FROM PIPELINE TO PRODUCT: **MALARIA** R&D FUNDING NEEDS INTO THE NEXT DECADE

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POLICYCURES

FROM PIPELINE TO PRODUCT: MALARIA R&D FUNDING NEEDS INTO THE NEXT DECADE

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CONTENTS

ACRONYMS

ACT	Artemisinin-based combination therapy
AIDS	Acquired Immunodeficiency Syndrome
ASAQ	Artesunate/amodiaquine
ASMQ	Artesunate/mefloquine
Australian NHMRC	Australian National Health and Medical Research Council
BS	Blood stage
E&E	Elimination and eradication
FDC	Fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
G6PD	Glucose-6-phosphate dehydrogenase
G-FINDER	Global Funding of Innovation for Neglected Diseases
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
ICMR	Indian Council of Medical Research
IRS	Indoor residual spraying
IVCC	Innovative Vector Control Consortium
Laos PDR	Lao People's Democratic Republic
LLINs	Long-lasting insecticide-treated bednets
malERA	Malaria Eradication Research Agenda
MESA	Malaria Eradication Scientific Alliance
MMV	Medicines for Malaria Venture
MVI	PATH Malaria Vaccine Initiative
NCE	New chemical entity
PATH	Program for Appropriate Technology in Health
PE	Pre-erythrocytic
PE-VIMTs	Pre-erythrocytic vaccines that interrupt malaria transmission
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
SSM-VIMTs	Sexual, sporogonic, or mosquito vaccines that interrupt malaria transmission
TBV	Transmission-blocking vaccine
TCP	Target candidate profile
UK DFID	UK Department for International Development
UK MRC	UK Medical Research Council
US DOD	US Department of Defense
US NIH	US National Institutes of Health
USAID	US Agency for International Development
VCTR	Vector-based Control of Transmission: Discovery Research
VIMT	Vaccine that interrupts malaria transmission
WHO	World Health Organization

EXECUTIVE SUMMARY

Introduction

Malaria is a major public health challenge that threatens approximately half of the world's population.[1] Malaria claims the life of a child in Africa each minute[1] and the life of a pregnant woman worldwide each hour.[2] In 2010, there were more than 219 million cases globally.[3]

However, the situation is now far better than it was even ten years ago. Thanks to increased funding for malaria programmes, better tools, and increased control efforts, worldwide malaria deaths have decreased by 26% since 2000.[3] Between 2001 and 2010, there were 274 million fewer cases and 1.1 million fewer malaria deaths.[3] New tools have made an important contribution to this progress and are the outcome of increasing investment in research and development (R&D) over the past two decades. The 2011 global investment of US$610 million in malaria R&D is nearly five times larger than the $131 million invested in 1993, and almost double the 2004 total of $320 million.[i]

With improvements in tools and coverage, and a comprehensive global framework for action—the Global Malaria Action Plan[6]—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 further still, 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.[3] Reaching these goals will require a sustained, long-term, and well-planned effort, and ongoing R&D will be critical to this.

There are, however, emerging issues that threaten the efficacy of current control methods. Resistance to first-line malaria drug treatment has emerged in the Greater Mekong Subregion and early resistance to insecticides has been reported in two-thirds of malaria-endemic countries. The *Plasmodium vivax* form of malaria is also growing as a problem, affecting adult males as well as the children and pregnant women traditionally targeted by the *Plasmodium falciparum* strain of malaria. Control, elimination, and eradication programmes will fail in the face of these emerging threats without continued R&D to improve existing tools and to develop new ones.

From Pipeline to Product: Malaria R&D funding needs into the next decade serves as a tool to guide policymakers' investment in new tools to control malaria, contain emerging threats, and move toward the goal of eradicating malaria from the world. It looks at the estimated funding needed for R&D of new malaria tools until 2022, including for basic research, drugs, vaccines, diagnostics, and vector control agents. The report provides an update to the 2011 *Staying the Course* report, which estimated R&D cost and R&D investments for all malaria R&D activities. All figures presented in *From Pipeline to Product: Malaria R&D funding needs into the next decade* have been adjusted for inflation and are reported in 2011 US dollars.[ii]

[i] The 1996 Wellcome Trust report put malaria R&D funding in 1993 at $84 million.[4] In 2004, total malaria R&D funding (including implementation research) was $323 million, according to the 2005 Malaria R&D Alliance report.[5] These figures have been converted into constant 2011 US dollars and implementation research removed from the 2004 total for comparative purposes.

[ii] This represents a change from the *Staying the Course* report, where figures were reported in 2007 US dollars.

Key findings

Overall funding landscape

Malaria R&D funding trended upward between 2007 and 2011, increasing from $531 million in 2007 to $610 million in 2011. The dominant areas of investment over the five-year period were drugs ($1 billion, 38% of total malaria R&D funding), basic research ($745 million, 26%), and vaccines ($742 million, 26%). Vector control products and diagnostics received, respectively, just 4% ($114 million) and 2% ($53 million) of malaria R&D funding in 2007-2011, although the amount each area received per year generally increased.

The period from 2007 to 2011 saw a trend away from funding of product development and toward basic research. Product development accounted for 76% of total malaria R&D funding in 2007, decreasing to 72% in 2011, although both basic research and product development experienced funding increases and the total funding pie became around $85 million larger. These trends were largely driven by public funders, which accounted for around half (51%) of all malaria R&D funding in 2007-2011. The philanthropic sector accounted for a third (32%) and industry for a fifth (17%). Philanthropic funding fluctuated substantially from year to year, as funding from this sector is particularly responsive to changes in the pipeline. However, at an individual funder level, malaria R&D funding is highly concentrated, with the top 12 organisations accounting for 90% of the funding over the 2007-2011 period.

Overall funding need

The overall funding need for malaria R&D in the next decade is projected at between $5.5 billion and $8.3 billion, with the midpoint averaging around $700 million on an annual basis. Around two-thirds of the projected funding need is for R&D to eliminate and eradicate malaria, including diagnostics for individual and population-level use, drugs to block transmission and prevent relapse, vaccines that interrupt malaria transmission between humans and mosquitoes, and vector control products aimed at killing mosquitoes before they ever reach humans. Of the total funding needed over the next decade, vaccines make up around 32%, drugs and basic research around 27% each, vector control products around 11%, and diagnostics just greater than 3%.

In the next decade, funding will need to be distributed amongst product areas as follows:

- Drugs: The focus on single exposure radical cure and prophylaxis and single exposure chemoprevention agendas means that drug development funding needs can be reduced sooner than projected in *Staying the Course*. The projections indicate that funding can decrease by 23% in 2013-2014 to around $180 million in 2015, but then funding will need to be maintained at that level until at least 2022.

- Vaccines: Funding for vaccine development will account for approximately 32% of funding needs over the next decade and will need to increase from their 2011 level of $150 million to $200 million in 2013. Steady increases thereafter to $250 million per year by 2017 will be required to make substantial progress toward all of the Malaria Vaccine Technology Roadmap targets.

- Diagnostics: There has been only a doubling of funding since 2009 instead of the quadrupling of funding recommended in *Staying the Course*, and now funding needs to double again immediately to around $34 million per year. Thereafter, diagnostics funding will gradually decrease and remain steady at around $15-20 million per year post-2018.

- Vector control products: Like diagnostics, vector control funding needs to almost double immediately to $52 million per year in 2013 and will increase steadily to a peak of $100 million in 2018.

Value for money

Research and development of global health products is a smart and effective area in which to invest money in order to save lives. Past investment in malaria R&D has produced tools—including long-lasting insecticide-treated bednets, a drug suitable for children, and more reliable diagnostic tests—that have contributed to an estimated 26% decrease in malaria deaths worldwide since 2000. In the last decade, at least nine malaria products were registered, including two insecticide formulations for vector control, seven drugs, and multiple diagnostics.

The current malaria R&D pipeline is very healthy, with at least 96 malaria products in development, including 13 new vector control active ingredients and new formulations, 37 drug candidates, and 46 vaccine candidates. The development of new malaria tools will be critical to ensuring that control strategies are effective, particularly in the face of resistance and other threats, and that the goals of elimination and eradication can be met.

Recommendations

This is a critical time for malaria R&D funding. The landscape is shifting to align with new global priorities for malaria control, elimination, and eradication; new research discoveries; and the challenge of resistance. Just as current malaria interventions must work together, the efforts around R&D—in diagnostics, vector control, drugs, and vaccines—need to be equally synergistic. With this in mind, we recommend the following:

1. Funding for malaria R&D must address the full continuum of control, elimination, and eradication.

2. Annual malaria R&D funding should increase to an average of $700 million per year—from as little as $550 million per year to as much as $830 million per year, on average—in order to satisfy the projected malaria funding need, estimated at between $5.5 billion and $8.3 billion over the next decade (through 2022). This equates to a relatively modest increase over current annual funding. Funding for vector control and diagnostics should double over the ten-year period.

3. Basic research needs to be better aligned with product development to maximise public health impact. Current donors can assist by working more closely with new donors to ensure that funding from research ministries results in increased funding for research in the service of product development. Public funders can also increase their commitments to product developers, including product development partnerships.

4. There should be a more coordinated approach to funding to maximise effectiveness and minimise delivery time. Indeed, the projected resource needs in this report assume a higher level of coordination than currently exists.

5. Funding should be flexible to support optimal portfolio management and diverse partnerships, and to maximise resources from endemic countries and emerging economies.

6. In order to broaden the funding base, more funders need to become engaged in malaria R&D, including more donor governments, philanthropic donors, and research and science and technology agencies.

INTRODUCTION

Malaria remains one of the world's great public health challenges, claiming the life of a child in Africa each minute[1] and the life of a pregnant woman worldwide each hour.[2] Notwithstanding impressive progress in the development of and access to new tools, backed by significant increases in funding over the last decade, there were still 219 million cases of malaria worldwide and at least 660,000 deaths in 2010.[3]

Malaria cases and deaths have decreased dramatically in recent years, with an estimated 274 million cases and 1.1 million deaths averted between 2001 and 2010 as a result of better tools and increased control efforts,[3] but resistance remains a constant threat to current control tools. As Dr. Margaret Chan, Director-General of the World Health Organization (WHO), noted in her address to the sixty-sixth World Health Assembly, *"[For] malaria, recent progress has been encouraging, but is increasingly threatened by the spread of resistance to mainstay medicines. If we are not careful, all the hard-won gains can go down the drain."*[7]

Resistance to drugs and insecticides and the increasing importance of *Plasmodium vivax* are substantial hurdles in the fight against malaria. The Greater Mekong Subregion, which includes Cambodia, Laos PDR, Myanmar, Thailand, Vietnam, and Yunnan Province of China, is the birthplace of drug-resistant malaria. It was here that resistance to chloroquine,[3,8] the previous first-line antimalarial, emerged before spreading to Africa, and it is here that resistance has now emerged to our newest and most effective antimalarial, artemisinin.

Vector (mosquito) control relies on insecticides for indoor spraying and treating bednets; however, insecticide resistance has now been reported in two-thirds of malaria-endemic countries, affecting all major vector species and classes of insecticides.[9] All long-lasting insecticide-treated bednets (LLINs) use just one class of insecticides—pyrethroids—which was developed more than 40 years ago and faces the most widespread resistance. All four classes of insecticides used for indoor residual spraying (IRS) are also facing increasing resistance.[3,9,10]

Children younger than five years and pregnant women are especially at risk of malaria. Malaria in pregnancy has two particularly devastating consequences—higher rates of maternal anaemia and low birth weight babies—which in turn increase neonatal deaths. There are still up to 200,000 newborn deaths each year due to malaria during pregnancy, and 86% of all malaria deaths in 2010 were in children younger than five.[11,12] Children who survive malaria face a high risk of developmental delay as a result of severe anaemia caused by malaria infection.[13,14]

Whilst most control measures focus on the deadly *Plasmodium falciparum* species of the malaria parasite, the less severe *P vivax* is also expanding its share of the global malaria burden. *P vivax* is the most geographically widespread malaria strain, with an estimated 2.6 billion people at risk globally,[15,16] and accounts for up to half of malaria cases in South & South East Asia, and as many as 81% of cases in Latin America.[17] The increasing relative prevalence of *P vivax* will require the development of new treatments to clear dormant parasites and prevent relapse, and new tools for diagnosis, which can be challenging if parasite numbers are small.

These threats seriously endanger global malaria control efforts. As the development of new tools can take more than 15 years (for new vaccines and drugs), research and development (R&D) efforts must be supported and scaled up now.

This report estimates the total funding need for malaria control, elimination, and eradication R&D until 2022, based on globally agreed R&D targets. It updates the 2011 *Staying the Course* report, including analysing the funding landscape between 2007 and 2011, providing revised projections of malaria R&D funding needs, and assessing whether these are on target to be met. All figures presented in *From Pipeline to Product: Malaria R&D funding needs into the next decade* have been adjusted for inflation and are reported in 2011 US dollars.[iii]

[iii] This represents a change from the *Staying the Course* report, where figures were reported in 2007 US dollars.

METHODOLOGY SUMMARY

This report describes the current landscape of funding for malaria R&D, analyses recent funding trends and future funding needs, and identifies gaps between the two. It provides an update to the 2011 malaria R&D report, *Staying the Course? Malaria research and development in a time of economic uncertainty.*[18]

A detailed analysis of malaria R&D funding over the period 2007-2011 was conducted using five years of G-FINDER survey data. For a full overview of this survey's methodology and scope, please refer to the G-FINDER 2012 report, *Neglected disease research and development: A five year review*, available at: http://policycures.org/g-finder2012.html. Malaria funding totals in this report are not directly comparable with G-FINDER however, as all funding has been converted to constant 2011 US dollars, and any core funding provided to product development partnerships and other multi-disease research groups has been apportioned to malaria (where appropriate) based on identified expenditure patterns.

Total funding figures for 1993 and 2004—taken from past surveys of malaria R&D funding[4,5]—were used for the purpose of long-term comparison. Both previous surveys also involved active collection of malaria R&D funding data and we consider their scope fully aligned with G-FINDER, with the exception of the 2004 total, from which implementation research has been removed to allow direct comparison. The totals have also been converted to 2011 US dollars.

Cost projections for malaria R&D funding need over the next decade (until 2022) have been modelled independently for each product area using inputs derived from expert consultations (a full list of the model inputs and experts involved appears in Annexe 2).

Key variables used in the model were:

- All products in the pipeline for malaria, including their current stage of development.
- Ideal portfolio targets (number of products needed in the next decade for each product development goal—determined through extensive consultations with experts in each area).
- Total direct cost per phase (excluding cost of failure).
- Phase duration.
- Probability of technical success (defined as percentage of candidates successfully reaching the next phase).

For a full list of how these variables were used when modelling different research categories, please see Annexe 2. All cost projections include minimum and maximum values to reflect the uncertainty range in the estimates provided by the experts, with the estimated average future funding need representing the midpoint of these two values. Total cost projections also include cost of capital and multipliers to account for uncertainty.

The methodology used in this report, including the modelling exercise, is complementary and aligned with the methodology used in *Estimating costs and measuring investments in malaria R&D for eradication.*[19] However, one difference is that historical funding data and cost projections in *From Pipeline to Product*—consistent with G-FINDER methodology—excludes health systems and operational research, as well as modelling and harmonised data systems.

All figures in the report are in 2011 US dollars.

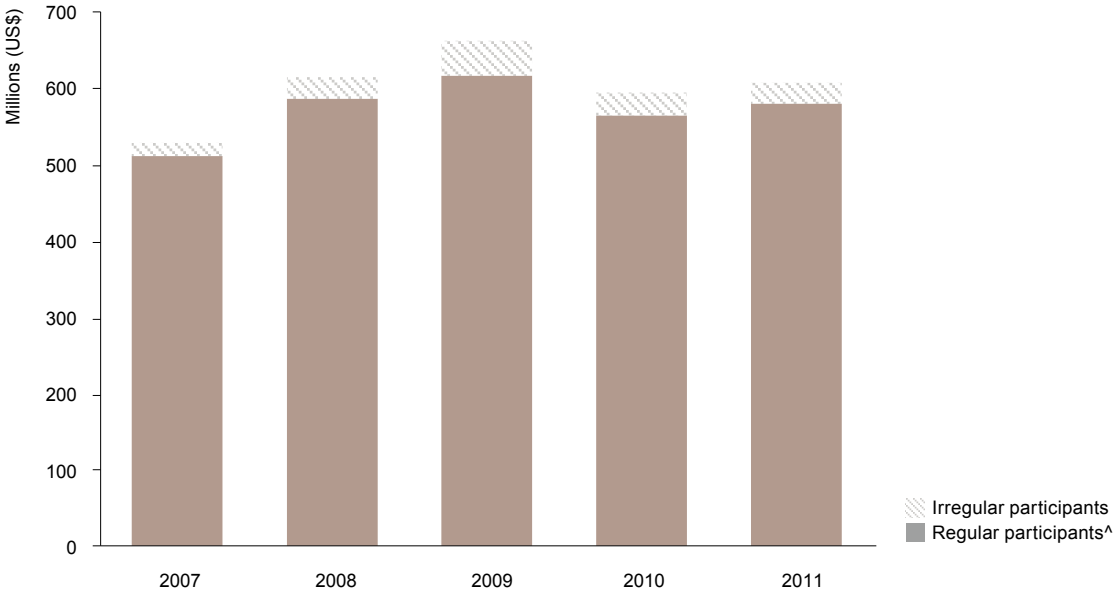
OVERALL MALARIA R&D FUNDING

OVERALL FUNDING LANDSCAPE

Globally, more than half a billion dollars a year is invested in R&D for malaria, and this figure generally is trending upward, from $531 million in 2007 to $610 million in 2011. This represents around a fifth of all funding for neglected disease R&D globally, placing malaria second only to HIV/AIDS in terms of funding received.

This represents a continuation of the upward funding trend revealed by previous surveys of malaria R&D funding. The 2011 global R&D investment of $610 million is nearly five times larger than the $131 million invested in 1993, and almost double the 2004 total of $320 million.[iv]

FIGURE 1
Overall malaria R&D funding, 2007-2011 (2011 US$)



^ Regular participants are those who have reported to G-FINDER in every year of the survey. In order to avoid artefactual changes related to data collection, funding from irregular participants is not included in our trend analysis.

Funding by product

Whilst the amount invested in malaria R&D is important, this investment also needs to be distributed appropriately between product areas (drugs, vaccines, diagnostics, and vector control) according to funding need.

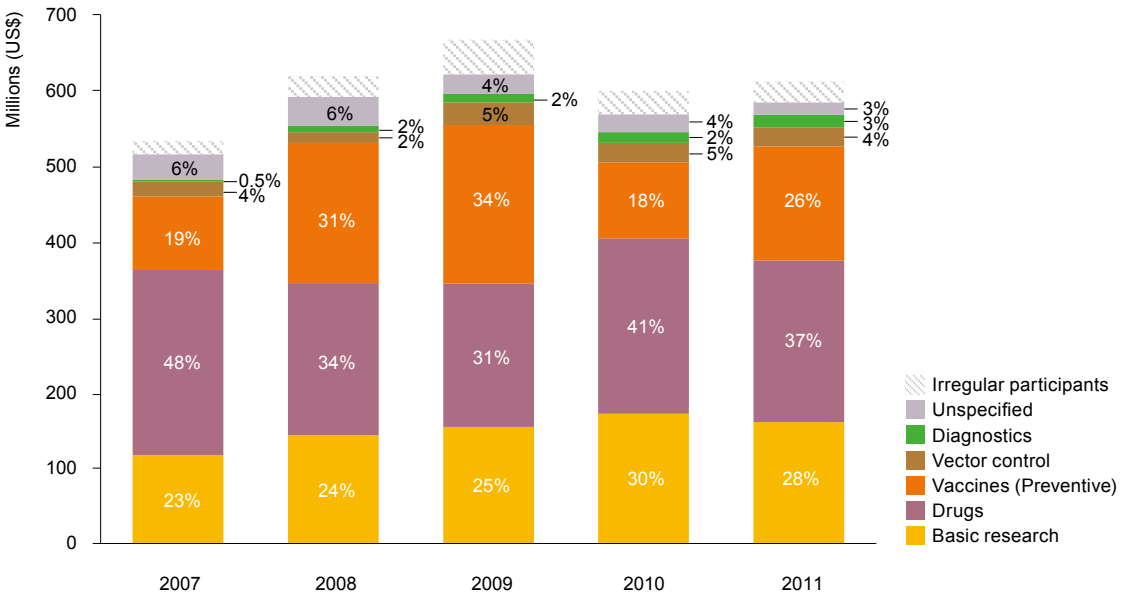
Funding requirements cannot be directly compared between product areas because different types of products have such different development timelines and R&D costs; they also may differ depending on the sector (e.g., private for-profit versus non-profit). Previous estimates in the literature suggest that the costs for the successful development of one product, including failures along the way, are as follows:[6, 18]

[iv] The 1996 Wellcome Trust report put malaria R&D funding in 1993 at $84 million.[4] In 2004, total malaria R&D funding (including implementation research) was $323 million, according to the 2005 Malaria R&D Alliance report.[5] These figures have been converted into constant 2011 US dollars and implementation research removed from the 2004 total for comparative purposes.

- One drug costs $150-250 million over 7-10 years.
- One vaccine costs $600-800 million over 10-15 years.
- One diagnostic costs $2-50 million over 3-5 years.
- One vector control product costs $60-65 million over 10-12 years.

Although funding cannot be directly compared, changes in funding of different product areas over time can be considered. On that basis, we note that R&D funding for drugs has been steady at between $200 and $250 million per year since 2007, whilst vaccine funding has fluctuated substantially due to evolution of the pipeline, in particular, late-stage development of one malaria vaccine candidate. Funding for diagnostics and vector control R&D has increased proportionally faster than for other areas, but this is from a low base and both areas are still underfunded even allowing for their lower development costs.

FIGURE 2
Malaria R&D funding by product type, 2007-2011 (2011 US$)



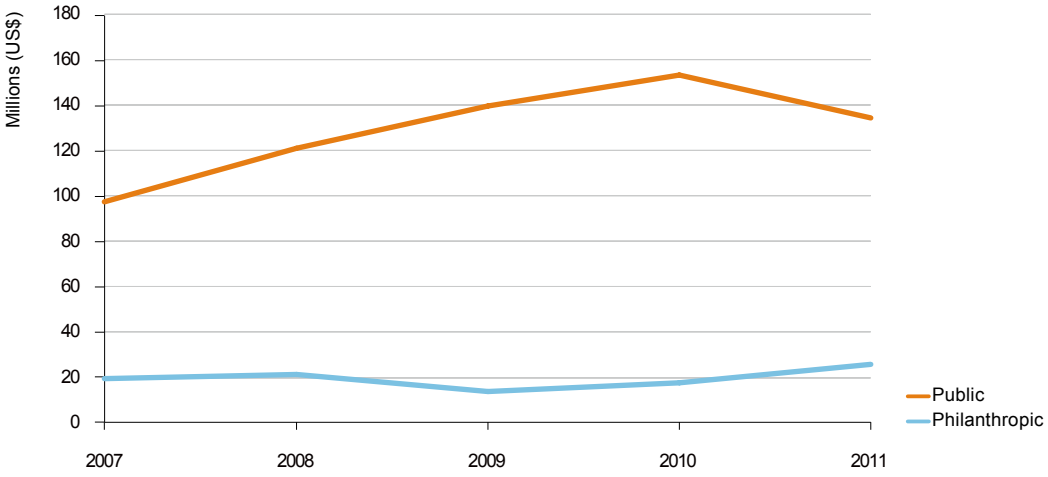
Basic research and product development

Malaria R&D activities can be grouped into two broad categories: basic research and product development.[v] Both are necessary to deliver new malaria tools, but the funding balance between the two must be appropriate, with product development generally requiring substantially more funding than basic research due to the high costs involved, particularly for large, late-stage clinical trials.

Basic research: Malaria basic research funding was $117 million in 2007, peaking at $171 million in 2010 and settling at $161 million in 2011. Basic research was predominantly (87%) funded by the public sector, and public funders were responsible for almost all (85%) of the increase in basic research funding over the five-year period. The philanthropic sector provided the remaining 13% of funding (around $20 million per year).

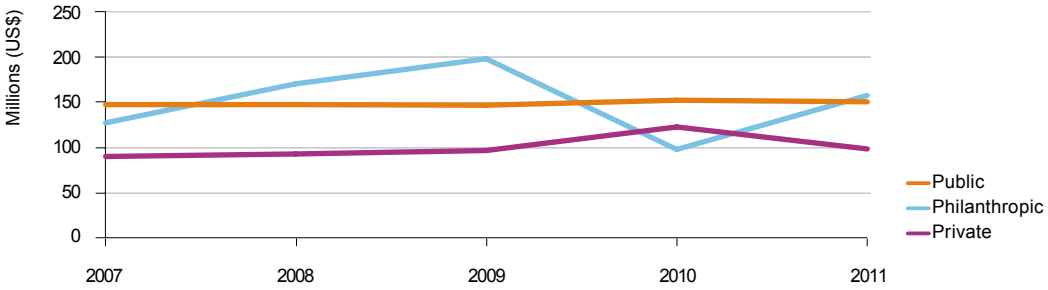
[v] Basic research refers to studies that increase scientific knowledge and understanding of the disease but does not yet target a specific product area. Product development involves identifying promising molecules, testing their abilities and effectiveness in combatting the disease, and eventually developing a successful, safe product.

FIGURE 3
Basic research funding by funder type, 2007-2011 (2011 US$)



Product development: The public and philanthropic sectors each invested approximately $750 million in product development in 2007-2011, but have demonstrated markedly different funding approaches. Public-sector funding has been steady at $150 million per year, with no apparent link to the evolution of the R&D pipeline. In contrast, philanthropic funding has been closely related to the pipeline, fluctuating between $100 and $200 million per year as product development was accelerated or completed—with movements largely driven by one investor, the Bill & Melinda Gates Foundation. Industry funding was entirely for product development.

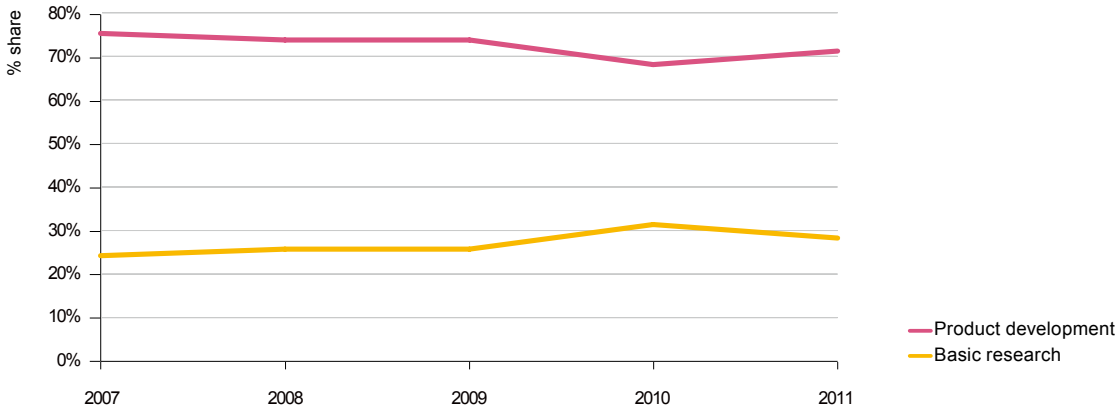
FIGURE 4
Product development funding by funder type, 2007-2011 (2011 US$)



A trend toward basic research

Despite the higher funding needs for product development compared to basic research, particularly as products advance into late-stage clinical trials, there is evidence of a trend in funding away from product development. Between 2007 and 2011, product development received between $370 and $440 million per year; the fluctuations evident in the intervening years (2009-2010) were due to a large cyclical disbursement from the Gates Foundation for late-stage clinical trials of a first-generation malaria vaccine candidate (RTS,S). Over the same five-year period, basic research funding increased by 37% ($44 million). Whilst both areas experienced increases, basic research fared better proportionally: product development accounted for 76% of total malaria R&D funding in 2007; by 2011 this proportion had decreased to 72%.

FIGURE 5
Basic research versus product development as a percentage of total malaria R&D funding, 2007-2011 (2011 US$)



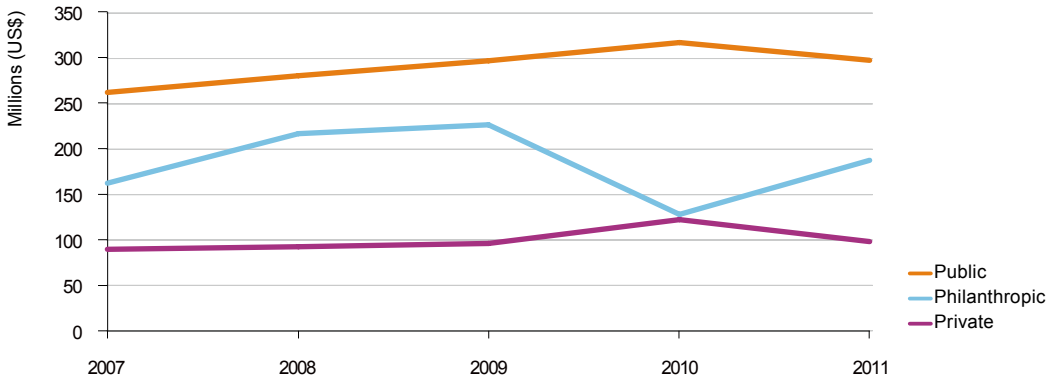
Funding by funder type

Overall, the public sector accounts for around half (51%) of all malaria R&D funding, the philanthropic sector for a third (32%), and industry for a fifth (17%).

Public funding has increased fairly steadily over the past five years, from around $260 million in 2007 to nearly $300 million in 2011. Philanthropic funding has been driven by two organisations—the Gates Foundation (84%) and the Wellcome Trust (15%)—and funding from this sector was also the most directly connected to developments in the malaria product pipeline, showing by far the largest fluctuations from year to year as products were catalysed, matured, or completed. For example, the almost halving of philanthropic funding from $226 million in 2009 to $128 million in 2010 reflects the timing of disbursements for the Phase III trial of RTS,S, now close to completion (funded jointly by GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative [MVI], with grant funding from the Gates Foundation to MVI).

Industry funders provided just less than one-fifth of malaria R&D funding at a relatively steady level of around $100 million each year.

FIGURE 6
Malaria R&D funding by funder type, 2007-2011 (2011 US$)



Top 12 funders

Malaria R&D funding is highly concentrated, with the top 12 funders (including an aggregate figure for industry)[v] accounting for 90% ($2.7 billion) of global malaria R&D funding over the period 2007-2011, and the top five funders alone—the Gates Foundation, the US National Institutes of Health (US NIH), industry, the European Commission, and the US Department of Defense (US DOD)—contributing almost three-quarters (74%).

[v] Industry investment is aggregated for confidentiality purposes, so 'aggregate industry' represents many individual funders.

The five-year period, however, has seen a clear divergence amongst the top five funders. Both the US NIH (up $41 million, or 45%) and Gates Foundation (up $22 million, 16%) have significantly stepped up their malaria R&D investments, in stark contrast to the US DOD (down $16 million, or 45%) and European Commission (down $12 million, 28%), which have cut their funding sharply. This trend has meant that the Gates Foundation and US NIH now account for nearly half (48%) of all malaria R&D funding, up from just greater than 40% just five years ago.

TABLE 1
Top 12 malaria R&D funders, 2007-2011 (2011 US$)

Funding organisation	Average annual funding (US$)^ 2007-2011*	Average % of total	2007*	2008*	2009*	2010*	2011
Gates Foundation	155,302,365	25.7%	134,823,544	189,972,464	199,315,338	95,397,069	157,003,409
US NIH	121,466,865	20.1%	91,449,280	113,515,618	125,659,609	143,980,466	132,729,353
Aggregate industry	105,875,544	17.5%	94,304,511	97,326,316	106,229,281	128,434,867	103,082,744
European Commission	34,423,344	5.7%	41,771,327	39,235,878	33,342,713	27,744,251	30,022,549
US DOD	30,765,281	5.1%	35,927,928	33,052,812	40,710,817	24,552,851	19,582,000
Wellcome Trust	27,521,000	4.6%	25,875,226	25,332,606	26,263,035	31,155,023	28,979,111
UK MRC	19,070,982	3.2%	17,028,345	17,991,100	19,320,005	22,195,835	18,819,627
UK DFID	13,362,716	2.2%	5,809,546	4,623,527	8,476,485	26,875,413	21,028,609
Australian NHMRC	13,362,180	2.2%	10,715,548	12,470,421	14,067,835	13,405,355	16,151,742
Institut Pasteur	9,702,558	1.6%	14,759,525	8,787,135	7,925,364	9,992,886	7,047,880
USAID	9,211,746	1.5%	10,019,784	9,267,054	8,845,663	9,486,998	8,439,233
Indian ICMR	7,033,715	1.2%		10,862,268	7,162,667	5,045,031	5,064,891
Top 12 subtotal#			490,136,668	563,634,654	597,318,810	538,266,044	548,499,307
Grand total			530,590,904	616,805,359	664,498,130	596,945,190	609,577,790

Australian NHMRC: Australian National Health and Medical Research Council; ICMR: Indian Council of Medical Research; UK DFID: UK Department for International Development; UK MRC: UK Medical Research Council; USAID: US Agency for International Development.
^ Averages calculated across years of available data.
* Figures are adjusted for inflation and reported in 2011 US dollars.
# Subtotals for 2007, 2008, 2009, 2010, and 2011 reflect the top funders for those years, not the average top 12.
Did not participate in the survey.

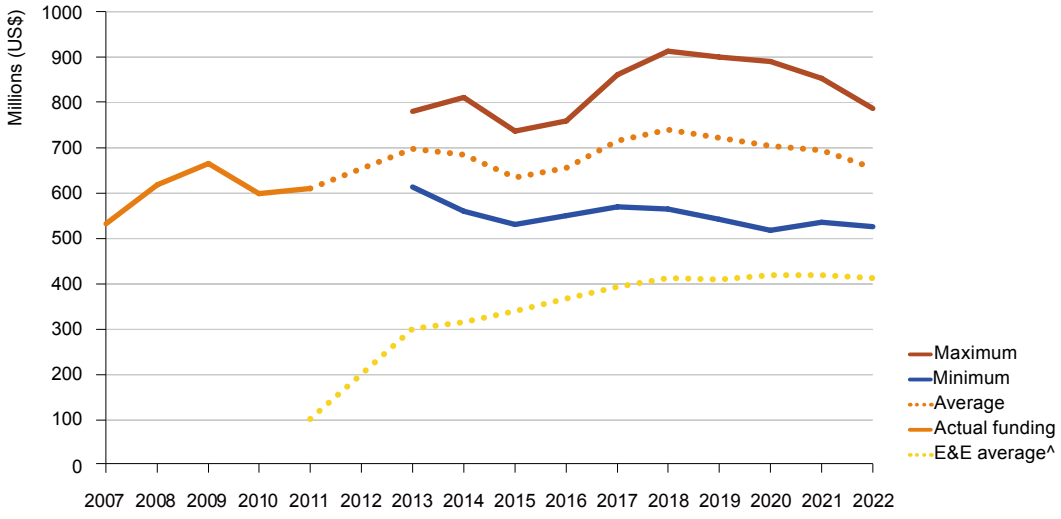
OVERALL FUNDING NEED

Malaria R&D in the next decade (2013-2022) is projected to require a total of $5.5 to $8.3 billion, with the midpoint averaging around $700 million per year for most of the decade.

Around two-thirds of the projected total cost in the next decade is for R&D to eliminate and eradicate malaria, including diagnostics for individual and population-level use, drugs to block transmission and prevent relapse, vaccines that interrupt malaria transmission between humans and mosquitoes,[vii] and vector control products aimed at killing mosquitoes before they ever reach humans. The remaining one-third of the total cost is made up of R&D for 'control' products—drugs and vaccines aimed at treating or preventing malaria in individual patients.

These projected elimination and eradication funding requirements appear far from today's reality. Investment in elimination and eradication R&D for 2011 was estimated at less than one-sixth of total malaria R&D funding, but would need to rise to about half of total funding by 2014, increasing to around two-thirds by 2022 to address the global malaria community's goals.

FIGURE 7
Projected malaria R&D funding need, 2013-2022 (2011 US$)

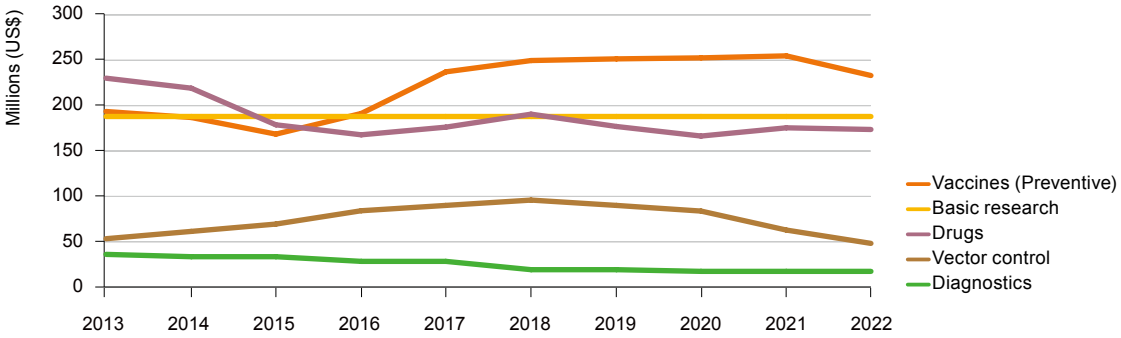


The full set of inputs and assumptions for the cost projections is included in Annexe 2.
^ The E&E (elimination and eradication) total shown here differs slightly from that in *Estimating costs and measuring investments in malaria R&D for eradication*,[19] which has a slightly broader scope.[viii]

Of the total funding needed over the next decade, vaccines make up around 32%, drugs and basic research around 27% each, vector control products around 11%, and diagnostics just greater than 3%, reflecting both the varying costs of developing each product type (from higher-cost vaccines to lower-cost diagnostics) and the state of each portfolio and the ambitiousness of scientific goals for each area. These are average figures, with funding (and thus funding percentages) in reality varying markedly from year to year. In particular, funding requirements for drug R&D are higher in the early years, with vaccine R&D funding needs taking over after 2015 or 2016.

[vii] There are two subtypes of vaccines that interrupt malaria transmission: those that target the pre-erythrocytic stage of the malaria parasite's lifecycle (PE-VIMTs) and those that target the sexual stage of the malaria parasite's lifecycle (SSM-VIMTs).
[viii] The elimination and eradication total differs from that quoted in: *Estimating costs and measuring investments in malaria R&D for eradication*, as the 2011 funding total in that report includes an extra $6 million in investment in two research areas (health systems and operational research and modelling and harmonised data systems) that are not within the scope of this report.

FIGURE 8
Malaria R&D funding need by product type, 2013-2022 (2011 US$)



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

A second point to note is the impact of one type of vaccines, in particular, transmission-blocking vaccines that are explicitly aimed at malaria elimination and eradication (the SSM-VIMTs). The potentially higher trial costs and uncertainty regarding the development and regulatory approval pathway of these particular vaccines is the main driver behind total vaccine development costs, and also overall funding requirements, accounting for around one-third of overall malaria R&D funding needs over the next decade.

We also note the very high uncertainty ranges in the total funding figures. This again reflects the high uncertainty surrounding development of elimination and eradication vaccines (which have a cost range, on average, of $100 million on either side), as well as the uncertainty around development of new drug approaches (costs of plus or minus around $50 million). The uncertainty ranges for vector control products (plus or minus $5 million) and diagnostics (plus or minus $5 million) are minor contributors to the wide ranges seen above.

Finally, we note that the impact of interactions amongst 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 rollout 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 TOOLS WILL WE HAVE BY 2022?

Ten years of investment in malaria R&D at the levels shown above will deliver a remarkable suite of new tools to attack, and begin to eradicate, malaria. It means that by 2022, those living in the world's malaria zones should have far better diagnostic, treatment, and prevention options than they do today, including:

- Two new single-dose malaria medicines that can treat all types of malaria, prevent relapse, and provide post-treatment prophylaxis against all malaria lifecycles and species (single exposure radical cure and prophylaxis).
- A single drug that can protect against malaria for up to a month, active against all species of malaria and suitable for mass administration (single exposure chemoprevention).
- Approval of drugs for use in several new patient groups, including pregnant women and infants.
- A first-generation *P falciparum* vaccine that has 50% protective efficacy for at least one year against severe disease and death from malaria.
- Possibly a more protective second-generation vaccine that responds to the updated Malaria Vaccine Technology Roadmap by preventing clinical disease and/or infection with one or both of *falciparum* and *vivax* malaria.
- A test that can be used to monitor the accuracy of rapid diagnostic tests used by health care workers in the field.
- A field test to detect low levels of malaria parasites, to help wipe out remaining foci of infection.
- An automated microscope that can be used by health workers to accurately detect malaria and quantify parasites.
- A malaria test that avoids the need to take blood from patients, including small children.
- Three improved new active ingredients (chemicals) for use in LLINs and IRS.
- A follow-on generation of new approaches to chemical and biological control of malaria-carrying mosquitoes.
- A healthy pipeline of backup products in all areas, including products that can further increase efficacy, counteract the malaria parasite's ability to develop resistance, and move us closer to the goal of eradication and elimination of malaria from the world.

MALARIA R&D FUNDING BY PRODUCT

BASIC RESEARCH

Funding landscape for basic research

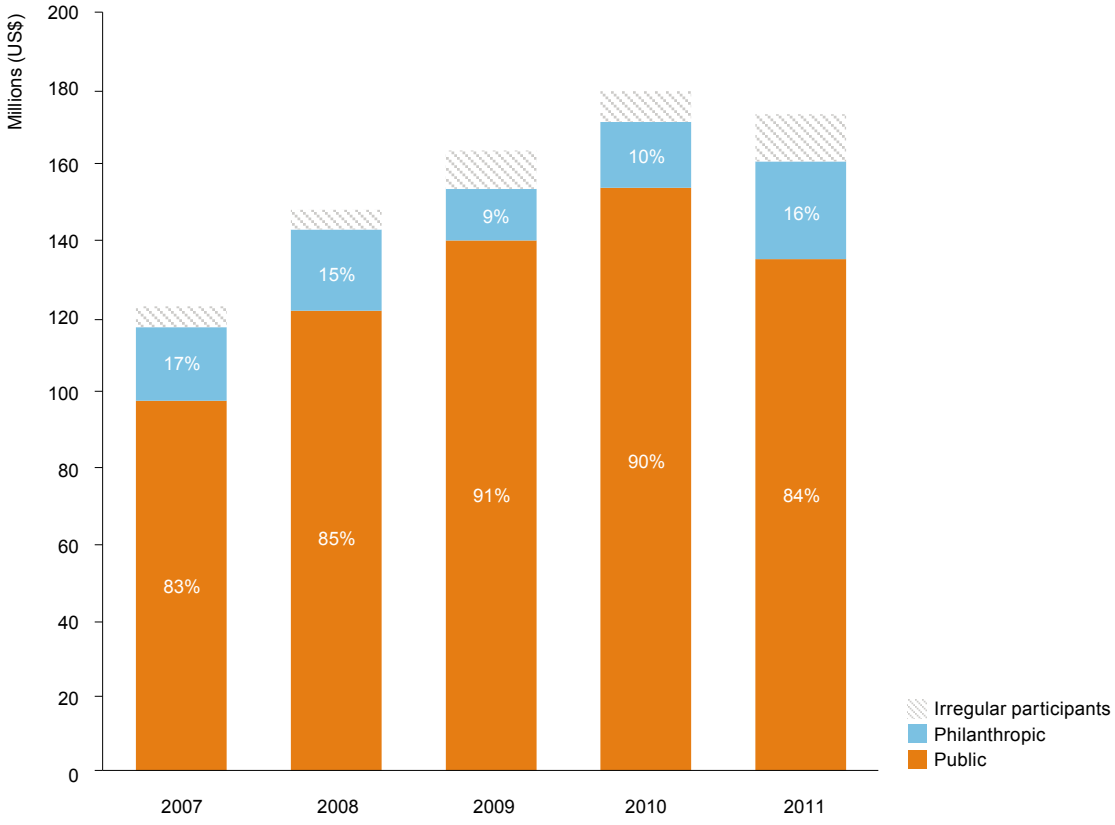
Basic research refers to the studies that increase understanding of malaria, including its disease processes, pathogen, or vector, but which are not yet directed toward making a specific product. Basic research received around one-quarter of global malaria R&D funding in 2007-2011, with the bulk of basic research funding and funding increases since 2007 driven by the public sector.

The public sector provided 87% of funding for basic research over the five years, with a striking contribution of just more than half (53%) coming from the US NIH. During that time, 90% ($585 million) of public funding for basic research went to public institutions and 64% ($416 million) specifically to academic institutions. Public funding for basic research increased by 38% ($37 million) in the period 2007-2011, very likely related to a government preference for investing in their own domestic institutions during periods of economic downturn.

Philanthropic organisations provided 13% of basic research funding, consistently providing between $14 and $26 million each year over the five years. Two organisations accounted for 98% of this funding: the Wellcome Trust (69%, $67 million) and the Gates Foundation (29%, $28 million). The majority of the Wellcome Trust's basic research funding (84%) went to UK institutions, whilst just more than two-thirds (69%) of the Gates Foundation's basic research funding went to US institutions.

Reporting on investment in basic research for different malaria strains (*P vivax* and *P falciparum*) continues to be fairly poor. Between 2007 and 2011, 48% ($354 million) of funding was reported as specifically invested in *P falciparum* research, whilst only 5% ($35 million) was specifically reported as *P vivax* research. However, half of all funding was reported as 'unspecified' (48%, $355 million); this included any malaria research not exclusively directed at one of these two strains, such as research that was relevant to both strains.

FIGURE 9
Basic research funding by funder type, 2007-2011 (2011 US$)



Funding needs

Consistent and sustained investment in malaria basic research will be required to support the development of the global product portfolio over the next decade and beyond. Constant investment in malaria basic research of between $180 and $195 million per year has been included in the model, which maintains funding at or just greater than the 2011 level. However, along with funding, the malaria community would also benefit from increased coordination between scientists conducting basic research and those involved in product development. This would enable a more targeted response to identified needs, which in turn would accelerate new products. For instance, a better understanding of the genetic markers for drug resistance could lead to better screening tests. More research in antigen discovery could propel the development of a highly efficacious malaria vaccine.

DRUGS

Drugs, along with vector control tools, are the mainstay of malaria control strategies, and are used to treat patients who have already contracted malaria as well as for prevention of malaria in pregnant women and children.[ix] At present, artemisinin-based combination therapies (ACTs) are recommended by WHO as first-line treatment for *P falciparum* malaria, as they offer significant advantages over alternatives: most malaria parasites are still sensitive to artemisinin, and since it rapidly clears the malaria parasite from the patient's blood, even before treatment is completed, transmission by biting mosquitoes is also reduced. The slower-acting partner drug in the combination therapy is then on hand to kill any remaining parasites and provide post-treatment prophylaxis for at least one month.[20]

Unfortunately, artemisinin resistance is now emerging in the Greater Mekong, the same subregion where resistance emerged to all previous frontline treatments, including chloroquine and sulfadoxine-pyrimethamine (Fansidar®).[3,8,21] There are no currently available replacement drugs for artemisinin and most of the new antimalarial drugs in the late stages of the pipeline are artemisinin-based or synthetic artemisinin-like compounds.[22]

There are also significant gaps in the malaria treatment armamentarium, particularly for *P vivax*. Currently, the recommended *P vivax* treatment is chloroquine (or an appropriate ACT in areas with chloroquine resistance) to treat the episode and a 14-day course of primaquine to prevent relapse.[3,16] However, primaquine cannot be used in patients with a certain enzyme deficiency (specifically, those with the relatively common glucose-6-phosphate dehydrogenase, or G6PD, enzyme deficiency, in whom it can induce haemolytic anaemia).[16] And it is often difficult for patients to complete lengthy treatment courses, such as the 14-day primaquine treatment for *P vivax* malaria.

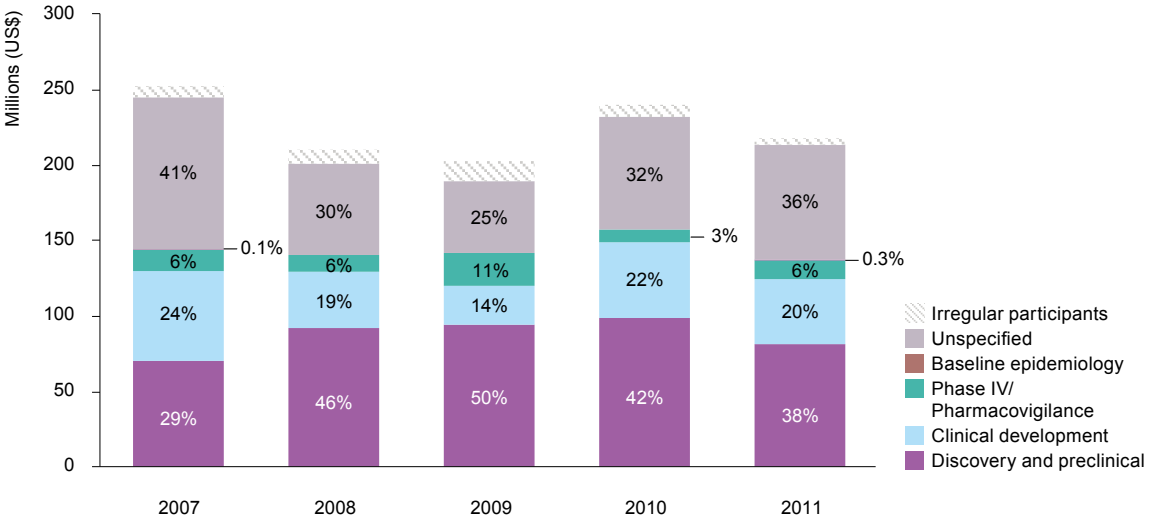
Sustained investment in malaria drug R&D is essential to confront the emerging threat of artemisinin resistance, to provide alternative *P vivax* treatments, in particular for patients with G6PD deficiency, and to develop a single-dose cure for all types of malaria to simplify treatment and ensure accurate dosing.

Funding landscape for drug R&D

Drug R&D for malaria has received $190-250 million each year since 2007, with funding fluctuations during that time largely reflecting developments in the drug pipeline. For instance, funding decreased from 2007 to 2009 due to completion of several new antimalarials, including artesunate/amodiaquine (ASAQ) in 2008, artesunate/mefloquine (ASMQ) in 2008, and Coartem® Dispersible in 2009, and has increased since then as the next generation of malaria drugs moved into clinical trials.

[ix] Malaria drug R&D includes research activities that are necessary to develop new compounds designed to prevent, cure, or treat the disease; these activities include drug discovery and design, preclinical or clinical development, and other activities that are important for successful drug development and uptake.

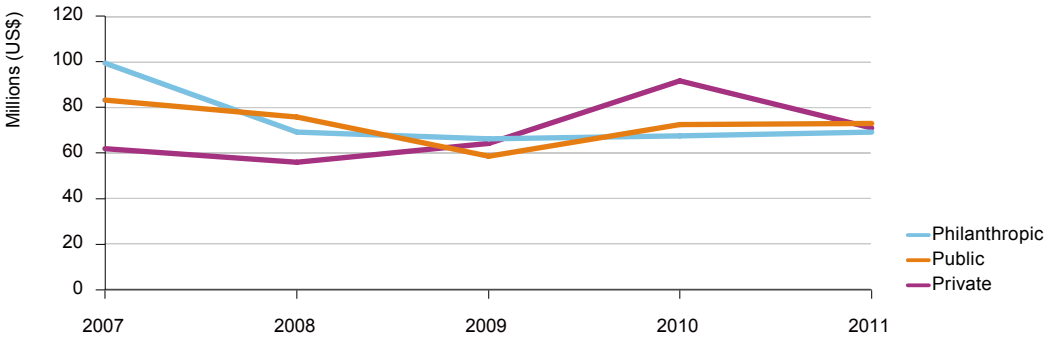
FIGURE 10
Drug funding by R&D stage, 2007-2011 (2011 US$)



Changes in sectoral funding patterns have also had an impact on malaria drug R&D funding. In general, in 2007-2011 public funding declined, industry funding increased, and philanthropic funding remained largely steady. As a result, each of the three sectors—public, philanthropic, and industry—now contributes around one-third of malaria drug R&D funding, a marked change from 2007.

We note a general decline in public funding for malaria drug R&D since 2007, exacerbated by the global financial crisis of 2007-2008. For example, between 2007 and 2011, European Commission funding decreased from $25 million to $6 million and US DOD funding from $18 million to $11 million. These decreases were partially masked by a major funding increase from the UK Department for International Development, which gave grants of $22 million and $19 million to Medicines for Malaria Venture (MMV) in 2010 and 2011 respectively.

FIGURE 11
Drug funding by funder type, 2007-2011 (2011 US$)



In contrast, industry funding for malaria drug R&D over the five years remained relatively resilient, with industry being the only one of three funding sectors that invested more in 2011 than 2007. Industry funding increased steadily from $62 million to $92 million between 2007 and 2010 as several industry drug candidates went through clinical trials, including four new ACTs (DHA-piperaquine, pyronaridine-artesunate, artesunate-amodiaquine, and arthemeter-lumefantrine dispersible), and decreased to $71 million in 2011 as ACTs reached registration and other industry funders moved their funding focus from clinical development to discovery and preclinical.

Philanthropic funding has been steady at around $65-70 million since 2008, after a 2007 peak partially reflecting a five-year cyclical grant to MMV from the Gates Foundation; this five-year cycle was just renewed in 2013, which will lead to a further peak and drop.

Funding by stage

Investment in clinical drug development halved between 2007 and 2009, from $60 million to $26 million, as a result of several drugs completing expensive late-stage clinical trials (as noted above), and the discontinuation of two unsuccessful candidates: isoquine in 2008 and chlorproguanil-dapsone-artesunate in 2009. In parallel, discovery and preclinical research have received substantial funding since 2008 to ensure the pipeline remains robust.

There has also been a marked shift in who funds clinical drug development—with public funding failing to match pipeline needs since the global financial crisis. Five years ago, public and industry had an almost equal investment in clinical development. However, since the financial crisis, public funding has been cut steeply to a quarter (23%) of previous levels (down from $23 million in 2008 to $5 million or less in each subsequent year), with many smaller government funders completely discontinuing funding for clinical drug development. Industry funding, on the other hand, has closely matched the progression of the pipeline, dropping from $27 million to $20 million between 2007 and 2009 as products concluded, and increasing to $34 million in 2011 as new candidates advanced.

The future of drugs

What drugs do we need?

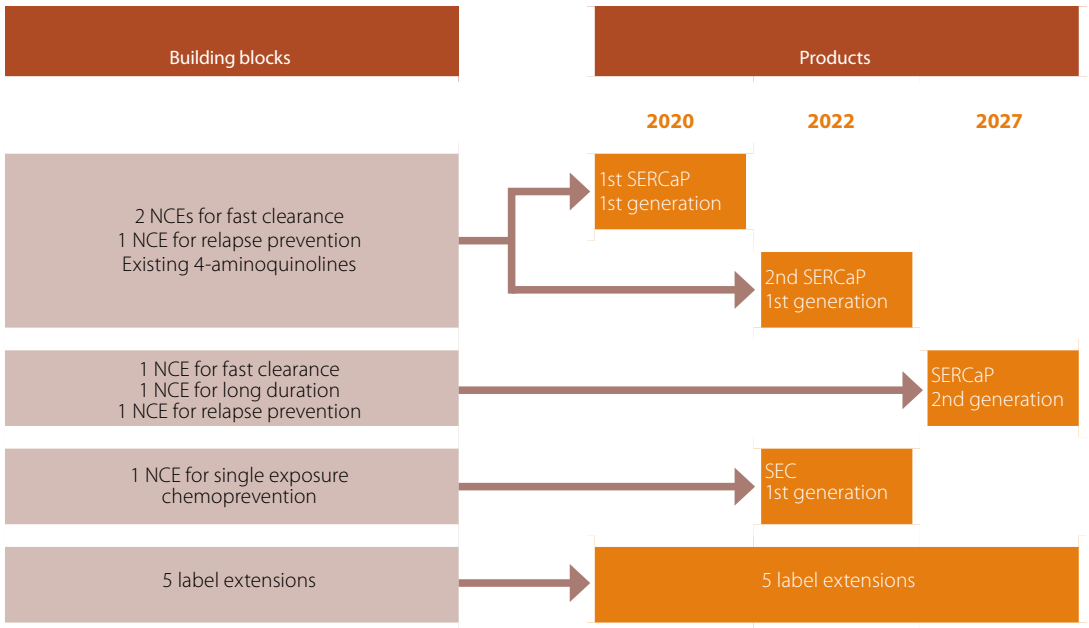
Two new types of drugs will be key to achieving malaria control, elimination, and eradication goals:

- *Single exposure radical cure and prophylaxis (SERCaP)*, a combination therapy able to radically cure all malaria lifecycle stages and species, whilst providing post-treatment prophylaxis in a single dose.
- *Single exposure chemoprevention (SEC)*, a compound ideal for prevention that provides month-long protection against all species of malaria with a single dose, suitable for mass administration, and has a different mechanism of action to medicines used for treatment.

These new single-dose 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 in addition to being fast acting and of long duration (qualities critical to malaria control) may have elimination-specific features to prevent relapse in the liver stages or block malaria transmission. These NCEs will feed into SERCaP therapies, two of which will be ready for patients by 2022.
- One NCE for SEC.
- Once these new NCEs are registered, development of several as label extensions (registration of an existing drug for new patient groups or uses).

FIGURE 12
Malaria drug building blocks and products expected in the future

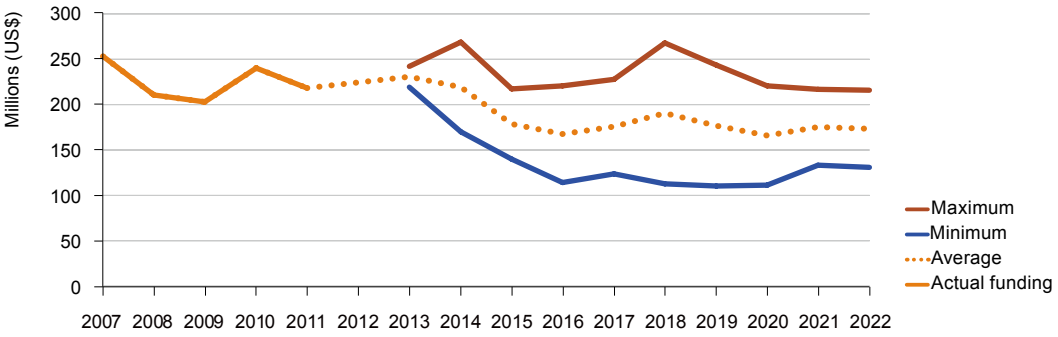


How much funding will be needed?

Between 2013 and 2022, malaria drug R&D funding will require $110-270 million per year. The funding fluctuations seen below, particularly in the maximum range, reflect the higher costs of late-stage clinical trials. For example, a Phase I or IIa trial can cost less than $5 million, Phase IIb around $10-15 million, and a Phase III trial up to as much as $40 million. These costs are reflected in the 2018 funding peak, when ten candidates enter Phase IIb.

In order to deliver two first-generation SERCaPs, a SEC, and several label extensions, drug R&D will require $1,364-2,333 million over the next ten years.

FIGURE 13
Projected drug funding need, 2013-2022 (2011 US$)



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

What products will this funding deliver by 2022?

Modelling suggests that funding malaria drug R&D at these levels will deliver the following products:

- Two first-generation SERCaPs that can treat all types of malaria and prevent relapse, with a single dose.
- A SEC drug that provides one month of protection from malaria in a single dose.
- Two to three label extensions that allow new or existing drugs to be given to new patient groups, including pregnant women and infants.

VACCINES

Vaccines are a vital tool in controlling, eliminating, and eradicating disease, and have proven to be highly effective, as seen with the polio and smallpox eradication campaigns.[x] They protect individuals who have not yet contracted the disease and can allow whole populations to be immunised against the threat of a disease. In other words, vaccines can both prevent new infections and assist in eliminating the disease from a region altogether.

Currently, no vaccine exists for malaria, despite decades of research. In 2006, the global Malaria Vaccine Technology Roadmap set for the R&D community the goal of developing an 80% effective vaccine against *P falciparum* malaria by 2025 that would provide protection for longer than four years, with an interim landmark of a 50% effective vaccine of one-year duration by 2015.[23] An effort to update the Roadmap, launched by WHO in 2012, has resulted in a revision of the longer-term strategic goals for vaccine development, whilst retaining the 2015 landmark goal.[24] The latter may be realised with the RTS,S malaria vaccine candidate, currently in late-stage trials in Africa. Initial modelling suggests that RTS,S could have a significant public health impact amongst children younger than five years who are most at risk of malaria, whilst a more highly efficacious vaccine targeting either disease and death or malaria transmission could make an even greater contribution to elimination and eradication.

TABLE 2
Malaria Vaccine Technology Roadmap updates[xi]

Vision	
2006	2013
An effective vaccine that prevents severe disease and death caused by *Plasmodium falciparum* malaria in children under five in sub-Saharan Africa and other highly endemic regions.	Safe and effective vaccines against *Plasmodium falciparum and Plasmodium vivax* that prevent disease and death, and prevent transmission to enable malaria eradication.
Landmark goal (remains unchanged)	
By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year.	
Strategic goals	
2006	2013
By 2025, develop and license a malaria vaccine that has a protective efficacy of more than 80% against clinical disease and lasts longer than four years.	By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* that encompass the following two objectives, for use by the international public health community: 1) Development of malaria vaccines with protective efficacy of at least 75% against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas. 2) Development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns.

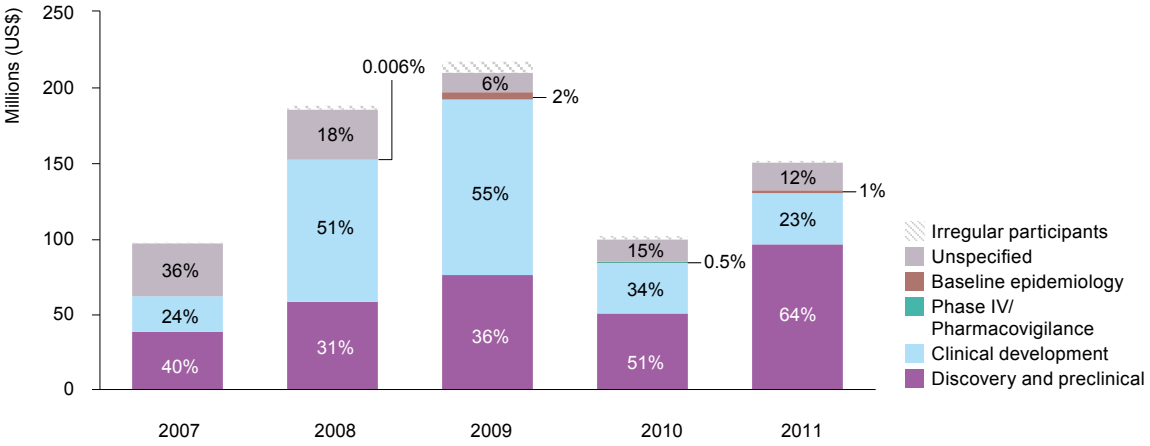
[x] Malaria vaccine R&D includes research activities and processes needed to develop and improve investigational vaccines specifically intended to prevent infection, such as vaccine design, preclinical and clinical development, and other activities essential for successful vaccine development and uptake.

[xi] The Malaria Vaccine Technology Roadmap is a shared effort of the malaria vaccine community and has evolved to reflect expanded priorities and new realities.

Funding landscape for vaccine R&D

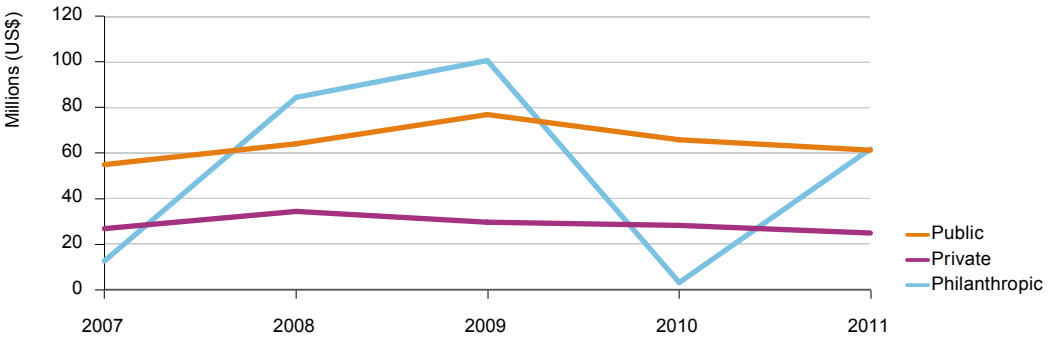
Vaccine development is an expensive and time-consuming activity, with costs heavily weighted toward late-stage clinical trials. The impact of this uneven weighting is seen in vaccine funding patterns in 2007-2011, with the large funding peak in 2009 reflecting the progression of a single, first-generation malaria vaccine candidate into a large, late-stage trial (Phase III), followed by a funding decrease as the trial headed toward completion and the focus shifted to earlier stages of development for second-generation candidates. However, given the greater scope of the revised Roadmap, funding needs will increase significantly again as the vaccine candidates envisioned move into later stages of development.

FIGURE 14
Vaccine funding by R&D stage, 2007-2011 (2011 US$)



From 2007 to 2011, public funders contributed 44% ($327 million) of malaria vaccine R&D funding, whilst philanthropic organisations accounted for 36% ($267 million) and industry for 20% ($148 million). Funding patterns also varied markedly between sectors, with philanthropic funding closely reflecting the progress of candidates through the vaccine pipeline and the timing of grant payments (largely disbursed in advance for this five-year period), whereas industry and public funding has been largely steady from year to year irrespective of vaccine developments on the ground (with donor disbursement more closely aligned with annual R&D spending).

FIGURE 15
Vaccine funding by funder type, 2007-2011 (2011 US$)



Public funders provided $55-80 million for vaccine R&D each year between 2007 and 2011. Public funding was dominated by US government agencies—the NIH, the US Agency for International Development (USAID), and the US DOD—which provided more than three-quarters (77%) of public funding for malaria vaccine R&D in this period.

Between 2007 and 2011, the Gates Foundation provided 99.9% of philanthropic funding for malaria vaccines. The large swings in philanthropic vaccine funding were driven by several factors, the two most important being the award of core funding to MVI in 2008 and the entry of the RTS,S vaccine candidate into Phase III clinical trials, which prompted a supplemental grant of $75 million to MVI in 2009. This latter grant was specifically to fund the Phase III clinical trials of RTS,S, the vaccine candidate under development by MVI in collaboration with GSK Vaccines (this grant accounted for 38% of total malaria vaccine funding in 2009). As noted above, the other major factor explaining the large funding swing over this time period is related to the timing of grant disbursements by the donor. For example, the RTS,S supplemental grant was paid out fully in 2009, with the funds intended for use over the entire length of the Phase III programme.

Industry investment remained steady at $25-35 million per year over the five years.

Funding by stage

As noted above, there was a nearly $100 million increase in funding for clinical development of vaccines (from $23 million to $116 million) between 2007 and 2009, reflecting in part the disbursement of funding for the RTS,S Phase III clinical trial. Thereafter, funding shifted strongly back to discovery and preclinical activities, reflecting the move to research for second-generation vaccine candidates.

The future of vaccines

What vaccines do we need?

Different vaccines may be needed to address both malaria control at the individual level and malaria eradication and elimination at the population or community level.

As per the updated Malaria Vaccine Technology Roadmap, the first target for malaria control is the original landmark goal of a first-generation *P falciparum* vaccine with 50% protective efficacy of at least one year in duration against severe disease and death by 2015 (this vaccine appears to be on the horizon). By 2030, the strategic goal is to have a second-generation *P falciparum* vaccine (which could also include a component against *P vivax*) with a protective efficacy of at least 75% against clinical malaria that lasts for at least two years.[24] These goals take into account the difficulty of developing vaccines against the malaria parasite target and the complexity of the human immune response to it. Whilst efficacy goals are lower than the demonstrated effectiveness of vaccines against measles, tetanus, or polio, for example, they are higher than those of vaccines against shingles or influenza.

In addition to vaccines that prevent malaria disease, the global malaria community has also committed to a new goal of developing vaccines by 2030 that target infection by blocking the transmission of malaria between humans and mosquitoes, one against *P falciparum* and one against *P vivax*. Transmission-blocking vaccines that specifically target human-to-mosquito transmission (SSM-VIMTs) may be more expensive to test in clinical studies than vaccines against malaria disease or that target infection when the parasite first enters humans (PE-VIMTs), because the clinical trial design may require large numbers of subjects—unless an

alternative development pathway is identified. Since their benefit to the individual is delayed and dependent on high levels of coverage across a community, clinical trials of SSM-VIMTs could require significantly more subjects, compared to the approximately 20,000 subjects in trials of vaccine candidates such as RTS,S, which target clinical malaria and have direct benefit to the vaccinated individual. Far fewer SSM-VIMTs have advanced to clinical development compared to pre-erythrocytic and blood-stage vaccines. Essentially, just one target antigen (*Pfs*25), delivered using different adjuvants and/or carriers, has reached clinical testing, and there are fewer than ten transmission-blocking approaches in this particular pipeline. Whilst early failure rates could be higher than for anti-infection vaccines—whilst scientists learn what works in this new research area and validate tools for evaluating vaccine efficacy prior to large-scale field trials—the focus on an antibody-mediated mechanism and promising preclinical results is indicative of a significant opportunity for development of a game-changing intervention.

Other desirable but not imperative targets include a standalone *P vivax* vaccine against clinical disease (rather than one targeting both *vivax* and *falciparum* malaria); a single transmission-blocking vaccine that would work against both *P falciparum* and *P vivax*; and a malaria vaccine for use in pregnancy.

How much funding will be needed?

Vaccine funding needs are more difficult to project than funding for other malaria products. This is because estimates must include projected funding for vaccines targeting both malaria disease and malaria transmission.

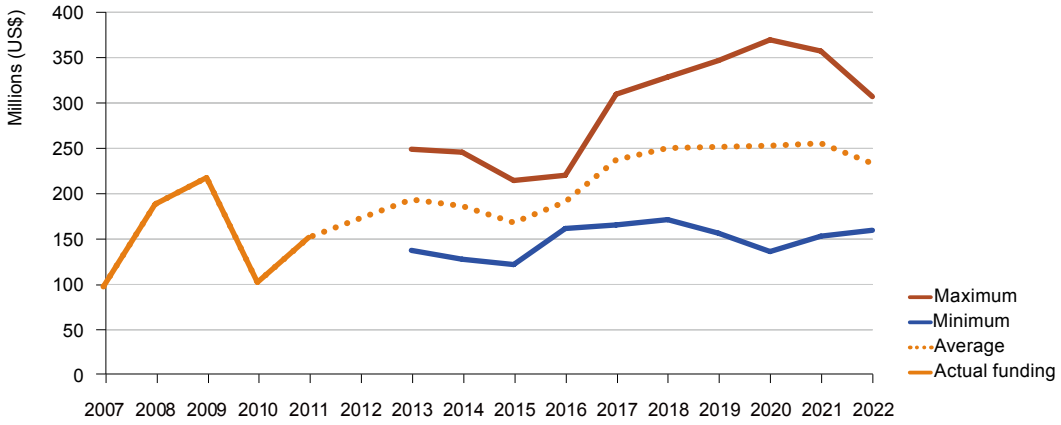
Funding projections for vaccines against malaria disease can be estimated with relative confidence, as this portfolio is relatively mature. A first-generation malaria vaccine (the RTS,S vaccine candidate) is anticipated to reach regulatory and policy review as early as 2015, and the current portfolio of second-generation candidates supports a measure of confidence that a second-generation vaccine targeting disease could be registered by 2030 at current attrition rates.

In contrast, vaccines that interrupt transmission face many unknowns. Attrition rates are unclear, and later-stage trial costs have yet to be determined. If existing vaccine regulatory pathways are followed, estimates suggest that Phase III trials could cost as much as $300 million—pointing to the need for exploration of alternate regulatory pathways. However, promising early-stage projects are under development despite this uncertainty, and the recent influx of development-stage resources into this area has significantly catalysed all areas of the development process.

In order to progress the current anti-disease portfolio and support a steady growth in the transmission-blocking portfolio, average funding needs to increase from $150 million today to around $240 million by 2017 and stay at this level until 2022 (the limit of our projections). The confidence ranges for this funding are quite wide—up to $100 million on either side—reflecting the uncertainty of both costs and attrition rates for this new vaccine approach. Total funding for the next decade under this scenario is estimated at $1,488-2,941 million.

The total amount of funding required will be affected by a number of factors, including the degree of coordination across the research community. The most cost-effective scenario is one in which research activities are coordinated, and there is smart down-selection of vaccine candidates in response to clearly defined go/no go criteria. If there is a diffuse, uncoordinated research effort without rational down-selection, then the amount of funding required will be higher and the likelihood of delivering within the Roadmap time frame reduced.

FIGURE 16
Projected vaccine funding need, 2013-2022, growth scenario (2011 US$)



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

What products will this funding deliver by 2022?

It is likely that the target of a first-generation vaccine against *P falciparum* disease will be delivered by 2022, with the RTS,S vaccine candidate expected to complete policy review as early as 2015. Further, based on the strength of the current pipeline, the likelihood that a second-generation vaccine against *P falciparum* disease and/or infection (possibly including a component against *P vivax*) could also have completed late-stage clinical trials by 2022 is high. Where there is still uncertainty, however, is whether any of the vaccine candidates in the current pipeline are capable of meeting the goal of greater than 75% efficacy.

The progress of transmission-blocking vaccines over the next decade will depend on funding and scientific breakthroughs, but assuming a steady growth in the portfolio, it is predicted that 16 transmission-blocking vaccine candidates could reach early-stage clinical trials by 2022.

DIAGNOSTICS

Effective diagnostics are essential tools for control, elimination, and eradication of malaria, with the ability to accurately and quickly identify malaria infections being critical to ensuring that patients receive appropriate treatment, to tracking the impact of interventions, and to allocating resources effectively.[xii] The development of rapid diagnostic tests (RDTs) has meant that suspected malaria cases can now be tested quickly and easily in the field by an unskilled worker, and that patients are able to quickly receive the drugs they need. It is estimated that 400 million unnecessary malaria treatments can be averted and 100,000 lives can be saved annually by using practical, field-appropriate malaria tests.[25]

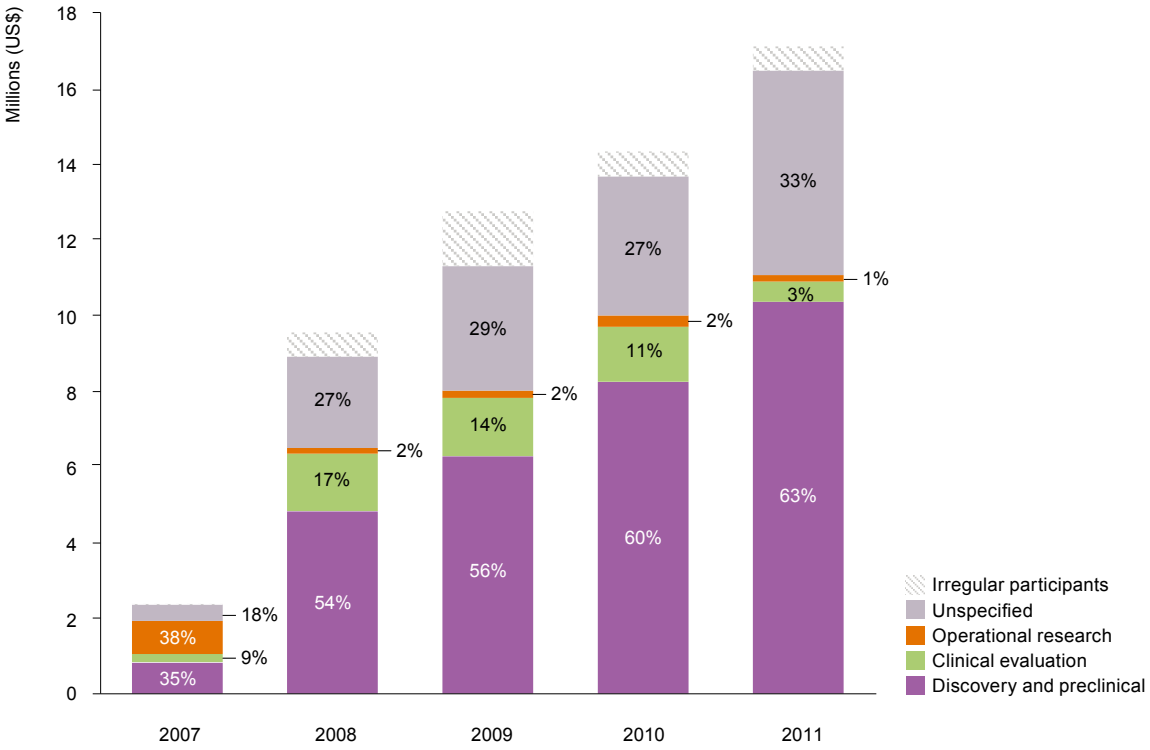
Research and development gaps still exist, however, including for detection of artemisinin resistance and reliable detection of *P vivax* malaria, and new screening tests to guide elimination. Currently, artemisinin resistance cannot be diagnosed by a rapid test or in a single encounter,[26] instead requiring a skilled microscopist to examine a blood sample taken 72 hours after the patient started drug treatment.[26] And, whilst *P vivax* is less likely than *P falciparum* to lead to severe malaria and death, it is also more difficult to control since current diagnostics cannot detect the dormant liver-stage or low-level blood-stage infections. An in-field diagnostic is also needed so that patients with G6PD enzyme deficiency can be identified and safely treated for *P vivax* malaria.[16,27] Finally, tests are required to identify foci of continued malaria transmission in elimination zones, and to identify asymptomatic low-density infections in these foci.

Funding landscape for diagnostics R&D

Despite malaria diagnostics presenting a much smaller funding challenge than other product areas due to their lower production costs and shorter development time, they remain severely underfunded. From 2008 to 2011, funding for malaria diagnostics increased by $8 million (a near doubling); however, this was far less than the quadrupling recommended by the 2011 malaria R&D funding report.[18]

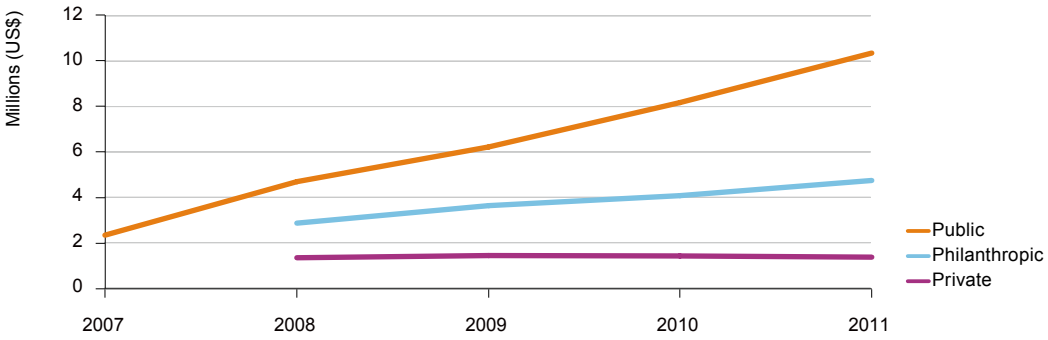
[xii] Malaria diagnostics R&D includes the research activities and processes necessary to develop, optimise, and validate diagnostic tests for use in resource-limited settings (less expensive, faster, more reliable, ease of use in field), including discovery and design, preclinical and clinical evaluation, and other activities essential for successful deployment for public health use.

FIGURE 17
Diagnostics funding by R&D stage, 2007-2011 (2011 US$)



Over the 2007-2011 period, public and philanthropic funders consistently increased their funding for malaria diagnostics R&D (albeit from a very low base), whilst industry funding was low but stable. Public funding increased approximately five-fold between 2007 and 2011, from $2 million to $10 million. Philanthropic funding increased by two-thirds, from $3 million to $5 million from 2008 to 2011, almost entirely reflecting funding changes from the Gates Foundation, which accounted for 97% of philanthropic investment. Industry funding remained steady from 2008 to 2011 at $1.4-1.5 million.

FIGURE 18
Diagnostics funding by funder type, 2007-2011 (2011 US$)



^ In 2007, no data were captured from philanthropic or industry funders for their investment in malaria diagnostics.

Funding by stage

Over the five years, 58% of diagnostics R&D funding was invested in discovery and preclinical research, which more than doubled between 2008 and 2011 (from $5 million to $10 million). The majority of the discovery and preclinical increase came from the public sector (up from less than $1 million in 2007 to $6 million in 2011), alongside a smaller increase from philanthropic funders (up from $3 million in 2008 to $4 million in 2011).

The future of diagnostics

What diagnostics do we need?

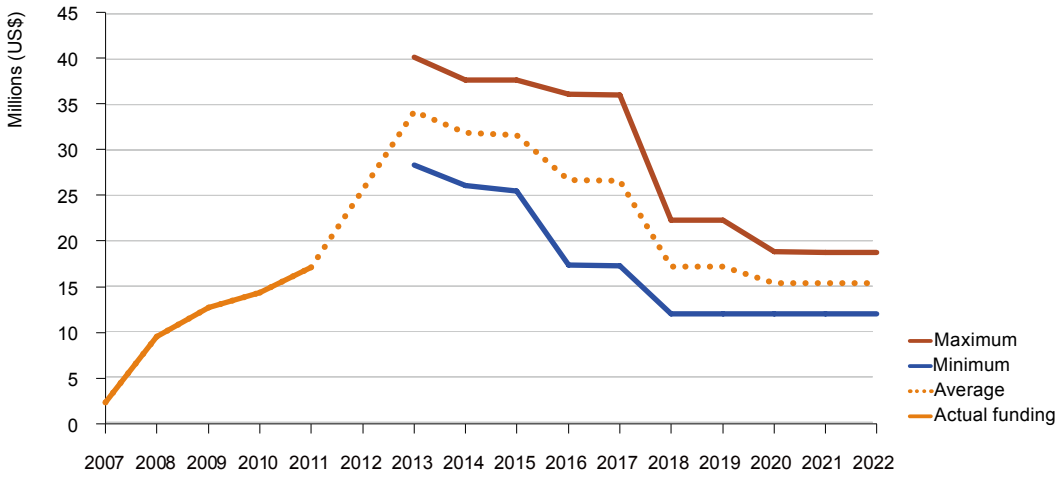
The gaps and threats described above will require a range of new diagnostic tests:

- Improved RDTs, particularly for non-*falciparum* species.
- New tools to perform quality control tests and evaluate RDT performance, to ensure their usability and efficacy before being used in remote locations. Without these tools, patients may be tested with ineffective RDTs that have been affected by climatic conditions or transportation, leading to misdiagnosis and inappropriate treatment.
- A highly sensitive field test that can rapidly detect even low levels of parasites in blood samples and can be used to help reach elimination by detecting asymptomatic ('hidden') infections.[28]
- Screening tools that can identify areas where transmission is continuing (e.g., a marker of recent infection).
- A field test to identify patients with *P vivax* malaria who are also G6PD deficient and thus may have severe side effects when treated with the frontline drug.
- A point-of-care 'fever' test to guide management in malaria-negative cases.[29]
- A test that conducts microscopy automatically, omitting the need for a highly trained medical practitioner, whilst providing the advantages of identifying not only the type but also the quantity of species.
- A diagnostic test that does not require blood samples to be taken, particularly from children.

How much funding will be needed?

Despite increases since 2007, malaria diagnostics remain severely underfunded. Funding levels urgently need to double from 2011 levels ($17 million) to reach the ideal funding target of $34 million (range of $28-40 million). If these increases are achieved today, annual funding needs will plateau at approximately $22 million per year from 2018, as a majority of the targets are expected to be met within the next five years.

FIGURE 19
Projected diagnostics funding need, 2013-2022 (2011 US$)



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

What products will this funding deliver by 2022?

At these funding levels, patients could see all of the listed diagnostic needs met by 2022, and some as early as 2017. Depending on which of the above projects donors initially choose to invest in, products potentially available in the next five years include:

- Two improved RDTs for non-*falciparum* parasites, each of which will require $3-18 million over five years.
- A low-cost quality control tool for RDTs in the field. This will require $1.5-4 million of funding to be ready by 2017.
- A field test for low levels of parasites. This will need $22 million to be in the field by 2017.
- A field test to detect G6PD enzyme deficiency. This will need $5-12.6 million of funding to be ready by 2017.

VECTOR CONTROL

Vector control products include LLINs, IRS programmes, and biological control products that target the mosquito (the vector) that transmits malaria.[xiii] There are four classes of insecticides currently used in vector control, but only one class, pyrethroids, is recommended for use in LLINs. Over the last ten years, the large-scale introduction of treated bednets and spraying has been a major factor in the dramatic reduction in malaria mortality and morbidity worldwide.

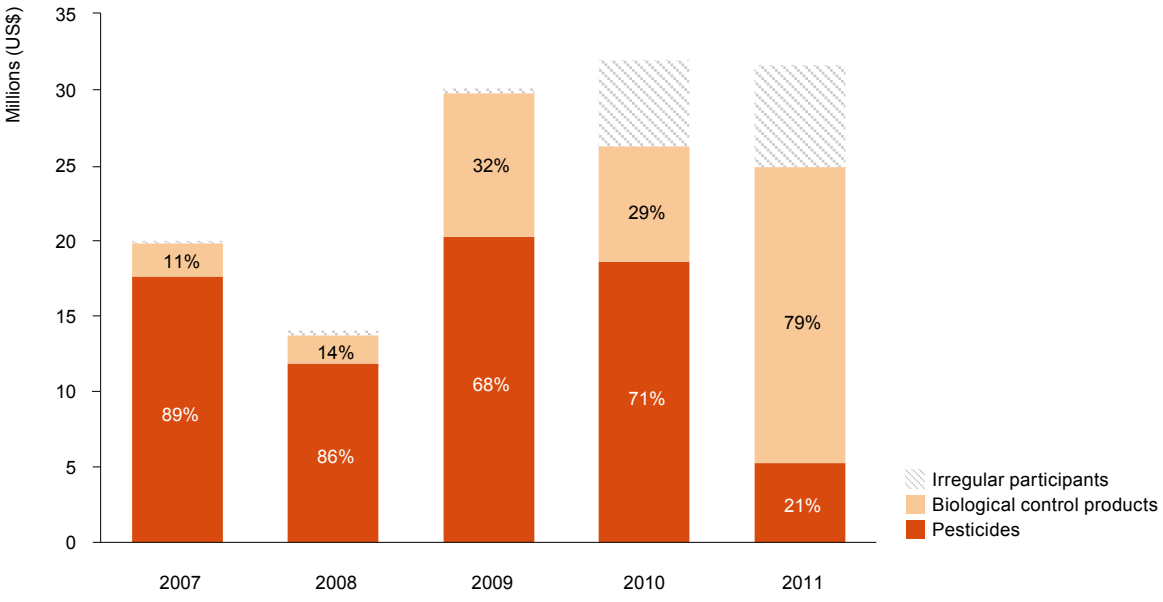
In recent years, significant insecticide resistance has been reported in two-thirds of malaria-endemic countries, affecting all major vector species and all classes of insecticides.[9] There is also evidence of cross-resistance: if a mosquito develops resistance to one insecticide, it becomes resistant to all insecticides in the same class. This significantly limits the available options for IRS.

Resistance to pyrethroids is especially concerning, as no other insecticide is available for use in LLINs. When pyrethroids fail to be effective, due to the rise of resistance, bednets will lose a substantial part of their value as vector control products (although the physical barrier they provide will remain). As there is no current alternative insecticide to pyrethroids, a new class of insecticide is urgently needed for use in LLINs, and three new active ingredients are needed to manage insecticide resistance in the future.

Funding landscape for vector control R&D

Vector control R&D receives only limited funding, and mostly from a single donor (the Gates Foundation, which provides 81% of the total); therefore, funding trends need to be interpreted with caution. The sudden rise in vector control R&D funding in 2009, for example, was due almost entirely to increased Gates Foundation investment, which has been maintained, resulting in fairly steady funding of around $30 million per year since then.

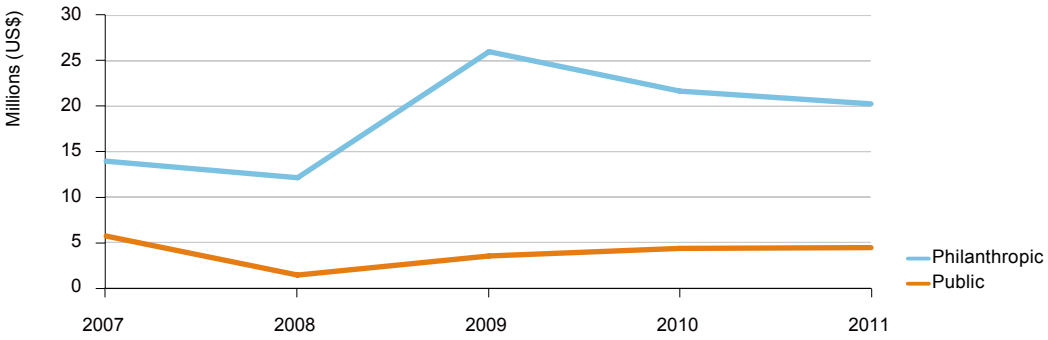
FIGURE 20
Vector control funding by product type (2007-2011)



[xiii] Malaria vector control R&D includes two product areas, pesticides and biological control products. R&D for pesticides includes only chemical pesticides intended for global public health use and which specifically aim to inhibit and kill malaria vectors. Likewise, the biological control product category only includes R&D of innovative biological control interventions that specifically aim to kill or control malaria vectors.

The philanthropic sector provided the vast majority of funding (83%) for vector control R&D between 2007 and 2011, with the Gates Foundation providing 98% ($92 million) of this investment. The public contribution was a modest $5 million or less per year. In 2008, the US DOD (previously the second largest vector control funder) stopped its vector control investments entirely, leading to a marked decrease in public funding. The subsequent recovery in public funding was due to small, uncoordinated grants from 12 other public funders. No data were available for industry funding between 2007 and 2009, and industry is therefore excluded from this analysis; it was only in 2010 and 2011 that industry funding of around $4-5 million was reported by irregular participants in the G-FINDER survey.

FIGURE 21
Vector control funding by funder type, 2007-2011 (2011 US$)



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

Funding by product type

Around two-thirds (64%) of vector control R&D investment over the past five years went to insecticides, but there has been a clear trend toward increasing investment in biological control products since 2009.

Insecticide R&D funding was steady at around $15 million per year between 2007 and 2010, with around 80% of annual funding coming from Gates Foundation investment in the Innovative Vector Control Consortium (IVCC) or its host organisation, the Liverpool School of Tropical Medicine. The sudden decrease in insecticide funding in 2011 was entirely due to a sharp drop in Gates Foundation funding (to $1 million), which is understood to be due to the grant cycle.

Biological control product funding increased ten-fold between 2007 and 2011. The vast bulk of this investment has been since 2009, and again the Gates Foundation is largely responsible. Of particular note is their funding to the Foundation for the National Institutes of Health for their Vector-based Control of Transmission: Discovery Research (VCTR) programme, which accounted for two-thirds of all investment in this area from 2009 to 2011 and covered both vector and biological control work. However, the jump in funding in 2011 was also entirely due to a $13 million increase in the Gates Foundation's investment in the biological control R&D activities of the VCTR programme.

The future of vector control

What vector control products do we need?

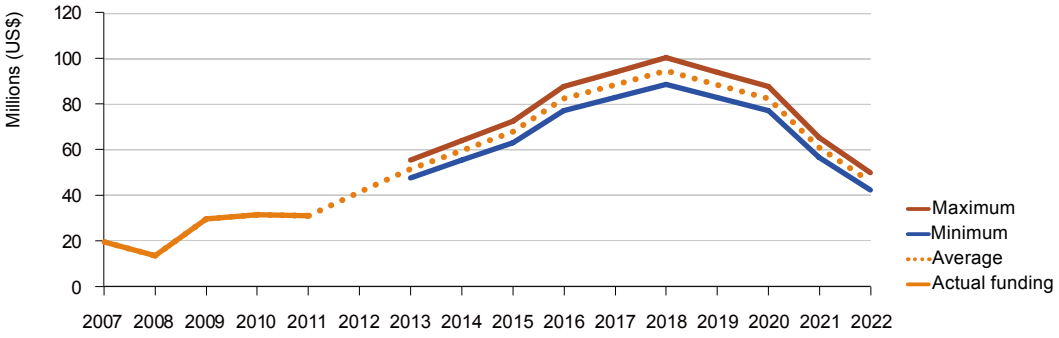
To counter the threat of insecticide resistance, the following new vector control tools are needed:

- New active ingredients (chemicals).
- Supportive research activities to identify promising molecules, develop stable and suitable preparations for new insecticides, identify new non-insecticide-based ways to control mosquitoes, and develop information systems.

How much funding will be needed?

Vector control funding has long been minimal and, despite increases, was still only $32 million a year between 2009 and 2011. Funding will need to almost double to reach the immediate target of $52 million (range of $48-56 million). Funding needs for the next decade will be driven by the development of three new active ingredients as they progress through optimisation, pre-trial development, and development and registration; projections also include supportive research costs, which are evenly spread across the ten years. The largest funding demand will be between 2016 and 2020, when all three new active ingredients will be in the development phase, requiring funding of $77-100 million per year during this time. Providing the immediate scale-up of funding is achieved, candidates will be in the less-expensive registration phase from 2020 and funding needs will thereafter decrease to less than $66 million per year.

FIGURE 22
Projected vector control funding need, 2007-2011 (2011 US$)



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

What products will this funding deliver?

At these levels of funding, the following products will be delivered by 2022:

- Three new active ingredients to be used in vector control products (LLINs and IRS). This will require $360 million over ten years.
- A follow-on generation of insecticides and biological control approaches. These activities will require $325-364 million over the next decade.

VALUE FOR MONEY

The benefits of funding R&D for global health products are clear, with investment from funders past and present having contributed to the development of a solid pipeline of new product candidates as well as a range of products with a demonstrable health impact. At least nine malaria products have been developed and reached the field in the last ten years, and there are at least another 96 in the pipeline. Malaria R&D funding has been driven largely by the public sector, which accounts for around half (51%) of funding, whilst philanthropy provides a third (32%) and industry provides a fifth (17%). Notable public funders are the United States ($165 million yearly average), the European Commission ($34 million yearly average), and the United Kingdom ($32 million yearly average), although most countries that invest in malaria R&D contribute on average less than $15 million per year.

Investing in malaria R&D has a quantifiable impact on those at risk of and infected by malaria. Amongst the interventions coming into widespread use over the past two decades are LLINs, ACTs for adults and children, and more reliable diagnostic tools. Past investment in malaria R&D has produced these tools, which have contributed to an estimated 26% decrease in malaria deaths worldwide since 2000.[3] Better tools and scaled-up use of interventions have also had an impact at the national level. For example, since 2007, malaria has been eliminated in four countries: Armenia, Morocco, Turkmenistan, and the United Arab Emirates.[3] In some subnational regions such as Zanzibar, where ACTs have been made freely available in public health facilities since 2003 and LLINs have been distributed to the entire population, deaths from malaria decreased by more than 90% between 2002 and 2009.[30]

REGISTERED PRODUCTS

There have been at least nine malaria products registered in the last ten years, which have contributed to the drop in malaria deaths:

- Two new insecticide formulations (Actellic® 300CS, K-Othrine® Polyzone™).
- Seven drugs, all from product development partnerships in collaboration with industry and non-industry partners:
    - Four new ACTs, including for easier once-daily dosage, and one for both kinds of malaria (Eurartesim®, Pyramax®, ASAQ, ASMQ).
    - One new paediatric treatment (Coartem® Dispersible).
    - One new treatment for severe malaria (artesunate for injection).
    - One intermittent preventive treatment for infants (sulfadoxine-pyrimethamine with amodiaquine).

Malaria diagnostics are less easy to count since R&D may not develop a standalone product but may involve improving the quality of existing products, such as variations to platforms to adapt them for new disease uses. For example, from 2007 to 2013, 54 RDTs were evaluated and approved to WHO standards of quality.

CASE STUDY: NEW MALARIA DRUGS

There has always been a paradox at the heart of drug treatment for acute *P falciparum* malaria: more than 85% of those who die are children younger than five years old, yet available drugs have always been developed as tablets for adults and therefore need to be broken up or crushed for children, making it difficult to give the exact dose. Additionally, many of the most widely available antimalarials are bitter to taste, causing children to gag or spit out the very medicine that could save their lives.

Even more challenging, after the first dose is given by a health care professional, parents or caregivers must continue to treat their sick children at home. This makes it hard to guarantee they will complete their treatment course, which is critical to ensure a complete cure and reduce the risk of emerging drug resistance.

Responding to the international community's call for the development of paediatric formulations of medicines, Medicines for Malaria Venture, a product development partnership, signed an agreement with the drug company Novartis in 2003 to develop the first antimalarial especially for children. The result was Coartem® Dispersible, a sweet-tasting, dispersible formulation which eases administration and ensures effective dosing for young children. Since its launch in 2009, more than 171 million treatments of this lifesaving medicine have been delivered to more than 30 malaria-endemic countries, at a cost as low as $0.38 per course of treatment.

Rose Aluoch Ngala and her daughter Shanrol, Kamagaga, Kenya.
Photo courtesy of Novartis

CASE STUDY: IMPROVED MALARIA DIAGNOSTICS

In 2007, Senegal started using rapid diagnostic tests (RDTs) to confirm malaria, instead of relying on the patient's symptoms to make a diagnosis. Over a three-year period, the use of RDTs increased from 4% of cases to 86%.

The impact was significant. By confirming whether malaria was really the cause of fever, Senegal reduced the use of malaria treatments from 72.9% of all fever cases to 31.5%, saving an estimated $1.57 million in drug procurement in 2009. The national malaria control programme is better able to predict the quantity of malaria drugs required, and to allocate antimalarial resources more efficiently between high- and low-burden malarial areas of the country.

Incorrectly treating people with antimalarials not only wastes drugs but also delays diagnosis and treatment of other life-threatening illnesses. With the use of RDTs, a negative malaria test means health workers know they should investigate further to identify the real cause of fever. When the test is positive, patients know they really have malaria, and must take a complete course of treatment.

Since 2007, the Foundation for Innovative New Diagnostics (FIND, a product development partnership), working with the World Health Organization and other partners, has evaluated more than 120 malaria RDTs available on the market. This has dramatically improved RDT quality and the market share of high-performing tests. FIND and partners also work to ensure that RDTs are implemented efficiently at national levels, that patients receive accurate results from good tests and adequate materials to support transport, and that training and good practice are available for even the most remote areas.

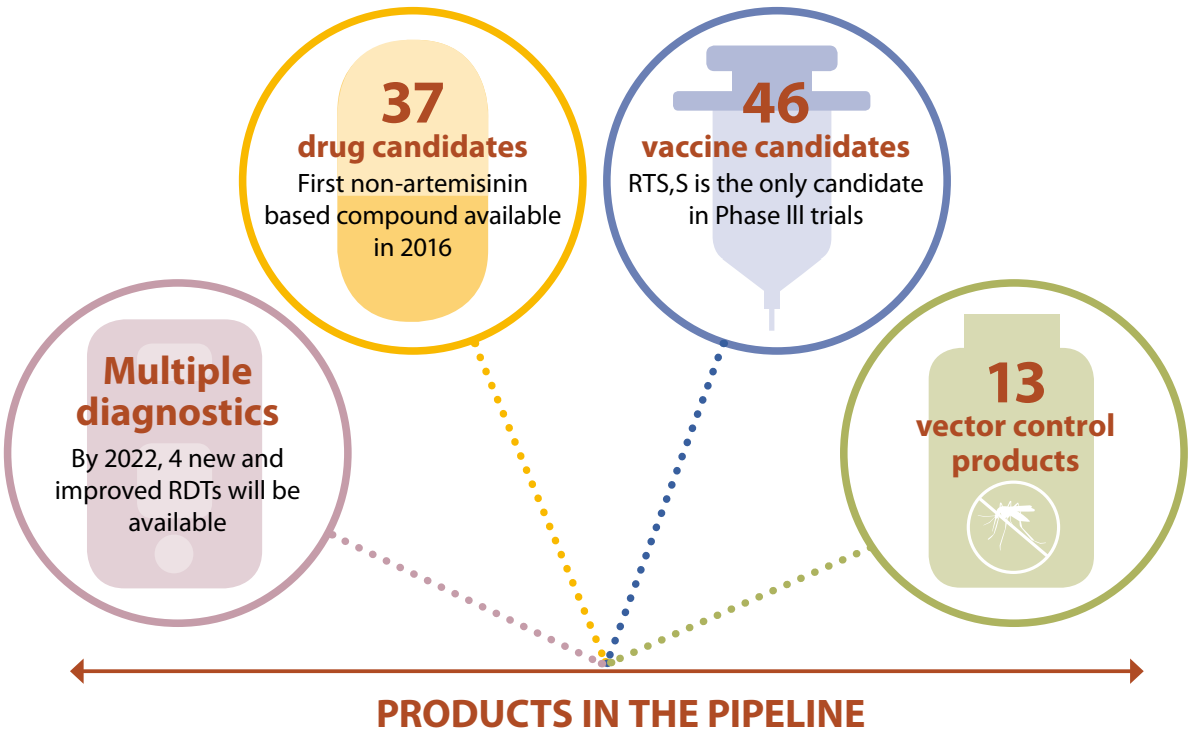
Laboratory technician in Senegal testing a patient's blood with a malaria RDT.
Photo courtesy of FIND/Sandra Incardona

PRODUCTS IN THE PIPELINE

There are at least 96 products in the malaria R&D pipeline that will be key tools in addressing emerging insecticide and artemisinin resistance, and reaching elimination and eradication goals:

- Five new active ingredients and eight new formulations of insecticides on the way.
- Thirty-seven drugs, with ten in late-stage clinical trials.
- Forty-six vaccine candidates, including one in late-stage clinical trials.

This list includes only drug and vaccine candidates that are already in preclinical or clinical studies; many more candidates are at the earlier discovery and lead optimisation stage. Whilst it is difficult to quantify the malaria diagnostics portfolio due to the nature of diagnostics R&D, the pipeline includes multiple tools for diagnosis of malaria, including five within a few years of registration.



CASE STUDY: MALARIA VACCINES IN THE PIPELINE

There is still no vaccine against malaria. To address this need, the PATH Malaria Vaccine Initiative (MVI) was established in 1999 to accelerate the development of malaria vaccines and catalyse timely access in endemic countries. In 2009, MVI, GlaxoSmithKline Vaccines, and their African partners launched the Phase III efficacy and safety trial of the RTS,S vaccine candidate, which enrolled more than 15,000 children at 11 sites in seven African countries. Whilst the final results from this trial are expected in 2014, results to date show that over a year of follow-up, RTS,S reduced cases of malaria by half in children 5-17 months old and by approximately one-third in African infants, on top of the protection provided by bednets.

The investments required to conduct the Phase III trial have improved health services for trial site communities in endemic countries, enhancing local capacity to develop solutions for malaria and other diseases for many years. For example, the RTS,S trial delivered laboratory improvements at Agogo Presbyterian Hospital in Ghana; helped to put the village of Nanoro in Burkina Faso on the electrical grid; and built a clinical research centre at Tanzania's National Institute for Medical Research in Korogwe.

Finally, MVI supports and invests in a vital but unsung area of vaccine research: tools to evaluate new vaccine approaches and candidates, including development and qualification of vital assays that allow researchers to directly and consistently compare immune responses elicited by different malaria vaccines. Progress in these activities has and will continue to provide robust data to inform decision-making in malaria vaccine development, thereby reducing both costs and risks of the development process.

First vaccination in the Phase III trial of the RTS,S malaria vaccine candidate.
Photo courtesy of PATH Malaria Vaccine Initiative/Dave Poland

CASE STUDY: NEW MALARIA VECTOR CONTROL PRODUCTS

Vector control has made a major difference to millions of the poorest people in the world, including indoor residual spraying (IRS) of insecticides and use of long-lasting insecticide-treated bednets (impregnated with pyrethroid), which will be critical to malaria elimination and eradication.

The Innovative Vector Control Consortium (IVCC) was established to produce improved insecticides and formulations, and to provide improved tools for vector control decision-making at the community level in malaria-endemic countries. It is on target to produce three new products within ten years.

Since 2005, IVCC has been working with the world's leading agrochemical companies and academic organisations to develop new insecticides. These include a collaboration with Syngenta to reformulate an existing non-pyrethroid insecticide into a new longer-lasting formulation, Actellic® 300CS; and with Bayer to reformulate an existing pyrethroid-based insecticide to make the longer-lasting K-Othrine® Polyzone™. These mean fewer spray campaigns in households and communities where IRS is taking place, and better control of resistance by providing more options to allow rotation of different insecticides.

Keeping the children safe: a mother and her healthy children under an insecticide-treated net in Uganda.

DISCUSSION

Funders of malaria R&D should take from this report three key messages. The first is one of reassurance: that malaria R&D will not require unlimited and ever-increasing funding, because it has defined goals and exit points, as defined by the Global Malaria Action Plan and the 2013 update to the Malaria Vaccine Technology Roadmap. Sustained and flexible funding will be needed over the next decade and beyond to reach these goals, but the total funding required will decrease with each goal that is achieved. The second message is one of caution: that whilst there have been increases in funding since the projections made in *Staying the Course* in 2011, there is still a long way to go. A concerted effort from the global malaria funding community will be needed to deliver tools that can make reaching the goals of malaria elimination and eradication a reality. The final message is one of promise: that policymakers should be assured that funding malaria R&D is a wise investment and represents value for money. Past investment has resulted in a strong malaria R&D community with many actively involved partners, a healthy pipeline of products in development, and more importantly, a suite of new products which have had a demonstrated impact.

Modest sustained funding growth is needed

Funding for malaria R&D has been on track to meet the global community's R&D product development goals, at around $600 million per year over the past five years. The total funding need for malaria R&D in the next decade is projected at between $5.5 billion and $8.3 billion, with the midpoint averaging around $700 million on an annual basis—a relatively modest funding increase to deliver the new tools necessary to effectively combat malaria. This funding level is similar to the need projected in *Staying the Course*, which reported an average projection of $600-700 million per year; the major difference is that funding will no longer decline post-2017 but will remain stable until 2022, the end of our projection period. This change—along with the bulk of the overall funding needs outlined here—is largely driven by R&D for elimination and eradication. In particular, the more ambitious drug and vaccine targets within the elimination and eradication agenda are responsible for greater minimum and maximum funding projections and also for a larger uncertainty range than the previous exercise. We must note, however, that funding for elimination and eradication appears far less than the projected funding need (an estimated $98 million[xiv] in 2011 with a projected need of at least $300 million in 2013), and is highly concentrated: in 2011, the Gates Foundation provided almost half (47%) of total funding specific to elimination and eradication R&D. A separate report analysing global funding flows for R&D for elimination and eradication products is currently being prepared under the guidance of the Malaria Eradication Scientific Alliance.

[xiv] The elimination and eradication total differs from that quoted in *Estimating costs and measuring investments in malaria R&D for eradication*,[19] as the 2011 funding total in that report includes an extra $6 million in investment in two research areas (health systems and operational research and modelling and harmonised data systems) that are not within the scope of this report.

Distribution of funding between product areas

A logical and effective distribution of funding between basic and applied research—and between the different product areas—is key to ensuring that products in the pipeline progress and are able to reach people on the ground as quickly as possible. Between 2007 and 2011 there was a trend in funding toward basic research and away from product development. Whether or not this is justified by need, it is a result of public funders moving away from funding product development, with a prime example being the 77% drop in public funding for the clinical development of malaria drugs following the global financial crisis.

In terms of product areas, whilst funding allocation has improved since the projections in *Staying the Course*, particularly for diagnostics, these increases have not reached the full funding need projected in 2011. In the next decade, funding will need to be distributed amongst product areas as follows:

- Drugs: The focus on SERCaP and SEC agendas means that drug development funding needs can be reduced sooner than projected in *Staying the Course*. The projections indicate that funding can decrease by 23% in 2013-2014 to around $180 million in 2015, but then funding will need to be maintained at that level until at least 2022.
- Vaccines: Funding for vaccine development will account for approximately 32% of funding needs over the next decade and will need to increase from the 2011 level of $150 million to $200 million in 2013. Steady increases thereafter to $250 million per year by 2017 will be required to make substantial progress toward all the Roadmap targets.
- Diagnostics: There has been only a doubling of funding since 2009 instead of the quadrupling of funding recommended in *Staying the Course*, and now funding needs to double again immediately to around $34 million per year. Thereafter, diagnostics funding will gradually decrease and remain steady at around $15-20 million per year post-2018.
- Vector control products: Like diagnostics, vector control funding needs to almost double immediately to $52 million per year in 2013 and will increase steadily to a peak of $100 million in 2018.

As the decade progresses and funding needs in one product area decrease, this funding should not cease altogether but should instead be redirected to where it is most needed.

Concentration and coordination of funding

As noted in *Staying the Course*, malaria R&D funding is still highly concentrated. The top two funders, the Gates Foundation and US NIH, accounted for nearly half (48%) of all malaria R&D funding in 2011, up from just more than 40% in 2007. This funding pattern has major implications for risk, funding security, and continuity of product development, as the investment decisions and preferences of a few major funders determine and sustain the global malaria pipelines. Funding sources need to be diversified, particularly if funding is to be sustained over the next decade.

A more coordinated approach to malaria R&D funding is also essential to reduce cost, improve efficiency, and increase the likelihood of success whilst reducing the time needed to reach malaria R&D goals.

One positive aspect of the concentration of malaria R&D funders is that it provides a real opportunity to improve information exchange, allowing better-coordinated funding decisions, forward planning, and project prioritisation. Whilst complete coordination is not possible, or even desirable, malaria funders can take steps to ensure their funding is aligned with global targets and coordinated with other funders working in the same product area.

Flexible funding

Unfortunately, funding decisions are often disconnected from the product development occurring on the ground. Ideally, funding should be flexible and should respond to changes in the pipeline: if a malaria vaccine candidate enters late-stage clinical trials, then the funding required is significantly higher than in the earlier stages of the development pipeline. Industry, and to an extent, philanthropic funders (particularly those with the resources to closely follow R&D developments or whose funding contracts are milestone based) tend to be responsive to these fluctuations in the pipeline and in funding needs. Public funders, however, are often much less responsive. Funders should be aware of R&D developments in the global portfolio and progress against agreed-upon goals in order to direct their funds to the areas where they are most needed.

RECOMMENDATIONS

This is a critical time for malaria R&D funding. The landscape is shifting to align with new global priorities for malaria control, elimination, and eradication; new research discoveries; and the challenge of resistance. Just as current malaria interventions must work together, the efforts around R&D—in drugs, vaccines, diagnostics, and vector control—need to be equally synergistic. With this in mind, we recommend the following:

1. Funding for malaria R&D must address the full continuum of control, elimination, and eradication.

2. Annual malaria R&D funding should increase to an average of $700 million per year in order to satisfy the overall malaria funding need, estimated at between $5.5 billion and $8.3 billion over the next decade (through 2022). This equates to a relatively modest increase over current annual funding. Funding for vector control and diagnostics should double over the ten-year period.

3. Basic research needs to be better aligned with product development to maximise public health impact. Current donors can assist by working more closely with new donors to ensure that funding from research ministries results in increased funding for research in the service of product development. Public funders can also increase their commitments to product developers, including product development partnerships.

4. There should be a more coordinated approach to funding to maximise effectiveness and minimise delivery time. Indeed, the projected resource needs in this report assume a higher level of coordination than currently exists.

5. Funding should be flexible to support optimal portfolio management and diverse partnerships, and to maximise resources from endemic countries and emerging economies.

6. In order to broaden the funding base, more funders need to become engaged in malaria R&D, including more donor governments, philanthropic donors, and research and science and technology agencies.

LIST OF ADVISORY COMMITTEE MEMBERS

Name	Organisation	Title
Geoffrey Targett	London School of Hygiene and Tropical Medicine	Professor of Clinical Tropical Medicine
Jo Mulligan	UK Department for International Development	Central Research Department
John Reeder	World Health Organization	Director, Special Programme for Research and Training in Tropical Diseases
Janice Culpepper	Bill & Melinda Gates Foundation	Senior Programme Officer
Charles S. Mgone	European & Developing Countries Clinical Trials Partnership	Executive Director
James Jones	ExxonMobil Foundation	Manager, Community Investments

ANNEXE 1: REFERENCES

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ANNEXE 2: METHODOLOGY

COST PROJECTIONS METHODOLOGY

Cost projections for drugs and vaccines are based on a risk-adjusted portfolio model designed by the Bill & Melinda 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) All products in the pipeline for malaria, including their current stage of development.

b) Ideal portfolio targets (number of products needed in the next decade for each product development goal).

c) Phase duration.

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

d) Probability of technical success—PTS (defined as percentage of candidates successfully reaching the next phase).

These variables were used differently when modelling different research categories.

- For basic research, annual projections were calculated as a proportion of total funding needs based on historical data. Constant investment of between $180 and $195 million per year were included in the model, which maintains funding at or just above the 2011 level.
- For diagnostics and vector control products, annual projections were calculated based on the following variables: activities in the pipeline, ideal portfolio targets, research and development (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: candidates in the pipeline and current stage of development, ideal portfolio targets, phase duration, direct R&D cost (excluding cost of failure), and PTS by phase.

In all research categories, minimum and maximum values have been included to 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).

All figures in the report are in 2011 US dollars.

Drugs

A list of R&D development goals was developed based on:

- Consultation with Medicines for Malaria Venture (MMV).

- Literature from the malERA Consultative Group on Drugs.
- Consultation with the MESA Task Force.

A list of matching products currently in the pipeline was compiled based on these development goals. 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 Advisory Committee, and/or existing Policy Cures contacts.

The following drug R&D 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 and vaccine goals for elimination/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 control versus elimination/eradication features.
- Total direct cost per product, per phase (minimum and maximum estimates), excluding cost of failure.
- Probability of technical success 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 of FSG participated in the discussions on the target candidate profiles with MMV, and Martin John Rogers from the US National Institute of Allergy and Infectious Diseases 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 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.

Vaccines

A list of R&D goals required for vaccines was developed based on:

- Malaria Vaccine Technology Roadmap.
- Literature from the malERA Consultative Group on Vaccines.

- Consultation with the MESA Task Force.
- Consultation with the PATH Malaria Vaccine Initiative (MVI).
- Consultation with other malaria experts.

Based on these development goals, a list of matching products currently in the pipeline was compiled based on the World Health Organization Rainbow List.

Expert consultation

In addition to the consultations conducted with MVI and the MESA Task force, other malaria experts were interviewed:

- Christian Loucq, International Vaccine Initiative.
- Charles S. Mgone, European & Developing Countries Clinical Trials Partnership.
- Geoffrey Targett, London School of Hygiene and Tropical Medicine.
- Janice Culpepper, Bill & Melinda Gates Foundation.
- Jo Mulligan, UK Department for International Development.
- Rip Ballou, GlaxoSmithKline Biologicals.

Experts were asked to comment on:

- Overall vaccine R&D goals and vaccine goals for elimination/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 R&D goal each addresses.
- Total direct cost per product, per phase (minimum and maximum estimates) and per vaccine type (pre-erythrocytic/blood stage and sexual stage), excluding cost of failure.
- Probability of technical success for candidate to reach next phase (minimum and maximum estimates).
- Phase durations (minimum and maximum estimates).
- Case studies.

Different questions were posed to different experts depending on their background and expertise.

Modelling

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

a) Direct cost of progressing the current pipeline 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 was conducted to outline a preliminary list of diagnostics R&D activities.

Expert consultation

The following diagnostics experts were interviewed:

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

Experts were asked to comment on:

- Diagnostics 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 was conducted to outline a preliminary list of vector control R&D activities.

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.

INPUTS AND ASSUMPTIONS

Variables and values (in 2011 US dollars) used to calculate future funding needs for each of the research areas included in the report are listed below.

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 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%

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 (fast clearance)	2	2	2022	MMV expects to register 2 NCEs for TCP 1 by 2022.
TCP 1 (fast clearance) 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 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.
TCP 2				
TCP 2 (long duration)	1	1	2027	First-generation SERCaP will use existing 4-aminoquinolines in combination with TCP 1. Novel TCP 2 NCEs will be developed for second-generation SERCaP.
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.
TCP 3				
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.
TCP 4				
TCP 4 (chemoprophylaxis)	1	1	2022	MMV expects to register 1 NCE for TCP 4 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; NCE: New chemical entity; SERCaP: Single exposure radical cure and prophylaxis; TCP: Target candidate profile.

Additional assumptions

- Funding for fixed-dose combinations and label extensions have been estimated as an independent add-on R&D category, and not included in the discovery, preclinical, clinical, or Phase IV costs.
- Combination products (including single exposure radical cure and prophylaxis) begin when all new chemical entities included in the combination have completed Phase IIa. New chemical entities (NCEs) are brought into combination as soon as they have demonstrated activities in subjects with malaria (Phase IIa). No NCEs will be registered as single entities unless they provide a specific interest (special population).

Vaccines

	Duration for model		Total cost for model ($)		% to reach next phase (PTS) (minimum and maximum)
R&D activity	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 1: First-generation *P falciparum* vaccine with 50% protective efficacy against severe disease and death, lasting longer than one year.	1	1	2015	Non-VIMT. RTS,S is the only vaccine in the current global portfolio that corresponds to this target.
Core 2: Second-generation *P falciparum* vaccine (with or without components that target *P vivax*) with protective efficacy of more than 75% against clinical disease and/or infection, providing protection for longer than two years.	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-or-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 includes only vaccines that target the sexual stage and do 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 includes only vaccines that target the sexual stage and do not provide direct, immediate benefit. Assumes cluster randomised trials required for licensure and deemed feasible.

BS: Blood stage; PE: Pre-erythrocytic; 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 ACTIVITIES		
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%

FROM PIPELINE TO PRODUCT: **MALARIA** R&D FUNDING NEEDS INTO THE NEXT DECADE

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