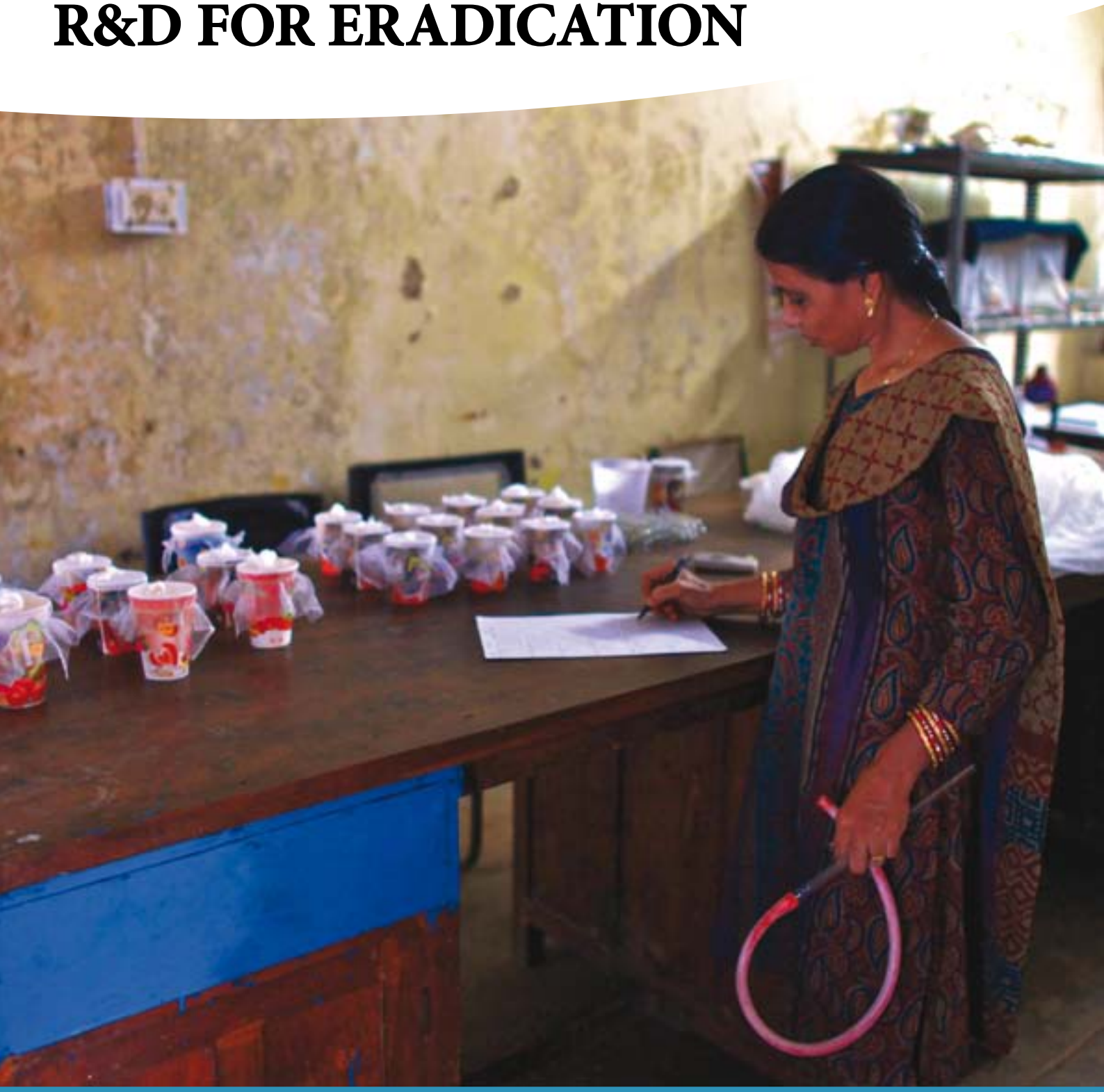
ESTIMATING COSTS AND MEASURING INVESTMENTS IN

MALARIA

R&D FOR ERADICATION



POLICYCURES

ESTIMATING COSTS AND MEASURING INVESTMENTS IN MALARIA R&D FOR ERADICATION

AUTHORED BY **POLICY CURES**

DR MARY MORAN

DR JAVIER GUZMAN

DR NICK CHAPMAN

LINDSEY WU

RACHEL HOWARD

DR PENNY FARRELL

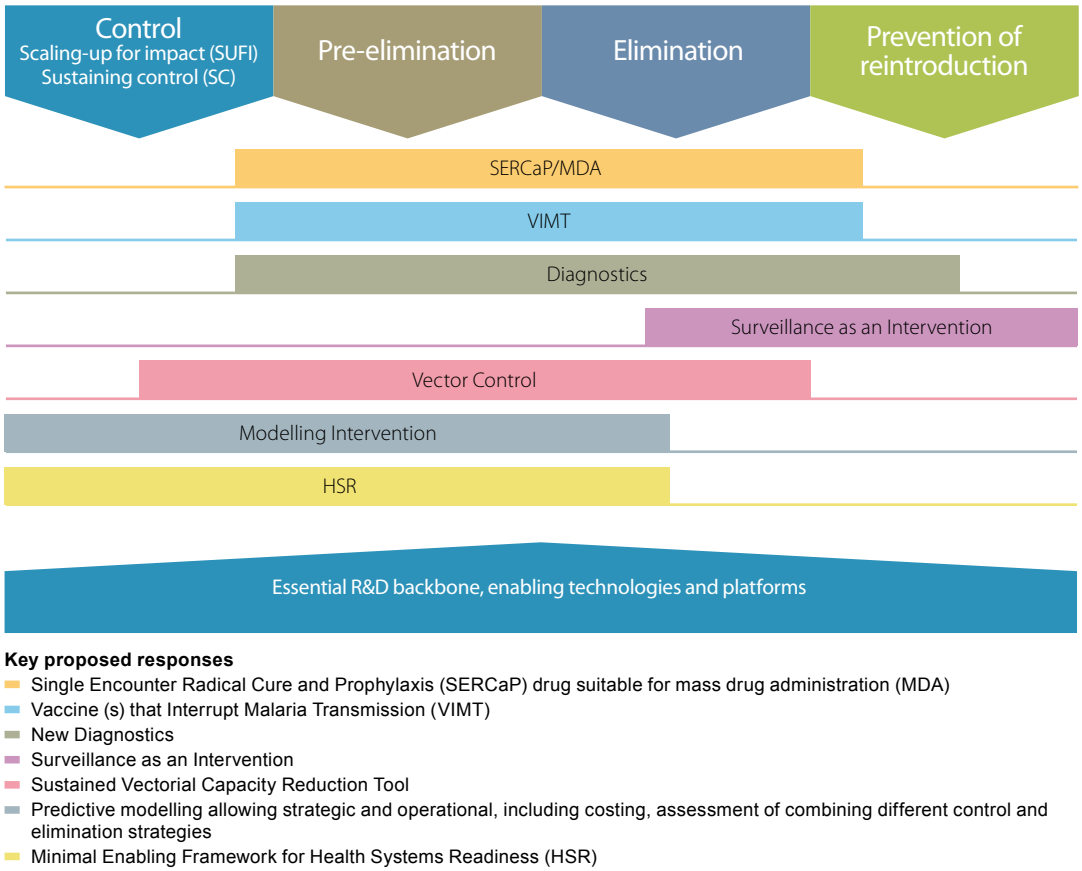
JACK LUXFORD

Cover photo: The Vector Control Research Center in Koraput, Orissa, India testing the LLIN's against the local vector (*Anopheles fluviatilis*) before distribution. © Anne Helsop

FOREWORD

Recent years have seen renewed interest in the concept of malaria eradication. This involves acceleration through enhanced malaria control to zero malaria deaths, cases and, eventually, infections. Currently available tools are sufficient to achieve elimination in some settings, as reflected by those countries certified malaria-free.[1] However, new tools are required in sub-Saharan Africa, where *P. falciparum* malaria exerts a huge burden of disease and death, and in large parts of south-east Asia and central and south America where elimination of *P. vivax* is a major challenge. The nature of the necessary innovations in tools, resource platforms, approaches and training was discussed and agreed during the malERA consultative process,[5] and are illustrated in the figure below.

Schematic of R&D categories pertinent to a malaria elimination research agenda[2]



The malaria eradication research agenda (malERA) consultative process resulted in a multifaceted R&D agenda for malaria elimination and eradication, encompassing basic research, vector control, diagnostics, drugs, vaccines, health systems and operational research, and mathematical modelling.

The levels of investment in malaria research and development (R&D) have been captured in recent years by the Policy Cures G-FINDER reports.[17] These present two sets of estimates: firstly the anticipated R&D investment needs, as determined through consultation with a broad array of stakeholders. Secondly, the actual investment in malaria R&D activities, captured through an extensive survey, developed over the last 5 years, of funders of malaria R&D. This information should enhance the ability of funders to co-ordinate efforts and improve the efficiency with which relevant products are developed.

The new report from Policy Cures, *Estimating costs and measuring investments in malaria R&D for eradication*, attempts to tease out from the overall R&D agenda the needs and investments which are specifically driven by malaria eradication. This has presented a number of technical challenges. Firstly, how is eradication-specific research to be defined? Many research outcomes relevant to eradication will have benefits for control, and vice versa. Funding for research activities and infrastructure, such as those provided as core funds to Product Development Partnerships or the National Institute of Health's support for International Centers of Excellence for Malaria Research, may also benefit both the control and eradication agendas. Secondly, malaria eradication will depend not only on the availability of new tools but also on a clear understanding of how best to deploy them. This implies the need for a portfolio of operational research that includes an enhanced understanding of how to overcome the bottlenecks in health systems which compromise the impact of tools. It is therefore important to include estimates for the costs and investments in operational and health systems research, neither of which have previously been captured. This requires a novel range of funders to engage with the investment survey and agreement on a set of assumptions surrounding the cost estimates. Thirdly, as it is not feasible to evaluate each potential combination of interventions in every setting to generate the evidence base for decisions relevant to elimination policy, there is a need to develop and use modelling techniques to tackle elimination questions. The related costs and investments of this research also need to be captured.

The Policy Cures report is the first attempt to quantify current investments and to estimate malaria R&D costs that are pertinent to the malaria elimination and eradication agenda. We trust this report will generate discussion and input for future work. The report is complementary and fully aligned with the overall malaria R&D funding analysis presented in *From Pipeline to Product: Malaria R&D funding needs into the next decade*.[7]

Estimates of resource needs will require an iterative process of revisions and updates over time, and this first report provides the baseline. As we look forward, we learn from the experiences from the Global Malaria Eradication Programme of the 1950s and 60s, and the ongoing efforts to eradicate poliomyelitis, which show that research requirements in an eradication programme do not diminish but increase overtime as new and unexpected challenges emerge.

Graham Brown, David Schellenberg, Kate Whitfeld, Marcel Tanner and Pedro Alonso.
On behalf of MESA (Malaria Eradication Scientific Alliance).
The MESA alliance works with the community to follow-up on the malERA agenda, and provides a dedicated platform to accelerate the translation of the science of malaria eradication for impact.[18]

EXECUTIVE SUMMARY

Introduction

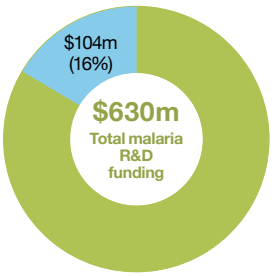
Malaria is one of the world's greatest public health challenges, with an estimated 219 million cases occurring in 2010.[1] Thanks to the rapid development of new tools, increased coverage of malaria control strategies, and a comprehensive global framework for action—the Global Malaria Action Plan[2]—there has been significant progress in malaria control globally over the last decade. Four countries have been certified free of malaria since 2007; and twenty-six additional countries are now in the process of moving from controlled low-endemic malaria to elimination.[1]

These successes spring from the research and development (R&D) that originally led to the key tools to combat malaria, such as long-lasting insecticidal nets, rapid diagnostic tests and artemisinin-based drug combination therapies. Innovation in R&D will be instrumental in achieving the ultimate goal of malaria elimination and eradication, and a coordinated R&D approach will be required to identify, develop and evaluate tailored approaches and new tools to interrupt malaria transmission. The Malaria Eradication Research Agenda (malERA) consultative process laid the foundation for this research effort, and the Malaria Eradication Scientific Alliance (MESA) follows in the footsteps of that process.

Estimating costs and measuring investments in malaria R&D for eradication presents a novel analysis of investments made in 2011 and estimates future funding needs until 2022 for malaria research pertinent to the elimination and eradication agenda. Also for the first time, costs in operational research and mathematical modelling, both research areas which will help maximise the impact of R&D, are presented here. The elimination and eradication focus of this report is complementary and fully aligned with the analysis of overall malaria R&D funding presented in *From Pipeline to Product: Malaria R&D funding needs into the next decade*.

Key findings: Overall R&D for malaria elimination and eradication

Funding in 2011



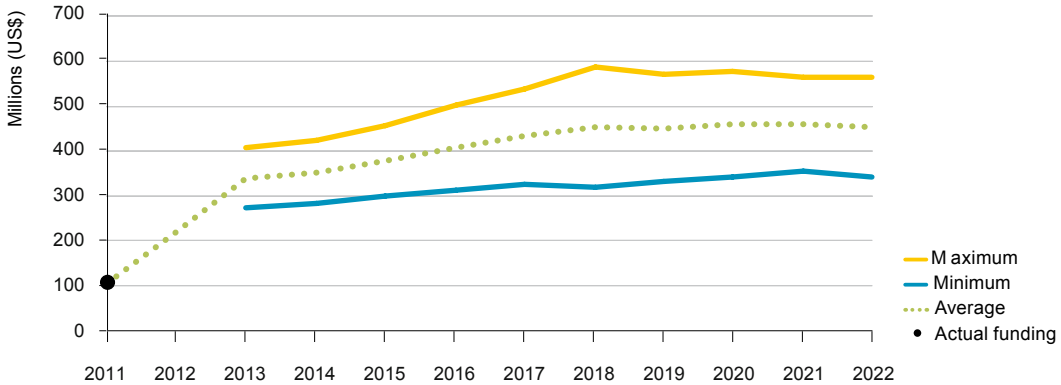
In 2011, funding for malaria elimination and eradication R&D was $104 million, 16% of total malaria R&D funding. There is a high concentration of funders, with the largest funder, the Bill & Melinda Gates Foundation, providing nearly half ($49 million, 47%) and the US National Institutes of Health (US NIH) coming in as the second largest funder ($16 million, 15%) of malaria elimination and eradication R&D overall. Although industry is a large player in malaria R&D overall, contributing nearly one-fifth of total malaria R&D funding, companies played a smaller role in elimination and eradication-specific R&D, contributing only $9.4 million (9%) of total funding for this work in 2011. Key findings for each product area include:

- Basic research: The largest funder was the US NIH ($2.0 million, 24%), followed by the Gates Foundation ($1.8 million, 21%) and the US Centers for Disease Control ($1.3 million, 16%). The majority of this funding was given to domestic academic research institutions.
- Drugs: The largest funders were the Gates Foundation ($15 million, 64%) and international aid agencies ($6.1 million, 26%). A substantial portion of this funding was given to the Medicines for Malaria Venture, which is the biggest product developer in this area, accounting for over three-quarters ($18 million, 77%) of elimination and eradication specific drug R&D.
- Vaccines: Three key funders (US NIH, the Gates Foundation and industry) accounted for 87% ($14 million) of vaccine R&D funding. These three funders contributed to transmission-blocking vaccines and some early stage *Plasmodium vivax* candidates targeting relapse prevention.
- Diagnostics: Two main funders, the Gates Foundation ($4.4 million, 26%) and US NIH ($3.3 million, 19%), provided almost half of the $17 million in funding given to malaria diagnostics R&D in 2011.
- Vector control products: Funding was dominated by the Gates Foundation which provided 63% ($20 million) of funding in 2011, followed by the public sector which provided 21% ($6.7 million).
- Novel analysis on health systems and operational research: Funding was minimal, with just 3% ($0.4 million) spent on elimination and eradication specific activities, consisting of three small grants. The total reported here is certainly an underestimate, as these figures do not capture grants from likely sources, such as the Global Fund for AIDS, TB and Malaria, or those endemic-country governments who did not provide data to G-FINDER.
- Novel analysis on modelling and harmonised data systems: the majority of funding came from the Gates Foundation ($3.9 million, 74%).

Future funding need

The overall funding needed for malaria elimination and eradication R&D is estimated at around $335 million per year in 2013, rising steadily to $450 million per year by the end of the decade, with slower growth after 2018. There is an immediate $200 million funding gap for malaria elimination and eradication R&D, as funding in 2011 was only $104 million.

FIGURE 1
Projected elimination and eradication R&D funding need, 2013-2022 (2011 US$)



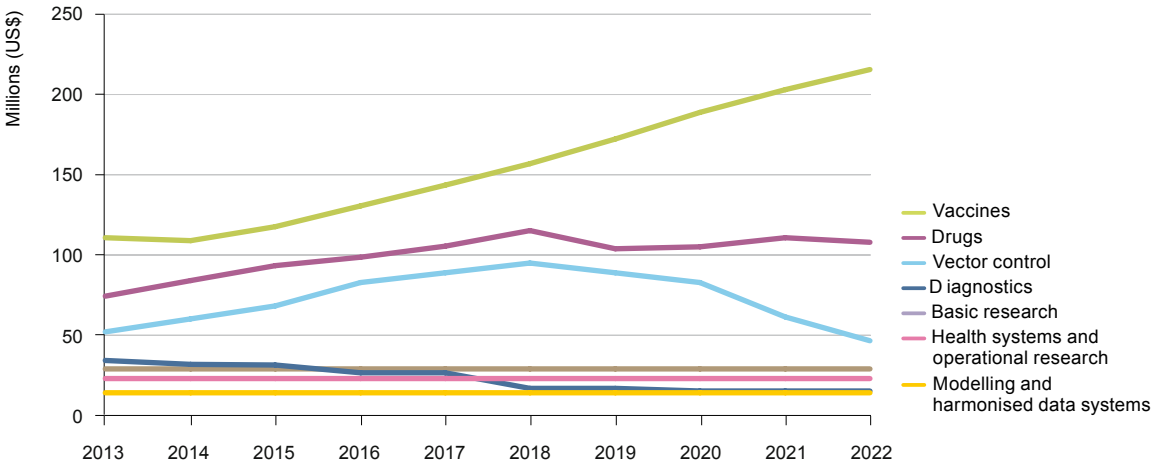
The full set of inputs and assumptions for the cost projections are included in Annexe 2.

The overall funding need and patterns are largely driven by R&D for vaccines and to a lesser extent, drugs, as these are the product areas that have specific elimination and eradication portfolios.

Vaccines account for around 37% of total funding needs over the next decade and will require a steady increase in funding: this reflects the need to rapidly build a pipeline of vaccine candidates if transmission-blocking vaccines are to be a reality in the next thirty to forty years. Drugs account for 24% of total funding needs, with funding needs increasing up to 2018, stabilising thereafter; this need will be driven by clinical trials of several late stage candidates and several expected combination drug trials, as well as the development of novel candidates (new chemical entities) to address resistance.

Vector control products account for 18% of total funding, and will require steady increases until a peak in 2018 at around $90 million, and will subsequently decrease significantly. Funding for other R&D areas has only a limited impact on overall elimination and eradication funding trends, with basic research accounting for 7% of the total funding need, diagnostics 6%, health systems and operational research 6%, and modelling and development of harmonised data systems just over 3%.

FIGURE 2
Projected average R&D funding need by product type, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

Snapshot: Funding in 2011 and future funding need

Funding needs for malaria elimination and eradication R&D are influenced by the development costs of each product type (from high cost vaccines to low cost diagnostics); the state of the science; the advancement of the product pipeline; and the novelty and ambitiousness of the scientific goals that need to be met to develop a product.

TABLE 1
Total and elimination and eradication (E&E)-specific malaria R&D funding by research area

Research area	Total malaria R&D funding 2011 (US$)	Malaria E&E R&D funding 2011 (US$)	E&E as a % of total malaria R&D investment 2011	Immediate annual E&E R&D funding requirement (US$)^	Total E&E R&D funding required over next decade (US$)^
Basic research	$173m	$8m	5%	$27-31m	$273-307m
Drugs	$218m	$24m	11%	$62-86m	$697m-1.3bn
Vaccines	$152m	$16m	10%	$100m	$1.1-2.0bn
Diagnostics*	$17m	$17m	100%	$28-40m	$175-288m
Vector control*	$32m	$32m	100%	$48-56m	$676-773m
HS&OR	$13m	$0.4m	3%	$14-31m	$147-$317m
Modelling and harmonised data systems	$7.4m	$5.3m	71%	$13-16m	$128-159m

^ Funding projections are expressed in 2011 US$.
* All malaria diagnostic and vector control R&D funding has been categorised as elimination and eradication specific.

What products will this investment deliver?

Ten years of investment in malaria elimination and eradication R&D at the levels shown above will deliver a wide range of new tools to move us towards the goal of eliminating and eradicating malaria, including:

- Two new single dose malaria tablets that can prevent relapsing infections, as well as treating all types of malaria (single exposure radical cure and prophylaxis).
- A single tablet that can protect against malaria for up to a month (single exposure chemoprevention).
- A field test to detect low levels of malaria parasites, to help wipe out remaining foci of infection.
- A malaria test that avoids the need to take blood from subjects, including small children.
- Three improved new active ingredients (chemicals) for use in insecticide-treated bednets and indoor spraying in houses.
- A follow-on generation of new approaches to chemical and biological control of malaria-carrying mosquitoes.
- A thriving pipeline of back-up products in all areas, including vaccine candidates to permanently block transmission of malaria.
- Mathematical models informing the design of randomised trials and programmes.
- Health systems and operational research spanning the spectrum from the health facility-level to the global level.

Recommendations

There is an opportunity to increase the focus on the goal of worldwide malaria elimination and eradication, and build on R&D successes to date. Researchers and funders need to work with aligned priorities in the areas of basic research, vector control, diagnostics, drugs, vaccines, health systems, and modelling. With this purpose in mind, we recommend:

1. Funding for malaria elimination and eradication R&D needs to increase by $200 million per annum in the immediate term, and $300 million per annum by the end of the decade.
    - Funding for elimination and eradication is currently less than a sixth of malaria R&D overall; when it should represent two-thirds of the total malaria R&D investment over the next decade.
2. Funders need to strengthen their coordination efforts towards meeting specific elimination and eradication targets in order to optimise the efficiency, cost and timeframes of this global endeavour.
3. New funders and funding models are required for diversification of malaria R&D funding for elimination and eradication.
    - More funders should become more engaged in progressing the elimination and eradication R&D agenda, including through the set-up of specific calls for proposals or funding streams.
    - The pharmaceutical industry should increase its role in malaria eradication and elimination R&D.
4. Funding should be flexible and linked to product development.
    - Funding should be dynamic and reviewed regularly so that it responds to product and portfolio developments across research and product areas. This is especially important for elimination and eradication R&D, where the wider landscape is still evolving in the face of product interactions yet-to-be fully identified.

ACKNOWLEDGEMENTS

We would like to extend our collective gratitude to the people who gave their time and expertise during the course of this project.

The report would not have been possible without the input of the following key organisations and individuals: Malaria Eradication Scientific Alliance – Pedro Alonso, Marcel Tanner, David Schellenberg, Graham Brown, Kate Whitfield and Anna Rebecca Oje; PATH Malaria Vaccine Initiative – David Kaslow, Ashley Birkett, Cynthia Lee and Theresa Raphael; Medicines for Malaria Venture – Tim Wells, Claude Oeuvray, Andrea Lucard and Matthew Doherty; Innovative Vector Control Consortium – Tom Mclean and Jed Stone; and the Foundation for Innovative New Diagnostics – Jerome St-Denis, David Bell and Mark Perkins.

We would also like to thank the Bill & Melinda Gates Foundation for assistance with our portfolio modelling, and the additional experts who provided input on the technical modelling aspects (see annexes for further detail).

Graphic design was provided by Shigemi Nakamura-Simms of Polkadot Graphic.

CONTENTS

ACRONYMS

ACT	Artemisinin-based combination therapy
AIDS	Acquired Immunodeficiency Syndrome
Brazilian FINEP	Brazilian Innovation Agency
CRTs	Cluster randomised trials
Danish DANIDA	Danish International Development Agency
E&E	Elimination and eradication
FIND	Foundation for Innovative New Diagnostics
G6PD	Glucose-6-phosphate-dehydrogenase
Gates Foundation	Bill & Melinda Gates Foundation
G-FINDER	Global Funding of Innovation for Neglected Diseases
GSK	GlaxoSmithKline
HS	Health systems
Indian ICMR	Indian Council for Medical Research
IRS	Indoor residual spraying
ITN	Insecticide-treated bednet
IVCC	Innovative Vector Control Consortium
malERA	Malaria Eradication Research Agenda
MESA	Malaria Eradication Scientific Alliance
MMV	Medicines for Malaria Venture
MVI	Malaria Vaccine Initiative
NCE	New chemical entity
OR	Operational research
PATH	Program for Appropriate Technology in Health
PDP	Product development partnership
PTS	Probability of technical success
R&D	Research and development
RDT	Rapid diagnostic test
SEC	Single exposure chemoprevention
SERCaP	Single exposure radical cure and prophylaxis
TCP	Target candidate profiles
UK	United Kingdom
UK DFID	UK Department for International Development
EIR	Entomological Inoculation Rate
UK MRC	UK Medical Research Council
US	United States
US CDC	US Centers for Disease Control
US NIH	US National Institutes of Health

INTRODUCTION

Despite impressive progress and significant increases in funding over the last decade, malaria remains one of the world's great public health challenges, claiming the life of a child in Africa each minute and the life of a pregnant woman worldwide each hour.[3,4] There were an estimated 219 million cases of malaria in 2010,[1] despite the fact that the disease is both preventable and curable.

Yet with improvements in tools and coverage and a comprehensive global framework for action—the Global Malaria Action Plan,[2] developed by the Roll Back Malaria Partnership and endorsed by the global malaria community in 2008—it has become possible to speak not only of controlling malaria, but also of eliminating and eradicating malaria. Whereas malaria control focuses on reducing malaria to a level where it is no longer a public health problem, malaria elimination seeks to reduce the incidence of malaria infection to zero through deliberate efforts within a defined geographical area. Malaria eradication goes one step further than elimination, aiming for the permanent reduction to zero of the worldwide incidence of infection caused by malaria parasite species, reaching a state where intervention measures are no longer needed (see Box 1).[1]

Box 1. Definitions[5]

Control: Reduction of disease incidence, prevalence, morbidity, or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction.

Elimination: Reduction to zero of the incidence (new cases of malaria) of locally transmitted malaria infection in a defined geographical area as a result of deliberate efforts. With elimination, continued intervention measures are required to prevent reestablishment of transmission.

Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate efforts. Intervention measures are no longer needed once eradication has been achieved.

Elimination and eradication of malaria worldwide is the ultimate goal and some countries are already proving successful in achieving their targets. Four countries have been certified free of malaria since 2007 (Armenia, Morocco, Turkmenistan and the United Arab Emirates) and were the first endemic countries to be declared malaria free since the 1980s.[6] Twenty-six additional countries are now in the process of moving from controlled low-endemic malaria to elimination.[1]

Scope of malaria elimination research

Research is, and will continue to be, a vital component of a successful malaria eradication effort. The successes we see today spring from the research and development that led to the key tools to combat malaria, such as long-lasting insecticidal nets, rapid diagnostic tests, and artemisinin-based combination therapies (ACTs). Malaria elimination and eradication require a research programme to identify, develop and evaluate tailored approaches and new tools to interrupt transmission and provide the necessary evidence to inform policy making.

The Malaria Eradication Research Agenda (malERA) consultative process laid the foundation for this research effort. The malERA process highlighted the need to tackle malaria at the level of infection, both symptomatic and asymptomatic, so that transmission is interrupted. It elevated the importance of *Plasmodium vivax*, the neglected human malaria parasite, which lies dormant in the liver and causes relapses over a person's lifetime. Grounded in these key concepts, a multifaceted R&D programme is needed for malaria elimination, encompassing basic research, vector control, diagnostics, drugs, vaccines, health systems and operational research, and modelling. Areas which stand out include: basic research of the *P. vivax* liver stage; new metrics to measure falling transmission; sensitive diagnostic tools for screening, surveillance, and response approaches; tools which protect against and clear infection including vaccines, vector control and drug combinations; and operational research to test the applicability of tools and to overcome constraints limiting the effectiveness of interventions. The Malaria Eradication Scientific Alliance (MESA) follows in the footsteps of the malERA initiative. MESA supports research which tackles some of the critical hypotheses in malaria eradication science. The alliance brings together scientists from all regions and multiple disciplines to advance the debate and take coordinated action.

Financing research: investing in tools and knowledge for eradication

The *Estimating costs and measuring investments in malaria R&D for eradication* report takes the first look at where investments are being made in support of the eradication research agenda. The report presents a novel analysis of investments made in 2011 and estimates future funding needs until 2022 for malaria research pertinent to the elimination and eradication agenda. The eradication focus of this report is complementary and fully aligned with the analysis of overall malaria R&D funding presented in the PATH MVI report *From Pipeline to Product: Malaria R&D funding needs into the next decade*.[7]

As there is a continuum from control to elimination, the categorisation of research activities for elimination is not an exact science. For the purposes of this report, research which was deemed 'primarily for elimination' according to the malERA research agenda formed the basis of the elimination and eradication dataset presented here. For most research areas, elimination and eradication specific activities are a subset of total malaria investment; this is true for basic research and enabling technologies, drugs, vaccines, health systems and operational research, and data modelling. In contrast, all research activities for diagnostics and vector control products are considered relevant for elimination and eradication, so in these two research areas there is no distinction made between control and elimination, and all funding is included (see Annexe 1 for more information).

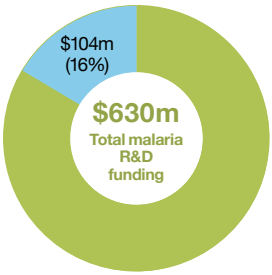
In this report, we present a novel focus on the malaria funding landscape:

- The scope of research encompasses basic research, vector control, drugs, vaccines, diagnostic and, for the first time for a financial analysis of malaria research, health systems and operational research, as well as modelling and harmonised data systems.
- The first quantification of research investments specific to elimination is presented for financial year 2011.
- Estimated cost ranges of elimination-specific research are projected for the next decade.

The authors present this analysis as a tool to indicate how and where the elimination and eradication R&D agenda is being supported, as well as demonstrating potential funding gaps that will need to be addressed in order to deliver the tools and knowledge necessary for malaria eradication. *Estimating costs and measuring investments in malaria R&D for eradication* aims to support policy makers and funders in making investment decisions, and research organisations in the development of strategic and high-impact malaria elimination research portfolios.

OVERALL R&D FUNDING FOR MALARIA ELIMINATION AND ERADICATION

Funding for malaria elimination and eradication R&D in 2011



In 2011, funding for malaria elimination and eradication R&D was $104 million, or 16% of total malaria R&D funding, with the Gates Foundation providing nearly half ($49 million, 47%). Around 90% of the Gates Foundation's funding went to not-for-profit organisations, including more than one-third to the Foundation for the National Institutes of Health ($18 million, 37%), and just over one-quarter ($13 million, 27%) to product development partnerships (PDPs) including the Medicines for Malaria Venture (MMV), PATH Malaria Vaccine Initiative (MVI), the Innovative Vector Control Consortium (IVCC) and the Foundation for Innovative New Diagnostics (FIND). A further quarter went to universities and academic institutions around the world ($13 million, 26%).

The US National Institutes of Health (US NIH) was the second largest funder of elimination and eradication R&D in 2011, providing $16 million (15%). Nearly two-thirds ($9.8 million, 61%) of its funding went to US universities via investigator initiated grants, and a further one-quarter ($3.9 million, 25%) was invested internally into US NIH vaccine candidates relevant to elimination and eradication.

Although industry is a large player in malaria R&D overall—it contributes nearly one-fifth of total malaria R&D funding—companies played a smaller role in elimination and eradication specific R&D, contributing only $9.4 million (9% of total funding) for this work in 2011. This included investment by small pharmaceutical and biotechnology companies into vector control and diagnostic R&D, and by multinational corporations into drug and vaccine candidates. Examples include Sanofi's work on primaquine; and GlaxoSmithKline's (GSK) work on *P. vivax* vaccines and partnerships with MMV on transmission-blocking platforms.

The UK Department for International Development (UK DFID) and the European Commission provided modest amounts to PDPs and European academic research institutions (respectively) for elimination and eradication specific R&D.

With the exception of the Gates Foundation, all top funders in 2011 (11 out of 12) indicated that the elimination and eradication agenda has not directly affected their funding priorities.

TABLE 2
Top 12 funders of malaria elimination and eradication (E&E) R&D in 2011 (2011 US$)

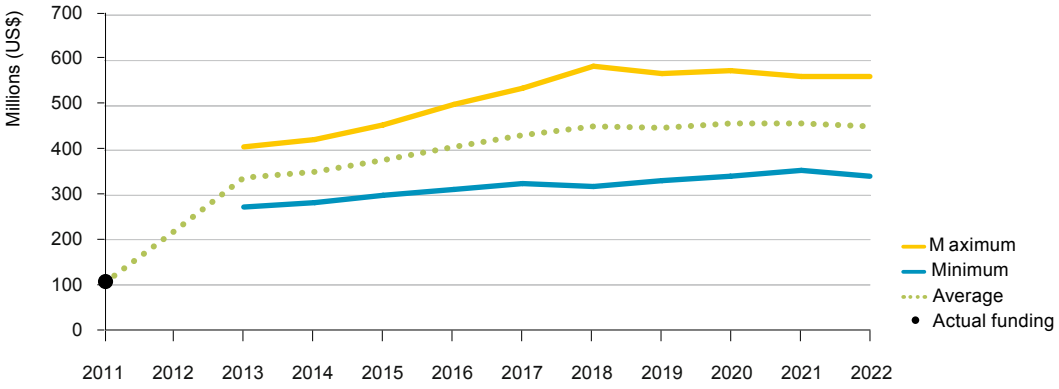
Funding organisation	Total malaria R&D funding 2011[7^]	Malaria E&E R&D funding 2011	% of total E&E-specific funding 2011
Gates Foundation	157,003,409	49,149,027	47.5%
US NIH	132,729,353	15,963,605	15.4%
Aggregate industry	97,998,839	9,393,666	9.1%
UK DFID	21,028,609	5,270,317	5.1%
European Commission	30,022,549	4,922,775	4.8%
UK MRC	18,819,627	2,795,601	2.7%
Danish DANIDA	4,499,202	2,240,466	2.2%
Wellcome Trust	28,979,111	1,876,240	1.8%
Institut Pasteur	7,047,880	1,669,361	1.6%
US CDC	2,781,117	1,557,316	1.5%
Indian ICMR	5,064,891	1,352,943	1.3%
Brazilian Innovation Agency (FINEP)	1,127,609	905,844	0.9%
Top 12 subtotal	507,102,196	97,097,161	93.9%
Grand total	609,577,790	103,581,334	100%

^ Does not include investment in health systems and operational research, and modelling and harmonised data systems.

Future funding needs

Overall funding needed for malaria elimination and eradication R&D is around $335 million in 2013, rising steadily to around $450 million per year by the end of the decade, although with slower growth after 2018. These patterns reflect a steady increase in vaccine R&D needs throughout the decade; while drug R&D funding needs increase to 2018, stabilising thereafter; and vector control funding demand decreases significantly after a 2018 peak. Funding for other R&D areas has only a limited impact on overall funding trends.

FIGURE 3
Projected elimination and eradication R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

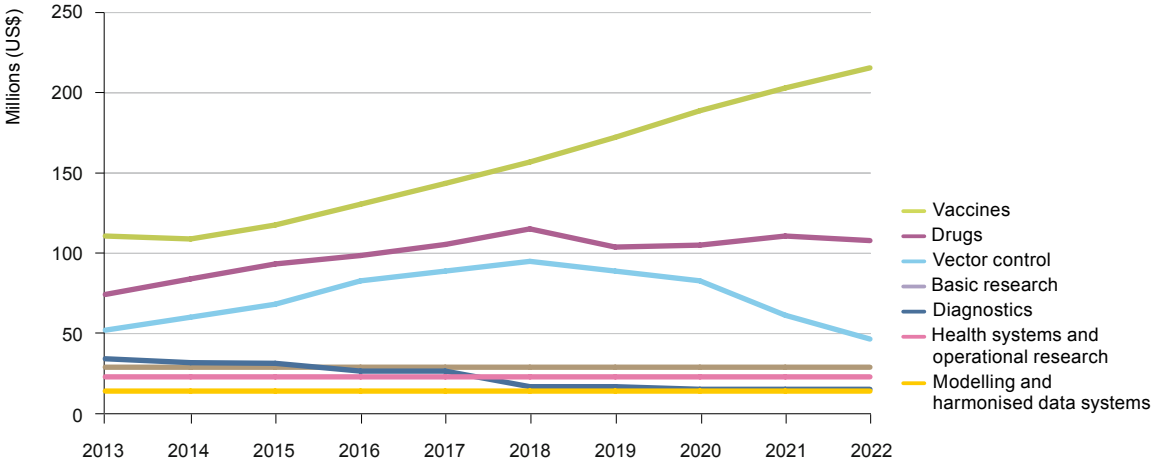
Vaccines account for around 37% of the total funding needs for the elimination and eradication agenda over the next decade and are the key driver behind overall increases in elimination and eradication R&D funding over that time: this reflects the need to rapidly build a pipeline of vaccine leads if transmission-blocking vaccines are to be a reality in the next thirty to forty years. Drugs account for 24% of total funding, driven by clinical trials of several late stage candidates and several expected combination drug trials, as well as the development of novel candidates (new chemical entities—NCEs) to address resistance. Vector control products account for 18% of total funding required over the next decade; basic research for 7%, diagnostics for 6%, health systems and operational research for 6%, and modelling and development of harmonised data systems for just over 3%.

TABLE 3
Total and E&E-specific malaria R&D funding by research area

Research area	Total malaria R&D funding 2011 (US$)	Malaria E&E R&D funding 2011 (US$)	Immediate annual E&E R&D funding requirement (US$)	Total E&E R&D funding required over next decade (US$)	% of total malaria E&E R&D over next decade
Basic research	$173m	$8m	$27-31m	$273-307m	7%
Drugs	$218m	$24m	$62-86m	$697m-1.3bn	24%
Vaccines	$152m	$16m	$100m	$1.1-2.0bn	37%
Diagnostics^	$17m	$17m	$28-40m	$175-288m	6%
Vector control^	$32m	$32m	$48-56m	$676-773m	18%
HS&OR	$13m	$0.4m	$14-31m	$147-317m	6%
Modelling and harmonised data systems	$7.4m	$5.3m	$13-16m	$128-159m	3%

^ All malaria diagnostic and vector control R&D funding has been categorised as elimination and eradication specific.

FIGURE 4
Projected average R&D funding need by product type, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

However, funding allocation between research areas does not only reflect the progress of candidates through each pipeline. It also reflects the varying costs of developing each product type (from high cost vaccines to low cost diagnostics) and the fact that only a fraction of the total cost of drug development is attributable to elimination and eradication studies, unlike transmission-blocking vaccines and vector control and diagnostic products, where all R&D costs are relevant to elimination and eradication.

Another critical factor determining how much funding is needed for each sector is the novelty and ambitiousness of its scientific goals. The more novel and ambitious a research area is, the more funding will be needed to build a product portfolio from scratch, and to test out new approaches until a successful way forward is discovered. For this reason, the very high uncertainty ranges in the above figures—up to $200 million on either side throughout the decade—are largely the result of scientific and cost uncertainties around the new transmission-blocking vaccines and the novel drug R&D approaches aimed at preventing relapse and potentially blocking transmission. By contrast, uncertainty ranges for more established product and research areas are far lower, less than $10 million on either side in each case.

Finally, we note that the impact of interactions among the different product areas is another area of uncertainty. Although most of the target product profiles used in the development of the interventions have been well defined, the wider landscape is still evolving in the face of a yet-to-be fully defined eradication agenda. The interactions between drugs, vaccines, vector control and diagnostics will have an impact on the types of interventions needed if the goal of eradication is to be achieved. This in turn will affect funding needs. For example, if a new diagnostic tool is necessary to accompany the roll out of a new vaccine, the funding requirements for diagnostics would be impacted. Therefore, current estimates of required funding may change as the portfolio of each intervention evolves.

Overall product development: What new malaria elimination and eradication tools will we have by 2022?

Ten years of investment in malaria elimination and eradication R&D at the levels shown above will deliver a wide range of new tools to move us towards the goal of eliminating and eradicating malaria including:

- Two new single dose malaria tablets that can prevent relapsing infections, as well as treating all types of malaria (single exposure radical cure and prophylaxis).
- A single tablet that can protect against malaria for up to a month (single exposure chemoprevention).
- A field test to detect low levels of malaria parasites, to help wipe out remaining foci of infection.
- A malaria test that avoids the need to take blood from subjects, including small children.
- Three improved new active ingredients (chemicals) for use in insecticide-treated bednets (ITNs) and indoor spraying in houses.
- A follow-on generation of new approaches to chemical and biological control of malaria-carrying mosquitoes.
- A thriving pipeline of back-up products in all areas, including vaccine candidates to permanently block transmission of malaria.
- Mathematical models informing the design of randomised trials and programmes.
- Health systems and operational research spanning the spectrum from the health facility-level to the global level.

BASIC RESEARCH AND ENABLING TECHNOLOGIES

Basic research includes activities that increase scientific knowledge and understanding about malaria but which are not yet directed towards a specific product, for example, studies of disease processes, the parasite causing the disease (the pathogen) and the organism transmitting the parasite (the mosquito vector). Enabling technologies include tools that are not product specific but will support the discovery and development of new vaccines, drugs, diagnostics and vector control products.

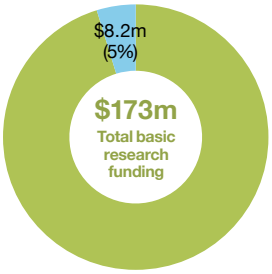
Ten-year priorities

Priorities for basic research and enabling technologies to support malaria elimination and eradication in the next ten years include:

- Innovative metrics to measure malaria transmission—as we move closer to elimination and malaria transmission levels decrease, new tools and indices will be needed. Traditional metrics such as the entomological inoculation rate (EIR) are not suitable for measuring very low levels of transmission densities.
- Improved animal models to study and validate biomarkers for transmission and immune responses.
- The development of *in vitro* cell cultures of liver stage *Plasmodium falciparum* parasites, and asexual and liver stage *P. vivax* parasites. Currently, we do not have stable and continuous cell cultures of these parasite stages and this prevents the systematic screening of chemical entities for activity against these parasite forms.
- Characterisation of the *Plasmodium* parasite metabolome (all the small molecules resulting from the metabolic processes in the parasite) to fully understand the metabolic processes of the parasite life-cycle.
- Identification of novel classes of molecules that can affect gene function during the transition stages of the parasite life cycle.
- New genetic technologies to identify gene functions and gene-drug interactions. Identifying scalable genetic technologies that allow for sharing genome-wide sets of genetically modified parasite lines will allow us to better understand the parasite's stage-specific biology to be targeted with drugs or vaccines, and will enable the systematic large-scale production of parasite samples for testing, avoiding duplication and increasing efficiency. This research can also inspire new experimental approaches to solve elimination and eradication specific questions;

- Characterisation of mosquito stages of the parasite life cycle; and development of techniques to suppress expression of mosquito genes which are needed for transmission of the parasite.
- Research of the glucose-6-phosphate-dehydrogenase (G6PD) genetic mutation and the susceptibility of the different genetic variants to different drugs.

Funding for basic research and enabling technologies in 2011



In 2011, 5% ($8.2 million) of malaria basic research funding was spent on elimination and eradication-specific activities. The main funders were the US NIH ($2.0 million, 24%), the Gates Foundation ($1.8 million, 21%) and the US Centers for Disease Control (US CDC, $1.3 million, 16%).

The majority of funding ($6.9 million, 84%) was provided as grants to academic research institutions. While the Gates Foundation gave targeted grants to organisations internationally, funding from government science and technology agencies such as the US NIH and the Australian National Health and Medical Research Council primarily went to domestic academic institutions and reflected investigator priorities.

The figures for malaria basic research funding analysis presented here may be slightly lower than the real totals. This is because:

a) This was the first attempt to measure elimination and eradication-specific investments, meaning that elimination and eradication criteria are still being defined—specifically in relation to detailed cut-off points between R&D categories and stages. Grey areas still exist and some criteria may need to be better categorised;

b) Some G-FINDER survey participants are unable to provide detailed, disaggregated data about basic research. This hampered our ability to identify and adequately categorise elimination and eradication-specific investments.

Future funding needs

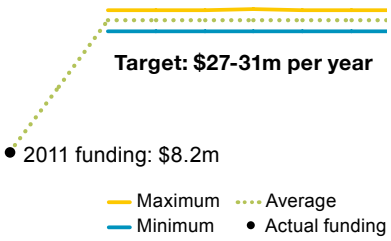
Box 1. Key model assumptions (see Annexe 2 for full details)

Total costs for R&D activities:

- Measuring malaria transmission - $84 million
- Distribution of severe G6PD variants - $2-4.7 million
- Characterisation of the entire *Plasmodium* metabolome - $17.5 million
- *In vitro* culture systems for *P. falciparum* - $10.5-15 million
- *In vitro* culture systems for *P. vivax* - $29-30 million
- Improved animal models - $15 million
- Identification of novel classes of molecules - $22.5 million
- New genetic technologies - $59.2 million

Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum; costs are spread evenly across 10 years

FIGURE 5
Projected elimination and eradication basic research R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

To achieve the ten-year priorities outlined above, annual funding for basic research and enabling technologies for malaria elimination and eradication will need to more than triple, from the current $8.2 million per year to around $27-31 million per year, and will then need to stay at this level throughout the decade (real life funding will, of course, fluctuate from year to year). Total funding needs for the next decade will be in the range of $273-307 million.

Within basic research and enabling technologies, the areas likely to require the most funding include:

- Measuring malaria transmission, estimated at approximately $84 million over the next ten years;
- New genetic technologies to identify gene function and gene-drug interactions, estimated at $59 million over the next ten years;

The data on the basic research investment in 2011 does not include the investments made into cell culture for *P. vivax* blood stage parasites. These investments, a total of $29-30 million over the next ten years, were categorised as 'drug discovery' through the G-FINDER survey and are presented here in the chapter on drugs.

DRUGS

Antimalarial drugs are primarily used to treat clinical malaria, but they are increasingly also being used as preventives in pregnant women and children in particular. However, existing antimalarials do not cure all parasite stages and are only effective in protecting against clinical malaria (as opposed to asymptomatic malaria infection). Meanwhile, drug resistance to ACTs is a growing threat.

New antimalarial drugs will be essential tools in the path towards elimination and eradication. Used in conjunction with other interventions, they will play a critical role in driving down malaria transmission, preventing reintroduction, and eliminating residual foci of infection.

Ten-year priorities

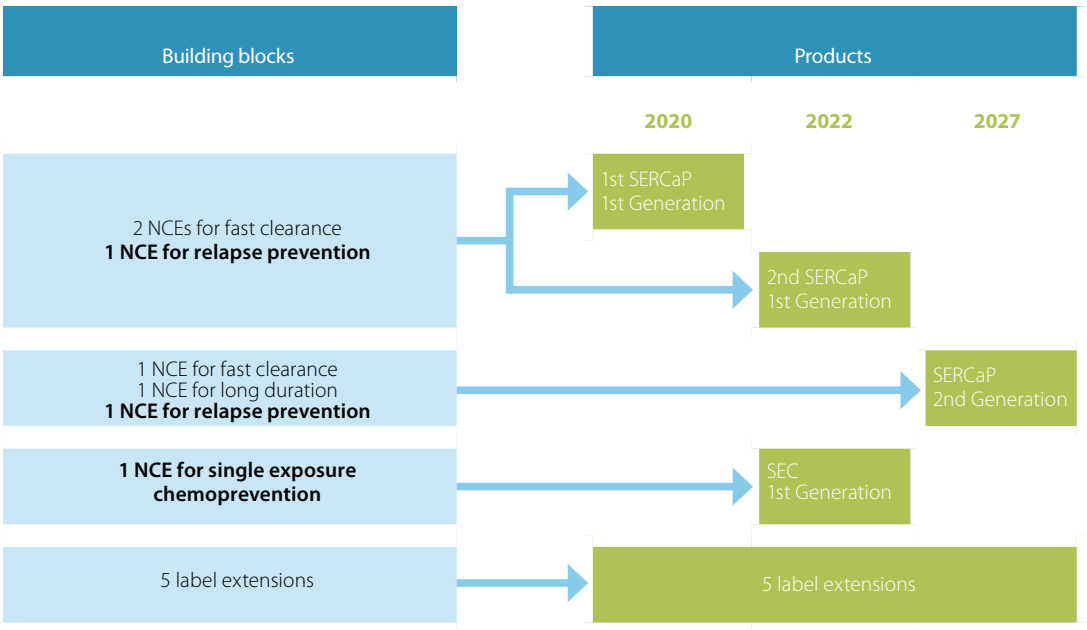
Ten-year priorities for drug R&D include the development of two new product types that will be key to achieving malaria elimination and eradication:

- **Single exposure radical cure and prophylaxis (SERCaP)**, combination therapies that are a radical cure against all malaria life cycles and species in a single dose, and prevent relapsing malaria infection; and
- **Single exposure chemoprevention (SEC)**, a compound ideal for prevention that provides month-long protection against malaria with a single dose and is suitable for mass administration.

These new combination malaria medicines will in turn require the development of several building blocks (see Annexe 2 for full information), including:

- Six new chemical entities (NCEs) that will feed into SERCaP therapies. (This includes early work on three NCEs to feed into a more advanced second-generation SERCaP, which should be ready for subjects around 2027.)
- One NCE for SEC.
- Once these new NCEs are registered, development of several of them as label extensions (registration of an existing drug for new subject groups or uses).

FIGURE 6
Malaria drug building blocks and products expected in the future

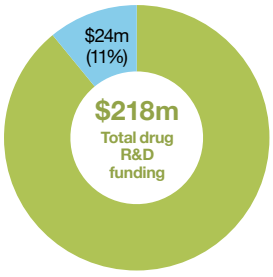


* The **bold NCEs** are being developed for use in elimination and eradication, focussing on prevention of relapse in the liver stage, transmission blocking and prophylaxis: their full costs are therefore attributed to elimination and eradication. All other drugs are being primarily developed for malaria control, but include modest additional studies (usually only Phase IIa trials) to test their elimination and eradication properties: only partial costs are therefore included for these.

Some of these elimination and eradication targets need to have their full development funded, including those for SEC and at least one NCE to prevent relapse. However, in most cases, the costs of developing products for elimination and eradication are heavily cross-subsidised. This is because most NCEs are already being developed for use in SERCaP as a malaria treatment, and only modest studies are needed to additionally test each compound for its potential elimination and eradication properties (usually only Phase II trials). This makes development of elimination and eradication specific drugs particularly cost-effective.

Funding for drug R&D in 2011

In 2011, 11% ($24 million) of funding for malaria drug R&D was spent on research specific to elimination and eradication. The largest funders were the Gates Foundation ($15 million, 64%) and international aid agencies ($6.1 million, 26%), including UK DFID, the United States Agency for International Development, Irish Aid and the Swiss Agency for Development and Cooperation. The US NIH also played a role, investing $1.1 million (5%) in 2011.



A significant portion of this funding was given as core funding to MMV, which in turn allocated around one-quarter of its investments to elimination and eradication-specific R&D ($7.6 million, 25%).[i]

MMV is the biggest product developer in this area, representing over three-quarters of all expenditure on elimination and eradication drug R&D ($18 million, 77%). MMV's candidates (such as NITD609, OZ439 and GNF156) are some of the most advanced in the pipeline. The

[i] Product development partnerships such as MMV are often financed through non-earmarked core funding grants. We therefore analysed each PDP's 2011 R&D expenditure to determine the proportion of core funding going to elimination and eradication-specific R&D.

remaining quarter of funding ($5.4 million, 23%) was disbursed to universities and research institutions including the Liverpool School of Tropical Medicine, the University of Oxford, Johns Hopkins University, Yale University and the Queensland Institute of Medical Research.

Future funding needs

Box 3. Key model assumptions (see Annexe 2 for full details)

Total costs, durations and probability of successful phase completion for individual R&D activities:

- Discovery -$5-7.5 million
- Preclinical - $1.8-2.1 million; 1.5-3 years; 55%
- Phase I - $1.5-1.7 million; 1-2 years; 60%
- Phase IIa - $1.2-2.3 million; 1.5-2 years; 30%
- Phase IIa TCP 4 - $2.4-4.6 million; 1.5-2 years; 30%
- Phase IIb - $10.7-14 million; 3.5-4 years; 75%
- Phase IIb SERCaP - $10.7-14 million; 3.5-4 years; 40%
- Phase III - $31-35.7 million; 2.5-4 years; 73%
- Phase III SERCaP - $31-35.7 million; 2.5-4 years; 40%
- Phase IV - $10-11.5 million; 5 years; 98%
- FDCs and label extensions - $5-11.5 million; 3 years

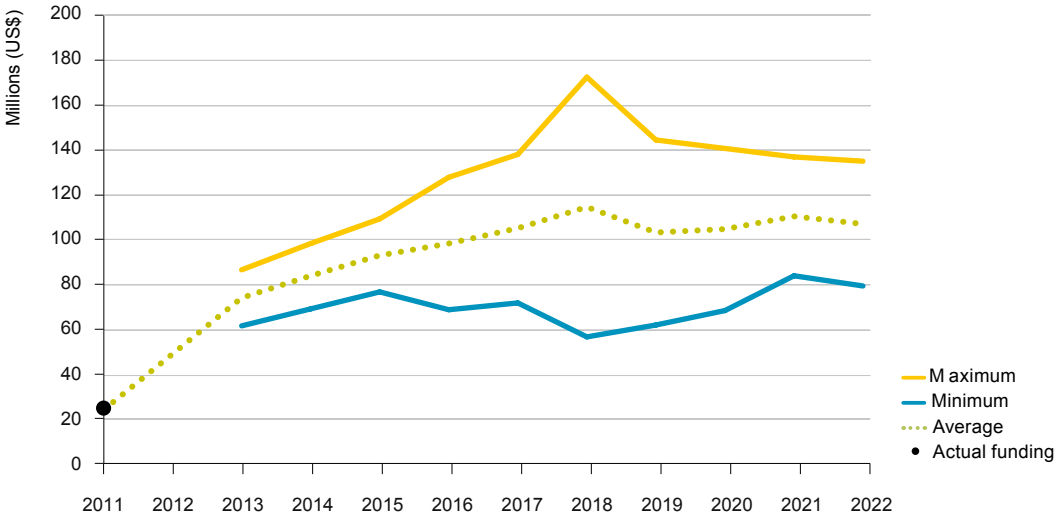
Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum

Drugs strategic goals are listed in Annexe 2

In 2011, investments in elimination and eradication drug R&D totalled $24 million. To meet immediate R&D needs, this investment will rapidly need to more than double to $62-86 million, which will include support for candidates already in late stage clinical trials such as tafenoquine (currently in Phase III), NITD609 (Phase IIa) and OZ439 (Phase IIa).

Funding needs will continue to rise steadily over the next decade to cover the cost of early stage preclinical candidates, late stage clinical trials, and the development of new combination products, including for SERCaP. Overall, drug R&D for malaria elimination and eradication will require $697-1,289 million over the next ten years.

FIGURE 7
Projected elimination and eradication drug R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

What will this investment deliver by 2022?

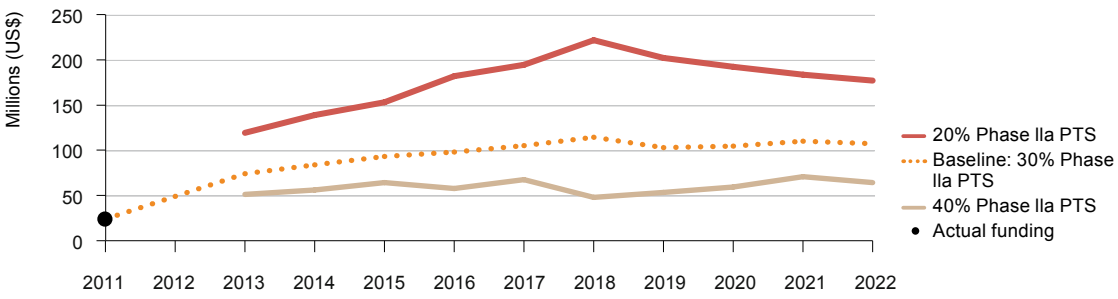
Modelling suggests that funding R&D at these levels will deliver five to six new antimalarial drugs by 2022, including two first-generation SERCaP drugs, one SEC drug, and two to three label extensions approved for new subjects groups or uses.

Factors that may affect future funding needs

Funding projections for drug R&D are influenced by a range of factors, in particular: a) new R&D strategies or technologies that increase the probability of technical success (PTS); b) agreement on more streamlined development paths for combination products; c) variation in the length of development phases; and d) changing the target global drug portfolio that the malaria community is aiming for.

Of these, the factor with the largest impact on funding is the probability of technical success. Improved R&D strategies such as innovative drug screening and design methods, or the use of more effective biomarkers in developing proof of concept, can help to better predict safety and efficacy and thus to improve the success rate and cost-effectiveness of drug development. For example, improving the success of Phase IIa 'proof of concept' trials from the current 30% to around 40%, would cut funding needs by approximately $400 million over ten years, while a drop in success rates from the current 30% to 20% would increase funding needs by over three-quarters of a billion dollars ($770 million) in the next ten years.

Figure 8
Projected elimination and eradication drug R&D funding need 2013-2022 (2011 US$) (Sensitivity: Increased PTS)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

VACCINES

Vaccine priorities for the elimination and eradication of malaria are primarily focused on the development of vaccines to interrupt transmission of both *P. falciparum* and *P. vivax* malaria, although the inclusion of *P. vivax* elements in control vaccines will also have some impact by preventing relapsing infection. No such vaccines exist, and the most advanced vaccine candidate now in development (RTS,S) does not address elimination and eradication, as it was instead designed to target *P. falciparum* malaria infection in individual subjects.

While vaccine development is always expensive, transmission-blocking vaccines that are explicitly aimed at malaria elimination and eradication—those that target human to mosquito transmission—will be particularly expensive to develop. Because their benefit to the individual is delayed, transmission-blocking vaccine trials may need to enrol up to 200,000 subjects in order to demonstrate efficacy, compared to fewer than 20,000 subjects for trials of vaccines like RTS,S that target individual malaria infection. As a result, significant costs would be incurred to license transmission-blocking vaccines if the standard regulatory endpoints and pathways are used.

While vaccines against malaria infection in individuals have been in development for over thirty years, the impetus to focus on vaccines for elimination and eradication of malaria at population level is relatively recent. As a result, the transmission-blocking pipeline is small and immature, with just a single target antigen currently under investigation in early stage clinical trials. This immaturity means that there are currently insufficient candidates to sustain the portfolio while scientists learn what works in this new research area. In order to generate a successful transmission-blocking vaccine, substantial additional funding will be needed to create a portfolio of promising vaccine leads sufficiently large to ensure that one or more candidates make it through to the finish line.

Ten-year priorities

Priorities for the next decade are to progress development of:

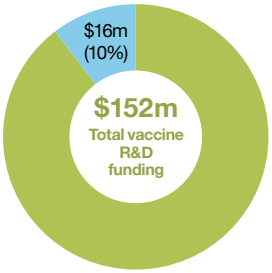
- A vaccine to interrupt transmission of *P. falciparum*.
- A vaccine to interrupt transmission of *P. vivax*.

Components targeting *P. vivax* are also being investigated for inclusion in vaccines under development for malaria control.[7] By preventing relapse, they will also have some impact on elimination and eradication, and the cost of these components is therefore included here.

The additional target of a single transmission-blocking vaccine that covers both *P. falciparum* and *P. vivax* is desirable, but not a priority.

Funding for vaccine R&D in 2011

In 2011, $16 million was invested in elimination and eradication-specific vaccine R&D (10% of total malaria vaccine R&D funding). There were only 10 funders active in this area. The three key funders were the US NIH ($5.8 million, 40%), the Gates Foundation ($3.8 million, 26%) and industry ($3.0 million, 21%). All three funded transmission-blocking vaccines and a few early stage *P. vivax* candidates targeting relapse prevention.



PDP involvement in elimination and eradication research is also only in the early stages. In 2011, the European Vaccine Initiative spent only 3% ($129,270) of its vaccine research funding on elimination-specific R&D, while MVI spent only 1% ($397,742), with this partly reflecting the low cost nature of early stage research. For example, MVI's AnAPN-1 candidate (developed in collaboration with Johns Hopkins University and Sabin Vaccine Institute) is still only in the preclinical stage. However, MVI has indicated that spending on elimination and eradication R&D will rise to 50% of their total expenditure in the next five to ten years as their elimination and eradication portfolio expands and moves into more advanced development stages.

Future funding needs

Box 4. Key model assumptions (see Annexe 2 for full details)

Total costs, durations and probability of successful phase completion for individual R&D activities:

Vaccine blood stage:

- Discovery - $3.8-6.3 million
- Preclinical - $0.05-0.5 million; 5 years; 53%
- Phase Ia - $0.5-1.8 million; 1 year; 55%
- Phase Ib - $1 - 4 million; 2.5-4 years; 88%
- Phase Ia/IIa - $0.8 million; 1 year; 25%
- Phase IIb - $15-20 million; 5-7.5 years; 50%
- Phase III -$140-280 million; 4-5 years; 70%
- Phase IV - $30-100 million; 5-8 years; 85%

Vaccine blood stage:

- Discovery - $3.8-6.3 million
- Preclinical - $2-5 million; 5 years; 30%
- Phase Ia - $3.8-10 million; 3.5-5 years; 20%

- Phase Ib - $3.8-10 million; 3.5-5 years; 20%
- Phase IIb - $50-100 million; 5-7.5 years; 50%
- Phase III - $300 million; 4-5 years; 70%
- Phase IV - $30-100 million; 5-8 years; 85%

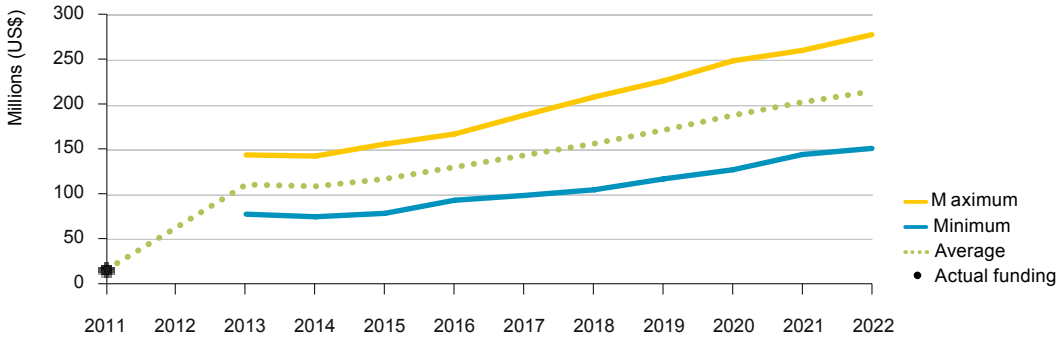
Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum

Vaccines strategic goals are listed in Annexe 2

The immature state of the elimination and eradication vaccine pipeline means that there is a very wide divergence between current investment and what will be necessary to deliver on the elimination and eradication vaccine targets set by the global malaria community for 2030, as outlined in the Malaria Vaccine Technology Roadmap. In order to achieve these targets there must be significant growth in the number of new transmission-blocking approaches under investigation, compared to the current pipeline. The uncertainty surrounding the development and regulatory pathway for this type of vaccine makes it difficult to precisely predict the growth trajectory required; the scenario presented here models the entry of sufficient new candidates into preclinical studies each year to account for attrition and allow for steady growth.

Under this scenario, funding needs gradually increase from around $100 million per year in 2013 to around $215 million per year by the end of the decade, as the pipeline of candidates grows progressively larger. Funding estimates also become more uncertain with a range of $50 million on each side, reflecting the uncertainty of costs and attrition rates for early stage development of transmission-blocking vaccines. Total funding for the next decade under this scenario is estimated at $1,057-2,006 million.

FIGURE 9
Projected elimination and eradication vaccine R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

What will this investment deliver by 2022?

Because of the uncertainties surrounding transmission-blocking vaccine development, it is difficult to predict when a transmission-blocking vaccine might be available. By 2022, however, the funding outlined above should deliver a robust pipeline of new transmission-blocking vaccine candidates—without which the 2030 goals of the Malaria Vaccine Technology Roadmap will be impossible to achieve.

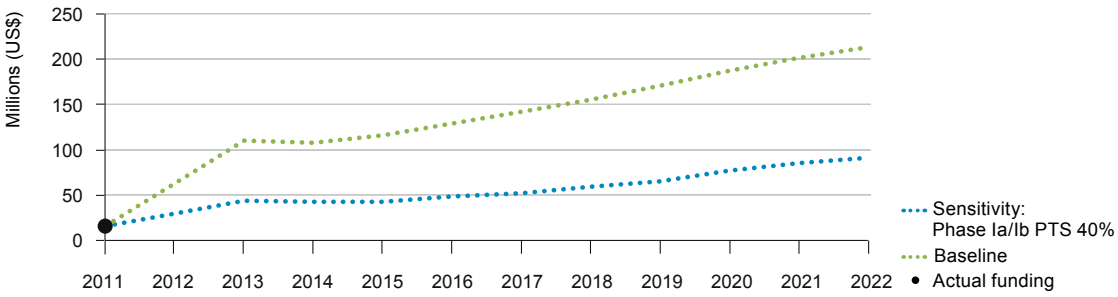
Factors that may affect future funding needs

As noted above, the ability to generate a robust pipeline of transmission-blocking vaccine candidates is the key factor driving likely future funding needs. However, there are two other driving factors behind projected vaccine R&D costs: the regulatory pathway for transmission-blocking vaccines, which is amenable to human intervention; and the probability of success, which is largely outside human control.

A review of regulatory pathways offers genuine possibilities for reductions in vaccine development cost—and may even be imperative for creation of a transmission-blocking vaccine. Conventional thinking suggests that safety and efficacy data from Phase III transmission-blocking trials currently generated through cluster randomised trials (CRTs) involving hundreds of thousands of people, will drive up costs to levels that may challenge funders. However, some experts suggest new trial design and regulatory pathways, including the use of earlier endpoints and therefore a reduced number of subjects needed for clinical evaluation. This could dramatically decrease Phase III costs, while also shifting some costs out to the Phase IV trials conducted once the vaccine is in use.

The probability of vaccine success or failure depends on the state of the science as well as on serendipitous breakthroughs, and there is a high degree of scientific uncertainty surrounding malaria vaccine development: the global community has yet to create a fully successful malaria vaccine against infection, and has only barely begun the attempt to create a transmission-blocking vaccine. Because probability of success is a strong driver of funding needs, this uncertainty has a major impact on the funding needed over the next decade. For example, if the success rates for early clinical trials (Phases Ia and Ib) of transmission-blocking vaccines are 20% higher than current estimates, then the funding need for elimination and eradication vaccine R&D would more than halve (in 2013 dropping from $110 million to just $44 million). Over the ten-year period, this change would mean a decrease in the vaccine funding required from $1.5 billion to $608 million.

FIGURE 10
Projected elimination and eradication vaccine R&D funding need 2013-2022 (2011 US$) (Sensitivity: Increased PTS)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

DIAGNOSTICS

The development of rapid diagnostic tests (RDTs) is helping to realise the World Health Organization recommendation to test every suspected malaria case. With continued R&D, improved and novel diagnostic tools can take us even further: diagnostics to identify asymptomatic individuals; diagnostics as a pillar of surveillance and response systems; and diagnostics for metrics of low transmission. For the purpose of this report, we considered all R&D in diagnostics to be pertinent to malaria elimination and eradication efforts.

Ten-year priorities

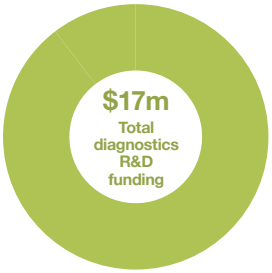
The ideal ten-year diagnostics portfolio includes development of a range of new products that will be critical to achieving malaria elimination and eradication, including[ii]:

- Highly sensitive tests that can rapidly detect:
  - low levels of parasites in blood samples and can help countries in the elimination stages clear the asymptomatic or 'hidden' infections.
  - the presence of *P. vivax* hypnozoites in the liver.
- New metrics to measure transmission levels in low and very low transmission areas would enable surveillance and know if transmission has really been interrupted.
- A field test to identify individuals who are G6PD deficient, to guide case management of *P. vivax* malaria, as side effects are possible with the current drug primaquine.
- Simple low-cost quality control tests to evaluate RDT performance in remote locations, including positive control wells and recombinant panels, as part of batch testing during manufacturing and stock testing.
- A diagnostic test that does not require blood samples. This would enable easy screening of large populations, e.g. migrating workers and other migrant populations, people crossing borders.
- An automated microscopy system, which does not need a highly-trained medical practitioner, but can differentiate *Plasmodium* species and accurate quantification.
- Improved RDTs, particularly for non-*falciparum* species. The goal is for two new RDTs for non-*falciparum* parasite species.

[ii] These diagnostics priorities are listed in order of importance for the elimination and eradication agenda.

Funding for diagnostics R&D in 2011

Malaria diagnostics R&D received $17 million in 2011, all of which is relevant to elimination and eradication efforts. The two main funders were the Gates Foundation ($4.4 million, 26%) and the US NIH ($3.3 million, 19%), although the majority of the funding was in the form of smaller amounts from many donors, including the Danish International Development Agency (DANIDA) ($2.2 million, 13%), the UK Medical Research Council (UK MRC) ($1.8 million, 11%) and others such as the Wellcome Trust all contributing less than 2% each.



Around half of diagnostic R&D funding was given as grants to academic institutions ($9.4 million, 55%), with a single PDP (FIND) – accounting for the next largest share ($2.7 million, 16%), followed by self-investment or grants to small pharmaceutical and biotechnology companies ($2 million, 12%).

Future funding needs

Box 5. Key model assumptions (see Annexe 2 for full details)

Total costs and durations for individual R&D activities:

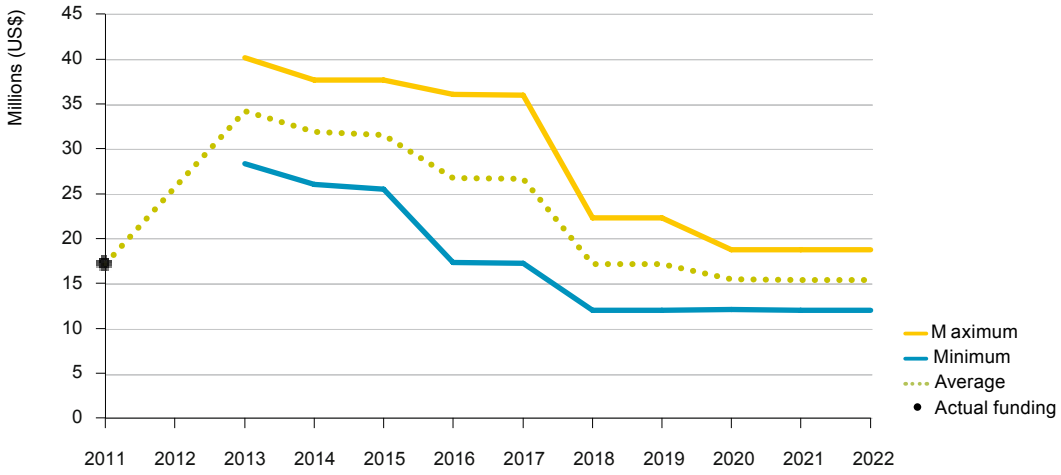
- Improved RDTs for non-*falciparum* parasites - $3-18 million each; 5 years
- Positive control wells - $1.5-2 million; 1 year (until completion)
- Recombinant panels - $1.5-4 million; 1.5-3 years
- RDT quality control - $9 million; 5 years
- High-throughput field molecular testing - $21.6 million; 3-5 years
- Serological screening tests -$4.0-12 million; 5 years
- Point of care G6PD detection - $5-12.6 million; 5 years
- Multiplexing - $5-20 million; 5-7 years
- Automated microscopy - $21.6 million; 10 years
- Improved RDTs for *P. falciparum* - $3-10.8 million; 5 years
- Non-blood testing - $72 million; 10 years

Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum

In order to achieve the ten-year goals set out above, funding for malaria diagnostics R&D needs to urgently increase, requiring an approximate doubling of funding from the current $17 million per year (2011) to around $28-40 million per year. However, due to much improved diagnostic R&D funding since 2009, (in particular from the Danish DANIDA, the UK MRC and the US NIH), this is far less than the quadrupling of funding recommended in the previous 2011 malaria R&D funding report.[8]

Once funding has reached optimal levels of $28-40 million, investment needs will gradually decrease over the following five years to a relatively steady state of between $12-19 million per year. Once good diagnostic tools are available and providing the functions needed in elimination settings, the need for further investment to develop new diagnostics is likely to decrease. Overall, the malaria community will need to invest between $175-288 million in R&D for new and improved diagnostics over the next ten years, with the majority of this funding needed upfront between 2013 and 2017.

FIGURE 11
Projected diagnostics R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

What will this investment deliver by 2022?

If donors fund in a coordinated manner and funding needs are met, a number of the above priority tools could be delivered with high certainty by 2022, and some as early as 2017:

- A field test for low levels of parasites. This will need $22 million of funding to be in the field by 2017. With these tests available, national malaria programmes would be able to strengthen the surveillance data and surveillance-response systems.
- A field test to detect G6PD enzyme deficiency. This will need $5-13 million of funding to be ready by 2017. With a G6PD deficiency test, programmes would be able to better map this genetic trait, which would serve in planning and implementing strategies around using low doses of primaquine to clear gametocyte of *P. falciparum* malaria.[9]
- Simple low-cost quality control tests to evaluate RDT performance in remote locations. These will require $3-6 million of funding to be ready by 2017.
- Two improved RDTs for non-*falciparum* parasites, which will each require $3-18 million over five years.

Factors that may affect future funding needs

Factors that affect diagnostic R&D funding needs include: a) what tools are prioritised by funders and developers; b) improved coordination of R&D pipelines; and c) shorter or longer development times.

For example, if quality assurance processes which evaluate RDTs are rapidly developed, malaria programmes may look towards purchasing and providing quality controlled RDTs together with quality assured antimalarial treatments. 'Bundling' these two interventions will likely involve pilot testing as well as operational research.

A further major factor driving up R&D costs is lack of coordination in the diagnostic field, with many projects being carried forward by multiple funders, rather than selection of – and investment in – the handful of optimal projects in each area. Any efforts to improve coordination will dramatically reduce R&D costs.

VECTOR CONTROL

Vector control works to block or decrease transmission of malaria. Hence, for the purposes of this report, all vector control R&D for malaria is considered relevant to the elimination and eradication agenda.

Vector control R&D includes development of new and improved insecticides and biological control products (including larvicides, mosquito sterilisation techniques and genetically-modified mosquitoes that are not susceptible to the malaria parasite[10]). Development of new vector control products is also lengthy, taking nearly as long as for a new drug. For instance, creation of a new active ingredient for an insecticide takes an estimated ten years: three years to optimise a promising chemical lead, two for pre-trial development, three for field trials and two years for registration.[8]

Ten-year priorities

Research priorities for vector control include the development of the new active ingredients for use in vector control products—insecticide-treated bednets (ITNs), indoor residual spraying (IRS), research for novel products (e.g. for use out of doors), as well as research for non-insecticide based vector control paradigms.

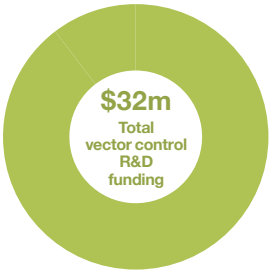
Research priorities for vector control include the development of new active ingredients for use as insecticides, as well as ongoing research to support other elements for new insecticide development and non-insecticide based vector control products. Priorities include:

- The development of three new active ingredients into formulations for new insecticides and vector control products. This includes:
    - Formulation development, where the active ingredient is combined with chemical coformulants to develop stable and effective insecticides.
    - Development of vector control products including ITNs and IRS. The products must be feasible to distribute and apply, and have good user acceptability.
- Screening for new candidates, aiming to identify new active ingredients that can be developed for use in vector control, including reviewing existing chemical compound libraries to select those for review and optimisation at a later stage.
- Strengthening information systems and tools, since accurate design and targeting of vector control products requires complete and up-to-date information on vector populations, including species, infection status, and insecticide resistance[iii].
- Research on three new paradigms, or non-insecticide based ways to control mosquitoes.

[iii] Even though this research area has been included under vector control in this report, it could also be considered part of the health systems and operational research category.

Funding for vector control R&D in 2011

In 2011, malaria vector control R&D received $32 million. The largest funder was the Gates Foundation ($20 million, 63%), which predominantly invested through the Vector-based Control of Transmission-Discovery Research Programme (a Grand Challenges extension programme). This programme is managed by the Foundation of the National Institutes of Health and focuses on biological control methods and the development of new insecticides and chemical compounds to control mosquitoes.



The public sector, led by the US NIH, provided 21% ($6.7 million) of vector control funding. Reported industry investment was restricted to small pharmaceutical and biotechnology companies ($4.3 million, 14%)[iv], mostly spent on joint R&D projects with the IVCC, which is a PDP. The industry-IVCC collaborations included new pesticide and IRS formulations, discovery programmes, and screening for new active ingredients.[11]

Future funding needs

Box 6. Key model assumptions (see Annexe 2 for full details)

Total costs for R&D activities:

- *New active ingredients*: Development of three new active ingredients from optimisation to registration with a total R&D development cost per active ingredient of $120 million and total duration of ten years
- *Ongoing research activities (costs spread evenly across ten years)*:
  - Screening new candidates - $26 million
  - Formulation development - $78 million
  - Three new vector control paradigms - $195 million
  - Information systems and tools - $26-65 million

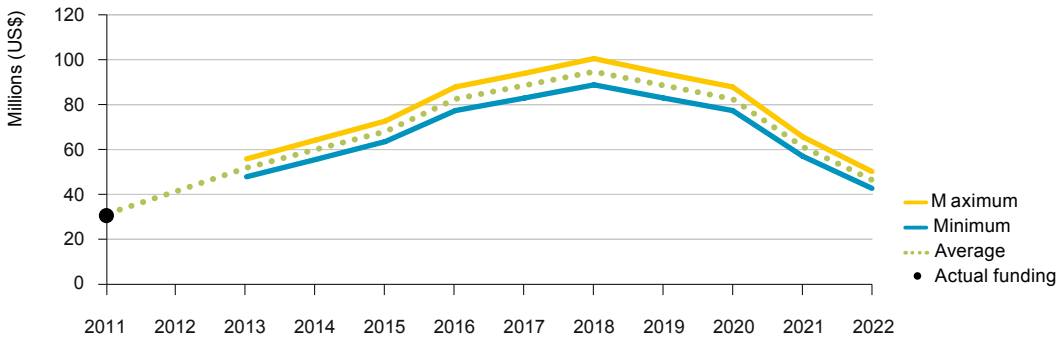
Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum

In 2011, funders invested almost $32 million in malaria vector control R&D, although we note that this figure may be atypically low due to the uneven disbursement of multi-year grants to IVCC, a major product developer in this area.

[iv] Investments by agrochemical firms are likely to be underreported as some companies active in this area did not participate in the G-FINDER survey 2011.

To meet immediate vector control funding needs, funding levels urgently need to increase by $16-24 million, to reach the ideal level of $48-56 million per year. Even if achieved today, funding needs would then continue to increase over the next five years, peaking at around $89-100 million in 2018, when the first new active ingredient in the current pipeline would be expected to complete its development. Funding needs would then decrease steadily as the remaining new active ingredients complete development in 2019 and 2020, and transition to registration. These funding patterns mean that R&D for new and improved vector control products would require $676-773 million over the next ten years.

FIGURE 12
Projected vector control R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

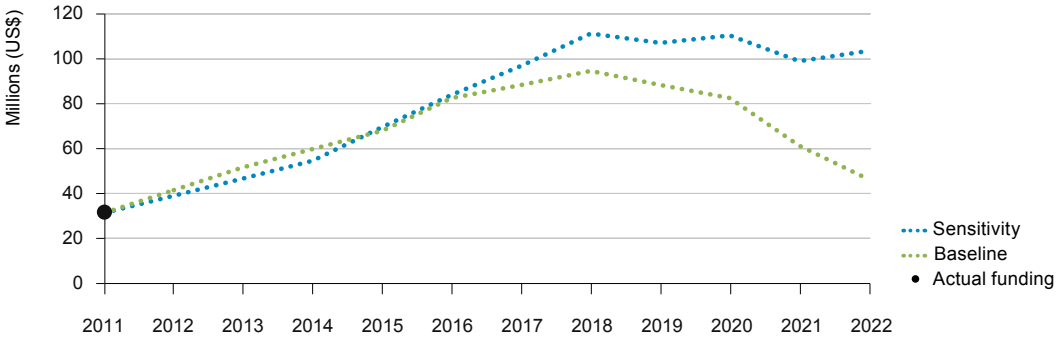
What will this investment deliver by 2022?

There is relatively little uncertainty with insecticide product development compared to other product areas. Funding vector control R&D at these levels for the next ten years will likely result in three new active ingredients for use as insecticides by 2022. New active ingredients are particularly important given that nearly two-thirds of malaria-endemic countries are reporting cases of resistance to existing insecticides, including to pyrethroids, which are the only insecticides used on long-acting bednets.[12] With three new active ingredients for use as insecticides, we would be able to apply them in mosaic patterns and in rotation cycles; minimising future resistance and minimising the mosquito population.[13] The more challenging work will be in developing new and effective ways to deliver the insecticides, including ways to protect people from being bitten when working and sleeping outside their homes.

Factors that may affect future funding needs

The most significant driver of future funding needs is the number of active ingredients that the global health community is aiming for in the ten-year vector control portfolio. For instance, if six active ingredients are developed instead of three, then ten-year funding needs will increase by $210-228 million, with the bulk of these additional funds required between 2018 and 2022.

FIGURE 13
Projected vector control R&D funding need, 2013-2022 (2011 US$) (Increased number of target new active ingredients)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

Other factors that might affect these projections include the inclusion of vector-related operational research and the rate of development of insecticide resistance. Vector-related operational research including optimising vector control in combination with other interventions and in various epidemiological settings and environmental management approaches to deal with breeding sites to reduce transmission has not been measured here. Also, a potential slower rate of resistance overtime due to fewer mosquitoes is likely to lead to effective insecticides for longer periods of time.

HEALTH SYSTEMS AND OPERATIONAL RESEARCH

Health systems are defined as all organisations, people and actions involved in promoting, restoring or maintaining health, including service delivery, governance and technological development.[14] Operational research is research that contributes to evidence-based decision-making at the health system level, where those decisions relate to the implementation of public health interventions and clinical care. Overall, health systems and operational research for the elimination and eradication agenda should address issues of governance, human resources, financing, information, service delivery, medicines and technology in the context of eventual eradication.

Countries in the malaria control phase, as well as the pre-elimination and elimination phases, require health systems and operational research, although each faces a different set of health systems challenges. For example, highly sensitive surveillance triggering a rapid response is critical in the pre-elimination or elimination phase, when preventing transmission becomes crucial. Methods for elimination of residual foci will also become critical as we approach elimination, requiring research to determine the scale, coverage period, and the frequency of the intervention required. Some health systems research questions will be generic and broadly applicable across different country settings, while others will be context-specific and asked at the country level.

Health systems and operational research needed to support elimination and eradication includes research to tailor and optimise the implementation of new and existing tools in a variety of epidemiological settings. For example, in the case of vector control, methods for control in areas with residual malaria foci will become critical as we approach elimination, requiring research to determine the scale, coverage period, and (in the case of indoor residual spraying) the frequency of the intervention required to achieve elimination.

One of the key priorities for malaria health systems and operational research will be to investigate the impact of new tools in concert with other interventions, as it will be the implementation of these tools in an integrated manner that will be critical for maximising their impact. Modelling will be a critical adjunct to operational research in this task.

Ten-year priorities

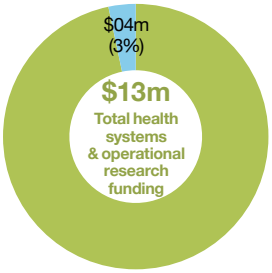
These include:

- Research at the health facility level to understand how to monitor, enhance and sustain health worker performance and compliance with best practice.
- Research at a district level to test hypotheses around the factors impeding greater use of existing tools, and approaches to district health system strengthening.

- Research at the national level, to strengthen health system components through experience in disease-specific programmes.
- Research at a regional and global level, to investigate the strengths and weaknesses of current malaria surveillance and subject management practices in malaria-endemic countries, and to examine the determinants of success of inter country collaboration for disease elimination.
- A holistic look at all components of the system, from providers to supply chain to surveillance systems and infrastructure; understanding mechanics; and mapping how infections are decreasing and pressures applied to different parts of the system can reduce infections further.

Funding for health systems and operational research R&D in 2011

In 2011, 3% ($0.4 million) of identified funding for malaria health systems and operational research was spent on elimination and eradication-specific activities.[v,vi] This funding consisted of three small grants, from the Swedish Research Council, the Inter-American Development Bank and the Wellcome Trust, aimed at elimination strategies for Mesoamerica and the Asia Pacific, as well as optimising drug combinations for *P. vivax* and *P. falciparum* co-endemic regions.



This is the first time that funding data on health systems and operational research for malaria has been collected from the institutions surveyed—which are mostly governments and organisations who fund R&D. The total reported here is therefore almost certainly an underestimate, as these figures do not capture grants for health systems and operational research from other likely sources, such as the Global Fund to Fight AIDS, TB and Malaria, or those endemic-country governments who have not provided data to G-FINDER. It can also be difficult to neatly distinguish operational research from other research categories or product areas, and in particular to delineate control-driven from elimination & eradication-specific research.

Future funding needs

Box 7. Key model assumptions (see Annexe 2 for full details)

Total cost for model:

- Countries where elimination is considered impossible with existing tools; and countries with focal malaria - $57.7-118.9 million
- Elimination ready countries - $0.5-1.0 million

[v] As the elimination and eradication-specific malaria health systems and operational research portfolio consists of only three grants, it is difficult to draw conclusions on this funding stream.

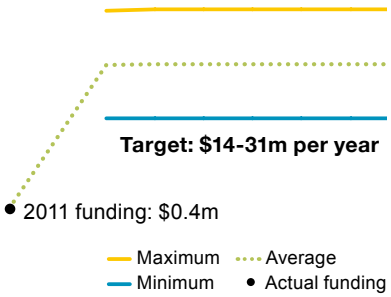
[vi] Figures are likely to be somewhat underestimated as general health systems strengthening grants from the GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis & Malaria may include a health systems and operational research component.

Number of countries in each group:

- Countries where elimination is considered impossible with existing tools; and countries with focal malaria: 80 countries
- Elimination ready countries: 19 countries

Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum; costs are evenly spread across ten years

FIGURE 14
Projected elimination and eradication health systems R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

Based on current data, funding for health systems and operational research for malaria elimination and eradication appears low ($0.4 million in 2011) and will need to rapidly increase by approximately $14-31 million in 2013 to meet immediate research needs and to be maintained at these levels for the next ten years. This means that health systems and operational research for malaria elimination and eradication would require $147-317 million in total funding for the decade.

Factors that may affect future funding needs

The rate at which countries transition from malaria control to malaria elimination will influence future funding needs for health systems and operational research, although we note that transition rates are currently poorly understood, and health systems and operational research is largely uncoordinated. Updated criteria used in the World Malaria Report will likely help to track phase transitions over time, and more research on how countries transition between stages will then allow more accurate projections. That said, the projections above assume a transition rate of 1-2% of countries per year; and, even if countries transition at the rate of 4-5% per year, funding needs would still increase by only $1-2 million in total over the decade.

MODELLING AND HARMONISED DATA SYSTEMS

Modelling and harmonised data systems are important tools to guide research for malaria products and to inform policy decisions at all stages of malaria elimination and eradication. Modelling includes developing and testing mathematical methods to define, quantify or extrapolate general patterns in epidemiology, transmission and the potential effect of interventions; and it also allows implementation strategies to be tested in different simulated epidemiological and socio-economic settings. Harmonised data systems involve developing and testing information and communication technologies, database or cyber-infrastructures that assist researchers to share the data used to build and validate these models.

Ten-year priorities

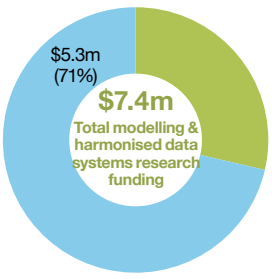
In the context of the malaria elimination and eradication agenda, modelling and harmonised data systems will be needed to synthesise information, quantify uncertainty and extrapolate current knowledge on:

- Optimal allocation of resources.
- Management of drug and insecticide resistance.
- Impact of new tools to interrupt transmission.
- Technical feasibility of interventions, including their target coverage levels and timelines.
- Use of operational feasibility assessments to weigh economic costs, capital investments and human resource capacities.[15]

Funding for modelling and harmonised data systems R&D in 2011

In 2011, 71% ($5.3 million) of malaria modelling and harmonised data systems funding was spent on elimination and eradication specific activities.[vii]

Most of this funding came from the Gates Foundation ($3.9 million, 74%), with more modest amounts ($0.3-0.5 million each, 5-10%) provided by the US NIH, UK MRC and Swedish International Development Agency.



[vii] The elimination and eradication-specific malaria modelling and harmonised data systems portfolio is small, consisting of only 15 grants. Therefore, it is difficult to draw conclusions on this funding stream.

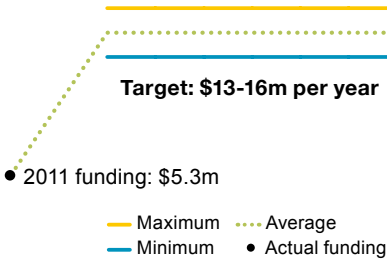
Box 8. Key model assumptions (see Annexe 2 for full details)

Total costs for R&D activities:

- Number of research groups: 7-8
- Annual cost per research group: $1.6 million

Assumptions: Cost of capital multiplier 4%; uncertainty multipliers of 10% for minimum and 20% for maximum; costs spread evenly over 10 years

FIGURE 15
Projected elimination and eradication modelling R&D funding need, 2013-2022 (2011 US$)



The full set of inputs and assumptions for the cost projections are included in Annexe 2.

Current funding ($5.3 million in 2011) will need to triple to $13-16 million to meet existing research needs, and to be maintained at this level for the next decade. The malaria community will need to invest $128-159 million in modelling and harmonised data systems research for malaria elimination and eradication over the next ten years.

DISCUSSION

This report examines for the first time where investments supporting the eradication research agenda are being made. It shows that there is a large underinvestment in malaria elimination and eradication R&D, both in absolute numbers, and relative to the amount spent on malaria R&D overall; that funding is very concentrated, with heavy reliance on a small pool of funders; and that the pharmaceutical industry plays a much less prominent role in malaria elimination and eradication R&D compared to malaria R&D overall.

Substantial funding growth is needed to deliver the tools and knowledge for malaria elimination and eradication

The total funding need for all malaria R&D (including for malaria control) averages around $600-700 million per year for most of the next decade.[7] Around two-thirds ($335-$450 million, 56-64%) of this annual funding requirement is for R&D to eliminate and eradicate malaria. However, in 2011, funding for malaria elimination and eradication R&D totalled only $104 million, or 16% of total malaria R&D funding. There is a funding gap for malaria elimination and eradication R&D of over $200 million per annum in the immediate term and of $300 million per annum over the next decade if funding for malaria elimination and eradication R&D does not increase.

To help reach elimination and eradication outcomes, the malaria community needs to maintain its focus on clear, defined targets (for example SERCaP in the area of drug R&D). With coordinated efforts towards meeting these specific targets, malaria elimination and eradication R&D funding needs will be finite—with defined goals and exit points.

Vaccines and drugs account for the majority of malaria elimination and eradication funding needed

Vaccines and drugs combined account for almost two-thirds of elimination and eradication R&D requirements over the next decade. Vaccines account for around 37% of total funding needs at present and are the key driver behind overall increases in elimination and eradication R&D funding over that time. There is a need to rapidly build a pipeline of vaccine leads for transmission-blocking vaccines, and the high cost and uncertainty regarding the development and regulatory approval pathway of these particular vaccines substantially increases the vaccine development funding requirements. Drugs account for 24% of total funding, driven by clinical trials of several late stage candidates and several expected combination drug trials, as well as development of NCEs to address resistance.

Overall, there is a steady increase in vaccine R&D needs throughout the decade; while drug R&D funding needs increase to 2018, stabilising thereafter. Vector control funding demand follows a similar trend—decreasing significantly after a 2018 peak—while funding for other R&D areas has only a limited impact on overall funding trends. By the end of the decade, the funding requirement for vaccines will be approximately the same as that for all other product areas combined.

The funding patterns for each product area reflect several R&D elements including the varying costs of developing each product type (from high cost vaccines to low cost diagnostics); the state of the science; the state of advancement of the product pipeline; and the novelty and ambitiousness of the scientific goals that need to be met to develop a product.

TABLE 4
Total and E&E-specific malaria R&D funding by research area

Research area	Total malaria R&D funding 2011 (US$)	Malaria E&E R&D funding 2011 (US$)	Immediate annual E&E R&D funding requirement (US$)	Total E&E R&D funding required over next decade (US$)	% of total malaria E&E R&D over next decade
Basic research	$173m	$8m	$27-31m	$273-307m	7%
Drugs	$218m	$24m	$62-86m	$697m-1.3bn	24%
Vaccines	$152m	$16m	$100m	$1.1-2.0bn	37%
Diagnostics^	$17m	$17m	$28-40m	$175-288m	6%
Vector control^	$32m	$32m	$48-56m	$676-773m	18%
HS&OR	$13m	$0.4m	$14-31m	$147-317m	6%
Modelling and harmonised data systems	$7.4m	$5.3m	$13-16m	$128-159m	3%

^ All malaria diagnostic and vector control R&D funding has been categorised as elimination and eradication specific.

Funding for malaria elimination and eradication is very concentrated

Funding for malaria elimination and eradication R&D is more concentrated than funding for malaria R&D overall, which is already very concentrated. This means that funding for malaria elimination and eradication R&D relies heavily on a small pool of funders, which is not likely to be the most reliable pathway towards ensuring the funding increases required by the end of the decade. In 2011, 63% ($65 million) of total funding for malaria elimination and eradication R&D was provided by two funding agencies, with the Gates Foundation providing nearly half ($49 million, 47%) and the US NIH providing 15% ($16 million). In the same year, the same two funding agencies were the top funders for malaria R&D overall, but their contributions represented 48% ($290 million) of total funding.[7]

Funding concentration for malaria elimination and eradication varies between the different product areas, with funding for vector control, vaccine development and basic research relying particularly heavily on a small number of funders. In 2011, the Gates Foundation alone provided nearly two thirds ($20 million, 63%) of R&D funding for malaria elimination and eradication vector control R&D. In the same year, two thirds of vaccine funding for elimination and eradication R&D came from the US NIH ($5.8 million, 40%) and the Gates Foundation (26%, $3.8 million); and almost half of basic research funding specific to elimination and eradication came from the same two funders: $2.0 million (24%) from the US NIH and $1.8 million (21%) from the Gates Foundation.

Although industry is a large player in malaria R&D overall, contributing nearly one-fifth of total malaria R&D funding, companies played a far smaller role in elimination and eradication-specific R&D, contributing only $9.4 million (9%) of total funding in 2011. This reflected investment by small pharmaceutical and biotechnology companies into vector control products and diagnostics, while multinational corporations invested in drug and vaccine candidates. Examples include Sanofi's work on primaquine; and GSK's work on *P. vivax* vaccines.

New funders and novel financing mechanisms such as the Global Health Investment Fund[16] are required for diversification of R&D funding. Increased funding support for malaria elimination and eradication R&D activities from malaria-endemic countries in areas such as health systems and operational research will also be essential.

If funding is maintained, critical research and potential game changers in malaria elimination and eradication R&D will be delivered in the short and long term

The goal of malaria elimination and eradication is intricately linked to the following list of short and long term product development goals. The greatest impact is expected if funding is maintained in an incremental and sustained manner.

TABLE 5
Malaria elimination and eradication product development goals in short and long term

Research area	Product to be delivered in short term (<5 years)	Potential impact	Product to be delivered in long term (>5 years)	Potential impact
Basic research	Continuous cell culture of blood stage *P. vivax*	Would provide well-characterised challenge strains for vaccine studies and a screening method for compounds against *P. vivax* and on hypnozoites	Sensitive and real time metric to measure low levels of malaria transmission	Coupled with surveillance and response, would enable mapping of recent infections and make a direct contribution to elimination of all malaria parasite species
Vector control	Development of 2-3 novel active ingredients to formulations and products	Impact would sustain the gains made with vector control and largely stave off hazardous consequences of mosquito resistance to pyrethroids	Research for novel applications of new insecticides targeting indoor and outdoor biting mosquitoes	With 2-3 novel insecticides, rotation and mosaic application in vector control products is possible and can be extended to outdoor biting mosquitoes
Diagnostics	Product development of sensitive molecular diagnostic for large sample numbers and wide-scale use	Would enable targeted treatment of symptomatic and asymptomatic individuals. As part of surveillance and response systems, and even during the validation process, would accelerate country's progression through elimination stages	Research for non-blood screening tool	Tool would enable mass screening for malaria infection, including asymptomatic infections, e.g. screening migrating populations
Drugs	Development of tafenoquine as a single dose radical cure against *P. vivax*	Would transform treatment and clearance of *P. vivax* infections and become an essential component of tailored response packages in surveillance-response systems	Development of well-tolerated, first generation SERCaP	Would enable large-scale administration to both symptomatic and asymptomatic infected populations including children and pregnant women
Vaccines	Identification and validation of biomarkers as surrogates for protection against malaria infection	Would increase our understanding of protection mechanisms and accelerate development of next-generation vaccines	Development of a relapse prevention vaccine against *P. vivax* which targets and eliminate hypnozoites	Would block malaria transmission, accelerating country's progression through elimination stages

Research area	Product to be delivered in short term (<5 years)	Potential impact	Product to be delivered in long term (>5 years)	Potential impact
Health systems & Operational research	Operational research, coupled with diagnostics and surveillance of the size and importance of the asymptomatic reservoir	Understanding of the importance of the asymptomatic reservoir in transmission will provide a building block for operational research assessing the impact of (combinations of) interventions to drive down transmission. This knowledge would impact on the validation of feasible and effective surveillance-response approaches in different endemic settings.	Research to identify and eliminate bottlenecks which cause reduced effectiveness of malaria interventions within the health system	Would impact on health systems integration and strengthening and support go/no-go decisions for malaria control and elimination programmes in different health and social settings.
Modelling & harmonised data systems	Consolidate and harmonise the different modelling approaches and create user interfaces to improve the effective application of models for prediction and feasibility studies for control and elimination programmes	Would optimise the effective use of models in predictions, forecasting and feasibility studies including the economic components	Mathematical modelling testing integrated interventions in epidemiological, health system and cost contexts	The model outputs together with malaria programme experience and surveillance would effectively inform and guide programme decision-making and thus accelerate progress

RECOMMENDATIONS

There is an opportunity to increase the focus on the goal of worldwide malaria elimination and eradication, and build on R&D successes to date. Researchers and funders need to work with aligned priorities in the areas of basic research, vector control, diagnostics, drugs, vaccines, health systems, and modelling. With this purpose in mind, we recommend:

1. Funding for malaria elimination and eradication R&D needs to increase by $200 million per annum in the immediate term, and $300 million per annum by the end of the decade.
    - Funding for elimination and eradication is currently less than a sixth of malaria R&D overall; when it should represent two-thirds of the total malaria R&D investment over the next decade.
2. Funders need to strengthen their coordination efforts towards meeting specific elimination and eradication targets in order to optimise the efficiency, cost and timeframes of this global endeavour.
3. New funders and funding models are required for diversification of malaria R&D funding for elimination and eradication.
    - More funders should become more engaged in progressing the elimination and eradication R&D agenda, including through the set-up of specific calls for proposals or funding streams.
    - The pharmaceutical industry should increase its role in malaria eradication and elimination R&D.
4. Funding should be flexible and linked to product development.
    - Funding should be dynamic and reviewed regularly so that it responds to product and portfolio developments across research and product areas. This is especially important for elimination and eradication R&D where the wider landscape is still evolving in the face of product interactions yet-to-be fully identified.

ANNEXE 1: REFERENCES

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ANNEXE 2: METHODOLOGY

G-FINDER ANALYSIS

Data collection

The 2012 G-FINDER online survey platform[viii] was used to collect FY2011 investments into malaria R&D from funding organisations, fund managers and product developers.

In 2012, 204 organisations across 36 countries participated in G-FINDER, including 23 organisations invited to participate in G-FINDER for the first time, as suggested by the MESA Task Force to try and better capture country contributions to malaria research, especially health systems and operational research. Of these, 93 organisations across 33 countries submitted malaria investments to G-FINDER, reporting a total of 2,018 malaria grants (this also includes 231 non-earmarked core-funding grants given to multi-disease R&D organisations known to conduct malaria research) see Annexe 3. Of these 93 organisations, 53 entered data on grants related to malaria elimination research activities.

Survey participants were asked to report on all research for malaria by research project or grant; with an exception that private pharmaceutical firms reported their annual malaria investment by number of staff, salaries and direct project cost. Participants categorised each malaria investment by:

- Strain (*P. falciparum*; *P. vivax*; other and/or unspecified malaria strains);
- Product/research category (basic research; drugs; vaccines (preventive); diagnostics; pesticides; biological control products; modelling & harmonised data systems; health systems & operational research).
    - Data on pesticides and biological control agents are reported as vector control.
    - Modelling & harmonised data systems and health systems & operational research were added to the G-FINDER survey this year for malaria as part of the adaptations conducted for the MESA project.
- R&D stage for investments in drugs, vaccines, diagnostics and pesticides:
    - Drugs/vaccines (discovery and preclinical; clinical development; Phase IV/ Pharmacovigilance; baseline epidemiology).
    - Diagnostics (discovery and preclinical; clinical evaluation; operational research).
    - Pesticides (primary and secondary screening and optimisation; development; WHOPES evaluation).
- For each malaria investment, participants were also asked to answer Yes/No to the question "Would this activity have been pursued in the absence of the renewed malaria eradication goal?" This question was included to find out whether the eradication

[viii] For full details on the G-FINDER survey platform, refer to the 2012 G-FINDER report, http://www.policycures.org/g-finder2012.html

agenda had any influence on an organisation's malaria research priorities in 2011. With the exception of the Gates Foundation, all top funders in 2011 (11 out of 12) indicated that the elimination and eradication agenda has not directly affected their funding priorities.

- Allocation of R&D investments to elimination and eradication was conducted by Policy Cures internally (see next section 'Allocating malaria investments to elimination and eradication').[ix]

A total of 2,018 investments entered into the G-FINDER platform by the survey recipients were marked as malaria research investments. This included 231 core-funding grants to multi-disease research organisations known to conduct malaria research. A portion of this core funding was allocated to the malaria total and included in the analysis; this apportioning was based on the aggregated expenditure of the recipient organisations according to the different diseases.

The data entered were quality checked by Policy Cures staff. Grants entered were checked against the standard G-FINDER inclusion/exclusion criteria, i.e. the G-FINDER survey captures investments that support pharmaceutical R&D aimed at preventing, treating or curing neglected diseases for subjects in developing countries. This criterion was not applied to malaria grants describing health systems and operational research, or modelling and harmonised data systems. Data entered were then cross-checked between that entered by the funding organisations and that entered by the fund recipients; these are standard G-FINDER processes, more detailed information can be found at (http://policycures.org/downloads/GF2012_Report.pdf).

Allocating malaria investments to elimination and eradication

Using grant descriptions and project abstracts provided by survey participants, Policy Cures staff allocated each malaria investment to one of three categories: primarily for control (meaning the grant was 70% or more driven by a malaria control research objective); primarily for elimination or eradication (meaning the grant was 70% or more driven by a malaria elimination research objective); cannot be allocated. As there is a continuum from control to eradication, there is a degree of subjectivity in defining research which is pertinent to the elimination and eradication agenda. The categorisation was carried out by Policy Cures staff and was based on malERA definitions. Examples of the primarily for elimination and eradication category are given in table 6.

[ix] Based on malERA.

TABLE 6
Examples of research categorised as being primarily for malaria elimination and eradication

Research category	Primarily elimination and eradication
Basic research	Study the dynamics of malaria transmission stages in host and vector in three non-African settings to determine their impact transmission
Vector control	All research considered relevant for control and elimination, e.g. develop and commercialise a tool that effectively reduces malaria vector populations and longevity
Diagnostics	All research considered relevant for control and elimination, e.g. develop a handheld, inexpensive battery-powered instrument that can rapidly diagnose malaria
Drugs	Identify potential drugs targeting the gametocyte or the liver stage of the malaria parasite life cycle
Vaccines	Identify biomarkers of correlates of protection against pre-erythrocytic malaria infection that will enable down selection of vaccine antigens
Health systems and operational research	Develop technical guidance for countries to transition from control to elimination; document practices for accelerating control to elimination; and support research needs for elimination
Modelling and harmonised data systems	Test predictions from an individual based simulation model on impact of transmission intensity by targeting interventions to malaria transmission 'hotspots' compared to untargeted interventions

For each recipient, the proportion of their malaria R&D investments which were primarily for elimination and eradication was calculated. This percentage was then used to apportion any core-funding received by the recipient.

COST PROJECTIONS

Cost projections for drugs and vaccines are based on a risk-adjusted portfolio (RAP) model designed by the Gates Foundation and further developed by Policy Cures. Cost projections for all other research categories are based on a model developed by Policy Cures.

Key variables used in the model

a) Elimination and eradication products in the pipeline and their current phase of development.

b) Ideal portfolio targets. Defined as desired number of products needed in the next ten years for each elimination and eradication product development goal (e.g. X vaccines interrupting malaria transmission, Y relapse-prevention drugs, etc.).

c) Phase durations.

d) Total direct cost per phase (excluding cost of failure).

e) Probability of technical success (PTS. Defined as percentage of candidates successfully reaching the next phase (i.e. the reverse of attrition rate).

These variables were used differently when modelling different research categories:

- For basic research, diagnostics and vector control product, annual projections were calculated based on the following variables: Elimination and eradication activities in the pipeline, ideal portfolio targets, R&D duration and start date, and total direct R&D cost (including cost of failure).
- For drugs and vaccines, annual projections were calculated based on the following variables: Elimination and eradication candidates in the pipeline and current phase, ideal portfolio targets, R&D duration, direct R&D cost (excluding cost of failure) and PTS by phase.
- For Health Systems & Operational Research, annual projections were calculated based on elimination and eradication research targets per country group (see group definitions in the Health Systems & Operational Research section below), R&D duration, number of countries in each group, total direct R&D cost (including cost of failure). For Modelling & Harmonised Data Systems, annual costs were estimated based on the number of research groups currently conducting malaria modelling research and the average annual cost per research group.

In all research categories, minimum and maximum values have been included that reflect the range of cost estimates provided by experts. Total cost projections also include cost of capital (4%) and multipliers to account for uncertainty (10% for minimum cost, 20% for maximum cost).

Basic research

Identification of relevant activities

Research activities relevant to malaria elimination and eradication were defined based on literature from the malERA Consultative Group on Basic Science and Enabling Technologies and in consultation with the MESA Task Force.

Once identified, basic research activities relevant to elimination and eradication were classified as a) primarily for elimination and eradication, b) 70% for elimination and eradication, c) primarily for control, or d) could not be allocated to any category. Activities either primarily or 70% for elimination and eradication were taken to malaria basic research experts for further consultation.

Expert consultation

Experts were identified based on either their participation in the malERA Consultative Groups and/or suggestions from the MESA Task Force. Experts interviewed included:

- Rhoel Dinglasan, Johns Hopkins University.
- Oliver Billker, Wellcome Trust Sanger Institute.

Experts were asked to comment on:

- Total cost for each research activity including cost of failure.
- Duration of each research activity.
- Expected start date of each research activity.

An additional expert (Kevin Baird, Eijkman Oxford Clinical Research Unit) was contacted and interviewed to provide estimates for the cost of G6PD deficiency research.

Drugs

Identification of relevant activities

A list of R&D development goals required for drugs for elimination and eradication was developed based on:

- Literature from the malERA Consultative Group on Drugs.
- Consultation with the MESA Task Force on R&D that is primarily or 70% for elimination and eradication.
- Consultations with MMV including discussion on what features of their target candidate profiles (TCPs) are relevant to elimination and eradication.

Based on these development goals, a list of matching products currently in the pipeline was compiled. This was based on a review of the literature and consultations with malaria drug R&D experts.

Expert consultation

Experts were identified based on either their participation in the malERA Consultative Groups, suggestions from the MESA Task Force, and/or existing Policy Cures contacts.

The following experts were interviewed:

- Steve Ward, Liverpool School of Tropical Medicine.
- Tim Wells and Claude Oeuvray, Medicines for Malaria Venture.

Experts were asked to comment on:

- Drug product development goals for elimination and eradication.
- Desired number of products to be developed in the next decade for each goal (ideal portfolio targets).
- List of current products in the pipeline and their associated elimination and eradication features.
- Total direct cost per product, per phase (minimum and maximum estimates) (excluding cost of failure).
- Probability of technical success (PTS) for candidate to reach next phase (minimum and maximum estimates).
- Phase durations (minimum and maximum estimates).

Three additional experts participated in specific discussions during the consultations: Sebastien Mazzuri and Simon Meier from FSG participated in the discussions on the TCPs with MMV and Martin John Rogers from the National Institute of Allergy and Infectious Diseases (NIAID) participated in the discussion on the current product portfolio.

Modelling

Drug R&D costs were calculated based on the sum of two estimates:

a) Direct cost of progressing the current pipeline of elimination and eradication specific products from their current R&D phase until the expected point of failure (determined by PTS values).

a) Cost of backup R&D (feed) required to account for attrition to reach desired number of successfully registered products.

Vaccines

Identification of relevant activities

A review of the literature from the malERA Consultative Group on Vaccines was conducted to outline a preliminary list of vaccine R&D relevant to elimination and eradication. Then, the MESA Task Force identified which of these R&D activities were a) primarily for elimination and eradication, b) 70% for elimination and eradication, c) primarily for control, or d) could not be allocated to any category. Activities either primarily or 70% for elimination and eradication were taken to malaria vaccine experts for further consultation.

Expert consultation

Experts were identified based on participation in the malERA Consultative Groups, suggestions from the MESA Task Force, and existing Policy Cures contacts.

The following experts were interviewed:

- Rip Ballou, GSK Biologicals.
- Christian Loucq, International Vaccine Initiative.
- Ashley Birkett, David Kaslow, Cynthia Lee, Katya Spielberg, Malaria Vaccine Initiative.

Experts were asked to comment on:

- Vaccine R&D goals for elimination and eradication.
- Desired number of products to be developed in the next decade for each goal (ideal portfolio targets).
- List of current products in the pipeline and the elimination and eradication R&D goal each addresses. List was compiled based on the latest WHO Rainbow list.
- Total direct cost per product, per phase (minimum and maximum estimates) (excluding cost of failure).
- Probability of technical success (PTS) for candidate to reach next phase (minimum and maximum estimates).
- Phase durations (minimum and maximum estimates).

Modelling

Total vaccine R&D costs were calculated based on the sum of two estimates:

a) Direct cost of progressing the current pipeline of elimination and eradication specific products from their current R&D phase until the expected point of failure (determined by PTS values).

b) Cost of backup R&D (feed) required to account for attrition to reach desired number of successfully registered products.

Diagnostics

Identification of relevant activities

A review of the literature from the malERA Consultative Group on Diagnoses and Diagnostics was conducted to outline a preliminary list of diagnostics R&D relevant to elimination and eradication. As nearly all diagnostics R&D was identified by the MESA Task Force as relevant to both elimination and eradication and control, cost projections include diagnostic R&D activities for malaria overall.

Expert consultation

The following experts were interviewed:

- David Bell and Mark Perkins, Foundation for Innovative New Diagnostics.

Experts were asked to comment on:

- Diagnostic R&D goals for malaria overall.

- Desired number of products to be developed in the next decade for each goal (ideal portfolio targets).
- Total cost per R&D goal (including cost of failure).
- Duration of each R&D activity.

Vector control products

Identification of relevant activities

A review of the literature from the malERA Consultative Group on Vector Control was conducted to outline a preliminary list of vector control R&D relevant to elimination and eradication. As nearly all vector control R&D was identified by the MESA Task Force as relevant to both elimination and eradication and control since vector control products are developed to interrupt transmission, which is a key aim in elimination and eradication strategies, cost projections for vector control includes R&D activities for malaria overall, rather than only the percentage that is specific to elimination and eradication.

Expert consultation

The following experts were interviewed:

- Tom McLean, Innovative Vector Control Consortium.
- Jo Lines, London School of Hygiene and Tropical Medicine.

Experts were asked to comment on:

- Vector control R&D goals for malaria overall, including:
  a) Development of new active ingredients.
  b) Ongoing research activities.
- Desired number of new active ingredients to be developed in the next decade (ideal portfolio targets).
- Total cost per active ingredient per phase (including cost of failure).
- Total cost for each ongoing research activity.
- Phase durations.

Health systems and operational research

Identification of relevant activities

A review of the literature from the malERA Consultative Group on Health Systems and Operational Research was conducted to outline a list of research activities relevant to elimination and eradication. Activities were described as relevant to one of more of the following groups:

- Group 1—countries where elimination is considered impossible with existing tools.

- Group 2—countries with focal malaria.
- Group 3—elimination ready countries.

Expert consultation

The following experts were interviewed:

- Taghreed Adam, Alliance for Health Policy and Systems Research, WHO.
- Fabrizio Tediosi, Università Bocconi.
- Don de Savigny, Swiss Tropical and Public Health Institute.

Experts were asked to estimate:

- Total cost for one country to conduct the activities in each group, as defined above (minimum and maximum estimates).
- Time required to conduct the activities in each group, as defined above (minimum and maximum estimates).

Modelling

The total cost for all countries was calculated by multiplying:

a) Cost per country to conduct each control or elimination research activities.

b) Number of countries in control or elimination phase.

Important methodological considerations included:

- Cost per country is adjusted based on each country's population at risk of malaria (e.g. countries with larger population at risk will have higher costs).
- Countries are also modelled to transition from control stage (Group 1 and 2) to pre-elimination stage (Group 3): 1-2% of Group 1 and 2 move into Group 3 each year starting 2014.

Initial number of countries in control or elimination phase at start of the model (2013), and population at risk of malaria in each country are based on the WHO World Malaria Report: http://www.who.int/malaria/world_malaria_report_2011/9789241564403_eng.pdf. Input on the transition rates was given by Aafje Rietveld (WHO GMP focal point in elimination) and Hoda Atta (WHO Regional Adviser in the EMRO Region).

Modelling and harmonised data systems

Expert consultation

Thomas Smith from the Swiss Tropical and Public Health Institute provided estimates for number of research groups and annual cost per research group.

INPUTS AND ASSUMPTIONS

Variables and values used to calculate future funding needs for each of the research areas included in the report are listed below:

Basic research

	Duration for model		Total cost for model	
R&D activity	Minimum	Maximum	Minimum	Minimum
Measuring malaria transmission	10	10	$84,000,000	$84,000,000
Distribution of severe G6PD variants	10	10	$2,000,000	$4,700,000
Characterisation of the entire *Plasmodium* metabolome	10	10	$17,500,000	$17,500,000
In vitro culture systems for *P. falciparum* liver stage	10	10	$10,500,000	$15,000,000
In vitro culture systems for *P. vivax* asexual and liver stage	10	10	$29,000,000	$30,000,000
Improved animal models	10	10	$15,000,000	$15,000,000
Identification of novel classes of molecules	10	10	$22,500,000	$22,500,000
New genetic technologies to identify gene functions and gene-drug interactions	10	10	$59,166,667	$59,166,667

G6PD: Glucose-6-phosphate-dehydrogenase.

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

Drugs

	Duration for model		Total cost for model		% to reach next phase (PTS) (minimum and maximum)
R&D activity	Minimum	Maximum	Minimum	Maximum	
Discovery^	N/A	N/A	5,000,000	7,500,000	N/A
Preclinical	1.5	3	1,800,000	2,070,000	55%
Phase I	1	2	1,500,000	1,725,000	60%
Phase IIa	1.5	2	1,200,000	2,300,000	30%
Phase IIa TCP 4	1.5	2	2,400,000	4,600,000	30%
Phase IIb	3.5	4	10,700,000	14,005,000	75%
Phase IIb SERCaP	3.5	4	10,700,000	14,005,000	40%
Phase III	2.5	4	31,000,000	35,650,000	73%
Phase III SERCaP	2.5	4	31,000,000	35,650,000	40%
Phase IV	5	5	10,000,000	11,500,000	98%
FDCs and label extensions	3	3	5,000,000	11,500,000	N/A

FDC: Fixed-dose combination; SERCaP: Single exposure radical cure and prophylaxis; PTS: Probability of technical success; TCP: Target candidate profile.
^ The model assumes that the R&D work starts in preclinical stage and calculates a feed (backfill) to simulate discovery based on the gap between the desirable targets and the outcomes reached by progressing the current portfolio. Thus, no duration or PTS are needed for this phase.

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

Drugs strategic goals	# products (minimum)	# products (maximum)	Date	Notes
First-generation SERCaP	1	1	2022	These targets will be fufilled by combining the TCP NCEs, so no backfill will be included for this
Second-generation SERCaP	1	1	2027	These targets will be fufilled by combining the TCP NCEs, so no backfill will be included for this
TCP 1				
TCP 1 (transmission blocking)	0	0		NCEs will be tested for transmission blocking, but there will be no backup R&D if testing is unsuccessful - no backfill included
TCP2				
TCP 2 (relapse prevention)	0	0		TCP 2 NCEs will be tested for relapse prevention, but there will be no backup R&D if testing is unsuccessful; no backfill included.
TCP 2 (transmission blocking)	0	0		NCEs will be tested for transmission blocking, but there will be no backup R&D if testing is unsuccessful; no backfill included.
TCP3				
TCP 3 (relapse prevention)	1	1	2022	MMV expects to register 1 NCE for TCP 3 by 2022.
TCP 3 (relapse prevention) second-generation	1	1	2027	Second-generation NCEs will need to be developed to counteract drug resistance and replace first-generation candidates that might fail.
TCP 3 (transmission blocking)	0	0		NCEs will be tested for transmission blocking, but there will be no backup R&D if testing is unsuccessful; no backfill included.
TCP4				
TCP 4 (chemoprophylaxis)	1	1	2022	MMV expects to register 1 NCE for TCP4 by 2022.
TCP 4 (transmission blocking)	0	0		NCEs will be tested for transmission blocking, but there will be no backup R&D if testing is unsuccessful; no backfill included.
FDCs and label extensions	5.25	5.25		1.5 for every 2 registered products (75% of NCE target). Incremental one-off R&D costs per product; no backfill included.

FDC: Fixed-dose combination; SERCaP: Single exposure radical cure and prophylaxis; TCP: Target candidate profile; NCE: New chemical entity.

Vaccines

R&D activity	Duration for model		Total cost for model		% to reach next phase (PTS) (minimum and maximum)
	Minimum	Maximum	Minimum	Maximum	
Vaccine blood stage					
Discovery PE or blood stage^	N/A	N/A	3,800,000	6,300,000	N/A
Preclinical PE or blood stage	5	5	50,000	500,000	53%
Phase Ia PE or blood stage	1	1	500,000	1,800,000	55%
Phase Ib PE or blood stage	2.5	4	1,000,000	4,000,000	88%
Phase Ia/IIa PE or blood stage	1	1	800,000	800,000	25%
Phase IIb PE or blood stage	5	7.5	15,000,000	20,000,000	50%
Phase III PE or blood stage	4	5	140,000,000	280,000,000	70%
Phase IV PE or blood stage	5	8	30,000,000	100,000,000	85%
Vaccine sexual stage					
Discovery sexual stage^	N/A	N/A	3,800,000	6,300,000	N/A
Preclinical sexual stage	5	5	2,000,000	5,000,000	30%
Phase Ia sexual stage	3.5	5	3,800,000	10,000,000	20%
Phase Ib sexual stage	3.5	5	3,800,000	10,000,000	20%
Phase IIb sexual stage	5	7.5	50,000,000	100,000,000	50%
Phase III sexual stage	4	5	300,000,000	300,000,000	70%
Phase IV sexual stage	5	8	30,000,000	100,000,000	85%

PE: Pre-erythrocytic; PTS: Probability of technical success.

^ The model assumes that the R&D work starts in the preclinical stage and calculates a feed (backfill) to simulate discovery based on the gap between the desirable targets and the outcomes reached by progressing the current portfolio. Thus, no duration or PTS is needed for this phase.

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

Vaccines strategic goals	# products (minimum)	# products (maximum)	Date	Notes
Core 2: Second-generation *P. falciparum* vaccine (with or without components targeting *P. vivax*) with protective efficacy of more than 75% against clinical disease and/or infection, providing protection for longer than 2 years. Note: Only R&D associated with *P. vivax* was included as being specific to elimination and eradication.	1	1	2030	VIMT – PE/BS. All blood-stage and pre-erythrocytic vaccines in the current global portfolio will be modelled as corresponding to this target using standard attrition rates. This target will include the development of P. vivax candidates for clinical disease, up to the proof-of-concept stage. It assumes that once the proof-of-concept is successful, the *P. vivax* candidate(s) will be combined with the *P. falciparum* vaccine leading candidate(s). Assumes different clinical development pathways for clinical disease versus infection endpoint.
Core 3: Transmission-blocking vaccine for *P. falciparum*	1	1	2030	VIMT – TBV. This target only includes vaccines targeting the sexual stage and does not provide direct, immediate benefit. Assumes cluster randomised trials required for licensure and deemed feasible.
Core 4: Transmission-blocking vaccine for *P. vivax*	1	1	2030	VIMT – TBV. This target only includes vaccines targeting the sexual stage and does not provide direct, immediate benefit. Assumes cluster randomised trials required for licensure and deemed feasible.

PE: Pre-erythrocytic; BS: Blood stage; R&D: Research and development; TBV: Transmission-blocking vaccine; VIMT: Vaccine that interrupts malaria transmission.

Diagnostics

R&D activity	# products	Cost (minimum) ($)	Cost (maximum) ($)	Duration (minimum)	Duration (maximum)
Improved RDTs for non-*falciparum* parasites	2	3,000,000	18,000,000	5	5
Positive control wells	1	1,500,000	2,000,000	1	1
Recombinant panels for lot testing (quality control of RDTs at country level)	1	1,500,000	4,000,000	1.5	3
RDT quality control	1	9,000,000	9,000,000	5	5
High-throughput field molecular testing	1	21,600,000	21,600,000	3	5
Serological screening tests	1	4,000,000	12,000,000	5	5
Point-of-care G6PD detection	1	5,000,000	12,600,000	5	5
Multiplexing	1	5,000,000	20,000,000	5	7
Automated microscopy	1	21,600,000	21,600,000	10	10
Improved RDTs for *P falciparum*	2	3,000,000	10,800,000	5	5
Non-blood testing	1	72,000,000	72,000,000	10	10

G6PD: Glucose-6-phosphate dehydrogenase; RDT: Rapid diagnostic test.

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

Vector control products

NEW ACTIVE INGREDIENTS	
# new active ingredients needed in next decade	3

Phase	Total cost per active ingredient (maximum and minimum) ($)	Duration for model (years)
Optimisation	17,000,000	3
Pre-trial development	25,000,000	2
Development	53,000,000	3
Registration	25,000,000	2
Total cost per product	120,000,000	

Ongoing research activity		
Ongoing research activity	Total cost (minimum) ($)	Total cost (maximum) ($)
Screening of new candidates	26,000,000	26,000,000
Formulation development	78,000,000	78,000,000
Three new paradigms	195,000,000	195,000,000
Information systems and tools	26,000,000	65,000,000

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

Health systems and operational research

Country grouping	Per country cost of full set of research activities	# countries	Total cost for model per country ($)		Total cost for model ($)		Duration for model	
			Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
Group 1 - countries where elimination is considered impossible with existing tools	1,486,500	80	720,750	1,486,500	57,660,000	118,920,000	Evenly spread across 10 years	
Group 2 - countries with focal malaria	1,441,500							
Group 3 - elimination ready countries	53,333	19	26,667	53,333	506,667	1,013,333	Evenly spread across 10 years	

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

Modelling and harmonised data systems

	Minimum	Maximum
Number of research groups	7	8
Annual cost per research group	1,600,000	1,600,000

Assumptions	Minimum	Maximum
Cost of capital multiplier	4%	4%
Uncertainty multiplier	10%	20%

ANNEXE 3: SURVEY RESPONDENTS LIST

Organisation Name

Anacor Pharmaceuticals
AstraZeneca
Australian Department of Industry, Innovation, Climate Change, Science, Research and Tertiary Education (DIICCSRTE)
- including data from Australian Research Council (ARC)
Australian National Health and Medical Research Council (NHMRC)
BASF Corporation
Bayer CropScience
Baylor College of Medicine
Belgian Ministry of Foreign Affairs
- including data from Belgian Development Cooperation (DGDC)
Bill & Melinda Gates Foundation
Bio Manguinhos
Brazilian Innovation Agency (FINEP)
Brazilian Ministry of Health: Department of Science and Technology (DECIT)
Burnet Institute (previously the Macfarlane Burnet Institute for Medical Research and Public Health)
Carlos III Health Institute
Catalan Agency for Development Cooperation (ACCD)
Celgene Corporation
Crucell
Dafra Pharma International Ltd.
Danish Ministry of Foreign Affairs
- including data from Danish International Development Agency (DANIDA)
DesignMedix, Inc.
Drugs for Neglected Diseases initiative (DNDi)
Dutch Ministry of Foreign Affairs - Directorate General of Development Cooperation (DGIS)
Dutch Organisation for Scientific Research (NWO)
European Vaccine Initiative (EVI)
European and Developing Countries Clinical Trials Partnership (EDCTP)
European Commission: Research Directorate-General
FK Biotecnológia
Foundation for Innovative New Diagnostics (FIND)
French National Research Agency (ANR)
Fundacio La Caixa
German Federal Ministry for Economic Cooperation and Development (BMZ)
German Federal Ministry of Education and Research (BMBF)
German Federal Ministry of Health (BMG)
German Research Foundation (DFG)
Ghana Health Service
GlaxoSmithKline (GSK)
GSK Bio
Health Research Council of New Zealand (HRC)
Indian Council of Medical Research (ICMR)
Indian Council of Scientific and Industrial Research (CSIR)
Indian Department of Biotechnology, Ministry of Science and Technology (DBT)
Infectious Disease Research Institute (IDRI)
Innovative Vector Control Consortium (IVCC)
Inserm - Institute of Infectious Diseases
Institut Pasteur
Institute of Tropical Medicine Antwerp/Prince Leopold Institute of Tropical Medicine (ITM)
International Centre for Genetic Engineering and Biotechnology (ICGEB), India
Irish Aid
ISGlobal
Liverpool School of Tropical Medicine (LSTM)
London School of Hygiene and Tropical Medicine (LSHTM)
Malaysian Ministry of Science and Technology (MOSTI), including the National Biotechnology Division (BIOTEK)
Medicines for Malaria Venture (MMV)
Merck and Co Inc
Mexican National Institute of Public Health (INSP)
Mymetics
Nicaraguan Ministry of Health
Novartis
OneWorld Health (OWH)
Papua New Guinea Health Promotion Branch
Partec GmbH
Pfizer
Program for Appropriate Technology in Health (PATH)
- including data from Meningitis Vaccine Project (MVP), Malaria Vaccine Initiative (MVI), Technology Solutions, Vaccine Development, Vaccine Access and Delivery
Royal Norwegian Ministry of Foreign Affairs and/or Norwegian Agency for Development Cooperation (NORAD)
Royal Tropical Institute (KIT)
Sabin Vaccine Institute
sanofi-aventis
South Africa Medical Research Council (MRC)
South African Department of Science and Technology (DST)
- including data from the Technology Innovation Agency
Spanish Clinical Foundation for Biomedical Research, Fundacio Clinic per a la Recerca Biomedica (FCRB)
Spanish Ministry of Foreign Affairs and Cooperation for Development (MAEC)
- including data from Agency of International Cooperation for Development (AECID)
Spanish National Research Council, Consejo Superior de Investigaciones Cientificas (CSIC)
Swedish International Development Agency (SIDA)
Swedish Research Council
Swiss Agency for Development and Cooperation (SDC)
Swiss National Science Foundation (SNF)
Swiss State Secretariat for Education and Research (SER)
Swiss Tropical & Public Health Institute
Syngenta Crop Protection AG
Thailand National Science and Technology Development Agency (NSTDA)
The Walter and Eliza Hall Institute of Medical Research
The Wellcome Trust
UBS Optimus Foundation
UK Department for International Development (DFID)
UK Medical Research Council (MRC)
United States Agency for International Development (USAID)
University of Cambridge
University of Dundee
US Centers for Disease Control (CDC)
US Department of Defense (DOD) including DOD Defense Advanced Research Projects Agency (DARPA)
US National Institutes of Health (NIH)
World Bank
World Health Organization: Special Programme for Research and Training in Tropical Diseases (WHO/TDR)