Bridging the gaps in malaria R&D

An analysis of funding—from basic research and product development to research for implementation

PATH

World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

malaria NO MORE united kingdom

MMV Medicines for Malaria Venture

FIND Because diagnosis matters

IVCC Building Partnerships Creating Solutions Saving Lives

POLICY CURES RESEARCH.

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Abbreviations

3GIRS	third-generation indoor residual spraying
ACT	artemisinin-based combination therapy
AIDS	acquired immunodeficiency syndrome
ANDI	African Network for Drugs and Diagnostics Innovation
CHMI	controlled human malaria infection
DFAT	Australian Department of Foreign Affairs and Trade
DNDi	Drugs for Neglected Diseases initiative
EC	European Commission
EDCTP	European & Developing Countries Clinical Trials Partnership
FIND	Foundation for Innovative New Diagnostics
G-FINDER	Global Funding of Innovation for Neglected Diseases
HCPC	Health Care Compliance Packaging Council of Europe
HIC	high-income country
HIV	human immunodeficiency virus
ICMR	Indian Council of Medical Research
IDRC	Canadian International Development Research Centre
IRS	indoor residual spraying
IVCC	Innovative Vector Control Consortium
KEMRI	Kenya Medical Research Institute
LMICs	low- and middle-income countries

MalaFA	Malaria Futures for Africa
malERA	malaria elimination and eradication
MMV	Medicines for Malaria Venture
MNC	multinational corporation
MSF	Médecins Sans Frontières
NgenIRS	Next Generation Indoor Residual Spraying (project)
PMI	US President's Malaria Initiative
R&D	research and development
SMEs	small- and medium-sized enterprises
ssART	semisynthetic artemisinin
TDR	The Special Programme for Research and Training in Tropical Diseases based at the World Health Organization
UK	United Kingdom
UK DFID	UK Department for International Development
UK MRC	UK Medical Research Council
US	United States
USAID	US Agency for International Development
US CDC	US Centers for Disease Control and Prevention
US DOD	US Department of Defense
US NIH	US National Institutes of Health
WHO	World Health Organization

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Foreword

The timing of this report could not be more critical. Progress against malaria has recently flatlined, and in some areas, malaria cases are on the rise. This is a threat to more than a decade of progress and investments in the global fight against malaria—and to the lives and livelihoods of millions of people. Valuable tools have been developed, and more are on the way, but lagging behind are the systems to ensure that they are implemented, used appropriately, and easily accessible to everyone in need.

Consequently, there is an increasing demand for research that can support broader and better implementation and thus greater impact. However, significant challenges exist to measuring the current effort—let alone accurately assessing the need.

Understanding the volume and uses of funds across malaria research and development—from basic research through implementation—is one way to identify potential gaps in the field. Past reports on funding patterns have shown their usefulness in prompting more attention and marshalling more resources.

In this study, we expand that effort to include data from a pilot survey on funding for research for implementation and the challenges to tracking the resources that support those efforts.

By integrating data on funding for basic research and product development with similar data on research for implementation, this report builds on previous work and provides a broader view of funding patterns. Although focused on malaria, it offers insights that are applicable across other disease areas.

This report is intended to inform ongoing discussions—among funders, policymakers, product developers, and program implementers—on how best to approach the challenge of improving specific health outcomes in a health system context, the role of resource tracking in meeting this challenge, and ways to fill critical data gaps. It provides recommendations on funding for malaria research and development, and a call to action: to ensure that tools to fight malaria are developed and deployed efficiently, effectively, for optimal impact.

In the end, it is about staying on course—ensuring that the many countries faced with high burdens of malaria have the right tools and strategies and use them—so that this scourge can be eliminated once and for all.

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Executive summary

After more than a decade of progress in reducing the burden of malaria disease and death, the total estimated number of malaria cases rose in 2016 by more than 5 million over the previous year.[1] Increases in malaria burden were reported from countries in all World Health Organization regions from 2014 to 2016.

As new tools have become available, health care systems face growing challenges in ensuring that the drugs, diagnostics, vaccines, and vector control products are designed for the conditions in which they are used; reach the right place, at the right time, in the right quantities; and are delivered appropriately.

In the past, there was more funding for basic research and insufficient investment in product development. Publicly reported funding data helped illuminate the gaps and raise commitments toward addressing what was called the valley of death.

Today, the questions are whether there is enough funding for research for implementation that would improve access to the health products and services now available, and how well what is funded is aligned to the product pipeline and health system needs. Is there a second valley of death?

This report covers findings from a pilot study on funding for malaria research for implementation, which includes implementation research, operational research, and health systems research. For the first time, these data are combined with data on funding for basic research and product development.

The 26 organizations surveyed have highlighted opportunities for improved monitoring and analysis of funding flows. There are significant challenges to getting complete data that cover research for implementation, including a lack of consensus around categories and definitions, and insufficient application of these categories and the geographic locations of research within funding databases.

Average annual funding for basic research and product development (as distinct from research for implementation) falls short of the need. WHO's Global Technical Strategy for Malaria estimated average annual investment needs at close to $700 million over the period 2016 to 2030.[2] Annual funding from 2014 to 2016 has averaged about $100 million less than that figure, and it remains to be seen if these funds will be made available.

This analysis shows that malaria research and development does not need an endless blank check, but rather, requires targeted funding to develop customizable toolboxes designed to meet the unique needs of each country and region.

The stalled progress against malaria (and in some areas rises in the number of cases) reminds the world of the need to stay on course. Thus, for funders, policymakers, product developers, and other malaria stakeholders, three overarching recommendations emerge from the research behind this report:

1. IMPROVE COORDINATION ACROSS INTERVENTION AREAS (FROM BASIC THROUGH IMPLEMENTATION RESEARCH).

Product developers must work together to ensure that next-generation interventions will fit together seamlessly. Although this is already happening periodically, a sustained and ongoing effort is needed to ensure that scarce resources have maximum impact.

2. DEVELOP MORE INNOVATIVE FUNDING APPROACHES.

There is little or no high-income market for the malaria interventions needed in endemic regions and the regions most affected are struggling with the systems required to implement, let alone monitor, them. While the maturity of the current product pipeline is an emerging success story, that success could be limited by the absence of sufficient resources to optimize the impact of new tools. New types and approaches of funding mechanisms and incentives are clearly needed.

3. CONTINUE EXISTING TRACKING OF FUNDING FLOWS AND STRENGTHEN SYSTEMS TO ADDRESS DATA GAPS.

Tracking efforts must be sustained for basic research and product development, and data gaps addressed—particularly for research for implementation. The findings in this pilot survey provide only a partial picture and do not address the evolving nature of malaria and tools required. Key stakeholders, including those who have experience tracking resource flows and conducting research, should work together—and, in particular—on research for implementation.

KEY DISCUSSION TOPICS ON RESEARCH FOR IMPLEMENTATION INCLUDE:

AGREE TO DEFINITIONS AND A CORE DATASET TO TRACK RESEARCH FOR IMPLEMENTATION.

The use of a range of definitions complicates and, in some cases, prevents tracking and analysis into funding flows. Few funders are doing this, and many who would like to do this do not have the systems or personnel to do it.

DETERMINE HOW TO COLLECT DATA ON RESEARCH FOR IMPLEMENTATION FUNDING AT THE INSTITUTIONAL, NATIONAL, AND SUBNATIONAL LEVELS.

This survey has been limited to a subset of organizations. However, there is a deep well of research to be mined at the local level that is necessary to complete the full picture. The *Malaria Futures for Africa* report of views from 68 key stakeholders in 14 sub-Saharan countries stated that "much more emphasis should be placed on operational research, which most respondents considered underfunded. They felt there should be much more emphasis on how interventions are best delivered through health systems."[3] Is it possible to track funding flows to this, ensuring investments are not double-counted? If not, could projects themselves be better tracked, using case studies to explore the funding requirements for implementing certain types of products or services, and how this differs by country or region?

INVESTIGATE THE VALUE OF TRACKING FUNDING FOR TRAINING AND CAPACITY-BUILDING FOR RESEARCH FOR IMPLEMENTATION.

Several organizations provided funding for building this capacity, yet this report (and others) have identified gaps in research capacity. Can the tracking of funding for training be useful for funders and program planners? A baseline is needed for further analysis on the gaps, which could also be applied to other diseases.

REVIEW DIAGONAL VERSUS HORIZONTAL RESEARCH FOR IMPLEMENTATION.

How can the outcomes of research for implementation be shared across health systems so that the learnings do not remain siloed within a particular disease area or type of intervention? Those working in other disease areas are thinking about this issue, and there is the general belief that working across diseases can increase the value of the research. Can this be monitored and evaluated through funding data?

CONSIDER A FUNDING TARGET FOR RESEARCH FOR IMPLEMENTATION AS PART OF ANY ELIMINATION OR CONTROL PROGRAM.

Review other disease elimination programs and how research for implementation was funded, such as with the Onchocerciasis Elimination Program for the Americas[4] and the Polio Eradication Initiative.[5] Is it possible to identify appropriate levels of investment in this area, and/or to prioritize topics or areas for research for implementation, or establish targets for percentages of the total research funding that should be devoted to research for implementation? The goal would be to increase funding to the areas with the greatest gaps, not to reallocate from within the current funding pool.

To provide more specific examples of research for implementation, six brief case studies are provided at the end of this report. They include past studies on improving the usability and uptake of three products—insecticide-treated bednets, artemisinin-based combination therapy, and rapid diagnostic tests; a study on operational research capacity-building for the malaria elimination program; and two current studies—one related to pilot implementation of the first malaria vaccine and another on expanding the use of new wall paint products as part of insecticide-resistance management strategies in Africa.

Introduction

This report combines, for the first time, funding disbursements for malaria basic research and product development with "research for implementation." This latter term includes implementation research, operational research, and health systems research, with the third element here referring to research focused on the systems to implement products and services into health care practices (definitions and examples can be found in Appendix 1).

The results provide a first picture of how funds are being spent across the different research for implementation fields. They also highlight opportunities for improved monitoring and analysis of funding flows. There are significant challenges to getting complete data that cover research for implementation, including a lack of consensus around categories and definitions, and insufficient application of these categories and locations of research within funding databases.

The systems and practices required to increase access to, and use of, malaria products and services are receiving increased attention, as seen in the World Health Organization's (WHO's) *Global Technical Strategy for Malaria 2016–2030*[2] the research agenda from the malaria elimination and eradication (malERA) Refresh Consultative Panel on Health Systems and Policy Research;[6] the Roll Back Malaria Partnership plan, *Action and Investment to Defeat Malaria 2016–2030;*[7] and the United Nations Sustainable Development Goals.[8] To more effectively monitor and evaluate investment impacts, however, data on funding levels for research for implementation are needed.

Understanding this area of funding has become increasingly important because new products are not being fully used or integrated into existing intervention packages. For example, programs currently testing mass drug administration to prevent malaria are providing evidence of the relevance of community engagement and the need for high uptake of interventions, but research to define the successful operational criteria is still needed; social science methods have not been fully applied to overcome these challenges.[6]

The 2017 updated malERA research agenda[6] pointed out that "a single approach will not work in all settings with the same efficiency." It also called for "locally tailored vector control, case management, and surveillance strategies."[6]

Maxine Whittaker wrote in Public Health Action:

> *Implementation research helps identify what modifications need to be made for the various contexts—ecosystems, social, political, geographical, health systems, cultural—to reach a pre-elimination and then an elimination phase. Building local capacity to address local problems and challenges is important to inform nuanced implementation of the national and international evidence-based guidelines in these local contexts.*[9]

However, data on funding for this field have not been readily available to determine if this type of research simply was not being done, was not funded at appropriate levels, or was deemed too difficult to track.

In early 2018, Policy Cures Research conducted a quantitative survey asking for data or access to publicly available databases on disbursements on research for implementation for the years 2014 to 2016, and a qualitative survey examining perceptions of, and commitments to, this field. Of the 26 organizations polled (the full list is in Appendix 2), 77% responded to the quantitative survey and 69% to the qualitative survey.

These data were incorporated into the broader malaria basic research and product development pipeline funding already tracked annually by Policy Cures Research for the G-FINDER (Global Funding of Innovation for Neglected Diseases) surveys.[10] The data provide a first picture of how donor funds are being spent across the different research for implementation fields.

This report also outlines the achievements and challenges for each area of research—basic research and development (R&D) of diagnostics, drugs, vaccines, and vector control products. These are often linked with each other and with research for implementation.

What is learned in malaria may also have important implications for other diseases and for working across diseases, as illustrated by some of the case studies in this report. Some case studies investigate how a single tool or approach can cover multiple diseases. Others document short- and long-term impact on improving the usability and uptake of insecticide-treated bednets, artemisinin-based combination therapies (ACTs), and rapid diagnostic tests. More recent studies provide a view of the next-generation vector control products and operational research focusing on reaching malaria elimination in southern Africa. Finally, a planned study that will support pilot implementation of the first malaria vaccine highlights new potential for this field of research.

The report on the findings of this pilot survey is intended to inform ongoing discussions—among funders, policymakers, product developers, and program implementers—on how best to approach the challenge of improving specific health outcomes in a health system context, the role of resource tracking in meeting this challenge, and ways to fill critical data gaps. It provides recommendations on funding for malaria R&D, and a call to action: to ensure that tools to fight malaria are developed and deployed efficiently, effectively, for optimal impact.

Report methodology

This report describes the current landscape of funding for malaria research and development. It provides an update to previous reports, the most recent of which was published in 2013,[11] analyzes recent funding trends, and identifies some key gaps and challenges for the malaria R&D field. This report includes data from several sources.

BASIC RESEARCH AND PRODUCT DEVELOPMENT FUNDING

A detailed analysis of malaria funding covering basic research and product development from 2007 to 2016 was conducted using G-FINDER survey data from that period. For a full overview of that survey's methodology and scope, please refer to the G-FINDER 2017 report titled *Neglected Disease Research and Development: Reflecting on a Decade of Global Investment.*[10]

Malaria funding totals in this report are not directly comparable with G-FINDER, however. In this report, core funding provided to product development partnerships and other multidisease research groups has been apportioned to malaria (where appropriate) based on identified expenditure patterns. Throughout the text, references to years in the context of funding refer to financial years.

Industry (pharmaceutical companies and biotechnology firms) investment in R&D is not grant-based, so the G-FINDER reporting tool was tailored for these participants. Instead of grants, companies entered the number of staff working on neglected disease programs, their salaries, and direct project costs related to these programs. Companies were required to exclude "soft figures," such as in-kind contributions and costs of capital.

For some organizations with very large datasets, the online survey and equivalent offline reporting tool were difficult to use. In those cases, Policy Cures Research used publicly available databases to identify the relevant funding. For the US National Institutes of Health (US NIH), information about grants was collected using the Research Portfolio Online Reporting Tools and the Research, Condition, and Disease Categorization process. Information about funding from the European Commission was retrieved from the Community Research and Development Information Service public database. Supplementary data were provided by the European Commission.

All participating organizations were asked to only include disbursements (or receipts), rather than commitments made but not yet disbursed. In general, only primary grant data were accepted. All entries greater than $0.5 million were verified against the inclusion criteria. Cross-checking was conducted using automated reconciliation reports—which match investments that were reported as disbursed by funders with investments that were reported as received by intermediaries and product developers—followed by manual grant-level review of the report outputs. Any discrepancies were resolved by contacting both groups to identify the correct figure. For grants from the US NIH, funding data were supplemented and cross-referenced with information received from the Office of AIDS Research and the National Institute of Allergy and Infectious Diseases.

UNSPECIFIED FUNDING

Some malaria R&D funding included in this report could not be allocated to a specific product area—for instance, when funders reported a grant for research to be for both basic research and drugs but did not apportion funding to a specific product category. This means that reported funding for some products will be slightly lower than actual funding, with the difference being included as "unspecified" funding. However, in cases in which unrestricted ("core funding") grants were given to an organization working on multiple diseases or product types, the malaria-specific share of this funding has been proportionally allocated to the relevant product categories, based on the organization's R&D activities.

DATA AGGREGATION

All pharmaceutical industry funding data have been aggregated and anonymized for confidentiality purposes. Rather than attributed to individual companies, pharmaceutical company investment is instead reported according to the type of company, with a distinction made between multinational pharmaceutical companies and small pharmaceutical and biotechnology companies.

INFLATION ADJUSTMENTS

Funding data have been adjusted for inflation and converted to US dollars to eliminate artifactual effects caused by inflation and exchange rate fluctuations; this allows accurate comparison of annual changes. All funding data in this report are reported in 2016 US dollars.

LIMITATIONS

While the survey methodology has been refined over the past decade, there are limitations to the data presented, including survey noncompletion, time lags in the funding process, an inability to disaggregate some investments, and noncomparable or missing data. Please see the G-FINDER methodology document, available online at www.policycuresresearch.org/gfinder-2017, for a more in-depth discussion of these limitations.

Data are limited to organizations that fund basic research and product development. Consequently, organizations that fund research for implementation but not these other areas are not included in the pilot survey.

RESEARCH FOR IMPLEMENTATION FUNDING

A subset of the G-FINDER database of organizations involved in funding, coordinating, or conducting malaria basic research and product development (26 organizations, listed in Appendix 2) were sent a survey in early 2018 that focused on funding of research for implementation for the three years from 2014 through 2016. Organizations were asked to provide data on disbursements in this area. The response rate was 77%. Given the limited nature of this pilot survey, which excludes organizations that fund research for implementation but not malaria R&D overall, it is important to note that this is not a complete accounting of all research for implementation.

The survey also queried the 26 organizations on their perceptions of the utility of research for implementation—how they defined it and their commitments to it. This garnered a 69% response rate (see Appendix 3 for the survey questions).

Background on malaria cases and recent trends

After more than a decade of progress in reducing the burden of malaria disease and death, the total number of estimated malaria cases rose in 2016 by 5 million over the previous year, with the WHO regions of the Americas and Africa accounting for nearly 70% of national increases of more than 20%.[1] Fifteen African countries carried 80% of the global malaria burden.

Increases in malaria cases were documented in high- and low-burden countries: of the 21 countries that have been on track to eliminate malaria by 2020, 5 countries reported an increase of more than 100 cases in 2016 compared with 2015. Malaria cases are on the rise, but not uniformly.[1]

"If we continue with a 'business as usual' approach—employing the same level of resources and the same interventions—we will face near-certain increases in malaria cases and deaths."[1]

– WHO Director-General Dr. Tedros Adhanom Ghebreyesus

This change is occurring despite commitments to eliminate malaria that have generated unprecedented support from both donors and national governments. It has been estimated that eliminating malaria could save 11 million lives and unlock an estimated $2 trillion in economic benefits from gains in productivity and health savings.[12]

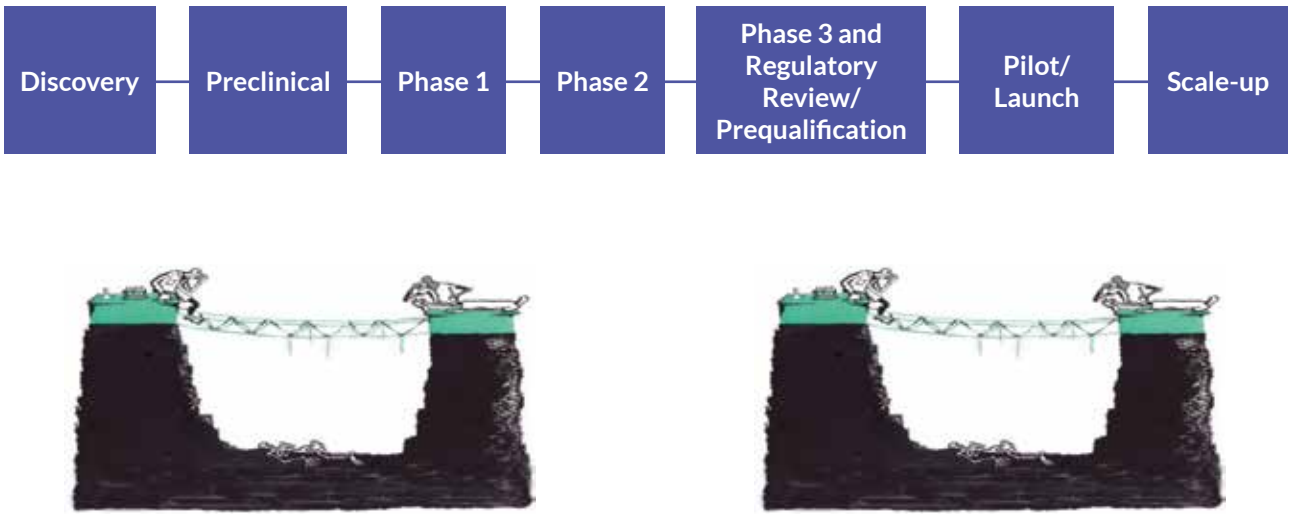
The WHO Malaria Policy Advisory Committee has recognized the need for more tailored support at the country level, focusing on the 11 countries that account for an estimated 70% of all malaria cases and deaths globally: Burkina Faso, Cameroon, Democratic Republic of the Congo, Ghana, India, Mali, Mozambique, Niger, Nigeria, Uganda, and the United Republic of Tanzania. At its April 2018 meeting, the committee called for "harmonized and complementary support" that gives countries the evidence to determine which interventions and combinations are best suited for their needs.[13] The guidance is moving from "implement all tools as much as you can" to tailored approaches that focus on the highest-burden areas within each country.

The challenges of enhancing access to effective interventions are shared with other diseases that affect low- and middle-income countries. A study on research funding for the 17 neglected tropical diseases identified the need for more social science research to improve delivery and use of drugs and technologies.[14]

A second valley of death?

There is growing recognition of a possible second valley of death (Figure 1). The first valley of death addressed the gap of translation from basic research into product development.[15] Funding data helped to illuminate the gaps and to raise commitments toward addressing that valley. Today, there appear to be challenges in translating the fruits of product development into access and health impact consistently across the countries burdened with high malaria rates.[16] The *MalaFA: Malaria Futures for Africa* report reinforces this. Sixty-eight key stakeholders in 14 sub-Saharan African countries, where malaria has the greatest burden, were surveyed on their views on what is needed to control and eliminate malaria. They recommended placing "much more emphasis" on operational research and how interventions are best delivered through health systems, areas they considered to be underfunded.[3] Research for implementation is perceived as a bridge over this valley, helping to ensure that tools reach the intended population and actually work in real-life settings with challenges such as harsh weather, remote conditions, and limited training. This research can also ensure that the investments already made are not lost, but rather are built on, thereby improving control and supporting disease elimination. Like any bridge, however, it has to be built and maintained—and this requires money.

Figure 1. **A second valley of death?**



The first valley of death: from basic research to product development[15]

The second valley of death: from licensure to routine use and scale-up[16]

Overall summary of findings

Table 1 and Figure 2 summarize funding trends from 2007 through 2016 for basic research and product development, based on data from the 2016 G-FINDER survey of 187 organizations. Research for implementation funding is tracked only from 2014 through 2016 among a subset of 26 organizations thought to either be funding or conducting this type of research.

Total funding for malaria basic research and product development peaked at $656 million in 2009. It has remained at a steady level since then—between $540 million and $600 million per year.

Funding of research for implementation increased from $99 million in 2014 to $123 million in 2016, bringing total malaria R&D funding (including basic research, product development, and research for implementation) to $689 million in 2016.

Funding is highly concentrated, with the top 12 funders in 2016 accounting for 93% of total malaria R&D funding and the top three funders (the Bill & Melinda Gates Foundation, US NIH, and industry) collectively contributing 71% of total investment.

Table 1. **Leading funders of malaria research and development by volume of funding provided** (in million US dollars, adjusted to 2016 dollars to account for inflation).

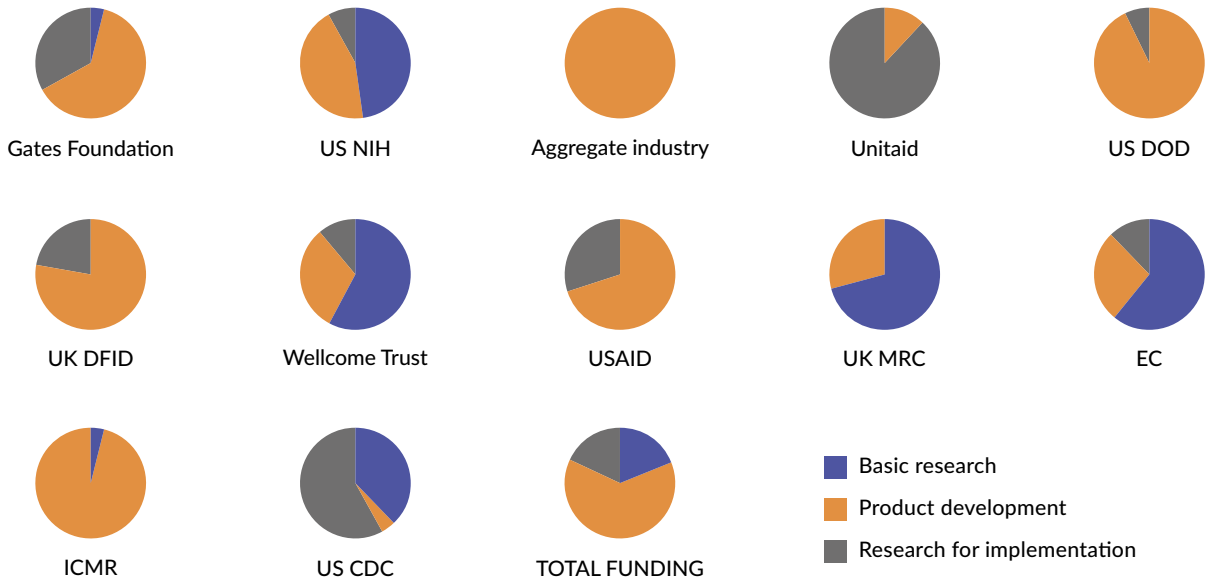
Funder	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Gates Foundation	146.0	206.0	215.0	103.0	170.0	137.0	127.0	178.0	155.0	176.0
US NIH*	99.0	123.0	136.0	156.0	144.0	177.0	144.0	161.0	168.0	174.0
Aggregate industry	83.0	85.0	96.0	115.0	93.0	106.0	76.0	118.0	142.0	137.0
Unitaid*	-	-	-	-	-	-	5.9	28.0	22.0	37.0
US DOD	39.0	36.0	44.0	27.0	21.0	11.0	23.0	19.0	30.0	31.0
UK DFID	5.3	4.2	6.6	25.0	19.0	6.0	27.0	20.0	21.0	17.0
Wellcome Trust	24.0	23.0	24.0	29.0	27.0	27.0	24.0	22.0	17.0	14.0
USAID*	11.0	10.0	9.6	10.0	9.1	12.0	6.6	11.0	14.0	12.0
UK MRC	16.0	17.0	18.0	20.0	17.0	16.0	16.0	14 .0	9.2	11.0
EC*	34.0	32.0	28.0	23.0	25.0	19.0	26.0	26.0	31.0	9.4
ICMR		10.0	7.0	5.0	5.1	6.7	7.5	7.0	7.8	9.0
US CDC	2.6	3.1	1.7	4.2	3.0	1.7	4.2	10.0	2.9	8.2
Subtotal of basic research and product development funding	518.0	606.0	656.0	581.0	600.0	587.0	544.0	562.0	567.0	566.0
Total funding	518.0	606.0	656.0	581.0	600.0	587.0	544.0	662.0	667.0	689.0

Funding organization did not participate in the G-FINDER survey for this year.

Funding totals include data from the pilot survey on research for implementation during 2014 to 2016 only.

*Research for implementation data were extracted from publicly available databases and were not verified by the organization.

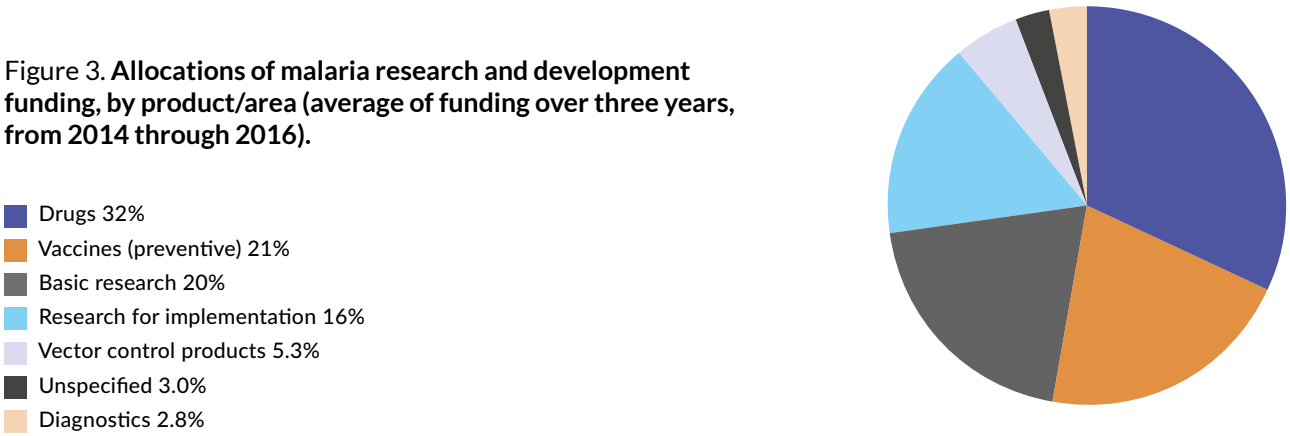
Figure 2. **Relative allocations of funding, by funder, by category of malaria basic research and product development (2016).**



Abbreviations: CDC = Centers for Disease Control and Prevention; DFID = Department for International Development; DOD = Department of Defense; EC = European Commission; ICMR = Indian Council of Medical Research; MRC = Medical Research Council; NIH = National Institutes of Health; UK = United Kingdom; US = United States; USAID = US Agency for International Development.

Figure 3 illustrates the three-year period from 2014 through 2016. The largest share of funding went into drug development (32%), with vaccines and basic research about equal (21% and 20% respectively), and research for implementation at 16% of the pie. Vector control and diagnostics comprise a small proportion of funding.

Figure 3. **Allocations of malaria research and development funding, by product/area (average of funding over three years, from 2014 through 2016).**



Types of funders

PHILANTHROPIC FUNDERS

As illustrated in Figure 4, the Gates Foundation has been a major contributor, providing 85% of all philanthropic funding for basic research and product development over the past ten years ($1.5 billion) and $152 million for research for implementation over the three years from 2014 through 2016. Its share of total global funding for basic research and product development peaked at 34% in 2008 but has since fallen to an average of 21% over the years 2014 through 2016, as funding from other sources increased. The Gates Foundation provided nearly half of all the funding for research for implementation that was reported by pilot survey respondents from 2014 through 2016.. However, it is not possible to draw any firm conclusions regarding the Gates Foundation's share of total global research for implementation funding due to the limited nature of the pilot survey.

PUBLIC-SECTOR FUNDERS

Public-sector funders provided about half of all basic research and product development funding over the past ten years, with 94% coming from high-income countries, and more than half of this from the US NIH. Funding by the US NIH increased steadily to a peak of $177 million in 2012 but fell to $144 million in 2013 as a result of the US government budget sequester. Since then, funding has again increased steadily, reaching $159 million in 2016 ($174 million when research for implementation is included).

GOVERNMENT FUNDERS

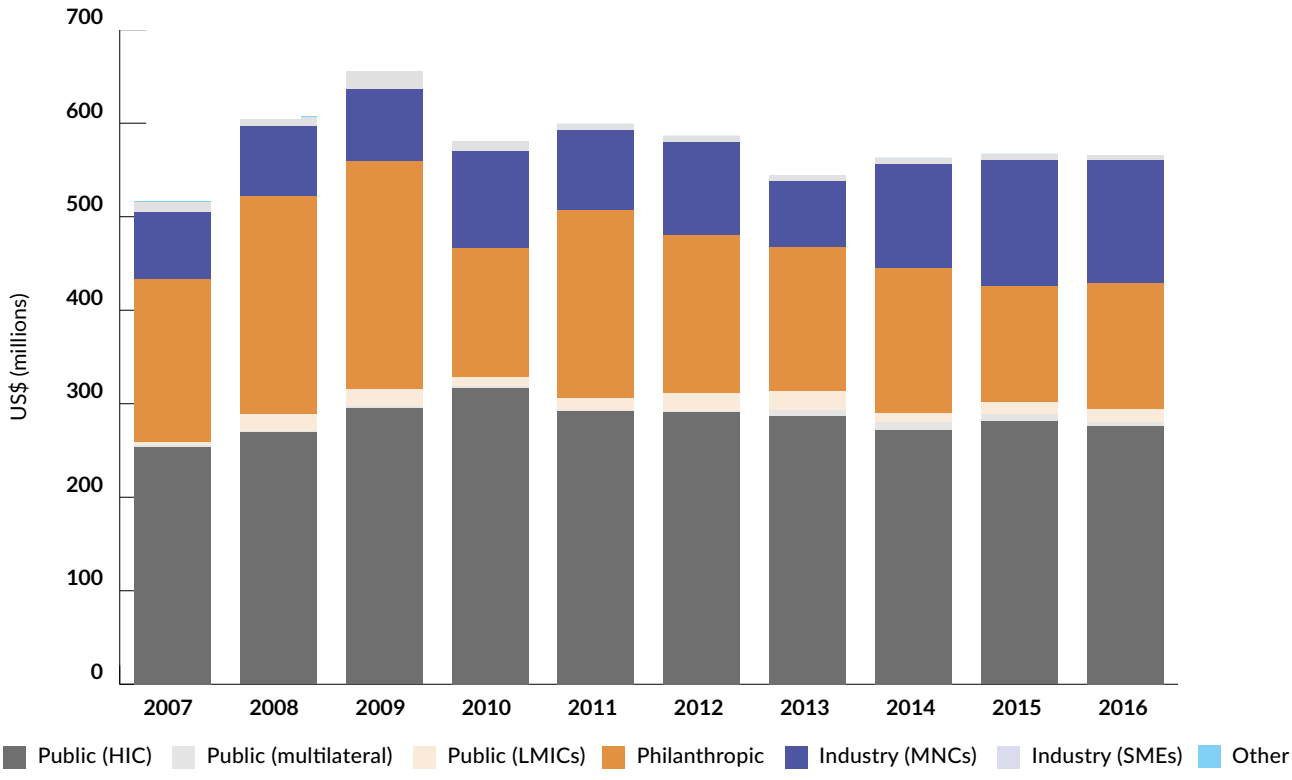
Only two government aid agencies were among the top 12 funders—the UK Department for International Development and US Agency for International Development—both of which focused on funding product development (drugs and vaccines, respectively).

Two funders from low- and middle-income countries have ranked in the top 12 in the past ten years: the Indian Council of Medical Research (every year but one since 2008) and the Brazilian Foundation for Support of Research in the State of Amazonas (Fundação de Amparo a Pesquisa do Estado do Amazonas) in 2013 ($8.3 million).

INDUSTRY FUNDERS

In 2015, funding from industry surpassed philanthropic funding for basic research and product development for the first time in the last decade, due mainly to industry's investment in drug development.

Figure 4. **Malaria basic research and product development funding, by sector** (excludes research for implementation).



Note: Does not include research for implementation.
Abbreviations: HIC = high-income country; LMICs = low- and middle-income countries; MNCs = multinational corporations; SMEs = small- and medium-sized enterprises.

© WHO. Laboratory in Kisumu, Kenya.

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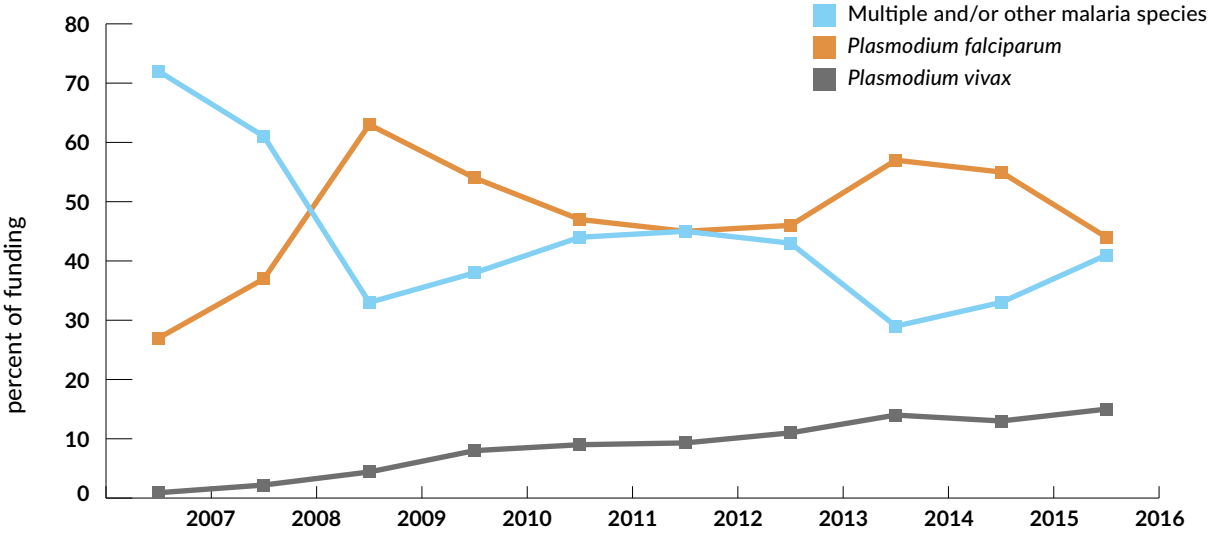
Where the funding is going

As of August 31, 2017, 576 products for infectious diseases (not just malaria) that disproportionately affect low- and middle-income countries were reported to be in some phase of development between preclinical and the end of phase 3 trials. With 141 products, the malaria pipeline had the second greatest number of products. Tuberculosis had 153 candidates and HIV/AIDS had 107. Together, these three diseases represented of 70% of all product candidates.[17]

Variations in funding levels for malaria basic research and product development have largely reflected the progression of the overall product pipeline, with spikes in vaccine funding in 2008 and 2009 (related to grants for phase 3 trials of the RTS,S malaria vaccine candidate and other vaccine development efforts at PATH) and again in 2014. There was a more recent peak in drug funding from 2015 through 2016 as product candidates entered late-stage clinical trials. This peak has also been reflected in the distribution of funding by parasite species (see Figure 5).

The product pipeline has been dominated by candidates targeting *Plasmodium falciparum*. Peaks in vaccine investment have been responsible for corresponding increases in the *P. falciparum*–specific funding share (it accounted for 63% of all malaria basic research and product development funding in 2009, and 57% in 2014). Similarly (although on a much smaller scale), *P. vivax*–specific funding has grown steadily over the past ten years, from less than 1% of total funding in 2007 to 15% in 2016. This was primarily driven by increased investment in *P. vivax* drug candidates as they progressed through the pipeline, but it also reflected more accurate reporting of species-specific funding flows over time.

Figure 5. **Malaria basic research and product development funding, by species** (excludes research for implementation).



Note: The low share of investment for Plasmodium falciparum (and corresponding high shares for multiple and/or other malaria species) in 2007 and 2008 is likely an artifact of less accurate species-specific reporting by respondents in the early years of the survey.

FUNDING RECIPIENTS

Less than a third of all funding for malaria R&D in 2016 ($223 million, 32%) was invested by funders in their own internal R&D activities (see Table 2). The largest funders of internal R&D activity were aggregate industry ($135 million, 61% of all internal investment), followed by the US NIH ($34 million, 15%) and US Department of Defense ($31 million, 14%).

The remaining 68% of all funding for malaria R&D in 2016 ($466 million) was either given directly to researchers and product developers, or channeled via product development partnerships and other intermediaries. The rest of this section focuses on the recipients of this external funding.

Product development partnerships represented three of the top four recipients of all external funding in 2016, although they received only a little more than a quarter ($128 million, 27%) of all external funding; three organizations (Medicines for Malaria Venture [MMV], Innovative Vector Control Consortium [IVCC], and PATH [mostly for product development, including diagnostics and vaccines]) received 93% of this total. The Malaria Consortium, Clinton Health Access Initiative, and University of California San Francisco were among the top 12 recipients largely because of their work in research for implementation.

The Malaria Consortium received $53 million for research for implementation from 2014 through 2016. Almost all of this was from Unitaid for the ACCESS-SMC project to evaluate the effectiveness of seasonal malaria chemoprevention among more than 6 million children across seven countries in the African Sahel region.

The Clinton Health Access Initiative was the top recipient of Gates Foundation funding for research for implementation ($26 million between 2014 and 2016).

The Gates Foundation was the only funder of the Clinton Health Access Initiative included in the pilot survey. The University of California San Francisco has been funded consistently by the US NIH for all areas of its research (particularly basic, drug, and implementation research). It also has received increased funding from the Gates Foundation for research for implementation in recent years, from $0.9 million in 2014 to $5.4 million in 2016.

In addition to the funds they invest in their own internal R&D programs, industry receives funding from external sources to support these activities. Collectively, aggregate industry received an average of $24 million of external funding each year from 2014 through 2016, mainly from a small group of funders, including the US NIH, Gates Foundation, Wellcome Trust, US Department of Defense, and European Commission.

For a list of the countries documented as receiving funding, see Appendix 4.

Table 2. **Leading recipients of external malaria research and development funding, by volume of funding received** (in million US dollars, adjusted to 2016 dollars to account for inflation).

Recipient	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Medicines for Malaria Venture	85.0	50.0	45.0	73.0	76.0	52.0	65.0	74.0	77.0	60.0
Innovative Vector Control Consortium	-	11.0	16.0	16.0	<0.1	5.5	14.0	6.4.0	18.0	32.0
Malaria Consortium	-	-	-	0.9	0.6	0.8	-	13.0	12.0	28.0
PATH	13.0	84.0	90.0	4.4	44.0	26.0	22.0	71.0	28.0	26.0
Aggregate industry	9.9	21.0	29.0	24.0	17.0	41	30.0	29.0	20.0	22.0
University of Oxford	13.0	12.0	17.0	13.0	10.0	8.0	16.0	26.0	17.0	20.0
University of California San Francisco	-	1.7	1.6.0	3.2	6.7	4.9	7.5	12.0	13.0	17.0
Imperial College London	1.4	2.0	2.2	2.3	3.0	1.9	3.5	4.2	1.9	16.0
Clinton Health Access Initiative	-	-	-	-	-	-	-	6.4	5.4	14.0
Liverpool School of Tropical Medicine	45.0	17.0	18.0	9.8	11.0	10.0	9.0	8.8	2.9	10.0
University of Maryland, Baltimore	-	3.0	1.4	2.6	2.2	5.6	5.4	5.0	8.4	9.6
Foundation for Innovative New Diagnostics	0.2	3.3	3.1	3.4	2.8	4.0	5.9	4.2	4.1	6.6
Subtotal of basic research and product development external funding	355.0	432.0	461.0	382.0	431.0	424.0	400.0	380.0	342.0	347.0
External R&D funding received	355.0	432.0	461.0	382.0	431.0	424.0	400.0	478.0	441.0	466.0

Funding totals include data from the pilot survey on research for implementation.

Note: G-FINDER is primarily a survey of funders. Therefore, recipient totals may underestimate the funds received by research organizations, particularly those that did not participate in G-FINDER surveys. Abbreviation: R&D = research and development.

Summary of funding by type of research

BASIC RESEARCH

Basic research refers to the studies that increase understanding of malaria, including the parasite, disease pathophysiology, and vector, but which are not yet directed toward developing a specific product. This early research is critical to understanding the biological mechanisms of disease and paves the way to developing new and effective interventions.

Basic research received one-quarter ($1.5 billion, 25%) of all global malaria R&D funding from 2007 through 2016, with, with the public sector providing the vast majority ($1.3 billion, 85%). As Figure 6 illustrates, funding for basic research peaked in 2013 and has trended downward over the last few years. This raises the question of whether current funding levels remain sufficient for the need.

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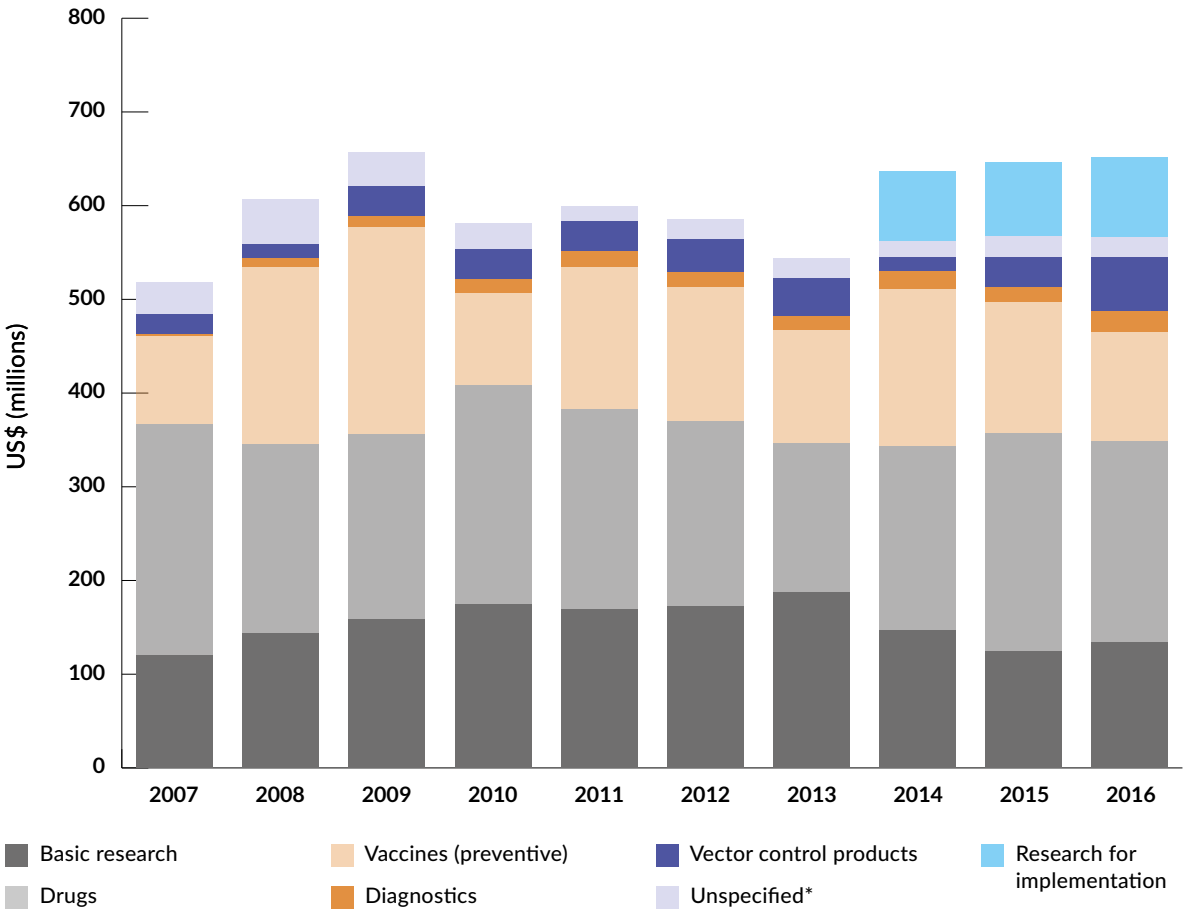
Reporting on investment in basic research for different malaria species (*P. vivax* and *P. falciparum*) tends to illustrate the gap in resource allocation between the two parasite species that predominate in humans. From 2007 through 2016, 50% ($762 million) of funding was reported as specifically invested in *P. falciparum* research, whereas only 6.4% ($98 million) was specifically reported as *P. vivax* research.

Figure 6. **Malaria research and development funding by product/area.**



** Unspecified funding refers to basic research and product development investments that could not be allocated to a specific product or research area.*

Note: Investments in research for implementation were not captured before 2014. What is illustrated here only represents funding reported by 20 organizations. The G-FINDER survey of basic research and product development funding was more extensive, with 187 participants in 2016.

However, less than half of all funding was reported as "unspecified" ($668 million, 44%); this included any malaria research not exclusively directed at one of these two strains, such as research that was relevant to both strains.

The US NIH was by far the single largest funder of malaria basic research from 2007 through 2016, providing half of all global investment in malaria basic research during this period ($792 million, 52%). It has consistently provided more than $60 million each year, peaking at $91 million in 2012. Total investment in basic research from all sources peaked a year later ($187 million in 2013), driven by record disbursements from the Gates Foundation ($31 million). As the Gates Foundation's contributions returned to pre-2013 levels (in the range of $5.5 to $8.6 million), and funding from non-US science and technology agencies (UK Medical Research Council, European Commission, and Australian National Health and Medical Research Council) declined, basic research funding fell, reaching $124 million in 2015 and rebounding slightly to $134 million in 2016.

Philanthropic organizations provided 14% of basic research funding, with the vast majority ($213 million, 96%) provided by two organizations: the Wellcome Trust provided $124 million, mostly to UK institutions, and the Gates Foundation provided $88 million, more than half of which went to US institutions.

What has been achieved

The malERA Refresh process provided a comprehensive analysis of recent achievements and future challenges across the malaria R&D field, including basic research.[6] Key areas of progress highlighted include greater understanding of both parasite and mosquito biology, as well as the interactions between the two; development of mouse models that facilitate understanding of the biology of the liver-stage parasite in both *P. falciparum* and *P. vivax* parasite species; and the ability to culture *P. vivax* hypnozoites in culture.

In addition, a key tool for evaluation of drugs and vaccines—the controlled human malaria infection (CHMI) or "challenge" model used to evaluate liver-stage interventions targeting the sporozoite—has been complemented by development of a blood-stage CHMI model and, more recently, by progress toward a model for evaluating transmission-blocking approaches. A second area of progress is in the various genome-editing systems, including CRISPR-Cas9. These have implications for drug and vaccine development, as well as vector control.

Challenges for basic research

The malERA update reported "significant gaps in the knowledge base and ability to tackle the non-*falciparum Plasmodium* species" and the need to apply "new technologies including CRISPR-Cas9 mediated gene drives, high throughput screening, metabolomics, and proteomics."[6] Other areas highlighted by the basic science panel included the need for in vitro cultures for mosquito-stage parasites and *P. vivax* gametocytes, and for understanding of persistence—of the parasite in the human and mosquito hosts, and of the mosquito in its habitat. Of CRISPR and similar technologies, the challenge is to identify the opportunities to intervene or disrupt interactions at the molecular or cellular level, and between the mosquito and human hosts, and thus foster the development of new tools to end malaria.

DIAGNOSTICS

Effective diagnostics are essential tools for the control, elimination, and eradication of malaria. The ability to accurately and quickly identify malaria infections is critical for ensuring that patients receive appropriate treatment, the impact of interventions is tracked, and resources are allocated effectively. The development of rapid diagnostic tests 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 could be averted and 100,000 lives saved annually by using practical, field-appropriate malaria tests.[18]

Diagnostic R&D investments grew between 2007 and 2016, from $2.1 million to $26 million—a more than tenfold increase, although this still represented only a small percentage (3.8%) of all malaria R&D funding in 2016.

What has been achieved

The Foundation for Innovative New Diagnostics, PATH, and their partners have made significant advances in developing innovative, ultrasensitive diagnostics to support the elimination of malaria. The first product from this portfolio was launched in 2017 (the Alere™ Malaria Ag P.f test), with progress under way on the others. These tests have the potential to significantly impact transmission of malaria, with point-of-care detection of low-density malaria infections.

Similarly, temperature-stable loop-mediated isothermal amplification (LAMP) kits and assays specifically for *P. vivax* detection that work in field conditions have already made it possible to effectively identify these infections, which may be low-density and asymptomatic. Both diagnostic tools—the ultrasensitive rapid diagnostic test and the LAMP—may be useful adjuncts to malaria elimination efforts.

Challenges for diagnostics development

The best-performing rapid tests for *P. falciparum* are currently based on the histidine-rich protein 2 antigen, which, due to gene deletions, is missing in a growing number of parasite populations. New biomarkers and tests based on novel ubiquitous markers are needed.

Improvements are also needed for non-falciparum diagnostics. Currently available rapid diagnostic tests for *P. vivax* infections have comparatively limited sensitivity. This challenge is currently being addressed on multiple fronts, including by improving the performance of diagnostic tests based on the *Plasmodium* lactate dehydrogenase enzyme, as well as by identifying new biomarkers and moving them into product development. *P. vivax* elimination is further complicated by the lack of tests for hypnozoites, the resting liver-stage parasite form that leads to chronic malaria relapses.

Quantitative tests for use at the point of care also are needed for glucose-6-phosphate dehydrogenase (G6PD) enzymatic activity. About 350 million people have a genetic deficiency resulting in low G6PD levels, which can result in rupture of red blood cells when certain antimalarials are taken for *P. vivax* treatment. PATH and partners continue to advance a product pipeline of diagnostics for G6PD deficiency that is able to support the use of these and next-generation treatment drugs.

Beyond the technical challenges, it is important to further strengthen the ecosystem surrounding diagnostic development. This includes improving access to specimen banks and decreasing the complexity of regulatory pathways.

DRUG DEVELOPMENT

Drugs, along with vector control tools, are the mainstay of malaria control strategies and used to treat patients who have already contracted malaria, and to prevent malaria in vulnerable groups. At present, 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 artemisinin 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 prevention for several weeks.

Funding for drug R&D had peaks in 2007, 2010, and 2015 to 2016, with the last peak reflecting an increased focus on clinical development as product candidates advanced through clinical trials.

What has been achieved

Since 2009, MMV has co-developed with R&D partners seven medicines that have saved at least 1.5 million lives, as well as taken stewardship for two products developed and launched by the Drugs for Neglected Diseases *initiative*. For uncomplicated malaria, this includes two formulations specifically for children: Novaritis' Coartem Dispersible and Shin

Poong Pharmaceutical's Pyramax® granules. Severe malaria treatments include Guilin Pharmaceutical's artesunate injection Artesun® and Cipla's and Strides Shasun's rectal artesunate suppository products. In addition, to protect children, MMV supported Guilin to obtain WHO prequalification for SPAQ-CO™ for seasonal malaria chemoprevention.

In 2014, a ten-year effort to establish and validate a manufacturing process to produce semisynthetic artemisinin (ssART) at industrial scale resulted in the first delivery of antimalarial treatments manufactured with a ssART derivative. The project, led by PATH's Drug Development program, brought together partners from academia, industry, and the public sector—including Sanofi—to address the historically volatile botanical supply chain and thus help to ensure that the global demand for ACTs can be met.

Challenges for drug development

Antimicrobial resistance is an increasingly serious threat to global public health and global health security, requiring urgent action across all government sectors and society. Parasite resistance has been identified to all but one of the malaria treatments.

Better antimalarials are needed to contain resistance, promote better adherence, and more effectively protect vulnerable populations.

Resistance to artemisinin, initially reported in 2008 in the Greater Mekong Subregion, has evolved into multi-drug resistance in some places. New therapeutic strategies are needed to address this threat in Asia, involving full deployment of the current portfolio of ACTs. New molecules are needed that target the malaria parasite with novel mechanisms of action that are also fully active against drug-resistant parasites. In addition, there is a need to prepare for the possible future spread of multi-drug-resistant malaria in Africa.

New medicines that simplify treatment of both *P. vivax* and *P. falciparum* malaria, and possibly act as a single-encounter radical cure, ideally with preventive properties, are also needed, as are new preventive treatments for use in seasonal malaria, and among infants (called IPTi).

To sustain this research effort, the capacity of researchers in the field of malaria (and across diseases) needs to be strengthened through scientific collaborations and open data-sharing platforms. One approach is "MMV Open," which helps grow the experience of researchers worldwide on issues of global and regional health security to improve the knowledge and the ability of the research community and practitioners to prepare for, and respond effectively to, epidemic threats.[19]

VACCINE DEVELOPMENT

A malaria vaccine has long been regarded as a critical missing tool in the malaria toolkit due to the dramatic impact of vaccination on public health around the world. During the twentieth century, vaccines saved more lives than any other health intervention; they have been credited with preventing 2 to 3 million deaths each year.[20,21] In the case of malaria, a vaccine is seen as an intervention that would complement, not replace, WHO-recommended interventions.

The malaria parasite has presented a challenging target for vaccine development due to its multistage life cycle and large genome (the parasite has more than 5,000 genes), the fact that even natural immunity does not fully protect against infection, the lack of a correlate of protection (meaning an immune response predictive of vaccine efficacy), and the speed with which the parasite invades—and thus is able to evade—the human immune system.

These factors combine to make development of a malaria vaccine a lengthy and resource-intensive activity, with costs heavily weighted toward late-stage development. The absence of a high-income market where sales could offset development costs requires the public and/or philanthropic sector to support the majority of development costs, as well as those associated with preparation for introduction.

The impact of late-stage vaccine development on funding flows is illustrated by funding patterns from 2007 through 2016. These included large funding peaks in 2008 and 2009, related to grants for the phase 3 trials of the RTS,S vaccine and other vaccine development efforts at PATH, and another in 2014.

Despite the challenges, malaria vaccine R&D remains an active area for scientific research and product development.

At any one time, there are roughly two dozen vaccine candidates undergoing testing in human volunteers, and others following behind in the pipeline, as illustrated by the so-called Rainbow Tables maintained by WHO's Department for Immunization, Vaccines and Biologicals.[22]

What has been achieved

Investments in malaria vaccine development have resulted in one vaccine, RTS,S, that is advancing toward introduction. Developed through a collaboration between GlaxoSmithKline and PATH's Malaria Vaccine Initiative, the vaccine, which targets the *P. falciparum* parasite, is intended to prevent disease in young African children. It has been positively reviewed by the European Medicines Agency (through the Article 58 procedure[23]) and recommended by WHO for pilot implementation, which is expected to begin in selected areas of Ghana, Kenya, and Malawi in late 2018. The Malaria Vaccine Implementation Programme is a country-led, WHO-coordinated initiative to assess—in the context of routine use—the feasibility of delivering the required four doses of RTS,S, its safety, and the vaccine's potential role in reducing childhood deaths.

To date, RTS,S is the only vaccine to show partial protection against malaria disease in young children, demonstrated in a large-scale phase 3 trial conducted by 11 research centers in seven African countries. The trial, which involved more than 15,000 infants and young children, found that among young children who received four doses of RTS,S, the vaccine prevented four in ten (39%) cases of clinical malaria and three in ten (29%) cases of severe malaria over four years of follow-up. Cases of severe malaria anemia were reduced by 62%. These benefits were in addition to those provided by long-lasting insecticidal nets, which were used by approximately 80% of children in the trial, and other interventions.[24]

A number of vaccine candidates targeting the pre-erythrocytic stage of the disease (the stage targeted by RTS,S) are currently being evaluated in humans, as are candidates targeting the parasite blood stage (when disease symptoms appear) and the sexual and/or mosquito stages of the parasite (so-called transmission-blocking vaccines). Pre-erythrocytic candidates include a whole-parasite approach, and another candidate that targets the same protein as RTS,S. Efforts are also underway to explore the potential for improving RTS,S efficacy by altering schedule and/or dosage.

Among blood-stage vaccine candidates, two target the VAR2CSA protein and are intended to protect pregnant women from pregnancy-associated malaria; they have completed phase 1 clinical testing. More recently, researchers completed a safety and efficacy study of RH5, regarded as a promising blood-stage candidate due to its potential for protection across different strains of *P. falciparum* malaria. Also worth noting is the first clinical assessment of a blood-stage vaccine against *P. vivax*, the results of which are expected to be published in 2018.

Development of transmission-blocking vaccines began attracting renewed attention in parallel with the global health community's growing support for malaria elimination. Clinical assessment of vaccine candidates aiming to block transmission of parasites from humans to mosquitoes has historically focused on surface proteins of the mosquito stage of the *P. falciparum* and *P. vivax* parasites, respectively. More recently, a candidate targeting the sexual stage of the parasite was shown to be able to significantly reduce transmission in humans.

Challenges for vaccine development

The *Malaria Vaccine Technology Roadmap*, first published in 2006 and last updated in 2013, represents the community's consensus around the vaccines needed along the continuum

from control through elimination and eventual eradication of malaria, as well as on specific aspects of vaccine development requiring focused attention.[25] The 2013 Roadmap targeted the development of vaccines against both *P. falciparum* and *P. vivax*, including vaccines targeting clinical disease (with at least 75% efficacy) and those able to reduce parasite transmission (to support malaria elimination) by 2030. The Roadmap also retained its landmark goal of a first-generation malaria vaccine by 2015 that has greater than 50% efficacy against severe disease and death and lasts more than one year.

While progress has been made over the past five years, several key challenges noted in the Roadmap remain. These include the chronic underfunding of vaccine development efforts targeting non-*falciparum* parasite species, most notably *P. vivax*; the lack of immune correlates of protection able to predict vaccine efficacy; and the need to support post-approval pharmacovigilance and effectiveness testing in malaria-endemic regions.

VECTOR CONTROL

Vector control products include long-lasting insecticide-treated nets, the spraying of insecticides on indoor walls (indoor residual spraying, or IRS), and biological control products that target the mosquito (the vector) that transmits malaria. There are five classes of insecticides currently used in vector control, but only one class, pyrethroids, is recommended for use in long-lasting insecticide-treated nets.

Investment in vector control product R&D nearly tripled from 2007 through 2016 (from $21 million to $58 million), almost entirely due to increased funding from the Gates Foundation.

What has been achieved

Since 2007, the IVCC and its industry partners have completed the development of three indoor residual sprays (K-Othrine® Polyzone [Bayer S.A.S.], Actellic® 300CS [Syngenta], SumiShield™ 50WG [Sumitomo Chemical]) and a dual active-ingredient insecticide-treated bednet (Interceptor® G2). These products are aimed at preventing the build-up of insecticide resistance in mosquitoes, as is a new bednet that includes the chemical piperonyl butoxide together with a pyrethroid.

Challenges for vector control

There are significant challenges to vector control product development and their use in low-resource settings.

> ***A complete toolbox of products needs to be developed to fight against insecticide resistance, protect people inside and outside of their homes, and adapt to a wide range of vectors.***

Currently, vector control tools are not able to interrupt all malaria transmission (indeed, no single tool is), and "residual transmission" can persist even in areas with good vector control coverage.[1]

Commitments from funders and innovators are needed to stay the course in long-term product development to reach and sustain malaria elimination, such as ZERO by 40, [26] a pledge from key industry partners to work collaboratively toward the eradication of malaria by 2040.

Basic research and product development challenges

The key challenges for these areas include:

Continued underinvestment in *P. vivax*, a parasite species that is growing as a proportion of the total malaria burden. This is seen in low investments in basic research, in limited numbers of diagnostics and drugs for this species, and in vaccine development.

Unpredictable or unknown regulatory and/or policy pathways, noted for vector control products, but also affecting other areas.

Resistance on the part of the parasite and vector to drugs and insecticides, respectively.

As the product portfolio has matured, all areas are finding issues around access to new or improved products. The challenges to testing a product in field conditions, and moving it through weak health systems, has led to new emphasis on research for implementation to better understand the obstacles and identify solutions. This is the key driver behind the study to begin to collect funding data in this area.

©WHO, Child receiving a rapid malaria diagnostic test in Kisumu, Kenya.

Research for implementation

Research for implementation can provide greater understanding of barriers and opportunities for strengthened disease control and implementation of new tools. It is also uniquely placed to support the final phases of disease elimination, where the challenges are not about the creation of new products but about how to get products and services implemented in very specific circumstances.

The qualitative survey results

The pilot survey also included questions that examined perceptions of, and commitments to, this field. Responses are included in the analysis for this report.

Reaching agreement on categorizations and definitions of research for implementation continues to be a challenge. The three types of research referenced in this survey are based on a 2010 paper that offered working definitions of research that strengthens health systems (see Appendix 1).

The survey attempted to assess whether these definitions were recognized and accepted. Although the majority of those surveyed agreed with the definitions, several leading funders used other categorizations. One indicated that health systems research is an umbrella term that includes operational and implementation research, whereas another stated that there is no distinction between these latter two.

Most organizations (both funders and recipients) reported that their organization included research for implementation in their strategy. The Special Programme for Research and Training in Tropical Diseases (TDR) based at WHO was one of the few to explicitly state that they had funding priorities for research for implementation, and PATH's Center for Vaccine Innovation and Access has a dedicated functional area (policy, access, and introduction) that supports work in this area. Others implicitly referred to this; for example, the *IVCC Annual Report 2016–17* states, "The Access Strategy is inseparable from the overall product development strategy and the consequent portfolio."[27]

Related to this, several organizations reported funding master's or PhD degrees in this area: the European & Developing Countries Clinical Trials Partnership, Fogarty International Center, TDR, Wellcome Trust, and WHO's Global Malaria Programme. WHO lists five high-priority areas for operational research, with capacity-building one of them. Tracking funding of research capacity may be just as critical as tracking the funding of the actual research itself. Lessons can be learned from other diseases. The WHO's *A Global Action Framework for TB Research in Support of the Third Pillar of WHO's End TB Strategy* provides case studies of how operational research capacity has been built in public health programs in low- and middle-income countries.[28]

Of the 18 qualitative survey respondents, 6 reported that research for implementation was their highest priority among all types of malaria research. It is, therefore, important to get more complete funding data to be able to see if disbursements are matching priorities.

All respondents noted challenges in reporting funding data on research for implementation. Few organizations were able to separate specific figures from overall funding, as has been done for basic research and product development over the last 10 years.

It was an insurmountable challenge for some organizations that fund activities across many countries and institutions; this type of tracking would require modification of financial planning and reporting tools.

Funding of research for implementation

The Gates Foundation provided $152 million for malaria research for implementation from 2014 through 2016, with funding almost evenly split between operational research ($82 million, 54%) and implementation research ($70 million, 46%) (see Table 3).

Unitaid provided $67 million for malaria research for implementation between 2014 and 2016. The majority was for implementation research (96%) and most of the remainder was for operational research (3.6%).

The US NIH contributed $40 million to research for implementation from 2014 through 2016. Like the Gates Foundation, its funding was almost evenly split between operational research (53%) and implementation research (47%). In 2016, Unitaid had the highest proportion of malaria research funding allocated to research for implementation of the top 12 funders (88% of its investment).

The Gates Foundation, the European Commission, the Wellcome Trust, the US Agency for International Development, and Grand Challenges Canada were the only funders in this limited pilot survey to report funding for health systems research in 2016.

Table 3. **Selected funders of malaria research for implementation, by volume** (in million US dollars).

Funder	2014	2015	2016
Gates Foundation	46.0	49.0	57.0
Unitaid*	19.0	14.0	33.0
US NIH*	13.0	12.0	15.0
US CDC	6.0	2.9	4.8
UK DFID	0.9	3.0	3.9
USAID*	5.3	5.1	3.7
US DOD*	-	-	2.1
Wellcome Trust	1.5	1.3	1.8
EC	3.9	7.9	1.2
WHO TDR**	1.4	2.3	0.5
Australian DFAT	-	-	0.3
WHO Global Malaria Programme***	1.1	0.5	0.3
Total funding	99.0	99.0	123.0

Abbreviations: CDC = Centers for Disease Control and Prevention; DFAT = Department of Foreign Affairs and Trade; DFID = Department for International Development; DOD = Department of Defense; EC = European Commission; Gates Foundation = Bill & Melinda Gates Foundation; NIH = National Institutes of Health; TDR = Special Programme for Research and Training in Tropical Diseases; UK = United Kingdom; US = United States; USAID = US Agency for International Development; WHO = World Health Organization.

– No reported funding.

** Data were extracted from publicly available databases and were not verified by the organization.*

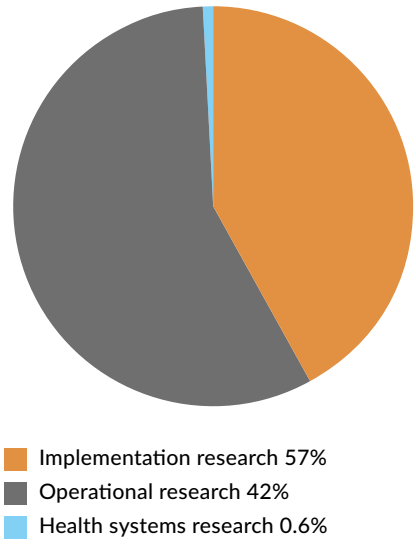
*** Funders of TDR include the UK Department for International Development, Swedish International Development Cooperation Agency, Belgian Directorate-General for Development Cooperation and Humanitarian Aid, German Federal Ministry for Economic Cooperation and Development, and Norwegian Agency for Development Cooperation. Contributions to TDR are not included in this table to avoid double-counting of this funding.*

**** The WHO Global Malaria Programme is funded by WHO Member States and voluntary contributions from other organizations. Contributions to the Global Malaria Programme are not included in the table above to avoid double-counting of this funding.*

More than half ($71 million, 57%) of all reported funding for research for implementation in 2016 was for implementation research, up from $61 million in 2014 (see Figure 7). The Malaria Consortium received 39% ($28 million) of implementation research funding. The University of California San Francisco, University of Oxford, and Clinton Health Access Initiative each received $5 million or more.

The share of research for implementation funding invested in operational research rose to 42% ($52 million) in 2016, an increase from 38% ($38 million) in 2014. Health systems research made up a tiny proportion (0.4%), reinforcing earlier reports like malERA 2017,[6] which complained that "too little investment and progress have been seen in this area" and called for a new tool to "identify bottlenecks (and) test different approaches to overcome them."

Figure 7. **Percentage allocations of malaria research for implementation funding, by type (2016).**



Note: These data are from the 20 responses received to the quantitative component of the pilot survey; they do not represent 100% of global research for implementation funding.

Where is research for implementation focused?

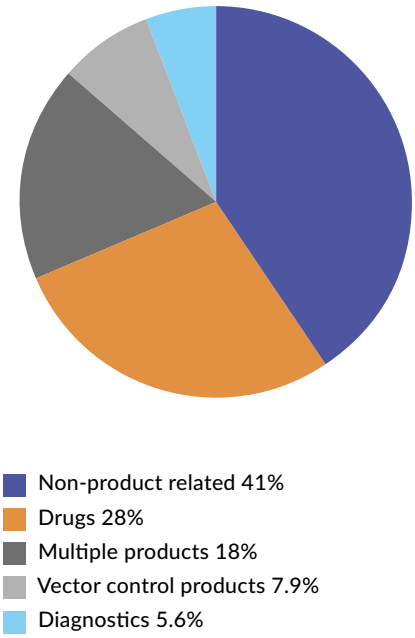
A large portion of research for implementation funding was invested in research that was not related to specific products ($52 million, 42%) (see Figure 8).

Almost a third of research for implementation funding ($38 million, 31%) was for drugs, whereas $10 million was invested in research for implementation for vector control products. Diagnostics received less attention ($3.4 million, 2.8%).

Very little funding of vaccine-related research for implementation was reported ($0.2 million), as research related to the pilot implementation of RTS,S, the malaria vaccine most advanced in development globally, had not yet started in 2016 and key organizations involved in funding vaccine R&D (i.e., industry) were not included in the pilot survey. The $240,000 reported from 2015 through 2016 by PATH was for preparatory work related to the health care utilization study profiled in case study 4.

Brief case studies of research for implementation are provided starting on page 36. These highlight past examples and their role in supporting changes to policy and practice, as well as current work that offers future potential.

Figure 8. **Malaria research for implementation funding, by product/area 2014-2016.**



Challenges in research for implementation

As new tools have become available, health care systems face growing challenges in ensuring that the drugs, diagnostics, vaccines, and vector control products are designed for the conditions in which they are used; reach the right place, at the right time, in the right quantities; and are delivered appropriately.

Results of the small pilot survey of research for implementation funding that are included in this report provide a first glimpse into the subject. They also raise questions on the R&D funding balance highlighted in previous G-FINDER reports, which cover research funding for all neglected tropical diseases (not just malaria):

> *Nearly two-thirds (59%) of all HIC [high-income government] and multilateral funding went to basic and early-stage research, with only a quarter (27%) going to clinical or field development and post registration studies.*[10]

For the 20 organizations that provided data on funding of research for implementation for this study, 20% of the funding went to research for implementation in 2014, and 25% in 2016. However, there are not enough data and years of collection to determine any trends and thus ascertain whether funding levels are consistent with stated priorities or sufficient to meet the need. In this small subset of funders, however, there were large discrepancies. Of those that said it was a priority, the percentage of funding for research for implementation ranged from 2.8% to 100%.

ACCESS TO DIAGNOSTICS

Diagnostics are hardly covered by research for implementation. Is the low level of funding reported an accurate representation of a lack of research, a reflection of the limited data, or an indication that research in this area is less expensive? Given the critical role of diagnostics in preventing the use of the wrong treatment—and thus delayed treatment, unneeded costs, and increased parasite resistance—it is important to get an accurate picture of how much research for implementation is being used and what it costs.

ACCESS TO DRUGS

Independent of the funding data received from survey participants, the justification for research for implementation is growing. WHO reported in *The World Malaria Report 2017* that almost one-third of patients who sought malaria treatment at a public health facility did not receive ACTs, the most effective antimalarial drug that is the result of years of R&D investment. The numbers who received this treatment were even lower in the private sector. And at antenatal clinics, 25% of pregnant women in sub-Saharan Africa still do not get even a single dose of intermittent preventive treatment.[1]

ACCESS TO VACCINES

As the first malaria vaccine moves toward implementation, key issues to be addressed include how to ensure that children receive all 4 recommended doses and that use of other malaria interventions—and other vaccines—is maintained. The evaluation components of the pilot implementation program, including the health care utilization study described in case study 4, are critical to answering these and other questions.

As noted earlier, the *Malaria Vaccine Technology Roadmap* included as one of its priorities the need for capacity in malaria-endemic regions to support post-approval pharmacovigilance and effectiveness testing.[25] The experience with RTS,S highlights the need for appropriate mechanisms to support implementation assessments of the kind recommended by WHO, as well as resource needs in other areas—such as pharmacovigilance and manufacturing—that may arise as a result. For products such as malaria vaccines, where the financial return is modest at best, it may not be reasonable to expect that the private commercial sector will self-fund all the costs.

ACCESS TO VECTOR CONTROL PRODUCTS

Investments in vector control R&D are now offering the possibility of new insecticides, which are urgently needed given increasing resistance to current insecticides. A comprehensive toolbox to prevent malaria is becoming available, but knowing how and when to best use these tools in many different settings is essential. Overall, training and documentation are required. As noted in the *IVCC Annual Report 2016–17*: "For products to be accepted by countries and implementation partners, evidence on their cost effectiveness and impact is imperative."[27]

Strategies to deploy, at scale, innovative products in resource-poor countries are needed. Questions still to be answered center on optimizing the process, the need for reactive case detection epidemiology trials, and how to fast-track safe, effective, and high-quality products to market.

The migration of vector control products review to the WHO Prequalification Team in January 2017 was a major change, adding more resources and a degree of predictability into the system.[29] Pathways from development to market uptake to incentivize innovation and to fast-track review and product launch have been proposed, such as the Vector Expedited Review Voucher[30]. Market-shaping platforms need to be broadened and supported, such as the Next Generation Indoor Residual Spraying project (see case study 6).

CHALLENGES FOR MALARIA PROGRAMS

African leaders have doubts that the 2030 targets for malaria elimination will be achieved without big changes in funding and delivery. The *Malaria Futures for Africa* report states that "new discoveries are adopted slowly, or not at all, because countries lack the operational research infrastructure to test different deployment methods and to assess the impact that each has." The report called for "more high-quality data on how to use the tools they already have as effectively as possible."[3] These leaders also expressed concern about the impact of increased trade and travel in speeding up resistance to ACTs, and about how to track substandard and counterfeit medicines.

A review of the literature on malaria control and elimination published from 2008 through 2013 (15,886 articles) revealed that less than 4% met the definition of operational research.[31] A commentary in *Malaria Journal* asked, "Why is so little operational research done when much of it would be straightforward and inexpensive and could be done within the context of routine malaria programme activities?"[32]

This is not unique to malaria. A report of a 2010 meeting of The Global Fund to Fight AIDS, Tuberculosis and Malaria noted that operational research was often absent or inadequately elaborated in proposals that clearly described bottlenecks to progress, and recommended that "Technical Partners work with applicants to help translate programmatic constraints and identified bottlenecks into relevant operational research to support implementation research and to formulate programmatic changes based on research results."[33]

This study raises questions as to whether there is enough funding going into research for implementation that would improve access to the health products and services now available, and how well what is funded is aligned to the product pipeline and health system needs.

Overall report reccomendations

Average annual funding for basic research and product development (as distinct from research for implementation) falls short of the need. As reported in the *Global Technical Strategy for Malaria 2016–2030*, WHO estimated average annual investment needs at close to $700 million from 2016 through 2030 ($673 million in 2014 US dollars).[2] Annual funding from 2014 through 2016 averaged about $100 million less than that figure; it remains to be seen if these funds will be made available.

This analysis shows that malaria R&D does not need an endless blank check, but rather, requires targeted funding to develop customizable toolboxes designed to meet the unique needs of each country and region. This includes, in particular, a toolkit to tackle *P. vivax* malaria.

The findings for malaria research for implementation and its funding have implications for not only this disease but across other diseases affecting low- and middle-income countries.

The R&D pipeline is dominated by three diseases—malaria, HIV/AIDS, and tuberculosis—which comprised more than half of all product candidates and received 70% of all R&D funding for neglected diseases, or more than $2.2 billion of the more than $3.2 billion invested in 2016.[10] Consequently, any evolutions in collection of funding data and balancing of portfolios within malaria could be applied to other diseases.

The stalled progress against malaria (and in some areas rises in the number of cases) reminds the world of the need to stay on course. Thus, for funders, policymakers, product developers, and other malaria stakeholders, this report makes three overarching recommendations on malaria basic and product development research, and five specific recommendations on research for implementation:

1. IMPROVE COORDINATION ACROSS INTERVENTION AREAS (FROM BASIC THROUGH IMPLEMENTATION RESEARCH).

Product developers must work together to ensure that next-generation interventions will fit together seamlessly. Although this is already happening periodically, a sustained and ongoing effort is needed to ensure that scarce resources have maximum impact.

2. DEVELOP MORE INNOVATIVE FUNDING APPROACHES.

There is little or no high-income market for the malaria interventions needed in endemic regions and the regions most affected are struggling with the systems required to implement, let alone monitor, them. While the maturity of the current product pipeline is an emerging success story, that success could be limited by the absence of sufficient resources to optimize the impact of new tools. New types and approaches of funding mechanisms and incentives are clearly needed.

3. CONTINUE EXISTING TRACKING OF FUNDING FLOWS AND STRENGTHEN SYSTEMS TO ADDRESS DATA GAPS.

Tracking efforts must be sustained for basic research and product development, and data gaps addressed—particularly for research for implementation. The findings in this pilot survey provide only a partial picture and do not address the evolving nature of malaria and tools required. Key stakeholders, including those who have experience tracking resource flows and conducting research, should work together—and, in particular—on research for implementation.

KEY DISCUSSION TOPICS ON RESEARCH FOR IMPLEMENTATION INCLUDE:

AGREE TO DEFINITIONS AND A CORE DATASET TO TRACK RESEARCH FOR IMPLEMENTATION.
The use of a range of definitions complicates and, in some cases, prevents tracking and analysis into funding flows. Few funders are doing this, and many who would like to do this do not have the systems or personnel to do it.

DETERMINE HOW TO COLLECT DATA ON RESEARCH FOR IMPLEMENTATION FUNDING AT THE INSTITUTIONAL, NATIONAL, AND SUBNATIONAL LEVELS.
This survey has been limited to a subset of organizations. However, there is a deep well of research to be mined at the local level that is necessary to complete the full picture. *The Malaria Futures for Africa* report of views from 68 key stakeholders in 14 sub-Saharan countries stated that "much more emphasis should be placed on operational research, which most respondents considered underfunded. They felt there should be much more emphasis on how interventions are best delivered through health systems."[3] Is it possible to track funding flows to this, ensuring investments are not double-counted? If not, could projects themselves be better tracked, using case studies to explore the funding requirements for implementing certain types of products or services, and how this differs by country or region?

INVESTIGATE THE VALUE OF TRACKING FUNDING FOR TRAINING AND CAPACITY-BUILDING FOR RESEARCH FOR IMPLEMENTATION.
Several organizations provided funding for building this capacity, yet this report (and others) have identified gaps in research capacity. Can the tracking of funding for training be useful for funders and program planners? A baseline is needed for further analysis on the gaps, which could also be applied to other diseases.

REVIEW DIAGONAL VERSUS HORIZONTAL RESEARCH FOR IMPLEMENTATION.
How can the outcomes of research for implementation be shared across health systems so that the learnings do not remain siloed within a particular disease area or type of intervention? Those working in other disease areas are thinking about this issue, and there is the general belief that working across diseases can increase the value of the research. Can this be monitored and evaluated through funding data?

CONSIDER A FUNDING TARGET FOR RESEARCH FOR IMPLEMENTATION AS PART OF ANY ELIMINATION OR CONTROL PROGRAM.
Review other disease elimination programs and how research for implementation was funded, such as with the Onchocerciasis Elimination Program for the Americas[4] and the Polio Eradication Initiative.[5] Is it possible to identify appropriate levels of investment in this area, and/or to prioritize topics or areas for research for implementation, or to establish targets for percentages of the total research funding that should be devoted to research for implementation? The goal would be to increase funding to the areas with the greatest gaps, not to reallocate from within the current funding pool.

The impact of research for implementation: A series of case studies

The following case studies document examples of research for implementation. This includes improving the usability and uptake of insecticide-treated bednets, artemisinin-based combination therapies, and rapid diagnostic tests—all of which have provided dramatic improvements in expanding access to malaria treatment and reducing the disease burden.

Some of these case studies go back more than ten years to show the impact over time. Others are very recent and illustrate how impact can occur very quickly. And some outline studies under way to provide a view into this field's potential for current challenges, such as rolling out a new vaccine and laying the groundwork for scaling up new-generation insecticides and bednets.

1 Case study 1: Drug packaging increases access to malaria treatment

THE PROBLEM

Malaria drug treatment was changing from one drug taken once a day to a combination treatment with four doses over three days. The packaging was critical: it needed to not only protect the drug from humidity and other damage in challenging environmental conditions but also be acceptable and easily understood by end users. Early studies showed poor comprehension of how to use the drug, and highlighted the risk of people not taking the correct or full course, which could lead to poor outcomes and also contribute to parasite resistance to the drug.

THE APPROACH

Studies were conducted on drug packaging labels and boxes in Malawi and Tanzania in 2001, and the following year on educational materials for health workers in Tanzania. Researchers identified which specific visuals worked to explain dosing and which did not. There was a critical need to help people understand why they needed to take the full course, even when they were feeling better. Malaria is translated as "fever" in some languages, so speakers of those languages tended to believe that once the fever went away, they did not need the treatment anymore. As a result, a lot of attention was paid to how to visually represent the need to finish a course of treatment, with the parasites taking center stage in explaining the crucial WHY question (see Figure 9).

The symbol of the sun was found to represent one day, so three suns meant take the pill for three days in a row. An image of a mosquito was most effectively understood when it was shown next to a person sleeping on a bed; lying on a bed did not signify the person was ill. These critical understandings informed the development of drug blister packs with drawings so that even someone who could not read could understand the dosing instructions. Color-coding helped to differentiate the treatment course required for different body weights.

THE IMPACT

Today, the use of blister packs with illustrative instructions continues (see Figure 10). New drug versions, such as (in 2007) formulations that can be dissolved in water for children, have undergone further packaging design and comprehension testing. This packaging won the 2009 Pharmaceutical Patient-friendly Packaging Design Award "for an innovative solution for what might appear to be a complex unsolvable problem."[34] It has increased the number of people choosing to adhere to the full treatment course, thereby reducing the risk of the parasites developing drug resistance.

This type of research for implementation has redefined treatment strategies for uncomplicated malaria in areas where health care access is poor. It has also allowed for expanded community case management programs by empowering community workers and, most of all, mothers and caregivers, to competently and safely administer lifesaving treatment to children.[35]

Figure 9. **Original research findings on Coartem Dispersible package illustrations.**

PARASITES PREFERRED—SQUARE ONES!

More than 95% of those involved in the testing preferred versions with parasites to explain why to complete treatment.

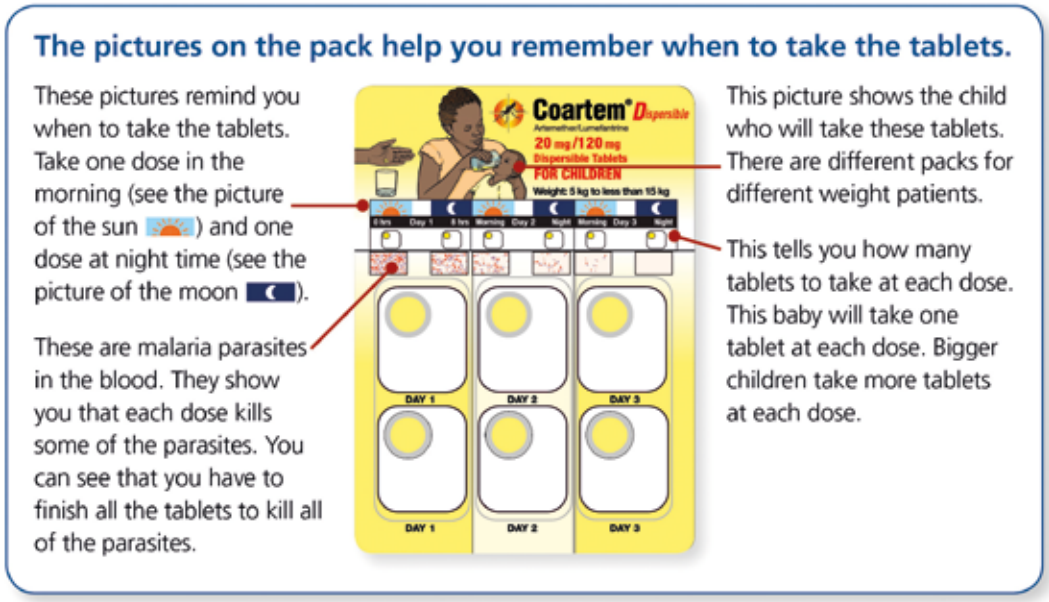
Details make a difference: Round parasites were often misunderstood for pills, balls, etc.

"It is better to give the whole dose, because on day 2 the wadudu are just drunk, and will start to kill again."
- Woman, 29 years, Tanzania

"When you see this, there is no way you fool yourself to think you have cured your child, until you have given the last dose."
- Woman 32 years, Tanzania

Source: Report to Novartis on research findings in 2007 and 2008, courtesy Ane Haaland.

Figure 10. **Explanation of pictorial guides for health workers on the Coartem Dispersible pack.**



Source: Innovation in malaria drug packaging: Coartem and Coartem® Dispersible, International Pharmaceutical Industry, Winter 2009/10 Newsletter. Winter 2009/10:84–88. Available at http://ipimediaworld.com/wp-content/uploads/2012/05/Pages-from-IPI-Volume-2-Issue-1-17.pdf.

PROJECT FUNDERS AND IMPLEMENTERS

The Special Programme for Research and Training in Tropical Diseases based at the World Health Organization initiated the pretesting in 2001. The research was planned and implemented by Ane Haaland, in cooperation with the ministries of health in Kenya, Malawi, Tanzania, and Uganda; Ifakara Health Research and Development Centre in Tanzania; KEMRI Wellcome Trust Research Programme in Kenya; Child Health and Development Centre at Makerere University, Uganda; and the Institute of General Practice and Community Medicine, University of Oslo.

The studies were funded by the pharmaceutical company Novartis and by Medicines for Malaria Venture.

Case study 2: Reducing deaths with bednets

THE PROBLEM

Research conducted in the 1990s showed that using insecticide-treated bednets reduced childhood mortality by up to 33%.[36,37] It was a game-changing finding, but it led to a new question: How could these bednets be scaled up to millions across all the countries at risk for malaria?[38]

In 1999, the United Nations Children's Fund and World Health Organization set the goal of providing 32 million bednets and 320 million bednet treatments per year for the following ten years to protect 80% of African households against malaria.[39]

THE APPROACH

Ensuring access to millions required work on many fronts. A number of research studies provided solutions to the many challenges to scale-up; these included the cost, availability, practicality, and acceptability of bednets in different settings. A few examples illustrate the range of studies that fall under research for implementation.

Helping people understand the value of the bednets was a first critical challenge,[40,41] which included motivating them to get the nets, care for them, and use them. Social research identified the motivators—it was not so much a concern about malaria but about the nuisance of being bitten by mosquitoes. That knowledge was built into educational materials, focused on giving families peace from the mosquitoes.[42]

Even the color and shape of the nets became a research topic.[43,44] Scientists found that the color affected how often nets were washed (more frequent washing reduced the effectiveness of the nets) and even whether they were used.

The insecticide needed to be re-applied to the bednets. In Tanzania, communal "dipping days," when nets were dipped in insecticide, were not working. A study thoroughly tested a set of instructions for safe and effective use of the treatment kits, even where literacy was low, in both urban and rural communities. The instructions were adopted by two social marketing projects. "Dipping it yourself" became the new way to have bednets effectively used.[45]

In The Gambia, the government introduced the National Impregnated Bednet Programme in 1992. A study examined the impact of a variety of activities, such as sensitization sessions, an educational campaign, staff training, and supply ordering and distribution. At the end of five months, overall bednet use was 73% and 83% of the nets had the correct amount of insecticide. More importantly, 25% fewer children between the ages of 1 and 9 died within the first year of intervention.[46]

© WHO/S. Hollyman. A woman hangs a mosquito net in a temporary dwelling in the fields (champka) that she and her husband are clearing to farm, Cambodia.

© WHO/S. Hollyman. A man and his mosquito bednet, United Republic of Tanzania.

Costs for the bednets and the insecticides became a concern. People could not afford them, so how could their provision free of charge be justified?[47,48] Research showed that the economic losses from malaria would be reduced by 37% over a three-year period in Malawi, while in Cameroon, a 9% to 11% reduction in the need for care was expected—justifying free distribution.[49] In The Gambia, research showed that distributing free insecticide through maternal and child health visits would reach the most vulnerable—young children—and that sales through private shops could reach others.[50]

In Latin America, research investigated the role of community and found that the local manufacture of bednets and their sale through village health workers, even in communities with low cash income, were viable ways of increasing bednet coverage.[51]

THE IMPACT

Today, bednets are attributed with saving millions of lives. Since 2000, 663 million cases of malaria have been prevented due to the combined effect of all approaches, with bednets contributing to 68% of the impact.[52]

Research for implementation—using a broad range of approaches encompassing implementation, operational, social, and economic research—took what was identified as a very effective tool and leapfrogged over deep systemic and logistical challenges to get it into the homes of millions of the most vulnerable across the world. The evidence generated by research for implementation was critical to mobilizing the funding for free bednets, expanding distribution schemes, generating investments in the diversity of products now available, and increasing capacity to continue these efforts at all levels.

© WHO. Community members build low-cost window and door screens in Colombia.

Case study 3: Two approaches to managing fever, a symptom shared by three diseases—malaria, pneumonia, and diarrhea

Using community health care workers

THE PROBLEM

More than one-third of all deaths in children younger than 5 years in Africa are due to malaria, pneumonia, or diarrhea.[1] Fever is often a symptom of all three, so accurate diagnosis and the correct treatment are critical. However, diagnosis and treatment have not been provided consistently and properly.

THE APPROACH

Integrated community case management of childhood diseases was recommended in 2012 by the World Health Organization and United Nations Children's Fund as an essential health service for children who live in hard-to-reach areas. The Rapid Access Expansion Programme trained almost 8,500 community health workers in five sub-Saharan African countries to manage childhood cases of malaria, pneumonia, and diarrhea, and underlying conditions like malnutrition.

Key elements of the program included recruitment of educated workers who lived in remote communities, worker training and regular supervision, sustained supply of high-quality medicines, and community support and engagement.

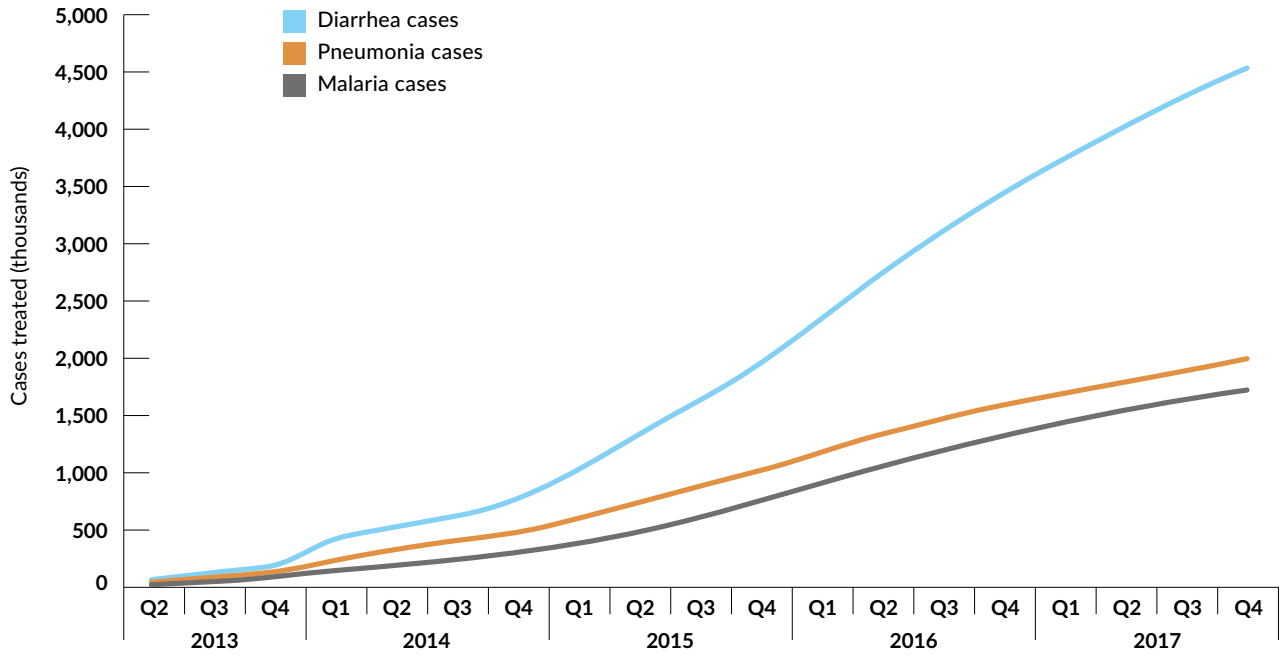
THE IMPACT

More than 8.2 million children were diagnosed and treated for pneumonia, diarrhea, and malaria (Figure 11). Each country also updated its national policies to facilitate the scale-up of integrated community case management of childhood diseases. The Democratic Republic of the Congo, Niger, and Nigeria are planning to expand these programs nationally.

PROJECT FUNDERS AND IMPLEMENTERS

The project was funded by the government of Canada and managed by the World Health Organization's Global Malaria Programme between 2012 and 2017. Ministries of health of the Democratic Republic of the Congo, Malawi, Mozambique, Niger, and Nigeria were involved. Nongovernmental organizations supported the implementation. Panels of external experts provided strategic guidance and review.

Figure 11. **Aggregate malaria, pneumonia, and diarrhea cases treated by community health workers through the Rapid Access Expansion Programme (2013 to 2017).**



Source: Rapid Access Expansion Programme Performance Management Framework, as reported by program grantees.

Using private drug shops

THE PROBLEM

Nigeria has one of the highest mortality rates among children under 5 years of age in the world, at 109 deaths per 100,000 live births.[1] Malaria, diarrhea, and pneumonia are among the leading causes, accounting for 40% of all child deaths in Nigeria. Diagnostic tools and treatments exist, but few children are treated appropriately. For example, just 18% of children diagnosed with malaria received the recommended treatment (ACTs).[53]

THE APPROACH

When a child has a fever, 34% of households seek treatment from private drug shops, called patent and proprietary vendors. However, few of the drug shop workers know how to appropriately manage the common childhood illnesses of malaria, diarrhea, and pneumonia. A quasi-experimental, controlled study was conducted in which more than 400 shops and 2,500 households were surveyed to test whether providing training and supervision to these community-based private providers could improve diagnosis and treatment of these common childhood illnesses on a population basis.

THE IMPACT

At drug shops where staff received the training and supervision, appropriate diagnosis and treatment for malaria dramatically improved, from 16% to 88%. However, only 29% of the drug shops in the study areas received the interventions; the majority of drug shops were not registered with the local regulatory body and were excluded from participation. Due to the low coverage of the intervention, a population-level impact was not achieved. Expanding shop registration, along with training, could lead to improved intervention coverage and quality of care.

The results and recommendations from the study are being used by Nigeria's Federal Ministry of Health, the US President's Malaria Initiative (PMI), and other implementing partners to guide the scaling of future training and supervision interventions for private drug shop owners.

PROJECT FUNDERS AND IMPLEMENTERS

The project was funded by the US Agency for International Development and PMI. The project was implemented through a partnership that included MalariaCare (a global PMI-funded project led by PATH over the five years from 2012 to 2017) and the Expanded Social Marketing Project in Nigeria (led by Society for Family Health), in close collaboration with the Federal Ministry of Health, the National Malaria Elimination Programme, and the Ebonyi State Ministry of Health. The Society for Family Health/Expanded Social Marketing Project was responsible for implementation of the study; MalariaCare provided technical assistance and led the evaluation.

© PATH/Kachi Amajor. A canvasser with the Expanded Social Marketing Project in Nigeria conducting routine monitoring at a private drug shop in Ikwo, Ebonyi State.

Case study 4: Ensuring appropriate health care use during malaria vaccine introduction

THE PROBLEM

The first malaria vaccine, RTS,S, will soon be rolled out in parts of Ghana, Kenya, and Malawi. There are a range of factors that could hurt or help uptake of the vaccine. It is unknown whether the vaccine will impact the use of other important malaria interventions—such as bednets, diagnostics, and treatment drugs—or other immunizations.

THE APPROACH

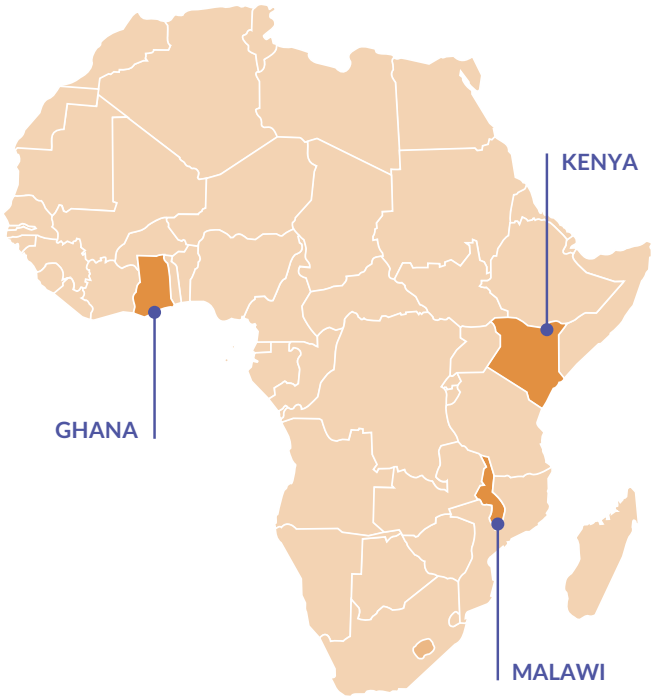
An intensive health care utilization study is one of the evaluation components comprising the Malaria Vaccine Implementation Programme. The Malaria Vaccine Implementation Programme is a country-led, World Health Organization–coordinated assessment of the feasibility, impact, and safety of RTS,S in routine use. Relying heavily on interviews with primary caregivers, health care providers, and other community members, the health care utilization study will use proven qualitative methods over several years to document adoption of and adherence to the recommended four-dose RTS,S schedule, malaria prevention behaviors, malaria care-seeking for febrile illness in children, and non-RTS,S immunization-seeking behavior.

THE IMPACT

Approximately 360,000 children will receive the RTS,S vaccine annually, across the three countries leading the pilot introduction. While the health care utilization study will be conducted in a small subset of the communities where RTS,S will be introduced, its research findings will inform health service, communications, and related strategies and practices across the implementation program.

PROJECT FUNDERS AND IMPLEMENTERS

The project is funded by the World Health Organization, with support from Gavi, the Vaccine Alliance; The Global Fund to Fight AIDS, Tuberculosis and Malaria; and Unitaid. PATH will lead the health care utilization study, working in collaboration with partners in Ghana, Kenya, and Malawi.



© PATH and Jordan Gantz Creative. Samuel Oduor is a community relations officer at the Kenya Medical Research Institute-Walter Reed Project in Kombewa, Kenya. He is shown here with his son.

@PATH/Doune Porter, Healthcare clinic in Sierra Leone.

Case study 5: Reaching malaria elimination through strengthened national research capacity

THE PROBLEM

Southern African countries are in the initial phases of malaria elimination, but getting to the very end and sustaining zero cases requires more discrete, localized solutions. Local capacity to identify the challenges, as well as to investigate and implement the solutions, is needed.

THE APPROACH

The Structured Operational Research and Training IniTiative (SORT IT) provided training in operational research to malaria control officers in Botswana, Namibia, South Africa, and Swaziland. In line with the *Global Technical Strategy for Malaria 2016–2030*,[2] senior malaria staff and academics from the four countries identified their national implementation challenges. Together with in-country and regional universities, their ministries of health, World Health Organization country offices, international organizations working in the countries and/or regionally, nongovernmental organizations, and private companies, these senior malaria staff and academics designed and conducted retrospective research studies during their training to address a broad range of issues. All studies used routinely collected malaria program data.

© PATH/Eric Becker. Family in Kenya with a bednet.

THE IMPACT

In Botswana, while larval control as a malaria intervention is used by at least 48 countries globally, its potential had not been studied or implemented in Botswana. This study showed that larviciding did indeed reduce the numbers of mosquito larvae and reduce the numbers of malaria cases in Botswana.

In Namibia, a study found that the main reason for households not having their walls sprayed with insecticide paint (indoor residual spraying, or IRS) was that residents were not at home during spraying times or that spray operators did not visit the households. Solutions to these problems included increasing community engagement and awareness of when spray operations were offered, and better targeting the highest risk areas.

In South Africa, what was once considered a minor malaria vector, the *Anopheles merus*, has been increasing transmission of malaria along the Tanzanian coast and Kenya, Madagascar and Mozambique. This study mapped the mosquito breeding sites in South Africa's Ehlanzeni District over a nine-year period; it found increasing numbers of this species, which should trigger additional, targeted vector control methods.

In Swaziland, although malaria incidence has decreased by 76% since 2009, the majority of new malaria cases result from limited use of prevention methods. Studies examined for the first time why the country had low levels of all three major preventive tools: long-lasting insecticide-treated nets, IRS, and the use of preventive medications by those traveling to malaria-endemic areas. The study provided evidence that helps policymakers and implementers see the steps needed for elimination, including distributing bednets beyond at-risk areas, addressing the cost and acceptability issues raised regarding IRS, and making chemoprophylaxis drugs more available and accessible to mobile populations, as well as screening and follow-up mandatory for all travelers from malaria-endemic countries.

Overall, this series of studies has led to actions being taken at the national level to address these obstacles to malaria elimination. The studies also show how training can lead to this type of research being sustainably conducted within normal, ongoing budgets of national disease control programs.

PROJECT FUNDERS AND IMPLEMENTERS

SORT IT is a global partnership led by TDR, the Special Programme for Research and Training in Tropical Diseases based at WHO. SORT IT includes a teaching component that was developed jointly by the International Union Against Tuberculosis and Lung Disease (The Union) and Médecins Sans Frontières. With a focus on those southern African countries that have the goal of eliminating malaria within the next decade, a specific SORT IT program was implemented by TDR in partnership with the WHO Regional Office for Africa; the WHO Global Malaria Programme; the Operational Research Unit (LuxOR), Médecins Sans Frontières, Brussels Operational Center, Luxembourg; the Centre for Operational Research, The Union, France; and the University of Nairobi, Kenya. Funding was provided by TDR, the WHO Global Malaria Programme, and the Bill & Melinda Gates Foundation.

Case study 6: Increasing access to new insecticidal products

THE PROBLEM

More than 80% of the reduction in malaria prevalence seen in Africa since 2000 has been attributed to vector control interventions—specifically, the indoor residual spraying (IRS) of insecticides inside homes and the use of insecticide-treated nets.[53] Unfortunately, insecticide resistance is spreading and threatening this control.[53] New insecticide products need to be developed and used.[55,56,57] Several third-generation indoor residual spraying (3GIRS) products are currently prequalified by the World Health Organization (WHO) for malaria vector control. However, the new products are more expensive; as a result, uptake has been slow, overall IRS coverage is low, and market stability remains a concern.

THE APPROACH

The Next Generation IRS (NgenIRS) project is a market-shaping initiative to expand the use of new IRS products in Africa. The project is designed to overcome five main conditions that create a challenging market: (1) limited demand; (2) market instability; (3) limited competition; (4) high prices; and (5) absence of a strong evidence base that shows cost-effectiveness and impact.

The project provides copayments that reduce prices for national malaria control programs, thereby allowing them to increase the volume of product they procure. In addition, the project provides consolidated forecasts and volume guarantees to manufacturers to address volatility in the market, and the manufacturers have reduced prices in response to the greater certainty of demand.

THE IMPACT

Malaria programs and implementation partners have been able to procure more than 4 million units of 3GIRS as prices dropped from $23.50 per unit to $15.00 per unit. More than 1 million additional units have been procured by partners outside of the co-payment mechanism at a significant discount, in return for volume guarantees to manufacturers; this shows the extended impact of the market-shaping intervention.

© Innovative Vector Control Consortium, 2016. A malaria spray operator in a village in Rwanda talking to household members before spraying their home.

Programs increased coverage, protecting an estimated 15 million more people than would have been possible if they were paying full price. The improved market has supported WHO prequalification listing of new 3GIRS products; a second insecticide was included in the project in 2018 after prequalification listing in 2017. Two additional products are currently under advanced WHO evaluation. The inclusion of a second 3GIRS product created needed competition in the marketplace; it has also allowed malaria programs to invest in subnational rotation as part of their insecticide-resistance management strategies.

The evidence thus far from observational analyses in Ghana, Mali, and Zambia, along with a randomized controlled trial in Mozambique, have shown a 22% to 40% reduction in malaria cases attributed to IRS. Further outcomes of these studies will be disseminated through journal publications, conference presentations, and workshops with key country- and global-level stakeholders in 2018 and 2019.

© Innovative Vector Control Consortium, 2018. Spraying the walls of a house in a village in Ashanti Region of Ghana to control mosquito vector populations and minimize contact between infected mosquitoes and people.

PROJECT FUNDERS AND IMPLEMENTERS

NgenIRS country partners include Benin, Burkina Faso, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Mali, Mozambique, Rwanda, Tanzania/Zanzibar, Uganda, Zambia, and Zimbabwe. Unitaid and the Innovative Vector Control Consortium have partnered with the US President's Malaria Initiative, Abt Associates, PATH, and The Global Fund to Fight AIDS, Tuberculosis and Malaria to work with industry and malaria programs in Africa to increase the uptake of 3GIRS products. The project is funded by Unitaid.

Appendices

Appendix 1. Research for implementation definitions

(Adapted from *TDR Strategy 2018–2023* [57] and "Defining research to improve health systems"[59])

In public health, research for implementation is used to understand the barriers that prevent access to lifesaving tools and to identify ways of removing those barriers. The research methodologies and tools that are used vary according to the type of problem to be addressed. For the purpose of this survey, three broad categories were used (Table 4):

OPERATIONAL RESEARCH is often carried out using data that are routinely collected by disease control programs. Operational research is done to provide ways to improve program operations and deliver more effective, efficient, and equitable care. Operational research is predominantly of use to health care providers. It tends to address a local problem, taking into account the particular context in which it occurs, with the goal of enhancing the quality, effectiveness, or coverage of the specific program being studied.

IMPLEMENTATION RESEARCH is the systematic approach to understanding and addressing barriers to effective and high-quality implementation of health interventions, strategies, and policies. It is driven by a range of stakeholders, such as health care practitioners, policymakers, researchers, and community members, all working together to frame the research questions based on local needs, conduct the study, and implement the results.

HEALTH SYSTEMS RESEARCH studies the health system as a whole (or one of its building blocks). It can address a wide range of questions, from health financing, governance, and policy to problems with structuring, planning, management, human resources, service delivery, referral, and quality of care in the public and private sectors. It is often highly multidisciplinary, with a strong emphasis on social sciences, economics, and anthropological investigations—for example, on community perceptions of health care. Health systems research is of most use to those who manage or need to make policy for the health system, generally being more amenable to adaptation and application in other contexts.

Table 4. **Examples of research questions for the three research for implementation domains.**[59]

RESEARCH DOMAIN	RESEARCH QUESTION
Operational	Can the "communication for behavioural impact" strategy improve compliance with mass drug administration for lymphatic filariasis elimination in Tamil Nadu, India?
	Which locations should be targeted for delivering HIV prevention services in Kawempe District, Uganda?
	Which of the current antiretroviral therapy payment strategies in use in Nairobi should be retained for the new, integrated program?
	Should the sleeping sickness program in Equator Nord Province, Democratic Republic of the Congo change its first-line drug?
Implementation	How to deliver ivermectin for onchocerciasis control and ensure sustained high treatment coverage in isolated rural communities?
	How to improve access to vaccination among children who are currently not reached by immunization services?
	How to implement antenatal syphilis screening — one-stop versus conventional service?
	How to effectively implement a new intervention package for kala azar elimination in the India subcontinent?
Health system	To what extent do health services reach the poor? How can this be improved?
	Should fees be charged to clients who use health centers for curative services?
	How effective are different policies for attracting nurses to rural areas?
	What has been the impact of the rapid scale-up of HIV programs on fragile health systems?

Source: Remme JHF, Adam T, Becerra-Posada F, et al. Defining research to improve health systems. PLOS Medicine. 2010;7(11): e1001000. doi: http://doi.org/10.1371/journal.pmed.1001000.

Appendix 2. List of "research for implementation" survey participants

Policy Cures Research sent a survey on research for implementation to the 26 organizations below, which had been identified as donors or recipients of funding for this type of research. Some of these organizations comprised several agencies; for the sake of clarity, the names of the individual agencies are listed here. Of the 26 organizations surveyed, 69% responded to the qualitative survey and 77% to the quantitative survey (either directly or by providing access to a database).

ORGANIZATION	QUALITATIVE SURVEY RESPONSE	FUNDING DATA PROVIDED
African Network for Drugs and Diagnostics Innovation	No	No
Australian Army Malaria Institute**	Yes	No
Australian Department of Foreign Affairs and Trade	Yes	Yes
Bill & Melinda Gates Foundation*	No	Yes
Canadian Institutes of Health Research	Yes	Yes
Drugs for Neglected Diseases *initiative*	No	Yes
European & Developing Countries Clinical Trials Partnership*	Yes	Yes
European Commission*	Yes	Yes
Fogarty International Center*	Yes	Yes
The Global Fund to Fight AIDS, Tuberculosis and Malaria**	Yes	No
Grand Challenges Canada	Yes	Yes
Innovative Vector Control Consortium	No	No
Canadian International Development Research Centre	No	No
Medicines for Malaria Venture*	Yes	Yes
Médecins Sans Frontières**	No	No
PATH	Yes	Yes
The Wellcome Trust	Yes	Yes
UK Department for International Development	Yes	Yes
UK Medical Research Council	Yes	Yes
Unitaid*	Yes	Yes
US Agency for International Development (including the US President's Malaria Initiative)*	Yes	Yes
US Centers for Disease Control and Prevention*	Yes	Yes
US Department of Defense*	No	Yes
US National Institutes of Health*	No	Yes
World Health Organization Global Malaria Programme	Yes	Yes
World Health Organization Special Programme for Research and Training in Tropical Diseases	Yes	Yes

** Quantitative dataset already available to Policy Cures Research.*
*** Unable to provide information at all (due to systems or confidentiality issues).*

Appendix 3. Research for implementation qualitative survey tool

PART A: YOUR ORGANIZATION'S APPROACH TO RESEARCH FOR IMPLEMENTATION

1. Does your organization have a strategy or policy relating to funding research for implementation?

   ☐ Yes (go to Question 2)

   ☐ No (go to Question 4)

2. How does your funding strategy/policy encompass research for implementation?

   ☐ It is explicitly included

   ☐ It is explicitly excluded

   ☐ It is implicitly included as part of a broader range of research activities

3. If your strategy/policy includes research for implementation, is this specifically for malaria?

   ☐ Yes

   ☐ No

4. Please rank, in order of priority for your organization, the following research areas:

Basic research	
Early-stage product development	
Late-stage product development	
Research for implementation	

5. Have the priorities in Question 4 changed since 2014? If so, please describe how.

6. Does your organization have a target amount (or percentage) within the research budget to fund research for implementation? If so, what is the value/percentage?

PART B: DEFINING RESEARCH FOR IMPLEMENTATION

7. Does your organization have (or use) any particular definitions of research for implementation? If so, please either include/link to these below, or attach relevant documents.

8. Whether or not you use specific definitions, do you agree with a taxonomy of "research for implementation" that includes (and separates) the fields of operational research, implementation research, and health system research? Please provide comments.

9. Please provide feedback on the following definitionsa:

Score out of 5, where 0 is very poor and 5 is excellent.

Definition	Score out of 5	Comments
Operational research is often carried out using data routinely collected by disease control programmes, to provide ways of improving programme operations, and deliver more effective, efficient and equitable care. Operational research is predominantly of use to health care providers. It tends to address a local problem, taking into account the particular context in which it occurs, with the goal of enhancing the quality, effectiveness or coverage of the specific program being studied.		
Implementation research is the systematic approach to understanding and addressing barriers to effective and quality implementation of health interventions, strategies and policies. It is driven by a range of stakeholders, such as healthcare practitioners, policy makers, researchers and community members, all working together to frame the research questions based on local needs, conducting the study and implementing the results.		
Health system research studies the health system as a whole (or one of its building blocks). It can address a wide range of questions, from health financing, governance, and policy to problems with structuring, planning, management, human resources, service delivery, referral, and quality of care in the public and private sector. It is often highly multidisciplinary, with a strong emphasis on social sciences, economics, and anthropological investigations, for example on community perceptions of health care. Health systems research is of most use to those who manage or need to make policy for the health system, generally being more amenable to adaptation and application in other contexts.		

[a]*World Health Organization (WHO). TDR Strategy 2018–2023: Building the Science of Solutions. Geneva: WHO; 2017. Available at http://www.who.int/tdr/publications/about-tdr/strategy/strategy-2018-23/en/.*

PART C: YOUR ORGANIZATION'S FUNDING OF RESEARCH FOR IMPLEMENTATION

10. In broad terms, how is your research for implementation investment divided?

Malaria alone		%
Malaria in combination with other diseases / health areas (e.g. HIV/AIDS, TB, maternal and child health, respiratory diseases, diarrheal diseases)		%
Other diseases / health areas (not malaria)		%
Comprising (if known)	Disease 1:	%
	Disease 2:	%
	Disease 3:	%
	Disease 4:	%
	Disease 5:	%

11. When did your organization begin funding malaria research for implementation? And (if known) why did the organization decide to begin this?

12. How does your organization fund malaria research for implementation?

- ☐ Open calls
- ☐ Targeted calls
- ☐ Other (please describe)

13. If your organization funds targeted calls, please provide more details on how these calls are targeted. For example, are they specifically focused on research for implementation, or do they also include other types of research? Are they restricted to malaria only, or do they include multiple diseases? Are there geographic restrictions (e.g., countries or regions)?

14. If your organization provides financial support for training in research for implementation, please provide details of this funding for the period between 2014 and 2016.

Please check all relevant boxes

- ☐ Master of science
- ☐ Doctor of philosophy, or PhD
- ☐ Training courses
- ☐ Other (please specify)

Is this funding malaria-specific?

- ☐ Yes
- ☐ No

Total financial support for training in research and implementation:

	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016
All Diseases			
Maleria Only			

Please specify currency

15. Are the results of your funded research for implementation in malaria made publicly available? If so, how? For example, this could be through an annual report or publication that your organization publishes, or through use of an online repository, or through requirements to grantees regarding their publication/posting of operational research/implementation research results/findings.

- ☐ Yes
- ☐ No

Appendix 4. Recipient countries of malaria research and development funding (2007 through 2016)

AFRICA
Algeria
Angola
Benin
Botswana
Burkina Faso
Cameroon
Congo
Côte D'Ivoire (Ivory Coast)
Democratic Republic of the Congo
Ethiopia
Gabon
The Gambia
Ghana
Guinea
Guinea-Bissau
Kenya
Kingdom of eSwatini
Madagascar
Malawi
Mali
Mauritius
Mozambique
Namibia
Nigeria
Rwanda
Senegal
Sierra Leone
South Africa
Sudan
Tanzania
Uganda
Zambia
Zimbabwe

EUROPE
Austria
Belgium
Denmark
Finland
France
Germany
Greece
Ireland
Italy
Luxembourg
Netherlands
Norway
Portugal
Spain
Slovakia
Sweden
Switzerland
United Kingdom

ASIA
Bangladesh
Cambodia
China (including Hong Kong)
India
Indonesia
Israel
Japan
Malaysia
Myanmar
Nepal
Philippines
Singapore
South Korea
Thailand
Vietnam

OCEANIA
Australia
New Zealand
Papua New Guinea
Solomon Islands

CENTRAL AND SOUTH AMERICA
Argentina
Brazil
Chile
Colombia
Guatemala
Mexico
Nicaragua
Panama
Peru
Venezuela

NORTH AMERICA
Canada
United States of America

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Bridging the gaps in malaria R&D

An analysis of funding—from basic research and product development to research for implementation

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