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The challenge of malaria eradication in the twenty-first century: Research linked to operations is the key

Joel G. Breman[a,*], A. David Brandling-Bennett[b,1]

[a] Fogarty International Center, National Institutes of Health, 16 Center Drive, Bethesda, MD 20892, United States
[b] Infectious Diseases Development, Global Health Program, Bill & Melinda Gates Foundation, Seattle, WA 98102, United States

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ABSTRACT

Interest and support for malaria control, eradication, and research has increased greatly over the past decade. This has resulted from appreciation of the huge medical, social, and economic burden that malaria exacts from endemic populations. Recent breakthroughs in drug development (artemisinin-based combination treatments), preventive interventions (long-lasting, insecticide-treated bed nets), improved diagnosis (rapid diagnostic tests), and community mobilization have resulted in deployment of new anti-malarial tools. National programs supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, the U.S. President's Malaria Initiative, and other donors have resulted in substantial reductions in malaria morbidity and mortality. Bill and Melinda Gates have given great impetus to eradication with support for the development of key research strategies and direct funding of innovative research projects, including malaria vaccine and drug discovery, that could decrease disease and transmission. Linking research to field operations is a strategy that succeeded for smallpox eradication and will be required for the demise of malaria.

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1. Introduction

Over the last decade there has been greatly renewed interest and actions supporting malaria research, control, and eradication. The huge-recurring medical, social, and economic burdens of malaria have been major factors in this increased attention. Estimates of malaria cases globally have ranged from 215 million to 659 million malaria cases per year [1–4]. *Plasmodium falciparum* causes the majority of clinical attacks but *Plasmodium vivax* is increasingly recognized as an important contributor to the malaria toll. The World Health Organization estimates the number of malaria deaths as over 780,000 annually – ~90 per hour – mainly children under five years of age suffering *falciparum* malaria in Africa [1]. Malaria and poverty are closely connected. In 2001, the productivity lost in malarious African countries was estimated at billions of dollars, with economic growth of endemic African countries impaired by over 1% per person annually from 1965 to 1990 [5,6].

Acceleration of anti-malaria activities over the past decade has been stimulated by the Multilateral Initiative on Malaria (MIM), the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), The U.S. President's Malaria Initiative (PMI), the Roll Back Malaria Partnership (RBM), the World Health Organization (WHO), and several other research and public health coalitions [7–10]. In October 2007, Bill and Melinda Gates hosted a malaria forum at which they announced passionately their reasons for supporting the goal of malaria eradication. This ambitious and audacious commitment, immediately joined by Margaret Chan, Director General of WHO, has invigorated malaria research and public health communities worldwide. This paper will review the special opportunities for advancing malaria control and eradication early in the twenty-first century and the need for research to be closely linked to field operations.

2. Biological and operational feasibility of eradication

The eradication of human malaria is feasible biologically. No known significant animal reservoirs exist for *P. falciparum*, *P. vivax*, *Plasmodium malariae*, and *Plasmodium ovale*; *Plasmodium knowlesi*, recently identified as causing human infections in Southeast Asia, is probably a zoonosis with long-tailed and pig-tailed macaques (*Macaca fascicularis* and *Macaca nemestrina*, respectively) their reservoirs. The female *Anopheles* mosquito is the vector for malaria; about 70 species are known transmitters. For many of these vectors, their indoor and outdoor biting and resting habits are not well known but are critical factors in efforts to reduce and interrupt transmission. The incubation period for malaria is about two weeks; persons with partial acquired immunity may have mild

* Corresponding author. Tel.: +1 301 496 4162.
E-mail addresses: joel.breman@nih.gov, bremanj@mail.nih.gov (J.G. Breman), David.Brandling-Bennett@gatesfoundation.org (A.D. Brandling-Bennett).
[1] Tel.: +1 206 709 3160.

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illness or be asymptomatic. Non-immune persons will typically have an acute febrile systemic presentation, and nearly all symptomatic persons will have parasites detectable in the blood, although the sequestration of parasites in the peripheral circulation may make infection difficult to detect using microscopy or rapid diagnostic tests. *P. vivax* and *P. ovale* can relapse (usually within a few months of the initial infection) requiring treatment of the dormant liver stages (called "hypnozoites") for complete elimination of the parasite [11]. Radical treatment to eliminate hypnozoites requires a two-week course of primaquine, a drug which can cause serious hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient persons. *P. malariae* (and very rarely *P. falciparum*) parasites have been detected in blood months or years after the original infection, but they do not have dormant liver stages like *P. vivax* and *P. ovale*.

Current antimalaria strategies launched in the early 2000s have been successful in numerous countries; these strategies have been drug use (treatment and prevention), classical vector control (insecticide residual spray and mosquito larviciding), preventive interventions [long-lasting, insecticide-treated bed nets (LLINs) and other materials, repellents], environmental modification (drainage and filling of mosquito breeding sites), and political and social mobilization (engaging global and local leadership and communities in elimination efforts). These strategies and related actions succeeded in freeing much of the world from malaria during the latter half of the twentieth century [12] (Figs. 1 and 2). For areas with low and moderate transmission the current interventions may be satisfactory for elimination, although achieving this for *P. vivax* will be very challenging because the parasite can persist dormant in the liver for months or years. For areas with high transmission improved and newer tools will be needed for eradication. The distribution of *falciparum* and *vivax* malaria is shown in Fig. 2; *falciparum* is essentially the main species in sub-Saharan Africa.

3. Lessons for eradication from history

Malaria eradication was first undertaken by the World Health Organization in 1955. This followed the appreciation of dichlorodiphenyl-trichloroethane (DDT) as a remarkably effective and safe insecticide, used extensively in the Second World War for control of malaria, typhus, and other vector-borne diseases. Chloroquine and quinine were fully effective antimalaria drugs for treatment and prevention, and primaquine was being introduced to prevent relapses. North America and Australia had become free of malaria in the mid-1950s and several European countries undertook very successful control and elimination efforts. By the 1960s, major declines in malaria were recorded in Asia and Latin America, most dramatically in India and Sri Lanka (ex-Ceylon) [12,13]. Paradoxically, sub-Saharan Africa was not included in the global program, because of its poor health infrastructure and intensity of transmission. Eradication in Africa was to be done at the end of the global program but was never attempted. Despite many gains made during the program, the eradication effort was terminated in 1969. This followed the awareness that eradication was not feasible in Africa and elsewhere because of the lack of political support, dearth of human and material resources, and the fact that the scientific, epidemiological, operational, and administrative strategies and tactics were inadequate and required reassessment. In addition, mosquito resistance to DDT had been noted in Europe since the 1950s. When the program stopped, devastating malaria epidemics began in countries that had achieved remarkable success, notably Sri Lanka and India [12,13].

A major problem throughout the 1955–1969 eradication program was that basic, clinical, and operational scientific research did not accelerate during the program, nor was disease surveillance prioritized highly. With the eradication program's termination, research and field malariologists, including critical parasitology and entomology specialists, entered other fields or retired; the

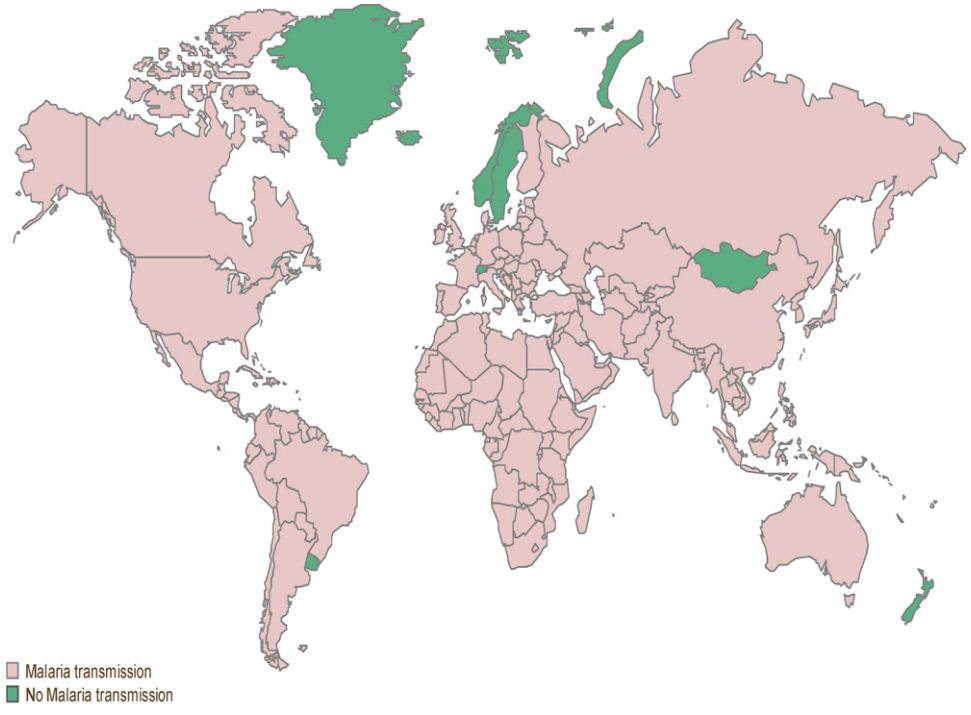

Fig. 1. Global extent of malaria transmission in 1945.
Source: Malaria Elimination Group of the Global Health Initiative, website: http://www.ghi.gov/.

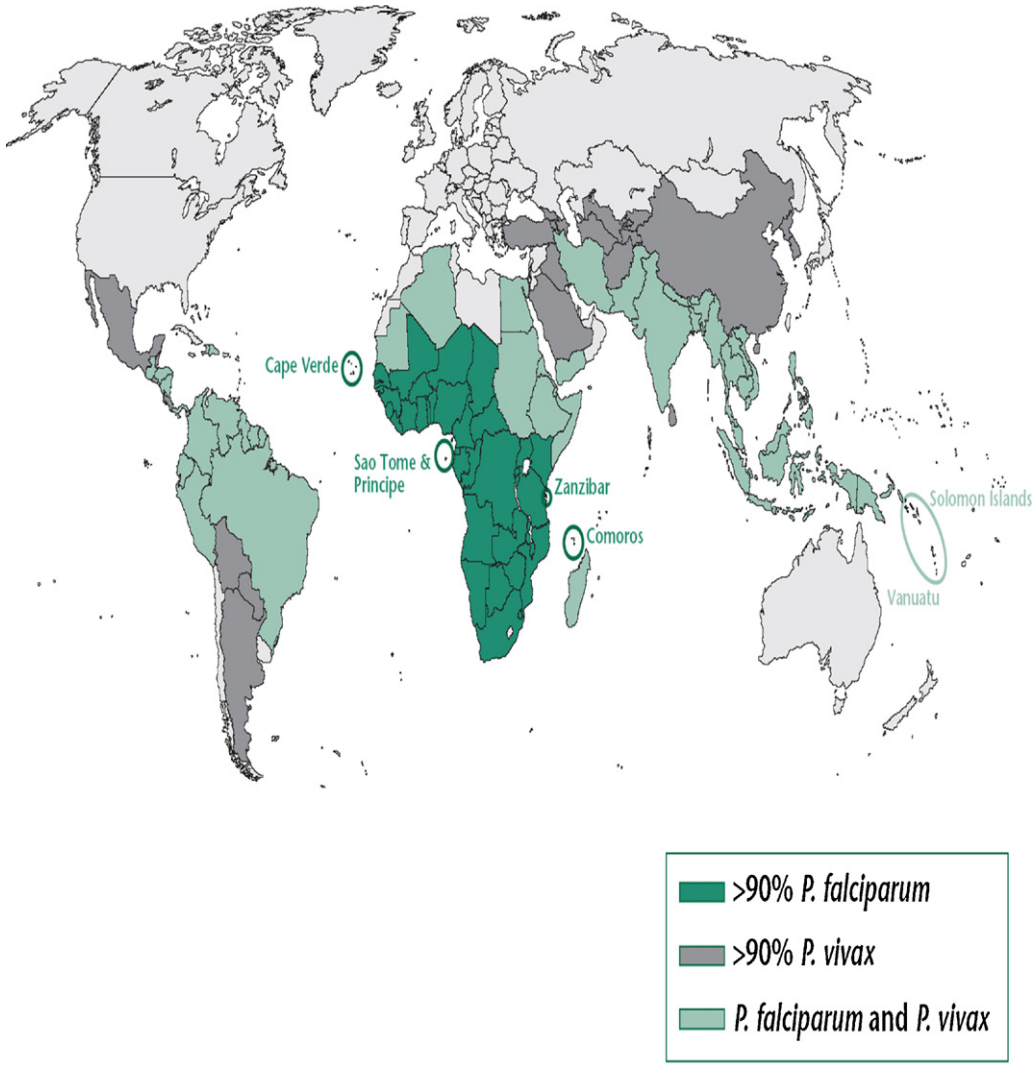

Fig. 2. Global distribution of *Plasmodium falciparum* and *P. vivax*, 2011.
Source: Malaria Elimination Group of the Global Health Initiative, website: http://www.ghi.gov/.

exception was a continuing antimalarial drug discovery program at the Walter Reed Army Institute of Medical Research, which had the primary objective of developing treatment and prevention measures for the military. In the late 1970s and early 1980s, the WHO recommendation was that the focus should be on reduction of malaria mortality in young children in areas of intense transmission; this meant assuring prompt and effective treatment. However, a new conundrum started surfacing and spreading – that of resistance of *P. falciparum* to chloroquine in Asia and South America in the 1950s and in sub-Saharan Africa in the 1980s and 1990s. A detailed review of malaria control programs over the past 100 years showed that the most effective control programs are those that have multilateral partners and are linked closely to research [14]. The smallpox eradication program has shown that focus on intensified surveillance, outstanding management along with focused research and innovations tied to field needs were the keys to eradication – and these will be the keys to malaria eradication [15].

4. Recent initiatives, successes and new strategies

Since the reinvigoration of all aspects of malaria research and control in the late 1990s there have been many notable successes. With knowledge that the main burden of malaria was in Sub-Saharan Africa, a cadre of African researchers working in support of malaria control needed to be strengthened and in most places created. African scientists required support; they established collaborative linkages with national control programs and with colleagues in advanced research settings and with each other through modern communications networks. The Multilateral Initiative on Malaria (MIM), an international coalition of research and funding agencies which began in 1997 [7,8,16], has led to over 100 African scientists from more than 25 institutions publishing over 120 articles in the past decade. MIM was initially hosted by North American and European institutions but is now based in Africa. Shortly after MIM began, the Roll Back Malaria Partnership began. RBM has been a successful coordinating and advocacy alliance drawing attention to the problem of malaria and need to control and eliminate the disease by eliciting support from high level political leaders, influential personalities (including celebrities), and funders. RBM is located at WHO, Geneva, and works closely with the Global Malaria Programme, WHO, responsible for policy and strategy formulation and supporting operational research and control activities in malarious countries. The major funds for malaria control have come through the Global Fund

Table 1
President's Malaria Initiative activities, 2006–2010.

Activity	Procured (millions)	Distributed (millions)
Insecticide treated nets (ITNs)	45.4	30.3
Intermittent preventive treatments/pregnancy (IPTp)	10.3	5.1
Rapid diagnostic tests (RDTs)	25.1	16.1
Artemisinin-based combination treatments (ACTs)	95.3	67.5
Insecticide residual spraying (IRS)	Number (millions)[a]	Houses sprayed (millions)[a]
People protected by IRS	100.3	24.2
Training	Number (thousands)[b]	
Antenatal care and IPTp distribution	45.9	
Malaria diagnosis (RDTs and microscopy)	23.2	
Case management	142.3	

[a] May have been protected by IRS more than once.
[b] May have been trained more than once.

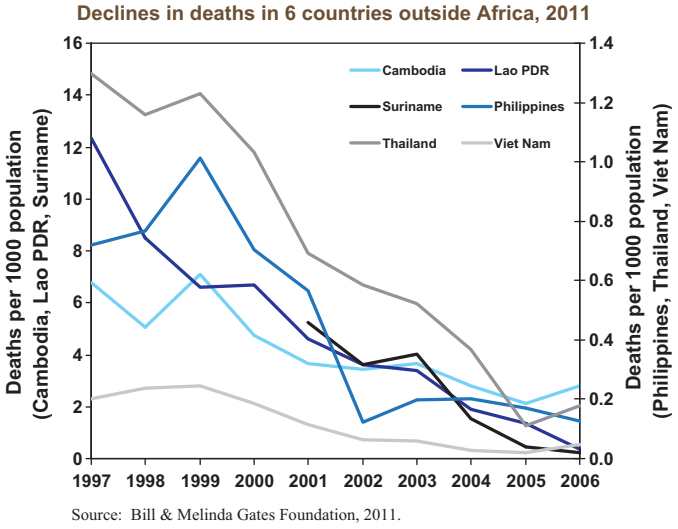

Fig. 4. Declines in deaths in 6 countries outside Africa, 2011.

which began in 2002. This fund has approved cumulative funding of $22.4 billion by 2011 of which about 30% has been for malaria programs in 50 malarious countries, mainly for bed nets, drugs, diagnostic materials and other support. Over 190 million LLNs and 170 million antimalarial treatments have been distributed via Fund support since 2004 [9]. More recently the U.S. Agency for International Development funded PMI has supported malaria control efforts in 17 African countries with implementation by the endemic nations and the Centers for Disease Control and Prevention [10]. Between 2006 and 2010 the PMI has provided major commodity and training support to those countries (Table 1) [10]. The PMI has distributed tens of millions of insecticide-treated nets (ITNs), intermittent preventive treatments during pregnancy (IPTp), rapid diagnostic tests (RDTs) and artemisinin-based combination treatments, in addition to protecting over 100 million people by insecticide residual spraying (IRS). These considerable accomplishments are the result of the first four years of PMI funding (FY 2006–2009) representing 60% of the $1.265 billion requested. The most recent World Malaria Report 2010 issued by WHO documents a major decrease in malaria cases following scale-up of long-lasting insecticide-treated nets (LLINs) and artemisinin-based combination treatments (ACTs) in several African countries since 2000, notably, Zambia, Eritrea, Ethiopia, Kenya, Rwanda and The Gambia [1]. Similar decreases in all-cause childhood mortality are reported from several PMI countries (Fig. 3).

Outside of Africa, a decrease of more than 50% in the number of confirmed cases of malaria between 2000 and 2009 was reported in 32 of the 56 malaria-endemic countries while downward trends of 25%-50% were seen in 8 other countries. The declines in death in six Asian countries since 1997 are shown in Fig. 4. Morocco and Turkmenistan were certified by WHO in 2009 as having eliminated malaria. These decreases reflect effective implementation of current technologies, establishment of malaria as a priority disease, and funding support.

5. Eradication strategy

The RBM Partnership and WHO have divided malarious countries into four groups: those that never had malaria or eliminated the disease; those that have recently qualified for certification of elimination or with conditions conducive to elimination (26 countries); countries with unstable malaria which are amenable to "sustained control" and ultimately elimination with current tools (32 countries); and, countries with intense stable transmission and relatively poor health infrastructure requiring "scale up for impact" (48 countries, 41 in sub-Saharan Africa) [1,4]. Countries with the

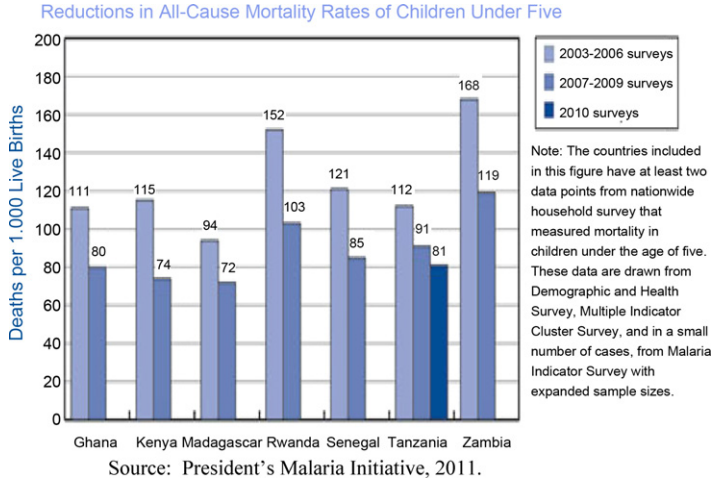

Fig. 3. Reductions in all-cause mortality rates of children under five in seven countries within the President's Malaria Initiative, 2003–2010.
Source: PMI website: http://www.pmi.gov/.

potential to achieve elimination with current technologies have been identified, advised, and supported by the Malaria Elimination Group, an international multidisciplinary group coordinated by the Global Health Group at the University of California San Francisco [17].

The malaria eradication strategy is based on three principles:

1. Elimination of infection and transmission in areas of low and moderate endemicity, primarily in countries "at the margins" of heavy transmission areas. *P. falciparum* elimination will be a priority and possibly easier than elimination of *vivax* because the latter is a relapsing infection.
2. Aggressive control in areas of high transmission. By scaling up delivery of available tools high coverage will be attained with reduction in cases and deaths. Once control is achieved major efforts will be required to sustain the gains and plan for interrupting transmission when feasible.
3. Research and development to protect and improve existing tools and provide new tools. Newer, better, and safe drugs, vector control, personal protection, and immunological (vaccine) interventions and delivery mechanisms will all be needed to progressively eliminate *vivax* malaria and maintain a malaria-free status in each country until global eradication of each parasite is achieved.

The immediate challenges to control, elimination, and eradication are parasite resistance to drugs, vector resistance to insecticides, human resistance to the use of available tools (nets and preventive drugs), lack of sensitive surveillance systems, and need for a trained cadre of researchers and operational personnel.

Table 2
Malaria eradication research agenda priorities: key conclusions.

1. Basic science
- Biology of liver stage and sexual forms (gametocytes)
- Vector ecology and behavior
- Immunology, especially tied to vaccines

2. Vaccines
- Transmission-blocking a priority for elimination and eradication

3. Drugs
- One formulation given at single encounter for radical cure and prevention or prophylaxis
- If not a single drug, need better and safe drugs to:
  - ◯ Overcome resistance
  - ◯ Attack latent liver stages (hypnozoites)
  - ◯ Be suitable for mass administration
  - ◯ Provide prevention or prophylaxis

4. New insecticides to avoid resistance
- For insecticide-treated nets and indoor residual spraying
- Long-duration formulations

5. New vector control tools
- Consumer and environmental friendly; cheap and easy to apply
- Target outdoor- and indoor-biting and resting mosquitoes
- Modified mosquitoes that reduce vectorial capacity permanently

6. Diagnostics
- Detect asymptomatic and low parasite levels
- Detect gametocytes

7. Monitoring and evaluation
- Usable, detailed and timely data to measure impact and manage programs
- Test different surveillance models: use "surveillance as an intervention"

8. Modeling
- Identify and characterize effect of key investments
- Address optimal intervention mix for different settings

9. Cross cutting: health systems and operational research
- Strengthen key components of health services
- Address financing, delivery, performance, engagement of communities and political leaders

6. The malaria eradication research agenda (malERA)

It is recognized that research will be needed to control and eradicate malaria particularly in the countries with the most intense transmission. A two-year exercise addressing research needs in support of eradication supported by the Bill & Melinda Gates Foundation was recently completed; over 200 malaria and public health experts considered nine areas where inventions and innovations for a renewed attack on malaria are needed. The findings were published in a special issue of *PLoS Medicine* [18–27]. The top priorities for several of the categories are listed in Table 2.

1. **Basic science**. Priorities include in vitro culture systems for the complete life cycle of *falciparum* and *vivax* parasites and a liver culture system to study hepatic stages. Genetic technologies for manipulation of *Plasmodium* need improvement, and the entire parasite metabolism needs to be characterized to identify new drug targets [19].
2. **Vaccines**. There are multiple sites in the parasite that are potential targets for vaccines, including parasite forms in the human liver and red blood cells and those that infect the mosquito (Fig. 5). Vaccines that interrupt transmission include both "classical" transmission blocking products that target the sexual stages of the parasite (called "gametocytes") that infect the mosquito and the parasite stages that infect and develop in the liver. The latter, called pre-erythrocytic vaccines, prevents infection of red blood cells, which causes the symptoms and complications of malaria [20]. The PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline Biologicals have jointly supported the development of RTS,S/AS01, which is now in phase 3 trials in African children. In a preliminary analysis of that trial, the vaccine has shown a 50% protective efficacy against clinical disease and a 35% protective efficacy against severe malaria. These results offer promise that there will be an efficacious malaria vaccine available for deployment in the near future [28]. Other vaccines, some of which are building on the RTS,S construct, are aiming to achieve a protective efficacy of at least 80%, which is the level needed to significantly impact transmission. By contrast, blood stage vaccines are being de-emphasized because they are less likely to contribute to reductions in transmission, although they could protect from illness, complicated malaria, and death.
3. **Drugs**. Antimalarial drugs will be essential in moving from control to eradication. The ideal eradication drug would be a co-formulated combination suitable for mass administration that could be administered in a single encounter at infrequent intervals; the treatment would result in a radical cure of all life cycle stages of all five malaria species infecting humans ("Single Encounter Radical Cure and Prophylaxis," or SERCaP) [21]. The Medicines for Malaria Venture (MMV) is a coalition of private and public partners devoted to drug discovery and has Gates Foundation support. An alarming recent finding is that artemisinin resistance has appeared in southeast Asia; a control action plan and research agenda have been developed and initiated to confront this perilous development [29]. Surveillance for drug efficacy remains essential for malaria control and elimination.
4. **Vector control**. Strategies and tools to address outdoor resting and outdoor biting mosquitoes are a top priority. Radically new approaches, such as the genetic modification of mosquitoes, may be needed to reduce the high vectorial capacity in many malarious regions. Active participation of individuals and communities at risk in vector control efforts will require innovative techniques and community leadership [22].
5. **Diagnosis and diagnostics**. Newer, improved tests for detecting low level parasitemia are priorities. More sensitive tests for *P. vivax* are needed as are gametocyte-specific tests. Field-ready G6PD deficiency tests and surveillance strategies will be

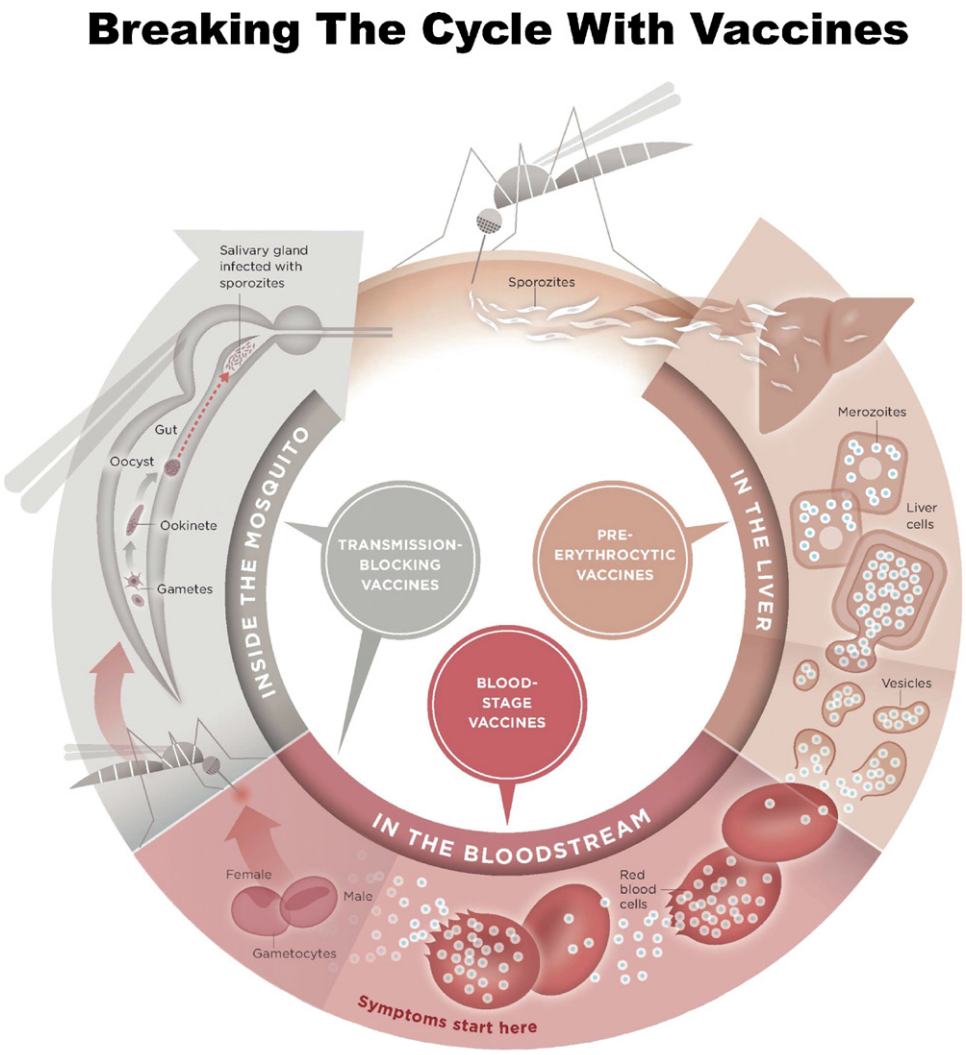

Fig. 5. Breaking the cycle with vaccines.

required when treatments with primaquine or similar drugs causing hemolysis in sensitive individuals are used widely to interrupt transmission [23].

6. **Health systems and operational research**. The effectiveness of a control or eradication program is defined by a cascade of factors, only one of which is intervention efficacy. Research must consider actions taken at the local health facility, district, national and regional levels, and at the home; these actions must assure optimal coverage and use of malaria services and compliance and adherence of providers and patients to treatment and prevention guidelines. Research is needed in the most effective means of improving governance, health workforce, health financing, health technologies, health information, and service delivery [24].
7. **Monitoring, evaluation, and surveillance**. More sensitive, prompt, feasible, and simple means of detecting infections and measuring transmission will be needed for eradication. Surveillance research to define actively and quickly hot spots and refractory areas will be a priority: passive surveillance methods used currently are too slow and inefficient. The use of maps, remote sensing, cell phones and other modern information technologies to report, analyze and feedback information for prompt actions is a requirement for eradication [25].
8. **Modeling**. A biomathematical modeling agenda needs to support operations by: determining how resources should be allocated optimally; informing how resistance of parasites to drugs and mosquitoes to insecticides can be mitigated; determining the impact of interventions – i.e. how can the tools, health systems, and social-economic settings be optimized for progressing toward eradication; and, assessing economic costs, capital investments and human resources required [26].
9. **Cross-cutting issues**. How can malaria eradication strengthen the health system? What training, information systems, and community engagement approaches and models are needed to achieve eradication [27]?

7. Conclusions: what lies ahead

The most immediate challenge is to sustain and extend the gains of the last decade, both in tropical Africa and elsewhere. Strategies and tactics to eradicate malaria will continue to focus on intensification of effective delivery of proven interventions in all endemic countries while improved and new tools are moved

from the laboratory to the field. RBM has set ambitious objectives of achieving near zero deaths by 2015, while reducing malaria cases by 75% compared with 2000, and eliminating malaria in 10 countries, including the entire European Region. Achieving those laudable objectives will be very difficult given the current global economic situation unless current donors increase their commitments and new, innovative sources of funding are found. All malarious countries, especially those in the heavily endemic "scale up-for-impact" category, will require long-term investments in operations, monitoring, and evaluation. Intensified research and development are needed to preserve and protect existing tools from the threat of resistance and to bring forward new, more effective and efficient tools, particularly ones that can interrupt transmission where it is most intense or persistent. It is likely that we will need multiple tools in most settings where transmission remains, and we must assume that finding a magic bullet such as a highly effective vaccine that provides life-long protection is unlikely. Global eradication will take sustained political will, commitment, and financing over several decades, during which time we must deploy effectively available tools to reduce the burden that malaria places on the most vulnerable.

The key to knowing how well control is occurring on the way to eradication will be an effective surveillance network; the network must cover disease trends, parasite prevalence, mosquito ecology, drug and insecticide resistance, environmental conditions and program services. Surveillance should use the most modern information technologies with program progress summaries available rapidly to decision makers for dissemination and mid-course corrections. Training of every level of health worker in malaria diagnosis, management and prevention will be another key to eradication. Drugs and vaccines that interrupt transmission will be crucial tools for hastening eradication. It is not known when these new interventions will be available in the anti-malaria arsenal or fully deployed. Even if the rapid progress made over the past decade can be maintained, the biological, technical, operational, and financial challenges, particularly in the final stages of elimination, are such that it would be the middle of the twenty-first century before eradication could be achieved.

Conflict of interest: The authors declare no conflict of interest.

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