

Malaria Control, Elimination, and Eradication: The Role of the Evolving Biomedical Research Agenda

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(See the perspectives by Miller and Pierce, on pages 1644–5, and Plowe et al, on pages 1646–9.)

Although it is an ancient and historical disease, malaria persists unabated in many parts of the world today. An estimated 3.3 billion people—approximately one-half of the world's population living in 109 countries—are at risk of contracting this serious and often life-threatening disease. Malaria accounts for ~250 million clinical cases and nearly 1 million deaths each year, the great majority of which occur in children younger than 5 years of age and in young, pregnant women. Malaria influences the social and economic well-being of societies in affected areas, draining scarce health and human resources, interfering with educational achievement, and causing persistent economic disadvantage [1].

In October 2007, Bill and Melinda Gates issued a call for a renewed effort at achieving global malaria eradication [2]. Whereas elimination involves ridding local and regional populations of the para-

site, eradication refers to the permanent elimination of the parasite throughout the world. Although skeptics have questioned the feasibility of malaria eradication, the Gates' call quickly galvanized support for a further expansion of malaria control and elimination programs. The World Health Organization endorsed such efforts, and the Roll Back Malaria (RBM) partnership launched its Global Malaria Action Plan in September 2008 [3]. In contrast to previous attempts at malaria eradication, current efforts explicitly acknowledge that to attain malaria eradication, a long-term effort must be undertaken, incorporating multiple activities and embracing multiple interventions, disciplines, approaches, and organizations.

Malaria eradication is a goal worth pursuing, and today, more than ever before, we are strongly positioned to make progress toward that goal. To this end, with initial support from the Bill and Melinda Gates Foundation, a new community-based initiative is supporting the development of a Malaria Eradication Research Agenda (MalERA) [4]. MalERA is intended to be an inclusive effort that encourages the global malaria research community to collectively think prospectively and innovatively about the tools, strategies, and implementation programs that will be required to achieve eradication.

MalERA has convened scientific and technical workshops and solicited Internet-based input on 7 distinct themes relevant to malaria eradication: (1) drugs, (2) vaccines, (3) vector control, (4) modeling, (5) monitoring and evaluation/surveillance, (6) integration strategies, and (7) health systems/operations. MalERA is also seeking engagement and dialogue with leading research agencies, including the National Institute of Allergy and Infectious Diseases (NIAID).

As we work toward the goal of malaria eradication, it will be important to use existing tools based on current best practices, which may change as we achieve success. Changes in the epidemiology of malaria (eg, decreased incidence and decreased transmission) and in the biological traits exhibited by the malaria parasites (eg, drug resistance) will require new tools and interventions. Development of these tools and interventions will depend on a sustained research effort to thoroughly understand the complex biology and epidemiology of malaria. Ultimately, these tools and interventions must be adopted and effectively deployed “on the ground” by implementation programs. Thus, the goal of malaria eradication cannot be achieved without a sustained commitment from multiple partners across disciplines and throughout the world. In this Per-

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The Biological Basis of Malaria Interventions

Understanding the basic parasite life cycle is essential for rationally designing and implementing interventions to effectively prevent infection and transmission as well as to treat malaria. The life cycle of malaria parasites is shown in Figure 1. At least 4 species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*) are responsible for malaria in humans. In addition, some human infections are caused by at least one species that naturally infects monkeys (*P. knowlesi*). All species are transmitted by female anopheline mosquitoes, which take a blood meal and simultaneously inject humans with infectious sporozoite-stage parasites. It is generally believed that only ~10–100 sporozoites are inoculated during a blood meal, and an even smaller number actually enter the circulation. Once in the circulation, however, sporozoites home to the liver, where they traverse the endothelium and invade hepatocytes. Over a period of ~6–16 days, depending on the species, the parasites undergo several rounds of replication and differentiate into invasive merozoite stages. In the case of relapsing forms of malaria caused by *P. vivax* and *P. ovale*, some intrahepatocytic stages also differentiate into dormant stages called hypnozoites. Hypnozoites may remain dormant for long periods—sometimes years—before they further differentiate into merozoites. While parasites are in the liver, infected individuals remain asymptomatic.

After their release from hepatocytes into the circulation, merozoites initiate the blood-stage of infection by invading susceptible red blood cells. Invasion is a complex but extremely rapid process. After entry into the red blood cell, the parasites undergo differentiation and replication over a few days, depending on the parasite species. Eventually, invasive merozoites are produced and rupture the red blood cell to gain access to the circulation and reinitiate the blood-stage cycle.

In some cases, the malaria parasites in the blood differentiate into sexual stages (gametocytes). After being taken up during a blood meal, these sexual-stage parasites undergo replication and maturation into microgametes (male) and macrogametes (female) in the mosquito gut. Microgametes and macrogametes undergo fusion to form a zygote, which in turn transforms over 18–24 h into an elongated, mobile form (ookinete) that passes between epithelial cells to form an oocyst on the outer surface of the mosquito stomach wall. Within the oocyst, the parasite again undergoes differentiation and replication to form elongated, motile sporozoites that eventually rupture the oocyst, enter the body cavity, and reach the salivary glands of the mosquito, which now becomes capable of transmitting malaria parasites to humans. The duration of the *Plasmodium* developmental stage in the mosquito can vary substantially, depending on the parasite species and environmental conditions.

As mentioned above, 4 species of malaria parasites are recognized as being responsible for human infection. Although there are common and shared clinical characteristics of disease (eg, fever, chills, and myalgias) caused by the different species, each is also capable of producing distinct clinical syndromes. *P. falciparum* is considered to be the most lethal species and is responsible for severe malaria anemia as well as cerebral malaria. *P. vivax* is associated with an increased risk of splenic rupture, which has a high mortality rate when it occurs. *P. malariae* causes an indolent, persistent infection that is often missed because of the low level of parasitemia but is associated with glomerulonephritis and nephrotic syndrome in chronic cases.

Although there are >400 species of *Anopheles* worldwide, only ~70 are capable of transmitting malaria under natural conditions, and only ~40 have generally been considered to be of major importance [19]. *A. gambiae* is considered to be the most important vector of malaria in sub-Saharan Africa, where the burden of disease is greatest, but other vectors, such as *Anopheles funestus* and *Anopheles arabiensis*, are also widespread in the same location and are capable of transmitting malaria. In other malaria-endemic areas, different *Anopheles* species are responsible for transmission.

spective article, we describe the crucial role that research agencies—specifically, the NIAID—can play in assuring that biomedical research is an enabling force for control, elimination, and eventual eradication of malaria.

ADDRESSING MALARIA CONTROL, ELIMINATION, AND ERADICATION FROM A BIOMEDICAL RESEARCH PERSPECTIVE

Malaria, as a disease and public health challenge, reflects an extremely complex set of interactions between the parasite,

the human host, and the vectors responsible for transmission (Sidebar and Figure 1). Environmental, social, economic, and behavioral factors enable and foster these interactions and, thus, support perpetuation of malaria as long as the life cycle of the parasite remains intact. In principle, any intervention that achieves a complete blockage at any point in the life cycle of the parasite would effectively interrupt transmission and facilitate eradication efforts. To date, however, no single intervention with such complete activity has been identified, and until that occurs, multiple interventions operating at vari-

ous points in the life cycle of the malaria parasite will be needed to maximally inhibit progression through the life cycle and prevent transmission.

From a biomedical research perspective, the key questions relate to understanding the complex features of the life cycle and identifying, validating, developing, and deploying countermeasures that will interrupt it. This task becomes particularly problematic in light of the fact that both parasites and the vectors are extraordinarily adaptable. Drug-resistant parasites have invariably emerged and spread when effective drugs have been deployed [5],

and similarly, insecticide-resistant mosquito vectors have emerged and continued to transmit malaria after the introduction of insecticides [6]. To address the complexity of the life cycle that sustains malaria, combinations of interventions and countermeasures currently are being deployed. For example, combination drug therapy to prevent emergence of drug resistance, the use of indoor residual spraying or insecticide-impregnated bed nets to prevent transmission, and prompt diagnosis and effective treatment have reduced transmission in many endemic areas [3].

As a result of these strategies, more than 25 countries where malaria has been endemic now have a low burden of disease and are in the preelimination or elimination phase of the malaria eradication effort [3]. Such successes, however, underscore the degree of complexity associated with truly eradicating malaria. Malaria eradication requires the elimination of every last vestige of disease in all regions of the globe. However, as the malaria burden is reduced in specific areas, it will become more difficult at the population level to diagnose malaria and deploy existing countermeasures effectively. The clinical and public health utility and cost-effectiveness of existing malaria countermeasures may change as the epidemiology changes. In addition, countries must remain ever vigilant to the possibility that malaria could be reintroduced from other endemic areas as long as the possibility for transmission persists.

A final level of complexity arises amid the wide range of players who are now engaged in malaria control and elimination efforts, including ministries of health, nongovernmental organizations, development assistance programs such as the President's Malaria Initiative [7], and multilateral organizations such as the World Health Organization and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Although the international attention to malaria elimination and eradication is certainly welcome, ensuring effective coordination of effort at

both the operational and organizational levels is a daunting task.

BIOMEDICAL RESEARCH ON MALARIA: THE ROLE OF THE NIAID

Considerable enthusiasm and momentum exist for moving globally toward malaria control, elimination, and possible eradication, but there is also widespread recognition that such an ambitious effort will need to be sustained for the duration of the eradication effort and will require a substantial research base. Therefore, it will be essential to engage the biomedical research community at multiple levels and to recruit its substantial intellectual capital to address this major global public health challenge. Malaria control, elimination, and eradication will require a multifaceted approach and extensive cooperation among the many organizations committed to this effort. The NIAID is committed to continuing and accelerating its support for both basic and applied malaria research, to develop the tools and interventions that will be required to

achieve this goal. We recognize, however, that as we work with our domestic and international partners in the malaria eradication effort, we have a strictly defined role—namely, to focus on the biomedical research required to develop the tools and countermeasures to sustain the fight against this fatal disease.

As a first step, in 2008, the NIAID published both a *Strategic Plan for Malaria Research* [8] and a *Research Agenda for Malaria* [9]. These planning processes continue, being further refined and expanded through the MalERA workshops. Key goals identified by the NIAID include research to:

1. Increase fundamental understanding of the complex interactions among malaria parasites, 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 the treatment, prevention, and control of malaria;
3. Enhance both national and international research and research training in-

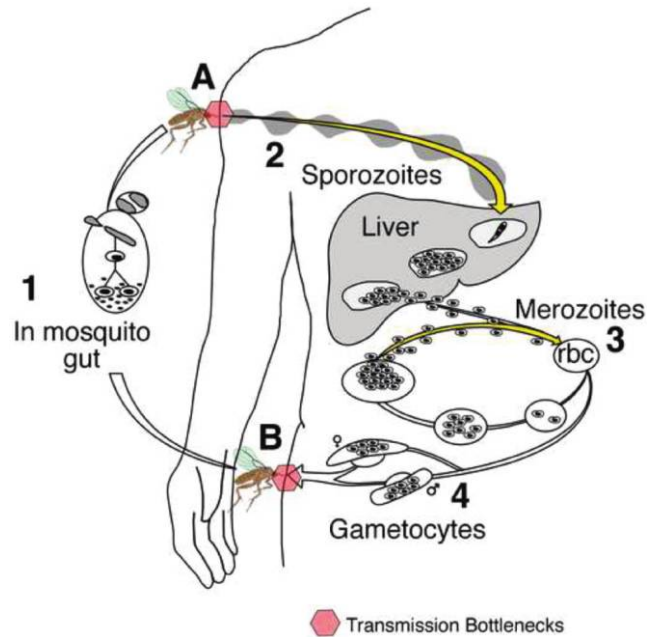


Figure 1. The life cycle of malaria parasites. A, Bottleneck in transmission of malaria from mosquito to man. B, Bottleneck in transmission of malaria from man to mosquito. rbc, red blood cell.

frastructure to meet malaria research needs, particularly for community-based and -supported clinical trials in malaria-endemic countries; and

4. Advance research to develop tools to support and sustain global efforts to control, eliminate, and eventually eradicate malaria.

In addressing these goals, it will be important to build on the substantial matrix of basic research currently in existence. For instance, complete, annotated genome sequences are already available for the human host [10–12], vector (*Anopheles gambiae*) [13], and both *Plasmodium falciparum* [14] and *Plasmodium vivax* [15]. Genome sequences also are available for rodent [16, 17] and simian [18] malaria parasites. One challenge, therefore, will be to translate these findings into new tools or strategies to intervene against human malaria.

A second challenge relates to improving our capability to diagnose malaria. The current reference standard is microscopy, although rapid diagnostic tests are increasingly being used. In the future, however, rapid, point-of-care diagnostic tests for asymptomatic, infected individuals will be required, especially in areas with decreasing or low incidence. It will be critical to identify individuals responsible for perpetuating transmission of parasites, to appropriately and effectively apply countermeasures.

Another challenge relates to blocking transmission. As illustrated in Figure 1, there are 2 bottlenecks in the life cycle, both involving the mosquito-human interface. One bottleneck occurs when the female *Anopheles* mosquito injects into a human host a limited number of sporozoites that home to the liver, where they establish infection before undergoing a replicative phase. The second bottleneck involves the uptake of sexual-stage parasites by the mosquito from the human host. These parasites undergo fertilization and then establish infection in the insect vector. To date, most interventions have focused on eliminating the mosquito

population (eg, insecticides) or reducing contact by physical barriers (eg, bed nets), but these biological processes clearly are amenable to other interventions that inhibit or prevent altogether development of the parasite in either the host or vector. Examples of such interventions currently being investigated include vaccines targeting the preerythrocytic stages and sexual stages of the parasite, transgenic mosquitoes that fail to support intravector parasite development, drugs that target the liver phase of infection, or the parasite sexual stages that are transmitted to mosquitoes.

It is also worth noting that, in some situations (eg, when transmission is seasonal), there may be ecological bottlenecks that reduce or limit interactions between the mosquito vector and the human host, and interventions that target such ecological vulnerabilities may have profound effects. Different vectors, however, may be responsible for transmission in different settings, and therefore, interventions that effectively target a vector principally responsible for transmission in one setting may be ineffective in other settings where transmission occurs via a vector living in a different biological niche and exhibiting different behavior. Thus, future research based on a better understanding of vector biology and ecology will be needed to provide not only new tools for vector management but also insights into how to better deploy such interventions.

A fourth and significant challenge involves expanding the research base for *P. vivax* and other human nonfalciparum malarias. The underlying biology and pathogenesis of these other malarias are distinct from those of *P. falciparum* (Sidebar), and there are significant scientific and technical hurdles to overcome to facilitate the study of these other malarias. Validated reagents and reliable cell culture systems still need to be developed and distributed broadly to accelerate the pace of research.

Despite recent advances in control and elimination, malaria will continue to be a

major clinical problem in many areas of the world for years to come. It remains imperative to continue to pursue pathogenesis research to identify new targets and processes for clinical intervention. As long as transmission of malaria persists, research to optimize clinical case management with currently available therapies (eg, combination drug treatment) and future therapies will be key to reducing malaria mortality and morbidity. Given the long projected time frame for malaria elimination and, hopefully, eradication, as well as the continuing threat of emergence and spread of drug-resistant parasites, a pipeline for the discovery and development of new therapies must be expanded and maintained so that hard-won successes are not negated in the future.

The final challenge is to ensure the vigor and sustainability of the substantial biomedical research efforts that will be required to eliminate and ultimately eradicate malaria. Such efforts must empower and support those investigators and public health officials working in areas at risk for malaria. Substantial collaboration with scientists in developing countries will be needed to identify and define (or redefine) key research areas as they evolve or emerge over time. Scientists working in malaria-endemic areas must enjoy the benefits not only of technology transfer but also of scientific rigor, debate, and a sense of shared purpose with their colleagues around the globe. Training programs and international connectivity to engage and sustain the “best and brightest” in the global scientific community must therefore figure prominently in future research efforts.

SUMMARY AND CONCLUSIONS

Malaria has proven to be a formidable adversary over many centuries; however, recent, hard-won successes in reducing its scope by means of a wide range of control programs have engendered a new sense of purpose and confidence in malaria elimination and, ultimately, eradication. Previous attempts at malaria eradication have

taught us significant lessons, so that today there is a greater recognition that a sustained and robust research foundation is absolutely required. New insights, new tools, and new thinking will be necessary as these efforts proceed.

As the lead agency in the US government charged with supporting biomedical research on malaria, the NIAID has long maintained robust and vibrant programs to better understand the fundamental biological aspects of malaria and to provide the research basis for identification, development, validation, and evaluation of new interventional tools and strategies. Last year, with the publication of the *NIAID Strategic Plan for Malaria Research* and the *NIAID Research Agenda for Malaria*, the NIAID outlined its vision of malaria research and development in the context of a changing landscape and provided a framework for future research directions, priorities, and efforts within its purview. We look forward to engaging broadly and working closely with the global research community and other partners to address the challenges and ambitious goals of a most important global public health priority: the elimination and eventual eradication of malaria.

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