Staying the course?

MALARIA RESEARCH AND DEVELOPMENT IN A TIME OF ECONOMIC UNCERTAINTY

ROLL BACK MALARIA

FIND foundation for innovative new diagnostics

IVCC COMBATING INSECT BORNE DISEASE

MMV Medicines for Malaria Venture

mvi PATH MALARIA VACCINE INITIATIVE

POLICYCURES

Staying the course?

MALARIA RESEARCH AND DEVELOPMENT IN A TIME OF ECONOMIC UNCERTAINTY

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Acronyms

ACT	Artemisinin-based combination therapy
AS/MQ	Artesunate/mefloquine
CQ	Chloroquine
CSR	Corporate Social Responsibility
DFID	UK Department for International Development
DGIS	Netherlands Directorate-General for International Cooperation
DNA	Deoxyribonucleic acid
DNDi	Drugs for Neglected Diseases initiative
DOD	US Department of Defense
EDCTP	European and Developing Countries Clinical Trials Partnership
FIND	Foundation for Innovative New Diagnostics
G20	Group of Twenty
G8	Group of Eight
G-FINDER	Global Funding of Innovation for Neglected Diseases
GMP	Good Manufacturing Practice
GMAP	Global Malaria Action Plan
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMF	International Monetary Fund
IPT	Intermittent Preventive Therapy
IRS	Indoor residual spraying
ITN	Insecticide-treated bednet
IVCC	Innovative Vector Control Consortium
LAMP	Loop-mediated isothermal amplification
LLIN	Long-lasting insecticidal net
LSTM	Liverpool School of Tropical Medicine
MAEC	Spanish Ministry of Foreign Affairs and Cooperation for Development
malERA	Malaria Eradication Research Agenda
MMV	Medicines for Malaria Venture
MNC	Multinational pharmaceutical company
MVI	Malaria Vaccine Initiative
NCE	New chemical entity
NIH	US National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
PATH	Program for Appropriate Technology in Health
PDP	Product development partnership
R&D	Research and development
RDT	Rapid diagnostic test
SME	Smaller pharmaceutical and biotechnology firms
SP	Sulfadoxine pyrimethamine
TDR	WHO-based Special Programme for Research and Training in Tropical Diseases
UK	United Kingdom
US	United States
USAID	US Agency for International Development
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme
WRAIR	Walter Reed Army Institute of Research

Foreword

The World Health Organization (WHO) launched a campaign to eradicate malaria in 1955. They used the tools that were considered most effective at the time: DDT for vector control and chloroquine for treatment and prevention. The campaign succeeded in eliminating malaria from Europe, North America, the Caribbean and parts of Asia and South and Central America.

However, drug and insecticide resistance emerged about a decade later. Tragically, there were no second-line antimalarial medicines and insecticides to replace the tools that had lost their efficacy, and countries like Sri Lanka, which had come close to elimination, experienced dramatic increases in malaria cases and deaths. By 1969, the political will to eradicate malaria globally faltered, and every year, malaria continued taking a terrible toll on the world's poorest people.

In 1998, the Roll Back Malaria (RBM) Partnership was launched by WHO, UNICEF, the World Bank and the United Nations Development Programme to mobilise a broad-based response to tackle this treatable and preventable disease. Today, the RBM Partnership is the global framework for coordinated action against malaria, made up of hundreds of governments, research and academic institutions and civil society and private-sector organisations.

The last decade saw remarkable progress in the fight against malaria. This once-neglected disease attracted unprecedented levels of attention and funds, and intervention coverage improved all over Africa and the world. Some areas, like the Tanzanian island of Zanzibar, KwaZulu Natal and Eritrea saw such spectacular decreases in the malaria burden that the highest-level representatives of the international community felt sufficiently encouraged to call for global eradication.

However, the lesson of history is clear: the malaria parasite is eminently adaptable. There is a great risk that it will develop new ways to outsmart the tools aimed at keeping it under control. Therefore, we constantly need to focus on developing new technologies for malaria control and elimination.

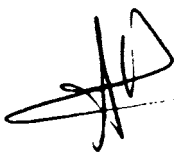
The 2008 Global Malaria Action Plan (GMAP) empowers the malaria community to put an end to this disease by articulating a three-pronged line of attack, which includes research and development (R&D) as one of its overarching strategic components.

To help ensure continued progress, it is helpful to know exactly how much we are doing. Who is funding malaria R&D and what are they funding?

Several years ago, the malaria community answered these questions based on funding estimates that were uncertain due to the lack of systematically collected and comparable data. In 2005, the Malaria R&D Alliance conducted a study to establish a baseline of global investment for malaria R&D; it was the most comprehensive report until that point and provided critical information for funders and researchers alike. This new report follows up the 2005 study and—using even better and more complete data—charts progress toward the goals set forth in the 2008 GMAP, which lays out a cohesive framework for global action against malaria.

As this report shows, malaria R&D is no longer neglected and underfunded. In recent years, a number of R&D consortia have been launched, like the Medicines for Malaria Venture, the PATH Malaria Vaccine Initiative, the Innovative Vector Control Consortium and the Foundation for Innovative New Diagnostics. New drugs, diagnostics and insecticides have been developed; a vaccine is in the third phase of testing; and hundreds of new tools for malaria control and elimination are in the R&D pipelines.

We truly have been coming together as a global community to put an end to this vicious disease once and for all. But we must remember that if we are to defeat malaria, not only must we fully deploy the tools we have today, it is equally important that we invest in the development of superior tools for tomorrow.



Awa Marie Coll-Seck
Executive Director, Roll Back Malaria Partnership

"…a dramatic increase in support for [malaria] R&D means funders are now well on the way to achieving global malaria control, treatment and elimination goals. However, these gains are fragile and may be reversed without continued funding and changes to funding patterns…"

Executive summary

MALARIA CONTINUES TO BE AN ENORMOUS ECONOMIC AND HEALTH BURDEN on developing countries, where more than three-quarters of a million deaths occur each year,[1] mostly among children living in Africa. However, for many decades, control efforts have been hindered by low levels of investment in research and development (R&D) of new products. Fortunately, a dramatic increase in support for R&D since the mid-1990s means funders are now well on the way to achieving global malaria control, treatment and elimination goals and, with maintained commitment, should reap the rewards in the next five to six years. However, these gains are fragile and may be reversed without continued funding and changes to funding patterns during this same time period.

Malaria R&D funding

Investment in malaria R&D has quadrupled in the past 16 years, from $121 million in 1993 to $612 million in 2009, with a particularly rapid increase since 2004. Funding is not spread evenly between product areas, reflecting differing costs of product development and differing levels of maturity of each portfolio, but also donor funding preferences. As a result, between 2004 and 2009, 38% of R&D funds were invested in drugs, 28% in vaccines, 23% in basic research, 4% in vector control products and 1% in diagnostics.

Malaria R&D funding by product

Between 2004 and 2009, nearly two-fifths ($752 million, 38%) of R&D funding was invested in the drug portfolio, although with a trend of steady decline in drug funding and funding share since 2007. Although this decrease is largely due to successful completion of several antimalarials, it also appears partially linked to a general trend away from product development funding and product development partnerships (PDPs). Vaccine development accounted for just more than one quarter ($544 million, 28%) of global R&D funding from 2004 to 2009, with a steep increase since 2007 associated with the progression of the RTS,S vaccine candidate into large-scale Phase III trials in Africa. R&D for vector control, which includes pesticides and biological control products, received only $72 million (4%), reflecting

both lower development costs and under-reporting, since no surveys have fully captured investment in this area by agrochemical firms. Expert estimates suggest these firms invested a likely additional $20 million in the 2007–2009 period; however, exact figures are unknown. Diagnostic R&D received $23 million (1%), reflecting both lower development costs and underfunding. While poor reporting of investment by malaria strain makes analysis difficult, only 3% of R&D funding was reported as dedicated specifically to *P. vivax*, compared to nearly 45% for *P. falciparum* (more than 50% of funding was not attributed to any strain).

Malaria R&D funders

Funding for malaria R&D is characterised by a heavy reliance on public and philanthropic funders, and a high degree of concentration. Public and philanthropic organisations provided 83% ($1.39 billion) of malaria R&D funding between 2007 and 2009, including public investment of $810 million (48%) and $577 million from philanthropic groups (35%). Public and philanthropic organisations also accounted for 94% of growth in malaria R&D funding during that time. Industry's reported collective investment totalled $281 million in 2009 (17%).

Two organisations—the Bill & Melinda Gates Foundation and the US National Institutes of Health (NIH)—provided a striking half of global malaria R&D funding in 2007–2009, and were responsible for 85% of the global increase in malaria funding. The Gates Foundation was the single largest funder, providing 30% of global funding in 2009, while the US NIH provided 19%. In the public sector, the United States dominated, providing more than half of all public investment each year, and five times more than any other government.

Malaria product developers

More than two-thirds ($945 million) of malaria R&D activity between 2007 and 2009 was conducted by public groups (academic, government and other public institutions), while industry was responsible for just less than a third ($468 million). Public groups accounted for virtually all basic research activity and 60% of global diagnostic R&D. Industry played a particularly dominant role in drug R&D, accounting for more than 60% of discovery and preclinical activity and just less than 40% of clinical development, while vaccine R&D was divided almost equally between public groups and pharmaceutical companies (51% and 44%, respectively). Reported data for vector control R&D suggested that public groups were responsible for three-quarters (78%) of all activity; however, when estimates of industry activity are used to supplement G-FINDER (Global Funding of Innovation for Neglected Diseases) data, public groups represented just more than half of all vector control R&D (53%), with industry responsible for a further third (34%).

PDPs played a central role, managing around one-quarter of all malaria R&D funding, nearly 40% of global grant funding and half of all drug and vaccine projects in the global malaria R&D pipeline. These PDPs relied heavily on only six donors, particularly the Gates Foundation, which provided more than three-quarters of malaria PDP funding in 2008–2009.

The malaria R&D funding gap

Overall, malaria R&D funding has been on track over the past five years to meet the global community's R&D product development goals. If this funding trend continues—with provisos—there will be no funding gap. This will require a modest 2% per year increase in malaria R&D funding each year, from $612 million in 2009 to a maximum of $690 million in 2015, with an investment spike of around 15% in 2016 to support late-stage products. Funders will then be able to decrease their malaria investments by about 5% per year from 2017 onward, as the fruits of their earlier investment come to registration.

The provisos: In particular, malaria R&D funding is not efficiently distributed and this urgently needs to be improved. Drug funding must remain at current levels until 2016 (and must stop its current decline), at which point it can begin winding back. (We note, though, that more accelerated drug delivery could be achieved with higher funding in the short to mid-term.) Vaccine funding needs to remain at or slightly less than current levels until 2016–2017 but will then need a major boost as next-generation vaccines move into advanced development. However, diagnostic funding needs to quadruple immediately to around $50 million per year in order to meet initial demand, while vector control funding needs to increase from its base of $28 million/$35 million in 2009[i] to a peak of around $90 million per year in 2016–2017 to make new products and paradigms available. These investment injections could be funded from the annual increases projected above.

Discussion

This analysis shows that malaria R&D does not need an endless blank cheque but rather requires realistic and feasible levels of funding, and has clearly defined goals and exit points as each desired product is brought to registration. It is also clear that maximum savings in lives and dollars will be achieved by adequate up-front funding, rather than provision of inadequate funds over many years.

However, much of this investment will be wasted without improved R&D funding policies. In particular, better distribution of funding between product areas; more responsive and flexible funding, particularly in the public sector; and far greater coordination of R&D funding between all sectors—public, private and philanthropic. Other areas of concern are the dependence on a very small number of funders, which has implications for funding security, and the plateau of funding for PDPs, which may reflect the impact of the global economic crisis, and is of concern given PDPs' central role in developing the global malaria portfolio.

[i] The lower figures are reported investment; the higher figure includes estimated unreported industry investment.

Conclusions and recommendations

Recent marked increases in malaria R&D funding have moved endemic countries closer to the drugs, vaccines, diagnostics and vector control products needed to control and progressively eliminate and eradicate malaria. Success is very close; however, it cannot be achieved without important changes to funding and funding patterns, as listed below:

1. Malaria R&D funding needs to increase modestly for the next five to six years (2% per year until 2015, 15% in 2016) and can then begin to decrease.
2. Funding must be better distributed between product areas. A high percentage of the proposed funding *increase* should be used to support the severely underfunded diagnostic and vector control areas, and greater funds need to be dedicated to *P. vivax* product development.
3. R&D funding, particularly in the public sector, must be more flexible and responsive to global portfolio developments and goals.
4. Funders must be given improved information and tools to allow them to better coordinate funding and portfolio decisions; this includes the public, philanthropic and private sectors.
5. More funders need to become engaged in malaria R&D, including more economically advanced countries (G8/G20/Organisation for Economic Co-operation and Development), and research and science and technology agencies in both existing and new donor countries.
6. PDP funding should be maintained, since PDPs account for nearly half of the current product pipeline and virtually all new malaria products delivered in the past five years.

"This report was developed to help funders see where they now stand, in particular how far the global community has progressed toward the GMAP targets and what more needs to be done."

Introduction

MALARIA REMAINS ONE OF THE WORLD'S GREATEST PUBLIC HEALTH CHALLENGES, and one of the few diseases for which death and infection continue to be measured in hundreds of millions of lives each year. In 2009, 765 million people in sub-Saharan Africa alone were estimated to be at risk of malaria.[1] There were just fewer than a quarter of a billion clinical cases of malaria in 2009, and a death toll of around 781,000 people.[1,ii]

It is still the case that an African child will have between one and five episodes of malaria fever each year on average,[2] and that many of these children will die. A staggering 85% of malaria-related deaths globally are in children younger than five years,[1] and malaria is still responsible for nearly one in every six child deaths in Africa.

Yet despite the enormous burden of malarial disease and the lack of appropriate drugs, vaccines and diagnostics, for many years, there were very low levels of investment in research and development (R&D) of new tools for malaria prevention and treatment. Fortunately, the past decade has witnessed renewed interest in malaria control, and consequent increases in funding for malaria research. As part of this, the global malaria community came together in 2008 to develop a Global Malaria Action Plan (GMAP),[3] which set out a cohesive and comprehensive global framework for action. It not only gave an overview of the malaria landscape, but presented an evidence-based approach to treatment and prevention, as well as an estimate of the funding necessary to achieve its goals. GMAP estimated malaria R&D funding needs between 2008 and 2050, both overall and for a range of R&D areas, including drugs, vaccines, diagnostics and vector control products. Importantly, it also changed the global focus to one of stepwise progress toward total eradication, as outlined in GMAP's three-part strategy: (i) scale-up of preventative and therapeutic measures to rapidly achieve global coverage and control, and then sustained control over time; (ii) progressive country-by-country elimination of malaria, toward a long-term goal of global eradication; and (iii) a research agenda to deliver the new tools necessary to achieve these aims, and to inform policy.

[ii] A 2005 study by Snow *et al.* concluded that the incidence of *P. falciparum* malaria was probably double the World Health Organization estimates, and possibly as high as 600 million episodes per year.

One of the key messages from the GMAP was that the best way to achieve these goals and to dramatically reduce future costs of malaria was to dedicate a short-term time window to increased investment in new tools now. This increased up-front investment in malaria R&D would create new tools that would more rapidly decrease the malaria burden, decrease future malaria control costs and decrease the need for future R&D funding. In other words, by investing in the short term, the global community would save a great deal in both human and financial costs in the mid- to long term. However, the onset of the global financial crisis and shifting government interests have the potential to undermine donor commitment and investments, threatening the significant progress already made toward the GMAP goals.

This report was developed to help funders see where they now stand, in particular how far the global community has progressed toward the GMAP targets and what more needs to be done. The report is structured in three sections. The first provides a detailed picture of malaria R&D funding over the past five years (2004 to 2009), including how much funding went to each product and research area, who provided the funding and how investments flowed from funders to recipients. Funding recipients were also examined: Who are they? Which groups dominate which research areas? How much funding do they receive? What types of R&D does each sector conduct? The second section uses this information to assess progress against the GMAP funding goals and to identify what more is needed in the next ten years. The final section discusses the implications of these findings and provides recommendations for the future.

In order to ensure integrity of the analysis in this report, we used only hard data, including the 2005 Malaria R&D Alliance report and the 2008–2010 G-FINDER (Global Funding of Innovation for Neglected Diseases) reports. Data were not available for 2005 and 2006. The exception is industry vector control funding, for which insufficient hard data were available; in this case, data were supplemented with estimates at some points (noted as such).

Disease background

HISTORY OF MALARIA CONTROL

Malaria is a global health threat that has caused economic hardship as well as the loss of millions of lives for centuries. The global malaria eradication programme established by the World Health Organization in 1955 led to elimination of malaria in temperate and sub-tropical climates through vector control with dichlorodiphenyltrichloroethane residual spraying.[4] However, the campaign was abandoned in 1969 due to concerns over environmental safety and insecticide resistance. Malaria management was further complicated in the early 1960s by emerging *Plasmodium* resistance to chloroquine (CQ), the main drug used for the prophylaxis and treatment of malaria at that time.[5] Increasing drug resistance to CQ prompted a change to other first-line regimens, commonly sulfadoxine pyrimethamine (SP)[1]; however, resistance to SP was quick to develop in endemic countries. These factors contributed to resurgence of malaria, especially in Africa and South-East Asia, where *P. falciparum* and *P. vivax* account for the bulk of malaria cases respectively.[6,7]

Significant progress in malaria control has been made over the last decade, with several countries reporting decreased malaria morbidity and mortality through intense malaria control efforts based on early diagnosis and treatment using new artemisinin-based combination therapies (ACTs), the use of long-lasting insecticidal nets and indoor residual spraying (IRS).[1] However, the recent appearance of resistance to ACTs, widespread resistance to pyrethroids[6] and the lack of a highly effective vaccine means there is still much to be done to achieve global malaria control, elimination and eradication.

THE ECONOMIC IMPACT OF MALARIA

Malaria significantly slows economic growth and development. As well as the direct costs associated with illness, treatment and premature death, malaria decreases workforce productivity, reduces school attendance and impairs childhood cognitive development.

In countries with high levels of transmission, it is estimated that malaria can reduce gross domestic product by as much as 1.3% per annum.[4] In Africa, malaria is now the fourth-leading cause of years of productive life lost to mortality and morbidity (disability-adjusted life years).[8]

Because it predominantly affects poor rural areas, malaria not only places a higher burden on those least able to afford it, but also on those who are least likely to be able to access adequate health care services. The problem of access to treatment is one of the major challenges in achieving global eradication.

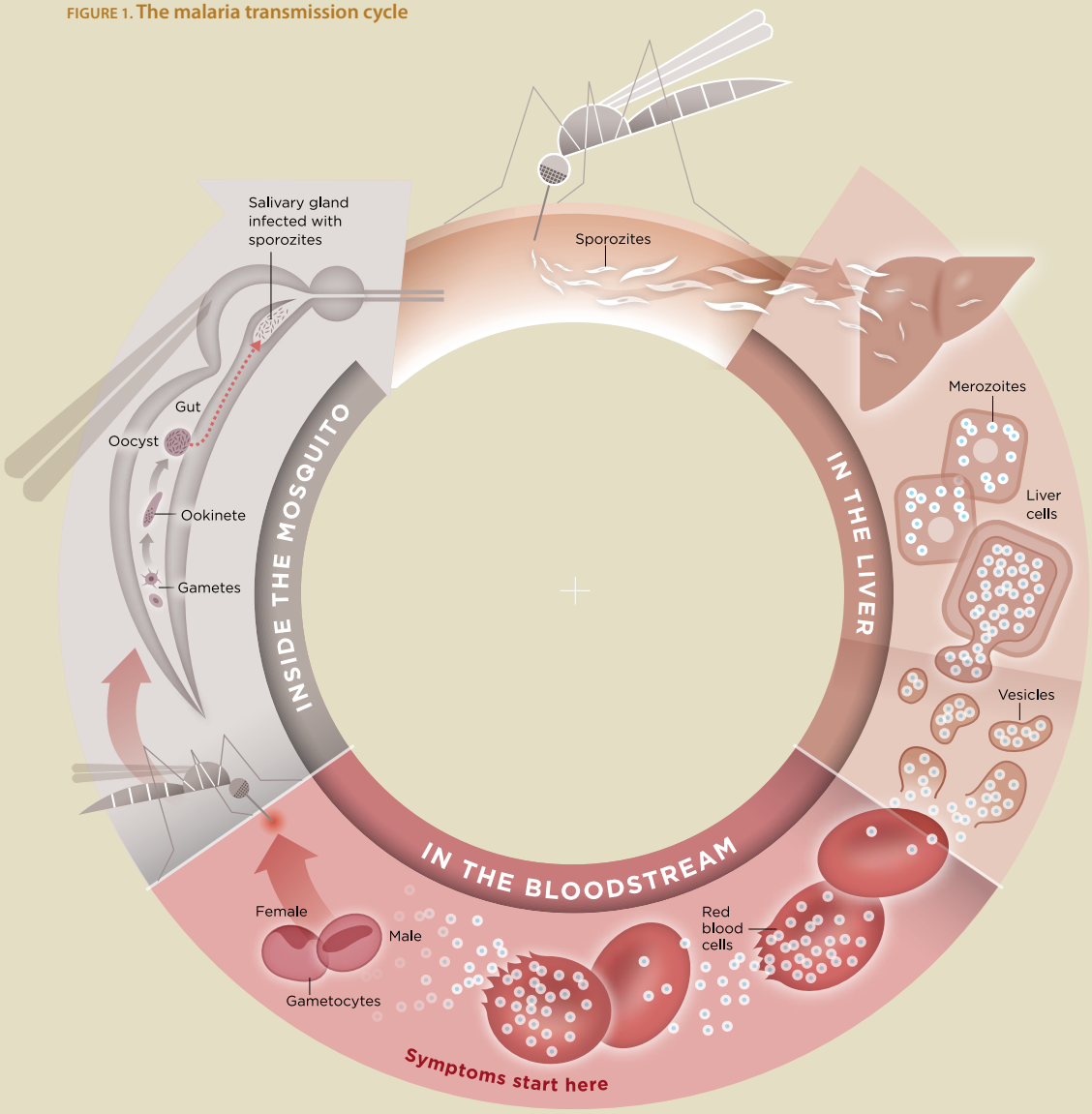
OVERVIEW OF DISEASE TRANSMISSION AND IMPORTANT STRAINS

Malaria is caused by the protozoan parasite *Plasmodium*, and the two major strains (*P. falciparum* and *P. vivax*) together account for virtually the entire global malaria burden. *P. falciparum* is by far the most deadly, and is also the dominant strain in sub-Saharan Africa, where it accounts for 98% of all malaria cases. Outside of Africa, *P. vivax* is often the dominant strain, accounting for up to half of all malaria cases in South-East Asia and as many as 70 to 80% of cases in South America.[7]

Malaria is transmitted to humans via the bite of the infected female *Anopheles* mosquito (Figure 1). Once inside the human body, the *Plasmodium* parasite multiplies in the liver (the pre-erythrocytic stage) and the blood stream (the blood stage), before being transmitted to the mosquito vector once again when it bites an infected human. Malaria presents as a febrile illness, with symptoms commencing 10–15 days after the original bite, and including high fever, chills, abdominal pain, headaches and nausea and vomiting. The acute attack lasts for around four to six hours, and recurs cyclically every one to three days.

Malaria is frequently associated with complications, some fatal. If not treated within 24 hours after the onset of symptoms, *P. falciparum* infection can progress to severe malaria, often leading to death. Patients with severe malaria may suffer anaemia as a result of widespread destruction of red blood cells, which can result in multi-organ failure. The disease may progress to cerebral malaria, which can result in permanent and severe neurological disability in children and is often fatal. Malaria during pregnancy can cause low birth weight and premature delivery, which are in turn associated with an increased risk of neonatal death and impaired cognitive development. The prevention of malaria during pregnancy links directly to Millennium Development Goals 4 and 5, which aim to reduce maternal and child mortality.[9]

FIGURE 1. **The malaria transmission cycle**



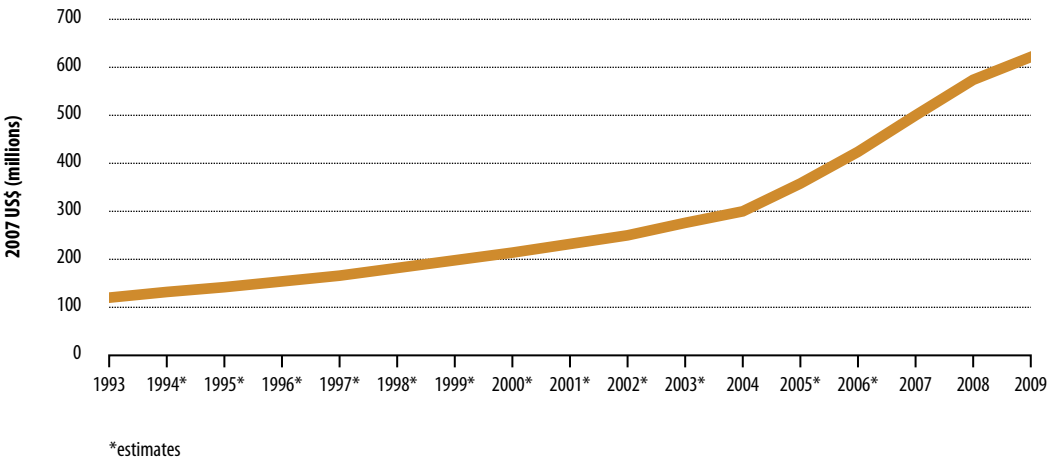
"Funding for malaria R&D more than quadrupled in real terms over 16 years due to a marked increase in commitment to development of new tools to control, eliminate or even eradicate the disease."

SECTION ONE

Malaria R&D funding today

FUNDING FOR MALARIA R&D MORE THAN QUADRUPLED in real terms over 16 years due to a marked increase in commitment to development of new tools to control, eliminate or even eradicate the disease. Wellcome Trust reported a $121 million annual investment (in 2007 US dollars) in malaria research in 1993.[10] Within 11 years, this had more than doubled, to $295 million in 2004, and in the past five years, doubled again, to $612 million in 2009.[iii]

FIGURE 2. **Overall malaria R&D funding, 1993–2009**



While some of this increase has come from the inclusion of data from more funders over the years, the majority is due to real increases in funding from a handful of 'top donors' that have remained consistent across all surveys, with close to 90% of global funding reported by the same 12 funders each year.

[iii] Total malaria funding in 1993 as reported in the 1996 Wellcome Trust report was $84 million, and in 2004 (reported in the 2005 Malaria R&D Alliance report) was $323 million. All figures have been adjusted for inflation and expressed in 2007 US dollars. Vector control funding may be up to $6 to 7 million per year more than reported in these surveys.

Malaria accounts for just less than one-fifth (18%) of global funding for neglected disease R&D, with its share remaining steady at this level since 2007, the first year that fully comparable cross-disease data were available.

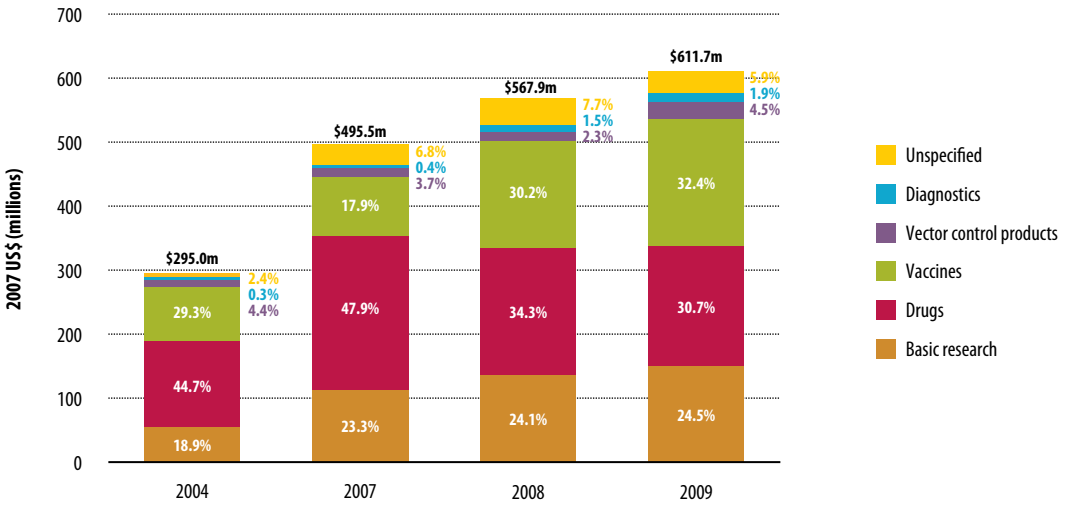
Malaria R&D funding by product

The total amount of funding provided for malaria R&D is important; however, it is also important that these funds are efficiently distributed to the different R&D areas.

Different products have very different development costs and timelines. Vaccine development is by far the most expensive and lengthy, estimated at $600–800 million[11,12] over 10–15 years[11] to create one successful vaccine. Creation of one new drug is estimated to cost $150–250 million[13,3] over 7–10 years,[14] while a new vector control product will cost an estimated $60–65 million[15] over 10–12 years.[22] One successful new diagnostic will cost around $2–5 million[16] and take three to five years[17] to create. The maturity of a pipeline is also important, since large late-stage clinical trials are far more expensive than early laboratory research. As a result, spending needs will be high in areas with one or more products in late-stage development and, as a corollary, are likely to decrease once these products are registered and the focus shifts back to development of early leads.

Analysis shows that from 2004 to 2009, drugs accounted for an average of 38% of total malaria R&D spending, followed by vaccines (28%), basic research (23%), vector control products (4%) and diagnostics (1%). This funding distribution was driven by a range of factors, in particular the type of product being developed and the relative maturity of each product pipeline; however, donor funding patterns and preferences also played an important role, as discussed below.

FIGURE 3. **Malaria R&D funding by product, 2004–2009**



Basic research funding

Basic research is an important part of malaria R&D, as it aims to increase our knowledge and understanding of the disease. A key difference between basic research and R&D into, for example, drugs or vaccines is that basic research is not yet directed toward a specific product.

Funding for basic research more than doubled between 2004 and 2009, increasing at a far faster rate than funding for drugs, diagnostics or vector control products. This is not explained by product type or portfolio maturity, but rather appears to reflect donor funding patterns. For example, many public funders, such as the UK and Australian governments, have a marked preference for funding basic research. Similarly, the US National Institutes of Health (NIH) invests about two-thirds of its malaria funding in external researchers, of which most goes to basic research.

Drug R&D funding

For most of the past half-decade, malaria drugs have received the majority of R&D funding, with marked increases between 2004 and 2007 (up $105 million, 80%). However, since 2007, there has been a steady decline in funding for drug R&D (down $49 million, 21%), as well as a redistribution of funds away from clinical development and toward discovery and preclinical activities.[iv]

These trends are largely, but not entirely, explained by the maturity of the drug portfolio, with successful registration of several new antimalarials, including artesunate/amodiaquine (2008),[18] artesunate/mefloquine (AS/MQ, 2008)[19] and Coartem® Dispersible paediatric formulation (2009),[20] and submission for registration of Eurartesim™ [21] (2010) and Pyramax® [22] (2010)—as well as the termination of unsuccessful drug candidates, including isoquine (2008) and chlorproguanil-dapsone-artesunate (2009).

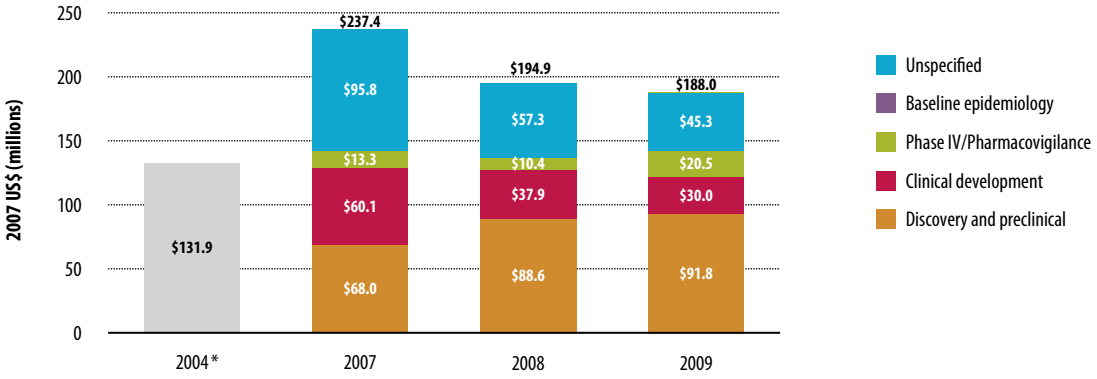
These registrations and terminations led to decreased funding needs as expensive late-stage trials were concluded. Instead, the funding emphasis shifted to discovery and preclinical projects designed to fuel the drug pipeline and improve portfolio composition in the longer run, as well as to Phase IV/pharmacovigilance studies to assess the ongoing safety of these newly registered drugs.

Many of these changes are efficient and productive, and provide a valuable example of the longer-term savings to be made by ramping up investment to achieve product goals. However, some of the funding decrease appears unrelated to portfolio development, but rather to a more general global trend from public and philanthropic funders toward basic research funding and away from product development.[v] For instance, the funding decrease for drug development does not align well with the global health community's agreement on the need for further new antimalarials, including a single-dose cure, treatments for pregnant women, a radical cure for *P. vivax*, novel compounds to tackle artemisinin resistance and transmission-blocking antimalarials.

[iv] A decrease in the 'unspecified' R&D area reflects better reporting by survey participants. We assumed that improved reporting of 'unspecified' funding was evenly spread across the development portfolio.

[v] See the findings of the 2010 G-FINDER report, *Neglected disease research & development: Is the global financial crisis changing R&D?* Available at: http://www.policycures.org/downloads/g-finder_2010.pdf.

FIGURE 4. **Funding for malaria drugs by R&D area, 2004–2009**



* Funding data for 2004 cannot be broken down by R&D area.

Vaccine R&D funding

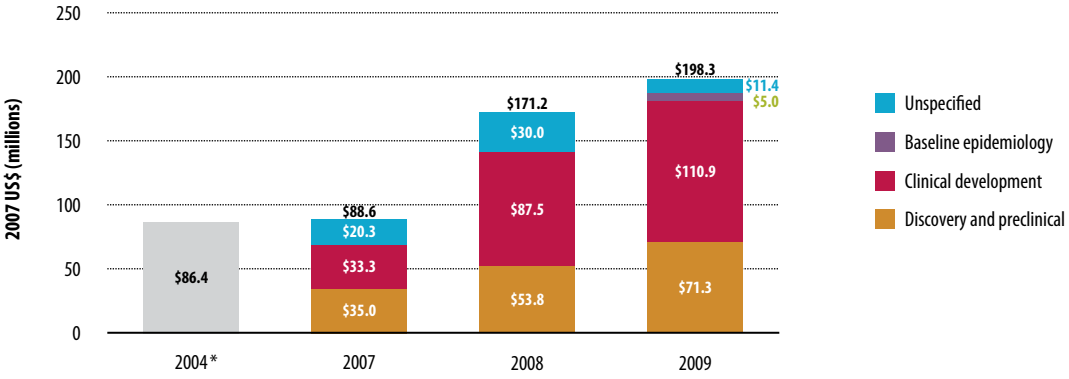
Vaccine funding shows a very different pattern, reflecting the different shape and maturity of the vaccine portfolio.

Investments in vaccine R&D more than doubled between 2007 and 2009 (up $110 million, 124%), and were predominantly directed toward clinical development. This was almost entirely due to the high investment demand associated with the move of the RTS,S malaria vaccine candidate, developed by the PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline, into large-scale Phase III trials in Africa. As a result, vaccine funding surpassed drug R&D funding for the first time in 2009.

While this increase went largely to the clinical development stage—large-scale vaccine trials are the most costly of all product development phases—investment in discovery and preclinical stages also doubled as work progressed to develop more effective second-generation malaria vaccines.

These shifts again reflect sensible funding patterns, with significant increases to support advanced candidates to registration that can likely be followed by funding reductions as the focus moves back to follow-on candidates at earlier stages of development.

FIGURE 5. **Funding for malaria vaccines by R&D area, 2004–2009**



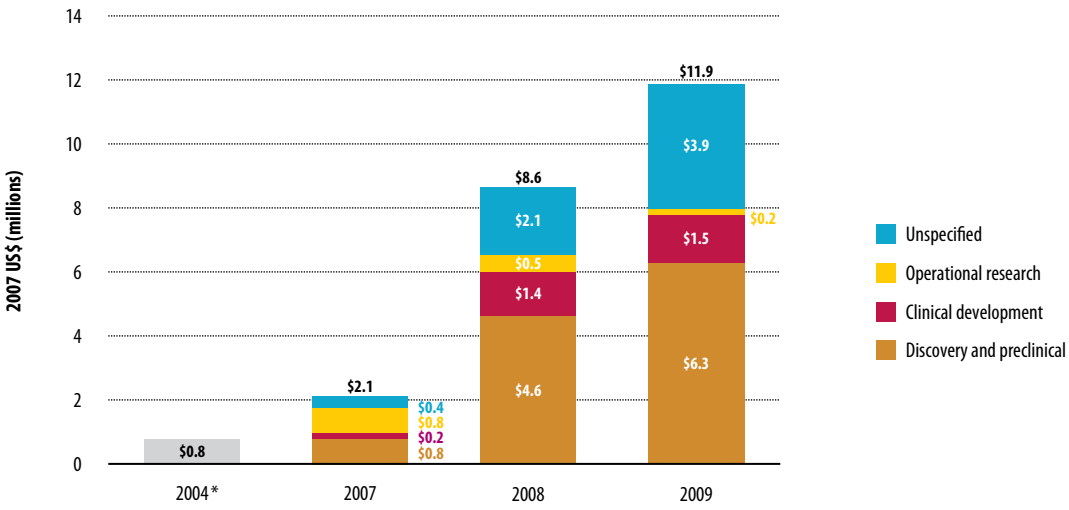
* Funding data for 2004 cannot be broken down by R&D area.

Diagnostic R&D funding

Diagnostics would be expected to require less funding than other malaria product development areas given their far lower development costs and times and lower regulatory burden. Nevertheless, diagnostic funding was remarkably low at just less than $12 million in 2009 (1.9% of total malaria investment). This is particularly troubling, as diagnostics are a cornerstone of good malaria control, and will increasingly be needed to manage artemisinin resistance and for active case detection as eradication efforts progress.

An analysis of diagnostic investment by R&D category cannot be reliably undertaken due to the small amounts involved and the high proportion of investment reported as 'unspecified.' We also note that the apparent growth in diagnostic funding between 2007 and 2008 is an artefact due to expansion of data collection in 2008 to include many more diagnostic firms, while the 2009 figure represents a small but real increase in diagnostic funding.

FIGURE 6. **Funding for malaria diagnostics by R&D area, 2004–2009**



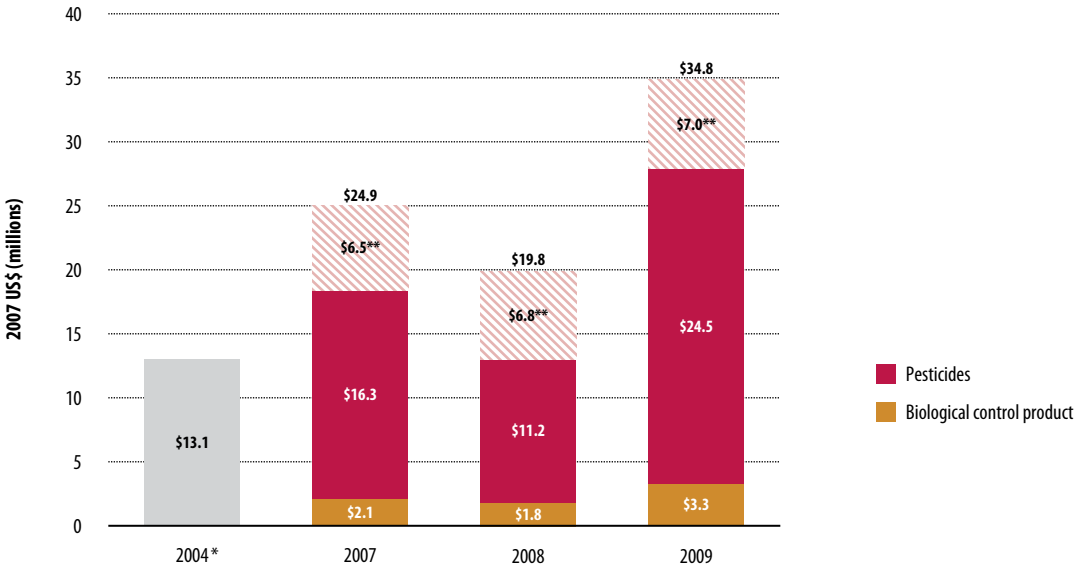
* Funding data for 2004 cannot be broken down by R&D area.

Vector control R&D funding

Vector control, which includes pesticides and biological control products, is in many ways the poor relation of malaria R&D funding. Data are limited and, when provided, are often of poor quality, with high levels of 'unspecified' funding reported. Available data also largely exclude private investments by agrochemical firms.[vi]

With these provisos in mind, it is nevertheless true that vector control products attract only a small proportion of overall spending on malaria R&D. Reported vector control R&D funding was $27.8 million in 2009, or 5% of the malaria total, with expert estimates suggesting the true figure may have been as high as $34.8 million. Although this represented a doubling of funding from figures reported in 2004 (up $14.7 million, 112%), the relative proportion of malaria R&D funding dedicated to vector control products increased only slightly over that time.

FIGURE 7. **Funding for malaria vector control products by type, 2004–2009**



* 2004 data cannot be broken down by product area.

** Estimated industry R&D investment not captured by surveys.

Reported investment in development of new vector control products is chiefly driven by the activities of the Innovative Vector Control Consortium (IVCC) and funding from the Bill & Melinda Gates Foundation. Thus, the activities of these two groups have a disproportionate effect on funding patterns; for instance, the drop in funding between 2007 and 2008 was largely a result of cyclical grant funding by the Gates Foundation.

[vi] G-FINDER is currently seeking to improve data collection from agrochemical firms working on vector control product R&D.

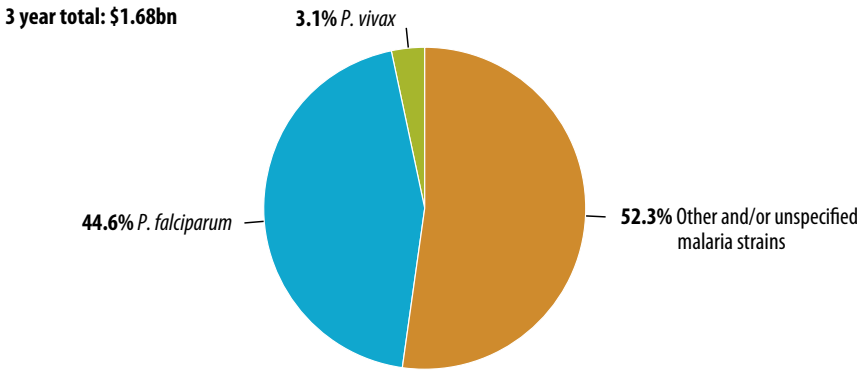
Funding by malaria strain

P. falciparum received the lion's share of malaria R&D funding, reflecting its status as the most deadly malaria strain, as well as its overwhelming dominance in Africa.

Nearly 45% of all malaria R&D funding from 2007 to 2009 was identified as being specifically targeted at *P. falciparum*, compared to just 3% for *P. vivax*, although we note that just greater than half of all funding during this time was not attributed to a specific strain (see Figure 8).[vii] This high proportion of 'unspecified' funding partly reflects the 'platform' nature of R&D areas like diagnostics and basic research, although there is, in general, poor reporting on investment by malaria strain. The weighting of funding toward *P. falciparum* is consistently high across all R&D areas, despite the high morbidity burden associated with *P. vivax* outlined earlier.

In order to eliminate or eradicate malaria, it will be important to ensure there is adequate R&D investment to address the challenges posed by all strains.

FIGURE 8. **Funding by malaria strain (three-year total, 2007–2009)**



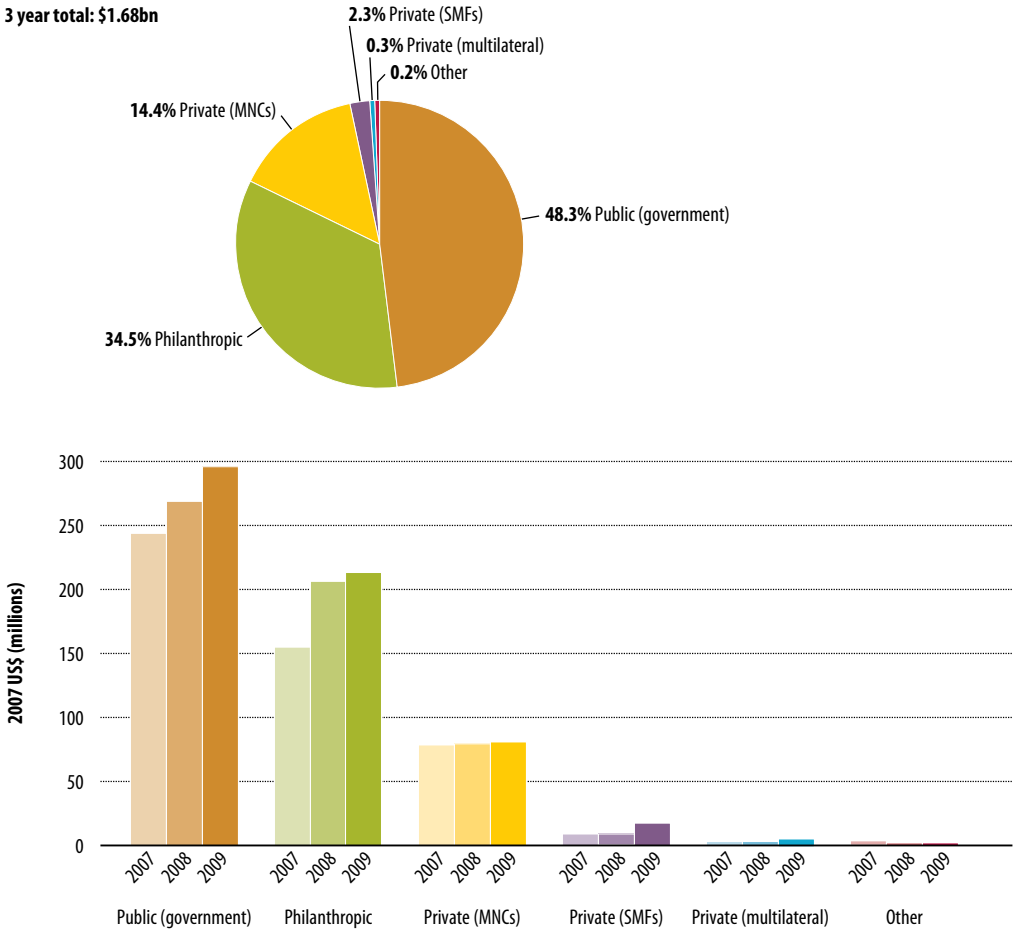
Malaria R&D funders

Funding for malaria R&D has been characterised by two key features: a heavy reliance on public and philanthropic organisations and a high degree of concentration. Public funders also showed markedly different preferences for funding basic or applied research. Public and philanthropic organisations provided 83% ($1.39 billion) of all malaria R&D funding between 2007 and 2009,[viii] including public investment of $809.6 million (48% of total funding) and $577.2 million from philanthropic groups (35%). While public funding continued to account for around half of total funding, philanthropic funding showed the strongest growth during that time, leading to a slight increase in their relative funding share at the expense of industry and government.

[vii] Funding for 'other malaria strains' could include both *P. falciparum* and *P. vivax* strains, multiple strains or strains other than *P. falciparum* or *P. vivax*. Funding categorised as being for 'unspecified malaria strains' generally reflects funders' inability to identify which strain was funded.

[viii] 2004 data were excluded from this analysis in order to keep the sample size for each year comparable, and because the Malaria R&D Alliance report did not break 2004 funding data into the same sub-categories as G-FINDER.

FIGURE 9. **Malaria R&D funding by funder type, 2007–2009**



MNC: multinational pharmaceutical company; SME: smaller pharmaceutical and biotechnology firms.

The apparent increase in SME investment in 2009 from 2007 is largely an artefact due to expansion of the data collection process to more small firms during that time, in particular companies in India, Brazil and the United States.

Together, public and philanthropic organisations were also responsible for essentially all growth (94%) in malaria R&D funding between 2007 and 2009, with philanthropic investments up more than a third ($58.2 million, 37%) and government funding up 21% ($50.9 million).

The contribution of industry was also significant, although smaller by comparison and remaining essentially static. Industry contributed $280.6 million (17%)[ix] between 2007 and 2009, a significantly higher proportion than the 12% of funding they provide to neglected diseases overall.[23] In addition to this direct R&D spending, companies also provided in-kind contributions that cannot easily be captured in dollar terms, including technology transfer, sharing of intellectual property and regulatory assistance. Although difficult to quantify, these inputs nevertheless represent a substantial value to their recipients and a significant cost to companies.

[ix] Inclusion of estimated industry vector control spending would increase this to $300.9 million (18%).

Funding is highly concentrated

The degree of concentration of malaria funding is striking. A small group of funders consistently provides almost all investment in malaria R&D, with two organisations—the Gates Foundation and the US NIH—dominating overall investment, and one government, the United States, dominating public investment.

Top funder organisations

Nine organisations (excluding the aggregate pharmaceutical industry) accounted for nearly three-quarters (72%) of global funding from 2007 to 2009. Half of global malaria R&D funding during that period was provided by just two organisations: the Gates Foundation and the US NIH. These two organisations were also responsible for 85% of the increase in malaria R&D funding between 2007 and 2009, with the Gates Foundation increasing funding by $59.8 million (48%) and the US NIH by $31.6 million (37%).

TABLE 1. Top 10 malaria R&D funders, 2007–2009

Funder	2007	2008*	2009*	2007 (%)	2008 (%)	2009 (%)	% Change 2007-2009
Bill & Melinda Gates Foundation	124,464,185	175,404,338	184,295,373	25.1	30.9	30.1	48.1
US National Institutes of Health	84,422,644	104,810,620	116,013,245	17.0	18.5	19.0	37.4
Aggregate pharmaceutical and biotechnology company respondents	90,793,583	90,611,134	99,230,024	18.3	16.0	16.2	9.3
US Department of Defense	33,126,578	30,518,142	37,585,617	6.7	5.4	6.1	13.5
European Commission	37,196,041	34,539,331	29,731,650	7.5	6.1	4.9	-20.1
Wellcome Trust	28,255,207	26,732,141	27,204,542	5.7	4.7	4.4	-3.7
UK Medical Research Council	18,594,597	18,985,044	20,712,331	3.8	3.3	3.4	11.4
Australian National Health and Medical Research Council	7,692,288	9,012,351	10,201,615	1.6	1.6	1.7	32.6
UK Department for International Development	6,343,903	4,878,960	8,582,482	1.3	0.9	1.4	35.3
US Agency for International Development	9,249,900	8,556,406	8,166,618	1.9	1.5	1.3	-11.7
Subtotal top 10 funders**	**446,937,912**	**508,083,475**	**541,723,498**	**90.2**	**89.5**	**88.6**	**21.2**
Grand total	**495,502,620**	**567,941,623**	**611,718,047**	**100.0**	**100.0**	**100.0**	**23.5**

* Figures are adjusted for inflation and reported in 2007 US dollars.

** Subtotals for 2007 and 2008 top 10 reflect the top funders for those respective years, not the top 10 for 2009.

Top government funders

Each year, ten governments provide more than 90% of total public-sector malaria R&D funding, with the United States providing more than half of all public funding and at least five times more than any other government. (Encouragingly, this is less concentrated than public

funding for neglected diseases overall, for which the United States provides 70%.[23]) We note that India was the sixth-highest public funder in 2009, contributing 3% of global public-sector funding for malaria R&D in 2009, and Brazil seventh with 2%—figures that place them well ahead of most Organisation for Economic Co-operation and Development (OECD) countries and several G8 governments.

Collectively, the top ten governments increased their funding by nearly 20% between 2007 and 2009, with the United States responsible for the vast majority (84%) of this rise. The United Kingdom and Spain were the only European governments that increased their malaria R&D investment during this time. Increased US funding also helped to offset reduced funding from many European governments, likely associated with the global financial crisis, with notable funding drops from the European Commission (down $7.5 million, 20%), France (down $3.5 million, 24%) and Ireland (down $3.2 million, 55%).

TABLE 2. **Top 10 government funders, 2007–2009**

Country	2007	2008*	2009*	2007 (%)	2008 (%)	2009 (%)
United States	129,615,489	147,454,629	164,805,181	53.0	54.8	55.7
United Kingdom	25,899,261	24,340,297	30,190,739	10.6	9.0	10.2
European Commission	37,196,041	34,539,331	29,731,650	15.2	12.8	10.1
Australia	7,805,463	11,130,221	11,391,587	3.2	4.1	3.9
France	14,477,350	9,170,260	11,027,001	5.9	3.4	3.7
India**	–	13,226,029	8,428,272	0.0	4.9	2.9
Brazil	2,175,502	839,041	6,541,161	0.9	0.3	2.2
Spain	1,407,821	8,124,088	6,526,248	0.6	3.0	2.2
Netherlands	6,381,857	5,265,113	6,185,521	2.6	2.0	2.1
Germany†	3,501,431	949,847	5,383,784	1.4	0.4	1.8
Subtotal top 10 funders§	**236,455,384**	**259,509,505**	**280,211,146**	**96.6**	**96.4**	**94.8**
Total public funding	**244,695,641**	**269,258,901**	**295,633,310**	**100.0**	**100.0**	**100.0**

* Figures are adjusted for inflation and reported in 2007 US dollars.

** Country not surveyed in 2007.

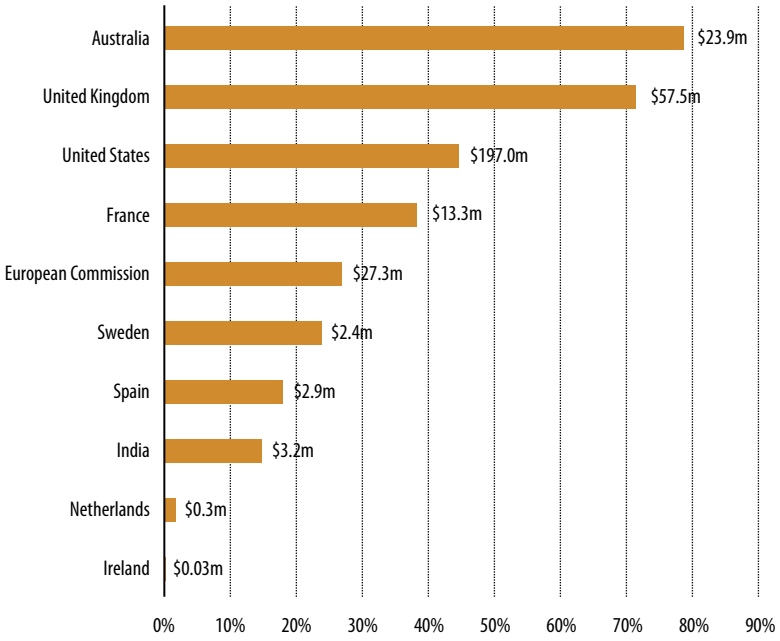
† The apparent drop in German funding in 2008 was mainly due to less comprehensive reporting.

§ Subtotals for 2007 and 2008 top 10 reflect the top funders for those respective years, not the top 10 for 2009.

Government funding patterns

Funding patterns differ markedly between governments, reflecting their differing agendas, funding structures and research capacities. By far the most striking difference is a marked preference in some countries for funding basic research while others predominantly fund applied research and product development.

FIGURE 10. **Investment in basic research for the top 10 funding countries, 2007–2009**



These funding patterns chiefly depend on the nature of the primary organisation funding malaria R&D in a given country, be it an overseas development assistance agency or a domestic research funding agency. Governments of countries such as Ireland and the Netherlands disburse much or all of their malaria R&D funding through their overseas aid agencies, which often fund product development partnerships (PDPs): this leads to a high level of funding for applied research into new product development. In contrast, governments such as those of the United States, the UK and Australia disburse the majority of their malaria R&D funding through health research agencies, which predominantly or entirely fund domestic academic groups: this leads to a high level of funding for basic rather than applied research.

Funding decisions are also influenced by domestic researchers: countries with larger and more developed malaria research communities (particularly academic communities) are more likely to direct a significant proportion of their funding to these researchers to conduct basic research.

Malaria product developers

Just who receives the funding to conduct malaria research and product development is the other side of the malaria coin.

Between 2007 and 2009, nearly two-thirds of malaria R&D by value was conducted by public institutions and academic groups, which received $945.1 million (63%) of the $1.7 billion invested in malaria R&D.[x] Industry was responsible for just less than a third ($468.2 million)[xi]

[x] The amount of funding invested in or by a group is used as a proxy for their activity.

[xi] This figure does not include the $20 million estimated industry investment in vector control R&D from 2007 to 2009.

of malaria R&D. The involvement of public and industry groups varied widely between R&D areas, with academic and public groups accounting for more than two-thirds of all basic research, while industry was more heavily involved in drug and vaccine R&D—accounting for about half the activity in each sector—and also in vector control R&D, for which estimates suggest industry might account for around one-third of all investment.

Many of these R&D groups were funded by PDPs, which also played a key role in portfolio and project management. Indeed, PDPs were responsible for managing around a quarter of all funding directed to malaria R&D, and as much as 40% of diagnostic R&D activity. We have therefore also noted for each area the extent to which the product developers were funded by PDPs.

When interpreting this information, please note that the amount of funding invested in R&D by each group has been used as a proxy for activity; however, this does not necessarily match the number of projects conducted by each group, since more advanced projects necessarily cost more than early-stage projects, while different R&D organisations and sectors can have very different cost structures.

Basic research

Virtually all basic research was conducted by public institutions and academic groups, with PDPs responsible for just 4% in 2009 ($5.4 million). Reflecting their focus on product development, this accounted for only 5% of all malaria R&D funding disbursed by PDPs. In contrast, 40% of all funds received by academic and public research institutes in 2009 went to basic research.

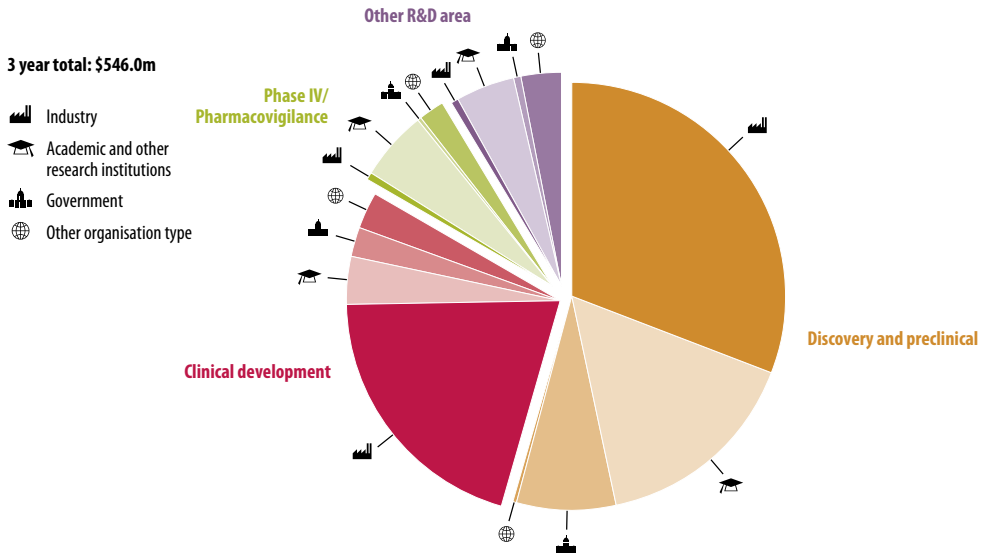
Drugs

Although industry represented only one-third of malaria research overall, it accounted for just more than half (52%, $283.8 million) of malaria drug development. Company activity was strongly focused on upstream research such as drug discovery and preclinical testing (60% of total industry activity), with a further two-fifths (39%) spent on clinical drug development. Industry played a dominant role in malaria drug discovery and preclinical and clinical development, but only a very minor role in Phase IV/pharmacovigilance studies in developing countries.

Government and academic institutes accounted for two-thirds of global malaria research but only 40% of malaria drug R&D. These groups mainly focused on drug discovery and preclinical testing (59% of total public group activity), while clinical drug development and Phase IV/pharmacovigilance studies accounted for 15% and 14% of total activity respectively. Government and academic groups played a key role in drug discovery and preclinical testing (42% of all activity), with two research institutes within the US Department of Defense (DOD), the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center, accounting for nearly all government activity in these areas ($37.6 million, 89%). Government and academic groups also took the lead in Phase IV/pharmacovigilance studies but, perhaps surprisingly, played only a minor role in clinical trials of malaria drugs in developing countries.

PDPs were collectively responsible for a quarter ($141.3 million) of all drug R&D funding, with one PDP alone—Medicines for Malaria Venture (MMV)—accounting for almost all of this ($123.4 million).

FIGURE 11. **Malaria drugs: Analysis of R&D activity, 2007–2009**



Vaccines

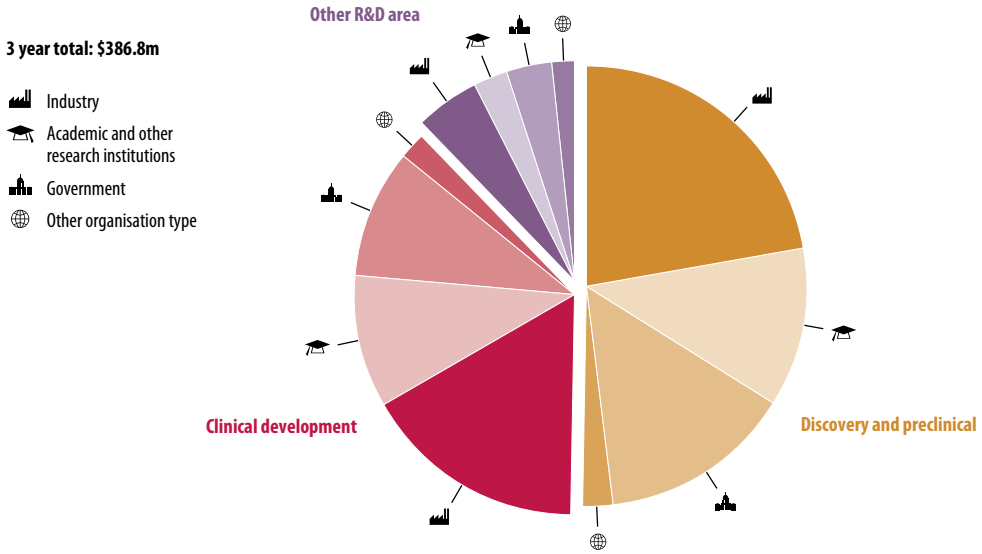
Although pharmaceutical companies also played a major role in vaccine development, there was not the same dominance as evident in drug R&D, with government and academic groups conducting as much or more activity than industry in every area of vaccine R&D (see Figure 12). This difference likely reflects the much higher costs of vaccine development, which industry can be reluctant to bear alone, as well as the presence of large malaria vaccine programmes within public research institutes.

Industry accounted for 44% ($168.3 million) of vaccine R&D activity divided fairly equally between multinational pharmaceutical companies (MNCs) and smaller pharmaceutical and biotechnology firms (SMEs), and between upstream discovery and preclinical (51%) and clinical vaccine development (38%)—likely reflecting GlaxoSmithKline's extensive involvement in clinical trials of the RTS,S vaccine.

Government and academic groups accounted for 51% of global vaccine activity, also divided fairly evenly between discovery and preclinical work and clinical product development. Within the government sector, US research institutions again dominated, in particular the Malaria Vaccine Development Branch of the US NIH and the Naval Medical Research Center and WRAIR at the US DOD, which accounted for 41% of all government activity and 21% ($79.9 million) of global vaccine R&D activity.

PDPs provided $108.9 million to vaccine development over the three years, accounting for more than a quarter of all malaria vaccine R&D activity, 82% of which came from MVI, which is co-developing the RTS,S vaccine.

FIGURE 12. **Malaria vaccines: Analysis of R&D activity, 2007–2009**



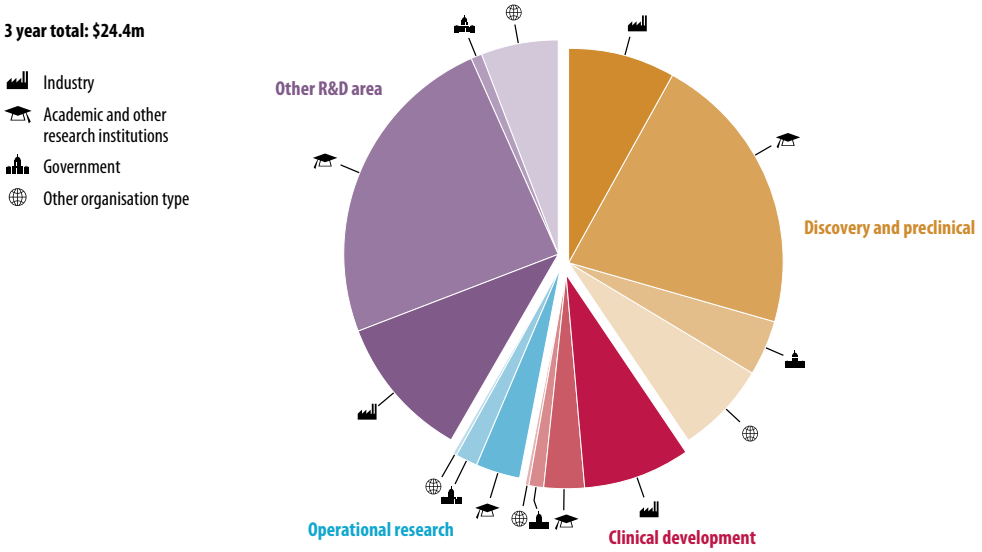
Diagnostics

The paucity of malaria diagnostic funding (around 1% of global malaria R&D funding per year from 2004 to 2009) means caution must be exercised in drawing conclusions. That said, a few salient points can be noted, in particular that diagnostic R&D activity was far more reliant on the public sector than was the case for drugs or vaccines. Public groups, both government and academic, were responsible for the majority of diagnostic R&D, accounting for 60% of global activity. Academic diagnostic funding tended to consist of small grants to many institutions; however, three academic institutions—Royal Tropical Institute, National Bioproducts Institute and the University of Oxford—accounted for more than one-third of global diagnostic activity, collectively representing more activity than all companies combined.

While a high level of public involvement in operational diagnostic research was to be expected (e.g., cost-effectiveness studies and large-scale demonstration studies to assess suitability in developing countries), the public sector also played an unexpectedly dominant role in diagnostic discovery and preclinical, accounting for 64% of all R&D activity compared to the same stage for drugs (29%) and vaccines (24%). This was particularly striking given that public costs can often be lower than private-sector costs, suggesting that the public sector was responsible for well more than two-thirds of all malaria diagnostic discovery and preclinical development projects.

PDPs provided 40% ($9.9 million) of total diagnostic R&D funding over the three years, with just more than half of this amount disbursed by the Foundation for Innovative New Diagnostics (FIND).

FIGURE 13. **Malaria diagnostics: Analysis of R&D activity, 2007–2009**



Vector control products

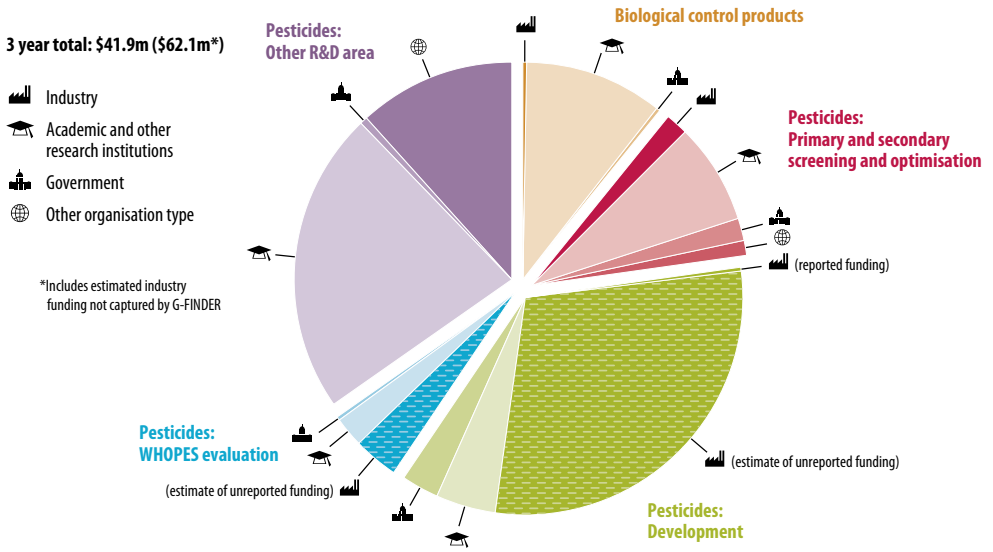
As noted earlier, uneven and patchy reporting and lack of complete industry data means R&D activity in this area cannot be reliably analysed using only G-FINDER data. In this section, expert estimates of industry investment are included to provide a better picture (see Figure 14).

Based on these supplemented data, public groups (academic and government institutions) were the main players in vector control R&D, conducting around half (53%) of all R&D and dominating biological control product development and early-stage pesticide R&D. Industry accounted for a third (34%) of all estimated activity, predominantly in the clinical development stage, but also accounting for around half of World Health Organization Pesticide Evaluation Scheme (WHOPES) activity.

PDPs provided $7.9 million for vector control R&D funding over the three years, accounting for a fifth of all reported malaria vector control R&D activity (13% if industry estimates are included), 86% of which came from IVCC.

Further analysis of vector control activity by R&D stage is unreliable due to the degree of uncertainty surrounding industry data and the lack of breakdowns for biological control R&D. This is partly because vector control R&D categories are not as well defined as for other products, with no clear consensus among product developers on the terminology for the different research stages.

FIGURE 14. **Malaria vector control products: Analysis of R&D activity, 2007–2009**



* Includes estimated industry funding not captured by G-FINDER.

Malaria R&D funding flows: How is malaria funding disbursed?

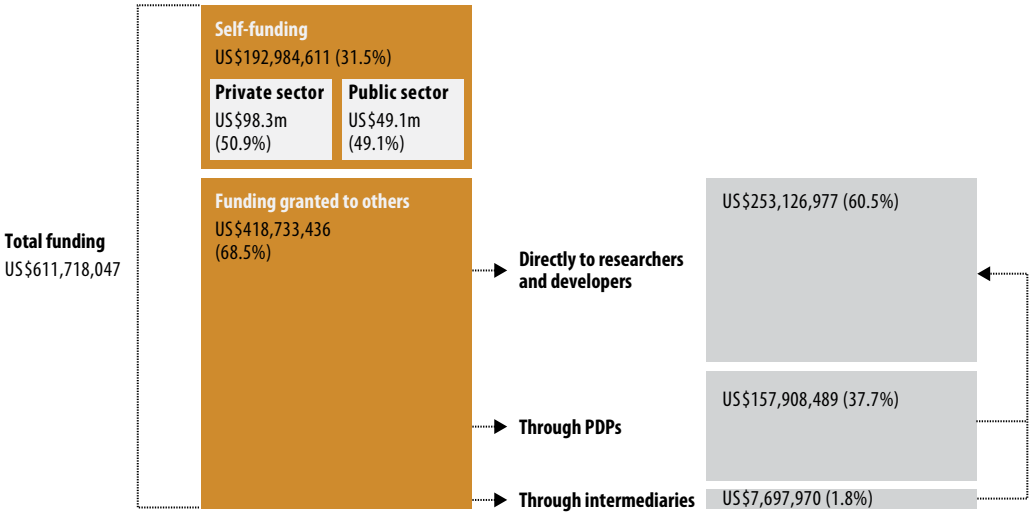
Although a picture now exists of who provides malaria R&D funding and which groups use this funding to create which new products, it is helpful to understand how funding moves from one group to the other, including the role of intermediary fund managers such as PDPs.

In practice, funders disburse their R&D investments in three main ways:

- Self-funders (internal investment)—typically large pharmaceutical firms, but also government institutions such as the US DOD—use their own budget to fund internal R&D programmes.
- Extramural funders provide grants either directly to external researchers and product developers, or through intermediary organisations like PDPs, which then distribute these funds onward to developers in their product portfolios.
- Some funders, such as the US NIH, use a mixed model of providing funding to external groups but also investing in their own internal research programmes.

More than two-thirds of malaria R&D funding in 2009 was in the form of extramural grants ($418.7 million), while internal investment (self-funding) accounted for the remaining third ($193.0 million) (see Figure 15). Around 60% ($253.1 million) of these external grants were given directly to researchers and developers, while just less than 40% ($165.6 million) was channelled through fund managers such as PDPs and other intermediaries, which then distributed these funds onward to selected researchers and developers. PDPs were by far the most significant fund managers in the malaria field, with other intermediaries managing less than 2% ($8 million) of external grant funding in 2009.

FIGURE 15. **Funding flows, 2009**



From 2004 to 2009, there was a modest trend toward both increased internal investment and increased funding through PDPs, compared to direct grants to researchers and developers. As a result, funds managed by PDPs and other intermediaries nearly doubled between 2004 and 2009 (up $79 million, 91%), representing a 3% increase in their overall funding share. This trend has since changed, as discussed below.

Self-funding (internal investors)

The public and private sectors each invested just less than $100 million in their own internal malaria R&D programmes in 2009. This represented virtually all the industry investment (since companies rarely provide grants to others) but less than a fifth (18%) of public investment in malaria R&D, since most public funders also provide extensive grants to external researchers and developers. In the public sector, more than two-thirds of all internal investment was accounted for by just three large public research institutes: the US DOD, US NIH and UK Medical Research Council.

Large multinationals dominated private-sector internal investment, since larger firms have far greater resources and capacity to devote to generally low-profit malaria research, which is often done under the banner of Corporate Social Responsibility (CSR). The significantly lower investment by SMEs is explained by their limited capacity to self-fund or to maintain CSR programmes, with small firms often relying on grants from public funders or PDPs to work in low-profit neglected disease areas (we also note that the apparent increase in SME investment in 2009 is mostly an artefact of survey expansion that year).

TABLE 3. **Top 10 self-funders for malaria R&D, 2007–2009**

Funder	2007	2008*	2009*	3-year average
Multinational pharmaceutical companies	80,102,177	80,629,333	80,785,723	80,505,745
US Department of Defense	26,260,000	22,581,732	34,621,473	27,821,068
US National Institutes of Health	19,874,188	26,900,727	23,349,745	23,374,887
Small pharmaceutical and biotechnology firms	10,102,063	9,489,843	17,480,377	12,357,428
UK Medical Research Council	14,400,659	13,428,850	16,983,582	14,937,697
Institut Pasteur	13,142,888	7,712,808	7,067,036	9,307,577
Indian Council of Medical Research**	–	8,913,969	6,500,473	7,707,221
Inserm–Institute of Infectious Diseases†	472,815	459,077	3,541,558	1,491,150
US Centers for Disease Control and Prevention	1,564,682	1,185,650	893,235	1,214,522
National Bioproducts Institute	–	351,370	789,441	570,406
Top 10 self-funders subtotal	**165,967,461**	**171,653,360**	**192,012,641**	**176,544,487**
Subtotal all self-funders§	**165,967,461**	**172,089,432**	**192,984,611**	**177,013,835**
Total R&D funding	**495,502,620**	**567,941,623**	**611,718,047**	**558,387,430**

* Figures are adjusted for inflation and reported in 2007 US dollars.

** New survey recipient in 2008; no 2007 data available. The drop in funding in 2009 was likely due to less comprehensive reporting by some of its institutes.

† The apparent increase in self-funding from Inserm is mainly due to more comprehensive reporting.

§ Subtotals for 2007 and 2008 top 10 reflect the top self-funders for those respective years, not the top 10 for 2009.

Grant funding to developers

Three-quarters ($182.7 million) of all direct malaria grants in 2009 went to academic researchers. Although distributed to more than 300 academic research institutions globally, this apparent diversity masked a high level of funding concentration, as 37% of all grant funding (and thus 15% of global malaria R&D funding) went to only ten academic and research institutions.[xii] These groups overwhelmingly focus on conducting basic research or early R&D for drugs and vaccines rather than clinical development.

As noted above, small companies rely heavily on grant funding to conduct malaria R&D. SMEs received 9% ($23.5 million) of malaria R&D grant funding in 2009, with three-quarters of these grants coming from just two organisations, the US NIH and the Gates Foundation. The US NIH provided nearly half ($11.1 million) of all SME grants, mainly through the Small Business Innovation Research scheme set up in 1983 to encourage scientific innovation in small business. A further quarter ($6.3 million) of direct grants to SMEs came from the Gates Foundation. Grant funding to SMEs far outweighed their own internal investments.

[xii] University of Oxford, Liverpool School of Tropical Medicine, World Health Organization Global Malaria Programme, Seattle Biomedical Research Institute, University of Ghana, the Walter and Eliza Hall Institute of Medical Research, University of York, Johns Hopkins University, INDEPTH Network and one undisclosed organisation.

TABLE 4. Top 10 malaria R&D researchers and developers, 2007–2009

Funder	2007	2008*	2009*	2007 (%)	2008 (%)	2009 (%)	% Change 2007-2009
Small pharmaceutical and biotechnology companies	11,749,536	16,927,917	23,495,673	6.1	7.5	9.3	100.0
University of Oxford	14,981,192	14,195,790	17,662,941	7.7	6.3	7.0	17.9
Liverpool School of Tropical Medicine (LSTM)**	39,632,036	15,718,819	17,257,106	20.5	7.0	6.8	-56.5
World Health Organization Global Malaria Programme	–	–	10,691,839	–	–	4.2	–
Seattle Biomedical Research Institute	7,887,861	8,396,879	9,338,221	4.1	3.7	3.7	18.4
University of Ghana	–	–	8,584,832	–	–	3.4	–
Foundation for the US National Institutes of Health	–	–	7,248,478	–	–	2.9	–
The Walter and Eliza Hall Institute of Medical Research	6,057,653	6,802,530	6,461,269	3.1	3.0	2.6	6.7
University of York	4,234,306	3,762,259	6,236,368	2.2	1.7	2.5	47.3
Johns Hopkins University	3,042,687	3,720,638	6,142,723	1.6	1.7	2.4	101.9
Top 10 researchers and developers subtotal†	**101,953,239**	**100,414,340**	**113,119,450**	**52.6**	**44.6**	**44.7**	**11.0**
Subtotal all researchers and developers	**193,796,077**	**224,957,704**	**253,126,977**	**100.0**	**100.0**	**100.0**	**30.6**
Total R&D funding	**495,502,620**	**567,941,623**	**611,718,047**				

* Figures are adjusted for inflation and reported in 2007 US dollars.

** The apparent funding drop for the LSTM in 2008 was due to funding for IVCC, which in 2007 was reported by the host organisation (LSTM), but in subsequent years was reported directly by IVCC.

† Subtotals for 2007 and 2008 top 10 reflect the top funders for those respective years, not the top 10 for 2009.

The role of product development partnerships

PDPs currently manage around one-quarter of all malaria R&D funding, and around half of all drug and vaccine projects in the global malaria R&D pipeline (56% of vaccine projects; 51% of drug projects).[xiii]

PDPs are defined here as public-health-oriented, not-for-profit organisations that use public and philanthropic funds to drive product development for neglected diseases. PDPs create new products by sourcing a portfolio of promising leads from industry and academia, utilising private-sector portfolio and project management practices (to a greater or lesser degree) to supervise and manage further development of these. Funding is, as noted, provided primarily by public or philanthropic funders, while R&D is generally conducted in collaboration with industry, public partners or contractors. Additionally, many PDPs conduct global advocacy

[xiii] This does not include the lead-generation phase, as it is not possible to accurately quantify project numbers. There are insufficient data on the global vector control and diagnostic pipelines to calculate the percentage managed by PDPs.

to raise awareness of their target neglected diseases. Although PDPs have greater similarities than differences, they nevertheless vary in some aspects: some are legally independent organisations (e.g., MMV), while others are programmes set up within larger international non-governmental organisations (e.g., MVI, a programme of PATH); some have their own laboratories, while others contract R&D development to external industry and academic partners; some see additional objectives such as capacity-building or technology transfer as a key component of their work, while others are mainly focused on product development.

The major PDPs working in malaria are MVI, the European Vaccine Initiative and the Infectious Disease Research Institute, developing malaria vaccines; MMV and Institute for One World Health, developing malaria drugs; IVCC, developing vector control products; and FIND, creating new malaria diagnostics (see Table 5).[xiv] While not a formal PDP, the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR) also has a malaria R&D programme.

There has been substantial growth in PDP funding since PDPs were first established in the late 1990s, to the point that by 2009, PDPs managed $157.9 million of malaria R&D funding, representing around a quarter of total malaria R&D funding and nearly 40% of all malaria grant funding. Malaria PDPs saw a significant *overall* funding increase between 2007 and 2009; however, virtually all of this was due to a seven-fold increase in funding for MVI (up $65.7 million) to support RTS,S vaccine development. This increase was, in turn, offset by funding drops for MMV and the Drugs for Neglected Diseases initiative (DNDi) coinciding with conclusion of large-scale Phase III clinical trials for several drugs that successfully progressed to registration. Once these portfolio-related funding changes are taken into account, most malaria PDPs are shown to have stable or even decreased funding over the period 2007 to 2009.

[xiv] DNDi developed two malaria drug reformulations, but has now moved out of malaria.

TABLE 5. **Funding to malaria PDPs, 2007–2009**

PDPs	2007	2008*	2009*	2007 (%)	2008 (%)	2009 (%)
PATH Malaria Vaccine Initiative	11,043,173	71,889,028	76,763,432	8.7	45.9	48.6
Medicines for Malaria Venture	75,982,931	46,030,619	41,804,090	59.7	29.4	26.5
Innovative Vector Control Consortium**	12,466,009	9,633,911	13,337,199	9.8	6.1	8.4
World Health Organization Special Programme for Research and Training in Tropical Diseases	9,884,600	8,605,136	7,781,139	7.8	5.5	4.9
Infectious Disease Research Institute	–	3,747,191	5,712,534	–	2.4	3.6
European Vaccine Initiative	7,745,898	4,398,783	3,877,131	6.1	2.8	2.5
Foundation for Innovative New Diagnostics	229,555	2,902,787	3,860,709	0.2	1.9	2.4
Institute for One World Health	7,242,438	8,751,847	3,855,569	5.7	5.6	2.4
Drugs for Neglected Diseases initiative	2,591,609	786,988	916,684	2.0	0.5	0.6
Total funding to PDPs	127,186,214	156,746,290	157,908,489	100.0	100.0	100.0

* Figures are adjusted for inflation and reported in 2007 US dollars.

** The IVCC figure for 2007 was reported by its host organisation, the Liverpool School of Tropical Medicine.

These figures represent only malaria-related funding. Many of these PDPs work in multiple disease areas, so amounts do not represent their full revenue.

Who funds product development partnerships?

The Gates Foundation provided more than three-quarters of malaria PDP funding in 2008 and 2009, while just six organisations provided more than 90% of PDP funding each year between 2007 and 2009, including smaller contributions (2% to 6%) from aid agencies of the United Kingdom (Department for International Development [DFID]), United States (US Agency for International Development [USAID]), Spain (Ministry of Foreign Affairs and Cooperation for Development [MAEC]) and the Netherlands (Netherlands Directorate-General for International Cooperation [DGIS]), as well as Wellcome Trust (see Table 6).

Several aid agencies used PDPs as their only channel to finance malaria R&D; for example, the UK, Spanish and Irish aid agencies provided all their malaria funding through PDPs. By contrast, the US NIH provided only 0.9% of its malaria funding through PDPs (compared to 67% of funding to external researchers and developers).

TABLE 6. Top malaria PDP funders, 2007–2009

Funder	To PDPs 2007*	To PDPs 2008*	To PDPs 2009*	% of 2009 malaria funds given to PDPs	Share of total PDP funding 2009 (%)
Bill & Melinda Gates Foundation**	83,567,215	122,359,675	120,046,430	65.1	76.0
UK Department for International Development	6,343,903	4,878,960	8,582,482	100.0	5.4
US Agency for International Development	5,325,000	4,726,926	4,373,248	53.6	2.8
Spanish Ministry of Foreign Affairs and Cooperation for Development	236,140	3,934,942	4,155,817	100.0	2.6
Netherlands Directorate-General for International Cooperation	5,928,209	3,450,753	3,985,396	84.6	2.5
Wellcome Trust	4,003,611	3,733,433	3,588,731	13.2	2.3
IrishAid	5,578,175	2,659,697	2,613,696	100.0	1.7
ExxonMobil Foundation†	1,543,173	1,298,296	1,352,914	100.0	0.9
Swedish International Development Agency	1,876,589	1,865,346	1,262,790	78.0	0.8
US National Institutes of Health	1,056,231	1,030,548	1,064,686	0.9	0.7
Subtotal top 10 PDP funders§	**119,518,666**	**150,209,897**	**151,026,191**		**95.6**
Total PDP funding	**127,186,214**	**156,746,290**	**157,908,489**		

* Reported in US dollars.

** The 2007 figure includes a grant reported by the Liverpool School of Tropical Medicine as a host for IVCC.

† Contributions compiled from grant information provided by funding recipients, so may be incomplete.

§ Subtotals for 2007 and 2008 top 10 reflect the top funders for those respective years, not the top 10 for 2009.

Several organisations increased their investment in malaria PDPs between 2007 and 2009, including the Gates Foundation ($36.5 million, 44%), Spanish MAEC ($3.9 million, 1660%) and UK DFID ($2.2 million, 35.3%). The increase by the Gates Foundation was related to RTS,S funding, as noted above, while DFID's increase was in line with its research strategy for 2008–2013, which includes increased funding to PDPs working in priority diseases.[24] Decreases in funding were observed over the same period from some aid agencies, including IrishAid ($3.0 million, –53%), DGIS ($1.9 million, –33%) and the Swedish International Development Agency ($0.6 million, –33%). In some cases, this was likely due to the impact of the global financial crisis; however, it may also partially reflect a general trend toward decreased PDP funding.[23]

Reliance on a small number of PDP funders can make life difficult and tenuous for malaria PDPs, since a policy shift by a single funder can have a potentially severe impact on portfolios that are mid-stream in the development process.

Who do product development partnerships fund?

Of the $157.9 million received by PDPs in 2009, $113.6 million was used to fund malaria R&D. The difference between the two figures can be attributed to administration, advocacy, communications, and fundraising costs, along with non-R&D access and delivery initiatives,

which are excluded from the assessment of R&D spending, as well as being a temporal artefact of the survey, caused by the delay between funds being received by a PDP and then disbursed in onward grants. In line with the $30.7 million increase in funding to malaria PDPs between 2007 and 2009, their R&D expenditure increased by $32.4 million (40%) over this time.

Expenditure fell into two categories: the first, funding disbursed to external partners (by far the majority of funding), such as academic research institutions, contract research organisations and private companies in developed and developing countries (91%, $102.8 million); the second, investment by PDPs in their own laboratories and R&D staff (10%, $10.8 million).

Around two-fifths of malaria PDP investment in 2009 ($49.2 million, 43%) went to the for-profit private sector, with well more than half this amount (58%, $28.4 million) going to SMEs and the remaining $20.8 million (42%, or 18% of the total) going to MNCs, a picture essentially unchanged since 2007. Academic and other research institutions received two-fifths of PDP R&D expenditure in 2009 ($47.8 million, 42%), although trends in academic funding cannot be analysed due to lack of detailed data from earlier years.

FIGURE 16. **Funding disbursed by PDPs, 2009**

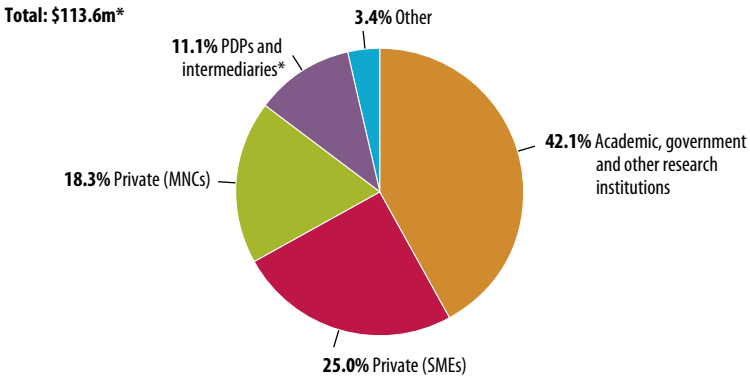


Figure differs from the $157.9 million reported as received by PDPs in 2009 due to exclusion of administration and advocacy costs from the assessment of R&D spending, as well as a temporal artefact of the survey, caused by the delay between funds being received by a PDP and then disbursed in onward grants.

*The 'PDPs and intermediaries' category includes both intramural investments (self-funding) and funding given from PDPs to other PDPs.

Other intermediaries

Like PDPs, other intermediaries also receive R&D funds and are dedicated to a specific non-profit research aim, but, unlike PDPs, they more often represent a consortium of organisations and do not normally use private-sector management practices. In general, they disburse these R&D funds to external product developers rather than conducting product development themselves. Examples of intermediary organisations include the European and Developing Countries Clinical Trials Partnership (EDCTP), a partnership of several European and developing countries that offers grants to support clinical trials for HIV/AIDS, malaria and tuberculosis products, and the Multilateral Initiative on Malaria, which aims to develop sustainable malaria research capacity in Africa and raise international awareness of the disease.

In 2009, these other intermediaries received $7.7 million, which represented 1% of total malaria R&D funding and 1.8% of all extramural funding. This was a two-thirds decrease from their 2007 funding level of $13.3 million. The EDCTP was the highest-funded intermediary, receiving $6.3 million; the European Commission was the key funder of intermediaries, providing $4.8 million.

If malaria R&D funding trends over the past five years continue on their upward path, we will stay well on track to meet the R&D funding target. However, very substantial funding gaps now exist for some malaria product portfolios, in particular diagnostics and vector control products. This discrepancy needs to be rectified if global malaria goals are to be met.

SECTION TWO

Estimating the funding gap

THIS SECTION USES THE R&D FUNDING DATA DESCRIBED IN SECTION 1 to assess progress against the GMAP R&D funding goals to date, and to identify what will be needed in the coming decade to deliver the suite of products needed to manage, eliminate and—ideally—eradicate malaria from the world.

Forward funding estimates use, as a starting point, assumptions in the GMAP[3] model, including projections of the number of new tools needed to achieve malaria elimination and eradication from 2008 to 2050, products needed, the time period in which they should be developed and their estimated cost of development. However, it is important to note that these assumptions and the model itself have been significantly amended and updated to reflect additional data and changes in the malaria field since GMAP's publication, including publication of Malaria Eradication Research Agenda (malERA) reviews.[25] This new model and the updated assumptions are referred to as GMAP-Plus to reflect our debt to GMAP, but also the substantial work to develop an updated model (see Annexe 2 for the full methodology).

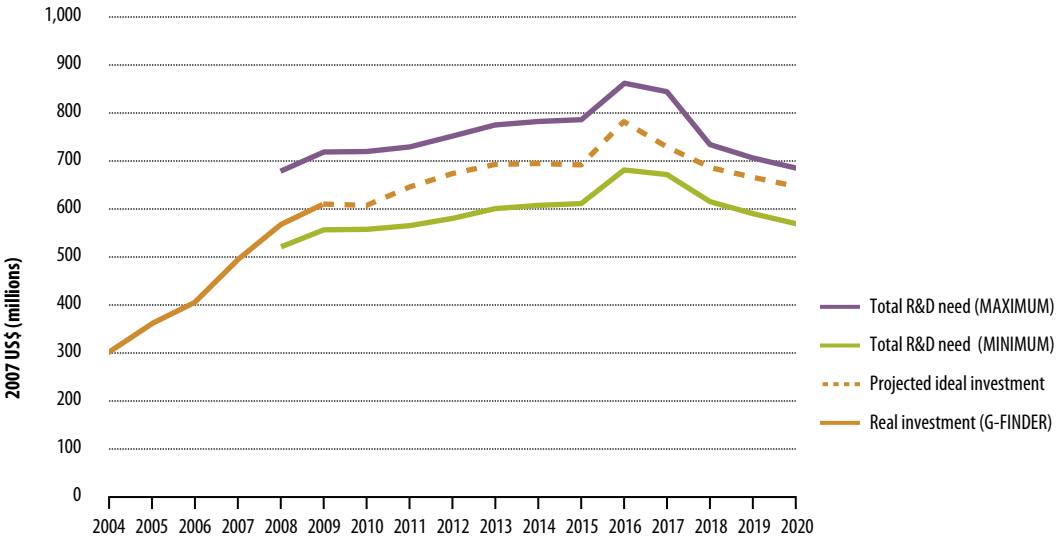
A key point to keep in mind when reading this section is that both GMAP and GMAP-Plus are based on estimations of the R&D funding needed to create an 'ideal' portfolio of new malaria products. In other words, they assume donors are working toward developing the ideal toolbox of new drugs, vaccines, diagnostics and vector control products defined by the international community as necessary for malaria management, control and elimination. The more that R&D activity deviates from this goal—for example, if donors fund duplicative projects or domestic projects that may not match these goals, or do not coordinate their funding efforts—the greater the R&D funding shortfall will be, since funding needed to achieve the ideal portfolio of products will instead be invested in potentially superfluous other projects. This would increase funding needs far beyond what is estimated here. This report (and its funding projections) assumes this will not be the case.

The overall funding gap

The good news is that malaria R&D funding for the past five years has been on track to meet the global community's R&D product development goals. In further reassuring news, if malaria R&D funding trends over the past five years continue on their upward path, we will stay well on track to meet the R&D funding target: there will be no funding gap. This would achieve two important outcomes: first, vital new products to deliver malaria control, elimination and eventually (and ideally) eradication will begin to sequentially appear in public health toolkits and be available to patients in the next few years (several already are); and, second, funders will be able to begin reducing their malaria R&D investments around six years from now, in 2017, as these product goals are achieved.

Total malaria R&D funding need is projected to increase at a modest 2% per year from funding of $612 million in 2009 to a maximum of $690 million in 2015. Investment needs then spike to around $785 million in 2016 (a rise of about 15%), largely due to the funding needed to develop the next generation of malaria vaccines (see Figure 17). Thereafter, funding needs are projected to decrease by about 5% per year as an increasing number of products finish costly late-stage clinical trials and become available for implementation in endemic countries.

FIGURE 17. **Projected malaria R&D funding need, 2004–2020**



However, this promising overall picture has significant provisos. In particular, while funding levels and targets are realistic and feasible, the apparent close match between current and projected funding needs is actually the net effect of high and low spending across different product areas, with very substantial funding gaps now existing for some malaria product portfolios, in particular diagnostics and vector control products. This discrepancy needs to be rectified if global malaria goals are to be met.

Funding gap by product

Drugs

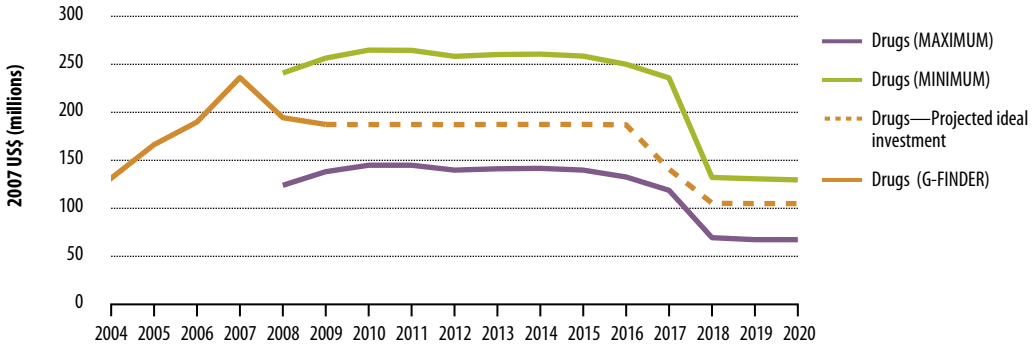
Spending levels for malaria drug R&D are on track, but only if the recent downward trend is halted now. Maintaining present levels of investment for the next five to six years would allow malaria drug R&D funding to then be roughly halved, from current levels of around $190 million per year to an average of a little more than $100 million per year from 2016 onward (see Figure 18).

Annual R&D funding for malaria drugs, including both preventives and therapeutics, needs to stay at current levels (in the range of $140 million to $260 million) until at least 2016 to cover the development cost of several products expected to become available. R&D is needed to develop new, improved therapies, such as a single-dose cure to replace the current three-day drug regimen and more formulations that are safe and suitable for children (there is currently only one registered paediatric formulation). Other drugs that are needed in the near future include more treatments for pregnant women (Pfizer/MMV's azithromycin-chloroquine is currently in Phase IIb/III), a radical cure for *P. vivax* (GlaxoSmithKline/MMV's tafenoquine is currently in Phase I) and novel compounds to tackle artemisinin resistance and transmission-blocking antimalarials. Phase III clinical trials for a number of new chemical entities (NCEs) will also likely be completed by 2016, hopefully resulting in the registration of a next-generation artemisinin-based combination therapy (ACT). R&D funding can then return to baseline levels averaging a little more than $100 million per year (in the range of $70–130 million) from 2018 onward to fund ongoing development of back-up novel compounds and reformulations to address the inevitable risk of resistance to any antimalarial.

However, if malaria drug R&D investment does not stabilise at current levels and continues its decline, we can expect to begin seeing discontinuation or slowing of drug projects now underway by 2014 or earlier, this being the point at which investment would fall to less than the projected level needed to maintain even the minimum necessary portfolio. This would result in substantial waste of prior investment in these projects.

A further point to consider is that the malaria community may want to accelerate development of new products, in view of resistance, among other factors. The funding projections shown here are based on current R&D timelines and delivery of products over the next five to six years. Accelerating these timelines and delivery goals would increase our short- to mid-term funding projections substantially; i.e., it would require more up-front funding. Evidence exists that additional funds can indeed lead to shorter R&D timelines, resulting in products reaching patients faster.[14]

FIGURE 18. **Projected malaria drug R&D funding need, 2004–2020**



Vaccines

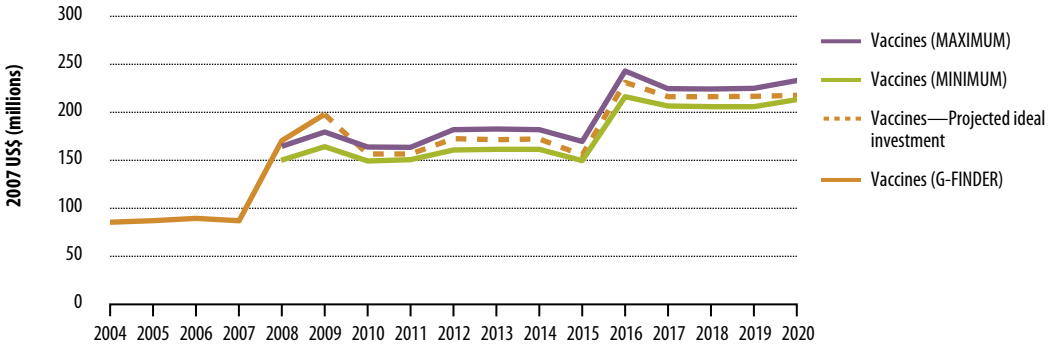
Vaccine R&D funding demand is far more irregular than for drugs, since vaccine development usually involves very small numbers of candidates going into highly expensive late-stage trials at widely spaced intervals. For instance, the 2010 funding peak reflects advanced trials of the RTS,S vaccine candidate, with a second peak not expected until 2016, when a second-generation *P. falciparum* malaria vaccine is expected to go into large trials (see Figure 19).

In fact, vaccine funding is relatively secure in the short term, with the recent disbursement of large, up-front, multi-year grants resulting in the current level of funding appearing to exceed projected funding need. Two large grants were disbursed in 2008 and 2009, to provide multi-year funding for Phase III clinical trials of the RTS,S vaccine candidate and research into the next-generation *P. falciparum* vaccines, and were responsible for much of the dramatic increase in investment in malaria vaccine R&D since 2007.

A significant drop in investment of up to 20% is therefore likely (and sensible) in 2010–2011 as these trials move toward conclusion. Steady investment of around $155–170 million per year will then be needed through to 2015 to fund a series of activities, including Phase IV trials of RTS,S, development of a more effective second-generation *P. falciparum* vaccine and new vaccine candidates targeting *P. vivax*. Funding will then likely need to ramp up considerably to $220–230 million per year from 2016 and beyond to fund late-stage trials of the anticipated second-generation *P. falciparum* vaccine, as well as early preclinical work associated with transmission-blocking vaccines, vaccines for pregnant women and candidate vaccines targeting both *P. vivax* and *P. falciparum*.

Although short-term vaccine R&D funding has been secured, allowing investment to drop to less than the projected funding need in the next few years would threaten the continuity of early- and mid-stage projects in the vaccine product pipeline. Funder flexibility will also be essential, especially in anticipating the jump in funding need in the latter half of the decade.

FIGURE 19. **Projected malaria vaccine R&D funding need, 2004–2020**



There are key qualifiers to consider when looking at these vaccine funding projections. As with all product areas, our model assumes a coordinated funding approach applied to a planned portfolio tailored to deliver the necessary products. To be efficient, funding in this high-cost, high-risk area must involve a portfolio-based approach rather than a project-based approach, particularly in those periods following successful registration of a vaccine, when the focus swings back to early-stage research. As a corollary, lack of coordination will require far more funding than projected here. Perhaps more significantly, there is uncertainty surrounding vaccine costs and attrition rates, as a successful malaria vaccine has never before been developed. If attrition is higher than assumed in the model, funding needs will increase commensurately.

Diagnostics

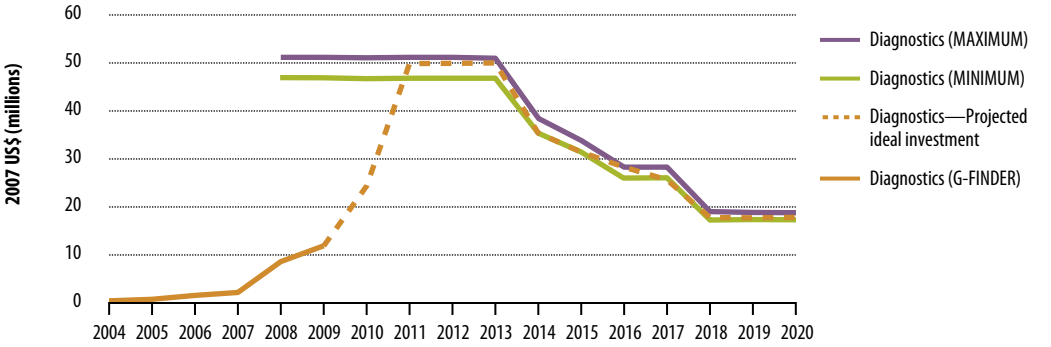
Malaria diagnostic R&D is currently severely underfunded, despite rising investment over the past few years (see Figure 20). Funding for diagnostic development will need to quadruple immediately, from investment of $11.9 million in 2009 to around $50 million per year.[xv] If this increase can be achieved, funding needs would then drop rapidly from 2014 onward, as the first new diagnostics are completed and made available, down to baseline levels of less than $20 million per year from 2018 onward.

Immediate product needs that necessitate an urgent and significant increase in funding include improved quality control methods to ensure the quality and stability of currently available rapid diagnostic tests (RDTs), improved RDTs targeting non-*falciparum* parasites, new and improved tools for field detection of very low-density parasitaemia (including non-*falciparum* parasites) and better screening for enzymatic deficiency (i.e., G6PD deficiency). Other important future targets include automated microscopy and non-invasive sampling (e.g., through analysis of saliva or urine). As countries come closer to elimination, it will become even more important to adapt screening and monitoring strategies so that a possible resurgence of malaria can be picked up rapidly, and to develop tests to detect non-malarial febrile disease pathogens, or markers of infection requiring specific treatment.

[xv] Operational research for diagnostic scale-up and implementation is not included in these figures, as funding estimates for these R&D activities were not available.

Insufficient funding is likely to not only threaten individual projects, but may lead to the demise of entire groups focusing on malaria diagnostic R&D.

FIGURE 20. **Projected malaria diagnostic R&D funding need, 2004–2020**

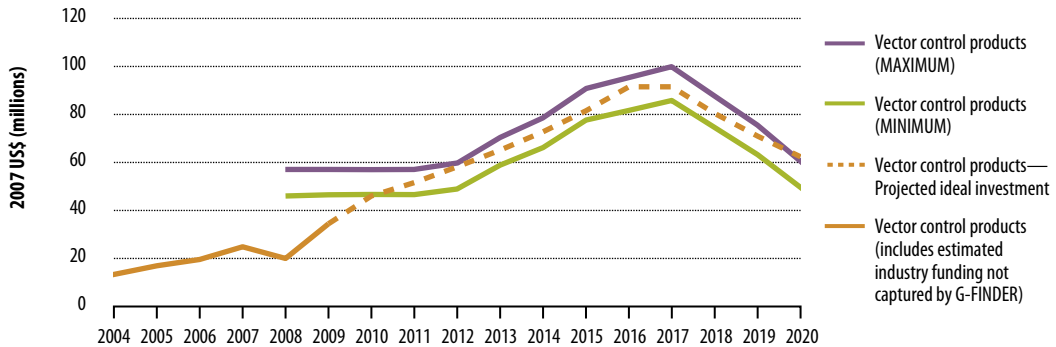


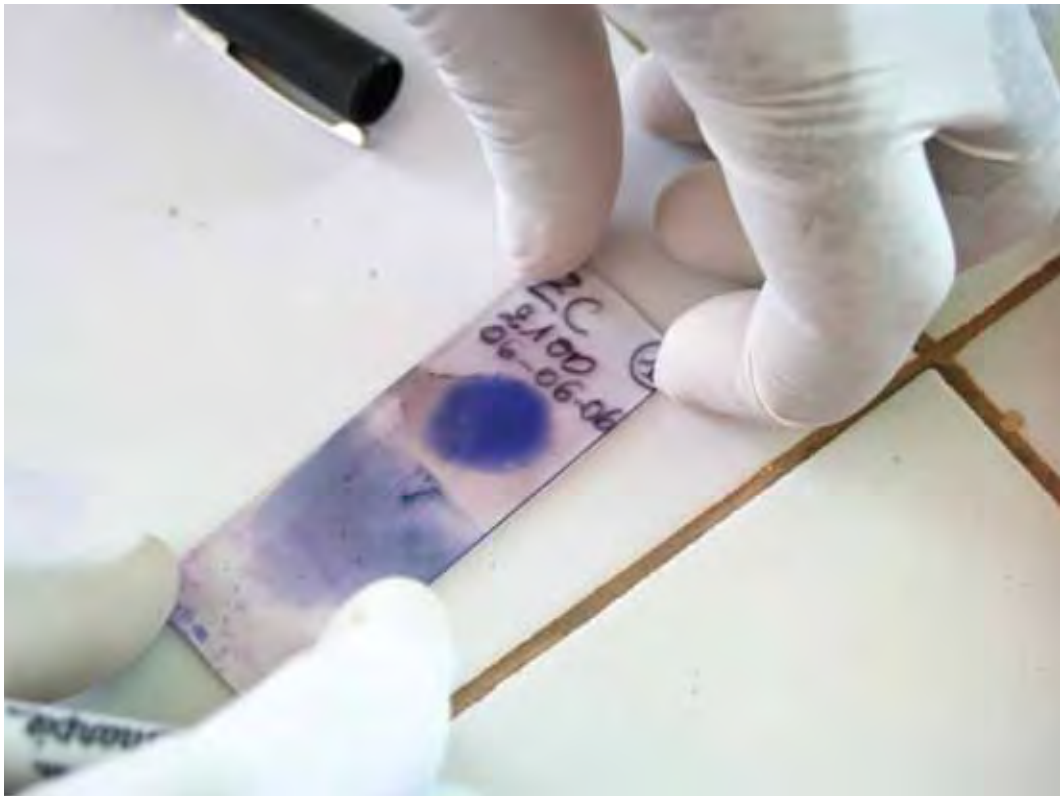
Vector control products

A sole reliance on pyrethroids for malaria vector control is a highly vulnerable strategy due to the risk of resistance, making the development of new active vector control ingredients crucial. However, although interest in vector control R&D has increased since 2008, funding today is still low and will need to increase two-and-a-half-fold in the next five to six years, to a peak of around $90 million per year in 2016–2017. (Estimates of historical industry investment, thought to be in the range of $6.5–7.0 million per year, have been factored into this projection in order to give a more realistic estimate of the funding gap.)

Once the most expensive stages of development of active ingredients have been completed and have resulted in several new compounds, funding needs will drop rapidly, declining by a third between 2017 and 2020. Although funding demand is likely to decline even further after 2020, we note that baseline funding levels will be needed to support proven paradigms such as novel active ingredients for bednets and indoor residual spraying (IRS), as well as exploring new paradigms in insecticide delivery—a field that has yet to gather momentum.

FIGURE 21. **Projected malaria vector control product R&D funding need, 2004–2020**





"Success is very close—closer than ever before in the history of malaria—however, it cannot be achieved without changes to funding and funding patterns…"

SECTION THREE

Discussion

SEVERAL IMPORTANT LESSONS CAN BE DRAWN FROM THIS ANALYSIS. The first is that malaria R&D will not require unlimited funding, but rather has clearly defined goals and known exit points. Several of these have already been achieved through increased investment in malaria R&D since the mid-1990s, which has underpinned development of the strongest-ever pipeline of antimalarial products. This funding has already resulted in the registration or submission to registration of four new ACTs, a new paediatric antimalarial formulation, a modestly effective first malaria vaccine close to registration and an increase in the variety of species-specific RDTs. Donors are well on the way to success, with only a further five to six years of sustained funding effort needed before they can begin to reap the rewards.

A further important lesson is that this R&D funding must be up front to deliver the maximum benefit. Delivering the right amounts of R&D funding in the next five to six years is the key to early delivery of needed products, and thus the saving of many tens of millions of lives. It will also allow donors to begin winding back their malaria R&D funding as early as 2017, as the fruits of their investments are reaped. Providing slow and inadequate amounts of funding over the next five to six years will not only delay the time when donors can begin to reduce their malaria R&D funding but—more importantly—will unnecessarily delay saving millions of lives in the developing world.

We note however that this promising overall picture has significant provisos. The full impact of the global financial crisis is yet to be seen; if this turns out to be severe, investment may rapidly end up off track, leading to delay or termination of promising projects and loss of investments to date. A high proportion of new malaria R&D funding may also be wasted without improved R&D funding policies. In particular, better distribution of funding between product areas; more responsive and flexible funding policies and practices, particularly in the public sector; and far greater coordination of R&D funding across all sectors, public, private and philanthropic. Other specific areas of concern are the dependence on a very small number of funders, and the plateau of funding for PDPs, which now manage just more than half of all products in the malaria product pipeline.

Key messages from these findings are highlighted below.

Modest sustained funding growth is needed

Funding for malaria R&D more than doubled between 1993 and 2004, and has doubled again since, to more than $600 million in 2009. As a result, the malaria R&D community is on track to deliver the new tools necessary to effectively combat malaria. In order to achieve this end, funding growth needs to be maintained over the next five to six years. However, due to the sustained donor effort to date, the rate of growth required in the next few years will be much lower than we have seen in the past decade, at around 2% per year until 2015, with a jump of 15% in 2016. Overall R&D funding demand will also drop substantially in the last half of this decade, as new tools are successfully completed and delivered. However, if funders wish to accelerate R&D timelines and delivery dates, for example, in light of growing resistance to current products, these funding projections will need to change to incorporate earlier peak funding.

Distribution of R&D funding between product areas

The modestly increased funding needs over the next five to six years need to be more efficiently distributed than in the past.

Vaccine and drug R&D each currently receive around a third of all malaria R&D funding. Projections show that drug funding can remain roughly at current levels for the next five to six years (unless accelerated product delivery is desired), while vaccine funding can remain at or even slightly less than current levels for the next three to four years. Funding increases greater than current levels over the next few years should therefore ideally be delivered to vector control and diagnostic R&D, both of which need significantly increased investment to meet even minimum R&D needs. In order to improve on the current generation of RDTs and meet the diagnostic challenges associated with decreasing levels of transmission, current funding for diagnostics should be quadrupled immediately. Similarly, resistance and the need for new vector control tools and paradigms mean vector control funding should increase two-and-a-half-fold over the next five to six years to a peak in 2016–2017.

Once diagnostic funding needs have peaked in 2014, and vector control needs in 2016–2017, the funds released by wind-back of these programmes should be redistributed to malaria vaccine R&D, which will then be seeing peak demand. As we progress toward elimination and eventual eradication of malaria, it will also be vital to ensure that sufficient funding within each product area is devoted to non-*falciparum* malaria strains, noting that just 3% of malaria R&D funding was reported as specifically directed toward *P. vivax* between 2007 and 2009.

We emphasise that redistribution does *not* mean funding for any area should decrease (beyond the already planned drops in vaccine funding related to conclusion of RTS,S trials), rather that proposed increases in funds greater than current levels should be redirected to the extent necessary to currently underfunded areas. We also caution that although funding for drug R&D is currently in line with need, this area has seen a sharp drop in funding over the last two years; this is a trend that will need to be arrested if strong recent progress in this area is to be sustained. Likewise, although vaccine funding appears relatively secure in the short term,

funders will need to maintain investment to underwrite development of new vaccines in the latter half of this decade.

Flexible and responsive funding

An unfortunate hallmark of funding, particularly public funding, is a frequent disconnect between funding levels and product development on the ground. R&D funding should increase when portfolio needs are high, for instance, to fund large-scale trials of new malaria vaccines, and decrease when these periods of peak demand have passed. This type of funding responsiveness is more often seen with industry groups, or with large philanthropic organisations that have the capacity to closely analyse and follow R&D developments by the groups they fund, or which may even fund certain products or stages of development on a contract or milestone basis. However, public funding less often demonstrates this responsiveness.

Public funders will need to be more aware of R&D developments in the global portfolio and of progress against goals, as well as more responsive and flexible in their funding patterns. The reality is that public groups will only be able to fund areas of increased R&D demand if they also wind back or maintain funding to areas in which R&D demand is slowing or steady.

Diversification of funding sources

Malaria R&D funding is troublingly concentrated. Almost three-quarters of global funding for malaria R&D is provided by only nine public and philanthropic organisations. Two of these organisations provided half of all malaria R&D funding—the Gates Foundation (30%) and the US NIH (19%)—and these two also accounted for a striking 85% of the global funding increase for malaria R&D between 2007 and 2009.

The highly concentrated nature of malaria R&D funding renders it extremely susceptible to changing investment decisions from major funders, with obvious implications for risk, funding security and continuity of product development. It also means R&D funding patterns reflect the policies and preferences of only a few organisations. For example, Australia, the fourth largest public funder of malaria R&D in 2009, directs more than three-quarters of its funding toward basic research and provides no funding to PDPs. Similarly, the US NIH gives two-thirds of its malaria funding to external researchers, of which three-quarters goes to basic research, but less than 1% to PDPs.

These preferences play out strongly due to the high concentration of public funding and the key role of a few organisations in malaria R&D funding, and have been an important factor behind the increased investment in basic research between 2007 and 2009. High levels of basic research grants can have implications for matching funding to product need, since grant criteria are often based on quality of the science rather than the degree to which the activity matches developing country application or need, or the overall global product development goals. Likewise, significant growth in internal investment by groups such as the US DOD could be potentially problematic if it results in a shift of R&D focus to military rather than developing country needs.

Coordination of R&D funding

The funding projections in this report are based on the assumption that funders will work together to invest in the desired portfolio of new malaria products. The greater the level of duplication and non-coordination between funders, the longer and more costly it will be to reach these goals—and many may not be reached at all.

Total coordination is not possible, and may not even be desirable; each funder necessarily makes their own funding decisions and must be responsible for their own investments. However, it is desirable and possible to provide enough information for funders to locate themselves on the global R&D funding map in order to voluntarily coordinate their decisions to the extent possible. Indeed, it would be entirely unreasonable to criticise funders for lack of coordination if the tools to make this coordination possible do not exist.

Some fora for coordination do exist, such as WHO's Malaria Vaccine Advisory Committee, an initiative of WHO/TDR and the Initiative for Vaccine Research, and the PDP Funders Group, a network of many of the world's donor governments and philanthropists, chaired by the UK DFID. But these groups do not cover all product areas or all funders, and they rarely incorporate private industry working in the field.

Even when their membership is more comprehensive, coordinating groups may lack the necessary tools. It can be difficult to get an up-to-date overview of all projects in a given field, although some sources now exist, such as the Bioventures for Global Health website, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) updates and the WHO "rainbow" list of malaria vaccine projects. Lack of standardised assays and trials can make comparison of projects difficult, and there are no commonly agreed metrics to review competing portfolios in order to identify which projects should be progressed and which terminated.

Some progress has been made, however. For example, the WHO/TDR targets database[26] and the *Plasmodium* genome resource (PlasmoDB)[27] provide a list of neglected disease drug targets that allows developers to voluntarily line up their activity with global goals (very helpful for investigator-initiated research and small company activity), and work continues on agreeing on standard assay approaches for malaria vaccines. Still, much more is needed; for example, information to identify how funding portfolios overlap, where future funding plans are synergistic/conflicting, progress of projects within the global portfolio and sharing data on project performance.

On a positive note, the concentration of malaria R&D funders may provide a real opportunity to improve information exchanges to allow better-coordinated funding decisions, forward planning and project prioritisation.

Plateau of product development partnership funding

PDPs manage just more than half the global portfolio of malaria products in the development pipeline and around two-fifths of all external grant funding for malaria R&D—a much higher proportion than the PDP average of 23% across all neglected diseases. This share

increased between 2004 and 2009, with total funds managed by PDPs doubling over that period. The strong position of malaria PDPs is reflected in their outcomes, including MVI and GlaxoSmithKline's success in bringing RTS,S to Phase III trials, and likely to registration, as the first-ever malaria vaccine; registration of Coartem® Dispersible (the first paediatric malaria medicine) by MMV; and registration or submission to registration of four new ACTs—Euartesim™, Pyramax®, Coarsucam™ and AS/MQ—by MMV and DNDi.

The plateau of PDP funding in 2008 and 2009 is therefore of concern, particularly within the context of an apparent general trend away from PDP funding, as reported in G-FINDER 2010.[23] With such a large proportion of the global malaria portfolio under PDP management, a significant funding cut to PDPs could have major implications for the future delivery of new products to combat malaria. Malaria PDP funding is also potentially precarious, as the Gates Foundation provides a staggering three-quarters of funding to malaria PDPs—bringing with it the attendant risks of highly concentrated funding, as outlined above.

Conclusions and recommendations

Recent marked increases in malaria R&D funding have moved endemic countries closer to the drugs, vaccines, diagnostics and vector control products needed to control and progressively eliminate and eradicate malaria. Success is very close—closer than ever before in the history of malaria—however, it cannot be achieved without changes to funding and funding patterns, as recommended below:

1. Malaria R&D funding needs to increase modestly for the next five to six years (2% per year until 2015, 15% in 2016) and can then begin to decrease.
2. Funding must be better distributed between product areas. A high percentage of the proposed funding *increase* should be used to support the severely underfunded diagnostic and vector control areas, and greater funds need to be dedicated to *P. vivax* product development.
3. R&D funding, particularly in the public sector, must become more flexible and responsive to global portfolio developments and goals.
4. Funders must be given improved information and tools to allow them to better coordinate funding and portfolio decisions; this includes the public, philanthropic and private sectors.
5. More funders need to become engaged in malaria R&D, including more economically advanced countries (G8/G20/OECD), and research and science and technology agencies in both existing and new donor countries.
6. PDP funding should be maintained, since PDPs account for nearly half of the current product pipeline and virtually all new malaria products delivered in the past five years.

Annexes

Annexe 1. 2011 status of malaria tools

Malaria drugs (by Medicines for Malaria Venture)

Scientific challenges around malaria drug development

Malaria can be cured if treated appropriately and on time. Today, the gold standard for treatment is fixed-dose artemisinin-based combination therapy (ACT).

The scientific hypothesis behind the development of these new, innovative ACTs is to associate the fast-acting artemisinin derivatives, which cure the fever in less than 24 hours and kill all malaria parasites within three days, with at least one month of protection against a new infection (prophylaxis) afforded by the partner drug.

The first challenge in the development of new ACTs was to prove that these drugs would provide a rapid cure as well as prophylactic effects for at least one month. This was proven by conducting clinical trials. With a strong commitment to developing ACTs to the highest possible international standards (International Conference on Harmonisation), MMV and other PDPs had to invest significantly in improving the infrastructure of existing clinical trial centres and in training highly skilled and motivated local teams.

Four ACTs have since been developed. The two frontrunners, which have been prequalified by WHO, are arthemether combined with lumefantrine and artesunate with amodiaquine. Although these drugs are now used to treat 130 million patients per year, they suffer from either twice-daily usage (artemether/lumefantrine) or existing resistance (artesunate/amodiaquine). Two next-generation ACTs, which are expected to gain prequalification by the end of 2011, are combinations of dihydroartesunate with piperaquine and artesunate with pyronaridine.

Malaria is a disease that primarily affects children, a population that requires specific drug formulation and/or treatments. However, for obvious safety and ethical reasons, no new drug is trialled on this special population, only therapies with well-known safety and efficacy profiles. Thus, the most at-risk population will either receive a new drug after a considerable lapse of time compared to adult patients (five to six years), or innovative and accelerated paths to registration of specific treatments must be found. Despite these challenges, child-friendly formulations have been developed and registered and are currently being used in developing countries, contributing considerably to malaria case management.

From a manufacturing perspective, developing ACTs was a challenge, as artemisinin derivatives contain a highly reactive chemical group (peroxide) that makes the final product relatively unstable, with a maximum shelf-life of two to three years. However, as extremely effective anti-malarials, they contribute to better public health management of the disease and have helped to significantly reduce the total number of cases in the region where they were initially deployed. In regions like Zanzibar and Zambia, they have contributed to the near elimination of the disease.

Progress in the past five to ten years

Over the last five years, ten Phase III clinical trials have been completed. Nine of these were sponsored by MMV, enrolling more than 10,000 patients to show that the ACTs being tested were safe and effective. The trials showed that more than 95% of patients had no parasite after 28 days, meeting the WHO criteria for effective malaria treatment.

As a result, two products, Coartem® and ASAQ Winthrop®, have been prequalified by WHO and are available through the public health network and can be procured using donor funds. Coartem® has also been registered by SwissMedic and the US Food and Drug Administration. Coartem® has been used to treat more than 300 million people. In 2010, we estimate that 80 million patients were treated with artemether/lumefantrine—as many as 40 million with the child-friendly medicine. A real breakthrough for the treatment of paediatric malaria was the development and launch of the first high-quality child-friendly formulation, Coartem® Dispersible, in 2009. This product has been enormously helpful to physicians and caregivers treating children younger than 5 years with malaria. As of September 2010, more than 40 million treatments had been distributed in 32 countries. An additional 25 million patients were treated with ASAQ Winthrop® in 2009, with an estimate of 50 million for 2010. This means, 140 million patients received a fixed-dose ACT; in other words, half of all malaria patients were treated with the gold standard treatment.

In November 2010, the WHO Prequalification of Medicines Programme approved an artesunate powder for injection, made to Good Manufacturing Practice (GMP) standards by Guilin Pharmaceutical Co. Ltd, China, in collaboration with MMV. It is now considered the first-line therapy for severe malaria, which affects 5% (12 million) of all malaria patients. Artesunate injection is an important option for patients with severe malaria, as they are often unconscious or likely to vomit an orally administered medication. Results from the largest global clinical trial in patients with severe malaria (AQUAMAT) showed that artesunate should now be the preferred treatment for the disease in both children and adults worldwide, instead of the centuries-old quinine. MMV has been working very closely with Guilin

Pharmaceutical to upgrade their production facilities to international standards as required by the WHO prequalification programme. The major limitation in the use of this product was its cost. Now, this newly prequalified artesunate injection will be available at the same affordable price as the current non-GMP material to countries using donor funds to procure anti-malarials.

Factors that have facilitated or impeded development

The key factors that have facilitated current success are the increased funding, political will and commitment from the international community to eradicate malaria. For example, in 2005, the Bill & Melinda Gates Foundation awarded the first five-year grant to MMV for a total of $137 million, which led to a significant increase in the number of malaria drug projects managed by the organisation. Long-term and sustained commitments to malaria drug R&D from committed donors, among them Wellcome Trust and the UK DFID, has enabled PDPs to secure long-term partnerships with renown academic and pharmaceutical global partners. This has enabled MMV to invest $40 million per year in R&D of new medicines. We estimate the cost to develop a new medicine at around $100 million. For several years now, pharmaceutical companies have been paying greater attention to neglected diseases, including malaria; many more of them are interested in collaborating with PDPs, sharing their capacity, cutting-edge facilities and knowledge of drug discovery and development, as well as offering a higher financial commitment to the process.

The PDP business model followed by MMV, FIND, IVCC and MVI has also been instrumental in the successful development of the malaria R&D portfolio. The strategic decision of industry and academia to collaborate and share the financial risk between donors and developers permitted a significant step forward in addressing the medical needs of neglected diseases of poverty.

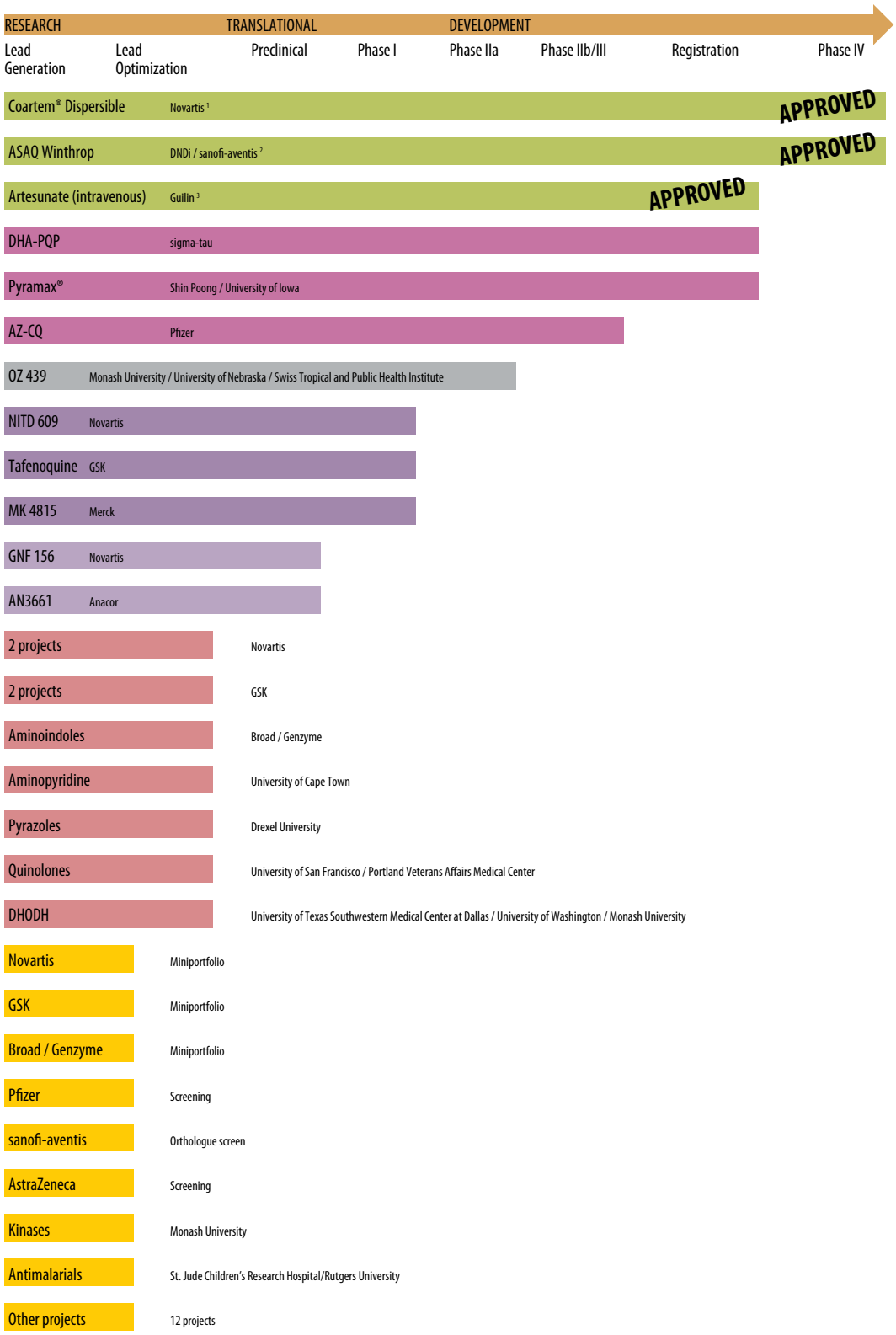
The PDPs have gained trust and respect from their stakeholders and have built strong relationships with key scientific partners in the field. The enhanced funding has allowed increased investment in developing countries as well as strong capacity-building to ensure high-quality standards for clinical trials. This clearly contributes to present and future success. The same efforts remain to be done in strengthening non-clinical research capacities.

The MMV portfolio

On one hand, the number of projects in late-stage development in the current portfolio reflects the initial emphasis on artemisinine-derived products either in combination for the treatment of the acute disease or alone by injection or in a suppository form for the management of severe malaria. On the other hand, there is an increasing number of projects in the portfolio in the early discovery phases, translating the switch of the investment in screening activities to address the eradication agenda.

MMV is currently sponsoring half of all late-stage projects in drug development. Of the remaining projects, we decided not to support 25% of them and are in active discussion regarding the remaining 25% of the total portfolio.

FIGURE 22. **The MMV portfolio**



1. Coartem Dispersible is in a Phase IV programme led by Novartis.
2. ASAQ Winthrop: This DNDi and sanofi-aventis product is in Phase IV trials with MMV.
3. MMV has worked with Guilin to achieve WHO prequalification for this vital medicine.

Expected yields of the portfolio

In addition to the two registered ACTs and prequalified artesunate injection, the portfolio is ready to deliver the following products within the next five years:

- New medicines for the treatment of pregnant women (AZ/CA in 2014).
- Two additional ACTs for the treatment of adults and children (Eurartesim™ and Pyramax® in 2011).
- Two new child-friendly formulations (Eurartesim™ and Pyramax®in 2012/2013).
- One treatment for the dormant form of *P. vivax* (tafenoquine in 2016).
- New medicines to replace artemisinin derivatives:
  - New combination to counter artemisinin resistance (OZ 439 with a long-acting partner).
  - Single-dose cure medicine (OZ 439 with a partner with high concentration in the blood).
  - NITD 609: First result of MMV's discovery work, which recently started Phase I.

The discovery strategy and the resulting portfolio are now fully focused on the eradication agenda. Our screening work—to date, of more than 5 million compounds—has resulted in the identification of more than 25,000 new chemical starting points whose data have been released into the public domain, an innovative way of sharing proprietary knowledge.

A number of collaborators are now commencing work on these highly innovative, promising compounds, and will help to feed the pipeline with at least three new molecules progressing to preclinical testing every year.

In parallel, assays have been developed to screen compounds for their activity against the key stages of the parasite, which will enable us to identify new molecules to block transmission and eliminate the hypnozoite of *P. vivax*. The combination of these two achievements will allow, for the very first time, the development of compounds or combination therapies that target different stages of the parasite's lifecycle.

Addressing long-term challenges

From a scientific perspective, the greatest challenge is the possibility of artemisinin resistance spreading to the new drugs that are currently being developed. The flexibility of the parasite's genome allows rapid acquisition of resistance by the parasite against any new compounds to which it is exposed. In terms of drug development, this means that the window in which to produce new therapies is extremely small. It requires constant effort to sustain the portfolio with NCEs that also target new mechanisms of action. This challenge is addressed by screening the compound libraries of six of the largest pharmaceutical companies (GlaxoSmithKline, Novartis, BroadGenzyme, AstraZeneca, Pfizer and Sanofi-aventis) and performing high-throughput screening. The screening has resulted in the identification of more than 25,000 positive hits (chemical entities) active against *P. falciparum* malaria that have been placed in the public domain. Priority can now shift to new sources of medicine that not only cure malaria but also target transmission and the dormant form of *P. vivax*.

The next major challenge is to move these very early-stage compounds toward becoming viable drug candidates ready for clinical testing. These activities will require more resources,

financial and human, and potentially new partners and alliances. However, we have demonstrated with the new compound NITD 609 that screening to Phase I can be done in less than four years.

The access by countries and patients to the new ACTs and artesunate injection is supported by very strong international initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID. The current forecast is that around 250 million people per year should be treated with ACTs. This raises the need to evaluate the safety of these medicines when available in the real world by closely following up their use in countries where pharmacovigilance systems are only starting to be implemented. The urgent need for the implementation and development of proper infrastructures, tools and systems to ensure proper pharmacovigilance should have a high priority, and the ethical responsibility of the international community should be raised. The mantra "No more poor drugs for poor people" should be accompanied by "No more poor pharmacovigilance for poor people".

ACTs are very efficient at curing malaria. Within the next five years, the availability of four new ACT medicines with different strengths and weaknesses and three child-friendly formulations will certainly save many more lives and benefit public health. This, however, might alter the perception of the urgent need to eliminate and ultimately eradicate the disease, and reduce the interest of donors. As mentioned above and underlined by this report, sustained funding is critical to target eradication by 2025. Drugs have a key role to play in the integrated approach to target eradication. Strong global advocacy to reverse a reduction in focus on malaria research will be critical if we are to succeed.

Malaria vaccines

Scientific and related challenges of malaria vaccine development

The parasite that causes malaria is complex and highly adaptable, and has survived for millennia. Today we use an array of malaria treatment and control measures—drugs to prevent and cure the disease, bednets to protect against bites and insecticides to reduce the mosquito population. While they have been effective in reducing malaria disease rates, the remarkably resistant *Plasmodium* has frustrated attempts to completely defeat it.

Despite recent progress, development of malaria vaccines remains complex. Developers face myriad challenges, including:

- The malaria parasite changes form as it moves between and through its human and mosquito hosts and has more than 5,000 genes (many more than the typical virus). No vaccine against a parasite has ever been approved for use in humans.
- We do not yet completely understand the specific immune responses that protect against malaria, and there are no known correlates of immunity (measurable signs that a person is immune). Therefore, vaccine candidates can only be shown to work through evaluation in humans, an expensive and time-consuming process.
- Because the malaria parasite is so complex, vaccine scientists are faced with a diversity of targets. The large number of potential targets (proteins) has not yet been systematically evaluated.

- The immune response to a target antigen can be enhanced through the use of a delivery platform (such as a weakened virus, or a nanoparticle), or an adjuvant (such as aluminum salts, long used in vaccines, or more novel cocktails of immunostimulant molecules). Use of novel delivery platforms and adjuvants may extend the time to regulatory approval.
- There are few rigorously qualified assays and models for assessing vaccine candidates to inform decision-making along the development pathway.
- The limited financial return anticipated from a market that is primarily in Africa and other developing countries holds little attraction for the private commercial sector.

Potential contribution of vaccines to controlling, eliminating or potentially eradicating malaria

From smallpox to polio to whooping cough, vaccines have offered a cost-effective and efficacious means of preventing disease and death. A pre-erythrocytic vaccine such as RTS,S would be a vaccine to aid control, as it either reduces the risk of infection, increases time to infection or cuts the number of malaria episodes, thereby reducing exposure to severe disease and death.

A more highly efficacious pre-erythrocytic vaccine could help reduce transmission. Other vaccine approaches currently in development, such as those targeting the portion of the parasite's lifecycle when it is transiting through the mosquito, could also potentially cut the transmission cycle.

A first-generation vaccine such as RTS,S would need to be used within the context of other interventions used against malaria, and while it is not possible to know how effective transmission-blocking vaccines would be at ending transmission, it is likely that coordinated use with other interventions would still be necessary, together with broad coverage for the vaccine itself.

Progress in the past five or ten years

A malaria vaccine candidate is in the final stages of development, thanks to the efforts of scientists and clinicians around the world and to the support of the Bill & Melinda Gates Foundation and other donors.

Early development of the RTS,S vaccine candidate was undertaken through a collaboration between WRAIR and what is now GlaxoSmithKline Biologicals (GSK). In 2001, GSK and MVI established a PDP to develop RTS,S for paediatric use. In Phase II trials, RTS,S was the first vaccine candidate to demonstrate substantial, if not complete, protection of young children and infants in malaria-endemic areas against infection and clinical disease caused by *P. falciparum*, the most deadly form of the malaria parasite.

Working in collaboration with African scientists, MVI and GSK launched a large-scale Phase III efficacy trial of RTS,S in May 2009; that trial is now underway in 11 sites in seven African countries. The target enrollment of more than 15,000 children and infants was reached at end-January 2011, making this the largest malaria vaccine trial to date.

If all goes well in Phase III testing—and results confirm the safety and efficacy of the vaccine candidate—WHO has indicated that a policy recommendation for RTS,S is possible as early as 2015, paving the way for implementation in countries through their expanded programmes on immunisation.

Currently, some 60 vaccine projects are underway worldwide, including two dozen in clinical trials. Since 2003, MVI has advanced 12 projects into first in human Phase I studies, including seven into Phase IIa challenge studies.

Another important area of progress has been evaluation technologies. Dozens of projects are underway to develop, improve or validate methods to evaluate the potential efficacy of malaria vaccine approaches, whether before or after they go into human testing.

The malaria vaccine field has also benefited from the existence since 2006 of the Malaria Vaccine Technology Roadmap, which established interim and final goals for malaria vaccine development efforts and identified the key hurdles to be overcome.

Factors that have facilitated or impeded development

Clearly, malaria vaccine development in the past decade has progressed faster and further than ever before, largely facilitated by significant increases in funding, especially from the Gates Foundation and the US government.

Factors that have inhibited the development of a malaria vaccine are rooted in the very nature of the malaria parasite, the *Plasmodium* protozoa that cause malaria: they have more than 5,000 genes and a complex lifecycle that takes place in mosquitoes (the vectors) and humans (the hosts).

Our greatest success to date has focused on the parasite's pre-erythrocytic stage—the period during which the organism, in the form of a sporozoite, enters a person's bloodstream and heads for the liver, where it matures and begins a prolific multiplication process. Vaccine developers are also working in two additional points in the cycle: blood stage and during transmission.

Other critical inhibiting factors include a lack of understanding of the specific immune responses associated with protection from malaria. This obstacle is intensified by the limited number of well-characterized target antigens and highly effective immune-enhancing adjuvants and vaccine delivery platforms available for use in humans. MVI's work has shown that new adjuvants are needed to enable a recombinant[xvi] malaria vaccine to elicit a sufficiently strong immune response and be acceptable for use in humans, particularly in children. There is also a clear need for new and diverse vaccine delivery platforms that provoke strong immune responses to parasite invasion.

A final impediment to developing a malaria vaccine is the paucity of rigorously qualified assays and models to evaluate vaccine candidates. Developing and maintaining effective preclinical and clinical evaluation technologies is essential to inform decision-making.

[xvi] A recombinant vaccine is a vaccine made through recombinant DNA technology, the technique by which genetic material from one organism is inserted into a foreign cell in order to mass-produce the protein encoded by the inserted genes.

The PATH Malaria Vaccine Initiative portfolio

MVI maintains a vaccine project portfolio (see below) with a diversity of preclinical, translational (early clinical) and at least one advanced clinical project. The portfolio illustrates MVI's multi-pronged approach to developing a next-generation vaccine by 2025. It includes:

- Pre-erythrocytic vaccine approaches that target *P. falciparum* and *P. vivax.*
- Transmission-blocking vaccine approaches that target *P. falciparum* and *P. vivax.*
- Blood-stage approaches targeting *P. falciparum* and *P. vivax.*
- Early-stage feasibility studies in which antigens, delivery systems and adjuvant formulations are evaluated for their potential as vaccine components.

Expected yields of the portfolio

MVI's primary focus has been the development of a vaccine against *P. falciparum* that is appropriate for use in young children. We hope that RTS,S—the first vaccine candidate to progress to late-stage clinical testing—will fulfill that intermediate goal.

Already, however, MVI is working to develop next-generation vaccines that would be more highly effective against disease and death. In addition, MVI has realigned its R&D strategy and further diversified its portfolio to target the long-term goals of eliminating and eradicating malaria. Thus, in addition to pre-erythrocytic vaccines (similar to RTS,S), MVI's range of vaccine approaches now includes those that seek to block malaria transmission. To further support efforts to eradicate the disease, MVI also is increasing its focus on *P. vivax*, the parasite that causes a less deadly—but more widespread—form of malaria than *P. falciparum.*

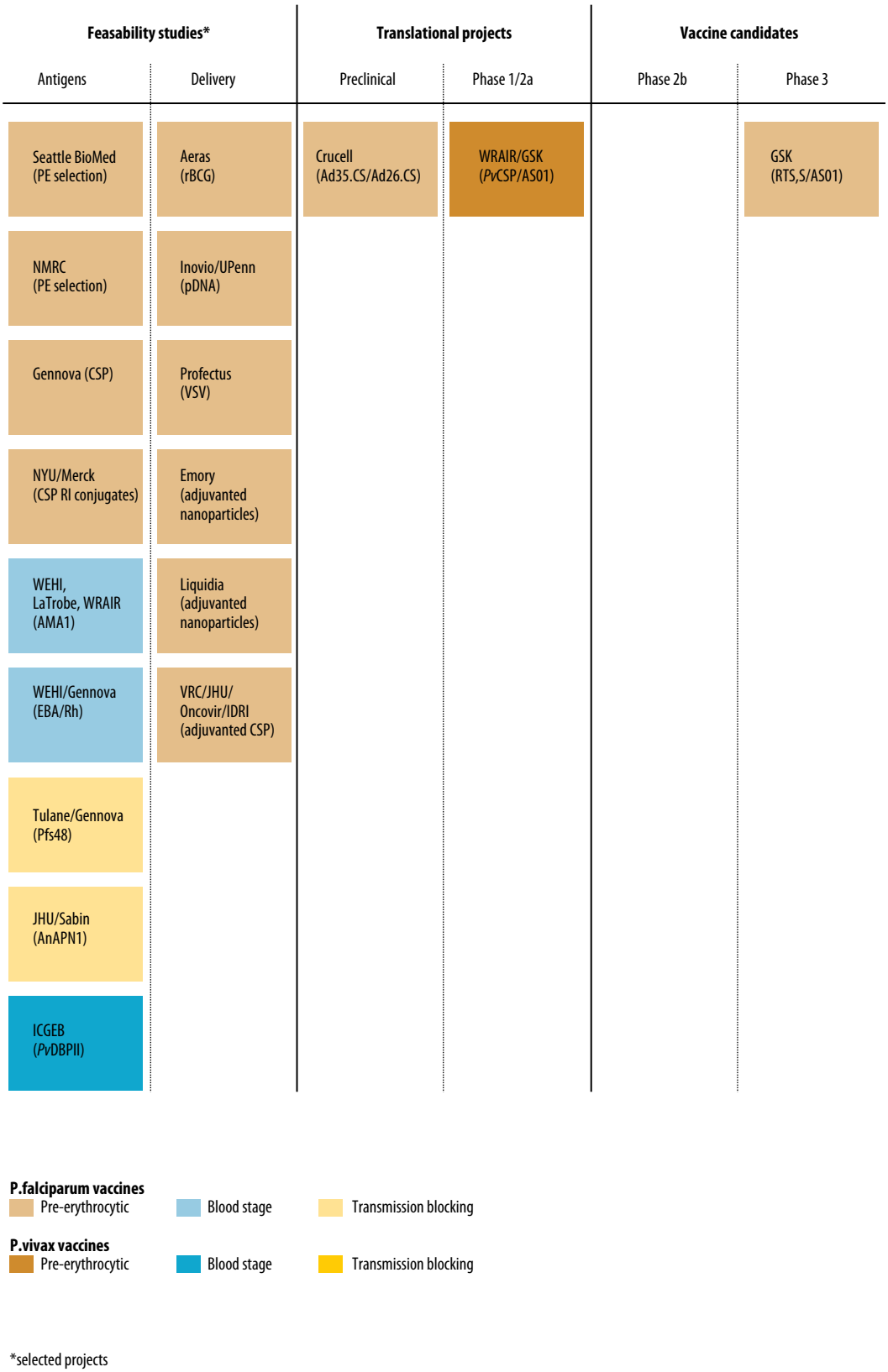
While it is not possible to predict the future, MVI anticipates at least two additional vaccine candidates advancing to Phase III trials over the next decade.

Addressing challenges

The most critical activities to achieving an effective malaria vaccine are:

- **Developing and supporting new evaluation tools and models.** To comparatively assess vaccine approaches, we must support the reference and service centres, improve assays, use human as well as non-human challenge models and enhance capabilities for infected mosquito challenges. Success in this area would provide robust data to inform decision-making and reduce investment risk.
- **Holding large-scale Phase III studies.** These costly trials monitor safety and potential side effects and evaluate efficacy on a large scale. They must ensure that the vaccine works under varied conditions, including different malaria transmission patterns. Based on the limited experience to date, Phase III malaria vaccine trials should be expected to last three to five years from trial enrollment through follow-up.
- **Testing prime-boost approaches.** When a single application of a malaria vaccine is insufficient, repeated immunisations are performed using different vaccine preparations to sequentially stimulate a better immune response. Essentially, one vaccine primes the immune system to attack malaria while the next one boosts the response.

FIGURE 23. **The MVI portfolio**



*selected projects

- **Developing *P. vivax* vaccines.** While there has been encouraging progress in *P. falciparum* malaria vaccines, much less progress has been made in development of vaccines against *P. vivax*, the second most serious malaria-causing parasite.
- **Developing transmission-blocking vaccines.** The development of vaccines that could block the cycle of transmission of *Plasmodium* species that infect humans is widely regarded as a key tool in the global control, elimination and eradication effort.

The cost to take a malaria vaccine from the laboratory through development and into endemic countries is estimated to be at least $500 million. This cost highlights the need for sustained, coordinated and gradually increasing funding until development of the needed vaccines is achieved.

Malaria diagnostics

Scientific and related challenges of developing malaria diagnostics

Current RDTs, as well as microscopy, are adequate for case management when sufficient quality assurance measures are in place, but will miss a high proportion of low-density asymptomatic infections and therefore can be inadequate for parasite surveys and active case finding. Even when RDTs are of good quality, issues such as antigen persistence after clearance of parasitaemia, deletions of the histidine-rich protein 2 target antigen in some parasites and poor detection of some species limit utility in specific situations. The most sensitive RDTs target *P. falciparum*, and more sensitive assays are needed that detect and discriminate other species, including *P. vivax* infections. Therefore, identification of new targets, together with improvements in manufacturing consistency, will have significant benefits to malaria control.

The development of low-cost field-ready platforms that detect very low parasite densities, such as molecular tests, would be invaluable for surveillance and resource targeting in low-transmission settings and are likely to be necessary to achieve and maintain elimination in areas of high vectorial capacity, such as sub-Saharan Africa.

A related challenge is the screening and diagnosis of malaria in pregnant women, who are at particular risk of asymptomatic infection and its consequences, including placental malaria, which can have major consequences on the newborn. Diagnostics that detect very low parasite densities in sampled blood will have increasing application as resistance to sulphadoxine-pyrimethamine (currently used for prophylaxis in pregnant women) spreads. Such tools will support the more effective targeting of efficacious anti-malarial treatment for asymptomatic pregnant women.

Malaria is a geographically highly heterogeneous disease, predominantly occurring in remote areas and low-resource settings. As such, conducting clinical trials on new diagnostics can be difficult and expensive, and trial results often are not easily extrapolated to the broader population. As the tools themselves are usually used by health care workers in community settings, it can be difficult to appropriately move new technologies from more traditional laboratory settings to this level, where they are most needed. In addition, reference standards

currently in use often lack accuracy and reproducibility in field settings, which further complicates trials of new tools.

Most fevers, even in malaria-endemic countries, are not caused by malaria. Improved fever management, and continued malaria testing in sites where malaria has been well controlled, will depend on the availability of tests that can detect other causes of fever, and aid clinical decisions.

There is a need for new tools to facilitate the early detection of resistance to anti-malarial drugs, to ensure that these drugs can retain their maximum efficacy in global malaria control programmes. Finally, as referenced elsewhere in this report, there is also a need for diagnostic tools to support the development and rollout of new drugs, vaccines and insecticides.

Potential contribution of malaria diagnostics to controlling and/or eliminating/ eradicating malaria

Effective, high-quality diagnostic tools are essential to control, eliminate and eventually eradicate malaria. It will be virtually impossible to address the disease if we do not have appropriate methods to determine who is being affected by it.

As described above, a large percentage of fevers are not due to malaria, and this percentage will continue to increase as malaria prevalence decreases. Therefore, effective control of the disease can only be achieved if there are appropriate and high-quality tools available in all settings to ensure that only actual malaria cases are being treated for the disease, and that individuals with other causes of fever receive appropriate care.

As countries come closer to elimination, and the political will and resources aimed at malaria potentially decrease, it will become more important to adapt diagnostic, screening and monitoring strategies and tools to lower-prevalence settings. As resource-intensive prevention and control programmes decrease in importance, countries will need to have tools to identify where conventional malaria control resources should be targeted and where other strategies should be employed. With the ability to detect very low concentrations of parasites in often asymptomatic individuals, it will be possible to consolidate gains from control programmes, and to help prevent any resurgence of the disease.

Appropriate diagnostic tools are also essential to support the rollout of other malaria control interventions. A case in point is in the development of new 8-aminoquinaline drugs, which are targeted at individuals infected with *P. vivax* but which can cause adverse effects in those with G6PD deficiency. The widespread use of these new drugs will only be possible if it is accompanied by diagnostics and strategies for their use that can detect G6PD deficiency at a field level and ensure safe drug targeting.

Progress in the past five or ten years

Over the past decade, the number of manufacturers of malaria RDTs has increased significantly, as has the variety of species-specific RDTs. WHO now recommends that malaria case management be informed by parasite-based diagnosis in all cases, which has increased interest from national malaria control programmes, donors and other stakeholders in scaling up diagnosis.

To support widespread use of RDTs, a rigorous programme to test the quality of existing RDTs has been put in place, and its results now inform purchasing decisions of large donors and implementing partners. In addition, tools now exist to test the quality of individual lots of RDTs as they are shipped to countries. There has also been a renewed interest in the quality assurance of microscopy, which is another method to ensure parasite-based diagnosis.

Factors that have facilitated or impeded development

As can be seen in the funding section of this report, investments in new diagnostic tools are woefully lacking, amounting to only about 1% of all R&D funding. Partly, this may be due to the nature of diagnostics; they are necessary, but not sufficient, for control and elimination efforts to function. However, there is a general lack of awareness on the importance of diagnostics, and they can be much less eye-catching or attractive to the donor community than other types of interventions.

More specifically, there is sometimes a perception that health care workers do not follow the results of RDTs. This can be addressed by a number of actions, including better training for health care workers; increased quality control of RDTs at global, national and community levels (such as those under development with Positive Control Wells at the community level to reassure workers that tests are working properly and give them confidence in the results); and more resources to develop strategies for the management of non-malarial fevers (i.e., giving health care workers tools to diagnose and treat their patients when an RDT shows that they do not have malaria).

The 2011 diagnostics portfolio

Despite the low levels of funding of malaria diagnostics, there has been some activity in this area, and a number of technologies are in the pipeline. Loop-mediated isothermal amplification (LAMP) of DNA for malaria is a novel molecular technology platform that can be used in basic laboratories to detect very low levels of parasite densities, thus making it suitable for sensitive detection and low-prevalence settings. The performance of this technology is currently in the evaluation phase, and a high-throughput version of the technology is being investigated. New serological tools, using antibody-detecting enzyme-linked immunosorbent serologic assays, have the potential to allow for the screening of large populations at low cost to identify sites where transmission is occurring, or has recently occurred.

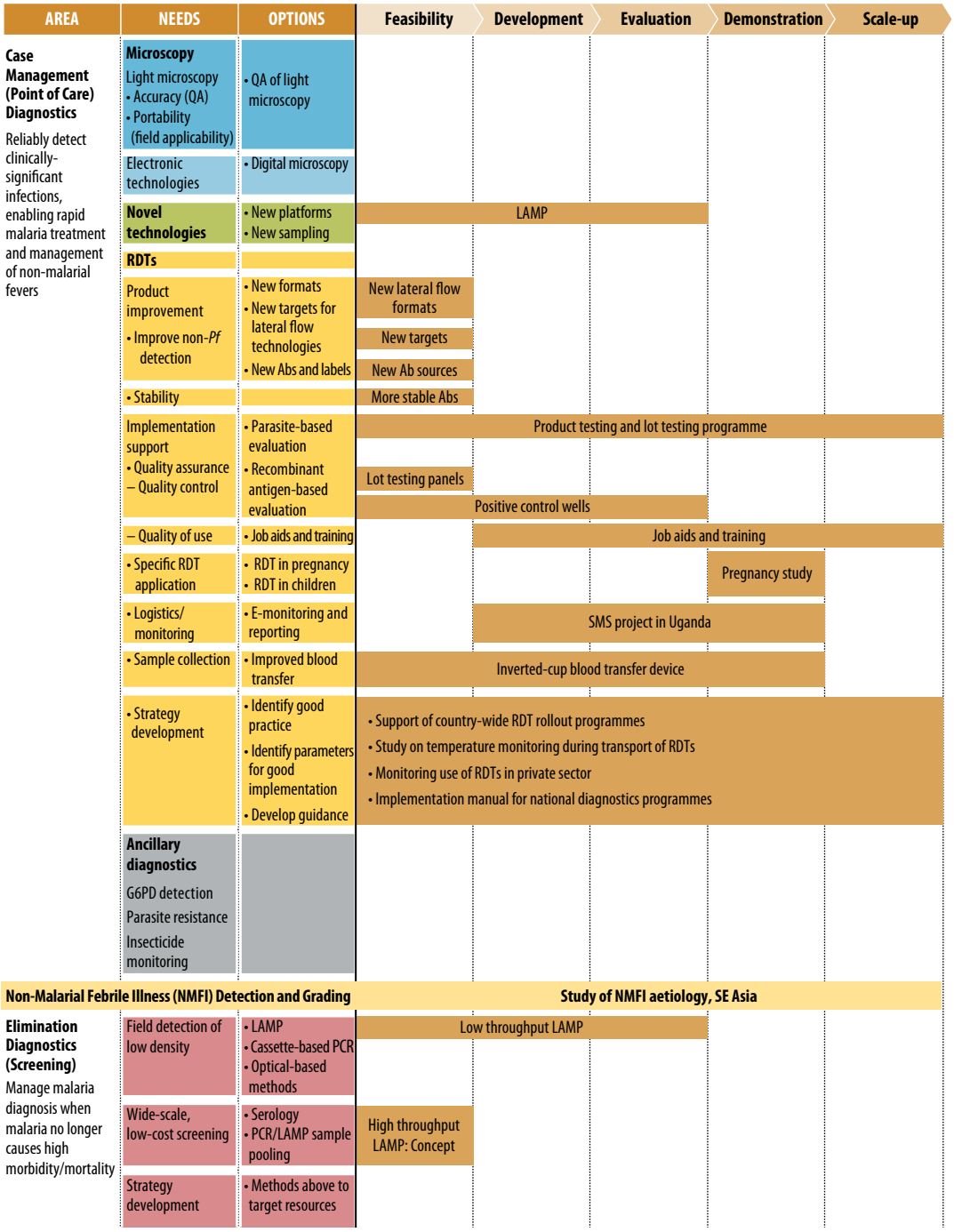
Tools are being tested for detection of malaria in pregnant women. Work is currently underway to improve existing point-of-care lateral flow assay platforms to address some of the drawbacks of existing RDTs, such as variability and instability at temperatures greater than 30°C. Additional research is also being conducted on the identification of new targets with specific diagnostic utility, which would be highly abundant, highly conserved and species specific.

To address the need for tools that can help health care workers address malarial and non-malarial fevers, a number of groups are working to develop multiplexing platforms, which could detect a range of diseases. Most of these projects are still in their infancy.

Finally, a number of other technological advances are being investigated, such as digital microscopy, polarized light microscopy, haemozoin detection systems and other methods such as spectrometry.

The chart below broadly describes the diagnostic needs for both case management and elimination, and shows FIND's portfolio of projects.

FIGURE 24. **Diagnostics portfolio**



Expected yields of the portfolio

The portfolio is expected to yield more stable and consistently reliable RDTs and more accurate and easy to use field-ready molecular tests. A multiplex assay, which can distinguish between malaria and other causes of fevers, will be invaluable for the management of malaria within the context of other pathologies present in different communities.

The portfolio is also expected to yield new tools that can address the diagnostic and surveillance needs of lower-prevalence settings. These include low-cost, accurate tools that can detect very low parasite densities, as well as tools to quickly and easily determine local prevalence in different settings, which will be necessary to inform the targeting of scarce resources to higher-prevalence pockets and prevent resurgence of the disease.

Addressing long-term challenges

As with R&D for all interventions, one major challenge will be a decrease in attention and resources devoted to malaria as prevalence decreases. However, history shows us that this will likely result in a resurgence of the disease.

As we move toward elimination, it is important to address the fact that we do not currently have the tools to address this phase in malaria control. However, if tools and strategies are not developed now to address lower-prevalence settings, any gains from the more aggressive malaria programmes currently in place are likely to be lost.

Given the variability in quality of existing diagnostics, quality assurance and quality control activities have proven invaluable in increasing confidence in the intervention, and have supported a much more targeted and rational use of resources. However, sustainability of these quality assurance efforts is a major challenge.

Finally, one of the major challenges in the development and use of diagnostics has been some confusion in the malaria community regarding the utility and need for these tools.

One important way to address the twin challenges of lack of understanding and lack of resources is with joint advocacy at all levels on the importance of diagnostics as an essential facet of malaria management. Malaria control programmes will fail if we continue to treat non-malarial cases with anti-malaria medication because RDTs are not used or are of poor quality. New drugs will be of no use if there are no diagnostics to screen out individuals susceptible to side effects. The development of new vaccines requires better screening and evaluation tools. The introduction of new insecticides will also require appropriate diagnostic tools to monitor efficacy and presence, for example, in treated bednets. Finally, elimination strategies will not be possible to implement if effective screening tools are not developed to determine where and how to target more stratified control programmes.

Malaria vector control

Vector control product development: The state of the art

Mosquito vector control is capable of spectacular results. The malaria eradication campaigns of the mid-1900s eliminated malaria in much of the world; however, the campaigns were discontinued because of concerns about drug and insecticide resistance and problems with sustainability.

IRS with insecticides and the widespread use of insecticide-treated bednets (ITNs) have been successful in reducing the burden of malaria, and eradication will require large-scale vector control over a sustained period to reduce transmission to a level that drugs and/or vaccines can be effectively deployed.

Sustainability of vector control measures is at risk, as a 30-year hiatus in public health pesticide development has left efforts heavily dependent on a single class of insecticides to which resistance is already widespread. Currently, only one insecticide class—pyrethroids—is licensed for ITN use, leaving the intervention vulnerable to resistance. High levels of pyrethroid resistance have already been detected in East, West and southern Africa. While insecticide choice is wider for IRS, only four classes of insecticides are registered for IRS use and resistance in some mosquito populations is already present in all classes.

In addition to supporting the proven paradigms of long-lasting insecticidal nets (LLINs) and IRS, innovation is required in the definition and evaluation of new paradigms for insecticide-based vector control. To date, the process for bringing new paradigms to the market has been ineffective, with interventions that need significant input to facilitate community uptake, taking many decades to scale up for impact.

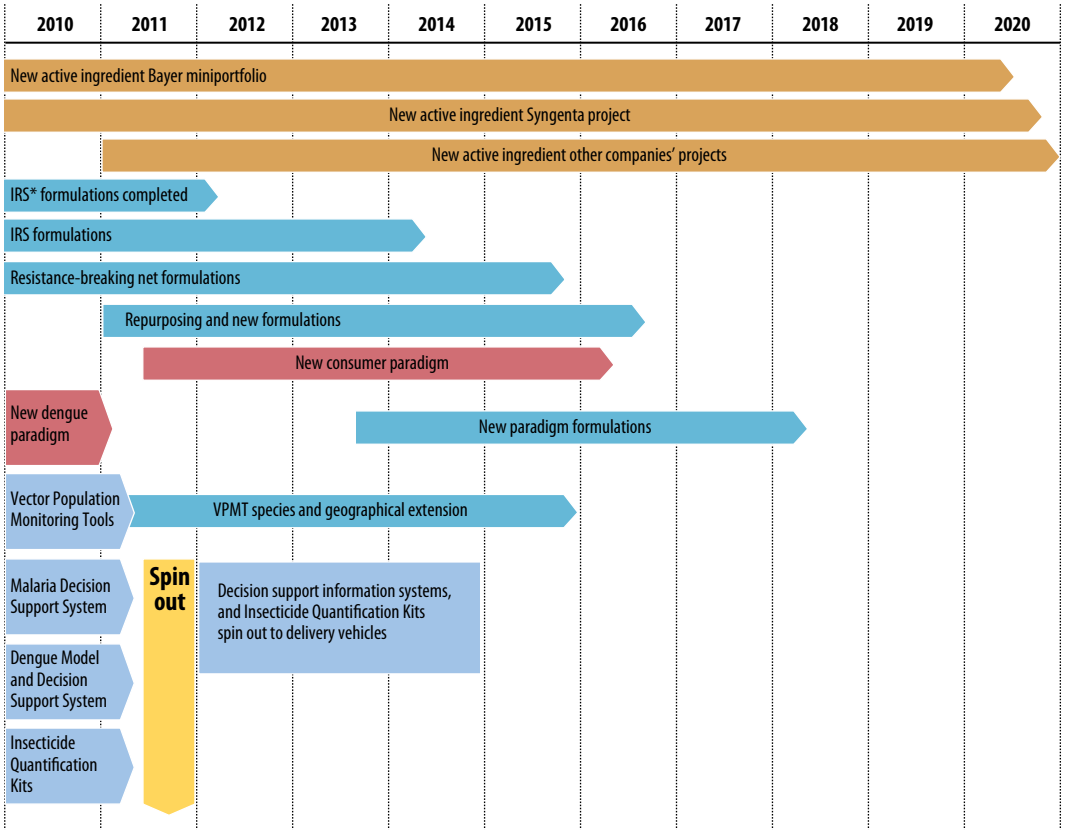
Monitoring and evaluation plays a crucial role in the success of vector control interventions, completing the information flow between intervention programmes on the ground, their managers at the ministry of health level and the global funders of public health interventions. By providing tools to create the raw monitoring and evaluation data and information systems that allow analysis, feedback and communication of the data, disease control programme managers are empowered to optimise performance of their programmes and communicate their needs and successes with their peers, managers and funders.

Insecticides for mosquito control are in short supply. In the1980s, a move away from contact toxicity and persistence has meant that many modern agricultural insecticides are not so easily re-purposed. High regulatory costs for new active ingredients and the relatively small market for public health insecticides make their development uneconomic. No new active ingredients have been registered for mainstream adulticide malaria PHP applications since the mid-1980s.

IVCC was established in November 2005 to facilitate the development of improved public health pesticides and formulations and to provide information tools and diagnostics to enable the more effective use of malaria and dengue control measures. In the first five years, through a mechanism of open calls, IVCC was remarkably successful at engaging industry, providing a robust pipeline of screens for new pesticides and supporting projects that establish a new industrial benchmark for formulations and provide alternative non-pyrethroid LLINs.

New diagnostic and information tools have also been created, which now need to be effectively delivered to the market. The first IVCC-supported IRS formulations will enter the market in 2011, with others coming to market over the next five years. These will increase the residual life of the treatment, dramatically reduce the cost and logistics involved in large-scale IRS and increase the choice of insecticide classes available for control.

FIGURE 25. **IVCC product development roadmap**

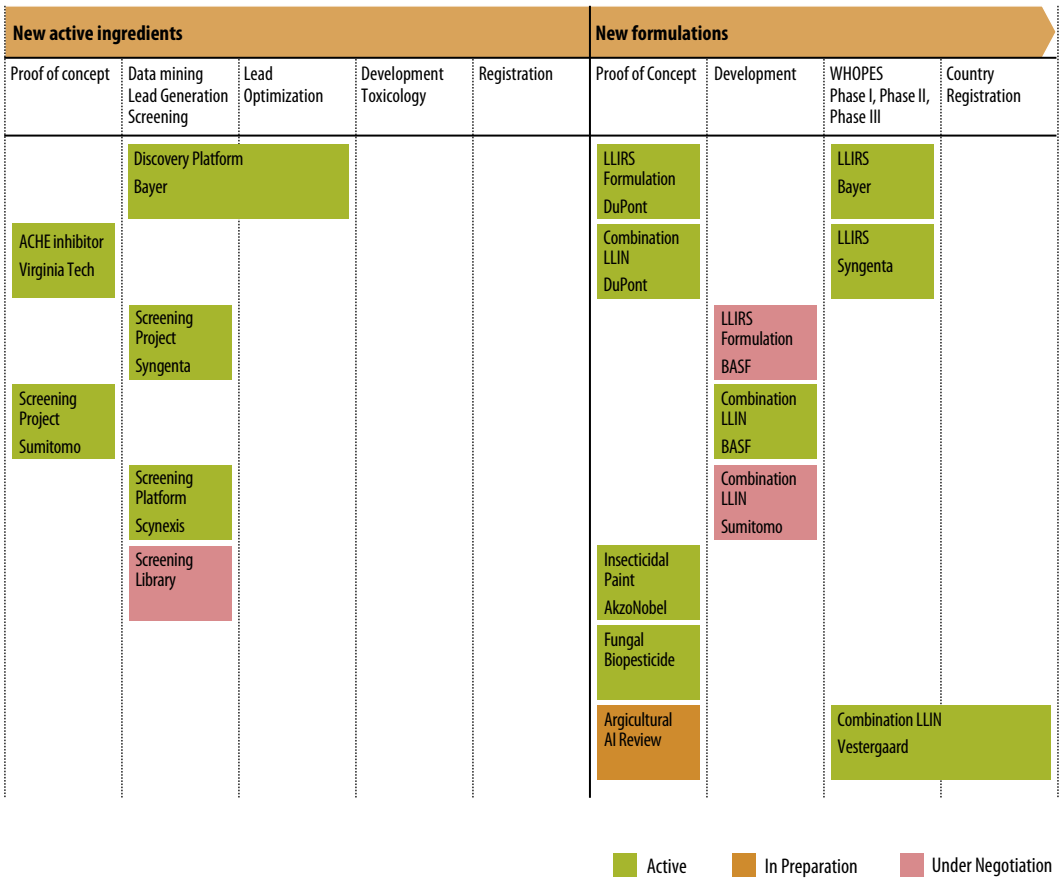


*Indoor residual spraying

The product development roadmap for vector control calls for development of:

1. Three new active ingredients with novel modes of action in order to provide effective resistance-management strategies.
2. New formulations for longer-lasting indoor residual sprays and bednets to provide alternatives to pyrethroids.
3. New paradigms in insecticide delivery in order to address uncontrolled mosquitoes and improve user demand.
4. Information systems and tools for effective monitoring and evaluation of vector control programmes.

FIGURE 26. **IVCC portfolio**



The current active ingredient and formulation portfolio represents the efforts of six of the world's largest chemical companies and all of those engaged in public health pesticides. While this represents a dramatic step-change in engagement of the chemical industry in vector control R&D, further discovery activity is required to ensure a sufficient pipeline for new active ingredients and exploration of the field of new paradigms has not yet gathered momentum.

New active ingredient screening projects are still at the earliest stages and are expected to deliver AI in 2020. Formulations are developed on a much shorter time scale, and the first of the IVCC-supported formulations is expected to be in use in 2011.

As industry is now engaging in development of public health pesticides *de novo* for the first time, IVCC has worked closely with this group to define the critical pathway to market for these compounds, and to estimate the R&D costs. A realistic estimate of cost is $67.5 million per compound brought to market, with a development time of approximately ten years. When amalgamated with the costs of information systems development and new paradigm development, the total requirement for vector control product development is on the order of $150 million for the period 2011–2015 and a further $150 million for the period 2016–2020. This product development component lies within a broader R&D estimate for the ten-year period of $600 million.

Annexe 2. Malaria product portfolio

This annexe gives an overview of the current malaria portfolio for drugs, vaccines, diagnostics and vector control products, based on:

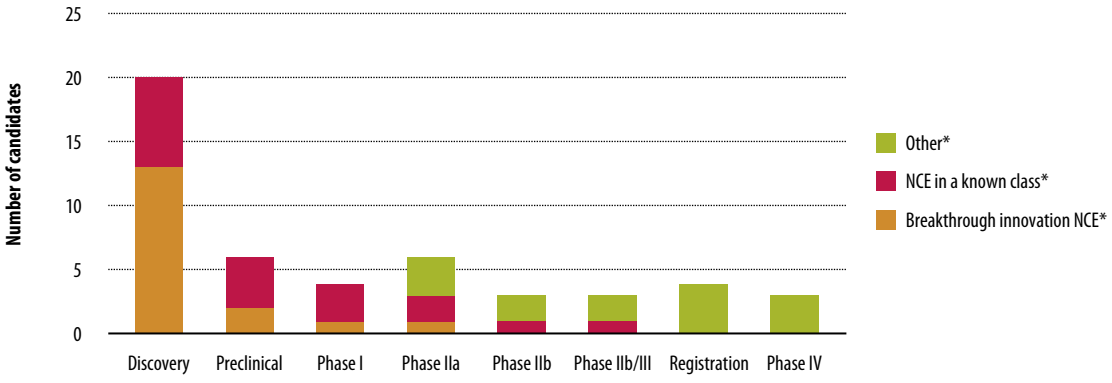
- Product portfolios, presentations and annual reports of the major PDPs, including MMV, MVI and the European Vaccine Initiative.
- Industry reports from the IFPMA.
- The WHO list of vaccine projects.[28]
- Personal communications with FIND, IVCC, MMV and MVI.

Identified projects were cross-checked to confirm their current status using the US NIH Clinical Trials database, the IFPMA's Clinical Trials Portal and websites of participating malaria organisations. Although effort was taken to make the list as comprehensive as possible, some active projects may not have been captured. This is particularly likely in the discovery stage, when results may not yet have been published. We also note that information on the diagnostic portfolio is patchy; nevertheless, this is the most up-to-date information available.

Drug portfolio

The current global malaria drug portfolio consists of at least 47 drug candidates, including 27 in the preclinical and clinical stages of development.

FIGURE 27. **Global malaria drug portfolio, Q4 2010**



* A 'breakthrough innovation NCE' is a novel candidate that targets malaria in a completely new way. An 'NCE in a known class' is a novel candidate, but with a non-novel method of action (i.e., it is an addition to an existing class of drugs). 'Other' includes fixed-dose combinations, label extensions, reformulations and re-registration of existing drugs to Western standards.

Of the 27 projects at or beyond preclinical, 20 are in clinical trials, with the remaining seven potentially entering clinical trials within the next five years. The majority of the most advanced projects contain artemisinin derivatives (all projects at registration and beyond,

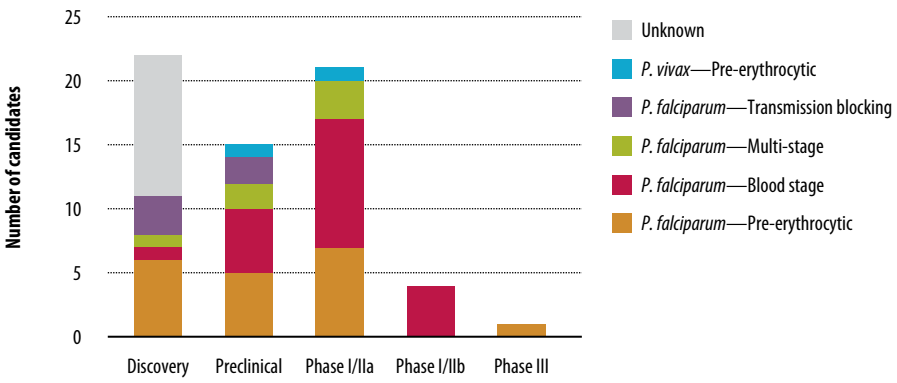
as well as two-thirds of those at Phase IIa or later). Other products in clinical trials include fixed-dose combinations (e.g., chloroquine/azithromycin for prevention in pregnant women), synthetic peroxides (e.g., arterolane piperaquine phosphate), aminoquinoline derivatives (e.g., tafenoquine) and other formulations. Examples of projects that are currently active include a single-dose cure, paediatric formulations, treatments for pregnant women, a radical cure for *P. vivax*, novel compounds to tackle artemisinin resistance and transmission-blocking antimalarials.

NCEs and breakthrough innovation now make up the majority of the upstream pipeline, a far healthier mix than in the past.[xvii] However, this is not the case in the preclinical and clinical stages, at which only four of the 15 NCEs are breakthrough NCEs, with the remaining 11 being new additions to a known class of drug.

Vaccine portfolio

The current global malaria vaccine portfolio consists of around 63 candidates, including 41 in the preclinical and clinical stages.

FIGURE 28. **Global malaria vaccine portfolio, Q4 2010**



Of the 41 candidates in preclinical or more advanced stages, 26 are in clinical trials, with the remainder potentially entering clinical trials within the next few years. To date, only one vaccine candidate, the MVI/GlaxoSmithKline candidate RTS,S, has successfully reached Phase III trials.

Most vaccine candidates in the clinical trial stages target the blood stage of the malaria parasite (14 out of 25), while eight target the pre-erythrocytic stage. The remaining three candidates target multiple stages of the malaria parasite.

Of the 41 vaccines in preclinical and clinical development, the overwhelming majority (95%) target *P. falciparum*, with only two vaccines targeting *P. vivax* (PvCSP AS01 by WRAIR/

[xvii] Compared to the 'two peak' profile identified in the 2007 report, *The Malaria Product Pipeline: Planning for the Future*, from the Health Policy Division at The George Institute for International Health (now Policy Cures).

GlaxoSmithKline and PvDBPII by the International Centre for Genetic Engineering and Biotechnology and MVI).

Diagnostic portfolio

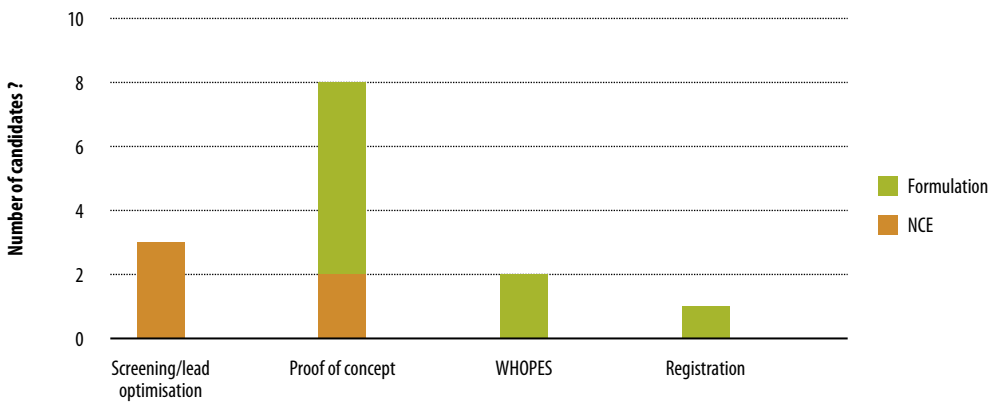
Information on the diagnostic portfolio is limited, and there are no data on numbers of candidates at each stage of the development process. However, a number of technologies are in the pipeline (mostly in their infancy). A LAMP of DNA to detect very low levels of parasite densities is currently being evaluated, while a high-throughput version of the same technology is in early development. Other technologies being evaluated as simpler, more sensitive platforms for malaria detection include point-of-care lateral flow assays (RDTs) with greater stability and new antigen targets.

Other diagnostic methods being investigated include new serological tools that use antibody-detecting enzyme-linked immunosorbent serologic assays for broad-scale screening and a number of other technologies, such as digital microscopy, polarised light microscopy, haemozoin detection systems and spectrometry, which have application in case management. Tools are currently being tested for detection of malaria in pregnant women; some work is being done on the identification of new targets with specific diagnostic utility; and a number of groups are working on the development of multiplexing platforms. Finally, low-cost quality control tools are under development to ensure diagnostic test safety in point-of-care situations.

Vector control portfolio

The reported global malaria vector control product portfolio consists of at least 14 candidates, including 11 in early stages of development (proof of concept, screening and lead optimisation). However, lack of complete private-sector data means this is almost certainly an under-estimate of the true number of products in development.

FIGURE 29. **Global malaria vector control products portfolio, Q1 2011**



Of the 11 known projects in early development, eight are at proof of concept and three in screening/lead optimisation; however, no products have progressed to the development stage. Three reformulations are in registration: Bayer's and Sygenta's long-lasting IRS products (WHOPES phase) and Vestergaard's LLIN candidate (registration phase).

Annexe 3. Methodology and limitations

Current status of malaria R&D funding

The status of malaria funding was assessed using investment data for 2004[xviii] from the Malaria R&D Alliance report[29] and investment data for 2007 to 2009 from the G-FINDER survey.[30,31,23] In the sections referring to vector control products, G-FINDER data were supplemented by expert estimates of industry investment (noted in each case).

Malaria R&D Alliance report methodology

The 2004 data presented in the Malaria R&D Alliance report were collected via an online survey completed by 79 organisations globally in May 2005.

Three categories of organisations were surveyed (funders, funding managers and researchers and developers), and funding was captured in six R&D categories (basic research, antimalarial drug discovery and development, vaccine development and vaccine trials, vector control research, development of malaria diagnostics and implementation research). These R&D categories overlap considerably with the product R&D categories used in G-FINDER, and for the purpose of this report, were assumed to be fully comparable. The only exception was implementation research that is not included in the G-FINDER survey and was therefore excluded from our analysis. Furthermore, the Malaria R&D Alliance report did not break the six R&D categories into sub-areas (such as discovery and development), which meant we were unable to include the 2004 data in our analysis of which organisations are conducting which types of research and product development.

For a full overview of its methodology and scope, please refer to the Malaria R&D Alliance's *Malaria research & development: An assessment of global investment* report, available at: http://www.malariavaccine.org/files/MalariaRD_Report_complete.pdf.

G-FINDER methodology

Below are relevant highlights of the G-FINDER methodology. For a full overview of this survey's methodology and scope, please refer to the G-FINDER 2010 report, *Neglected disease research and development: Is the global financial crisis changing R&D?*, available at: http://www.policycures.org/publications.html.

The 2007, 2008 and 2009 funding data included in this report were derived from the annual G-FINDER survey of neglected disease R&D funding. This annual online survey collects funding information from donors, fund managers and recipients, and is believed to capture the vast majority of global R&D funding of neglected diseases. Table 7 gives an overview of the scope of data captured for malaria product R&D.

[xviii] All years in this report refer to financial years.

TABLE 7. G-FINDER survey scope

Product R&D scope	R&D areas
Basic research	
Drugs	Discovery and preclinical development
	Clinical development
	Phase IV/pharmacovigilance
	Baseline epidemiology
Vaccines	Discovery and preclinical development
	Clinical development
	Phase IV/pharmacovigilance
	Baseline epidemiology
Diagnostics	Discovery and preclinical development
	Clinical evaluation
	Operational research for diagnostics
Vector control products	Primary and secondary screening and optimisation
	Development
	WHOPES evaluation

The online survey-based format of G-FINDER allows all organisations to enter their own data according to the same definitions and categories, with the same inclusions and exclusions. Survey participants were asked to enter every neglected disease grant they had disbursed or received in 2007, 2008 and 2009 into a password-protected online database, including the grant amount, grant identification number, a brief description of the grant and the name of the funder or recipient of the grant. An exception was the US NIH, for which data were collected from the Institute's online Research Portfolio Online Reporting Tools Expenditures & Results and Research, Condition and Disease Categorization systems. Private pharmaceutical companies reported their investments in a variation of the online tool that allowed them to record staff, salaries and direct project costs.

In 2007, funding information on malaria R&D was provided by 60 respondents, which reported 1,159 individual grants. This grew to 89 respondents and 1,209 grants in 2008, and 102 respondents and 1,599 grants in 2009. Using reconciliation reports, investments were matched and discrepancies resolved through contact with both funder and primary recipient (e.g., UK DFID and MMV).

Total funding figures reported in the 'Malaria R&D funders' section differ from those reported in the section 'Malaria product developers', as the latter analysed the data from the end recipients' perspective. (In other words, PDP running and administration costs were included in the 'Malaria R&D funders' section, as this section covers all funding given to PDPs by funders, independent of how PDPs then disbursed it. These costs were excluded in the 'Malaria product developers' section, as this section includes only funding that was disbursed by PDPs.) Time lags between the disbursement of funding from funders and expenditure of

funding by recipients also contribute to the difference in total funding reported between these two sections.

Additionally, the following key principles were used when reporting R&D investments:

- All figures quoted in this report were adjusted for inflation and expressed in 2007 US dollars using yearly inflation figures from the International Monetary Fund (IMF) World Economic Outlook Database, available at: http://www.imf.org/external/pubs/ft/weo/2010/01/weodata/index.aspx.
- Foreign currencies were converted to US dollars based on the 2007 average annual exchange rate as reported in the IMF Exchange Rates Database, available at: http://www.imf.org/external/np/fi n/data/param_rms_mth.aspx.
- For confidentiality reasons, industry investments were aggregated into MNCs and SMEs.
- All data in this report adhere to conditions as laid out in confidentiality agreements, which were signed with the relevant funder or recipient.

G-FINDER definitions of funding organisations

Figure 30 gives an overview of funding flows for malaria R&D, while Table 8 defines the main roles of funders and provides some examples.

FIGURE 30. **Overview of funding flows for malaria R&D**

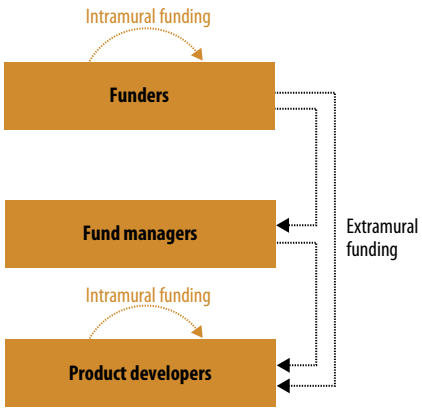


TABLE 8. Roles and involvement in malaria R&D funding and investment

Funding role	Organisation type	Role in malaria R&D	Examples
Funder	Public-sector government	Governments or government agencies and branches providing original funding to other organisations to support malaria R&D	UK DFID, USAID, Brazilian Ministry of Health
	Public-sector multilaterals	International financial institutions, United Nations agencies or multi-country entities that are funded by contributions from member state governments, utilising these funds to support malaria R&D	World Bank, WHO
	Private-sector philanthropic	Private organisations, including not-for-profit trusts, foundations, corporations and individuals, providing original funding to others to support and carry out malaria R&D	Bill & Melinda Gates Foundation, Wellcome Trust
Fund managers	Product development partnerships	Public-health-oriented, not-for-profit organisations that typically use private-sector management practices to drive product development for neglected diseases in conjunction with external partners	MVI, MMV, FIND, IVCC
	Intermediaries	Often a consortium of organisations that receive funds dedicated to a specific non-profit research aim and disburse them to external product developers rather than undertaking product development themselves	EDCTP
Product developers	Self-funded	Government research institutions, private companies and publicly traded corporations that conduct malaria R&D with their own funding (not received from others)	GlaxoSmithKline, Pfizer, US NIH intramural
	Externally funded	Research institutions, universities and some private companies that conduct malaria R&D with funding provided by donors or funding managers	London School of Hygiene and Tropical Medicine, Swiss Tropical Institute, GlaxoSmithKline

The role of 'core funding' in this report

In the original G-FINDER survey, 'core funding' (meaning non-earmarked funding given to recipients that do not have a single disease focus) was reported as a separate category. However, for the purpose of this report, a proportion of this core funding was attributed to malaria if the recipient was known to work in the malaria field. This proportion of core funding attributable to malaria was calculated as follows:

Recipient organisations active in malaria that received funding under the category 'core funding' were identified for each of the three years.

In order to estimate the proportion of the core funding allocated to malaria, we calculated, for each recipient, the proportion of their funding that went to malaria relative to other neglected diseases within the G-FINDER scope and allocated core funding proportionally. This was done by strain (e.g., *P. falciparum* versus other strains), product (e.g., drugs versus diagnostics) and R&D area (e.g., clinical development versus baseline epidemiology).

Limitations

The key methodological limitations are those associated with any data collected by survey, including survey non-completion, time lags in the funding process, inability to disaggregate

investments, non-comparable data and missing data. Of specific importance for this report is the likely under-estimation of funding disbursed to malaria vector control R&D, as several industry players in this field did not participate in either the Malaria R&D Alliance or the G-FINDER surveys. For a full overview of the limitations of the Malaria R&D Alliance and G-FINDER data, please refer to the respective reports.[23,29] Additionally, there may have been small methodological differences between the Malaria R&D Alliance and the G-FINDER surveys, as well as slight variations in the list of organisations that participated in these projects.

Finally, the methodology behind the allocation of 'core funding of a multi-disease organisation' grants to malaria may have under- or over-estimated investments made by some organisations in malaria R&D.

Estimating the funding gap

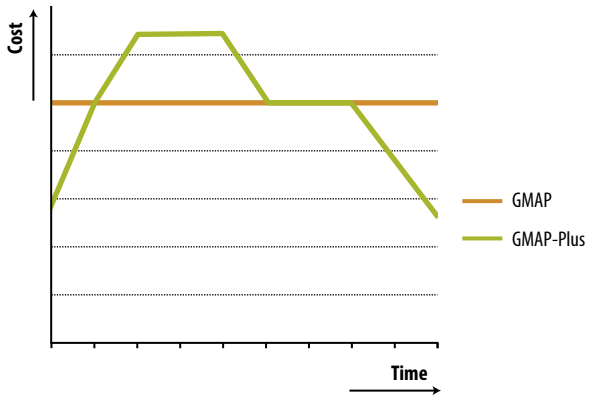
Step 1: Assessing funding needs

The model used to project the funding needs up to 2020 was based on GMAP; however, significant amendments were made to reflect additional data and changes in the malaria field since the publication of GMAP, resulting in the GMAP-Plus model. The GMAP model's authors (Boston Consulting Group) provided a detailed understanding of the underlying assumptions and modelling, and these were then either verified or amended. All assumptions underlying the GMAP-Plus model are specific to each product category, and include both portfolio assumptions (malaria products needed) and cost assumptions (malaria R&D costs).

Drug and vaccine funding needs were included from 2008, as the portfolio assumptions underlying these product categories mainly came from the original GMAP model, which started at 2008. However, diagnostic and vector control funding needs were based on our own consultations, not on GMAP assumptions, and thus start only from 2011. In order to compare the same time periods for all product categories, we assumed funding needs for diagnostics and vector control products in 2008–2010 were the same as in 2011 for both the minimum and maximum scenarios. This can be seen as two straight lines for 2008–2010 in Figure 20 for diagnostics and Figure 21 for vector control products. Immediate product needs that necessitate an urgent and significant increase in funding include improved quality control methods to ensure the quality and stability of currently available RDTs, improved RDTs targeting non-*falciparum* parasites, new and improved tools for field detection of very low-density parasitaemia (including non-*falciparum* parasites) and better screening for enzymatic deficiency (i.e., G6PD deficiency). Other important future targets include automated microscopy and non-invasive sampling (e.g., through analysis of saliva or urine). As countries come closer to elimination, it will become even more important to adapt screening and monitoring strategies so that a possible resurgence of malaria can be picked up rapidly, and to develop tests to detect non-malarial febrile disease pathogens or markers of infection requiring specific treatment. Insufficient funding is likely to not only threaten individual projects, but may lead to the demise of entire groups focusing on malaria diagnostic R&D. There are three further key differences between the GMAP and the GMAP-Plus models:

- The GMAP-Plus model projects minimum and maximum funding scenarios for each product category, resulting in projected funding ranges. This approach reflects the high level of uncertainty associated with the development of malaria products. By contrast, the GMAP model projected only one estimate for each product category and overall.
- The GMAP-Plus model takes Phase IV expenditures for new vaccines and drugs into account, while GMAP did not. These costs were estimated in consultation with malaria experts and are listed in the product tables below.
- The GMAP-Plus model projects the expected costs of each product individually, while the GMAP model averaged total product portfolio costs over a specified time period. For example, both GMAP-Plus and GMAP estimated development costs of ten reformulations in the therapeutic drug portfolio to be $250 million over the next ten years. However, GMAP-Plus staggered the development timeline over a ten-year period, so that 'reformulation 1' and 'reformulation 2' started development in 2008, 'reformulation 2' and 'reformulation 3' in 2009 and so on, while GMAP spread the total amount evenly over ten years ($25 million per year) (see Figure 31). This staggering of product forecasts allowed us to more precisely capture fluctuations in funding needs, with a ramp-up and ramp-down period more likely to reflect real R&D cost patterns.

FIGURE 31. **Example of the difference in approach to product projections between GMAP and GMAP-Plus***



* This is merely an example and does not reflect the full extension of the GMP-Plus model.

For further information on the methodology behind the GMAP-Plus model, see the section entitled 'Specific assumptions underlying the GMAP-Plus model' later in this annexe.

Step 2: Historical levels of malaria R&D funding

Historical levels of malaria funding came from the Malaria R&D Alliance report for 2004 and from the G-FINDER survey for 2007–2009. As noted, the vector control section supplements these data with estimates of industry funding (see earlier methodology sections for more information). These retrospective funding data were then matched to ideal funding needs for the same period in order to identify the funding gap for each product type in 2008 and 2009. This can be seen where the solid green line overlaps the minimum and maximum scenarios in Figure 18 for drugs, Figure 19 for vaccines, Figure 20 for diagnostics and Figure 21 for vector control products.

Step 3: Future projections of funding needs

Ideal funding was estimated out to 2020 based on the minimum and maximum scenarios created under Step 1 above. The ideal funding pattern was matched to the minimum and maximum scenarios of each product category and can be seen as a dotted line in Figure 18 for drugs, Figure 19 for vaccines, Figure 20 for diagnostics and Figure 21 for vector control products.

Specific assumptions underlying the GMAP-Plus model

Drugs

Portfolio assumptions

Separate assumptions were developed for therapeutic and preventive drugs. Almost all assumptions came from GMAP, with the exception of those related to Intermittent Preventive Therapy (IPT) drugs.

With regard to therapeutic drugs, the GMAP-Plus model uses the same target product needs as the GMAP model, and the same number of NCEs and reformulations (see Table 9):

- Next-generation ACTs for *P. falciparum*.
- Therapy targeting the hypnozoite of *P. vivax* in the liver.
- Drugs blocking *P. falciparum* and *P. vivax* transmission (gametocytocides/sporontocides).
- Drugs aimed at avoiding resistance.

With regard to preventive drug needs, GMAP-Plus differs from GMAP. GMAP assumed that many IPT drugs would be novel candidates developed specifically for IPT use. However, the majority of products being developed for IPT are first developed as therapeutic drugs, and later tested for use in IPT (a label extension), rather than being developed *de novo* for IPT. Unlike GMAP, GMAP-Plus therefore assumes we need one NCE and two reformulations of IPTs in the next decade under our maximum scenario (see further details in Table 10), rather than all novel IPTs.

As the main portfolio assumptions were taken from GMAP, the products forecasted for the 'next decade' refer to those predicted to be developed and registered between 2008 and 2018. Products for 'subsequent decades' refer to those that will be initiated after 2018.

R&D cost assumptions

The R&D cost per NCE was estimated to be $250 million in the maximum scenario, which includes cost of failure, as per GMAP. However, review of R&D costs from the 2002 MMV annual report[32] and our internal database of malaria drug and vaccine clinical development costs suggested a realistic minimum scenario of $150 million per NCE, which was included in the minimum scenario of the GMAP-Plus model. In both scenarios, the development time of an NCE was assumed to be ten years, with an additional three years to account for Phase IV activities. The costs of Phase IV were assumed to be $1.5 million, spread out evenly over these three years.

Drug reformulations have far fewer R&D cost variables, and were therefore assigned a fixed cost of $25 million, including cost of failure (rather than a cost range), as per GMAP. However, where GMAP assumed the development time per reformulation to be two to six years and spread out the portfolio cost evenly over ten years, the GMAP-Plus model assumes a development time of an average of four years and staggers each drug over the ten years (see explanation under Step 1: Assessing funding needs). The Phase IV costs and time frame were assumed to be the same as for NCEs.

TABLE 9. **Therapeutic drug assumptions**

	MAXIMUM SCENARIO			MINIMUM SCENARIO		
	Number of products registered	**Cost of development per product**	**Cost of Phase IV per product**	**Number of products registered**	**Cost of development per product**	**Cost of Phase IV per product**
Next decade (2008–2018)	6 NCEs	$250m	$1.5m	6 NCEs	$150m	$1.5m
	10 reformulations	$25m	$1.5m	10 reformulations	$25m	$1.5m
Subsequent decades (after 2018)	2 NCEs	$250m	$1.5m	2 NCEs	$150m	$1.5m
	6 reformulations	$25m	$1.5m	6 reformulations	$25m	$1.5m

TABLE 10. **Preventive drug assumptions**

	MAXIMUM SCENARIO			MINIMUM SCENARIO		
	Number of products registered	**Cost of development per product**	**Cost of Phase IV per product**	**Number of products registered**	**Cost of development per product**	**Cost of Phase IV per product**
Next decade (2008–2018)	1 NCE	$250m	$1.5m	–	n/a	n/a
	2 reformulations	$25m	$1.5m	2 reformulations	$25m	$1.5m
Subsequent decades (after 2018)	1 NCE	$250m	$1.5m	–	n/a	n/a
	1 reformulation	$25m	$1.5m	1 reformulation	$25m	$1.5m

Vaccines

Portfolio assumptions

The assumptions for the vaccine portfolio were largely taken from GMAP and are outlined in Table 11. The only change to these assumptions relates to development of a *P. vivax* vaccine, which was assumed to be initiated in 2010 rather than 2012. There was no difference in the assumptions underlying the minimum and maximum scenarios with regard to the portfolio.

R&D cost assumptions

The estimated cost of developing a vaccine was $800 million, spread over 13 years (75% over the first ten years as part of the R&D work pre-Phase III and 25% over the following three years to account for the more expensive Phase III trials) and included cost of failure, as per GMAP. The timeline for the second-generation *P. falciparum* vaccine was lengthened to 17 years and the cost increased to $1 billion, as in GMAP.

The most important change to GMAP's cost assumptions concerns projections for the RTS,S malaria vaccine, which is nearing the end of its development process. GMAP-Plus extended the time frame for Phase III trials by one year compared to GMAP, to 2014, to reflect the most recent information available. Remaining development funding needs were front loaded, to reflect the higher expenditures required to set up the RTS,S Phase III trials that commenced in May 2009. Furthermore, additional costs of $50.4 million in the minimum scenario and $75.6 million in the maximum scenario were added to account for RTS,S Phase IV expenditures, assumed to be evenly spread between 2012 and 2016.

TABLE 11. **Vaccine assumptions**

	MAXIMUM SCENARIO			MINIMUM SCENARIO		
	Number of products registered	**Cost/Remaining cost of development per product**	**Cost of Phase IV per product**	**Number of products registered**	**Cost/Remaining cost of development per product**	**Cost of Phase IV per product**
Currently ongoing	RTS,S for *P. falciparum*	$210m	$75.6m	RTS,S for *P. falciparum*	$210m	$50.4m
From 2008 onward	New vaccine for *P. falciparum*	$1bn	n/a*	New vaccine for *P. falciparum*	$1bn	n/a*
From 2010 onward	Vaccine for *P. vivax*	$800m	n/a*	Vaccine for *P. vivax*	$800m	n/a*
From 2016 onward	Other vaccine	$800m	n/a*	Other vaccine	$800m	n/a*

* Phase IV activities fell outside the forecasting period.

Diagnostics

Portfolio assumptions

Portfolio assumptions for diagnostic products were based on research needs in the next decade as described by the malERA[25] and discussions with FIND on prioritisation of diagnostic R&D (see Table 12).

As the portfolio assumptions did not come from GMAP, the products forecasted for the 'next decade' refer to those predicted to be developed and registered between 2011 and 2020. Where more than one of the same type of product was included, such as 'more heat stable RDTs' and 'improved RDTs for *P. falciparum*', individual products were evenly staggered within the 2011–2020 time frame (see explanation under Step 1: Assessing funding needs). Development time frames were based on GMAP estimates and discussions with FIND (see Table 12).

R&D cost assumptions

Cost estimates were developed in cooperation with FIND and represent costs to progress products to registration, but not subsequent activities. Assumptions for the minimum and maximum scenarios were the same and all estimates include cost of failure.

TABLE 12. **Diagnostics assumptions**

	MAXIMUM AND MINIMUM SCENARIOS		
	Number of products registered	**Cost of development per product/programme**	**Development time frame per product**
Next decade (2011–2020)	2 improved RDTs for *P. falciparum*	$10.8m	5 years
	2 improved RDTs for non-*falciparum* parasites	$18m	5 years
	Positive control wells	$9m	3 years
	Recombinant panels for lot testing (quality control of RDTs at country level)	$14.4m	4 years
	Product testing programme	$9m	5 years
	Non-blood testing	$72m	10 years
	Automated microscopy	$21.6m	10 years
	Multiplexing	$54m	7 years
	G6PD detection	$12.6m	5 years
	High-throughput field molecular testing	$21.6m	3 years

Vector control products

Portfolio assumptions

Portfolio assumptions for malaria vector control products can be divided into two groups: development of a specific number of new active ingredients (see Table 13), and ongoing annual costs (see Table 14). These assumptions were developed in collaboration with IVCC and are the same for the minimum and maximum scenarios.

As the portfolio assumptions did not come from GMAP, the products forecasted for the 'next decade' refer to those predicted to be developed and registered between 2011 and 2020. In the case of new active ingredients, products were evenly staggered within the 2011–2020 time frame (see explanation under Step 1: Assessing funding needs). The time to develop a new active ingredient was estimated by IVCC to be nine years in total (two for optimisation, two for pre-trial development, three for development and two for registration), not including the discovery stage.

R&D cost assumptions

Costs were estimated in collaboration with IVCC and were generally the same for the minimum and maximum scenarios. The only exception was the ongoing cost of pre-development R&D, which was assumed to be $10 million per year for the minimum scenario and $15 million per year for the maximum scenario. All cost estimates include cost of failure.

TABLE 13. **Vector control product assumptions (new active ingredients)**

	MAXIMUM AND MINIMUM SCENARIOS	
	Number of products registered	**Cost of development per product/programme**
Next decade (2011–2020)	3 new active ingredients	$62.7m

TABLE 14. **Vector control product assumptions (annual ongoing costs)**

	MAXIMUM SCENARIO		MINIMUM SCENARIO	
	Ongoing programmes	**Ongoing costs**	**Ongoing programmes**	**Ongoing costs**
Next decade (2011–2020)	Screening of new candidates	$4.5m	Screening of new candidates	$4.5m
	Formulation development	$4m	Formulation development	$4m
	3 new paradigms	$15m	3 new paradigms	$15m
	Information systems and tools	$5m	Information systems and tools	$5m
	Pre-development R&D	$15m	Pre-development R&D	$10m

Other assumptions

Cost of capital

An additional 4% (based on the rate of return for US government bonds) was added to all the cost estimates listed above to account for the cost of capital.

Uncertainty multiplier

As in GMAP, Policy Cures included a multiplier of 1.2 in the maximum final cost estimates to account for uncertainty. An uncertainty multiplier of 1.1 was included in the minimum cost estimates.

Information needs

Estimates of the cost of implementation research, effectiveness studies and resistance monitoring were included in GMAP under 'Information needs R&D' but excluded from the GMAP-Plus model.

Basic research

Both the minimum and maximum scenarios included in GMAP-Plus assumed that basic research funding needs start at $133 million annually, as per GMAP, but increase at an annual

rate of 5% to 2018 to reflect likely increased basic research needs during the early years of global portfolio development. We also separated out basic research as an independent category, rather than allocating it to each product category as in GMAP. This was done to allow comparison between G-FINDER data and cost projections on basic research.

Limitations

The key limitation to the funding gap methodology relates to the underlying assumptions. Specifically, the assumed R&D costs per product, time it takes to develop a product and attrition rates in each development stage are estimations based on available data and expert approximations. This is particularly the case for malaria vaccines and new malaria diagnostic techniques such as multiplexing, which have never previously been registered.

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