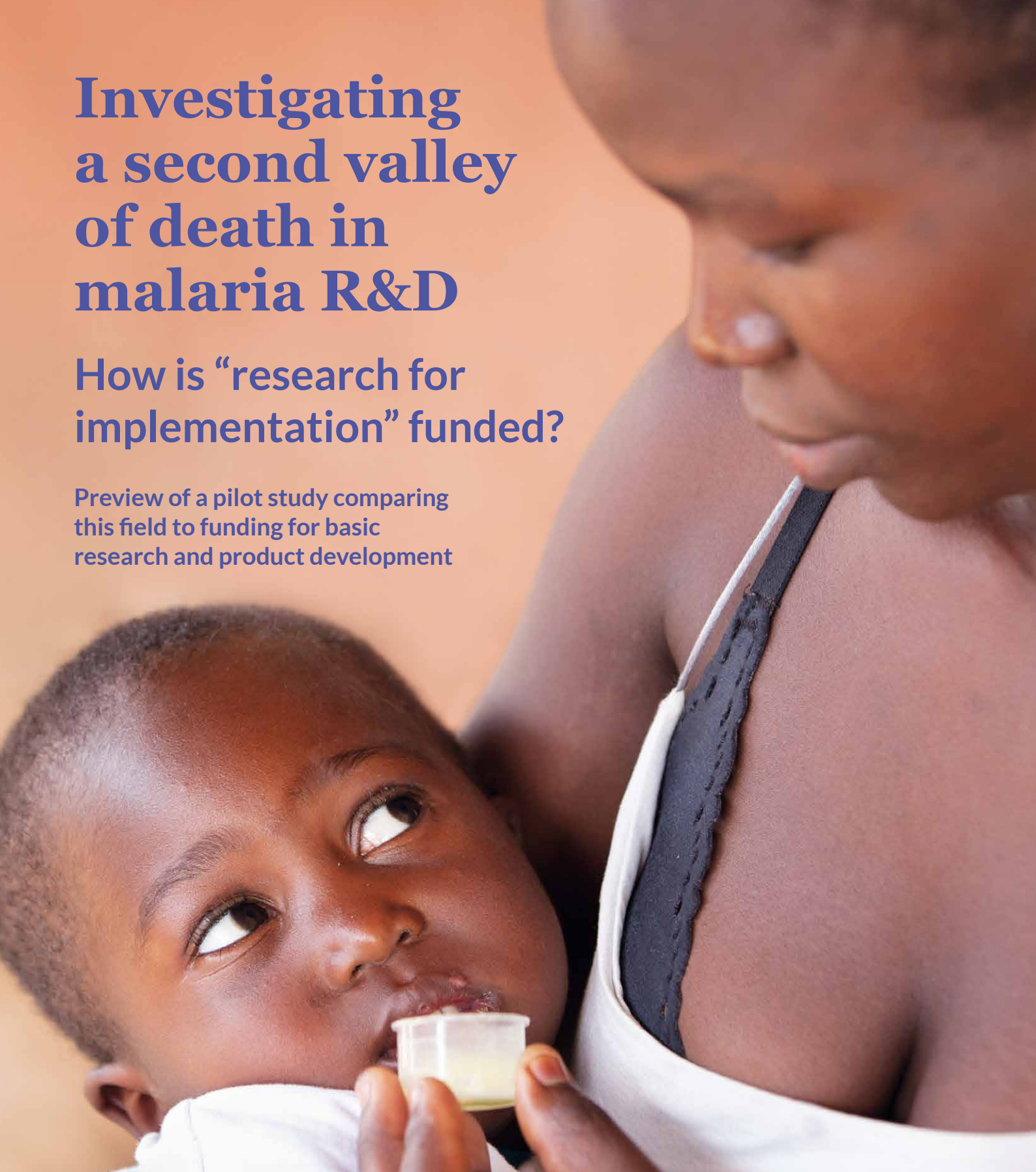


Investigating a second valley of death in malaria R&D

How is “research for implementation” funded?

Preview of a pilot study comparing
this field to funding for basic
research and product development



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Executive summary

After a decade of progress in reducing the burden of malaria disease and death, the total number of malaria cases rose in 2016 by more than five million over the previous year.¹ Increases in malaria burden were reported from countries in all regions of the World Health Organization (WHO) between 2014 and 2016.

As new tools have become available, there are growing challenges to the health care systems to ensure 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.

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

Today the question is whether there is enough funding 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. Is there a second valley of death?

This report covers initial findings from a pilot study on malaria research for implementation funding, which includes implementation research, operational research, and health systems research. For the first time, these data were combined with what has already been reported for basic research and product development. Also, four brief case studies are provided at the end of this report.

A final report with more data from funders will be published in June, 2018, but in the meantime, the initial findings from about half of the 26 organizations surveyed have highlighted challenges and changes that need to be made in order to provide a complete picture.

Donors and recipients need to improve their monitoring systems to better track the funding flows; there are significant challenges to getting complete data. However, this can only be done effectively when there is a clearer consensus around categories and definitions, and more complete and regular monitoring of the funding.

RECOMMENDATIONS

The following recommendations for policymakers and malaria research organizations are already clear from this pilot study:

1. **AGREE ON RESEARCH FOR IMPLEMENTATION DEFINITIONS.**
2. **IMPROVE TRACKING OF RESEARCH FOR IMPLEMENTATION FUNDING AT THE INSTITUTIONAL, NATIONAL, AND SUBNATIONAL LEVELS, INCLUDING IN LOW- AND MIDDLE-INCOME COUNTRIES.**
3. **TRACK FUNDING FOR TRAINING AND CAPACITY BUILDING FOR RESEARCH FOR IMPLEMENTATION.**
4. **CONTINUE TO BUILD THE DATABASE ON FUNDING OF RESEARCH FOR IMPLEMENTATION.**

To provide more specific examples of this field of research, four brief case studies are provided at the end of this report. They include past studies improving the usability and uptake of three products—insecticide-treated bednets, artemisinin-combination treatments (ACTs) and rapid diagnostic tests—and a future study related to the pilot implementation of the first malaria vaccine.

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. This is research focused on the systems to implement products and services into health care practices (definitions and examples can be found in Annex 1).

The systems and practices required to increase access to, and use of, malaria products and services are receiving increased attention through the World Health Organization’s Global Technical Strategy,² the research agenda from the Malaria Eradication Research Agenda (malERA) Consultative Group,³ the Roll Back Malaria plan, Action and Investment to defeat Malaria 2016-2030 (AIM),⁴ and the United Nations Sustainable Development Goals.⁵ To effectively monitor and evaluate investment impacts, data on funding levels for research for implementation are needed.

Understanding this funding has become important because new products are not being fully used. There are regulatory and market issues, and product implementation is slow with significant gaps in coverage. Malaria cases are on the rise, but not uniformly. Research for implementation can provide greater understanding of these challenges. However, data on funding for this field have not been readily available to determine if this type of research simply was not being done, not being funded at appropriate levels, or was deemed too difficult to track.

To address this information gap, a new pilot survey was conducted in March 2018 by Policy Cures Research, specifically on funding of research for implementation for the three years between 2014 and 2016. Twenty-six organizations were asked to provide data on disbursements in this area (a full list is in Appendix 2), with 54% of them responding.

The survey also queried the strength of organizations’ commitments to research for implementation, their perceptions of the utility of the research, and how they defined it, with 65% responding.

To provide more specific examples of this field of research, four brief case studies are provided at the end of this report. They include past studies improving the usability and uptake of insecticide-treated bednets, artemisinin-combination treatments, and rapid diagnostic tests; and a planned study that will support implementation of the first malaria vaccine.

Background on malaria cases and recent trends

After a decade of progress in reducing the burden of malaria disease and death, the total number of malaria cases rose in 2016 by five million over the previous year, with the WHO regions of the Americas and Africa accounting for nearly 70% of the increases of more than 20%.⁶ Fifteen African countries carried 80% of the global malaria burden.

Increases were documented in high- and low-burden countries: of the 21 countries that have been on track to eliminate malaria by 2020, five countries reported an increase of more than 100 cases in 2016 compared with 2015.¹

WHO Director-General Dr Tedros Adhanom Ghebreyesus said: "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

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 utilization of drugs and technologies.⁷

There is growing recognition of a second valley of death which affects products that have been developed for diseases of poverty like malaria—how can these products reach the people who need them? Research for implementation can bridge this valley and translate efficacious products into effective public health strategies. The research can ensure that the investments already made are not lost and build upon them, improving control and supporting disease elimination.

Overall summary of findings

The following summarizes funding trends between 2007 and 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 between 2014 and 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 US\$656 million in 2009, and has remained at a steady level since then—between \$540 million to \$600 million per year.

Funding of research for implementation increased from \$75 million in 2014 to \$86 million in 2016, bringing total malaria research and development (R&D) funding (including basic research, product development, and research for implementation) to \$652 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 National Institutes of Health [NIH], and industry) collectively contributing 75% of total investment.

Funding data has been adjusted for inflation and converted to the equivalent of 2016 US dollars (US\$) to eliminate artefactual effects caused by inflation and exchange rate fluctuations, allowing accurate comparison of annual changes. Due to these adjustments, historical G-FINDER data in tables and figures in this report will differ to data in previous G-FINDER reports.

Figure 1a. Largest funders of malaria basic research and product development. (US\$ million, adjusted to 2016 dollars to account for inflation)

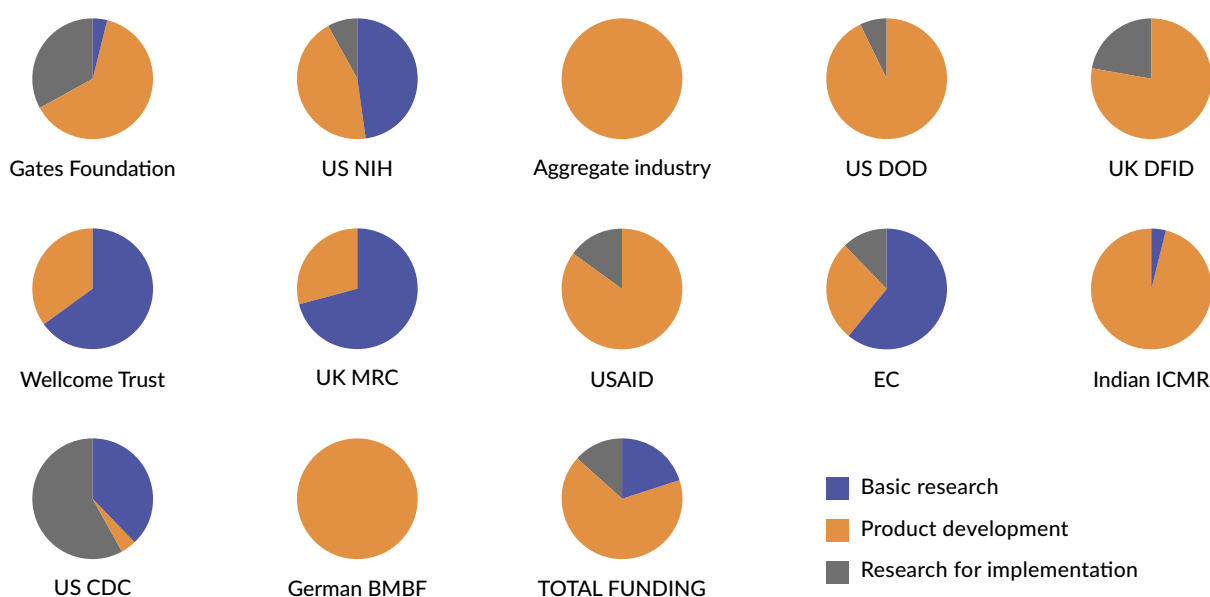
Funder	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Gates Foundation	146	206	215	103	170	137	127	178	155	176
US NIH	99	123	136	156	144	177	144	161	168	174
Aggregate industry	83	85	96	115	93	106	76	118	142	137
US DOD	39	36	44	27	21	11	23	19	30	31
UK DFID	5.3	4.2	6.6	25	19	6.0	27	20	21	17
Wellcome Trust	24	23	24	29	27	27	24	22	17	14
UK MRC	16	17	18	20	17	16	16	14	9.2	11
USAID	11	10	9.6	10	9.1	12	6.6	9.0	11	10
EC	34	32	28	23	25	19	26	26	31	9.4
Indian ICMR		10	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	2.9	8.2
German BMBF	0.8	0.6	1.6	1.6	2.0	2.6	2.8	3.4	5.8	6.9
Subtotal of basic research and product development funding	518	606	656	581	600	587	544	562	567	566
Total funding	518	606	656	581	600	587	544	638	647	652

■ Funding organization did not participate in the G-FINDER survey for this year. Any contributions listed are based on data reported by recipients and so may be incomplete.

■ Funding TOTALS include data from the pilot survey on research for implementation during 2014-2016 only.

Note: Funder acronyms listed at bottom of page.

Figure 1b. Relative allocations of funding, by funder, by category of malaria basic research and product development (2016).



EC = European Commission; German BMBF = German Federal Ministry of Education and Research; Indian ICMR = Indian Council of Medical Research; UK DFID = UK Department for International Development; UK MRC = UK Medical Research Council; USAID = US Agency for International Development; US CDC = US Centers for Disease Control and Prevention; US DOD = US Department of Defense; US NIH = US National Institutes of Health.

PHILANTHROPIC FUNDERS

The Gates Foundation has been a major contributor, providing 85% of philanthropic funding for basic research and product development over the past ten years (\$1,461 million), and \$152 million for research for implementation over the three years 2014–2016. Its share of funding for basic research and product development has fallen from a peak of 24% in 2008 to an average of 21% over the last three years, 2014–2016. In the absence of more complete data, it is not possible to draw any conclusions regarding the foundation's share of research for implementation funding.

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 over half of this from the NIH. Funding by the 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

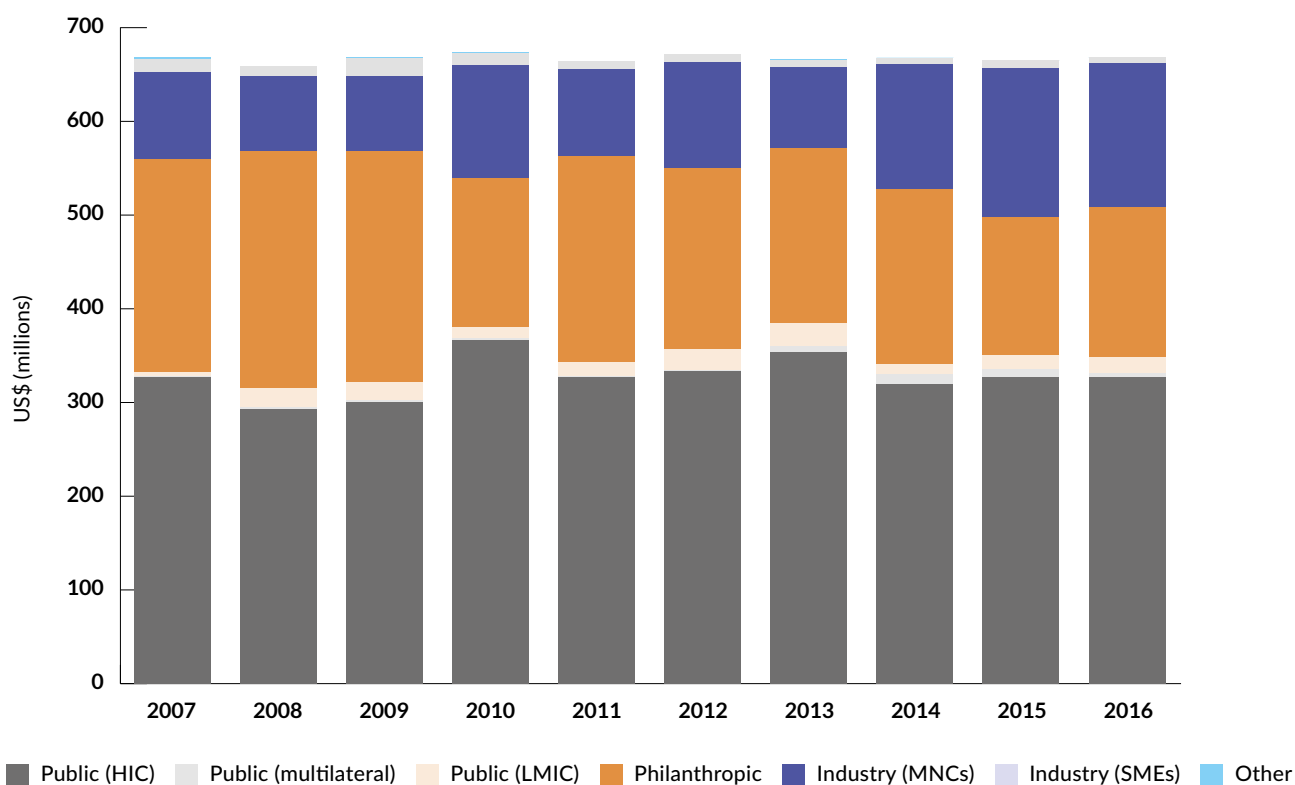
Only two government aid agencies were among the top 12 funders—the UK Department for International Development (DFID) and US Agency for International Development (USAID)—both of which focused on funding product development (drugs and vaccines, respectively).

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 since 2008), and the Brazilian Support Foundation for Research in the State of Amazonas (Fundação de Amparo a Pesquisa do Estado do Amazonas) in 2013 (\$8.3 million).

INDUSTRY FUNDERS

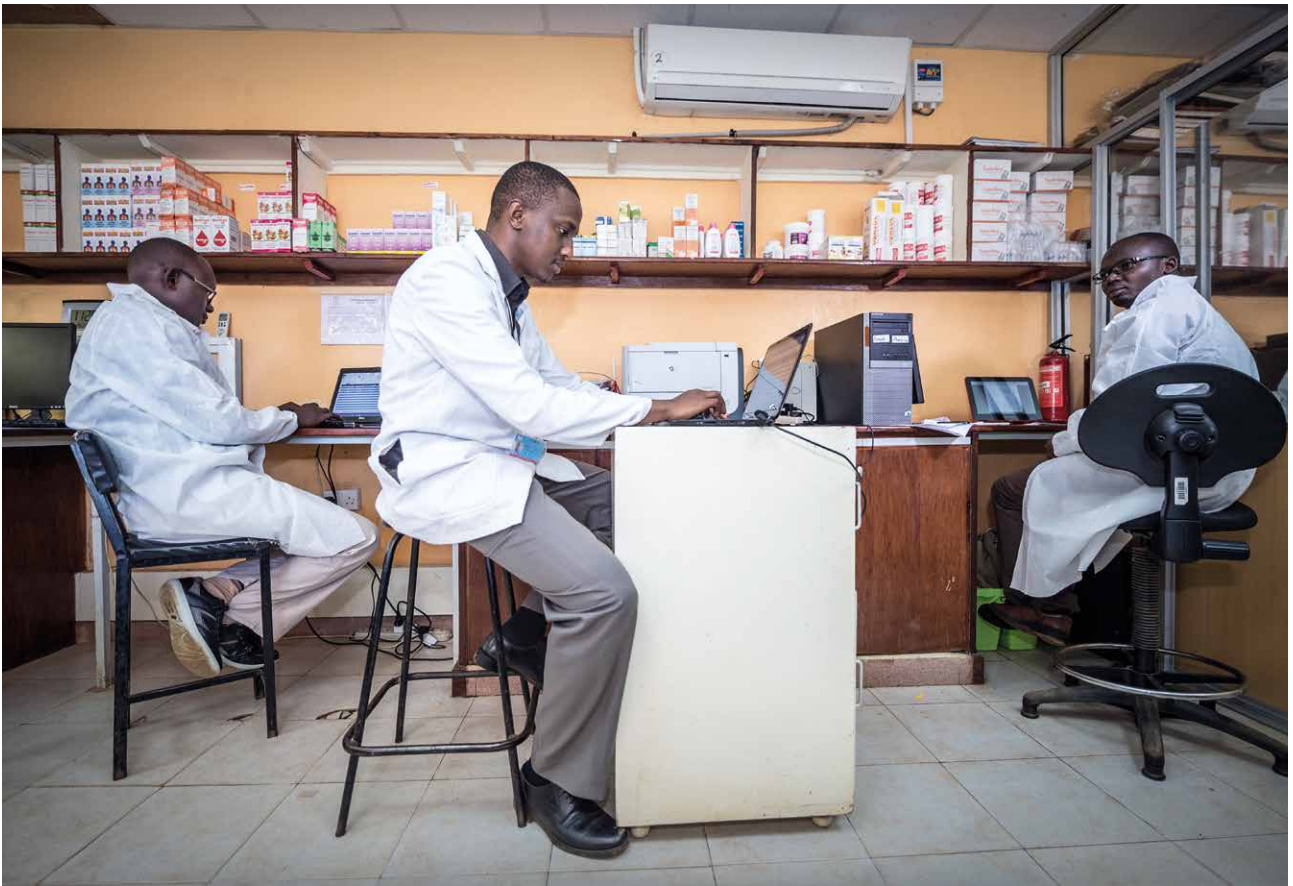
In 2015, funding from industry surpassed philanthropic funding for basic research and product development for the first time in the last decade, due mainly to industry's investment in drug development.

Figure 2. Malaria basic research and product development funding by sector.



Note: Does not include research for implementation

HIC = high-income country; LMIC = low- and middle-income country; MNCs = multinational corporations; SMEs = small- and medium-sized enterprises.



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Where the funding is going

Changes in malaria basic research and product development have largely reflected the progression of the overall pipeline, with a spike in vaccine funding in 2008–2009 (related to grants for Phase 3 trials of the RTS,S malaria vaccine candidate) and a subsequent sharp drop. Reductions in vaccine investment have driven research funding for the *Plasmodium falciparum* species down to the second lowest level since 2009 (44% of all malaria basic research and product development funding).

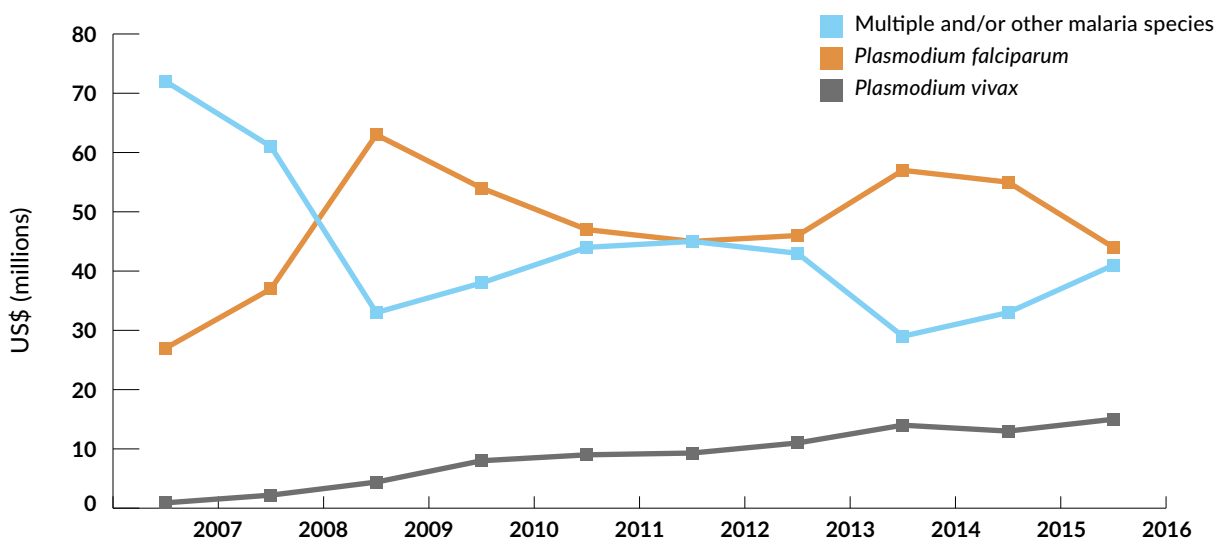
Note: The low share of investment for *Plasmodium falciparum* (and corresponding high shares for multiple and/or other malaria species) in 2007 and 2008 is likely an artefact of less accurate species-specific reporting by respondents in the early years of the survey.

Plasmodium vivax-specific basic research and product development funding has grown steadily over the past ten years, from under 1% of total funding in 2007 to 15% in 2016.

Investments in vaccine development have resulted in one vaccine, RTS,S, that is advancing toward introduction. Developed through a collaboration between GSK and the international nonprofit PATH, the vaccine has been positively reviewed by the European Medicines Agency and recommended by WHO for pilot implementation, expected to begin in late 2018.

Funding for drug R&D had peaks in 2007, 2010, and 2015–2016, with the latter peak reflecting an increased focus on clinical development as product candidates advanced through clinical trials. Medicines for Malaria Venture (MMV), with many partners, used its investment to develop and bring forward seven new medicines. For uncomplicated malaria, this includes two formulations specifically for children: Coartem® Dispersible, and Pyramax® granules as well as Pyramax® tablet and Eurartesim®. Severe malaria treatments include Guilin’s artesunate injection Artesun® and Cipla 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.

Figure 3. Malaria basic research and product development funding by species.



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 artefact of less accurate species-specific reporting by respondents in the early years of the survey.

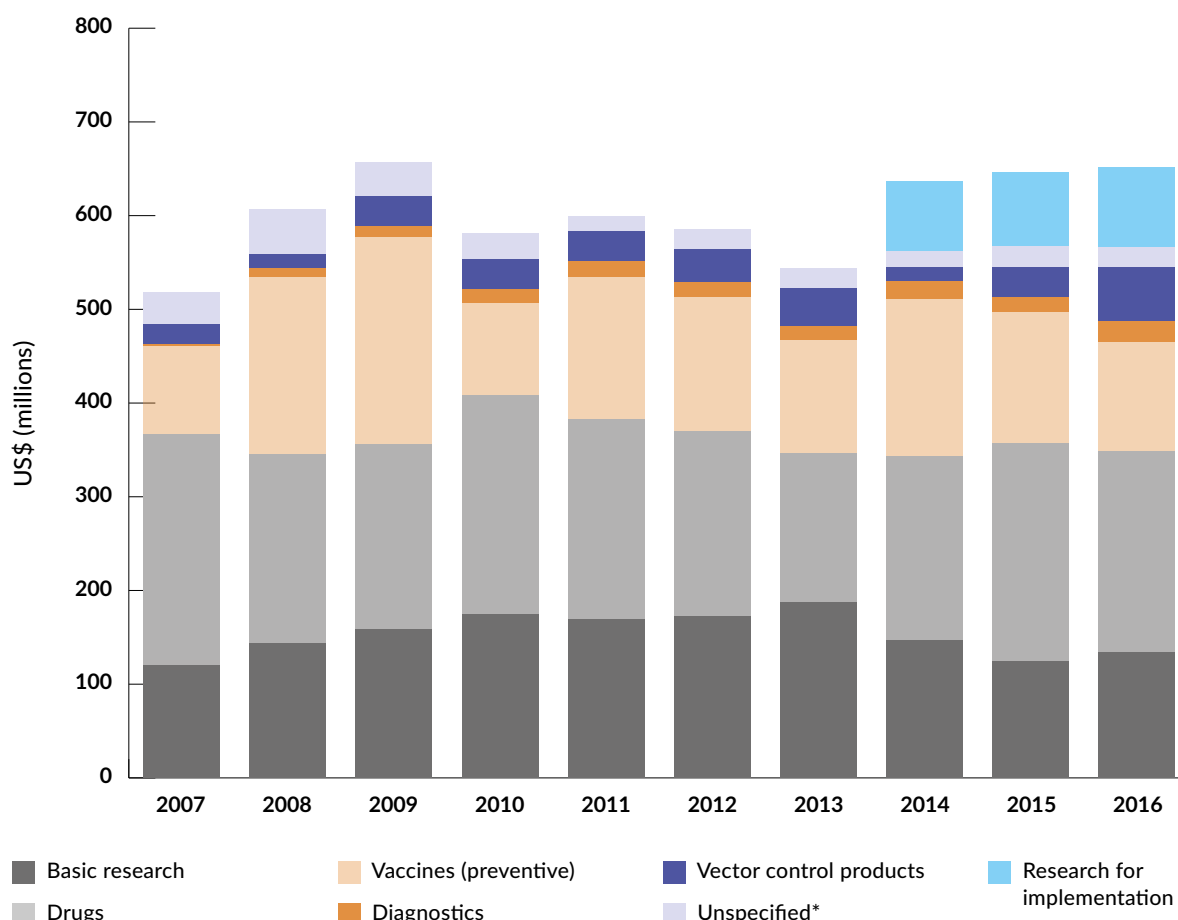
Investment in vector control product research and development nearly tripled over the period 2007–2016 (from \$21 million to \$58 million), almost entirely due to increased funding from the Bill & Melinda Gates Foundation. Over this time, IVCC (the Innovative Vector Control Consortium) and its partners have completed the development of three indoor residual sprays (K-Othrine Polyzone, Actellic 300CS, SumiShield 50WG) and a dual insecticide bed net (Interceptor G2). These products are aiming at preventing the build-up of mosquitoes' insecticide resistance.

Basic research and product development investments into diagnostics also grew between 2007 and 2016, from \$2.1 million to US \$23 million—a ten-fold increase—although this still represented only a small percentage (3.5%) of all malaria research and development funding in 2016.

The Bill and Melinda Gates Foundation, working directly with manufacturers and in partnership with PATH and FIND, have advanced a portfolio of innovative ultrasensitive diagnostics in support of malaria elimination, the first product of which was launched in 2017. In addition, PATH and partners have advanced a product pipeline of diagnostics for G6PD deficiency in support of radical cure of *Plasmodium vivax* malaria.

In the March 2018 survey of 26 organizations, investments of \$75 million in research for implementation were documented in 2014, amounting to 12% of total malaria funding, increasing slightly to 13% of the total amount in 2016. However, these are preliminary data, since only about half of the organizations were able to provide data in time for this publication.

Figure 4. 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: The research for implementation investments were not captured before 2014, and what is here only represents funding reported by 12 organizations, compared to the more extensive G-FINDER survey of basic research and product development funding (187 participants in 2016).

Research for implementation

THE QUALITATIVE SURVEY RESULTS

A qualitative survey, sent to 26 organizations that provide or receive funds for research for implementation, attempted to examine their perceptions of, and policies regarding, this field (see the definitions in Appendix 1). Fifteen responses are included in the analysis for this report (56%).

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. While the majority of those surveyed agreed with the definitions, several leading funders use other categorizations. One indicated that health systems research is an umbrella term that includes operational and implementation research, while 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. Although the Special Programme for Research and Training in Tropical Diseases (TDR) was one of the few to explicitly state funding priorities for research for implementation, others implicitly referred to this, such as in Dr Tom McLean's report in the Innovative Vector Control Consortium's 2016-2017 Annual Report: "The Access Strategy is inseparable from the overall product development strategy and the consequent portfolio."⁸

Related to this, only TDR reported funding capacity building/training in this field. The Programme is doing this because it has found low levels of capacity to conduct this type of research at the national and sub-national level. Tracking this type of funding may be just as critical as tracking the funding of the actual research itself.

The majority of funding for research for implementation is not related to a specific product (Figure 7).

Frequently, funders find increased value with this type of research because it can improve access to health products and services more broadly. However, the limitations on how funders document and/or monitor this research within their overall portfolios currently, prevent more detailed analysis.

Of the 15 qualitative survey respondents, nine reported that research for implementation was their highest priority among all types of malaria research, so it is 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 ten years. It was an insurmountable challenge for some organizations that fund activities across many countries and institutions, and this type of tracking will require modification of financial planning and reporting tools.

FUNDING OF RESEARCH FOR IMPLEMENTATION

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

The NIH contributed \$40 million to research for implementation between 2014 and 2016. Like the Gates Foundation, its funding was almost evenly split (53% operational research, 47% implementation research). In 2016, the US Centers for Disease Control and Prevention (CDC) had the highest proportion of malaria research funding allocated to research for implementation (58% of their investment).

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

Figure 5a. Initial list of malaria research for implementation funders and their funding. (2014-2016, in US\$ millions).

Funder	2014	2015	2016
Gates Foundation	46	49	57
US NIH	13	12	15
US CDC	6.0	2.9	4.8
UK DFID	0.9	3.0	3.9
US DOD	-	-	2.1
USAID	3.5	1.3	1.5
EC	3.9	7.9	1.2
WHO TDR*	1.4	2.3	0.5
Australian DFAT	-	-	0.3
Grand Challenges Canada	0.1	0.3	<0.1
Swedish SIDA		0.5	
UK MRC		0.4	
Total funding	75	79	86

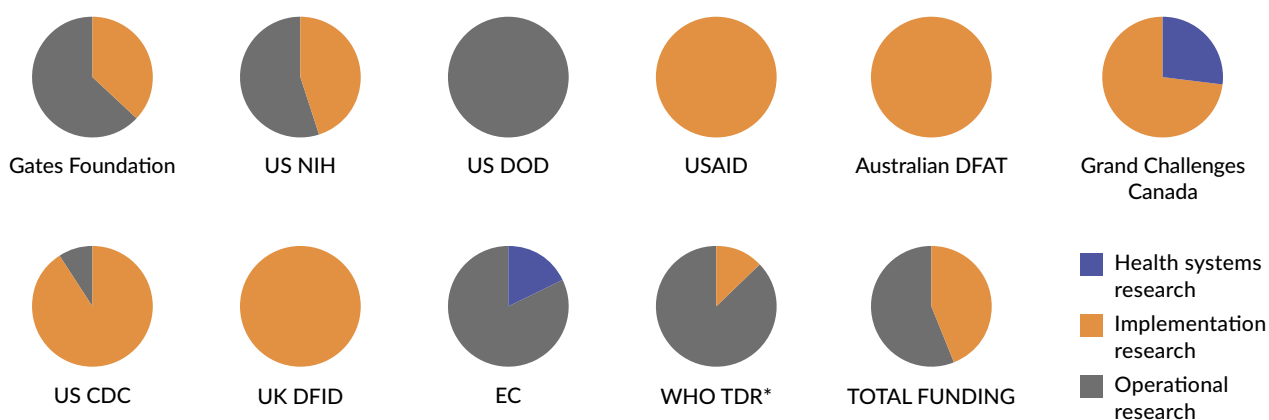
Funding organization did not participate in the pilot survey. Contributions listed are based on data reported by recipients and so may be incomplete.

- No reported funding.

* Funders of TDR include DFID, SIDA, DGDC, BMZ and NORAD. Contributions to TDR are not included in the table above, to avoid double counting of this funding.

Australian DFAT = Australian Department of Foreign Affairs and Trade; Belgian DGDC = Belgian Directorate-general Development Cooperation and Humanitarian Aid; German BMZ = German Federal Ministry for Economic Cooperation and Development; NORAD = Norwegian Agency for Development Cooperation; Swedish SIDA = Swedish International Development Cooperation Agency; UK DFID = UK Department for International Development; UK MRC = UK Medical Research Council; 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 TDR = Special Programme for Research and Training in Tropical Diseases at the World Health Organization.

Figure 5b. Relative allocations of funding, by funder, among categories of research for implementation (2016).

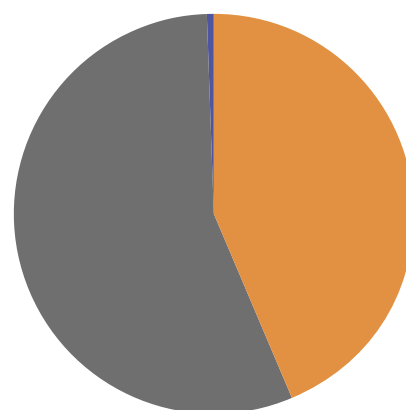


The share of research for implementation funding available for operational research rose to 56% (\$48 million) in 2016, an increase from 47% (\$35 million) in 2014. Health systems research made up a tiny proportion (0.4%).

Figure 6. Type of malaria research for implementation funding. Known funding in 2016: US\$ 86 million.

- Health systems research 0.4%
- Implementation research 44%
- Operational research 56%

Note: These data are from the 12 responses received to the pilot survey; they do not represent 100% of global research for implementation funding.



Where is research for implementation focused?

The majority of research for implementation was not related to specific products (\$51 million, or 59%). Almost a quarter (\$17 million, 20%) was for multiple products.

Diagnostics received little attention, even though studies on which diagnostics work in which specific settings could have been expected.

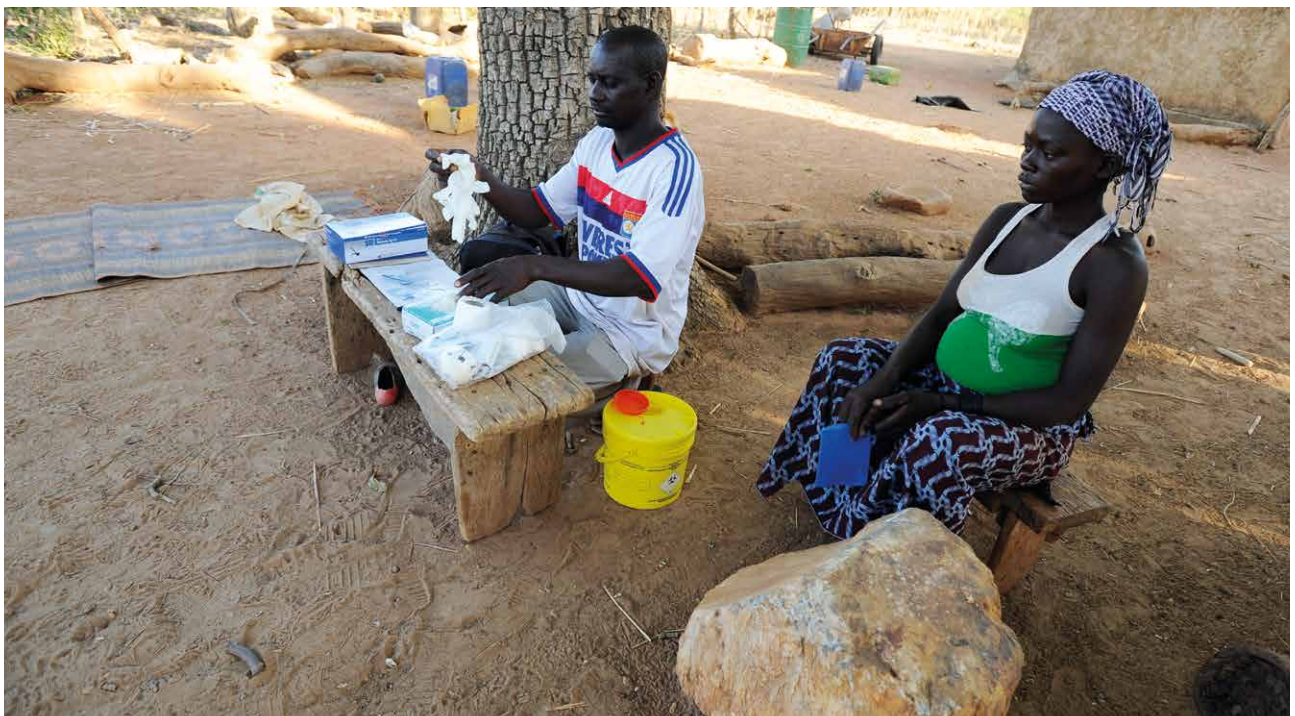
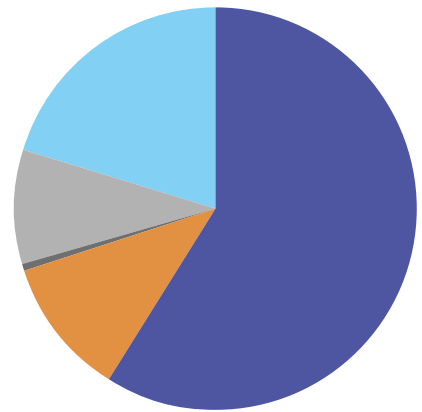
There was no funding of vaccine-related research for implementation reported by time of publication, as the research

related to the pilot implementation of RTS,S, the malaria vaccine most advanced in development globally, had not started in 2016 and key organizations involved in funding vaccine R&D (i.e., industry) did not participate in the study.

There were some expenditures in 2015-2016 in preparation of the intensive health care utilization study for the malaria vaccine implementation programme, but are not included in the funding data.

Figure 7. Malaria research for implementation funding by product type (2016). Known funding in 2016: US\$ 86 million.

- Non-product related 59%
- Drugs 11%
- Diagnostics 0.5%
- Vector control products 9.4%
- Multiple products 20%



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Challenges

As new tools have become available, there are growing challenges to the health care systems to ensure 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.

This small pilot study of research for implementation funding provides a first glimpse into the subject. It also raises 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 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.”⁹

This also appears to be the case for malaria. Yet of the 15 organizations which completed the survey on where research for implementation fits within their priorities, nine of them reported this to be the first or second priority. It would be valuable to compare these priorities with actual funding disbursements, but until this type of reporting is accepted and systems are in place, such an analysis is not possible.

The justification for research for implementation is growing. The World Malaria Report 2017 found that almost one-third of patients who sought malaria treatment at a public health facility did not receive artemisinin-combination treatments (ACTs), the most effective antimalarial drug that is the result of years of R&D investment. The numbers receiving this treatment are even lower in the private sector.

Investments in vector research are now offering the possibility of new insecticides, which are urgently needed, given increasing resistance to current insecticides. A broader toolbox to prevent malaria is available, but how will caregivers be able to assess which ones to use, and implement them in the many different settings? Training and documentation are required. Dr Tom McLean wrote in The Innovative Vector Control Consortium’s 2016–2017 annual report: “For products to be accepted by countries and implementation partners, evidence on their cost effectiveness and impact is imperative.”¹⁰

As the first malaria vaccine moves towards implementation, key issues to be addressed include how to ensure that children receive all four 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.

Diagnostics are hardly covered by research for implementation. Is the lack of funding an accurate representation of a dearth of research, or a reflection of the limited data set, or 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 utilized and what it costs.

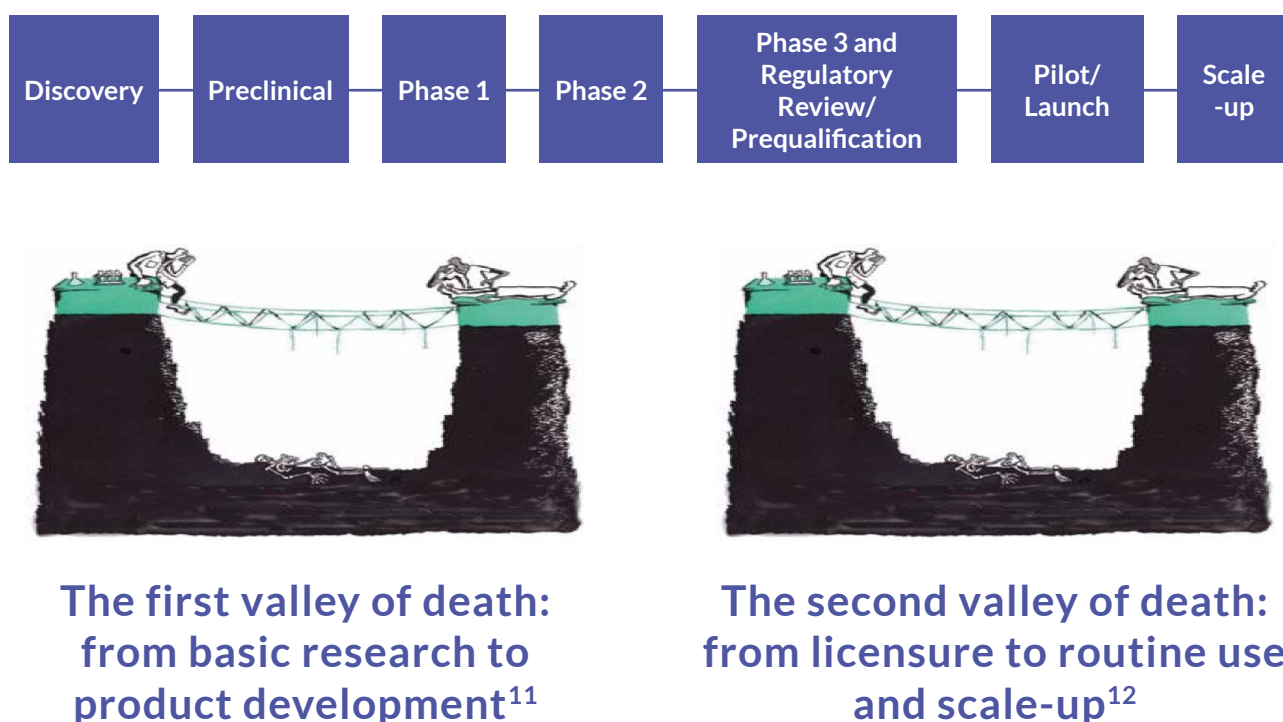
A SECOND VALLEY OF DEATH?

The trend toward increasing malaria cases, despite the number of product innovations, suggests that a second valley of death is already with us. Previously, there was more funding in basic research and insufficient investment into product development. Funding data helped illuminate the gaps and increase funding to address that valley.

Today the question is whether there is enough funding 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.

This report provides a first view of initial findings from about half of the 26 organizations surveyed. The full report, which will include funding data from more of the survey recipients, will be available in June 2018, but there are issues already identified that will require commitments from funders and funding recipients to fill out the broader picture.

Figure 8. A second valley of death?



Recommendations

To ensure that health systems in the highest burden countries are equipped to implement new tools, research for implementation funding needs to be aligned with the product pipeline. However, it is impossible to analyze whether this is being done because the funding data are missing.

Donors and recipients need to improve their financial monitoring systems to get a more accurate picture, both of the funding and the impact research for implementation has on the ground.

Consequently, the following initial recommendations for policymakers and malaria research organizations are already clear from this pilot study:

1. AGREE ON RESEARCH FOR IMPLEMENTATION DEFINITIONS.

Definitions for this field need to be agreed to track funding flows. The issue is not about controlling the way the research is conducted, but about reporting accurately what is being funded. This will require commitments by funders and those receiving funding to develop systems to track these money flows. Currently, few are doing this, and many who would like to do this do not have the systems or personnel to do it.

2. IMPROVE TRACKING OF RESEARCH FOR IMPLEMENTATION FUNDING AT THE INSTITUTIONAL, NATIONAL, AND SUBNATIONAL LEVELS, INCLUDING IN LOW- AND MIDDLE-INCOME COUNTRIES.

This survey has been limited to a subset of major funders. However, more research for implementation funding can and should be allocated locally, since it is designed to identify local solutions to local problems. Given the limitations of this pilot survey, it is likely that important work that has been undertaken is not included. Excluding these projects prevents analysis of the broader impacts of this type of research. For example, what level of funding is needed to implement certain types of products or services, and how does this differ by country or region? What are the appropriate levels of investment in this area, and how can funding data be used to prioritize research for implementation options?

3. TRACK FUNDING FOR TRAINING AND CAPACITY BUILDING FOR RESEARCH FOR IMPLEMENTATION.

Only one organization responding to this survey, TDR, provided funding for building this capacity. Research can only be conducted locally if there is the capacity to do this, so tracking this funding is a necessary support to the research.

4. CONTINUE TO BUILD THE DATABASE ON FUNDING OF RESEARCH FOR IMPLEMENTATION.

This follows on from a 2017 G-FINDER recommendation to provide organizations with improved information and tools that help them better coordinate funding and portfolio decisions. A key component—research for implementation—is missing.

The impact of research for implementation: a series of case studies.

Given that research for implementation is a new or unfamiliar field to some, the following case studies document some examples of past research and the resulting impact. This includes improving the usability and uptake of insecticide-treated bednets, artemisinin-combination treatments (ACTs), and rapid diagnostic tests—all of which have provided dramatic improvements in expanding access to malaria treatment and reducing the disease burden.

A fourth case study outlines a planned study that will support implementation of the first malaria vaccine, providing a current example of this field's potential for impact.

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 using 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 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 drugs.

THE APPROACH

Studies were conducted on drug packaging labels and boxes in Malawi and Tanzania in 2001, and the following year on health workers' educational materials 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 after they were feeling better. Malaria is translated as "fever" in some languages, so speakers of that language tended to believe that once the fever went away, they did not need the treatment anymore. So 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 explaining the crucial WHY question (Figure 9).

and 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 (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 HCPC-Europe's Drug Packaging Design Award for "an innovative solution for what might appear to be a complex unsolvable problem".¹³ 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 was poor. It also allowed for expanded community case management programs by empowering community workers and, most of all, mothers and caregivers, to competently and safely administer life-saving treatment to children.¹⁴

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,

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

PARASITES PREFERRED - SQUARE ONES!

More than 95% preferred versions with parasites to explain why to complete treatment.

Details make a difference: Round parasites 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.”

- Women, 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”

- Women 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.

The pictures on the pack help you remember when to take the tablets.

These pictures remind you when to take the tablets. Take one dose in the morning (see the picture of the sun ☀️) and one dose at night time (see the picture of the moon 🌙).

These are malaria parasites in the blood. They show you that each dose kills some of the parasites. You can see that you have to finish all the tablets to kill all of the parasites.

This picture shows the child who will take these tablets. There are different packs for different weight patients.

This tells you how many tablets to take at each dose. This baby will take one tablet at each dose. Bigger children take more tablets at each dose.

Source: Innovation in malaria drug packaging: Coartem® and Coartem® Dispersible, International Pharmaceutical Industry, Winter 2009/10 newsletter.

PROJECT FUNDERS AND IMPLEMENTERS

TDR, The Special Programme for Research and Training in Tropical Diseases 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 Research and Development Center in Tanzania; KEMRI-Wellcome Trust in Kenya and Child Health and Development Centre; 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 Medicines for Malaria Venture (MMV).

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%.^{18, 19} 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?²⁰

In 1999, the United Nations Children's Fund and WHO set the goal of providing 32 million bednets and 320 million bednet treatments a year for the following 10 years to protect 80% of African households against malaria.²¹

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.²² 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,²³ which included motivating them to get the nets, care for them, and use them. Social research identified the motivators—it wasn't so much a concern about malaria, but about the nuisance of being bitten by mosquitoes. That knowledge was built into educational materials, focusing on giving families peace from the mosquitoes.²⁴

Even the color and shape of the nets became a research topic.^{25, 26} Scientists found 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, and in Tanzania, communal "dipping days" were not working. So a study thoroughly tested a set of instructions for safe and effective use of the kits, even where literacy is 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.²⁷

In The Gambia, the government introduced the National Impregnated Bednet Program 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 during the first year of intervention.²⁸



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



© WHO, Kisumu, Kenya.



© WHO, Kisumu, Kenya.

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?^{29, 23} 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%–11% reduction in the need for care was expected—justifying free distribution.³¹ 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.³²

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, was a viable way of increasing bednet coverage.³³

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.³⁴

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, expanded distribution schemes, investments in the diversity of products now available, and increased capacity to continue these efforts at all levels.



© WHO/TDR, Colombia.



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

3 Case study 3: An integrated approach to multiple diseases with a shared symptom

THE PROBLEM

More than one-third of all African childhood deaths in children under the age of five are due to malaria, pneumonia, and diarrhea. Fever is often a symptom of all three, so accurate diagnosis and the correct treatment are critical, but were not consistently provided properly.

THE APPROACH

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

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

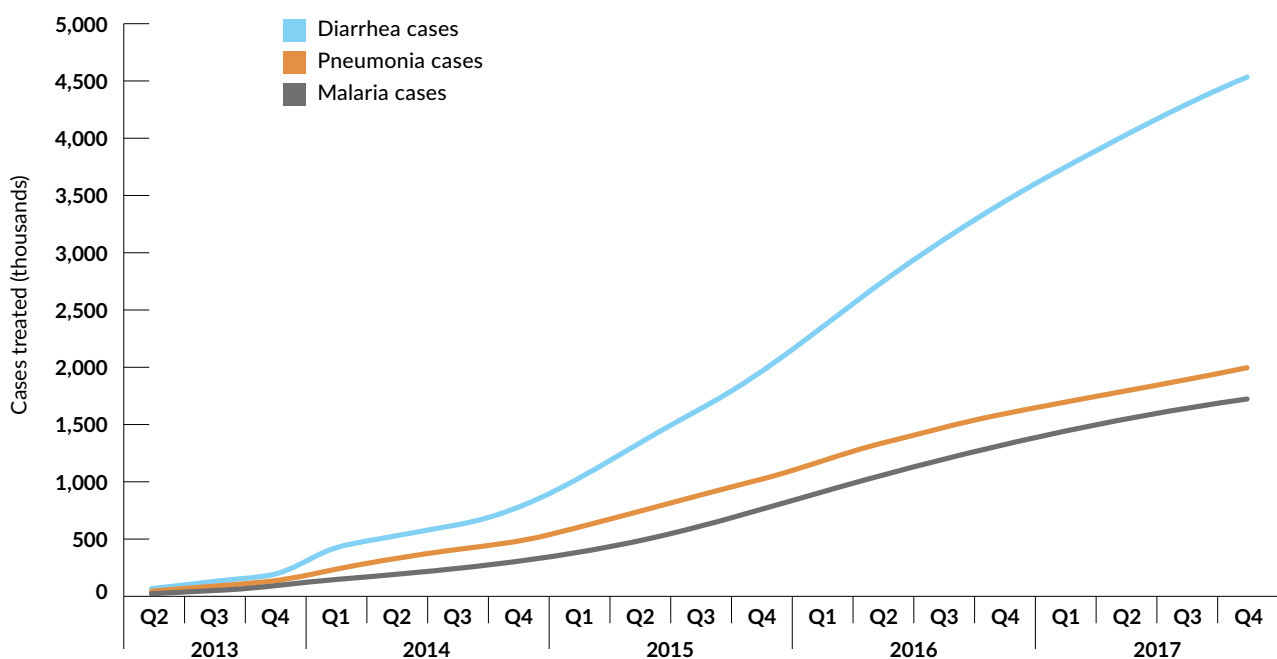
THE IMPACT

More than 8.2 million children were diagnosed and treated for pneumonia, diarrhea, or malaria. Each country has also updated its national policies to facilitate iCCM scale-up, and the Democratic Republic of the Congo, Niger, and Nigeria are planning to expand these programmes nationally.

PROJECT FUNDERS AND IMPLEMENTERS

The project was funded by the Government of Canada and managed by the WHO's Global Malaria Programme between 2012 and 2017. Ministries of health from the Democratic Republic of the Congo, Malawi, Mozambique, Niger, and Nigeria were involved; nongovernmental organizations supported the implementation; and panels of external experts provided strategic guidance and oversight.

Figure 11. Aggregate malaria, pneumonia, and diarrhea cases treated by community health workers through the RAcE Programme (2013-2017).



Source: RAcE Performance Management Framework, as reported by program grantees.

4

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, and 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

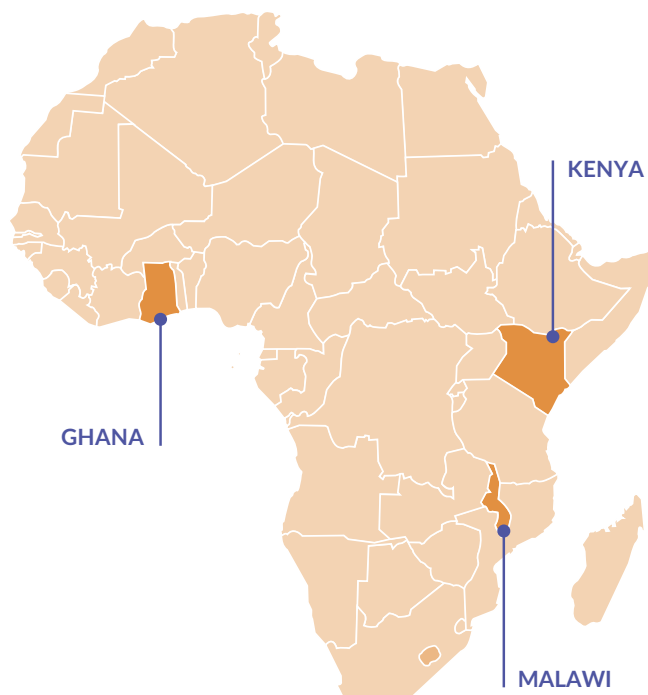
An intensive health care utilization study (HUS) is one of the evaluation components comprising the Malaria Vaccine Implementation Programme (MVIP). The MVIP is a country-led, WHO-coordinated assessment of the feasibility, impact and safety of RTS,S in routine use. Relying heavily on interviews with primary caregivers, health care providers, and other community members, the HUS will use proven, qualitative methods over several years to document adoption 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 HUS research, working in collaboration with partners in Ghana, Kenya, and Malawi.



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

Appendices

Appendix 1. Research for implementation definitions

(Adapted from TDR 2018–23 Strategy³⁵ and Remme et al, 2011³⁶):

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

OPERATIONAL RESEARCH

is often carried out using data routinely collected by disease control programs, to provide ways of improving 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 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, conducting the study and implementing 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 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.

Figure 12. Examples of research questions for the three research for implementation domains.³⁶

RESEARCH DOMAIN	RESEARCH QUESTION
Operational	Can the “communication for behavioural impact” (COMBI) strategy improve the poor compliance with mass drug administration for LF elimination in Tamil Nadu, India?
	Which locations should be targeted for delivering HIV prevention services in Kawempe district, Uganda?
	Which of the current ART payment strategies in use in Nairobi should be retained for the new integrated program?
	Should the sleeping sickness program in Equator Nord province, DRC, 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 centres to 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 programmes on fragile health systems?

Appendix 2. List of “research for implementation” survey participants

A survey on research for implementation was sent to 26 organizations identified as donors or recipients of funding for this type of research. Some of these organizations comprised several agencies, so for the sake of clarity, the names of the individual agencies are listed here. Of the 26 organizations surveyed, 65% responded to the qualitative survey and 54% to the quantitative survey, but responses from two organizations could not be included in time for this analysis. The full report, expected to be published in June 2018, will include responses from more of the 26 organizations surveyed.

ORGANIZATION	QUALITATIVE SURVEY RESPONSE	FUNDING DATA PROVIDED
African Network for Drugs and Diagnostics Innovation (ANDI)	No	No
Australian Army Malaria Institute	Yes	No***
Australian Department of Foreign Affairs and Trade (DFAT)	Yes	Yes
*Bill & Melinda Gates Foundation	No	Yes
Canadian Institutes of Health Research	Yes	No
Drugs for Neglected Diseases initiative (DNDi)****	No	No
*European Commission (EC)	Yes	Yes
*Fogarty International Center	Yes	Yes
Global Challenges Canada	Yes	Yes
Global Fund to Fight AIDS, TB and Malaria (GFATM)	Yes	No***
Innovative Vector Control Consortium (IVCC)	No**	No**
International Development Research Centre (Canada IDRC)	No	No
Médecins Sans Frontières (MSF)	No	No***
Medicines for Malaria Venture (MMV)	Yes	No
PATH	No**	No**
*The European & Developing Countries Clinical Trials Partnership (EDCTP)	Yes	Yes
The Wellcome Trust	No	No
UK Department for International Development (DFID)	Yes	Yes
UK Medical Research Council (MRC)	Yes	Yes
Unitaid	Yes	No***
US Agency for International Development (USAID) (including President’s Malaria Initiative)	Yes	No**
US Centers for Disease Control and Prevention (CDC)	Yes	Yes
*US Department of Defense (DOD)	No	Yes
*US National Institutes of Health (NIH)	No	Yes
World Health Organization: Global Malaria Programme	No**	No**
World Health Organization: Special Programme for Research and Training in Tropical Diseases (TDR)	Yes	Yes

* Quantitative dataset already available to Policy Cures Research.
 ** Unable to provide in time for publication. Review in process.

*** Unable to provide at all (due to systems or confidentiality issues).
 **** Portfolio transitioned to MMV.

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