient impact)

A detailed example from Vietnam, supported through DFAT, is provided below, reflecting the outcome and impact of investment in building country level systems and services.

Vietnam; EQA for GeneXpert MTB/RIF

- **Sustained FIND involvement**
- FIND working with Vietnam's National TB Control Programme (NTP) since 2013 on Xpert MTB/RIF EQA Proficiency testing (PT) scheme
- **Results of FIND intervention**
 - Positive impact of PT on testing quality evident after first five rounds (post training).
 - All site scores increased by 5.1%, and sites that previously received an unsatisfactory score by 10.4 %.
 - Successful in-country pilot production of PT panels (11 sites)
- **Outcomes**
 - Full local ownership after programme handed over to the NTP in March 2017.
- **Sustainability:**
 - The NTRL will progressively enrol all 75 Xpert MTB/RIF testing sites into the NTRL; an initial 35 sites to be enrolled by July 2017.
- **Impact:** To ensure the sustainability of the PT programme the NTRL will be applying for ISO 17043 accreditation with the goal of expanding its programme to regional countries.

Test 3: Australia's value-add and leverage

- How is FIND collaborating with Australian research institutions and what are the benefits of such collaboration?***

Academic/ research institutions and laboratories: Partnerships with top research institutions allow FIND to access the most cutting edge science and turn it into usable products. They also conduct studies that allow institutions to better understand the needs of the region. Laboratory partners (often supra-national reference laboratories (SRL) in industrialised countries) are very sophisticated with extended facilities that allow for early validation work, trouble-shooting and root cause analyses, i.e. critical assessments that are essential in early stages for product development. Partner research institutions and projects are listed below.

- **Queensland Mycobacterium Reference Laboratory (QMRL)**, the SRL for TB in Australia, is a WHO Collaborating Centre, and a partner to FIND.
- **The Burnet Institute** and FIND's future Omni studies in PNG will provide evidence that will be essential to drive further investment and uptake in TB and TB diagnosis to detect patients early and prevent spread of disease both in the region and globally. They are very strong on diagnostics and have local and regional know-how that FIND could not do without; they have access to partners critical for successful regional collaboration.
- **Woolcock Institute** allows FIND to leverage a unique opportunity to collect samples from TB household contacts with 2-year follow up information, which will be essential to development and evaluation of incipient TB tests.
- **The Walter and Eliza Hall Institute of Medical Research (WEHI)** is a recognised institution working on *P. vivax* malaria and conducting clinical trials and field research in PNG. They are pioneers in the evaluation of serology as a diagnostic approach for detection of *P. vivax* hypnozoites.
- **Queensland University of Technology (QUT)** have expert bio-statisticians for data analysis for the FIND-WHO RDT evaluation program; report is published annually.
- **QIMR Berghofer Medical Research Institute (QIMR)** is responsible for the expert production of recombinant proteins derived from *Plasmodium falciparum* parasites and that are currently used as global positive controls and reference materials for evaluation of performance of malaria RDTs.
- **AAMI** is a globally recognised reference laboratory for sequencing of genetic material of malaria parasites for the detection of mutant parasites that do not produce the key protein (HRP2) detected by most malaria rapid diagnostic tests (RDTs).
- At **Menzies School of Health Research**, a researcher is working with FIND to develop a novel diagnostic test that can identify people at high risk of carrying these dormant stages by confirming their recent previous exposure to *P. vivax*. Such tests will allow to screen population for *P. vivax* exposure and the selectively target those with confirmed exposure with the appropriate drug treatment for radical cure of both blood- and liver-stage parasites.

Advocacy partners in Australia:

- **RESULTS International Australia** is instrumental in helping build awareness on the need to address TB, in Australia and elsewhere.
- **Policy Cures** has expertise in tracking funding trends has been highly useful in developing cases for investments both in Australia as well as elsewhere in the world.

ii. *Is the total level of financial and technical resourcing of FIND from all sources appropriate to have an impact?*

FIND currently has 30 open grants with US\$133.8M available for the 4-year period 2017 to 2022. FIND estimates that sufficient funding to deliver on all the work currently planned is around US\$50M.

2017 percentages for allocation of funds by FIND's strategic pillar is as follows:

Overhead	13%
Catalyse Development	46%
Guide Use & Policy	16%
Accelerate Access	24%
Shape agenda	1%

Grand Total	100%
<p>FIND spend nearly half of its funding on early research and R&D and a quarter on access.</p> <p>Under this investment, impact has not been clearly defined and has not been measured. For this evaluation, the highest level of outcome measured was new or modified products being registered in the Asia Pacific. This context does not allow for an assessment of how resources (financial and technical) relate to impact.</p> <p>Also related to the definition of impact, there is a need for greater clarity on prioritisation of projects/products, possibly streamlining the number of projects and partners and focusing on those with potentially the highest impact and add dimension of time.</p>	
<p>iii. <i>Does FIND have funding gaps that could be usefully be supported by Australia?</i></p> <p>As DFAT funding has previously been core funding FIND has been able to assign funds across the organisation. Should DFAT commit earmarked funding (in addition to the core funding), FIND would welcome discussing DFAT priorities and determining a specific scope of work (to complement core funding).</p> <p>While FIND's preference is to maintain core funding from DFAT to enable a dynamic and agile portfolio, new areas of interest include AMR and outbreak preparedness and may be suitable for Australia to consider targeting with their funds as they align with strategic priorities under the Regional Health Security Initiative. For example:</p> <ul style="list-style-type: none"> • Addressing complex issues such as AMR through advocacy: DFAT investment in FIND's "shaping the agenda" would be very valuable. To deal with complex issues such as AMR, significant advocacy is needed. DFAT investment in targeted communications/ advocacy in AMR could help enhance use of diagnostics and have an impact on prescribing practices. • Supporting cross-sectoral collaborative platforms for R&D, implementation and scale-up: Cross-sectoral collaborative platform investments could also be very impactful, both for R&D and implementation and scale-up. For example, FIND has recently established a mini "arm" of CEPI, CEPIdx, taking the scope of the consortium beyond vaccines and into diagnostics for priority outbreak pathogens. Both these investment examples would be hugely beneficial regionally and globally, and would also raise DFAT's profile in this space as these undertakings are very "visible". 	
<p>iv. <i>Is FIND likely to demonstrate results in the shortest possible time (within 3-5 years)? At what stage are the clinical trials, if applicable?</i></p> <p>FIND has ambitious targets for the next five years based on its pipeline (see Annex x) and strategy. Overall deliverables (to end 2022) as stated by FIND include:</p> <ul style="list-style-type: none"> • Bringing new TB XDR assays to scale in select geographies (Xtend; Hain XDR; NGS) • Running an RFP to identify the next testing platform (multi-disease, but perhaps starting with TB) and supporting development of at least one • Taking at least 1 POC TB triage test through development to WHO endorsement • the same for top three tests to address AMR • the same for at least two assays for priority pathogens 	

- For all new R&D, doing the work that is needed to drive access and uptake, such as addressing market and needs understanding; providing evidence to drive policy change; and catalysing market pull mechanisms.

In more detail, FIND's top 5 priorities for the next 5-7 years which are expected to be game changes are:

- True point of care test for fever management
- Diagnostic for prompt fever treatment to prevent AMR
- True point of care test for TB, given the 4 million missed cases every year.
- Paradigm shift for diagnostics from closed diagnostic systems to semi-open instrument platforms with multiple manufacturers producing tests for this platform.
- CEPI Dx – a platform to answer diagnostic needs on outbreaks, hosted by FIND in collaboration with CEPI

It is important to note that new priorities in the next 5 years for FIND will be to include AMR and outbreaks through a focus on non-malarial fevers in light of reduced malaria numbers, and the cross cutting identification of pathogens to identify outbreaks and provide targeted treatment.

v. ***What is the likelihood of the research succeeding?***

The likelihood of success varies for each product, specifically products in late stages have a higher degree of success. Key challenges to product development include:

- Small research community working on diagnostics
- Thinning TB diagnostics pipeline - few tests make it into the last phases of development and trials, and some manufacturers have discontinued their engagement due to insufficient funding for both development and trialling
- Tests to support malaria elimination have been identified as a global need and their development is current a priority. However, since their use would be targeted to foci of transmission and populations at risk, their market would be small
- Identifying sites that have capacity to perform complex fever diagnostic studies critical to R&D

Key challenges to product introduction include:

- Unclear regulatory pathways for AMR and outbreak tests
- Equally unclear procurement / reimbursement mechanisms

Key challenges to uptake and scale up include:

- Need for engagement of donors and procurement agencies to guide and subsidise the use of diagnostics – developing new tools for diseases outside the ‘big 3’ (HIV, TB, and malaria) has revealed challenges in implementation and commercialisation of new products, as there is no global procurement mechanism
- Lack of local political will and /or heavy bureaucracy in some high-need countries
- For AMR, entrenched prescriber and patient behaviour

Test 4: Making performance count

i. ***To what extent is FIND demonstrating quality results?***

In general, products in the pipeline have progressed through the relevant stages of development successfully, and FIND has met the overall DFAT investment's outcome and output on its own.

Along with other PDPs, due to the lack of standard definitions related to Outcomes and Outputs, reporting of results has presented challenges. Specific indicators should be operationally defined in the future together with PDPs. Outcomes and outputs at FIND have been defined through their PFG logframe that was developed with DFID originally and has been used to report results to PDP funders. Under their new DFID funding (to 2021) they have a new logframe that is closely aligned with their corporate logframe.

ii. ***To what extent is FIND able to demonstrate value for money?***

FIND's 2015-2020 strategy includes value for money initiatives such as extending the use of technology platforms across diseases (i.e. multiple disease assays that can run off the same testing platform).

Since Australia started supporting FIND in June 2013, the organisation has been able to generate funding from other public and private donors, through in-kind contributions from partners and through fee-for-service offerings. This has been made possible in part because DFAT's flexible funds were used to support programmatic staff who were able to further develop projects and programmes that were attractive for other donors.

Overall, FIND is able to demonstrate good value for money, however, there are areas of improvement including measuring the selected cost-effectiveness metrics, clearly defining impact, as well as related opportunities to streamline processes and projects by utilizing aligned and more standardised health and economic impact measurement frameworks with other PDPs and partners when these are developed.

Economy

- **Investment leverage:** a key component of FIND's value for money is its ability to negotiate and build relationships with partners from private and public sector and garner cash and in-kind contributions; from 2014-2016 in-kind contributions in the form of facilities, staff and supplies represented on average 11.3% of FIND's total annual spend. FIND targets a cash investment ratio of 1:3 with partners (to be validated).
- **Leveraging trial platforms or alternate approaches:** request-for-application model for large-scale, multi-country uncontrolled studies to demonstrate use in intended settings shown to result in cost savings of up to 16%.
- **Focus of resources and low support costs:** FIND remains a lean organisation in the context of change and organisation growth, operating strong financial controls and practices to improve efficiency and productivity to ensure that limited resources are focused on program delivery, illustrated by:
 - a) Target - at least 55% of total FTEs focused on program related activities, which is comparable with peer organisations; In 2016, the number stood at 60%.
 - b) Support costs remained consistently less than 15% of total spend.

Efficiency

- **Catalysing innovation through FIND's support platform:** FIND provides researchers and developers with enabling materials, (e.g. specimens – data on usage available on website); tools (e.g. panels) and

information (e.g. databases; TPPs; trial guidance) to facilitate R&D. Two examples of support during the grant period were for development of: 1) a highly sensitive malaria RDT (completed in 2016); and 2) tests to meet the remaining key diagnostic gaps for TB, i.e. POC detection or triaging tests (biomarker-based) and drug susceptibility testing.

- **Products successfully developed (meeting TPPs):** There are currently 17 TPPs relevant to FIND's portfolio, 13 of which FIND recognises as high priorityⁱ. IVD products developed during this period address 3 priority TPPs (one each for TB, malaria and HAT), and FIND's current portfolio covers all the TPPs; hence resources target needs identified by the global health community, as per the FIND strategy.
- **Systematic technology review:** Fully established toward the end of 2014 and in use from 2015, with 159 submissions reviewed by end 2016 and 8 included in FIND portfolio after SAC review and approval, ensuring appropriate investment of resources.
- **WHO or regulatory authority approved products:** 8 WHO recommendations, across diseases, were made during this period (3 above target); the potential impact and value is high as WHO recommendation is considered one of key drivers of product uptake. 12 FIND-supported products were registered through an SRA (one for emergency use only).

Effectiveness (A critical measure of effectiveness is uptake of products)

- **Number of LMICs implementing FIND co-developed tests:** TB: 125 LMICs including all WHO high burden TB countries; HAT: 18 (out of 36 endemic countries recognised by WHO); Malaria: QA RDTs in 43 malaria endemic countries and new tools in 5.
- **Number of co-developed tests provided to LMICs (uptake):** Over the 3y period 2014-2016, ~32.8 million IVD products were provided to LMICs, with an average increase 8.3%/ year.
- **Cost reduction in FIND target markets compared to high income countries:** Negotiated prices (ex-factory to LMIC public sector) for FIND-supported products are available on the website. These prices are ~60 to 80% lower than those to high-income countries (the variation being a function of the cost structure of the product).
- **Extent to which tests are procured based on FIND/partners QA results:** By the end of the grant period 43/48 endemic countries (~90% of the target) were procuring quality assured RDTs. In 2016 >200 million malaria RDTs were lot tested through the WHO/FIND programme prior to global distribution, with ~90% destined for sub-Saharan Africa where 90% of global malaria deaths occurred in 2013.
- **Number of cited open access research publications:** FIND has increased efforts to build an evidence based argument for diagnostics to improve uptake. During the grant period, 163 papers were published in peer reviewed journals. The total for 2016 was 67 (target was 40) of which 90% were in open access platforms. The research published in 2015-2016 was cited a total of 595 times over same period, amplifying the Value for Money of this research as the reach of the message is increased.

Cost effectiveness

- **Cost effectiveness of new tools in LMICs: HAT:** Screening algorithms that use the HAT RDT are most cost-effective in all countries irrespective of HAT prevalence. These algorithms have also been found to be optimal for case detection in both passive and active screening settings (pub). **Malaria:** Molecular LAMP test for malaria can be competitive (vs. PCR) but is most cost effective in high workload laboratories (pub). This may make the test more suitable for use in elimination programmes, as is intended. **TB:** Xpert MTB/Rif testing costs in India have, as expected, come down since 2010, and larger labs achieve the lowest testing costs (economies of scale). FIND/ partners have now provided a solid methodological base for estimating resource requirements and cost-

effectiveness of wide-scale Xpert roll out in India (pub). Also, using Xpert in paediatric populations has been shown to reduce turnaround time, with infants in India put onto treatment within 2 days of diagnosis.

- **Impact on incidence/transmission:** Building capacity for uptake of TB diagnostics in public (primarily) and private (India) sectors. Impact delivered included 3 to 8 fold increase in MDR-TB detection. Modelled impact: 7.5% (public sector); 13.7% (public and private) reduction in incidence, and 20.1% (public); 35.3% (private and public) reduction in mortality by 2021. Activity: Development of more sensitive Xpert Ultra and Omni instrument (decentralised care). Modelled impact (10y): 12.4% (public sector); 20% (public and private) reduction in incidence; and 32.4% (public sector); 37.8% (public and private) reduction in mortality. [NOTE: this modelling includes assumptions about treatment initiation of between 85 and 100%].

iii. ***How is FIND managing risk and working in partnership with other PDPs and others to achieve results and avoid duplication?***

Partnerships with other PDPs

FIND has had good collaborations with other PDPs, which has increased over years. However there is room for improvement, such as better alignment of projects with systems view as well as joint definition and alignment of impact and M&E frameworks, to jointly achieve highest impact combining resources for best synergies between diagnostics and treatment, as well as advocacy and capacity building. Examples of collaboration include:

- TB and MDR TB** - collaboration with TB Alliance and its two new regimens that will enable decentralised MDR and XDR TB care. Decentralised diagnostics that can confirm TB and identify resistance to rifampicin and fluoroquinolones are needed to accompany these new regimens to ensure their impact and preservation. One of the intended outcomes of this project is WHO guidance on an integrated testing and treatment approach for TB and DR-TB.
- Diagnostics for outbreak preparedness** – collaboration with CEPI (CEPIdx formed, limited seed funding secure and initial projects in discussion) where FIND will develop diagnostics for pathogens that are vaccine targets for CEPI as well as other Blueprint pathogens.
- HAT (sleeping sickness)** - FIND-supported HAT RDT is the first-ever rapid test for HAT that can be used at POC. Its development has enabled decentralised testing, which fits very well with the new oral drug, fexinidazole, that DNDi is developing, which is also intended to be used in more basic health facilities. FIND and DNDi are now conducting their diagnostic and drug trials at the same sites in DRC, where mutual efforts in capacity building through training, providing equipment also result in synergies and value for money. FIND and DNDi also collaborate by participating to the same WHO meetings to define needs for new tools and develop integrated strategies combining Dx and treatments for disease control/elimination.
- Leishmaniasis** - FIND and DNDi have just secured EDCTP funding for a project in Kenya, Uganda, Sudan and Ethiopia. FIND will take advantage of a large multi-centric clinical trial (in DNDi LEAP sites) for a new combination for VL (Miltefosine/Paromomycin) to evaluate new tools to be used in two different companion diagnostic contexts: i) primary diagnosis and enabling treatment (RDTs developed by other groups), ii) treatment monitoring and use as pharmacodynamics tools in clinical trials (different tools, among them LAMP developed with FIND support). More generally, FIND (and DNDi and other partners) is

regularly invited by WHO to participate in the WHO bi-regional meeting on leishmaniasis control in East Africa, and with DNDi, MSF WHO and others are part of the working group: “Access to medicines and diagnostics for leishmaniasis control”

Managing Risk

In 2016 FIND undertook a review of all key process cycles to identify risks where potential financial misstatement, errors, omissions and (or) fraud could arise. The internal controls system framework was redesigned and controls were strengthened to address the various risks identified. An ICS monitoring template was also developed to facilitate regular monitoring of the ICS system. The internal risk matrices cover: Accounting & Financial, Revenue to Cash, Purchase to Pay, HR & Payroll, IT Application & General Controls and Entity Level Controls.

Based on recommendations from previous evaluations (i.e. MoFA Netherlands and DFID UK/BMGF Germany) a formal risk register was added to existing systems with a minimum of annual review by the Board

Risk assessment is performed at two main levels at FIND: i) organisation-wide “priority” assessments, which are performed on an annual basis and updated 6-monthly, and ii) project, program and business unit-specific assessments, which are undertaken and updated with greater frequency. For projects, this would occur at project initiation, prior to each project management meeting; and at each milestone.

iv. Governance & Ethics

FIND is an international non-profit organisation, as such organised as a Swiss Foundation with a Board of Director, Scientific Advisory Committee (SAC), management team and staff.

FIND has built a solid organisation over the past 12 years. Overcoming several challenges FIND maintained good balance of core competencies in staffing and has matured operationally, establishing and maintaining best practices, providing careful stewardship of donor funds and striving for efficiency and effectiveness. FIND is able to successfully leverage donor funding to attract investment from other groups and partner in-kind contributions. Starting with one donor in 2003, FIND now (2017) receives funding from 15 different public and private funders.

FIND has a **Code of Conduct and Ethics** (the “Code”), which is part of the contract terms of all directors and members of staff, and of consultants, suppliers, service providers and project partners that work with FIND (unless such partners already have similar, published rules which they are held accountable). FIND staff and external partners have access to several channels to report violations of the Code as well as other key policies (e.g. Anti-Fraud Policy) or any other concerns, whether real or perceived, relating to activities in which FIND is involved or considering involvement.

Decision-making practices at FIND are transparent and robust; decisions on the selection of partners and products, and on transitioning of products through the development pathway are evidence-based and, beyond defined thresholds, subject to external validation through SAC. FIND’s portfolio and project management system is stage-gated, allowing for pruning or expansion of the pipeline to maintain a balance that is appropriate from both technical and needs perspective, and again with all decisions having to be based on the data.

FIND significantly changed the format of its SAC meetings in 2016, allowing for greater efficiency and focus. These changes were very well received given the SACs expanded responsibilities vis à vis reviewing technology and partner assessment reports, a requirement at the time for any investments >\$50,000. SAC recommended that the investment threshold be moved to \$200,000, which was ratified at the Board meeting in January 2017.

Another change was to include participants from industry at the September 2017 SAC meeting to provide input – this practice will continue but these attendees do not have any rights afforded SAC members with regard to making recommendations. All conflicts of interest (COIs) are declared ahead of each meeting that are noted by FIND and the Chair of the SAC; participants who declare potential conflicts are excluded from relevant discussions.

Recognising the growing importance of focusing on access, FIND hired its first Chief Access in 2016. FIND continues to focus on more comprehensive analysis of the pillars of global access for diagnostics, i.e. acceptability; availability; affordability; and geographic accessibility.

FIND undergoes regular organisational and multiple donor-specific financial audits every year, which includes governance. Based on these assessments and recommendations, FIND has strengthened governance processes in the past 5 years.

v. *Sustainability & health for development*

With donor support, FIND strives to create products and platforms that attract industry partners and de-risk their investments. These may generate value for the industry and the markets FIND operates in. However, with increased focus on access and considering some products with viable markets, new approached and markets research needs to be considered.

FIND has continuously endeavoured to assess and integrate potential revenue generating opportunities. Of course, these are fraught with challenges because of the PDP structure and deliverables.

Through an internal analysis in 2016, FIND examined 8 potential revenue-generating opportunities for FIND, and participated in Tideline's study for BMGF which looked at the opportunities for PDPs in attracting return-seeking investment as well as the challenges to doing so. With the understanding that the PDP model most likely will not be financially self-sustainable in the near term, FIND continues to assess and integrate financial sustainability into FIND's work.

For example, FIND's biorepositories have value – BCG has taken a first stab at quantifying that value and FIND continues to try to build a business case for its collections (particularly extensive TB collection). FIND currently charges minimal administration fee for providing the samples, the approach is good but amount to only a symbolic income.

FIND has been receiving financial industry contributions for trials, the amount, and the range of IVD companies that are willing to provide contributions are increasing. This is largely driven by FIND's understanding of target markets, knowledge of pathways to market as well as ability to provide useful market data.

With regard to potential partnerships for local production of tests, some of the best quality malaria RDTs are produced in India and Ethiopia. In general, the production of sophisticated diagnostic tools is often less readily transferable to resource -poor settings, as quality assurance and evaluation is complex and

often requires a significant investment in customised equipment. FIND has looked at the possibility of technology and know-how transfer from a Japanese developer to a manufacturer in Brazil, but the economics were prohibitive. Some of the work that FIND will be doing over the next 5 years, particularly around outbreak preparedness, will necessitate further assessment of local reagent manufacturing in outbreaks. FIND builds capacity in SMEs in LMICs that have promising technologies for local markets, match-makes them with developed-world experts to solve their design, manufacture or commercialisation problems. FIND also uses, whenever possible, a range of manufacturing partners in developing countries: there are currently 24 commercial partners based in Africa and Asia.

Market access activities

FIND has recently hired Chief Access Officer to increase activities and partnerships in this critical area. In the future, FIND intends to support the countries through implementing connectivity solutions to help aggregate national level data and support more diligent planning. This includes targeting to implement molecular platforms as well as integrating them in the private sector. FIND expects to see major trends towards increased use of large data and integrated platforms and planning in the access space. Working together, this can allow for less siloed, more optimised lab networks across diseases that should promote efficiency and substantially transform access.

Interventions outside of R&D and their results include the following examples below:

India India is a regional leader, particularly for infectious / communicable diseases like HIV, TB and malaria, less so in the NCDs and maternal and child health space. With diagnostics, FIND believes that India will play instrumental role in implementation approaches, more so than in R&D. FIND has been working with a manufacturer to develop a competitive TB molecular test (to the Xpert), but it seems that there is a long way to go for IVD industry to become truly competitive at global level. FIND will continue to support new developers who have promising technologies to help drive diversity in the market. Also, one of FIND's main commercial partners, Cepheid (now part of Danaher), will be building manufacturing capacity in India – starting with some of components for the Omni device in the following years.

Myanmar The political climate in Myanmar has not been supportive of international interventions. Through advocacy and on the ground presence FIND was able to work successfully by building strong relationships and trust with the Ministry of Health and the national disease programs, support malaria projects have HCV projects in planning stages). By following the local protocol, FIND has a long-term consultant on the ground who acts as a senior advisor to FIND helping to navigate political and cultural hurdles, a must have.

Indonesia The second largest high burden country for TB after India, Indonesia is a challenging country to work in due to its highly bureaucratic system with limited political commitment. The majority of the TB/MDR-TB diagnostic activities have been driven by partners. Access to rapid quality assured diagnostic services has been therefore primarily restricted to facilities where partners work. When FIND engaged in laboratory strengthening activities in Indonesia, most were poorly staffed and there was no mechanism in place for referring samples from the facilities or regions outside the vicinity of the culture laboratories. KNCV has become an important partner with USAID /GFTAM funding support, and WHO SNRL role has been given to TB labs situated in Adelaide and Queensland, giving them a very important role in lab strengthening for Indonesia. Australian aid is now also available to Indonesia. There is a great need for

improved diagnostic services and treatment services in Indonesia as the country appears on all three lists for TB, TB/HIV and MDR-TB HBC.

Vietnam Also one of the 22 high burden countries. FIND has conducted controlled trials with the Regional Lab at Ho Chi Minh City for a very long time, and established a formal presence there in 2016. There is strong political commitment in the country to both, improve access to rapid diagnostic technology and to ensure that it happens in a quality assured manner within laboratories that meet nationally-specified quality standards, in line with international quality standards. Fortunately, the NTP sees that value of diagnostics and has recognised that there are more gaps in diagnostics than in treatment in Vietnam. The country is committed to improving the quality of testing in the SEA region through establishment of an EQA program that will serve other countries in the region. (The WHO SNRLs situated in Australia also provide QA support). Operating in the country requires significant understanding of the nuances of the culture, the operating environment, and the other players, many of which are very well funded (this latter factor being one of the major issues that FIND has had to overcome as it has had to work very hard to prove ourselves when there are much better-resourced teams operating in the same disease space).

Annex 8. Evaluation of MMV

Investment outcomes
<p>Definition of outcomes used by PDP</p> <p>New/modified PDP products registered in Asia Pacific with DFAT support: MMV considers a product registered in a country when they receive either a letter from the Ministry of Health or a communication from the pharma company involved indicating that the product has been added to the national list of registered medicines.</p> <p>New/adapted products successfully completing late stage clinical trials with DFAT support: a product is considered as successfully trialled based on a list of criteria, notably primary outcomes set at the inception of the project by MMV with the R&D partner based on internationally recognised targets (e.g. from WHO).</p> <p>Information on these products in Annexes * and *</p>
<p>Outcome: New/modified PDP products registered in Asia Pacific with DFAT support: 2</p> <p>Pyronaridine artesunate; Dihydroartemisinin-piperaquine</p> <p>Output: New/adapted products successfully completing late stage clinical trials with DFAT support: 2</p> <p>Tafenoquine (with GlaxoSmithKline); Dihydroartemisinin- piperaquine dispersible (with Alfasigma/Pierre Fabre)</p>
Test 1: Pursuing national interest and extending Australia's influence
<p>i. <i>Advance Australia's national and regional interests in terms of addressing risks to health security, stability and prosperity?</i></p>

Drug resistant malaria poses a serious threat to regional security, trade and investment in the Asia and Pacific region. Australia's MMV investment is addressing the market failure development problem for malaria. The introduction of new drugs is crucial to treat relapsing malaria from *P. vivax* – a relapsing form of the disease that is particularly endemic to the Asia Pacific region. In the case of malaria, which puts at risk 1.4 billion people in SE Asia, elimination is a realistic goal over the next decade, even in countries threatened by multi-drug resistance.

The importance of addressing malaria is also recognised by industries that are central to Australia's economic interests, including the mining and energy resource industries. The partnerships developed by MMV can incentivise private sector investment in diseases of poverty.

ii. **Extending Australia's Influence**

With reference to Australia's influence, MMV noted:

“Australia has an international leadership role in global health, due to its strong political commitment, its world-class medical research capability, and its focus on innovation and public-private collaboration.... Over the last decade Australia has become a global leader in malaria research. Australia is now a leading player in the global expertise chain, a mutually beneficial network that strengthens international and Australian research...”

One of the most critical aspects for Australia's influence has been its decision to invest in malaria from multiple angles. Australia's co-founding and continued engagement in the APLMA allows it the opportunity for regular interaction with heads of state in the region in a non-controversial setting. MMV's engagement with APLMA both as a technical partner and as the source of provision of products helps Australia underpin that relationship. This is especially important in light of emerging multi-drug resistance to anti-malarials in the region. Similarly, with Australia's funding of the Global Fund, by continuing to fund MMV—the source of the future products needed by the Fund—Australia helps to underpin its investment in this important international body... This is an investment that will help reap long-term rewards in regional health and international diplomacy. “

-- MMV

Although a small organisation, MMV has a broad reach internationally, both in the Asia Pacific region and elsewhere. Australia's continued and visible support of MMV demonstrates the reach, the concern and the engagement of the country in combatting a disease of world-wide concern. Australia is the only donor in the region (apart from some highly restricted funding from Japan).

Australia's investment in MMV is notable for its political engagement in the Asia Pacific Leaders Malaria Alliance (APLMA), and its support for the Global Fund. The investment in MMV is important for the future of both of those engagements, providing the technical expertise in drug development and access and the next generation of tools for malaria treatment and elimination. This is an investment that will help reap long-term rewards in regional health and international diplomacy.

Over the last decade Australia has become a global leader in malaria research. Australia is now a leading player in the global expertise chain, a mutually beneficial network that strengthens international and Australian research. MMV and its Australian scientific partners have been working together since 1999 to discover and develop new, effective and affordable antimalarial drugs.

An example of how Australia is influencing the region through MMV is through an ongoing (since 2012) partnership with Australia's Newcrest Mining Ltd in PNG. Given the threat to regional security, trade and investment that drug resistant malaria poses, MMV has been working with Newcrest Mining, IS Global, International SOS, and staff from a local medical centre in Lihir (New Ireland province, PNG) to eliminate

malaria from the island by 2020⁵⁷. This work requires significant engagement with local stakeholders and health authorities to achieve near-elimination. Once implemented, the malaria elimination initiative should serve as a case-study for other elimination projects in different provinces in Papua New Guinea. It could also incentivise further private sector investment in diseases of poverty, and should be leveraged as an example of how Australia is extending its influence.

Test 2: Impact on promoting growth and reducing poverty

i. ***Based on past reporting and current work plans, what is the potential of MMV to impact on growth and poverty reduction?***

Mortality and morbidity due to malaria dramatically affect communities and have a considerable economic impact on low-income and middle-income countries. Annual economic growth in countries with high malaria transmission is lower than in countries without malaria, and malaria is responsible for a 'growth penalty' and constrains the economic growth of the entire region. By investing in eliminating diseases such as malaria in the Asia Pacific region, Australia is contributing to the social and economic development of the entire region.

Because the investment in R&D is a long-term one, and because Australia's funding dates back only since 2013, it would be disingenuous to attribute any specific impact on growth and poverty reduction in the region thus far. Instead, Australia's investment should be seen as foundational to growth and poverty reduction in the region—with the development and delivery of the appropriate tools, the region can, in future years, combat one of the major causes and consequences of poverty.

More than 100 clinical trials have taken place, are ongoing or are planned in countries of the region (Australia, Cambodia, India, Indonesia, Laos, Papua New Guinea, Philippines, South Korea, Thailand and Vietnam).

ii. ***Based on past reporting and current work plans, to what extent is MMV focused on targeting the poorest and most vulnerable populations?***

MMV's mission is to include the health concerns of vulnerable populations groups (such as children and pregnant women) by designing its target product profiles for them and promoting research for treatment formulations adapted to their specific needs. By the end of 2015, MMV partnerships had delivered close to 350 million malaria treatments to 50 countries, the majority of recipients being children, helping to reduce suffering and saving the lives of people living in some of the least developed and most challenging environments in the world. The MMV response to this concern has been successful so far, notably in developing customised medicines for children. This concern remains a major priority for MMV and its 2017–2021 business plan aims to further customise medicines for women and children, and use innovative methods to provide tools to maximise their protection.

The involvement of the poorest and most vulnerable populations in the uptake and delivery of innovative medications for malaria is very important. An example of partnership that MMV has developed to help marginalised populations increase access to needed medications is the T3-TR programme, which was rolled out by NVBDCP2 Odisha, NIMR3 and MMV in India in June 2013, with the objective of training 41,000 women as community health workers (called ASHAs, a Sanskrit word that means "hope") across 30 districts in Odisha, to provide basic care in TB, malaria and leprosy, use bivalent RDTs to test for both species of *P. falciparum* and *P. vivax* malaria, treat malaria patients in line with national treatment guidelines and strengthen the link between the public health system and rural communities. In addition to the important public health benefit, this type of activity also empowers women and marginalised groups and gives them an important role and a status in their communities.

⁵⁷ <https://www.mmv.org/access/products-projects/supporting-malaria-elimination-papua-new-guinea>

Looking ahead, the risk of antimalarial resistance, combined with the movement of populations, will be a major challenge for the malaria community. New antimalarials for the protection of other vulnerable groups, such as migrant and mobile populations, will be essential components of malaria control and elimination strategies moving forward.

iii. ***Based on past reporting and current work plans, to what extent is MMV engaging effectively with the private sector to achieve better population health?***

MMV's fundamental model is to engage with the private sector to help bring private sector expertise and goods to the fight against malaria. Over the years, MMV has established contractual relations with more than 100 private entities in Asia and the Pacific, from pharma and other commercial companies, consultants, contract research organisations and legal firms, in Australia, Cambodia, China, Hong Kong, India, Indonesia, Japan, Malaysia, New Zealand, Singapore, South Korea, Sri Lanka, Taiwan, Thailand and Vietnam.

MMV leverages the facilities, knowledge and expertise of the pharmaceutical and biotechnology industries, drawing on their valuable experience and resources at every stage of the drug development process. This includes gaining access to novel and proprietary compound libraries to boost the diversity of candidate drugs in discovery research or benefiting from industry experience in manufacturing and distribution in preparation for the launch of one of products. Where MMV is funding a research programme the organisation expects the industry partner, at a minimum, to match the value of the contract through in-kind contributions (for example staff costs, laboratory space, equipment, overheads), thus maximizing MMV's financial resources. Increasingly, pharma provides at least a 50/50 cash match to research programs.

- MMV has also many examples of private sector collaboration outside of R&D and manufacturing. Below are three examples:
 - Malaria elimination with mining companies in PNG
 - Multi-sector partnership for access to severe malaria treatment with Chinese and Indian manufacturers for a WHO pre-qualified product.
 - Partnering with major international information and technology services company to provide market information in Zambia and Uganda.
- MMV collaborated with partners to consolidate data regarding the flow of malaria medicines at national levels and to help health authorities routinely analyse data on the importation and local manufacturing of all pharmaceuticals, including value and volume. The routine data entry and analysis of this information allows monthly market trends information to be sent to the Ministry of Health, MMV and IMS Health. In June 2016, MMV concluded a three-year sub-project in collaboration with IMS, with support from Tess Development Advisors that enabled the Uganda National Drug Authority to complete the development of a system for monitoring pharmaceutical flows at a national level that is comparable to Zambia's.

iv. ***Based on past reporting and current work plans, to what extent is MMV effectively addressing gender equality and empowerment of women and girls, and if so, how?***

MMV has prioritised the development of medicines to treat and prevent malaria in women and, in the face of cultural gender biases in access to healthcare, it has several projects that aim to ensure equal access to gender responsive health services and health education, especially for women caregivers and community healthcare workers.

MMV is working to find new antimalarial medicines for treatment and prevention that are well tolerated in pregnancy for pregnant women and has developed a strategy that allows for earlier testing of

suitability in pregnancy. This approach has been successfully used by MMV in the development of two drug candidates to date.

MMV is also working towards making safety in pregnancy one of the first safety tests performed in the development of a new malaria drug. It is hoped that this will allow for earlier identification and prioritisation of medicines to protect this vulnerable population.

Internally, MMV believes that employees from diverse backgrounds are important in achieving its mission and objectives and will not, therefore, discriminate against an employee on the basis of any personal characteristic, such as gender. MMV upholds an equity policy that promotes fairness in the way staff members are treated, regardless of personal characteristics. MMV policies are reflected by the gender composition of its current staff: women represent 66% of the total number of MMV staff and four out of nine members of its Executive Leadership Team.

v. ***Capacity building in support of country- level systems and services***

To date, MMV has built up a network of 107 clinical centres, increasing the research capacity of 30 malaria-endemic countries. For example, in the context of the work in Indonesia on Tafenoquine, MMV has provided support to strengthening the laboratory capacity of Indonesian partners. The team working on the project has been trained on good clinical practices in the Mahidol University in Bangkok. Also, a pharmacokinetics laboratory has been set up at the Faculty of Medicine of the University of Indonesia to enable data to be directly analysed in the country. The laboratory is also planning to reinforce its capacity and purchase new equipment to carry out gas chromatography/mass spectroscopy analysis, a more powerful technology, needed for the PK assessment of tafenoquine, which has so far required exporting samples to a laboratory abroad. The setting up of this technology at the Faculty of Medicine is expected to offer better cost effectiveness and bring the Indonesian laboratory capacity to a higher level of expertise which would be available not only for research on malaria but also on other infections which are major public health concerns in the region. In this context, the new laboratory has the potential to be used to centralise the analysis of clinical samples of ongoing MMV trials in South-East Asia.

The training of Indian women as community health workers across 30 districts in Odisha is another example of a positive approach to strengthen the link between the public health system and rural communities.

MMV also focuses on providing the most effective technologies (medicines) adjusted to the needs of the various parts of the health systems. The synergistic sequencing of the administration of rectal artesunate and injectable artesunate, respectively, to community-based referral services and to central health services, is a remarkable example of a comprehensive approach to supporting health systems for the effective management of severe malaria.

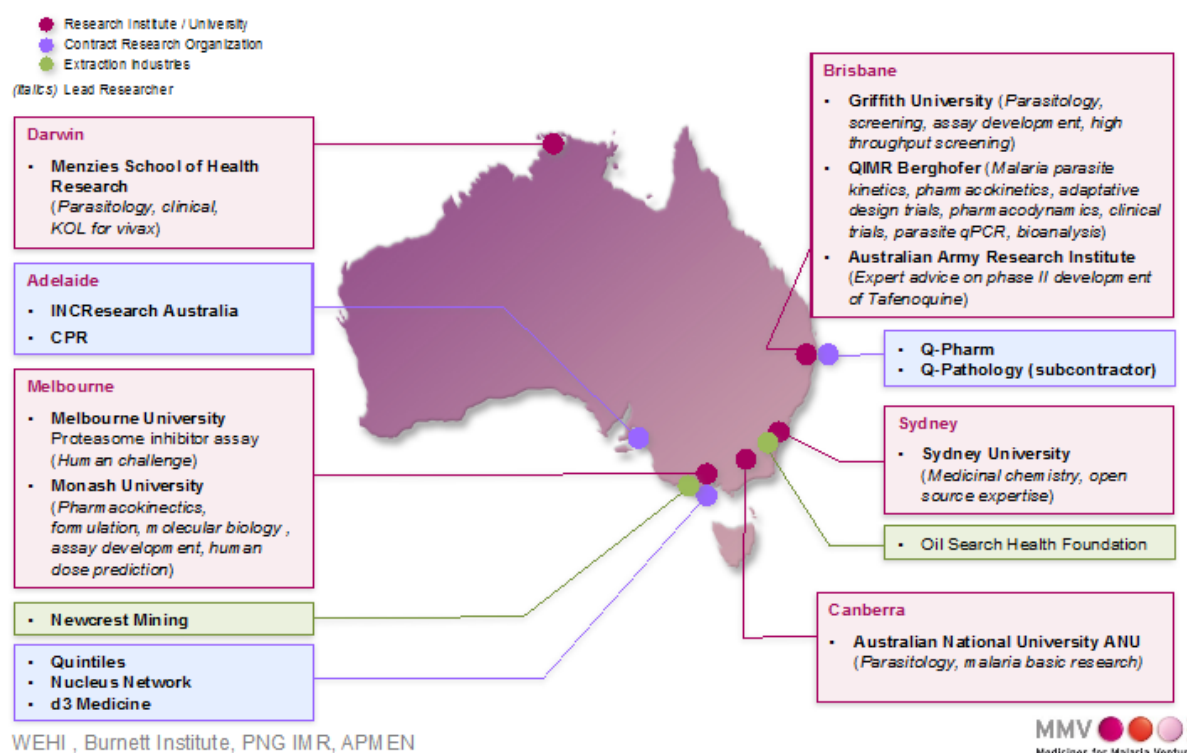
Through MMV, Australia has supported capacity building activities in Asia Pacific countries including India and Indonesia. As an example, MMV supported good manufacturing practices (GMP) assessment of Chinese manufacturer, Guilin Pharmaceutical, to enable them to become the first company to achieve WHO pre-qualification for their Injectable AS product – Artesun®. Since prequalification in 2010, 75 million vials of Artesun have been dispatched saving an estimated 450,000 to 500,000 additional young lives compared to treatment with quinine. More recently, MMV supported a second manufacturer, Ipca Laboratories from India, to enable submission of its dossier to WHO for prequalification review in 2016. This will help to ensure a sustainable global supply of Injectable AS and mitigate against the risk of having a sole-source of WHO prequalified medicine. This is in addition to capacity building done through numerous R&D trials in the region.

Test 3: Australia's value-add and leverage

i. **How is MMV collaborating with Australian research institutions and what are the benefits of such collaborations?**

MMV likely has the strongest relationship with Australian researchers out of all PDPs. As of today, MMV has entered into agreements with some 20 Australia-based entities on R&D and Access, has contributed almost AU\$33 million to Australian-based malaria research and has significantly increased research capacity in the region. MMV-supported research in Australia has generated 138 primary journal articles and six PhDs have been granted.

MMV's collaborators in Australia R&D centers, CROs and extraction sector



Examples of successful research collaborations with MMV include:

- Long-term MMV partner and international Australian scientist David Fidock, Professor of Microbiology & Immunology & Medical Sciences, Columbia University, received the 2016 Advance Global Australian of the Year Award in Life Sciences at the Advance Global Australian Awards and Summit for his contribution to malaria research. MMV's support for Australian science has generated significant synergies in research collaboration, the development of new products and capabilities, and support for policy initiatives related to regional economic development and innovation.
- A **Monash** researcher has been working with MMV over the past 17 years including:
 - Multi-institutional collaboration to explore new class of synthetic peroxide antimalarials, with potency comparable to artemisinin and improved exposure properties which led to discovery of OZ277 (arterolane); licensed and commercialised by Ranbaxy Laboratories; marketed as Synriam™; has been used to treat over a million malaria patients

<ul style="list-style-type: none"> - Continued work on this series of compounds that have potential for curing malaria with single dose; led to selection of OZ439 (artefenomel) for clinical development based on its potency, safety and long biological half-life; currently in Phase II clinical trials and is being developed as a single dose combination treatment with ferroquine by MMV and Sanofi - novel compound series was identified that selectively targets plasmodial dihydroorotate dehydrogenase (DHODH), a key enzyme for the parasite's survival and a new target for the treatment of malaria. The lead compound from this program, DSM265, is currently in Phase II clinical trials and is being developed jointly by MMV and Takeda Pharmaceuticals. • A Menzies researcher has been working with MMV on proving that malaria elimination can be accelerated even in areas with high <i>P. vivax</i> transmission by applying targeted approaches of mass drug administration combined with appropriate vector control and health systems interventions. If this approach is proven successful, it will be possible to directly aim for elimination even in areas with relatively high transmission and poor health systems (e.g. PNG, Solomon Island, Cambodia, Laos or Myanmar) without having to go through a lengthy process of reducing burden and strengthening health systems. 	
<p>ii. <i>Is the total level of financial and technical resourcing of MMV from all sources appropriate to have an impact?</i></p> <p>Total MMV investment between 2000 and 2016 has been USD 778 million, out of which USD 616 million have been invested in R&D and USD 64 million (since 2006) have been invested in access and product management.</p> <p>Under this investment, impact has not been clearly defined and has not been measured. For this evaluation, the highest level of outcome measured was new or modified products being registered in the Asia Pacific. This context does not allow for an assessment of how resources (financial and technical) relate to impact. Impact could be measured from public health and / or economic perspective (e.g. disease burden, costs per life saved, DALYs, etc.) This level of analysis would require knowledge of access and uptake level indicators.</p> <p>In 2016, 72.4% of MMV funding was allocated to R&D (within which: 71% to the private sector, 17% to academia, 12% to MMV direct activities); 14.7% went to Access and Product Management (within which: 59% private sector, 22% academia, 19% to MMV direct activities). Overheads counted for the remaining 12.9% of the resources.</p> <p>Australia has contributed USD 10.1 million 2013-2017. Its support has been for the unrestricted operations of MMV, and thus the specific question relates to the overall performance of MMV R&D and Access portfolio.</p> <p>The proportion of DFAT funding for MMV as a percentage of total funding has been on average 2.9%, since Australia started contributing in 2013. Australian funding has been stable at around 1.6% on average in 2013-2015, and has increased subsequently, reaching 5.6% in 2017.</p> <p>MMV allocated DFAT's funds according to the greatest need of the organisation at the time. Since inception of DFAT support in 2013 that allocation has included:</p> <ul style="list-style-type: none"> • R&D: Pyramax, Tafenoquine, DSM265, DSM421, MMV048, MMV253, OZ439, UCT943, Pathogen/Stasis box. • Access: Artesunate, Eurartesim, Pyramax, Tafenoquine 	
<p>iii. <i>Does MMV have funding gaps that could be usefully be supported by Australia?</i></p>	

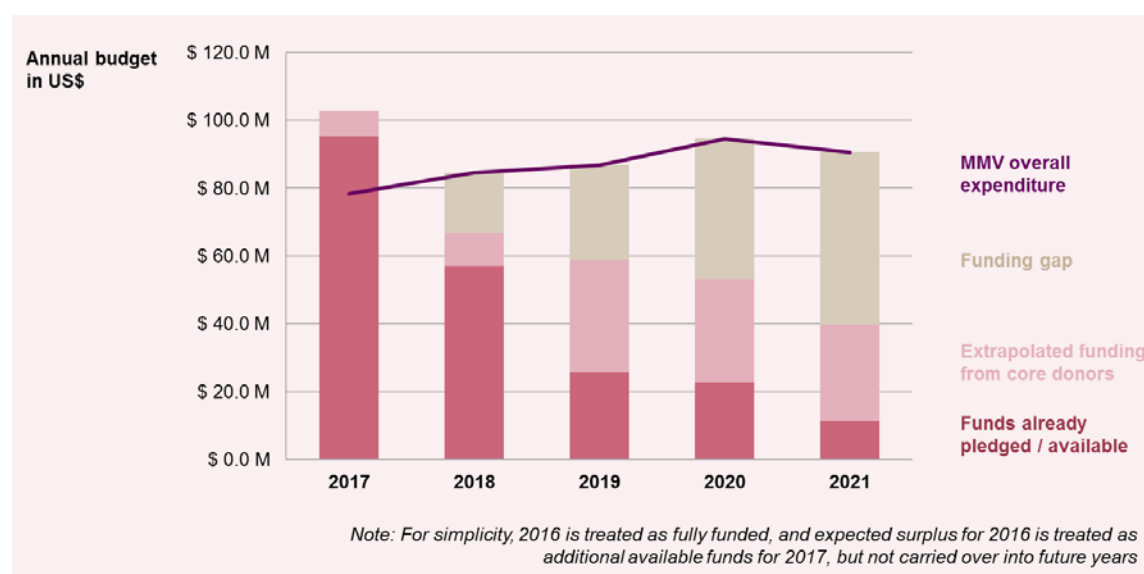
The most important investment for MMV continues to be in un-earmarked funds, allowing for flexibility of allocation according to what is most needed. This allows Australia to legitimately claim support for the totality of MMV's portfolio of R&D and access projects.

The major breakthrough in the region that Australian funding would help MMV achieve is access to Tafenoquine and making progress on new anti-malarials that will be the next defence against the spread of multi-drug resistant malaria—both issues of significant concern for Australia.

Important step would be operationalizing finalisation of the development process for Tafenoquine and its launch and cooperation with regulatory authorities across Asia and the Pacific through TGA to support access activities. Australia's leadership in APLMA and APMEN is crucial for advocacy purposes, as is the Australian Parliament commitment (Senate, House of Representatives and relevant Committees).

Also, an area for increased and continuous advocacy development is awareness about fighting anti-microbial resistance. Anti-microbial resistance is a problem across any area of disease that already has medicines that are available and deployed. This includes tuberculosis (of national concern in Australia), HIV and malaria as well as gram-negative bacterial infection. The tactics used to keep ahead of AMR in all areas is similar—judicious use of current tools, appropriate diagnosis, functioning health systems, and the development of new tools ahead of need. For Australia to keep that understanding as central to its upcoming health security strategy will be critically important for its own country and for the region. Keeping close to the product developers that already have experience in this area (in particular the three funded PDPs) will help with their emerging strategies.

Estimated MMV funding gap 2017 – 2021 is presented below:



MMV's core funding over the next five years will continue to come largely from the major donors already supporting the organisation, of which Australia is a very important part. Thus, continuing to deliver value to these major donors is the first pillar of addressing the future funding gap. Even as the majority of funds are likely to come from current donors, MMV will vigorously seek additional funding from new bilateral donors, as diversity of donors is one of the most important aspects of stability and scientific independence.

MMV continues to be engaged in conversations about new funding models (for example in advance market commitments or priority review vouchers) as they are developed to see how they may help MMV fill this funding gap.

The addition of Australia to the portfolio of funder was an important strategic pillar for MMV. As the only major donor to MMV in the Asia Pacific region (with the exception of the highly-restricted funding from GHIT Japan) Australia has a key role to play in the development of new anti-malarials—addressing one of the most important public health challenges affecting over one billion people within its sphere of influence. Without funding from Australia before 2013, it was difficult to make the argument that the country was engaged in cutting edge R&D on the global stage to combat this regional scourge. The addition of Australia to MMV’s donor base, and MMV to Australia’s funding portfolio, has allowed MMV to make visible the role of Australia with governments, industry, academia and NGOs in the region in the area of cutting-edge medical R&D.

One of the most critical aspects for Australia’s influence has been its decision to invest in malaria from multiple angles. As a health area of concern for many countries in the region, Australia’s co-founding and continued engagement in the Asia Pacific Leaders Malaria Alliance allows it the opportunity for regular interaction with heads of state in the region in a non-controversial setting.

MMV’s engagement with ALPMA both as a technical partner and as the source of provision of products helps Australia underpin that relationship. This is especially important in light of emerging multi-drug resistance to anti-malarials in the region. Similarly, with Australia’s funding of the Global Fund: by continuing to fund MMV—the source of the future products needed by the Fund—Australia helps to underpin its investment in this important international body.

Finally, MMV has established strong relationships throughout Australia with scientists and bodies such as the TGA, as well as with parliamentarians and the private sector there is a certain pride that has accompanied the investment in MMV. MMV is an effective, flexible, cutting-edge organisation with a well-respected business model which is very active in the country. MMV has seen a kind of pride of “ownership” in its interactions that has grown with the amount of funding contributed. Australia is no longer only the recipient of such funds from MMV but is also a contributor.

iv. ***Is MMV likely to demonstrate results in the shortest possible time (within 3-5 years)? At what stage are the clinical trials, if applicable?***

MMV maintains a portfolio of projects in both the R&D and Access arenas. See Annex x for a schematic that shows the type of product that will be investigated, supported, rolled out or developed over the next 5 years. MMV has a deep and varied pipeline, with some promising products at late stage trials. In particular, MMV is putting a lot of effort behind its product Tafenoquine.

v. ***What is the likelihood of the research succeeding?***

In order to mitigate the risks of failure inherent in drug development, MMV works both on “lead” and “backup” compounds for each of the areas of need, which allows the organisation to rapidly terminate projects that are not meeting required milestones and replace them with backup compounds. This maximises the potential for success by removing failing products earlier in the process, improving the likelihood of success for products that are able to move further along the development lifecycle.

Test 4: Making performance count

i. ***To what extent is MMV demonstrating quality results?***

MMV has met DFAT’s overall investment outcome on its own, with two products being registered for use in high-burden Asia Pacific countries.

In general, products in the pipeline have been progressed through the relevant stages of development successfully.

By supervising a whole portfolio of R&D projects, MMV is able to ensure the most efficient allocation of funds to fulfil their mission and avoid duplication of effort. Since its establishment in 1999, MMV has taken on an increasing share of the global malaria R&D and access portfolio. This has been recognised in a number of different areas. For example, in 2015, MMV took over the stewardship of two approved artemisinin combination therapies developed by Drugs for Neglected Diseases initiative (DNDi) and partners – artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMQ). This stewardship came at the request of DNDi, which recognised that MMV had established the expertise and network required to best manage these products.

- Along with other PDPs, due to the lack of standard definitions related to Outcomes and Outputs, reporting of results has presented challenges. Specific indicators should be operationally defined in the future together with PDPs.

ii. ***To what extent is MMV able to demonstrate value for money?***

MMV's project selection processes, management and prioritisation allow the organisation to deliver value for its donors' money and benefit the global community.

Overall, MMV operates under a strict value-for-money approach, striving to maximise the impact of funding. MMV estimates that every USD1 of donor funds leverages an additional USD2.50 of matched and in-kind contributions from partners. In addition, and specifically on Australia, MMV allocated \$49.6 m to Australian science, including \$16.8 million in direct grants, which have attracted a further \$32.8 million to MMV from agencies such as Japan's Global Health Innovative Technology Fund (GHIT).

MMV has demonstrated that it can:

Deliver value for money through efficiency and stringent portfolio management. MMV applies stringent portfolio management principles, including assessment of projects at key milestones by an independent expert scientific advisory committee. This process allows prioritisation of the projects that are most likely to meet Target Product Profiles (TPPs), as well as early termination of sub-optimal projects.

MMV employs staged financing and partnering strategies aimed at keeping the cost of bringing a new drug to market significantly lower than MMV's mainstream pharmaceutical partners.

Reduce clinical development costs - MMV has an efficient and cost-effective model for developing drugs. They effectively leverage donor funds to secure matched funding and in-kind support from industry. For a donor, this means investing in a full development programme for a drug at a fraction of traditional industry costs.

- Based on the clinical development costs of current MMV pipeline drugs, it is estimated that an annual investment of USD4.5 million per drug is required. While it is difficult to benchmark these numbers across the industry, it is generally accepted that candidate development costs between USD12.5m and USD25m per drug. These differences reflect the leverage factors: the co-investment provided by MMV's partners, reductions in supplier costs and, of course, the lower overheads caused by working in a largely virtual organisation.
- The pharmaceutical benchmark for clinical development (Phases I– III) of a new anti-infective is estimated to be USD180m; MMV, by leveraging in-kind support from industry, was able to develop and bring to market its antimalarial Pyramax with an investment of only USD53m.
- For preclinical studies, MMV's benchmark is USD1.8m for completion of a full Good Laboratory Practice preclinical package (as reflected in the costs for MMV048 and DSM265). MMV's pharmaceutical partners, however, typically budget between USD2.5m and USD4m for such activities.

MMV is a lean organisation, keeping a low overhead expense ratio of 13% of annual expenditures

iii. ***How is MMV managing risk and working in partnership with other PDPs and others to achieve results and avoid duplication?***

Partnerships and avoiding duplication

MMV's success in the research and development of new medicines, as well as in its access and product management approach, comes from the synergies created by its extensive partnership network in over 50 countries. It has worked with over 400 (~160 active) leading global academic, industrial, donor and policy organisations to catalyse innovation and ensure delivery and rational use of essential antimalarials

MMV has assembled a network of assays to test and compare drug candidates within the laboratories of academic and industry partners, eliminating the need for each partner to independently develop and maintain the platforms. This reduces cost and inefficiency, as well as allowing standardised comparison of drug candidates for portfolio and investment prioritisation. Current teams include: Swiss Tropical and Public Health Institute (TPH) and Syngene for blood-stage assays; GSK for in vitro Standard Membrane Feeding Assays and in vivo *P. falciparum* severe combined immunodeficiency mouse studies; University of California, San Diego for liver-stage assays; and Imperial College London for transmission-blocking assays. These centres are reviewed annually, with the goal of achieving cost reductions wherever possible.

Benefit other parties through increased capacity and infrastructure at clinical study sites. A key example of this is the malaria vaccine initiative PATH/MVI, which has trialled the RTS, vaccine at several clinical study sites supported by MMV and its partners (including the QIMR Berghofer Medical Research Institute, where the CHMI model is up and running). By collaborating effectively, MMV can share its clinical insights with other interested parties and benefit from reciprocal sharing. This open, knowledge-sharing ethos accelerates the discovery and development process.

The financial rationale for collaboration is clear: by working with other parties/organisations to improve the capacity of clinical trial sites in malaria-endemic countries, overall expenditure on clinical development can be reduced. The investment made by one party/organisation leads to improved infrastructure and/or staff skills, which automatically benefits other users of the same facilities.

Challenge partners' costs - MMV seeks to engage service providers as partners in its mission, and leverages this engagement to negotiate discounts for agreements that, in some cases, rival those offered to the largest pharmaceutical companies. Alternative bids obtained by MMV from contract research organisations (CROs) were more than 80% lower than cost estimates provided by a pharmaceutical partner. These data led to a successful renegotiation of costs with one of MMV's major partners, resulting in a significant reduction in cost and providing a benchmark for future studies of this type. MMV's collaboration agreements commit partners to launch products in malaria-endemic countries at affordable prices, with MMV reserving the right to audit and verify production costs and mark-ups.

MMV also works with consortia such as the Global Health Clinical Consortium, in which PDPs that receive funding from the Bill and Melinda Gates Foundation can negotiate significantly discounted rates with some of the largest global clinical CROs.

Leverage donor funds - One of MMV's key success factors is its ability to leverage matched funding and in-kind support from academic and industry partners, which generates an additional ~ USD1.5– USD2.5 from each USD1 of donor funding it receives.

In still another example, MMV is pioneering work with open access and open data in discovery, providing the platform for researchers to share compounds and data. Access to open data for research encourages synergies: in the Malaria Box project (also referenced above), MMV provided 400 diverse molecules active against malaria free of charge for researchers to work on and share their results.

Following the success of this initiative, MMV then launched the Pathogen Box, with 400 different compounds active against malaria or one of a range of neglected disease pathogens. MMV awarded seven challenge grants to researchers working on each of them. In 2016 all of the Pathogen Box grant recipients, together with four additional runners-up, were invited to attend a 2-day drug discovery workshop organised by MMV, the Cape-Town based H3D Drug Discovery Centre and the South African Medical Research Council at The International Conference on Pure and Applied Chemistry 2016 in Mauritius. Through these initiatives MMV aimed to not only provide access to compounds but also create an open and collaborative forum for researchers.

MMV funding has also led to the application of **Open Source Science** models to the development of new malaria drugs at the University of Sydney. The “open source” method of collaborative research aims to address research and commercialisation issues that have not been solved via traditional approaches. It draws on principles from open source IT and puts complete methodology and all relevant data into the public domain. This reduces duplication of efforts; enables people to work in their own time and from their own locations; provides an avenue for scientists in developing countries to participate in major collaborative projects; and enables people with diverse skills sets to participate.

Managing Risk

At the end of 2012, MMV established an integrated framework to manage risk. The risks are recorded in risk registers that capture the likelihood, impact and owner of a given risk, and detailed any potential mitigation activities. Two broad types of risks are identified:

- Operational risks (risks that impact day-to-day operations but are unlikely to fundamentally jeopardise MMV)
- Strategic risks (risks that have the potential to fundamentally impact MMV’s ability to achieve its strategic objectives).
- MMV updates its Strategic Risk Register on a monthly basis (19 strategic risks were being monitored as of March 2017). The Operational Risk Register listed 78 potential operational risks in March 2017. Key operational risks (there were 7 in March 2017) are also tracked on a monthly basis. MMV’s Board is updated on mitigation activities on all strategic risks and on key operational risks on a monthly basis. In addition, all operational risks are being reassessed every other year and key changes are highlighted to the Board.

iv. **Governance & Ethics**

MMV is governed by a Board of up to 18 members, chosen for their scientific, medical and public health expertise in malaria and related fields, their research and management competence as well as their experience in business, finance and fundraising.

To advise the CEO there are two advisory boards of external advisors:

- MMV’s Expert Scientific Advisory Committee (ESAC) helps to identify the best projects worthy of inclusion in the portfolio and continues to monitor progress through an annual review of all projects.
- The function of the Access & Product Management Advisory Committee (APMAC) is to advise MMV’s Access team on appropriate strategies to achieve its goals.

MMV has established robust management structures to oversee the portfolio based on an ethos of open information sharing and objective-driven product prioritisation. The organisational objectives and the target candidate profiles, developed with its partners in consultation with WHO and the wider malaria community, outline the identified medical needs that MMV is working to overcome.

MMV has a multi-level performance objective and evaluation process across five-year, one-year, and quarterly evaluations with a rigorous internal process for goal-setting. MMV's advisory committees meet and evaluate progress on R&D and access, and work with donors on a per-project and overall organisational evaluation. This process is similar with both R&D and Access.

Governance and risk management related to the development phase and clinical trials

Along the discovery and development process, MMV has well-defined stage-gates with internal and external expert reviews. Every project is systematically reviewed by MMV's Global Safety Board before first-in-human and at the end of Phase IIa. An additional review takes place before engaging in major investment for Phase III and decision to file with the stringent regulatory authority (Board of Directors ratification of decisions is required). At each stage, essential safety/toxicity, efficacy and exposure data are reviewed. Feasibility of production and cost of goods are key considerations throughout the development process.

Key learnings from recent projects have contributed to the ongoing improvements in MMV's monitoring and evaluation processes. For example, as a result of formulation challenges experienced in the development of artefenomel, MMV has begun front-loading its formulation development work, with a particular focus on paediatric formulation development. The above MMV stage-gate criteria have been updated to include requirements for suitable availability of paediatric formulations prior to starting Phase II studies in children.

Governance and risk management related to market introduction phase

One of the most important aspects of MMV's functioning is continuous quality improvement. For example, during 2016, sequential manufacturing and quality issues were encountered that impacted on drug supplies, as well as continuity and timelines. MMV's in-house Chemistry Manufacturing and Controls and Quality staff worked with partners to conduct audits and resolve these issues. Risk-mitigation measures for the future will include building redundancy into drug supply manufacturing for clinical trials, and transferring responsibility as early as possible to MMV partners.

Governance and risk management related to the scale up of products

With a very small access team that has a large remit to help make sure that MMV medicines are available at the place and time and form they are needed around the world, MMV is particularly engaged in large scale partnerships with on-the-ground actors. Projects are significantly different; thus the monitoring and evaluation is tailored for the approach.

MMV follows and applies in all of its activities the values of respect, integrity, transparency and excellence. The **MMV Code of Ethics** seeks to safeguard high standards of behaviour and maintain independence and effectiveness in the pursuit and achievement by MMV of its mission. This includes a stringent ethical review process for all trials, where MMV adheres to best practice as per pharmaceutical industry-led trials.

MMV has a zero-tolerance policy towards bribery and corruption and has a policy in place for fraud detection and prevention. The organisation also has an equity policy and a child protection policy in place, which is designed to create awareness about the need to protect children and to set up a mechanism through which MMV will handle reports of activities that go against the principles set out in this policy (Fraud Detection and the Child Protection policies available on the MMV website).

v. Sustainability

Financing sustainability

DFAT funding represents significant geographic diversity in the funding of PDPs—the majority of MMV funding comes from Europe and the USA, and yet malaria represents a very significant burden in the Asia Pacific region. Keeping that engagement and leadership allows MMV more freedom to operate in the region, with the imprimatur of the leading funding agency in Asia Pacific. This is augmented by DFAT’s involvement and funding of the Asia Pacific Leaders Malaria Alliance (APLMA, as noted above). DFAT’s visibility of funding, its engagement with the PDP Funders’ group, its publicizing of its funding and the positive results from that funding are all helpful in continuing to the diversity of funding of MMV and its ability to operate in the region.

Over the past several years, MMV has engaged not only with DFAT but also other areas of the Australian government, most notably the NHMRC to try to find joint funding opportunities for both departments. This has proven very difficult to pursue, although it may be that the regional health security initiative will overcome these difficulties. Being able to diversify funding even within Australia would increase the diversity and thus the sustainability of the model.

Also, engagement with the private sector broadly will play increasingly important role. MMV’s fundamental model is to engage with the private sector to help bring private sector expertise and goods to the fight against malaria. Over the years, MMV has established contractual relations with more than 100 private entities in Asia and the Pacific, from pharma and other commercial companies, consultants, contract research organisations and legal firms, in Australia, Cambodia, China, Hong Kong, India, Indonesia, Japan, Malaysia, New Zealand, Singapore, South Korea, Sri Lanka, Taiwan, Thailand and Vietnam.

Market access

MMV’s vision and mission reflect the need to address both access and delivery. Access strategy requires iterative development with input from a wide range of key stakeholders and partners, including the Board. Conceptual guidance was received from BCG during development of the 2008-2012 business plan. Simplicity of conceptual framework – the 3 pillars of Acceptance, Expansion, Measure/Evaluate/Feedback required to reach Health Impact Readily linked to annual access plans for each MMV product Firm but not rigid – adaptable over time because the landscape changes and there will be pressure to re-visit access and delivery strategy. Local manufacturing may be an evolving priority. There may be a case for accelerating generics to expand affordable access.

With currently MMV’s very small access team that has a large remit to help make sure that MMV medicines are available at the place and time and form they are needed around the world, MMV is currently engaged in large scale partnerships with on-the-ground actors. Each project for access is significantly different as each problem must be approached differently; thus the monitoring and evaluation is tailored for the approach.

For example, with the Improving Severe Malaria Outcomes Project, MMV sat at the centre of a UNITAID-funded project that included the Malaria Consortium and the Clinton Health Access Initiative. In this case, the deliverables of the project (for example, number of health workers trained, tenders for procurement reviewed, etc.) were agreed in advance with the donor and partners and monitored on a quarterly basis.

Annex 9. Evaluation of TB Alliance

Investment outcome and output
<p>Definition of outcome and output used by PDP</p> <p><u>Registered product in the Asia Pacific:</u> Any product, approved by a stringent regulatory authority and/or through WHO PQ (including the expert review panel) for use in TB treatment. Accessibility gets defined as approval plus availability through either direct order or through global procurement mechanisms like the Global Drug Facility (GDF)</p> <p><u>Successfully trialled new or modified product:</u> any phase 2 or phase 3 clinical trial that, based on the scientific review of its data, allows for a continuation of the development of the product for TB treatment. Unsuccessful trials are those studies that do not meet its primary endpoint defined (non-inferiority, superiority etc). However, significant learning for future treatment and studies can make “unsuccessful” studies extremely important for future treatment, like the learnings on moxifloxacin in Remox.</p>
<p>Outcome: New/modified PDP products registered in Asia Pacific with DFAT support: 2</p> <p>Paediatric Fixed-Dose Combinations (FDCs): HRZ and HR (rifampicin + isoniazid + pyrazinamide)</p> <p>Output: New/adapted products successfully completing late stage clinical trials with DFAT support: 5</p> <p>Evaluating the efficacy of combination of bedaquiline, pretomanid and linezolid for XDR-TB (BPaL); Evaluating the efficacy of combination of bedaquiline, pretomanid, moxifloxacin and pyrazinamide (BPaMZ); Linezolid dose-ranging study; Evaluating the efficacy of combination of bedaquiline and pretomanid (PA-824) and pyrazinamide (BPaZ); PaMZ - Combination treatment for DS-TB and MDR-TB Information on these products in Annexes</p>
Test 1: Pursuing national interest and extending Australia's influence
<p>i. <i>Advance Australia's national and regional interests in terms of addressing risks to health security, stability and prosperity</i></p> <p>TB Alliance works on new, faster-acting, and affordable compounds as well as novel treatment regimens. This is helping to address critical challenges including adherence, acceptability and drug resistance. Today there are over half a million new cases of drug-resistance TB (DR-TB) every year. The tools available to treat TB have not changed much since 1948 and the current standard treatment is long, toxic, expensive and has poor patient outcomes.</p> <p>Currently, TB treatment requires a minimum of three different classes of antibiotics, thus multiple new antibiotics are required. Two new antibiotics (bedaquiline and delamanid) recently came to market. However, these were developed independently of each other, and were added to the existing two-year regimen. As a result, we have not seen dramatic improvements in DR-TB treatment duration, side effects, or cost.</p> <p>ii. <i>Extending Australia's Influence</i></p> <p><i>“TB Alliance seeks to help actualise Australia's priorities, including expanding its influence, particularly in research and innovation for effective health response to the TB pandemic. TB Alliance will tackle the health security challenges created by the emerging threat especially of drug resistant TB and, in parallel, enhance</i></p>

Australia's influence, reputation and relationships internationally. The novel, transformative new regimens will simultaneously decrease the further emergence of drug resistant TB and markedly enhance the treatment and cure rates of all existing drug resistant TB... Our advocacy efforts in Australia and the region in 2017 will continue to focus on highlighting the positive impact of DFAT's medical research funding and its near-term impact regionally."

-TB Alliance

In addition to the product-specific outcomes achieved due to TB Alliance innovations (see Test 4), through TB Alliance, Australia has influenced the TB therapeutics landscape and the Asia Pacific, in particular, through capacity building, developing new treatment regimens and development of partnerships.

This is in addition to numerous relationships that TB Alliance is garnering with generic manufacturers as part of its unique commercialisation strategy, including with manufacturers in India and China, two of Australia's top ten bilateral trading partners.

Test 2: Impact on promoting growth and reducing poverty

- i. ***Based on past reporting and current work plans, what is the potential of TB Alliance to impact on growth and poverty reduction?***
- ii. ***Based on past reporting and current work plans, to what extent is TB Alliance focussed on targeting the poorest and most vulnerable populations?***

TB Alliance states a commitment to developing novel TB treatments that will save the lives of women and children.

As a disease of poverty, TB affects the poor and vulnerable disproportionately. TB Alliance's focus on TB this investment inherently promotes reducing poverty and improving growth.

- iii. ***Based on past reporting and current work plans, to what extent is TB Alliance engaging effectively with the private sector to achieve better population health?***

TB Alliance has contractually binding relationships with several major industry players and ongoing information sharing with all the major pharmaceutical companies engaged in TB drug research and/or development. Their joint program with GSK, Johnson & Johnson and Sanofi are examples of such industry partnerships.

The only *a priori* requirement by the Alliance for entering into contractual relationships with industry partners is a binding commitment by the partner to their Adoptability, Availability and Affordability principles.

This collaborative approach has allowed them to leverage their research investments with in-kind contributions from these partners. In-kind contributions include, but are not limited to, qualified personnel, laboratories, clinical drug supply, manufacturing capacity and general know-how in all areas of R&D.

Through the Global Health Innovative Technology Fund (GHIT), TB Alliance collaborates with Japanese pharmaceutical companies, whose compound libraries are made available to screen against TB. Under two new projects, TB Alliance and Japanese partners will work on preclinical discovery.

The key private sector partner for the development of paediatric FDCs were McLeods and Lupin.

<p>TB Alliance worked in collaboration with PepsiCo to improve treatment for children with TB. PepsiCo applies its proprietary flow and sensory expertise to develop strategies that will counter the bitter taste of TB drugs, thus making it easier for caregivers to administer drugs to children.</p>
<p>iv. <i>Based on past reporting and current work plans, to what extent is TB Alliance effectively addressing gender equality and empowerment of women and girls, and if so, how?</i></p> <p>TB Alliance’s approach to gender is limited.</p> <p>The TB Alliance acknowledge the limitations in their ability to address issues such as gender equity and access for vulnerable populations. They note this is because they are essentially dependent of national level partners. Nonetheless, TB Alliance is committed to the AAA mandate, that all products are adopted, available and affordable and so play a role in ensuring lifesaving products reach vulnerable populations.</p> <p>TB Alliance also facilitates product adoption and dissemination through engagement and advocacy, including in discussions that determine access for women, children and vulnerable populations.</p>
<p>v. <i>Capacity Building in support of country-level systems and services</i></p> <p>TB Alliance plays an important role in capacity building of clinical trial sites for drug development, and contributing to sustainability.</p> <p>Their role as “sponsor” of trials for stringent regulatory authorities (SRAs) and national regulatory bodies, as well for internationally agreed standards for clinical trials, provides a framework within which site capacity is markedly strengthened.</p> <p>They work closely with Clinical Research Organisations (CROs) for clinical trial site monitoring and support, clinical trial management and pharmacovigilance. They have been heavily involved in various assessments, evaluations and capacity development that ensure clinical trial sites and laboratories meet the highest global standards as defined by the International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (ICH-GCP) and Good Laboratory Practice (GLP).</p>
<p>Test 3: Australia’s value-add and leverage</p>
<p>i. <i>How is TB Alliance collaborating with Australian research institutions and what are the benefits of such collaborations?</i></p> <p>TB Alliance has had significant interactions with academic institutions in Australia and the Asia Pacific region. Key strengths of Australia’s academic institutions working on TB are around treatment, modelling and health systems strengthening.</p> <p>There most intense collaborations have been with Burnet Institute and University of Melbourne. Professor Steve Graham, who has been a key collaborator of their paediatric project and a Member of their Paediatric Advisory Group.</p> <p>As TB Alliance gets closer to roll-out of further regimens they expect these partnerships will expand; e.g. expansion of the roll-out of the paediatric TB treatment as well as the introduction of new DR-TB treatment, especially in PNG. For the paediatric TB introduction in PNG they also worked together with Health and HIV Implementation Services Provider [HHISP].</p> <p>TB Alliance has also had collaborations and exchanges with Griffith University, University of Queensland, Monash University and University of Sydney.</p>

<p>TB Alliance is engaging with the Australian TB Forum and the TB-CRE (the Tuberculosis Centre of Research Excellence) and together with FIND have discussed becoming a formal partner.</p> <p>In policy research they have a longstanding relationship with Policy Cures and for advocacy on TB R&D they work together intensely with Results Australia.</p>
<p>ii. <i>Is the total level of financial and technical resourcing of TB Alliance from all sources appropriate to have an impact?</i></p> <p>TB Alliance has a good pool of dedicated funders with long-term financial support and commitments, however, the estimated US\$ 300 million investment needed to progress all potential products to the finish line over the next 5 years is not met. They note that significant additional investment will be needed to ensure they can deliver without delays. Given the nature of contracts with funders the situation for year 4-5 is a somewhat uncertain because they will be expecting to renew a few contracts with major funders (including BMGF and DFID).</p> <p>Under this investment, impact has not been clearly defined and has not been measured. For this evaluation, the highest level of outcome measured was new or modified products being registered in the Asia Pacific. This context does not allow for an assessment of how resources (financial and technical) relate to impact. Impact could be measured from public health and / or economic perspective (e.g. disease burden, costs per life saved, DALYs, etc.)</p>
<p>iii. <i>Does TB Alliance have funding gaps that could be usefully be supported by Australia?</i></p> <p>In addition to core funding to ensure the future TB drug pipeline continues to mature, an additional proposal, separate from continued core funding, was made to DFAT in early 2017 about the most impactful regionally focused investment they could make. Key features of the proposal include investment into ensuring completion of the development and rapid early introduction of two novel, highly complementary therapeutic regimens that will dramatically alter the treatment of all types of active TB (BPamZ and BPAL). These two novel regimens hold the potential to address the full spectrum of TB treatment needs. Both regimens are built around a common backbone of bedaquiline and pretomanid. This work would include two confirmatory clinical studies, registration and introduction of the two regimens. It would require a total of approximately US\$ 115 million, of which AUD \$20 million is requested of DFAT (2017-2021).</p> <p>Reasoning cited for why this had to be separate funding included a need to maintain access to the most effective current treatments and to ensure even better and faster acting regimens will continue to be developed. However, it is unclear why this work could not just be supported through core funding.</p> <p>Whether through continued core funding, or in support as an additional separate project, these new regimens appear to be priorities for the potential promise they hold.</p>
<p>iv. <i>Is TB Alliance likely to demonstrate results in the shortest possible time (within 3-5 years)? At what stage are the clinical trials, if applicable?</i></p> <p>The current TB Alliance product development pipeline is in Annex 10, with particular promise shown by their upcoming regimens BPamZ and BPAL. Importantly, however, even though TB Alliance has a dedicated pool of committed funders, they note a shortfall of approximately AUD\$30m over the next three years which could lead to some delays.</p>

v. ***What is the likelihood of the research succeeding?***

As with the other PDPs, there was little information provided on the likelihood of success. Several of TB Alliance's current clinical trials are showing promising results that have the potential to dramatically shorten the cure time for DR-TB with as little as a tenth of the cost of the current treatment.

TB Alliance have undertaken important work to anticipate regulatory introduction of products in 30 countries to improve the likelihood of achieving wide market access.

Test 4: Making performance count

i. ***To what extent is TB Alliance demonstrating quality results?***

TB Alliance has been successful in contributing to DFAT's investment outcome and outputs, with a product being registered in a high-priority Asia Pacific country and with 5 products progressing through late stage trials.

In addition, since 2015, TB Alliance have been working with Indonesia to develop clinical partnerships and invest in clinical research capacity in order to jointly implement TB treatment trials that meet the highest clinical and regulatory standards. In PNG, support of TB Alliance ensures Australia is strengthening health systems to reduce TB and MDR-TB from multiple angles through three investment mechanisms: PDP funding, Global Fund, and direct bilateral support. Australia's support for PNG's plans for national TB scale-up in 2017 is also well aligned with the Paediatric FDC launch and rollout. TB Alliance works closely with local partners, including national TB programs, regulatory authorities, NGOs, etc. which will strengthen these efforts.

Along with other PDPs, due to the lack of standard definitions related to Outcomes and Outputs, reporting of results has presented challenges. Specific indicators should be operationally defined in the future together with PDPs.

ii. ***To what extent is TB Alliance able to demonstrate value for money?***

TB Alliance has estimated their projected cost for a registration trial, which accounts for the vast majority of development expense, to be USD70 million.

The TB Alliance's virtual model minimises overhead cost, and they leverage funding with significant non-cash contributions from partners, including those from the pharmaceutical industry. While no formal studies have been done to look at the correlation, pharmaceutical industry investment in the field of TB increased post-2000, after the creation of TB Alliance.

For donors, TB Alliance provides risk sharing, provides disease specific expertise, reduces entry barriers for other organisations to work in the field, and leads global and local regulatory efforts. As a result, donors such as DFAT have been able to augment their investments with other public and private sector funding that would otherwise have been unavailable. An analysis of their latest financials shows that partner contributions enabled the TB Alliance to leverage at least \$0.68 for every dollar of donor funds invested.

Costs savings (potentially up to 90%) as a result of promising new regimens are likely to be increasingly significant and will allow funders to recover their investments relatively quickly as the cost of health care delivery and traditional development aid for TB drops considerably.

They are continuing to actively pursue in-kind contributions from an expanding list of partners, including those from TB endemic emerging economies. Therefore, from a purely economic perspective, funding of the TB Alliance has a significant financial return on investment for donors.

Apart from the economic benefits of the new treatments, TB Alliance's clinical development work has an economic impact in the places where clinical trials are conducted. In order to conduct registration-standard clinical trials, laboratories must be upgraded, laboratory and clinic staff must be trained in the conduct of registration-standard research and in certain cases, hospital facilities must be refurbished and diagnostic and other equipment purchased. These capacity building efforts allow for further research to be conducted in these facilities and improved medical care to be delivered at the trial centres.

TB Alliance works with numerous companies and research institutions in endemic countries, thereby supporting the local biomedical industries.

iii. ***How is TB Alliance managing risk and working in partnership with other PDPs and others to achieve results and avoid duplication?***

Collaboration

TB Alliance has a number of strong contractual relationships with Australian research institutions and private sector partners. Relationships with research institutions are expected to expand as the rollout of further treatment regimens progress.

In addition, through the Global Health Innovative Technology Fund (GHIT), TB Alliance (along with MMV and FIND) collaborates with Japanese pharmaceutical companies, whose compound libraries are made available to screen against TB.

Managing Risk

Addressed under governance.

iv. ***Governance & Ethics***

In relation to drug trials managed by TB Alliance, numerous processes are in place to ensure sound governance. Assessments to ensure trial sites meet the highest global standards as defined by the ICH-GCP-GLP are a continuous process, occurring initially as part of the pre-selection due diligence for a site considered for a clinical trial, and after a site is selected multiple interim assessments along with any required training and remediation are provided to ensure consistency in research quality and capacity for the duration of the trials. This entails thorough evaluations of both research, clinical, laboratory and health care personnel, and material appraisals such as medical equipment, facility and laboratory capacity.

Through these processes, TB Alliance identifies possible issues and training needs of both clinical and laboratory staff. TB Alliance is involved in training staff at the site and supporting the purchase of necessary equipment as well as defining and providing funds for infrastructure needs, with all of this being integrated into their research budgets.

TB Alliance has brought many sites to the level of competency and capability of conducting TB drug trials to meet ICH-GCP guidelines, in addition to FDA, EMA, MCC and other stringent regulatory authority registration standards. The ICH-GCP and GLP guidelines set standards pertaining to various aspects of

laboratory practices and ensure uniformity, consistency, reliability, reproducibility, quality and integrity of tests.

Findings from site evaluations and assessments are made public, so that information is transparent and shared with other organisations interested in TB drug development. This helps further overall capacity building through resource exchange that benefits the overall global TB research system, patients, and research.

TB Alliance with its partners engage in a tiered assessment process that involves both internal quality control assessments as well as formal audits conducted by external independent auditors and regulators.

- Each trial has a carefully crafted set of **Standard Operating Procedures (SOPs)** that define roles of all parties and responsibilities of various staff members, quality control requirements, monitoring plans as well as a clearly defined communications plan. These SOPs provide a framework for defining capacity needs as well as a monitoring tool for its implementation.
- **Internal Monitoring and Quality Control:** TB Alliance performs quality control of clinical trial sites and laboratories through regular monitoring visits. Utilizing various control checks such as Monitoring Plans, Quality Assurance/Control Plans, and Communication Plans. Primary goal is to confirm adherence to study protocols.
- During the investment period TB alliance conducted multiple rounds for quality control assessments of clinical trial sites, including in the Asia Pacific, Africa, and Eastern Europe.
- **External Inspections and Audits:** Independent inspections and audits by external vendors and regulatory bodies are conducted to triangulate findings that provide confidence in the quality of data collected at trial sites.
 - E.g. – TB Alliance created a close working relationship with the Indonesian clinical trial network “INA-RESPOND” and, with their support, partnerships with Indonesian hospitals, research centres, laboratories, and universities treating TB patients. ClinActis, a contract research organisation (CRO), conducted an independent and full clinical assessment at sites identified together with the INA-RESPOND leadership. Initial review of the site assessments suggested 2-3 hospitals with TB and research experience may be suitable for development and capacity building for the implementation of TB clinical drug trials by 2018.
- **International Audits:** International audits are occasionally scheduled by SRAs like EMA and FDA, but these typically occur only when a problem arises. No audit by a regulatory agency has been conducted on any TB Alliance trial.
- Based on findings from previous assessments including those by Irish Aid, a due diligence review by DFID, and an Assurance Review by BMGF, one key focus for TB Alliance was to evaluate the process relating to their procurement policy and practices. This is being undertaken and strengthened.

v. **Sustainability**

The sum of all of the routine quality control assessments and related processes have contributed towards long term sustainability for clinical trial capacity for the development of drugs in LMICs, not just for TB Alliance, but for the local health systems, and the international community as a whole (see sections on Capacity Building and Governance above for more detail).

In view of MacLeods engagement to develop the new paediatric FDCs, there seems to be confidence that the manufacturer will continue responding to new orders. In view that India is the largest TB market, that

the leading manufacturers of TB drugs are based in India, and that the Indian government is committed and has been very collaborative with the STEP-TB project, a recent evaluation of STEP-TB concluded that progress will continue to be made towards establishing a sustained supply of the new formulations. Securing additional suppliers is likely to be beneficial and this has been deemed likely to happen⁵⁸.

According to the evaluation cited above, there seems to have been significant efforts to develop integration strategies for procurement and supply chain of the paediatric FDCs. Roadmaps were developed for several countries, WHO also held training of trainee workshops for in-country partners to create similar roadmaps in other countries; all these activities contributed to some impact on the supply and delivery dimensions. The STEP-TB Project also contributed to identification of suboptimal functioning of the supply chain such as inadequate quantification and forecasting, and procurement of medicines as a mechanism to spend unspent grant money, which raised issues that could then be addressed. Market research activities have also provided a better understanding of the supply chain in the non-NTP sector.

In reference to implementation of the new paediatric FDCs, there are reported difficulties in co-administering the dispersible FDC with non-dispersible Ethambutol¹. This is likely to be a challenge in countries where HIV is also prevalent because the WHO recommendation in high HIV prevalent settings is to treat children with HRZE. The dispersible Ethambutol has been developed and currently in the WHO prequalification process (see Outputs table - Annex 5). Until these are made available, there remains a potential risk of continued difficulty for use in these high risk populations.

Roll Out:

TB Alliance's partners are typically responsible for undertaking final formulation development, manufacturing of product, registration of regimen with WHO prequalification and with virtually all countries as well as the marketing of the new treatment regimens. Their technical and implementation partners lead on helping to ensure the issuing of timely global and especially local policy guidelines, country preparedness for adoption and introduction. They also assist in aligning planning for the development, availability, and roll-out of the appropriate diagnostic tools and driving scale up of resistance studies, which help ensure optimum use of new drugs. It is through their partnerships that the on the ground efforts to drive adoption and uptake efforts are carried out.

Their market access and commercialisation program aims to:

- Secure multiple commercialisation and manufacturing partners to enhance affordability, access, and adoption (they completed a significant landscape analysis of the generics market to look at creating potential new partnerships and competition to drive down prices).
- Execute and support all chemistry, manufacturing and control (CMC) work required for studies, registration and roll-out of the new products, including for fixed dose combination and paediatric products.
- Ensure pre-approval compassionate access (e.g. for BPaL)
- Develop country-by-country launch strategies
- Obtain early stringent regulatory authority registration and WHO prequalification

⁵⁸ UNITAID Final Evaluation of STEP TB project, 2017. Available at: <https://unitaid.eu/assets/UNITAID-STEP-TB-Final-Evaluation-04July2017.pdf>

- Drive guideline endorsement by the WHO
- Ensure timely regimen eligibility for funding by agencies such as the Global Fund
- Leverage the Global Drug Facility (GDF), WHO country offices, and local partnerships

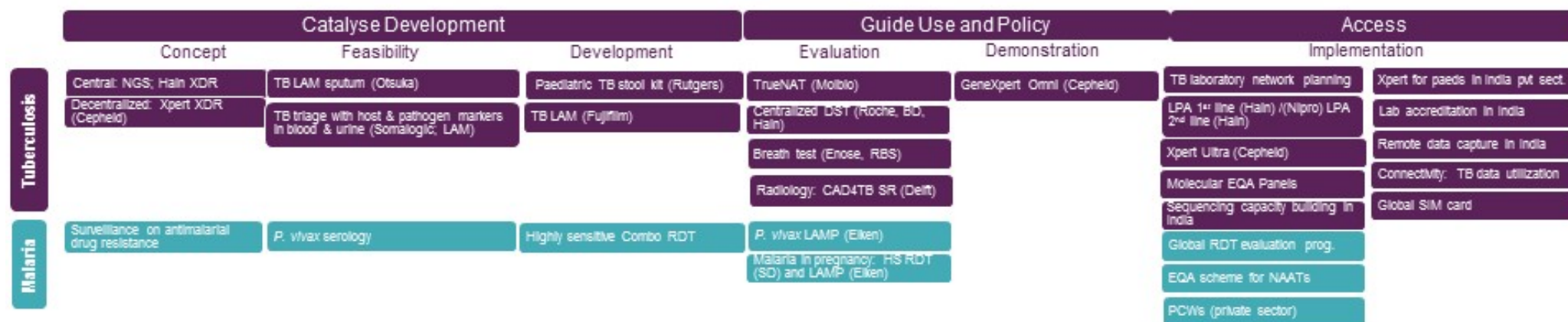
Examples of this program in action include:

- Assessment of the TB drug market in 2016. This study analysed data from the public and private sectors in 12 countries (India, Indonesia, China, Russia, South Africa, Philippines, Pakistan, Thailand, Vietnam, Brazil, Nigeria, and Ethiopia) in an effort to determine the current size and value of the TB drug market, to inform commercialisation strategy, and to support planning for forthcoming regimens.
- Engaged IMS Health, CHAI, MSH, and Mapping Health to support this study. The study included a review of the commercial landscape in the countries to understand the key players in the TB market, delineate commercial pathways for market access, and to inform global and regional commercial partnership strategies
- Worked with the Clinton Health Access Initiative (CHAI) to prepare high-level adoption readiness assessments in four priority countries (Nigeria, Myanmar, India, and South Africa). These assessments examined potential facilitators and barriers to introduction for new regimens in the selected countries, then proposed potential strategies for addressing key hurdles.
- Country-specific regulatory profiles have been completed for 30 countries to inform introduction planning of new products. Profiles contain information on registration requirements and timelines, exemptions and accelerated pathways, BE requirements, excipient restrictions, stability data and batch requirements, document requirements, and filing processes.

Annex 10: Product Development Pipelines Snapshot

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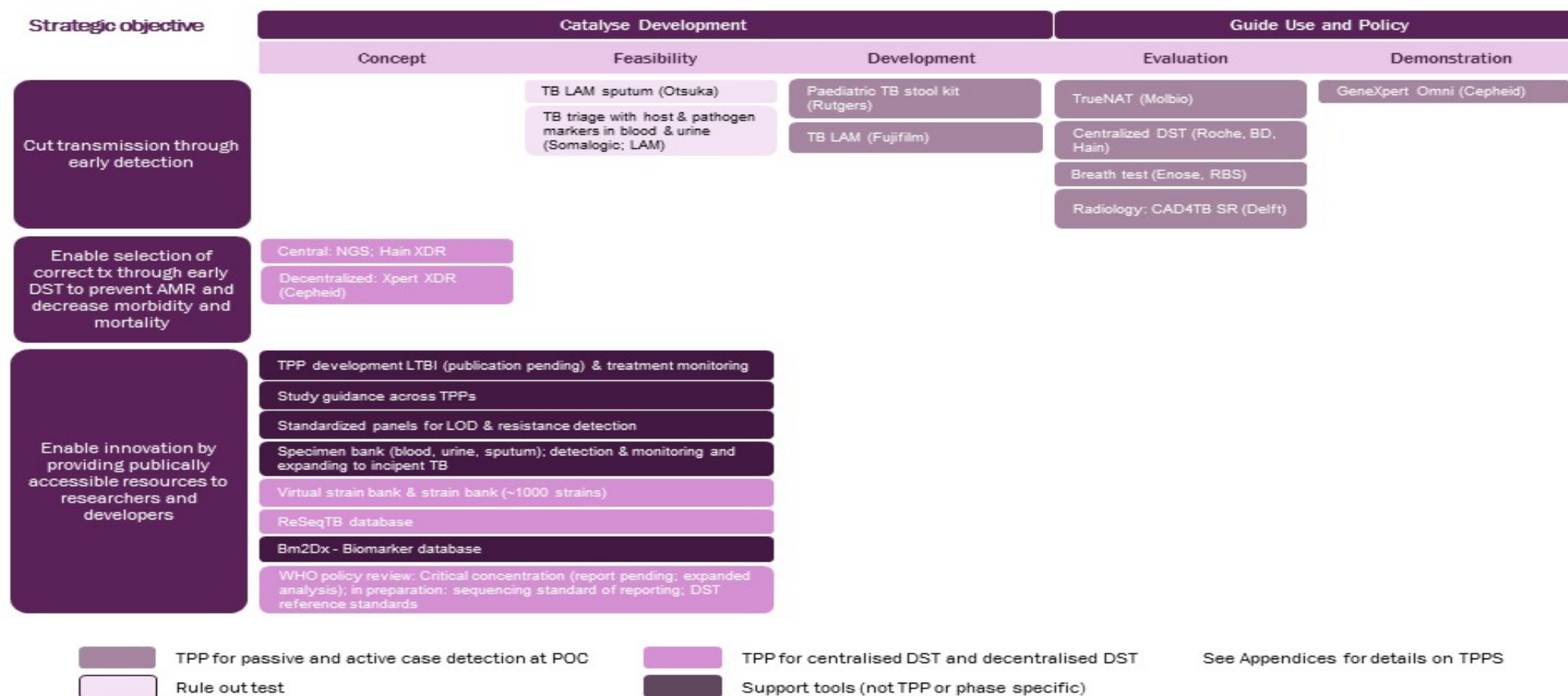
Project portfolio – TB Malaria



FIND:



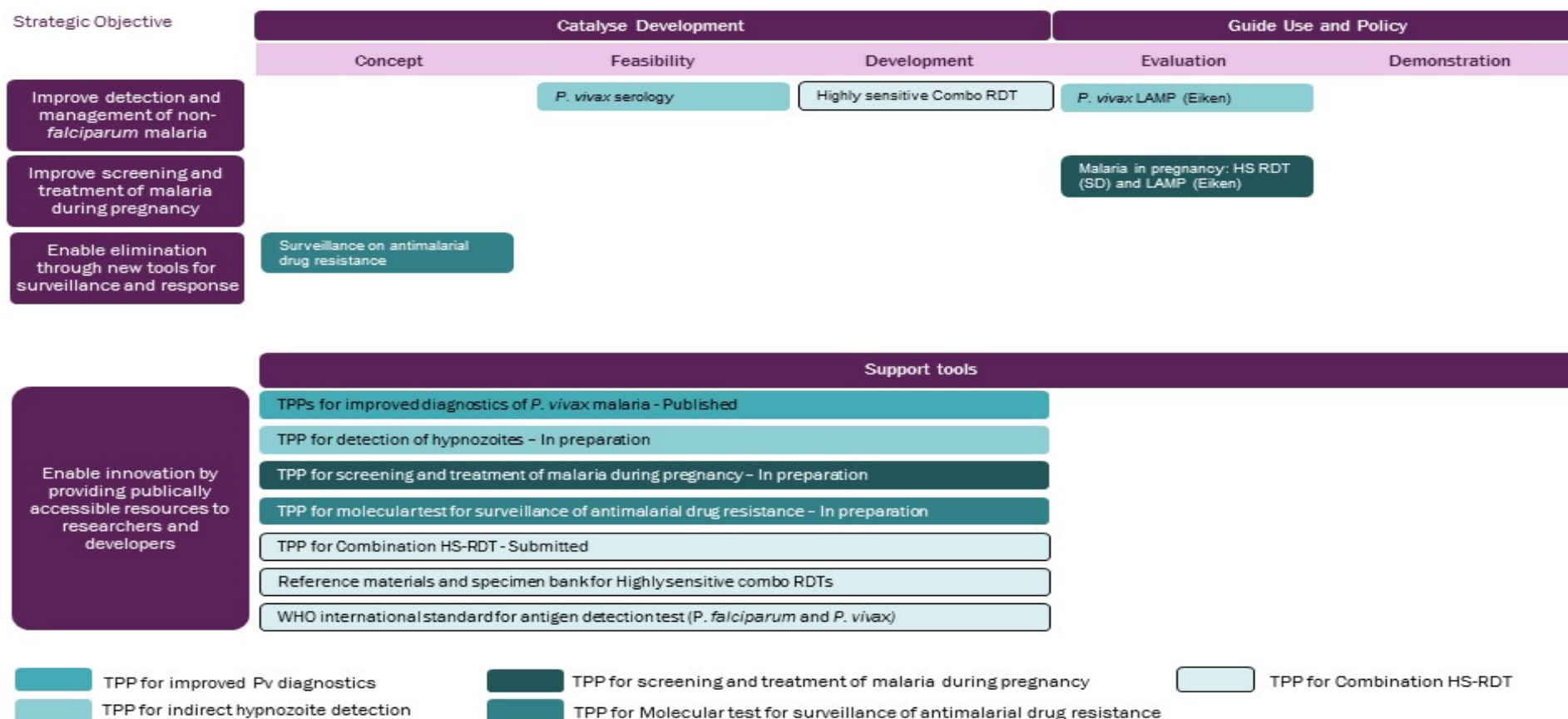
TB portfolio by strategic objective

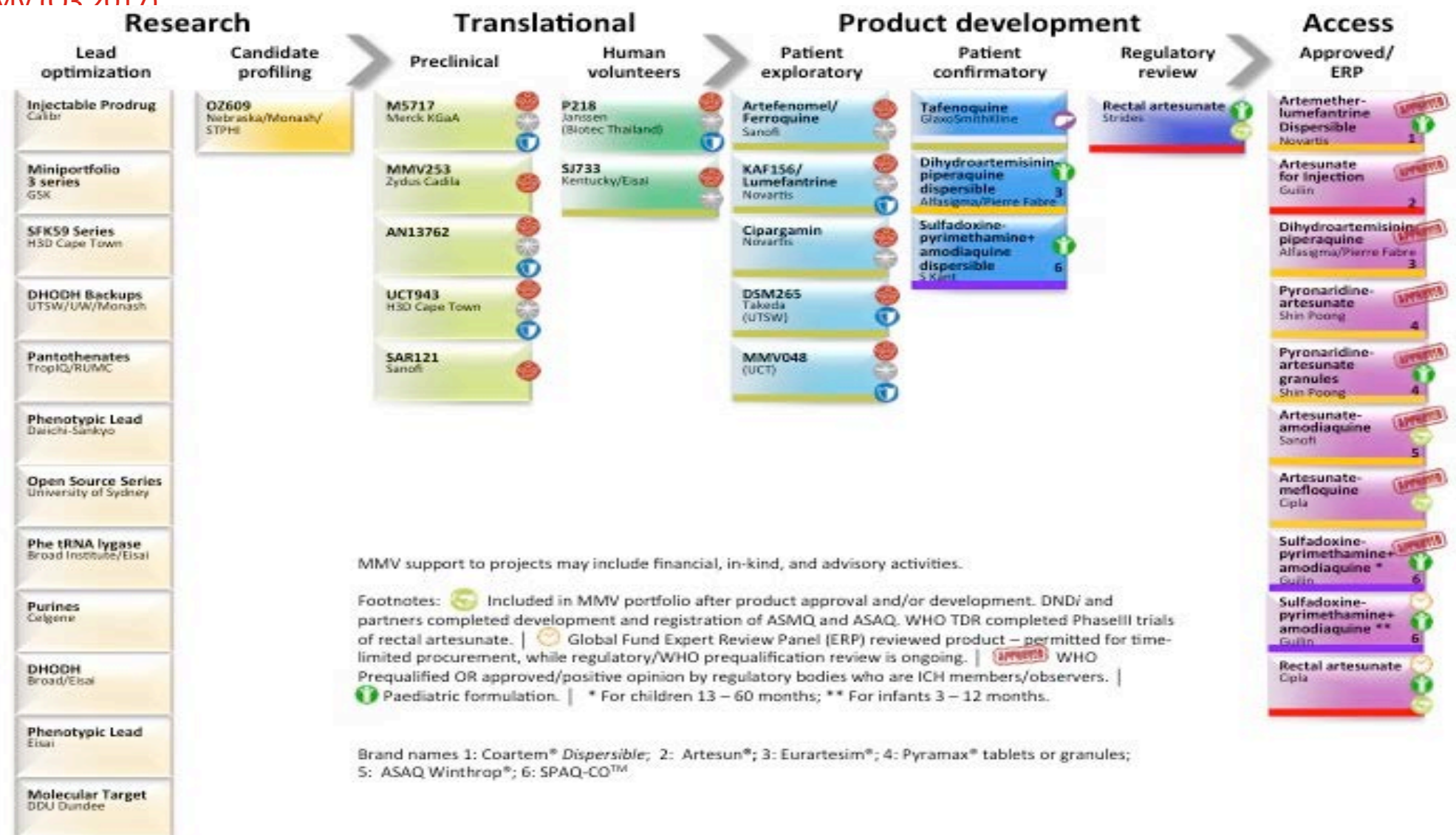


FIND:



Current malaria portfolio by strategic objective





TB Alliance (Q2 2017):

