MALARIA

OUR MISSION
Guided by the principle that all lives have equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program supports this mission by seeking to ensure that life-saving advances are developed and reach those who need them most.

We focus on problems that have a major impact on poor people in the developing world but get too little attention and funding. Where proven tools exist, we support sustainable ways to improve their delivery. Where they don’t, we invest in research and development of new interventions such as vaccines, drugs, and diagnostics. Our financial resources, while significant, represent a very small fraction of the overall funding needed to improve global health on a large scale. We therefore advocate for the policies and resources needed to provide people with greater access to health solutions. Strong partnerships are essential to our success in making a difference and saving lives.

THE OPPORTUNITY
Recent successes demonstrate that the fight against malaria can be won. In the last decade, more than a third of the 108 malaria-endemic countries saw a 50 percent decrease in their malaria burden. They achieved this by using a combination of effective interventions—reliable diagnostics, indoor residual spraying, long lasting insecticide-treated bed nets, and treatment with artemisinin-based combination drugs. The global response to malaria has also improved dramatically in the last decade, with malaria funding increasing almost sixfold since 2003, and the global malaria-fighting community, led by the Roll Back Malaria Partnership, coordinating a response to control, eliminate, and eventually eradicate this deadly disease through the Global Malaria Action Plan.

However, even with the array of tools and treatments available, malaria caused 243 million cases of fever and about 863,000 deaths in 2008, mostly among young children in Africa. While effective tools are being successfully scaled up and are reducing the burden of malaria in some endemic countries, coverage rates remain low in many areas. Additionally, parasite resistance to antimalarial medicines and mosquito resistance to insecticides are major threats to the effectiveness of existing tools. Whether used alone or in combination, current tools are simply insufficient to reach the goal of global eradication.

Malaria control: reducing the malaria disease burden to a level at which it is no longer a public health problem.

Malaria elimination: the interruption of local mosquito-borne malaria transmission. A country is certified by the World Health Organization as having eliminated malaria after transmission by anopheles mosquitoes has been fully interrupted for at least three consecutive years.

Malaria eradication: permanent reduction to zero of the worldwide incidence of infection caused by a particular malaria parasite species. Intervention measures will no longer be needed once eradication of all human malaria species has been achieved.
OUR STRATEGY
We aim to improve existing tools and discover new ones to reduce and prevent malaria transmission, and in the long term, eradicate malaria worldwide. Our efforts support the Global Malaria Action Plan’s targets of reducing global malaria deaths to near zero by 2015, eliminating malaria in 8–10 countries by 2015, and in the long term, eradicating malaria globally by reducing the incidence of malaria to zero through progressive elimination.2

Our strategy is based on our assumption that the preventive and curative tools that are currently available are insufficient to achieve global eradication, especially in the face of emerging resistance to drugs and insecticides. With eradication as the aim, our strategy focuses not only on improving current approaches, but also on intensive research and development toward the creation of new vaccines, vector-control tools, drugs, and diagnostics to prevent and interrupt transmission of both major species infecting humans, P. falciparum and P. vivax. We are also engaged in modeling to better understand the potential impact of new tools and the optimal combination of such tools in achieving eradication in various settings. Underlying these efforts is our ongoing advocacy for sustained financing and supportive policies that facilitate the fight against malaria.

INTERVENTION AREAS
Develop effective malaria vaccines
The most significant achievement in malaria vaccines to date has been the clinical development of the RTS,S vaccine, a pediatric vaccine that reduces the number of clinical malaria episodes experienced by children. In Phase II trials, RTS,S conferred up to 65 percent protection against malaria infection and 53 percent protection against malaria illness and was associated with a reduced risk of death, severe malaria, and pneumonia.3

Assuming the current timelines remain on track, RTS,S could be approved for use by 2015. However, there are a number of challenges to the licensure and rapid uptake of RTS,S, including a lack of data on the cost-effectiveness of the vaccine, a lack of awareness about RTS,S in endemic countries, and a lack of financing to ensure its delivery.

Additionally, if malaria is to be eradicated, second-generation, more efficacious, vaccines are needed that can not only reduce malaria in various target groups, but block its transmission across the entire population at risk.

To ensure that RTS,S is available and accessible to populations at risk and develop new vaccines to protect the broader population, we are currently making a number of investments to:
• facilitate licensure and gather cost-effectiveness data on the RTS,S vaccine and develop an investment plan for the appropriate delivery of the RTS,S vaccine
• develop vaccines that can interrupt malaria transmission, including a second-generation RTS,S vaccine or new vaccines based on transmission-blocking antigens
• conduct research that can guide rational vaccine development, including the development of a P. vivax culture system and the study of immunological correlates of infection

A key outcome measure in this area will be the number of additional vaccine-candidate antigens, new adjuvants, and new formulations that progress through development. Together with our partners, particularly the Malaria Vaccine Initiative at PATH, we will continue to apply industry standards to monitor outcomes.

Develop effective drugs and diagnostics
Globally, artemisinin-based combination therapies (ACTs) are the preferred treatment for malaria and are both effective and well tolerated in patients. However, ACTs are expensive due to the high and unstable cost of artemisinin. Patients thus often purchase cheaper, less effective drugs, artemisinin monotherapies, or poor-quality counterfeit drugs, increasing the risk of developing drug resistance. Alarmingly, resistance of P. falciparum to artemisinin has been observed in Southeast Asia and may be spreading.4

There is a need to tackle the high cost of artemisinin and spread of resistance, and at the same time diversify the drug pipeline so that there are new non-artemisinin combinations developed for various indications.

Our strategy supports the effective delivery of ACTs, the containment of artemisinin resistance, and the discovery of novel malaria drugs. The Medicines for Malaria Venture (MMV) is our major grantee for this effort, and has developed what is now the largest malaria-drug pipeline in history. We also support efforts to determine the appropriate use of accurate diagnostics. We are currently making investments to:
• ensure a stable supply of quality assured artemisinin through the introduction of high-yield plants and biosynthetic artemisinin
• ensure greater access to ACTs through the Affordable Medicines Facility for Malaria, which will make ACTs more affordable to public, private, and non-profit buyers
• prevent the spread of resistance through the elimination of poor quality or counterfeit drugs and monotherapies and the promotion of improved surveillance systems and malaria control programs
• develop new non-artemisinin-based treatments for several indications, including prevention, long-lasting prophylaxis, liver-stage infection, and transmission blocking
• determine the role of diagnostics in treatment, monitoring impact, and elimination

We will monitor success in this area based on the number of drugs and diagnostics that successfully make it through all stages of development, licensure, and timely delivery to those who need them. We will also assess their impact on artemisinin-tolerant parasites in Southeast Asia.

Develop effective vector-control tools
Indoor residual spraying (IRS) and long-lasting insecticide-treated bed nets (LLINs) are the two most effective interventions to reduce and interrupt malaria transmission available today.

Unfortunately, their success may be threatened by the mosquitoes’ resistance to the pesticides used in both tools. Additionally, both tools are less effective against species of mosquitoes that do not rest or feed indoors.

Our strategy supports efforts to improve existing tools or develop new vector-control tools required to interrupt transmission in all settings. We are currently making investments to:
• improve the impact of current vector-control tools, by developing longer-lasting IRS, insecticides to be used in combination, and active ingredients that avoid known resistance mechanisms
• identify new tools and strategies for malaria elimination and eventual eradication that exploit the novel aspects of the ecology or behavior of vectors, including spatial repellants, sugar-baited traps, and animal treatments
• determine which tools, alone or in combination, are the most effective for eliminating malaria in different settings

Together with our partners, particularly the Innovative Vector Control Consortium, we will monitor success in this area by the number of improved tools and new tools that progress through development and the identification of the optimal package of vector-control tools to interrupt malaria transmission.

Model and test approaches for the elimination and eventual eradication of malaria
The global malaria community now has a number of highly effective interventions to control malaria, but there are many unanswered questions on how and where to deploy these to achieve sustained control, elimination, and eventual eradication. Questions include: What is the impact of intensifying coverage of existing interventions on malaria control? In which countries is elimination currently feasible? What combination of tools will be optimal to accomplish elimination of malaria in specific transmission settings?

Our strategy supports gathering evidence about which set of interventions will have the most impact on interrupting malaria transmission and modeling to inform the optimal combinations of tools for specific geographic and transmission settings. We are currently making investments to:
• capture and share lessons learned on the impact on malaria control of scaling-up and sustaining high coverage of existing interventions
• learn how to sustain financing and commitment to malaria control and elimination as the disease burden declines
• identify countries where malaria elimination is feasible through the development and application of a tool to assess the feasibility of malaria elimination
• capture and share lessons learned on effective strategies to accomplish malaria elimination
• identify the optimal packages of existing and new tools to achieve elimination

Advocate for effective policies and financing
In the past decade, funding for malaria control has increased dramatically, rising from approximately US$ 0.3 billion in 2003 to an estimated US$ 1.7 billion in 2009.1 The massive increase was made possible by the Global Fund and commitments by the United States President’s Malaria Initiative, UNITAID, the World Bank, and other bilateral and multilateral agencies.

Despite the increase in resources, costing data in the Global Malaria Action Plan (GMAP) indicates a significant US$5 billion annual funding gap to achieve and sustain universal coverage and pursue research and development (R&D).2 The momentum gained by the remarkable growth in partners, political will, and funding needs to be sustained over the long term to maintain progress on sustained scale-up, enable further progress in R&D for transformative new tools, and support countries in their efforts to eliminate and eventually eradicate malaria.

Our strategy includes advocacy for effective policies at the global and national levels that support malaria elimination
and eradication and sustained financing to cover R&D and implementation efforts. We are currently making investments to:

- encourage continued funding commitments by current major donors and mobilize new donors for malaria R&D
- support efforts to track countries’ progress against malaria
- disseminate success stories about meeting GMAP targets
- capture and disseminate lessons learned on effective policies to improve global and country-level efforts

Progress on malaria policy and advocacy will be evaluated by the level of global funding for malaria control and R&D (through bilateral, multilateral, and private sources) and the implementation of effective policies to improve malaria control as well as documented successes at the country level.

**PROGRESS**

The following is a snapshot of some of our partners’ recent successes:

**Vaccines**
- The PATH’s Malaria Vaccine Initiative, in partnership with GSK Biologicals and the RTS,S Clinical Trials Partnership Committee, evaluated the safety, immunogenicity, and efficacy of the RTS,S vaccine, and found a vaccine efficacy in African infants of 65 percent under field conditions.\(^3\) RTS,S entered Phase III field trials in 11 sites in seven African countries in 2009, and its launch is expected in 2015.

**Drugs and Diagnostics**
- The Medicines for Malaria Venture and Novartis launched Coartem\(^®\) Dispersible, the first high-quality ACT formulated especially for children. As of September 2010, almost 42 million doses of this life-saving treatment have been delivered to 32 countries.\(^5\)
- The Medicines for Malaria Venture also submitted Pyramax for regulatory approval. If approved, Pyramax will be the first ACT registered to treat acute malaria attacks of both P. falciparum and P. vivax. This is particularly significant for treatment in Southeast Asia and India, where the two species are prevalent and initial diagnosis is often unable to distinguish between them.\(^6\)
- The Global Fund, along with several key partners, launched a pilot of the Affordable Medicines Facility—malaria (AMFm), an innovative financing initiative to expand access to affordable ACTs by subsidizing their cost, improving the supply chain, and strengthening the incentives for providers to provide effective malaria treatment at a low cost.\(^7\)

**Vector control**
- Field trials by the Innovative Vector Control Consortium and Syngenta show that their product Actellic\(^®\) 300CS can effectively control pyrethroid-resistant mosquitoes on treated construction materials for more than eight months. The product is now being reviewed by the World Health Organization Pesticide Evaluation Scheme for independent performance and safety assessment.\(^8\)
- A global team of researchers led by The Hebrew University of Jerusalem demonstrated through proof-of-principle studies the impact of sugar-baited traps on malaria vector species in several settings.\(^9\)
- A global team from Ifakara Health Institute and other leading research institutions demonstrated that spatial repellency is an important and distinct mode of action for controlling malaria vectors in Africa, Asia, and Central America.\(^10\)

**Advocacy**
- United Against Malaria used the draw of football, in the lead up to the first World Cup in Africa, to raise awareness about malaria with more than a million football fans and bring new allies, including corporate partners and football federations, into the fight against malaria. The campaign amplified the global voice about progress on malaria and the importance of continuing to prioritize control efforts.\(^11\)

**CHALLENGES**

History has demonstrated that an overreliance on a small number of tools to combat malaria is dangerous. With the emerging spread of parasite resistance to antimalarial medicines and mosquito resistance to insecticides, the challenge is to develop an array of tools that do not rely too heavily on any one active ingredient, as resistance to that ingredient is likely to occur over time. We hope our investments in controlling resistance and developing replacement drugs and insecticides will help to overcome this challenge.

The P. vivax species is responsible for a significant number of malaria cases in large parts of the world outside Africa, but its epidemiology and burden are not well documented. P. vivax is anticipated to be more challenging to eradicate than P. falciparum because it provokes a relapsing infection with an undetectable latent stage. While some tools are effective against both parasites, there is a significant gap in the tools available for P. vivax. We hope that our modest efforts to focus on P. vivax in our research and discovery efforts will help close this gap.
A high degree of uncertainty exists about the pathway to eradication. For example, we do not know in which endemic areas the currently available tools are adequate for elimination or what additional tools are needed in those areas where they are not. We hope that our and others’ investments in operational research, data analyses, and modeling for critical decisions will help surmount this challenge.

**WHAT WE’RE LEARNING**
Achieving and sustaining malaria control in a country largely involves crafting solutions based on the human and financial resources available and adapting these to the unique malaria transmission patterns characterizing the area. We are learning that the uniqueness of each setting can make it difficult to transfer lessons learned and scale up successes from one country to another. However, we have also learned that there are common features to success, including building strong partnerships under ministry leadership, careful five- and one-year planning, prompt identification and resolution of bottlenecks in program execution, and anticipation of procurement and logistics challenges.

In the area of vaccines, we are learning the hard lesson that the development of a highly effective malaria vaccine will likely take several decades. The scientific community lacks an understanding of the mechanisms of immunity which could facilitate more rational development of candidates to proceed to clinical trials. Thus, researchers can only test vaccine candidates by undertaking expensive and time-consuming clinical trials. We hope that our investments in trying to identify correlates of protections will enable more rapid development of vaccine candidates. Based on lessons we have learned in past vaccine trials, we will also invest in more standardized preclinical testing, and more predictive testing in human volunteers using the experimental malaria challenge model, and pursue a diversity of vaccine platforms.

Lastly, we are learning that gains in funding for and political commitment to controlling malaria over the last decade should not be taken for granted. Given the long timeline associated with achieving eradication, sustaining momentum will be challenging. We are renewing our efforts to better communicate successes in the fight against malaria and engage in strategic advocacy; through the use of our voice and that of our grantees, to maintain political commitment and ongoing funding in the implementation of malaria control efforts and increased funding for malaria R&D.

**THE WAY FORWARD**
Malaria eradication is feasible but will require a long, sustained effort over several decades. Available tools to control malaria are unlikely to work indefinitely. Government, donor, private-sector, research, nongovernmental, and community partners all have a stake in the solution. Partnerships are especially important in the development of safe and effective malaria vaccines, drugs, and vector-control tools. We look forward to working with all our partners in giving every individual the opportunity to live a healthy and productive life free of malaria.
REFERENCES


Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people’s health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people—especially those with the fewest resources—have access to the opportunities they need to succeed in school and life. Based in Seattle, Washington, the foundation is led by CEO Jeff Raikes and Co-chair William H. Gates Sr., under the direction of Bill and Melinda Gates and Warren Buffett.

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