NIAID Strategic Plan for Malaria Research

Efforts to Accelerate Control and Eradication of Malaria Through Biomedical Research

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National Institute of Allergy
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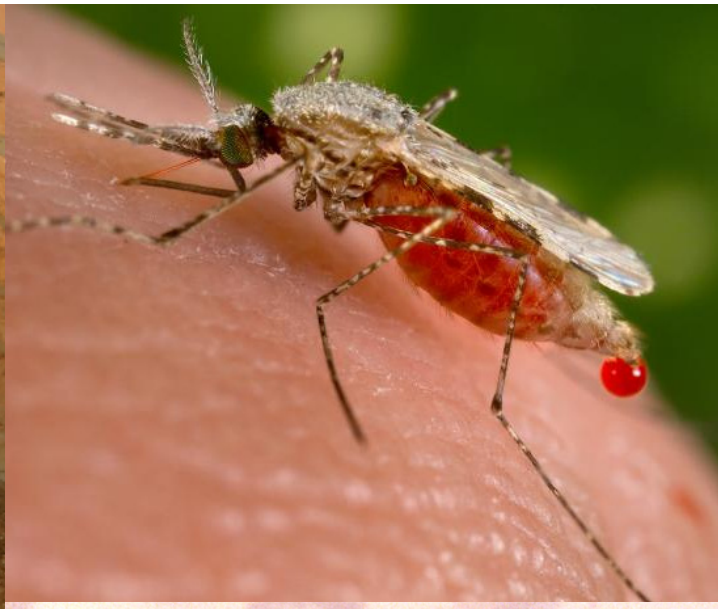

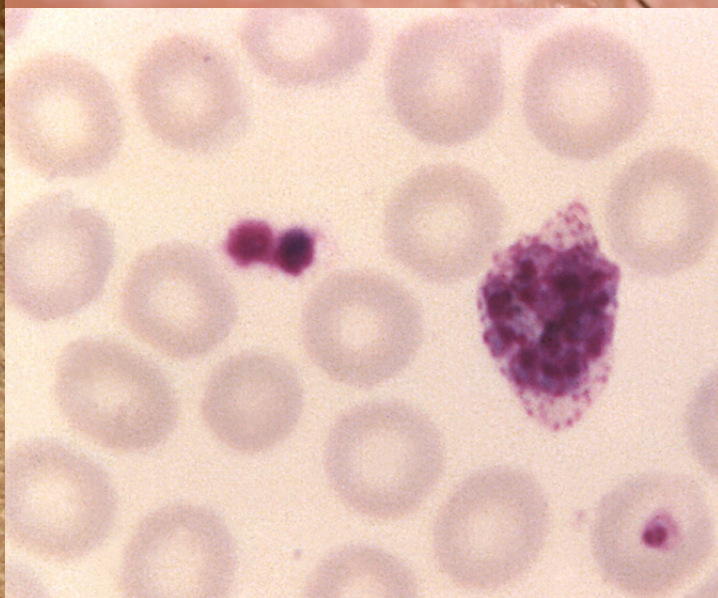

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Executive Summary

Malaria remains a leading global public health concern. Although there have been prior attempts to control malaria—and it has been successfully eliminated in parts of the world—close to half of the world's population still lives in areas where there is a risk of contracting malaria. As malaria is a global problem, reducing its burden will require a global solution. Fortunately, over the past decade a convergence of factors, including scientific and technical progress, globalization, increased appreciation of the enormous toll exacted by malaria, and the emergence of new programs and entities to support malaria research and development (R&D) and control efforts, have led to increased interest in better controlling and possibly eventually eradicating this disease. Thus, the landscape in which malaria R&D can be implemented today has changed dramatically from a decade ago.

Accomplishing this ambitious objective, however, will require long-term commitment and diligent application of a multi-pronged approach, involving appropriate tools and intervention strategies that target different aspects of the malaria parasite's complex lifecycle. Moreover, as progress is made, epidemiologic shifts can be expected, stemming from changes not only in the incidence and prevalence of malaria, but also from parasite and vector adaptations to drugs, insecticides, and other interventions. Thus, the landscape in which malaria R&D will be carried out in the future will continue to change, requiring ongoing re-evaluation and adaptation of the R&D effort to ensure its relevance and effectiveness to support the goals of control, elimination, and ultimately eradication. These changes will require not only strategic adjustments to the mix of tools and interventions, but also the development of new and improved interventions that are more appropriate to the prevailing epidemiologic state.

The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) is the lead agency in the U.S. government charged with supporting biomedical research on malaria. *The NIAID Strategic Plan for Malaria Research: Efforts to Accelerate Control and Eradication of Malaria Through Biomedical Research*[*] outlines the Institute's vision of malaria research and development in the context of a changing landscape and provides a framework for future research directions, priorities, and efforts within the Institute.

The Evolving Context of Malaria Research and Development

Although a disease of antiquity, malaria has persisted to the present day, despite efforts to control it. While the incidence and prevalence of malaria have been greatly reduced—and in many parts of the world the disease has even been eliminated—in other regions malaria has demonstrated remarkable tenacity, and in some areas in recent years, it has resurged, reversing hard-won public health successes. Today more than 40 percent of the world's population lives in areas where there is a risk of contracting malaria. The World Health Organization (WHO) has estimated that 300-500 million cases of clinical malaria occur each year, although some researchers (Snow et al., 2005) have suggested these estimates are low, as many infections outside of Africa are not included. Nevertheless, more than 1 million people die of malaria every year, mostly infants, young children, and pregnant women, and the great majority of these deaths occur in Africa. Malaria accounts for at least $12 billion in economic losses each year in Africa, and a reduction in annual economic growth is estimated at 1.3 percent.

The Endemic Nature of Malaria

Malaria has persisted in many regions for a variety of reasons, including the emergence of drug and insecticide resistance. Inadequate support for malaria control programs and poor environmental management have also contributed to the ongoing endemicity of malaria.

[*] Updated 4/30/08

Although increased globalization has generated extraordinary new opportunities and economic benefits for many malaria-endemic countries, increased travel and commerce also have created increased opportunities for malaria to spread and establish itself in new settings. Fortuitously, the growth of international communications that has greatly facilitated global business and trade has also increased global public awareness of the persistence, extent, and burden of malaria.

Partnerships for Treatment and Control

Over the past decade a renewed interest in malaria has emerged in both the public and private sectors. Government-sponsored activities, such as those under the aegis of NIAID's 1997 *Plan for Research to Accelerate Development of Malaria Vaccines* and the recent European Commission Framework Programs for Research on Poverty-Related Diseases, have grown in response to a need to establish a research base and toolbox of interventions to combat malaria. Similarly, the Multilateral Initiative on Malaria (MIM) was formed in 1997 to address the need to strengthen biomedical malaria research capacity in endemic countries through training and scientific collaborations. Philanthropic organizations such as the Bill & Melinda Gates Foundation and the Wellcome Trust have identified malaria as an important area in which to invest their time, resources, and efforts. The expansion of the research base has also been pursued by organizations such as the Special Programme for Research and Training in Tropical Diseases (TDR) and the Initiative for Vaccine Research (IVR), both located at the World Health Organization. In addition, private sector global corporations such as Exxon Mobil and Chevron have realized the burden that malaria inflicts on personnel and profits in malaria-endemic areas, and have made malaria a priority in their corporate responsibility programs.

Novel Efforts

Perhaps most exciting has been the emergence of new public-private partnerships, such as the Medicines for Malaria Venture (MMV), the Malaria Vaccine Initiative (MVI), and the Foundation for Innovative New Diagnostics (FIND), which are bringing together expertise from the public health and private sector communities to accelerate development and deployment of effective new malaria tools. In addition, biotechnological and pharmaceutical manufacturing capacity is experiencing accelerated growth in the rapidly emerging economies of countries such as Brazil, India, and China, which have political and economic incentives to address malaria in endemic areas. New programs, such as the World Bank's Global Strategy and Booster Program for malaria, the Roll Back Malaria Partnership, WHO's Global Malaria Program, the President's Malaria Initiative, and the Global Fund for AIDS, Tuberculosis, and Malaria, have arisen to provide support for malaria control programs and public health efforts to reduce the burden of disease in affected populations. Political support to address the burden of malaria also has been forthcoming as demonstrated by the commitment of African heads of state in the Abuja Declaration (2000) to halve malaria mortality by 2010, and by the United Nations Resolution, later the same year, to reverse the toll of malaria by 2015. Project appraisal analyses carried out in 2004 by the Copenhagen Consensus, a group of leading economists, identified malaria treatment and control to be among four leading global challenges with a very favorable cost/benefit profile, which has encouraged public and private sector groups to consider further investments in this area. Finally, the issue of inadequate market incentives for malaria R&D and control programs also is being addressed by novel mechanisms for procurement, access, and financing which have emerged in response to this urgent global public health need.

Thus, momentum to address the global burden of malaria has been gradually building over the past decade. Multiple groups have identified malaria as a shared priority, and a continuum of research and control activities sponsored by these groups has been established. As a result, the landscape in which malaria R&D needs to be conducted has fundamentally changed.

Building Momentum for Control and Eradication

This momentum, and the revitalized hope that malaria as a global problem could be addressed, reached a pinnacle in 2007. Despite the failures of previous attempts to eradicate malaria globally, interest in this lofty goal was revived at the Bill & Melinda Gates Foundation Malaria Forum held in Seattle in October 2007, when the founders of the Foundation recognized the impressive achievements that had been made in

combating malaria, and issued a renewed call for malaria eradication. In their comments they also noted that eradication would require a long-term commitment as well as the development and deployment of new tools.

In response to this call, the WHO announced that it would support such an effort. Shortly thereafter, the Roll Back Malaria Partnership announced that it would develop a new Global Malaria Business Plan, taking into account the long-term goal of malaria eradication. In January 2008, Malaria No More and McKinsey & Partners released a report calling for a scale-up of malaria control programs in 30 countries in Sub-Saharan Africa at a cost of 11 billion dollars.

The Evolution of Research Needs While Striving for Eradication

Only one human disease, naturally occurring smallpox, has been eradicated worldwide, although others, such as polio and dracunculiasis ("guinea worm"), are approaching eradication after years of sustained effort. Historically, efforts to eliminate and eradicate malaria have been undertaken, but have had only limited or short-term success. Following successes in eliminating *Anopheles gambiae*, the vector mosquito of *P. falciparum*, from Brazil and Egypt, and elimination of malaria from Sardinia in the 1940s, WHO in 1955 launched a malaria eradication program that produced significant reductions in some endemic areas. This program was based largely on a single intervention, spraying of the insecticide dichlorodiphenyltrichloroethane (DDT). Despite substantial successes in some areas, malaria eventually resurged due to increasing costs and a lack of administrative support for ongoing control programs, concerns about the environmental toxicity of DDT, and the emergence of insecticide resistance in mosquitoes and drug resistance in some parasites. Nonetheless, the fact that malaria has been eliminated from certain parts of the world is indisputable, and thus fulfills one of the scientific feasibility criteria identified by the International Task Force on Disease Eradication.

Characteristics Favoring Eradication

Biological characteristics of a disease that favor eradication reflect the epidemiologic vulnerability of that particular disease. Such characteristics include: low level of transmissibility; acute, self-limited infection (defined as short period of incubation and infectiousness); long-lasting immunity elicited by a naturally occurring initial infection; easy, rapid, specific diagnosis; and the absence of non-human reservoirs. In addition, appropriate effective interventions must be available, and the political will to eradicate the disease must be sustained over the many years that will be required for success. The favorable analyses reported by the Copenhagen Consensus, and more recently by Malaria No More and McKinsey & Co., indicate that malaria control is economically very beneficial, thus providing additional incentive for expanded efforts in malaria control and elimination. Additional studies may be required to evaluate more fully the potential economic benefits of eradication.

The Malaria Life Cycle: Opportunities for Intervention

The life cycle of malaria parasites (see Figure 1) presents numerous potential targets for intervention. In particular, two "bottlenecks" in the cycle occur. The first is when female mosquitoes, while taking a blood meal from a human, inject into the bloodstream small numbers of sporozoites* that go on to establish infection in the human host (see Figure 1/Bottleneck A). The second is when the female mosquito is taking a blood meal from an infected individual, resulting in ingestion of limited numbers of gametocytes† that go on to establish parasitic infection in the mosquito vector (see Figure 1/Bottleneck B). Any intervention at either of these bottlenecks could reduce transmission. Examples of current interventions operating at these bottlenecks include insecticide-treated bed nets and indoor residual spraying (both of which reduce mosquito-human contact). The stage in which the parasite is replicating, resulting in the development of parasitemia, represents an additional susceptible point in the lifecycle (see Figure 1/Box 3). Interventions such as drugs that can reduce the overall level of asexual erythrocytic parasite stages as well as the sexual stages (gametocytes) would reduce clinical disease and human-to-mosquito transmission, respectively (see Figure 1/Boxes 3 and 4). Importantly, any single intervention with 100 percent efficacy in interrupting the lifecycle would be capable of supporting eradication if applied in a timely manner. Unfortunately, no single intervention to date reaches this level of efficacy, and thus simultaneous multiple imperfect interventions

will be required to maximize their combined impact on reducing the life cycle. This likely will involve identifying and developing more effective interventions for each of the stages of the life cycle.

Multiple Species and Changing Conditions Require a Variety of Strategies

Much discussion of malaria is often focused on that caused by *Plasmodium falciparum*, largely because it accounts for the majority of malaria-related deaths in young children in Africa. It is important to recognize, however, that at least three other *Plasmodium* species (*P. vivax*, *P. malariae*, and *P. ovale*) infect humans. This is especially noteworthy when considering global elimination or eradication of malaria. In many cases these species co-exist with *P. falciparum* and may be targeted by the same interventions. However, they also exhibit unique features that may require alternative interventions and strategies, such as different drugs to attack the relapsing malaria species, or earlier administration of drugs with gametocidal activity for parasites with shorter time requirements for developing gametocytes. Finally, it is important to remember that malaria is a global disease and to recognize that malaria control, elimination, and ultimately eradication strategies may require adjustments to effectively address the predominant species of parasite, variations in vector biology and ecology, and different epidemiologic and geographic settings.

In the process of moving toward eradication, the disease will transition through a variety of epidemiologic states, including: control (reduction of disease burden to a pre-defined low level), elimination of disease, and, subsequently, elimination of infection. Since each of these states is epidemiologically distinct, it should not be assumed that the tools and strategies appropriate for one state are necessarily optimal for other states. As a consequence, any strategic approach to eradication must incorporate the development of new tools and interventions that anticipate the evolving epidemiology and perform effectively and efficiently in those settings.

Given the complex nature of the life cycle of the malaria parasite, the multiplicity of parasite and vector species involved, the evolving nature of elimination and eradication efforts, and the impact of these efforts in changing the underlying epidemiology of malaria, it is clear that efforts to eliminate and ultimately eradicate malaria will need to be highly focused on the end objectives in order to ensure timely progress.

Guiding Principles and Goals of the NIAID Strategic Plan

Role of NIAID

NIAID is the lead institution in the U.S. government charged with supporting malaria research and development. It is clear, however, that the targeted outcomes of malaria control, elimination, and eventual eradication rely not only on the research-related goals of improving the knowledge base and availability of effective tools and strategies for intervention, but also on the relevance and successful application of those tools and strategies in malaria-endemic settings. Viewed in this context, NIAID seeks to support research activities within its mission that will provide partner organizations and collaborators with appropriate knowledge, tools, and evidence-based strategies to support their intervention and control programs. Thus, the guiding principles of the *NIAID Strategic Plan for Malaria Research: Efforts to Accelerate Control and Eradication of Malaria Through Biomedical Research* are:

- To define and implement a structured set of R&D activities that will support and sustain momentum toward global malaria control and eventually eradication
- To develop, expand, and support the human, intellectual, and social capital and networks, both nationally and internationally, that in turn can support and sustain the long-term commitment for efficient and effective R&D activities to achieve global elimination and eradication of malaria.

In order to move the malaria R&D effort forward within these guiding principles, NIAID commits to the pursuit of the following goals:

1. Increase fundamental understanding of the complex interactions among malaria parasites, the mosquito vectors responsible for their transmission, and the human host.
2. Strengthen the ability to identify, develop, validate, and evaluate new tools and strategies for treatment, prevention, and control of malaria.

3. Enhance both national and international research and research training infrastructure to meet malaria research needs, particularly for community-based and -supported clinical trials in malaria-endemic countries.
4. Advance research to develop tools to support and sustain global efforts to control, eliminate, and eventually eradicate malaria.

Prioritizing Research Activities Based on a Changed and Dynamic Landscape

The design and implementation of research programs to address the overarching objectives and goals need to be framed in terms of the changed landscape. A decade ago, when there were fewer players involved in malaria R&D and control efforts, a large proportion of the R&D activities were focused on fundamental research and activities to demonstrate that new tools and interventions could be identified. While many fundamental aspects of malaria still deserve scientific investigation, R&D mechanisms are now in place to develop and evaluate new tools and interventions. Indeed, the key question now is whether the tools and interventions that are applied in research and development will be appropriate for field conditions. As a result, a major shift in focus must occur so that priority is given to addressing key research questions in clinical and field-based situations. Such research should also define which interventions are working, which are failing, and which are threatened by changes in the parasite population, mosquito vectors, and epidemiologic shifts. Answers to these questions will not only inform prioritization of R&D activities, but will also assist public health officials on the ground in modifying programs and devising new strategies with available tools and interventions to sustain reductions in malaria morbidity and mortality.

Specific activities to address implementation of the goals listed above are detailed in a separate, companion document, the *NIAID Research Agenda for Malaria*.

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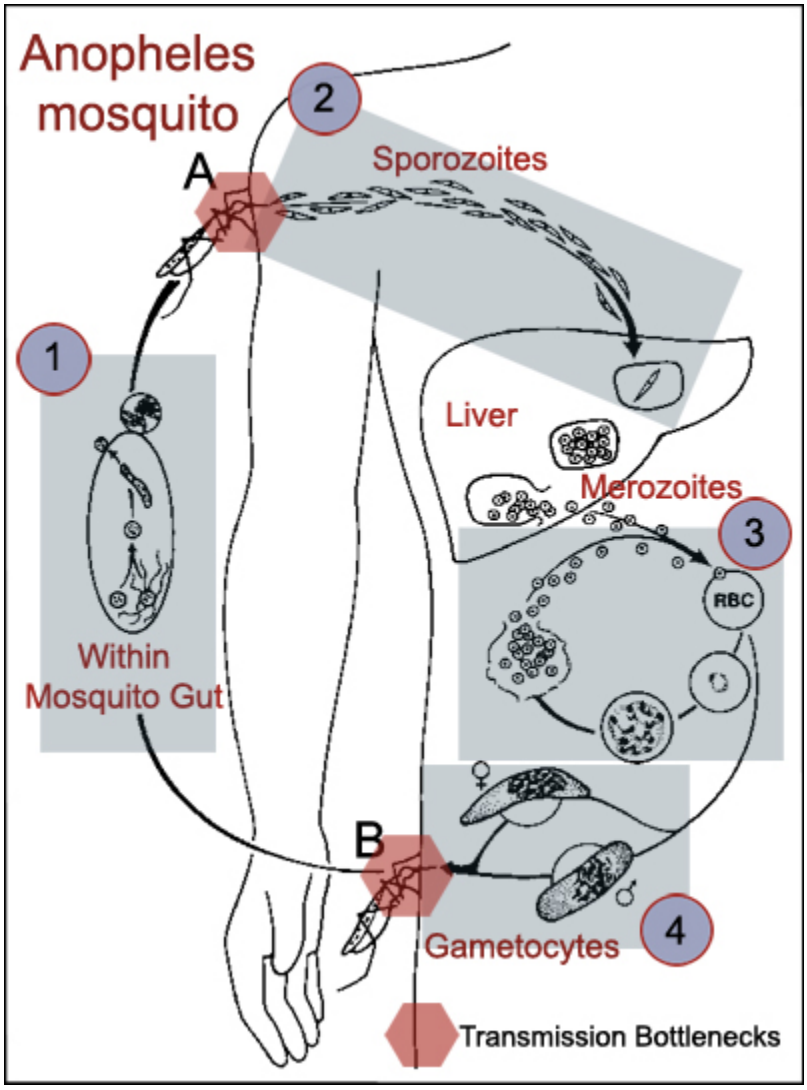

Figure 1. Stages in the Plasmodium Life Cycle That Serve As Potential Targets for Intervention

1. The stage during which the malaria parasite develops within the mosquito gut provides a target for interventions that target the mosquito vector directly. Interventions could interfere with the mosquito's ability to acquire, support, and transmit parasites; they could reduce a mosquito's "vectorial capacity" (i.e., affecting features such as a mosquito's host preference feeding behavior); or they could reduce the size of a mosquito population.

2. The stage that includes transmission of parasite sporozoites into the human bloodstream via the bite of the mosquito serves as a potential target for interventions that would reduce transmission of the parasite to the human host and interrupt the development of pre-erythrocytic parasite stages.

3. In the "erythrocytic" parasite stage, the parasite is infecting red blood cells and reproducing asexually. Targeting this stage with an intervention would reduce the rate of replication and development of asexual parasite stages, as well as reduce clinical disease manifestations

4. The stage in which the parasites leave the asexual reproduction cycle and develop into male and female gametocytes (sexual stage parasites) serves as a potential target for interventions that would interfere with the development of these sexual stage parasites or would block transmission of gametocytes from human hosts to mosquito vectors.

Table 1. Epidemiologic States and Examples of Priority Research Requirements

Status		Epidemiologic Features	Examples of Priority Research Requirements
Current Situation		1.3 M deaths/year (mostly young children) 300-500 M clinical cases/year Children and young pregnant women are primary at-risk populations 4-5 species infecting humans, including *P. falciparum* and *P.vivax and P. knowlesi* Some areas with very high entomological inoculation rates (EIRs) Widespread drug resistance	Expand research on non-falciparum malaria Expand research on combination drug therapy Expand research & development for malaria vaccines Expand research on vector biology and ecology of non-gambiae Anopheline mosquitoes
*Status According to International Task Force on Disease Eradication**	1. Control	Ongoing surveillance documents: Decreased incidence and prevalence of disease in areas where control has been implemented	Assure & expand pipeline of available interventions (drugs, vaccines, insecticides/ repellents, diagnostics) Assess degree of parasite population diversity to determine scope of tools/interventions needed Support multidisciplinary research approaches to discover, identify, validate, evaluate, and optimize interventional tools and strategies. Develop mathematical models based on emerging field data that will help guide product development and optimize combinations of interventions
	2. Elimination of Disease	Ongoing surveillance documents: No deaths directly attributed to malaria Incidence and prevalence of uncomplicated malaria is falling and/or low EIRs can still sustain infection	Assess changing epidemiology of malaria, including shifts in burden of disease and source of gametocytes Adapt tools and interventions to situation of decreasing incidence and prevalence
	3. Elimination of Infection	Ongoing surveillance documents: No deaths directly attributed to malaria Low and falling prevalence of parasitemia Low incidence, mainly due to short epidemics that are rapidly identified, treated and contained Low EIRS, whether due to low rates of infection in mosquitoes, decreased vectorial capacity or reduced biting behavior Drug and insecticide resistance is identified prospectively, and managed	Assess changing epidemiology of malaria, including shifts in burden of disease and source of gametocytes Adapt tools and interventions to situation of low incidence and prevalence, e.g., improved diagnostics for surveillance in mosquito populations Evaluate utility of transmission reduction strategies, e.g., transmission blocking vaccines, transgenic mosquitoes
	4. Eradication	No malaria deaths Prevalence =0 Incidence =0 EIR=0	Validated, rapid, highly sensitive diagnostics for detection of human and mosquito infections during surveillance period

*In order of progression from earlier to later.