The FasterCures Philanthropy Advisory Service

FasterCures / The Center for Accelerating Medical Solutions

FasterCures / The Center for Accelerating Medical Solutions is a nonprofit “action tank” whose mission is to identify and implement global solutions to accelerate the process of discovery and clinical development of new therapies for the treatment of deadly and debilitating diseases. FasterCures, as a center of the Milken Institute, is nonpartisan, nonprofit, and independent of interest groups.

Barriers to progress in accelerating cures exist all along the research continuum—from basic research to development, from medical education to medical practice, from investment capital to human capital. FasterCures is working to clear the path to faster progress, not just by analyzing barriers, but by overcoming them through action. A force to catalyze systemic change, FasterCures:

- Evaluates current systems of disease prevention, research, development, and treatment;
- Identifies barriers to efficiency, effectiveness, and expediency in those systems;
- Creates achievable action plans to improve those systems; and
- Provides seasoned leadership and expertise in implementing those action plans in concert with organizations searching for new medical solutions.

To guide its efforts, FasterCures developed a Blueprint for Change focused on the transformation needed in three areas of medical research: research leadership and innovation; research tools and resources; and the medical research environment. The Philanthropy Advisory Service (PAS) aims to promote progress in all three areas through more informed philanthropic investment.

Helping Philanthropists Make Informed Investment Decisions

The lack of independent, reliable data about nonprofit disease research opportunities is a major barrier to encouraging significant support for such research and to improving the efficiency and productivity of philanthropy. With grants from the Bill & Melinda Gates Foundation and the Pioneer Portfolio of the Robert Wood Johnson Foundation, FasterCures has developed the PAS to address this problem.

The objectives of PAS include:

- Helping philanthropists align their goals and expectations with the capabilities and approaches of research organizations;
- Identifying gaps in funding for areas crucial to the success of specific disease research efforts; and
- Promoting among potential donors a "continuum of cure" perspective that can help develop cures for deadly and debilitating diseases.
PAS creates an information marketplace to support informed philanthropic investment. It improves the efficiency and productivity of both philanthropists and the nonprofit disease research organizations that depend on their support, especially in areas where there are demonstrated funding gaps in research and development.

**Philanthropy Advisory Service Analyst Reports**

PAS provides two types of reports—disease and organization reports.

- **Disease Reports** discuss the burden, progression, and existing treatments for a given disease; highlight priority research areas; and provide an overview of relevant activities in the commercial and nonprofit research sectors. These reports provide a broader understanding of the disease, its toll on the greater society, and any potential products in the pipeline, as well as describe promising research areas. This information establishes the contextual knowledge for readers to consider as they evaluate nonprofit organizations in a specific disease area, particularly with regard to whether an organization is addressing key research areas and challenges.

  PAS develops disease reports using desktop research. Each report is reviewed and validated by a Scientific Advisory Board, or SAB, composed of leading researchers and clinicians in that disease area.

- **Organization Reports** are developed describing the activities of nonprofit organizations involved in disease research. For diseases primarily affecting the developed world, organizations reviewed include those funding research, as well as those providing tools to support research efforts. For diseases primarily affecting the developing world, the organizations reviewed include product development partnerships as well as academic and private research organizations.

These reports provide detailed information on strategy, research portfolio, management, and financials. They also include an assessment of the organization’s practices according to a set of metrics that FasterCures believes contribute to the acceleration of biomedical research. Readers can use this information together with the context outlined in the disease report as an aid to making philanthropic investment decisions.

Organization Reports are developed based on information collected in the public domain, augmented by discussions with representatives of the organization, with input from the relevant PAS SAB.
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Summary

Disease Definition
Malaria is a parasitic disease that is transmitted when a human is bitten by a female Anopheles mosquito infected with one of five parasite species from the genus Plasmodium. In most cases, symptoms appear 9 to 14 days after the infectious mosquito bite and typically include fever, headache, vomiting, and other flu-like symptoms. If drugs are not available for treatment or the parasites are resistant to them, the infection can rapidly become life-threatening.

Disease Statistics in Africa
Malaria has a staggering impact on the populations and economies of Africa, where the vast majority of infections and deaths occur. Malaria:

- yields 90 percent of 300 to 500 million annual global cases
- causes 20 percent of under age-five mortality
- accounts for 10 percent of the overall disease burden
- costs an estimated total of $12 billion in direct costs per year
- consumes 40 percent of all public health spending
- is responsible for an annual "growth penalty" of up to 1.3 percent.

Current Prevention and Treatment
Recently, a call for global efforts to eradicate malaria has become a rallying cry for the world community. Experts agree that the tools and techniques currently in use to prevent and treat malaria infection are insufficient to achieve eradication. Current interventions aimed at prevention include vector control, measures to reduce exposure to mosquitoes, and prophylactic use of certain malaria drugs. Interventions aimed at treatment focus on the current, first-line drugs known as artemesinin-based combination therapies (ACTs). All have varying levels of success due to rising rates of resistance, lack of effectiveness, and inadequate health systems to properly disseminate therapies and educate users. There currently is no vaccine against malaria.

Key Research Areas
Research efforts are underway in the nonprofit, government, academic, and commercial sectors to understand malaria better in order to develop more effective tools for prevention, diagnosis, and treatment. Efforts can be categorized according to the following:

- Understanding the various facets of malaria, including parasite behavior, human immune response, other issues
- Developing new vaccines and other tools for use in preventing infection
- Developing new interventions designed to block transmission
- Improving the sensitivity and cost-effectiveness of diagnostic tools
• Discovering and advancing new treatment options, particularly new types of drugs that can replace ACTs as resistance emerges
• Effective methods for delivering patient care

Challenges
Malaria researchers face significant scientific challenges, including:

• a complex and diverse parasite and life cycle that presents significant challenges for the development of new treatments and vaccines
• incomplete understanding of both parasite behavior and the human response to it
• insufficient innovation in technology platforms, lack of production skills, failing adjuvants,¹ and lack of access to newer, more potent ones
• the threat of emerging resistance that varies by region and time.

In addition, systemic challenges such as funding gaps, weak market incentives for investment, and gaps in health and trial capacity impede efforts to develop new tools to aid the fight against malaria.

Key Nonprofit Players
There are 13 major nonprofit organizations that fund malaria research, outlined below.

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Key For-Profit Players
The lack of a commercial market for antimalarial drugs has severely limited investment from for-profit industry. However, the growth of public-private partnerships aimed at developing new products for malaria and other developing world disease has led to a resurgence of involvement from the pharmaceutical industry. Major industry players in malaria product development consist of companies that either have a significant, branded drug on the market or those that are involved in major research and development activities aimed at producing new drugs and vaccines. These major players include:

¹An adjuvant is a pharmacological agent added to a drug to increase or aid its effect.
- Genzyme
- GlaxoSmithKline (GSK)
- Novartis
- Sanaria
- Sanofi-Aventis

The diagnostics field also is attracting significant interest from established and newer for-profit groups like Roche and Orchid Biomedical Systems.
Disease Burden

Overview

Malaria continues to plague vast regions and populations of the world. It is endemic in more than 100 countries and causes at least one million deaths annually. Every hour nearly 100 children around the world die of severe malaria infections, with the vast majority of deaths in sub-Saharan Africa. It is estimated that between 250 and 500 million episodes occur each year, imposing a stark human and economic burden on households, communities, and countries. Resistance is rendering current treatment options increasingly ineffective, and the new therapies under development are 10 times as costly. Scientists believe a partially protective vaccine may become available in 2013, but significant challenges lay ahead. Given the high incidence of the disease, the development of successful antimalarial products and therapies will provide enormous human and economic returns on investment.

Burden

Population Burden

Total annual mortality estimates for malaria range from about 1 million to as many as 2.7 million deaths per year. More than 90 percent of those deaths occur in sub-Saharan Africa. In endemic regions, malaria predominantly affects children, who make up 85 percent of all cases and two-thirds of all deaths from malaria each year. In highly endemic areas, malaria accounts for approximately 25 percent of the deaths for children under the age of five.

Half of the world’s population lives in the 109 disease-endemic countries, and an estimated 250 million to 500 million malaria infections are reported worldwide every year. Figure 1 shows the global distribution of malaria cases worldwide in 2006. It is estimated that an African child has on average between 1.6 and 5.4 episodes of malaria fever each year. Infections that

Figure 1: Estimated malaria incidence per 1000 people, 2006. Source: WHO World Malaria Report 2008.
do not lead directly to death may result in lifelong disability or other conditions that can cause death. Some experts say that indirect deaths resulting from malaria may be approaching 3 million per year in Africa alone. The last decade also witnessed a worsened epidemic in Asia, where health status is negatively affected by political conflict, collapsing health systems, and growing resistance to existing malaria treatments.

Recognizing the heavy burden that malaria imposes on the developing world, Bill and Melinda Gates in late 2007 issued a new call for global eradication of the parasite. Achieving this goal would require complete elimination of the parasite from existence in the natural world, which experts say is impossible using current tools.

Economic Burden
Malaria disproportionately affects the poor, perpetuates economic repression, and can trap families and communities in a downward spiral of poverty, impaired learning, and decreased school and work attendance. Figure 1 illustrates that malaria is clustered in Africa, Asia, and Latin America. Studies show that eliminating malaria would have a strong positive impact on economic development in these regions.

- In Africa, malaria imposes direct costs, including a combination of private and public expenditures on both prevention and treatment of disease, of approximately $12 billion every year.
- In some countries with a very heavy malaria burden, the disease may account for 30 to 50 percent of inpatient admissions, and 60 percent of outpatient visits, and up to 40 percent of total health expenditures.
- Malaria is suggested by some economists to be responsible for a “growth penalty” of up to 1.3 percent per year in some African countries. When compounded over the years, this loss leads to substantial disparities in GDP between countries with and without malaria.
- At the household level, the World Health Organization (WHO) estimates that a poor family in Africa can spend a quarter of its income on preventing and treating malaria.

Eradication, Elimination, and Control
Given the tools and resources available for global malaria control activities, malaria experts hold varied opinions on the desired end goals of such efforts. The WHO has defined three possible targets: control, where disease burden is reduced to the point of no longer being a public health problem; elimination, where transmission is reduced to zero within a defined geographical area, but interventions still are needed to maintain that status; and eradication, where malaria incidence is reduced to zero worldwide, and malaria-related interventions no longer are necessary.

The global eradication call issued by Bill and Melinda Gates in 2007, which they acknowledge will require significant investment in developing new technologies, has served as a rallying point for malaria advocacy groups, funders, and a number of international organizations. However, many malaria experts question the feasibility of this goal even if new technologies are introduced. For opponents of the eradication push, the complications of malaria—including having five species of parasite transmitted by multiple species of vector, coupled with a very complex life cycle that involves over 5,000 genes and a non-human host—make success so unlikely that they think control
and elimination are the most viable objectives. Even those who think eradication is a feasible goal do not expect it to be reached in the near term. Most estimates of the timeline for eradication focus on completion by 2050.

Historically, global efforts to control or eliminate malaria have largely excluded the areas most affected by the disease. Significant scientific developments during the first half of the twentieth century—including the introduction of chloroquine treatment in 1946 and the insecticide DDT in 1939—led to regional “eradication” efforts beginning in the 1940s and a $2 billion Global Malaria Eradication Program that spanned from the late-1950s to the 1970s. These activities resulted in the parasite’s elimination from 37 of the 143 endemic countries, notably ones with unstable transmission patterns, including 27 from Europe and the Americas. Several other countries, particularly in Asia, saw massive reductions in malaria incidence as a result of the global program. For example, India’s incidence fell from 110 million cases in 1955 to fewer than 1 million in 1968.

However, the campaign excluded most of sub-Saharan Africa (including Madagascar) because policymakers did not think the methods employed would be feasible there. Despite its successes, the eradication effort ultimately hastened the malaria parasite’s development of resistance to the drugs and insecticides on which it relied. The long-term impact of resistance, coupled with a period of disillusionment and neglect of malaria control programs, had devastating effects in Africa. While deaths from malaria in the rest of the world shrank from about 3.5 million in 1930 to less than 50,000 in 1990, within Africa they rose from about 300,000 to 1 million over the same time period.

Current calls for malaria elimination and eradication are based on significant technological and epidemiological inroads made over the last two decades. The period since 1992 has seen renewed interest in addressing malaria on a global scale, including the founding of the Roll Back Malaria Partnership (RBM) in 1998, the inclusion of malaria in global target-setting activities like the U.N. Millennium Development Goals, and massive increases in funding for malaria control and research. Simulations done by a World Health Organization (WHO) technical group suggest that worldwide scale-up of existing interventions could lead to a major reduction in malaria incidence worldwide and risk in many places; however, the proportion of the population at risk for malaria in Africa would remain close to the same, albeit at a lower level of risk. Even if current tools maintain their efficacy, elimination in areas of stable, high transmission will require both the development of more effective tools for malaria prevention and treatment and sustained global commitment to funding and implementing malaria control.

Despite the lack of consensus about whether eradication is the right objective for global malaria control efforts, this goal currently is driving the malaria research agenda. In November 2008, the Bill & Melinda Gates Foundation (Gates Foundation) and RBM launched a global effort to identify critical research gaps and develop a Malaria Eradication Research Agenda (MalERA). The interdisciplinary, consultative process will examine gaps in basic knowledge, novel technological approaches, the importance of non-\textit{falciparum} malaria, and the role of different sectors in the research process. The results of this effort will be published early in 2010. On the implementation

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2 Assuming continued efficacy of existing technologies (i.e., no significant resistance) and sustained attention to malaria control even after transmission is interrupted
Malaria Disease

Risk Factors

Geographic Distribution
Risk of malaria infection is directly related to the prevalence of infected Anopheles mosquito populations. Over half of the world’s population (3.3 billion people) is at some level of risk of becoming infected because they live in areas where malaria is endemic either seasonally or year-round. Of these, approximately one-third (1.2 billion people) live in areas that are considered to be high-risk, meaning that more than one case of malaria is reported annually per 1,000 people. These high-risk areas account for more than 99 percent of all malaria cases each year. A map showing P. falciparum risk is shown in Figure 2. Efforts are underway to develop a similar map showing P. vivax risk.

Although mosquitoes capable of transmitting malaria are still present in much of the United States and Europe, the malaria parasite has been eliminated from the developed world. As a result, malaria currently is endemic only in tropical and subtropical climates, which correspond with many of the world’s poorest communities. These communities frequently do not have adequate healthcare infrastructure, compounding the negative impact of the disease.

Individual Risk Factors
In endemic areas, children and pregnant women face the highest risk from malaria infection in terms of severity and mortality. In addition, some individual characteristics may decrease or increase a person’s ability to fight off malaria infection.
Age
Because they have not yet developed adequate naturally acquired immunity to the disease-causing parasite, children under the age of five years are most vulnerable to malaria and suffer the most severe form of the disease. Adults who remain in areas with stable epidemics generally develop immunity during childhood that protects them from the most severe forms of infection. However, natural immunity to malaria is not long-lasting, so adults who spend a significant amount of time in a non-endemic area or whose work exposes them to high risk of infection may become more susceptible. The lack of acquired immunity in areas of unstable transmission leaves both children and adults vulnerable to epidemics of infection that result in high mortality and morbidity.

Pregnancy
Depending on the severity of the epidemic (stable or unstable), malaria during pregnancy can range from an asymptomatic infection to a life-threatening illness. Most women living in regions with stable epidemics already have acquired natural immunity sufficient to protect them during pregnancy. If infected, however, these women likely will suffer from malaria-related anemia caused when parasites invade the placenta. This condition can result in low birth weight, which, in turn, impairs development and can increase mortality of child once it is born. Women living in regions with unstable epidemics have developed little to no natural immunity and are therefore at significant risk of experiencing severe malaria and death.

Other Characteristics
Host characteristics can influence the risks associated with malaria. Differences in general health status, nutritional state, genetics, and immunity all contribute to the manifestations of malaria. People whose red blood cells lack a surface protein known as the Duffy antigen have been found to be fully resistant to *P. vivax*, which is why this species of the parasite is absent from most of sub-Saharan Africa and cannot infect most African Americans. Meanwhile, those with an existing HIV infection face increased susceptibility to malaria.

Biology

Cause
Malarial fever is caused by infection with one of five species of *Plasmodia* parasites: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. *P. falciparum*, which accounts for the majority of malaria cases worldwide, is the most virulent and deadliest species of the parasite. It is most common in Africa, while the less-lethal *P. vivax*, which is still highly disabling, accounts for about 50 percent of all malaria cases in South and Southeast Asia and 70 to 80 percent of cases in Latin America. Estimates suggest that 132 to 391 million cases of malaria are attributable to *P. vivax* each year, and that the population at risk for *vivax* malaria actually slightly exceeds that for *falciparum* malaria (2.6 billion and 2.5 billion, respectively). The remaining strains of the parasite account for only a small proportion of illnesses; however, they remain scientifically distinct and eradication and control efforts must continue to take them into account.
Infection occurs when a female *Anopheles* mosquito bites an infected human and then feeds on an uninfected one, thereby transmitting the parasite from the first to the second. There are approximately 430 species of mosquitoes in the *Anopheles* genus, of which only 30 to 40 can infect humans with malaria causing parasites. Some species, particularly *A. gambiae* from Africa, are especially efficient vectors of the parasite, leading to increased transmission in areas where they are found.

**Progression**

**Life cycle of the Parasite**

Inside the human host (Figure 4), the malaria-causing parasite undergoes a series of changes as part of its complex life cycle. Its various stages allow *Plasmodia* to evade the immune system, infect the liver and red blood cells, and finally develop into a sexual form that is able to infect a mosquito that bites the infected person. Once it is transmitted back to the mosquito, the sexual stage of the parasite matures until it can again infect a human host when that host is bitten by the infected mosquito, 9 to 14 or more days later.

The stages of the parasite life cycle each present their own opportunities for interventions to prevent and treat malaria infection. The time the parasite spends in the liver is known as the pre-erythrocytic, or liver, stage of infection. This first phase of infection is asymptomatic and is characterized by low numbers of parasites. In *P. falciparum* and *P. malariae* infections, the liver stage progresses fairly rapidly, typically lasting for about six days; however, *P. vivax* and *P. ovale* infections have an extra liver stage that can persist in a dormant state for weeks or even years, delaying the onset of symptoms, giving rise to relapse infections, and making it more difficult to eliminate the parasites.

After some period of time, the parasite reproduces to the point that the liver cells burst and daughter cells are released into the bloodstream. This marks the beginning of the blood stage of infection, also referred to as the erythrocytic stage. This is the stage during which the infected person displays symptoms of clinical malaria, although *P. malariae* can lay dormant in the blood stage for decades. The released cells continue to multiply within the red blood cells until
they, too, burst, releasing new daughter cells into the bloodstream so that they can infect additional blood cells. Blood-stage replication produces both cells that are capable of asexual replication within the human host and those that can be transmitted to mosquitoes for the sexual reproduction process that produces new parasites to infect new humans, beginning the cycle again.

**Symptom Development**

Incubation for a period of 7 to 30 days is typical following an infective bite. The incubation periods for *P. falciparum* tend to be shorter, while *P. malariae* incubations tend to be longer. This corresponds to the faster or slower multiplication during the blood stage of the parasite. Increased incubation time following administration of prophylactic drugs to travelers can occur, as drugs can delay the appearance of symptoms by weeks or months.

Malaria may result in a wide variety of symptoms ranging from cold-like conditions (chills, fever, body aches, vomiting) to fatal conditions including serious organ failures. Clinicians tend to classify malaria as either “uncomplicated” or “severe” based on the types of symptoms experienced by the patient. Uncomplicated malaria typically is characterized by a fever and other symptoms that resemble many other infectious diseases, making it difficult to distinguish without the use of diagnostic tools.

**Severe Malaria**

Severe malaria occurs when serious organ failures or blood and metabolism abnormalities are present. These are caused, directly or indirectly, by the infection and destruction of red blood cells by the parasite. This blood-stage destruction can result directly in anemia, hemoglobinuria and coagulation problems, among other conditions. The host inflammatory response to high concentrations of the parasite in the bloodstream also can cause capillary blockage, leading to comas, strokes, heart failure, and other organ problems. Severe malaria cases are caused predominantly by *P. falciparum* infections, although *P. vivax* is increasingly recognized as a cause of serious illness.

Cerebral malaria (CM) is the most dramatic complication of severe malaria cases. Patients suffering from this neurological syndrome may experience seizures and loss of consciousness, which can result in symptoms ranging from confusion to a fatal coma. These symptoms can progress very quickly, leading to unresponsiveness to visual, verbal, or pain stimuli. CM is caused by sequestration of infected red blood cells in the brain, the resulting inflammation that occurs, and bleeding and swelling in the brain. With an estimated mortality rate of 25 to 50 percent in the absence of treatment and 10 to 15 percent even with prompt treatment, CM is a leading cause of death in children suffering from malaria. Further, a quarter of all children who survive a bout of CM exhibit permanent neurological defects within three to seven years.

**Interventions**

Prevention and treatment tools can intervene at four points in the life cycle of the mosquito to prevent an individual’s infection or death. Interventions include:

- Preventing mosquitoes from biting susceptible people;
- Preventing those who have been bitten from becoming infected;
Preventing those who have become infected from transmitting malaria to mosquitoes that bite them; and
Treating those who have been infected to alleviate symptoms and prevent death.

**Prevention Mechanisms**

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Current malaria prevention efforts rely predominantly on environmental and vector control techniques, measures to reduce exposure to mosquitoes, and preventive antimalarial drugs. No vaccine currently exists for malaria, severely limiting the options available for preventing infection.

**Environmental management**: One of the oldest approaches to preventing malaria is taking measures to interrupt the parasite life cycle through environmental control. This includes efforts to reduce the habitat required for malaria-bearing mosquitoes to live and breed, as well as efforts to improve human living conditions to reduce interaction between the mosquitoes and their potential victims.

Mosquito breeding requires the presence of standing water where females can lay their eggs and the resulting larvae can hatch and develop. This may include large-scale activities aimed at limiting sources of such water, such as draining marshes, creating channels for water to flow, and re-grading rivers and streams. Such environmental modification efforts were an important part of malaria control in the southern United States and other developed countries prior to elimination, and they continue to be employed in parts of the developing world today. However, such projects often require maintenance, the lack of which can actually have deleterious effects on vector control.

In addition to this long-term modification of the environment, malaria control efforts also may rely on shorter-term environmental manipulation techniques. These include water management activities to reduce standing water sources and vegetation management that targets the predilection of some vector species toward sunny conditions for larval development. Proper planning and alignment with local conditions are key to the success of these vector-control methods.

Environmental management of malaria also includes taking steps to change the conditions under which at-risk populations live. On a large scale, this may mean locating populations farther away from the breeding grounds of malaria-bearing mosquitoes. However, these measures also may involve targeting individual living conditions by covering windows and other openings with screens that allow for ventilation but prevent mosquitoes from entering. The potential impact of these techniques is limited by the housing structures available and the extent to which people sleep within structures at all.

**Indoor residual spraying (IRS)**: When sprayed onto the walls and ceilings of homes once a year, long-acting insecticides can kill mosquitoes when they land on treated surfaces. IRS has a track record of reducing uncomplicated clinical cases of malaria by 50 percent and can also reduce all-
cause childhood mortality by 20 percent. Forty-nine countries have adopted WHO-recommended policies that rely on IRS as a primary vector control method, and more than 100 million people were protected by IRS in 2006.

Many insecticides can be used for IRS, with the most effective being those that remain on the surface of the house rather than being absorbed, are highly toxic to the vector while remaining safe and acceptable for humans, and are easy and fairly inexpensive to apply. Historically, DDT has been the most commonly used insecticide for IRS; however, its use fell off due to environmental and safety concerns. Many IRS programs now use pyrethroids instead. The specific insecticides used in a given setting are determined by the susceptibility of the specific mosquito type and its feeding pattern, working best when the mosquitoes prefer to rest and bite indoors.

IRS is considered to be advantageous because it can be deployed rapidly and does not require individual behavior changes to achieve results. However, there are questions about sustainability associated with IRS because houses must be sprayed regularly in order to maintain protection, leading to recurring costs and problems with community fatigue. For a household of six people, a medium-priced insecticide costs about $6.50 plus shipping. With maintenance and parts, one spray pump costs $125 and can protect approximately 10,000 individuals for seven years. These are cost-effective prices; however, costs for local delivery, training, and labor for spraying are factors.

Effective IRS implementation requires an organized system for logistics, delivery, and coverage. The right insecticides must be selected, and they must be applied using appropriate techniques as identified by the WHO. Other factors, such as housing structure and building materials, also may limit the effectiveness of IRS. Further, there is evidence that malaria-transmitting mosquitoes have developed resistance to DDT, pyrethroids, and other insecticides used for IRS and in treating bednets in many malaria-endemic countries. As a result, research may be needed to identify new insecticides that could replace the older ones as they become less effective. Additionally, increased monitoring of resistance would allow malaria control experts to prolong the effectiveness of insecticides by rotating them.

**Insecticide-treated nets (ITNs):** Bednets are mesh coverings that are hung over beds to create a full, canopy-like enclosure to keep mosquitoes from landing on and biting anyone sleeping underneath. Most nets distributed are treated with an insecticide so that they provide both a physical and a chemical barrier to night-biting mosquitoes. Conventional nets require reapplication of insecticide every six months to continue full effectiveness; however, several options for long-lasting insecticide nets (LLINs) that retain their effectiveness for three to five years without reapplication have been developed recently.

ITN implementation requires community-based programming for education, deployment, and maintenance. Sixty countries have adopted policies that rely on ITNs as a primary vector control method, with all targeting children and 54 targeting adults. ITN coverage has increased significantly in recent years; however, WHO’s Global Malaria Programme estimates that only about 10 percent of Africans who are at risk for malaria are protected. Further, possession of a bednet does not always imply full protection, and household surveys in Africa have found that in some countries nearly half of all people who possessed a bednet did not sleep under it the night prior to being surveyed.
The unit cost is approximately $7.00 per net delivered to the end user, or $1.17 per person-protected per year (as two to three people can use one net, and a net lasts three to five years). Additional costs would also be required for public health messaging and continued education to ensure proper usage.

Insecticide resistance is a challenge for ITN effectiveness as it is for IRS, and research is needed to identify and develop new classes of rapid, long-acting insecticides for use in such vector control methods.

**Intermittent preventive treatment (IPT):** IPT involves giving several scheduled doses of antimalarial medications to high-risk groups, such as pregnant women and infants, to prevent malaria illness. Treatment is given without regard to whether the person is infected at the time, with the idea that infection will be prevented for sometime after the treatment is given. IPT during pregnancy involves giving a pregnant woman two to three doses of an antimalarial drug \(^3\) during her second and third trimester prenatal visits, and IPT in infancy is given along with routine immunizations.

A review of studies using SP found that IPT effectively decreased the incidence and density of placental malaria in all women and decreased the incidence of low-birth weight infants in low-parity women. There is a concern that resistance to SP is growing and studies are needed to assess the impact of resistance, as well as alternative regimens for pregnant women. A recent Institute of Medicine review concluded that IPT is likely to benefit infants, and that its potential benefit when given to young children is being assessed.

For one pregnant woman, the unit cost of three doses of three tablets of SP is about $0.18 (one tablet is about $0.02). This includes costs for procurement, delivery, education, and staffing for health clinics and prenatal programs.

**Larval control:** Interventions aimed at preventing the development of mosquito larvae are less common, but also may be important. Methods for larval control include biological interventions like the introduction of larva-eating fish and bacteria, as well as the use of chemical larvacides. These methods are most effective in urban areas, where there are fewer mosquito breeding sites and they are easier to identify.

**Traditional approaches:** At-risk populations also practice a variety of traditional approaches to preventing malaria infection, although these methods have not been fully evaluated. Several plant oils are used to reduce populations of *Anopheles* mosquitoes, including the Neem tree, which kills the larvae of *A. gambiae*, Ocimum suave and Ocimum kilimandscharicum, which kill several species, and other plant varieties (e.g., Eucalyptus species, Lantana camara, and Azadirachta indica). Some populations in areas where the disease \(\alpha^+\)-Thalassemia genotypes appear in individuals who are simultaneously developing resistance to malaria also practice consanguineous marriage (inbreeding), which reduces the overall mortality rate of the population even though it increases the frequency of \(\alpha^+\)-thalassemia allele and the loss of life due to homozygosis of recessive lethal alleles.

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\(^3\) Initially sulfadoxine-pyrimethamine (SP), although increasingly artether-lumefantrine (Coartem®) is used,
**Vaccines and drug prophylaxis:** Vaccines provide protection and immunity to a given disease. Currently, there is no licensed vaccine for malaria. Travelers are protected by taking daily or weekly effective antimalarial medications on a temporary basis. Unfortunately, travelers’ antimalarial medications cannot be a long-term solution for people who are exposed daily to malaria infected mosquitoes throughout their lives.

**Diagnostics**

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<tr>
<td>Rapid diagnostic tests (RDTs)</td>
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<tr>
<td>Other tests</td>
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The high prevalence of malaria in many regions, coupled with the fact that an effective treatment for the parasite exists, has led to a common practice in many places of treating all childhood febrile illnesses with antimalarial drugs. Accurate and cost-effective diagnostic products are available, but they are met with skepticism by health workers. Still, their use is becoming more common along with concerns that overuse of antimalarials leads to resistance.

**Clinical diagnosis:** Clinical diagnosis, in which health workers base malaria diagnoses on the symptoms the patient displays during the visit, is the basis of therapeutic care in endemic areas where laboratory support is often out of reach. A malaria module is included in Integrated Management of Childhood Illness, a strategy created by the WHO and the U.N. Children’s Fund (UNICEF) that provides clinical algorithms for diagnosing and treating common childhood afflictions. However, malaria symptoms—fever, chills, headaches, muscle pain, nausea, and vomiting, among others—often overlap with other tropical diseases and diagnoses often are imprecise. Further, there is pressure on health workers to diagnose malaria because an effective treatment is known to exist, where many febrile illnesses are caused by viruses that must run their course. This encourages the indiscriminate use of antimalarials for febrile conditions in endemic areas, which increases expenses and hastens the development of drug-resistant parasites.

**Microscopy:** The current laboratory standard for malaria diagnosis is microscopy, a technique through which the diagnosis of malaria is confirmed by examination of stained thick and thin blood smears. The thick smear is more sensitive, but the thin smear allows for species identification so that the right treatment can be administered. The test is relatively simple and inexpensive. However, the technique is not very reliable in developing countries because the microscopists are insufficiently trained, the laboratory equipment is of poor quality, and often the supply of electricity is unreliable. Furthermore, in many areas with multiple plasmodium species, mixed-species infections commonly confuse expert microscopists.

**Rapid diagnostic tests (RDTs):** Concerns about microscopy’s effectiveness in resource-poor settings led to the development of devices known as rapid diagnostic tests (RDTs), which can detect malaria antigens in a fingerprick blood sample. RDTs are similar to home pregnancy tests and use an immunochromatographic assay with monoclonal antibodies directed against the target parasite antigen. The use of an RDT enables health workers to determine if a patient is infected with malaria parasites more rapidly and under less stable conditions than are needed for microscopy.
Several types of RDT currently are on the market, with all targeting one or more species of malaria parasite. The quality of these tests and reliability of their diagnoses varies significantly, with some of them prone to deterioration in tropical climates. However, several RDTs have been shown to detect more than 90 percent of malaria cases presented. Some, but not all, of the tests currently on the market also are able to determine the species of parasite, which is key to determining the appropriate treatment.

RDTs are considered to be both cost-effective and reliable; however, antimalarial treatment use still far outpaces RDT use worldwide. This pattern is changing along with the widespread introduction of artemisinin-based combination therapies (ACTs), as malaria control experts are attempting to stave off resistance by limiting misuse of the new drugs. Further, even where RDTs are employed, mistrust of their results and pressure from patients to prescribe often leads health workers to ignore test results and treat for malaria even when results are negative.

**Molecular diagnostics:** Concerns about the sensitivity and specificity of microscopy and RDTs have led to development of new molecular approaches to diagnosing malaria. Among the most sensitive and specific methods is polymerase chain reaction (PCR)-based diagnosis, now considered the gold standard for laboratory diagnosis. However, the cost and skill requirements for accurate application of PCR-based diagnostics have been seen as a major impediment to widespread use in the developing world. However, adequate laboratory facilities are available in virtually all malaria endemic regions and these tools may grow in importance as elimination and eradication efforts advance.

**TREATMENTS**

<table>
<thead>
<tr>
<th>Treatment:</th>
<th>A variety of drugs currently are on the market for the treatment of uncomplicated malaria. While ACTs are recommended based on their efficacy, several older, less expensive therapies remain in use in many endemic countries.</th>
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<td></td>
<td><strong>Artemisinin-based combination therapies (ACTs):</strong> Because of their high efficacy and minimal reported resistance, herbal extract ACTs are the newest and most recommended treatment for malaria caused by all five species of <em>plasmodium</em> parasites. ACTs are formed by combining an artemisinin compound—derived from a Chinese shrub—with another effective drug (e.g., mefloquine, amodiaquine). Combinations, ideally presented in a fixed-dose form, are used because it is more difficult for parasites to develop resistance through specific gene mutations simultaneously to two or three drugs compared to one drug in a monotherapy application.</td>
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![Figure 5: Unprocessed artemisia annua. Source: Birgit Betzelt/action medeor.](image)
Artemisinin compounds have many other advantages, including:

- a rapid therapeutic response,
- excellent tolerability by patients,
- activity against gametocytes (the sexual form responsive for continued transmission),
- effectiveness against multi-drug resistant strains of malaria, and
- rapid clearing of the blood, which reduces transmission back to mosquitoes.

Despite these advantages, many ACTs are not ideal treatments because of side effects, pharmacokinetic mismatch, and cost. Further, malaria control experts are concerned that, as with other antimalarial drugs, resistance to ACTs is likely to occur over time and with expanded use. Some first reports of resistance in Southeast Asia already are under investigation. As a result, research is needed to develop compounds to overcome these concerns.

ACTs are the WHO-recommended first-line treatment regimen for *P. falciparum* malaria, and the majority of malaria-endemic countries have adopted policies to deploy them widely. However, in many countries ACTs remain a small, albeit growing, portion of the antimalarial drug market. This is largely attributable to cost and supply-chain issues. One course of ACT treatment costs between $0.60 for a young child to $1.70, or more, for an adult. As with most treatments, early use is more expensive, and it is expected the cost of ACT will decrease with increased adoption.

**Standard antimalarial drugs:**
Chloroquine is the most common and least expensive antimalarial therapy on the market at $0.10 per average dose. Widespread resistance to chloroquine emerged in the 1960s and spread rapidly, such that now resistance is reported in almost all malaria-endemic countries. As a result, the WHO announced in 2005 that chloroquine should be replaced with ACTs as a first-line treatment for malaria caused by *P. falciparum* parasites. Chloroquine remains a recommended treatment in many places for *P. vivax*, *P. malariae*, and *P. ovale*, although there is some evidence of emerging resistance.

Other older antimalarials like sulfadoxine/pyrimethamine (SP), mefloquine, and amodiaquine also may be used to treat malaria; however, resistance to these therapies is increasing in prevalence. A combination therapy using both SP and amodiaquine continues to show efficacy in some places. Resistance patterns in the geographic region need to be considered in selecting appropriate therapies.
Primaquine is the only currently available antimalarial drug that kills the liver-stage hypnozoites of *P. vivax* and *P. ovale*. Evidence from Southeast Asia suggests that *vivax* malaria parasites may be developing resistance to primaquine.

**Treatment of severe malaria:** Cases of severe malaria are treated using the same classes of drugs as uncomplicated malaria, only they are delivered intravenously to ensure adequate absorption into the blood. The artemisinin derivative artesunate is the preferred treatment in most cases because it has been found to be more effective and have fewer side effects than older drugs.
Research

Overview
Recognition of the need for new drugs and vaccines has led to an influx of resources for malaria research in the last several years. This increase in resources has allowed researchers to expand their efforts to better understand the disease and to develop new products to aid in global malaria control and eradication efforts. Key areas of research include disease understanding, vaccines, other prevention mechanisms, diagnostics, treatment, and care delivery.

Global investment in malaria research in 2007 was estimated to be around $468.4 million, with about 45 percent of that coming from two funders: the Gates Foundation, and the U.S. National Institutes of Health (NIH). As of March 2009, there were 175 ongoing clinical trials on malaria, with a heavy focus on developing new drugs and vaccines. The number of projects in discovery and preclinical research far exceeds this due to concerted efforts to expand the pipeline.

Scientific Research

Summary
Table 1 summarizes the major areas of biomedical research in malaria and areas where more investment is required to overcome challenges and accelerate research. Although this report focuses on biomedical research, important efforts to develop new tools and interventions to block transmission of malaria parasite also are ongoing. The areas of current research and the challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for malaria.

Table 1: Major Area of Scientific Research and Challenges in Malaria

<table>
<thead>
<tr>
<th>Research continuum</th>
<th>Current research foci</th>
<th>Challenges or areas requiring investment</th>
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</table>
| Cross-cutting Challenges | • Complexity posed by parasite biology, including multiple species and strains of malaria parasites, multi-stage life cycles of the parasites, multiple antigens displayed in different stages, variety of human responses to the different antigens, and regional diversity | • Incomplete understanding of how the malaria parasite develops and interacts with the human host  
• Lack of knowledge about non-*falciparum* malaria strains, including genetic mapping and potential for extended dormancy |
| Disease Understanding | • Understanding and disrupting the vector life cycle  
• Understanding how the parasite invades and hijacks red blood cells  
• Characterizing the human immune response, including innate and natural immunity  
• Identifying and targeting individual risk factors  
• Exploring interactions with other diseases |                                                                                                         |
<table>
<thead>
<tr>
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</thead>
</table>
| Vaccines           | • Developing vaccine candidates to target the whole parasite and its antigens at individual stages, including blood, liver, and transmission  
• Expanding the pool of building blocks for vaccines  
• Identifying new tools for evaluating vaccine candidates  
• Examining inexpensive, scalable production methods  
| • Incomplete understanding of the human immune response and how the malaria parasite evades it  
• Parasite diversity, which most likely requires that separate vaccines be developed for each species of malaria  
• Lack of immune correlates of protection, which makes the testing of malaria vaccines lengthy and expensive  
• Limited diversity of vaccine components, including target antigens, adjuvants, and vaccine platforms  
| | Source: FasterCures. |
**Disease Understanding**

Despite decades of work and the development of effective interventions, researchers still are trying to understand the mechanisms through which malaria parasites interact with their human host and lead to illness and death. The variety of species of parasites and clinical presentations of illness, along with the complex parasite life cycle, complicates these efforts, as different mechanisms and interactions likely determine different manifestations of disease. A number of factors contribute to this complexity, including multiple species and strains of malaria parasites, multi-stage life cycles of those parasites, multiple antigens displayed in different stages, and the variety of human responses to the different antigens. Regional diversity, requiring that research be conducted in a variety of geographic settings, further complicates efforts to develop new treatments and preventive vaccines.

Further, a historical focus almost exclusively on *P. falciparum* has left large gaps in understanding relating to the other three strains of parasite that hinder the development of new treatment and preventive products. In particular, research on *vivax* and *ovale* malaria is limited by a lack of knowledge about the dormant liver stage of infection, which is key to the development of vaccines and radical cures for infection with these species of malaria parasites. More research on the biology of the non-*falciparum* species will be essential for the eradication agenda.

The following sections outline the major areas of ongoing research to better understand malaria:

**Vector Biology**

Much research is being conducted to understand the life cycle of the vector and how vulnerabilities within that cycle might be exploited by malaria control efforts. One area of inquiry is the impact environmental and weather factors (i.e., climate, topography, and wetness) have on transmission. Other studies aim to understand how predators that feed on *Anopheles* mosquitoes impact malaria transmission. Still more vector research focuses on the feeding behavior of the mosquitoes that transmit malaria, including where and when they feed and rest (i.e., inside vs. outside, dawn/dusk vs. night) and whether they feed on humans, animals, or both.

Better knowledge of vector biology is feeding into development of new control strategies and tools, such as new pesticides and longer-lasting bednets and IRS strategies. In addition, researchers are working to develop ways to modify *Anopheles* mosquitoes to reduce their ability to transmit malaria parasites. These efforts include examination of genetic factors that affect transmissibility, including understanding the mechanisms that cause an immune response that kills the parasites in some mosquitoes and identifying mosquito traits that are required for transmission to take place. Studies are looking at whether genetically manipulated viruses could be used to reduce the susceptibility of mosquitoes to malaria parasite infection. Broad-based analysis of vector genomes and pathogens linked to their population structures are on the forefront of research aimed at generating long-term solutions.

**Parasite Biology**

Progress has been made in recent years toward sequencing the human, parasite, and mosquito genomes associated with malaria. The *P. falciparum* genome sequence was published in 2002 and the *P. vivax* and *P. knowlesi* genome sequences followed suit in 2008. Genetic sequencing activities have not yet been conducted for *P. ovale*, and *P. malariae*. For those parasites for which the genome
sequencing work is complete, further research is needed to understand what the individual genes do in order to identify targets for prevention and treatment interventions.

Armed with these tools for genomic analysis, researchers are working to understand the cell biology of malaria-causing parasites. The focus of these efforts is improving knowledge about the processes by which the parasite selects, invades, and modifies red blood cells and the role those processes play in immune system evasion. Malaria parasites produce and secrete proteins that enable them to “hijack” red blood cells, changing their physiological structure. The parasite is able to control surface proteins on the cell, flipping switches that make the cells rigid and sticky. These altered cells are then sequestered away from the spleen, where they otherwise would be destroyed. Recent studies have identified the genes thought to be responsible for this process in *falciparum* malaria infection, which could be important targets for the development of new vaccines and/or treatments.

Additionally, genetic diversity provides the basis for research on resistance, as genetic differences among malaria parasite strains even within the same species have been shown to account for some forms of drug resistant malaria. This research has yielded molecular markers that can be used to track the spread and extent of resistance. Similar approaches are being used to tackle the anticipated problem of vaccine resistant malaria, which may emerge as new vaccines are tested and deployed.

**Host Response**

Studies in both humans and animal models have looked to better understand innate and naturally acquired immune responses to malaria. One key target is the mechanisms that lead to natural protection after repeated exposure to infection. Researchers hope that understanding the development of natural immunity will allow them to reproduce this response using vaccines. Despite many years of research, the precise mechanisms of development of natural immunity remain poorly understood.

Resource-mediated factors, particularly the availability and penetrability of the red blood cells in which the parasite must reproduce, are one major area of pathogenesis research. A second key focus is the factors that govern the human immune response to the parasite, such as the role of T-cells and toll-like receptors that fight parasitic infection. Pathogenesis of malaria during pregnancy also is important, with researchers trying to understand why pregnant women are particularly vulnerable to infection and how that infection can lead to maternal anemia, low birth weight, and other complications. Additionally, researchers are working to develop better models and tools to aid their efforts to understand the pathogenesis of malaria infection.

**Epidemiology**

Data on malaria transmission and infection rates and other epidemiological considerations remain weak due to limited use of diagnostics and poor local data collection in endemic areas. However, researchers are working to improve data collection and supplement it with accurate modeling techniques that can be used to extrapolate beyond the available data. Some key focal areas of this work include efforts to assess the impact of malaria control efforts, predict epidemics in areas of unstable transmission, track the spread of drug resistance, and understand the impact of environmental changes. Additionally, a better understanding of the epidemiology of *P. vivax,*
including disease versus infection, immunoepidemiology, and parasite diversity, is considered essential for development of a preventive vaccine against the parasite.

**Risk Factors**

Understanding the individual risk factors that affect malaria can help to control and manage the disease. Studies have been done to understand the stratification of the disease by age group in order to understand where prevention and treatment efforts should be focused. Further research has looked at the role of nutrition in malaria morbidity and mortality. Researchers have found that severe malnutrition in children weakens their immune response and thus reduces their ability to fight infection. Another study shows that giving children a combination of Vitamin A and zinc reduces the risk of fever and clinical malaria episodes in endemic areas.

Other risk factor research focuses on genetic factors. Human genome-wide association studies are enabling scientists to begin to understand the molecular basis of differences in susceptibility to malaria. For example, research has shown that individuals who lack the Duffy blood antigen, predominantly those of black African descent, are not susceptible to *vivax* malaria. Various other human red blood cell polymorphisms also have been shown to provide varying degrees of resistance to different forms of malaria.

There also are significant research efforts regarding malaria in pregnancy. Specific risk factors have been studied, including age, parity, and blood type. Studies also have been conducted that examine the relationship of placental malaria with maternal anemia, low birth weight, and preterm delivery. Even more specific studies have identified proteins to which malaria parasites bind when they invade the placenta, thus informing the development of potential vaccine candidates.

**Co-morbidity**

Co-infection with some other pathogens, such as HIV and certain bacteria, results in higher rates of disease and death. Infection with others, such as the worms that cause schistosomiasis and the parasites that cause sleeping sickness, paradoxically provide some protection against malaria. Field and laboratory researchers are working to understand the mechanisms of these interactions and their public health significance.

**Vaccines**

Introduction of an efficacious malaria vaccine, or multiple vaccines to prevent the different species of parasite, would reduce the current reliance of malaria control efforts on methods that require regular intervention and are subject to significant human error (e.g., bednets and IRS). To have a real effect on the disease, a malaria vaccine needs to be highly effective, be delivered in ideally one and perhaps two or three doses at the most, give prolonged protection (in years), be affordable, and not rely on a cold supply chain to maintain stability and efficacy. Ideally, a vaccine also would protect against all five species of malaria parasite, although it seems likely the four or five separate vaccines will be needed. Additionally, to be an effective tool for elimination of malaria parasites in a region, a vaccine must be effective at preventing the build up and transmission of parasites not only in children who may be most vulnerable to infection, but also in adults who may be a reservoir for parasites even after they have developed natural immunity to infection.
Malaria vaccine development efforts are stymied by a lack of diversity in the various components that go into formulating a vaccine, including target antigens, powerful adjuvants, and delivery platforms. In addition, the tools that vaccine developers have to assess candidates at the various stages of development are insufficient and lead to longer and more complicated testing scenarios. This includes quality models and assays for use in laboratory testing, as well as a lack of identified immune correlates of protection that could be used to make clinical trials shorter and less expensive. In addition to developing full vaccine candidates, the malaria vaccine community also is dedicating significant attention to improving the building blocks and assessment technologies they employ in their work.

The following sections outline the major areas of ongoing vaccine research.

**Vaccine Candidates**

Almost all ongoing vaccine research efforts have focused on prevention of malaria caused by *P. falciparum* parasites, although a few efforts are beginning to target *P. vivax* malaria. Many past efforts have focused on vaccines targeting the liver stage of the infection cycle, during which there are smaller numbers of parasites to eliminate. Recently, however, there has been a shift toward developing both blood-stage and transmission-blocking vaccine candidates in addition. Ultimately, it is hoped that a single multistage vaccine could prevent infection, disease, and transmission.

Many past research efforts have focused on vaccines targeting the liver stage of malaria infection, during which there are fewer parasites to eliminate. Such vaccines are designed to prevent the parasite from ever taking hold in the infected person. **Liver-stage vaccines** continue to receive significant attention from researchers, who employ a variety of approaches to targeting proteins encountered during the liver stage. Several liver-stage vaccine candidates have shown promise in preclinical and early clinical studies. Most notably, the RTS,S vaccine has shown short-term efficacy rates ranging from 30 to 65 percent in infants and young children, and is expected to enter Phase 3 trials in 2009.

Recently, there has been a shift toward developing vaccines that target other stages of the parasite life cycle as well. **Blood-stage vaccines** focus on reducing the severity of malaria infection by limiting the replication of the parasite, rather than preventing all infection. In particular, the majority of activity to develop a vaccine against *vivax* malaria has focused on the blood stage, as researchers hope to duplicate the natural immunity shown in humans lacking a specific antigen on the surface of their blood cells that is thought to be the sole receptor for malaria parasite invasion. The blood-stage approach also is thought to hold promise in developing other targeted vaccines, such as for pregnant women. There is some concern that blood-stage vaccines could lessen the early symptoms of malaria infection, thus delaying diagnosis and treatment and allowing the parasite to take firmer hold.

**Transmission-blocking vaccines** target the spread of the parasite rather than the individual infection, conferring protection on the community rather than the vaccinated individual. The theory behind these vaccines is that antibodies produced in the human and ingested by the mosquito would prevent the parasite from taking hold in the vector. Although little clinical work has taken place on these types of vaccines to date, the theory has shown promise in the laboratory using animal models. Work on transmission-blocking vaccines thus far has focused on both *P. falciparum* and *P. vivax* malaria parasites.
Ultimately, it is hoped that a single **multi-stage vaccine** could prevent infection, disease, and transmission. A multi-stage vaccine approach could combine individual protein targets that are important to each stage of the parasite life cycle, or they could rely on whole, weakened sporozoites extracted from irradiated mosquitoes to stimulate immune response. To date, researchers have not been able to find a practical way to deliver such sporozoites; however, efforts are underway to address the challenges for using a needle or other device.

**Building Blocks**

Recognizing certain weaknesses in their research toolbox, the malaria vaccine community also has identified several priorities for research beyond vaccine candidates.

Researchers are working to identify and assess new **antigens** through which vaccine candidates could stimulate an immune response. Most past malaria vaccine candidates have relied on a small group of antibody-generating (antigen) targets; however, new antigens now are advancing in the development pipeline. The complete mapping of the *falciparum* genome has paved the way for further efforts targeted at discovering additional antigens with the ability to provide protective immunity against the parasite. Further efforts are ongoing to expand the pool of antigens being targeted by potential vaccines against *vivax* malaria. Another trend is toward combining multiple antigens in one vaccine to increase the likelihood that the vaccine will stimulate an immune response that can effectively target the wide variety of genetically diverse parasites found in nature.

Several current malaria vaccine candidates rely on an array of older **adjuvants** to amplify their immune response. Novel adjuvants developed in other vaccine areas have proven more potent than these traditional formulations; however, many of these are proprietary to private industry and the malaria vaccine community has had difficulty gaining access to them. Efforts are underway to develop and test new adjuvants to improve the potency of malaria vaccines.

**Delivery platforms** also are a key focus area of preclinical malaria vaccine research, with a focus on live viruses that have been weakened so that they will stimulate an immune response without making recipients ill.

**Related Technologies**

The lack of an accurate animal model to test malaria vaccines has led to a reliance on **human “challenge” models**. A good challenge model exists for testing liver and multi-stage candidate vaccines; however, a shift in approach toward targeting the blood stage of the malaria life cycle has led to a need for a new model to evaluate vaccine candidates in this area. Researchers are working to develop, test, and build consensus around potential models to meet this new need.

Further, through a collaborative process that concluded in 2006, the malaria vaccine community has launched an effort to **standardize the assays and procedures** used to test immune responses of vaccines to allow for better comparison across studies. Other efforts to increase the comparability of research focus on standardization of clinical trial design and assessment.
Researchers also are examining cheap, scalable methods for *vaccine production* once a malaria vaccine has been developed and approved.

**Diagnostics**

Rapid, accurate diagnostics are critical elements for malaria eradication. Malaria control efforts continue to be hampered by the shortcomings of existing diagnostic tools, particularly given the environment in which such tools are employed. One of the key challenges facing diagnostic development for malaria is that the conditions under which tests are produced and administered varies widely and can affect the accuracy of the tools. Climate factors such as temperature and humidity can reduce the sensitivity of RDTs, as can variable quality assurance efforts. Meanwhile, limitations on the equipment and personnel available, along with high costs, can hamper the administration of laboratory-based tests.

As with other malaria research areas, the existence of multiple species of parasites and the ability of those parasites to adapt presents additional challenges for diagnostic development. Just as the ideal malaria vaccine would prevent infection with all five species of malaria, the ideal diagnostic would detect and distinguish among the species in order to facilitate administering the most effective treatment. Further, in order to be truly useful for control and elimination of the parasite tests should be able to determine whether the parasite infecting a patient is resistant to treatment with specific drugs.

In addition, a lack of biomarkers—particularly for specific high-risk types of malaria—limits the tools available to diagnostics researchers. Recent gains have been made in identifying biomarkers for specific types of malaria such as placental and cerebral infections; however, further work is needed in this area. Advances in knowledge about biomarkers for malaria also could help speed the development of new tools for use specifically in the prevention and treatment of malaria. Clearly defined biomarkers can facilitate efficacy measurement in clinical trials, allow for smaller trial sizes, enable targeted trials based on clinical profiles, and test for preventive measures if surrogate markers that measure the risk of the disease are developed.

The following sections outline the major areas of ongoing diagnostics research:

**Rapid Diagnostic Tests (RDTs)**

RDTs are advantageous tools, as they are easy to use and offer timely diagnostic feedback. However, as long as the results of RDTs remain suspect and their cost is not significantly below that of antimalarial treatments, widespread adoption and adherence seems unlikely. Studies are being conducted to better understand how *environmental factors* (e.g., storage, transport, end user performance) affect the quality of the measurement. Several studies also are being conducted to evaluate RDTs for diagnosis of *non-falciparum malaria*, particularly *P. vivax*. The sensitivity of RDTs in asymptomatic populations also has been studied to determine if these tools would be effective in overall monitoring as part of mass *surveillance and management* programs. *Cost-effectiveness* studies also are in progress to understand the economic savings opportunity if RDTs are used to better target costly ACT treatment. Further studies have been conducted to test the variability of RDTs across *variances in endemicity*. 
Molecular Diagnostics

As the population of malaria parasites drops in response to the scale-up of malaria control efforts, infection will become even harder to detect using existing diagnostic tools. Current methods like blood smear microscopy and RDTs are not sensitive, specific, or efficient enough to chase down even low-level parasite infections, the elimination of which is essential for eradication. Thus, in addition to needing better point-of-care diagnostic technologies, there also will be a growing need for a truly effective, high-throughput screening tool. Although it is likely to be laboratory dependent, such a tool would facilitate quality control of field-ready RDTs and allow for better monitoring to inform decision making about malaria control efforts.

Studies have shown that PCR is more sensitive than standard microscopy for detecting all species of malaria parasite, making it the gold standard for diagnosis and surveillance if cost and complexity can be reduced. High-volume use, as would be required for effective surveillance as parasite levels fall, makes PCR much more cost effective than single-use disease diagnosis. As an alternative, researchers also are exploring simpler and less expensive molecular diagnostics like loop-mediated isothermal amplification (LAMP), microarrays, and flow cytometry, among others. However, each of these tools has certain drawbacks that must be overcome before they can be implemented more widely in the field. Additionally, rapid, sensitive, robust, and inexpensive molecular diagnostic methods that have been developed to detect agents of bioterror might provide models for new approaches to be used in diagnosing malaria.

Microscopy

Comparison studies were conducted to determine the variances in accuracy between microscopy diagnosis and clinical diagnosis in order to reduce the unnecessary prescription of antimalarials and improve disease management. Microscopy results have also been compared to RDT and PCR results to better understand the agreement in measures across transmission environments and clinical settings. Finally, new techniques such as magnetic deposition microscopy (MDM) are being studied that concentrate parasites on slides using magnets yielding measurements with acceptable sensitivity and clarity, but requiring less time to conduct.

Treatment

Most treatment research focuses on drugs for falciparum malaria; however, some new efforts are targeting other forms, with a particular emphasis on vivax malaria. Although the ACTs currently recommended for first-line treatment of falciparum malaria are considered highly efficacious, there is a continued need to conduct research on potential new treatments.

A number of clinical research programs still are looking at improving and expanding the range of ACTs available. This includes efforts to develop new fixed-dose combinations that can ensure that combinations are taken properly, as well as efforts to overcome deficits in global capacity to produce artemisinin. Further, researchers are trying to better understand and track drug resistance to help them stay ahead of the curve in treatment science.

Meanwhile, researchers are working to fill the treatment pipeline with new chemical treatments to replace artemisinin-based ones of resistance emerges. These efforts are slowed by the need to develop new compounds in combination so that resistance will not emerge as quickly as if they were introduced. This implies the need for a much larger pipeline of candidates in order to produce...
a single treatment, as well as a stronger understanding of the way that various compounds in development interact with one another.

The following sections outline the major areas of ongoing drug/treatment research.

**ACTs**

Many ongoing research efforts are aimed at developing new ACT formulations for use in both adults and children. Several new ACTs currently are in clinical development, including two in Phase 3. At the same time, researchers are continuing to assess and try to improve ACTs already approved and in use in developing countries. This includes efforts to develop new formulations specifically for use in children, to improve dosing and drug formulation to increase efficacy, and to understand and prevent potential adverse effects.

Other ongoing research efforts relating to ACTs are focused on increasing the global artemisinin supply to ensure that it is affordable and available for use in the therapies. Researchers are looking into a number of biotechnological and biosynthetic approaches to producing artemisinin, as well as increasing the effectiveness of processes for extracting artemisinin from the herb that produces it.

Additionally, many studies are being conducted to compare existing ACTs to make context-specific determinations about which are the most efficacious and best able to reduce the likelihood of malaria transmission. The possibility of deploying multiple first-line combination therapies at once also is being investigated as a strategy for overcoming resistance to individual drugs. Further work is needed to establish a biological rationale for choosing ACTs and assist in minimizing selection for resistant parasites.

**Novel Compounds**

Despite the use of combination therapies to slow the emergence of resistance to ACTs, researchers expect that these currently potent treatments eventually will be resisted. Unless new treatments are available to replace them, the accompanying decline in ACT efficacy could be catastrophic for affected populations and global malaria control efforts. As a result, researchers are working to develop new antimalarial drugs that are fast-acting, highly potent against asexual blood stage infections, minimally toxic, and affordable to residents of endemic regions.

Many new classes of antimalarial drugs are under investigation both individually and in combination, although this research is concentrated in the earlier phases of the R&D pipeline where attrition rates are higher and time to registration is longer. In order to maximize the potential for success in delivering novel malaria treatment options, researchers are conducting more than 80 activities aimed at discovering and optimizing completely new treatment leads.

**Standard Antimalarials**

Although ACTs are now the recommended first-line treatment for most populations, researchers continue to explore the use of non-ACT antimalarials like chloroquine and SP. One important target for this research is the treatment of pregnant women, in whom ACTs have not been proven to be a safe option. Although safety testing in this group is rare, some studies do seek to evaluate the risk of specific drugs in comparison with the risk posed by malaria infection.
A special subset of this research is focused on exploring the possibility that certain experimental malaria treatments—including chlorpheniramine, primaquine, and HIV protease inhibitors—could contribute to reversing chloroquine resistance. Researchers recently found that chloroquine resistance disappeared from an African country several years after the drug was replaced by SP, raising the possibility that drugs could be rotated to overcome resistance.

**Non-falciparum Malaria**

The emergence of *vivax* resistance to current first-line treatments such as primaquine and chloroquine, which has occurred more slowly than for *falciparum* malaria, has drawn attention to the need for more research to develop new treatments for non-*falciparum* malaria. Although ACTs are effective at treating immediate *vivax* infection, none provide a radical cure that completely clears the parasites from the system and prevents recurrence. Few products currently in preclinical or clinical studies specifically target a radical cure for *vivax* malaria, with the notable exception of tafenoquine, a novel treatment undergoing Phase 1 trials. A couple of compounds that target *falciparum* malaria also may act against *vivax*, including pyridones, a new class of drug that is in preclinical studies. Further efforts are underway to feed the pipeline with newly discovered compounds that show promise against *P. vivax*.

**Drug Resistance**

Researchers are working to understand and track the emergence of resistance to ACTs. These efforts include studies to understand the determinants and causes of resistance and what indicators can be used to predict it, as well as the recent creation of a World Wide Antimalarial Resistance Network (WWARN) to provide comprehensive, quality-assured information on drug resistance. Additional research is focused on improving ways, including biomarkers, in vitro methods, and genomic approaches, for monitoring the emergence of resistance. These efforts are particularly urgent in light of the recent reports of declining ACT efficacy in Southeast Asia and the possible emergence of ACT resistance there.

**Care Delivery**

Regions where malaria is highly prevalent often lack adequate health system infrastructure, which reduces access to facilities where diagnosis and disease treatment can be overseen by a qualified professional. For new prevention mechanisms and treatments to be truly effective, a health system needs to be in place to administer to patients. In the case of malaria, even when chloroquine was effective, it did not reach everyone who needed it because the health system was not broadly accessible.

Further, weak health systems frequently lack the capacity to coordinate multi-intervention efforts, which are key to successfully controlling malaria in endemic countries. A lack of funding and political will to address malaria-specific and system-wide shortcomings severely hinders malaria control efforts.

To circumvent these challenges, malaria researchers are searching for new ways to use existing tools and interventions to prevent vulnerable populations from ever getting infected with malaria.
In addition, researchers are trying to understand and improve diagnostic and treatment methods that do not rely on up-to-date facilities or even, in some cases, healthcare personnel.

The following sections outline the major areas of ongoing care delivery research.

**Intermittent preventive treatment**

Intermittent-preventive treatment (IPT) with SP has been tested extensively to protect expectant mothers (IPTp) from placental malaria infections that can lead to complications and threaten the health of their fetuses. Ongoing studies in this area focus on which drugs are best for IPT and how such care should be delivered to pregnant women. Researchers hope that better, longer-lasting drugs like ACTs might be safe and efficacious for use in IPTp, as they would confer more protection on the expectant mother.

Additionally, new research efforts focus on using IPT for infants (IPTi) and young children to prevent complications from malaria while they develop protective immunity. Studies have found that IPTi is efficacious in preventing illness when given during the first 12 months of life. Despite some encouraging results, IPTi during infancy and early childhood is still being evaluated due to concerns about its efficacy in the face of increasing resistance, the possibility that malaria risk may rebound after IPTi is stopped, and questions about whether it is beneficial and cost-effective in areas with different levels of malaria risk.

**Malaria in Pregnancy**

Malaria in pregnancy is understood to be one of the leading causes of maternal mortality in endemic areas, and also may lead to increased susceptibility among the children born. Further, pregnant women cannot be treated using first-line ACTs, so prevention is the key strategy for reducing maternal and child deaths due to malaria in pregnancy. IPT is one effective way of preventing malaria in pregnant women, as are ITNs and IRS. Researchers are evaluating different approaches to delivering IPT to expectant mothers. Some of these studies focus on what intervention or combination of interventions is most effective for preventing malaria, while others look at cultural considerations and try to develop appropriate education and dissemination techniques.

**Home-based Management**

Home management of malaria (HMM), in which children exhibiting symptoms of malarial fever are treated presumptively by community workers or parents, is used widely to disseminate chloroquine. Provision of ACTs through this delivery mechanism has been slow due to concerns about treatment protocol adherence and its contribution to resistance, cost, adverse effects, and other factors. Despite these concerns, researchers are implementing and evaluating pilot programs to learn more about whether and how to introduce ACTs through HMM.

**Diagnostic Practices**

Because diagnosis needs to be conducted in remote areas without access to some of the standard diagnostic tools, research is being conducted to identify symptoms for use in clinical diagnosis. For example, one study looked at the correlation between symptoms such as joint pain, headache, abdominal pain and vomiting, and the presence of malaria infection. Specific social factors that
guide healthcare workers’ decisionmaking processes also have been studied to better understand how training, peer influence, patient preferences, and diagnostic support can lead to over diagnosis.

Other research studies are looking at the risk of “perceived malaria” as identified by patients themselves as well as the economic cost for the over diagnosis of the disease. The impact of training, especially for expatriate populations, has been studied as an intervention for raising awareness and leading to better self-diagnosis. Additionally, health-seeking behaviors and the socioeconomic barriers for patients to access health care services for diagnosis and treatment have also been studied.

Research Infrastructure
Table 2 summarizes the major tools available for malaria research and areas where more investment is required to overcome challenges and accelerate research. Major tools and associated challenges were identified and prioritized through consultation with FasterCures’ PAS Scientific Advisory Board for malaria.

Table 2: Major Research Tools and Resources for Malaria and Challenges

<table>
<thead>
<tr>
<th>Tool category</th>
<th>Existing tools and efforts</th>
<th>Challenges or areas requiring investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biospecimens and data</td>
<td>• The Malaria Research and Reference Reagent Center (MR4) provides access to a variety of specimens&lt;br&gt;• Several genomics databases, including PlasmoDB, aggregate and analyze genomic and proteomic data on multiple species of malaria parasite</td>
<td>• Insufficient insectories to produce mosquitoes for research purposes&lt;br&gt;• Lack of tools for growing and studying non-falciparum malaria, including laboratory culture methods</td>
</tr>
<tr>
<td>Research capacity</td>
<td>• Multiple efforts to expand and support clinical trial capacity, particularly in Africa&lt;br&gt;• Several training and capacity-building programs, particularly targeting African scientists</td>
<td>• Need for sustained investment in maintaining clinical trial infrastructure after it has been developed&lt;br&gt;• Insufficient funding opportunities to entice new scientists to get involved&lt;br&gt;• Few postdoctoral training opportunities for scientists in or from endemic countries</td>
</tr>
<tr>
<td>Experimental models</td>
<td>• Four rodent models, including one that has been genetically modified to mimic human immune response&lt;br&gt;• Several strains of human malaria parasites that have been adapted to be infective in non-human primates</td>
<td>• Poor comparability of the mouse parasites and immune response to that of humans&lt;br&gt;• Lack of accessible models that effectively represent non-falciparum malaria&lt;br&gt;• Limited access to primate models, particularly the impending shortage of chimpanzees infected with P. ovale&lt;br&gt;• Inadequate challenge models for non-liver stage infection, non-falciparum malaria</td>
</tr>
<tr>
<td>Data standards</td>
<td>• Community-driven efforts to standardize assays, procedures, and reagents, as well as clinical trial design, among vaccine researchers</td>
<td>• Difficulties in comparing experimental results due to the proliferation of multiple testing models, limited availability, and lack of standard</td>
</tr>
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</table>
### Tool category

<table>
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<tr>
<th>Communication/Collaboration</th>
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<tbody>
<tr>
<td>Existing tools and efforts</td>
</tr>
<tr>
<td>The WorldWide Antimalarial Resistance Network (WWARN) tracks drug resistance</td>
</tr>
<tr>
<td>Issue-specific research collaborations such as the Malaria in Pregnancy Consortium</td>
</tr>
<tr>
<td>Online networking opportunities</td>
</tr>
</tbody>
</table>

**Source:** FasterCures.

Research infrastructure in developing countries is still in its infancy and is mostly funded by organizations from the developed world. However, the recent expansion of funding for malaria research and the emergence of public-private partnerships has led to increased investment in developing this capacity. These groups also are invested in other key resources to facilitate the work of malaria researchers globally.

**Biospecimens and Data**

Data and specimen banks provide important tools for standardization of research to produce comparable results. The malaria community has developed a number of these resources in the past several years, providing access to biospecimens, genomic data, and epidemiological information.

The U.S. National Institute on Allergies and Infectious Diseases (NIAID), the Multilateral Initiative on Malaria (MIM) and other partners have collaborated to create a Malaria Research and Reference Reagent Resource Center (MR4). Launched in 1998, the MR4 is meant to provide researchers access to low-cost reagents that can be used as reference standards or from which they can generate renewable reagent sources. The reagents distributed by the MR4 include parasites, proteins, molecular biology reagents, immunologic reagents, mosquitoes, and others. Scientists who request reagents from the MR4 pay only the shipping costs associated with their orders.

Efforts aimed at mapping the genome sequences for several species of malaria parasite have expanded the knowledge base for researchers at the basic and translational levels of inquiry. Several electronic databases provide researchers access to these genome maps and the research and analysis they have supported. One key database is NIAID’s PlasmoDB, genomic, proteomic, and other data for multiple species of Plasmodium parasites. In addition to the work on parasite genomics, researchers also have mapped sequences for a variety of species of Anopheles mosquito, which are aggregated and made available through AnoBase, a database developed by the UNDP/UNICEF/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR) and supported by NIAID.

Despite the availability of some resources, however, gaps remain that hinder research efforts. The lack of reliable methods for growing non-falciparum malaria in the laboratory severely limits the ability of researchers hoping to study these still-neglected species. Some research has gone into developing culture systems for vivax malaria; however, these efforts have failed to produce a method for long-term culture of the asexual blood and gametocyte stages of vivax infection. Additional challenges are posed by a lack of insectaries that can produce the mosquitoes required for malaria research efforts.
**Research Capacity**

Serious deficits in research capacity in countries where malaria is endemic have traditionally hindered efforts to develop better knowledge about the disease and to translate that knowledge into new tools. This capacity has been limited by a lack of investment in research infrastructure and human capital. Several networks and partnerships have been established to develop capacity and conduct research on malaria in developing countries, particularly in Africa.

**Clinical Trial Networks**

The Malaria Clinical Trials Alliance (MCTA) was created in 2006 to build clinical trial infrastructure and capacity in Africa. The Alliance, which is supported by the Medicines for Malaria Venture and the Malaria Vaccine Initiative, currently includes 17 sites in 10 sub-Saharan African countries. These sites are used to conduct ongoing clinical trials and train trial investigators.

Established in 2003, the European and Developing Countries Clinical Trial Partnership (EDCTP) is an organization that brings together 16 European and 46 sub-Saharan African countries to build clinical trial capacity. The partnership focuses its efforts on supporting development of new vaccines, drugs, and diagnostics for HIV/AIDS and tuberculosis (TB), along with malaria. Projects supported by the EDCTP take a multi-center approach and combine clinical trials, capacity building, and networking. EDCTP funding is being used to start up a new Central Africa Network on Tuberculosis, HIV/AIDS, and Malaria for the Conduct of Clinical Trials (CANTAM), which was announced in late February 2009.

The Africa Malaria Network Trust (AMANET) was created in 2002 to continue earlier activities carried out by the African Malaria Vaccine Testing Network relating to the development of clinical trial sites in Africa. AMANET has several ongoing activities, including a network to develop standardized immunological assays to assess vaccine candidates, long-term capacity building at four clinical trial sites, and publication of a directory of potential clinical trial sites in Africa. AMANET also conducts its own research on malaria vaccines.

Clinical trial sites in Asia are not as comprehensively organized as those in Africa, although significant capacity exists. The Wellcome Trust South-east Asia Programme supports malaria research centers in Laos, Thailand, and Vietnam and coordinates multi-center drug trials that cover sites in five countries. The Asia Clinical Trials Portal (ASCTP) is an online network and information resource for sites that conduct malaria, HIV/AIDS, and TB clinical trials in Asia. The portal provides information on trial site capacity and ongoing trials, as well as news and other information that might be useful for trial sites. As of December 2008, five sites (none of which is part of the Wellcome Trust program) were listed as having ongoing malaria trials, all of which were focused on drug development. The ASCTP is not yet a comprehensive resource; however, its sponsors hope to expand the breadth and depth of information provided.

Recent analysis conducted by the George Institute suggests that the attention paid to increasing clinical trial capacity has paid off, resulting in sufficient trial centers to advance the current pipeline of malaria-related products. However, there is concern that investments may not be consistent and sustainable, leaving room for capacity to degrade as time goes on. Ongoing support for existing clinical trial centers is therefore crucial to ensuring that investments in capacity have not been for naught.
Research Training

In addition to investments in infrastructure, several initiatives currently are seeking to bolster human capacity to conduct malaria research in endemic countries. AMANET and MIM offer and support a variety of training programs to develop new experts and to increase the skills of existing ones in Africa. Other groups provide fellowships and study exchanges meant to bolster human capital for research endemic-country. Despite these efforts, training opportunities still are not sufficient to attract researchers and develop their skills in malaria. There are few centers of excellence in endemic countries where new investigators can build skills and experience and pursue postdoctoral training. There also are only very limited opportunities for scientists from endemic countries to pursue high-level academic study outside of their home countries. Those who do take advantage of outside education often see little incentive to return home, opting instead to work in the countries where they have trained.

Experimental Models

Animal models are the key media through which potential treatment targets and methods are first identified and then studied, though it should be noted that animals typically do not develop the exact same disease as humans. In some cases, animal models are based on a similar disease that animals contract; in other cases, scientists artificially induce the disease to create animal models.

The first level of research typically focuses on small animals, particularly mice and other rodents. Malaria researchers commonly rely on four species of rodent malaria as models for studying different aspects of human malaria. The most widely used of these is *P. berghei*, which was the first rodent model to be isolated. In 2007, scientists developed modified versions of both *P. berghei* and the immune system in mice, which together are thought to be the closest correlate so far for use in vaccine research. *P. chabaudi* is commonly used to model drug resistance and *P. yoelii* is commonly used for developing and testing vaccine candidates. Use of a fourth model, *P. vinckei* is less common.

Non-Human primates, although more expensive, typically provide the closest match to human disease pathogenesis. Strains of *falciparum* and *vivax* malaria, along with *P. malariae*, have been adapted to infect owl and squirrel monkeys. Chimpanzees, meanwhile, may be infected with *vivax*, *ovale*, and *malariae*, and on rare occasions with *falciparum*. However, the chimpanzee model has declined in use amid concerns about using the endangered species for research. Instead, New World monkey models and blood from infected humans have been used for research on non-*falciparum* malaria, though these options both have limitations. In addition, several species of *Plasmodium* parasite that naturally infect non-human primates also may be used in malaria research.

Despite the existence of an array of animal models for use in malaria research, key gaps remain. First is the lack of an accurate model to replicate the human immune response to the malaria parasite, which limits the usefulness of animal research in testing new vaccines. Instead, vaccine researchers often must rely on human challenge models, which only exist for the liver stage of infection at this time. New challenge models for testing blood stage and non-*falciparum* candidates could provide important tools for vaccine development. Further, the rodent malaria models all provide some level of comparability for *falciparum* malaria but not for other forms. Similar models
for *vivax*, *malariae*, and *ovale* remain unavailable. Currently employed non-human primate models for testing these species of parasite are not adequate to meet the research needs of the field.

**Data Standards**

The quality and comparability of research data is important for efforts to improve knowledge sharing and collaboration. Recently the malaria research community has been working toward standardization of research and data protocols to improve the comparability and quality of research results. These activities are particularly strong in the area of vaccine research, where the major players collaborated on the 2006 release of a Malaria Vaccine Technology Roadmap, which included a commitment to developed standardized assays, procedures, and clinical trial protocols. Efforts to meet this commitment are underway, although the community has not yet achieved standardization.

**Communication/Collaboration**

Networks that bring together researchers and support their collaboration can play a key role in facilitating global research on malaria. Several networks have been created to focus on specific research questions relating to malaria, such as the WWARN network to track resistance and the Malaria in Pregnancy Consortium to connect scientists working on issues relating to pregnant women and malaria. MIM also hosts an online discussion forum for malaria researchers, although this community does not appear to be well-utilized. While it is clear that some networking resources do exist, opportunities and tools for networking and communication remain inadequate to bring together a research community that is quite dispersed and would benefit from greater global interaction.

**Clinical Trials**

As of March 2009, there were 175 ongoing clinical trials for malaria. Malaria has an unexplained, disproportionately high share of trials for which phase data are not available, perhaps due to differences in international data collection practices and the fact that a slightly higher share of malaria trials are observational and have no associated phase. Slightly higher shares of trials in Phases 3 and 4 are present as compared with other diseases, while a smaller proportion of trials are in Phase 2 (Figure 7).

![Trial distribution by phase](source)

**Figure 7: Clinical trials on malaria by phase.**  
Source: ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), FasterCures analysis.
In terms of sponsors, investments from the United States and other governments were especially strong, with their share of malaria being several times that for all trials. In addition, three times as many malaria trial sponsors are listed as unknown than for all trials, which may reflect difficulties in classifying PDPs and other international organizations. Six trials have PDPs listed specifically as sponsors, with many more likely but not reported as such. Another 10 list multilateral organizations like WHO and the Global Fund for AIDS, TB, and Malaria, while an additional 22 trials list foundations based in the United States and Europe as direct funders. Industry investment in malaria trials is significantly lower than all trials, and NIH and other sponsors lag behind as well (Figure 8). This reflects the lack of market incentives to encourage industry investment in malaria research, as well as the heightened role of nonprofits and multilateral organizations in filling the investment gap.

Trials involving drugs or biologics accounted for the largest shares of trials for all type of sponsors except NIH. About half of all NIH trials were controlled experiments focused on drugs or biologics, while the remainder were observational, or uncontrolled, studies. NIH’s portfolio includes almost three quarters of all observational trials, while organizations classified as “other” are involved in all but one of the nine behavioral studies registered, all six of the studies on procedures, and six out of eight studies classified as “other.”

**Funding**

The total amount of money spent fighting malaria in 2007 was estimated to be $1.5 billion. According to the Global Malaria Action Plan, approximately 34 percent of the funds came from national governments and another 20 percent from the sale of antimalarial drugs and ITNs, mostly from the private sector. International donors, including governments and foundations, contributed an estimated $701 million representing approximately 46 percent of the total funds. In September 2008, funding organizations pledged a total of $3 billion for malaria control and research.

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4 Trials with multiple types of sponsors are accounted in each sponsor type.
Global funding commitments to malaria initiatives have increased tremendously over the past four years, reaching an estimated $1.1 billion in donor disbursements in 2008 (Figure 10). This primarily is a result of the increased scope of the U.S. President’s Malaria Initiative (PMI) and disbursements from Phase 1 of the World Bank Booster Program. The PMI supported malaria control efforts in 10 African countries in 2007 and 15 countries in 2008.

**Research and Development**

Funds for malaria research have increased steadily, reaching about $468.4 million in 2007. Government and philanthropic funders, led by the Gates Foundation and NIH, provided about 80 percent of the total. These two sources combined to account for approximately 40 percent of total research funding. It should be noted that funding from NIH has remained virtually flat over the past five years, while funding from the Gates Foundation increased rapidly over this same period. Funding from industry sources accounted for over 19 percent ($90.8 million) of the total.

The development of new malaria drugs is the largest area of R&D investment, receiving 45.7 percent ($214.1 million) of all funds in 2007. This was followed by 24.1 percent ($112.9 million) for basic research and 18.9 percent ($88.4 million) for vaccines. Development of new products for use in vector control received 3.8 percent (17.7 million) of all funds. Meanwhile, diagnostics research accounted for a meager 0.3 percent ($1.6 million) of spending.

Current funding levels fall far short of the R&D funding requirements suggested by the Global Malaria Action Plan. According to the plan, R&D to increase the arsenal of tools to aid the fight against malaria will require an estimated $750 million to $900 million annually between 2008 and 2018. The total spend covered in these projections is $8.9 billion, including $1.2 billion for vector control, $3.5 billion for drugs, $2.6 billion for vaccines, and
$140 million for diagnostics (Figure 11). These numbers do not include $1.5 billion in funding for early research and information that can help in impact assessment.
Market Analysis

Overview
A number of initiatives are underway to develop drugs and vaccines for malaria. Because of international product development partnerships (PDPs), the malaria R&D pipeline is currently populated with a number of promising drugs, though few promising vaccines. Financing the pipeline is of concern to industry developers working to replace skeletal private markets in the poor regions of the world where malaria products are in highest demand.

Market
Today, there is no vaccine to prevent malaria. Vaccines are being developed (particularly by GSK), but few are in late-stage clinical trials. In contrast, a number of antimalaria drugs are currently on the market and are in clinical trial stages.

Organized by active ingredient, Table 1 provides a sample of internationally approved and recommended malaria drugs currently available. Many of these drugs have different marketing strategies, depending on the market type. For example, Novartis markets artemether/lumefantrine as Riamet in commercial markets and Coartem in low-income markets and endemic countries. A wide variety of additional antimalarials are sold in endemic countries, particularly Africa; however, many of them do not meet international standards or are not recommended for use as first-line treatments.

Table 1: Sampling of Antimalarials Currently Recommended for Use

<table>
<thead>
<tr>
<th>Active ingredient(s)</th>
<th>Recommended Intervention</th>
<th>Brand(s)</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>artemether IM</td>
<td>Treatment/Prophylaxis</td>
<td>Paluther®</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td>artemether-lumefantrine</td>
<td>Treatment</td>
<td>Riamet® Coartem®</td>
<td>Novartis</td>
</tr>
<tr>
<td>artemether-amodiaquine</td>
<td>Treatment</td>
<td>Arsucam® ASAQ</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td>artesunate-mefloquine</td>
<td>Treatment</td>
<td>Artequin™ ASMQ</td>
<td>Mepha Pharmaceuticals Farmanguinhos</td>
</tr>
<tr>
<td>atovaquone-proguanil</td>
<td>Prophylaxis</td>
<td>Malarone®</td>
<td>GSK</td>
</tr>
<tr>
<td>Active ingredient(s)</td>
<td>Recommended Intervention</td>
<td>Brand(s)</td>
<td>Company</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>chloroquine phosphate</td>
<td>Prophylaxis Treatment (P. vivax)</td>
<td>Aralen</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>halofantrine</td>
<td>Treatment</td>
<td>Halfan®</td>
<td>GSK</td>
</tr>
<tr>
<td>mefloquine</td>
<td>Prophylaxis Treatment</td>
<td>Lariam®</td>
<td>Roche</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primaquine phosphate</td>
<td>Treatment (P. vivax and P. ovale)</td>
<td>Primaquine</td>
<td>Sanofi-Aventis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>sulfadoxine-pyrimethamine</td>
<td>Prophylaxis Treatment</td>
<td>Fansidar®</td>
<td>Roche</td>
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Sources: Moran, Ropars, Guzman, Diaz, & Garrison, 2005; WHO Model List of Essential Medicines (updated March 2007).

The antimalarial drug market is segmented into four categories: public, private, travelers, and military/defense. Pricing is similar across all market segments. The public market is comprised of bulk purchases of drugs by governments of endemic countries to be distributed in their health care systems. The private market refers to purchases by individuals in endemic countries who pay out of pocket. Travelers from non-endemic countries to malaria endemic countries constitute the travelers market, excluding military personnel who fall into the military/defense market.

Although there is substantial need and potential demand across all four market segments, specific requirements for product profiles vary significantly by country (e.g., efficacy thresholds, minimum duration of drug action, and the species of malaria being dealt with, cost and targeted species). Additionally, the type of intervention—prophylactic versus therapeutic—plays a role in the type of product that is purchased. While some products can be used for both, this is not always the case.

Dividing antimalarial treatments by public and private shares shows vast discrepancies in the purchasing behavior of different market segments. Of the 546 million antimalarial treatments consumed in 2006, 27 percent were purchased by governments and the remaining 73 percent were purchased by private sources. While governments had switched over to purchasing mostly ACTs, the private market still overwhelmingly used less expensive drugs like chloroquine, SP, and artemisinin monotherapies.

The antimalarial drug market was estimated to be between $145 million and $290 million in 2008. The higher figure, from the International Federation of Pharmaceutical Manufacturers association (IFPMA) estimates the size of the travelers market to be $73 million and the public market within developing economies to be $218 million. These numbers are close to those reported by the Boston Consulting Group. By volume, 90 percent of antimalarials purchased are generic formulations; however, by purchase value the same percentage are branded drugs.
Estimates of the potential market for a malaria vaccine vary by market and vaccine profile.

**Financing Mechanisms**

The recent global interest in accelerating R&D activities to produce new tools in the fight against malaria and other diseases that primarily affect developing countries has led to the emergence of new funding mechanisms designed to stimulate investment and induce participation. This section focuses on R&D oriented mechanisms that are designed to create direct incentives, particularly for industry contributions. There also are numerous market-focused financing mechanisms that could be used to ensure that new products will be purchased and distributed once they become available.

- **Advanced market commitments (AMCs):** An AMC is a market-based mechanism designed to accelerate the development, production, scale-up, and use of vaccines by establishing “pull” incentives for private industry investment. Credible sponsors (e.g., large foreign aid donors) would commit in advance to a minimum price paid per person immunized up to a certain number of individuals. In exchange, industry would commit to produce additional doses in the longer-term at a low price. If no product is developed, no payments are made. The AMC concept currently is being tested on the development of a vaccine against pneumococcal disease. Even if it succeeds, large questions remain about whether it could be applied for malaria.

- **Priority Review Voucher (PRV):** A PRV entitles the holder to expedited review of a new drug application that does not meet the criteria typically required for priority review status, which can shorten approval time by four months to a year. The U.S. Food and Drug Administration recently announced that it will offer PRVs to companies that develop new products targeting neglected tropical diseases, including malaria. Under the program, PRVs will be transferable, allowing the rights to be sold if the recipient does not have another product for which it would like to secure priority review. Industry guidance on the PRV program was released in draft form in October 2008, with a public hearing held in December 2008.

**Pipeline**

**Vaccines**

In 1985 no malaria vaccine candidates were in clinical trials; by late 2006, the global malaria vaccine portfolio included 47 candidates in preclinical or clinical studies, and by 2009, 21 to 26 of them are expected to be in clinical trials (Figure 12). The location of projects will most likely shift toward Africa, because later stage trials need to be conducted in endemic regions (Figure 13). Shifting parameters such as project location will have funding implications.

RTS,S, a candidate that is under development by GSK and MVI, is expected to enter Phase 3 clinical trials in 2009, with anticipated registration as a partially effective malaria vaccine near 2012.
Between 1975 and 2004, 1,556 new drugs were approved for public use. Only eight were for malaria. Drug development is expensive and time consuming, but critical to combating drug resistance. As of the fourth quarter of 2008, there were 13 malaria drugs in clinical trials, including three in Phase 3 and three in registration or Phase 4 (Figure 14). Another eight products were in preclinical. Additionally, large scale efforts were underway to feed the pipeline by identifying and optimizing new drug leads, with eight leads in the optimization stages and more than 75 ongoing discovery projects.

The weighting of the portfolio toward either early or late-stage research results from a shift in global policy during 2000 to ACT as the standard treatment for malaria, and the entrance of several PDPs into the drug development arena. The drugs in Phase 3 are composed of new combinations or reformulated antimalarials already on the market and will continue to evolve through the pipeline as they will experience little to no attrition. As a result, policymakers will face an unprecedented level of Phase 4 studies in coming years and each will need to enroll tens of thousands of patients.
An ideal product portfolio image is triangular with a large number of preclinical products being whittled away and only one or two products remaining from which policymakers can choose.

A 2008 status report on pharmaceutical industry R&D activities targeting diseases of the poor showed that as of November 2008, 28 drug development efforts and four vaccine development projects were underway involving industry players. Three industry efforts, all undertaken in conjunction with PDPs, have resulted in a product registration (ASAQ, ASMQ, and Coartem-D) since 2005, while seven such efforts had been halted. Nineteen of the ongoing efforts were reported as having a PDP partner, showing the influence of PDPs on malaria R&D.

Pharmaceutical and biotechnology companies in developing countries often work with Western partners to bring malaria products to market, frequently through PDPs. In fact, nearly one-quarter of the documented 47 PDP neglected disease projects reviewed in a 2005 report, as well as the three drugs registered between 2000 and 2005, involved developing country firms as either the main or subsidiary partner.

Table 2 lists malaria drugs and vaccines currently in clinical trials.

<table>
<thead>
<tr>
<th>Sponsor/Implementer</th>
<th>Product</th>
<th>Project/Drug Name</th>
<th>Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEMRI, Wellcome Trust</td>
<td>Drug</td>
<td>Methotrexate</td>
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<td>Drug</td>
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<td>Drug</td>
<td>Isoquine</td>
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<td>Immtech, Tulane University</td>
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<tr>
<td>AMANET</td>
<td>Vaccine</td>
<td>GLURP (long synthetic peptide)</td>
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<td>Vaccine</td>
<td>GLURP+MSP-3</td>
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</tr>
<tr>
<td>WRAIR</td>
<td>Vaccine</td>
<td>NMRC-M3V-Ad-PfCA</td>
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<tr>
<td>NIAID, Crucell</td>
<td>Vaccine</td>
<td>Ad35, CS</td>
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<td>Vaccine</td>
<td>AMA1 (PfAMA-1-FVO[35-545])</td>
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<tr>
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<td>Vaccine</td>
<td>AMA1-C1/Alhydrogel + CPG 7909</td>
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<tr>
<td>Sponsor/Implementer</td>
<td>Product</td>
<td>Project/Drug Name</td>
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<td>Vaccine</td>
<td>AMA1-C1/ISA 720</td>
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<td>Vaccine</td>
<td>FMP1</td>
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<tr>
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<td>Vaccine</td>
<td>LSA-3-rec</td>
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<tr>
<td>MVI, Sanaria</td>
<td>Vaccine</td>
<td>Sanaria Pf SPZ</td>
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<tr>
<td>WRAIR</td>
<td>Drug</td>
<td>Tinidazole (vivax)</td>
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<tr>
<td>MMV, WRAIR</td>
<td>Drug</td>
<td>IV artesunate</td>
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<td>Fosmidomycin-azithromycin</td>
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<td>Pfizer</td>
<td>Drug</td>
<td>Arterolane PQP</td>
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<td>Pfizer</td>
<td>Drug</td>
<td>Blue AQ</td>
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<td>Drug</td>
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<tr>
<td>Ruprecht-Karls-University, Heidelberg, DSM Fine Chemicals</td>
<td>Drug</td>
<td>Methylene blue, chloroquine</td>
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<tr>
<td>MMV, Hong Kong University of Science and Technology</td>
<td>Drug</td>
<td>Artemisone (Artemefone)</td>
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<tr>
<td>Jomaa</td>
<td>Drug</td>
<td>Fosmidomycin-clindamycin</td>
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<td>Drug</td>
<td>SAR97276</td>
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<td>Sanofi-Aventis</td>
<td>Drug</td>
<td>Artesunate-ferroquine</td>
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<td>MMV, GSK</td>
<td>Drug</td>
<td>Tafenoquine (vivax)</td>
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<tr>
<td>GSK</td>
<td>Vaccine</td>
<td>Malaria Vaccine 257049</td>
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<td>Vaccine</td>
<td>MSP-3 LSP</td>
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<td>WRAIR, GSK, USAID</td>
<td>Vaccine</td>
<td>FMP2.1/AS02A</td>
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<td>Product</td>
<td>Project/Drug Name</td>
<td>Trial Phase</td>
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<td>Ranbaxy</td>
<td>Drug</td>
<td>Rbx11160-piperaquine</td>
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<tr>
<td>Gates Malaria Partnership</td>
<td>Drug</td>
<td>Azithromycin-artesunate</td>
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<tr>
<td>MMV</td>
<td>Drug</td>
<td>Azithromicin-chloroquine</td>
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<tr>
<td>MMV, Shin Poong</td>
<td>Drug</td>
<td>PYRAMAX® (pyronaridine-artesunate)</td>
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<tr>
<td>MMV, Sigma Tau, Chongqing, Holley</td>
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<td>DHA piperaquine (Artekin, Eurartesim™)</td>
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<tr>
<td>MVI, GSK, WRAIR</td>
<td>Vaccine</td>
<td>RTS,S/AS02 (A,B,E)</td>
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<td>WHO/TDR</td>
<td>Drug</td>
<td>Rectal artesunate</td>
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<td>MMV, Novartis</td>
<td>Drug</td>
<td>Artemether-lumefantrine</td>
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<td>DNDi, Farmanguinhos</td>
<td>Drug</td>
<td>Artesunate-mefloquine</td>
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<td>DNDi, Sanofi-Aventis</td>
<td>Drug</td>
<td>Artesunate-amodiaquine (ASAQ)</td>
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<td>USAID, CDC</td>
<td>Drug</td>
<td>Sulfadoxine-pyrimethamine</td>
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</tbody>
</table>

Sources: ClinicalTrials.gov, MVI, MMV, GAVI (2008), Genton (2008), Olliaro and Wells (2009), BVGH, IFPMA Status Report.
Commercial Players

Overview
This section provides a brief summary of selected companies that are active in malaria R&D. Companies were included in this survey that have major malaria products on the market, are involved in two or more research projects relating to new malaria products, and/or have dedicated facilities for malaria or neglected disease R&D. It is important to note that most commercial players involved in malaria R&D are not pursuing a profit objective, but rather view their investment from a philanthropic and/or public relations standpoint.

For each company, a brief discussion includes its investment in R&D broadly and in malaria specifically, as well as any other ties that make the company an important player.

Key Companies

Major Pharmaceutical Companies

Genzyme is a pharmaceutical company based in the United States that produces almost 4 billion product packs every year and reported $3.8 billion in revenues on 2007. In 2006, Genzyme launched its Humanitarian Assistance for Neglected Diseases initiative, through which it devotes resources to malaria, Chagas disease, and African sleeping sickness, among others. For its work on malaria, Genzyme is focusing on drug discovery through a partnership with the MMV and the Broad Institute of Harvard and the Massachusetts Institute of Technology.

GlaxoSmithKline (GSK) is a research-based pharmaceutical company with offices in over 100 countries making almost 4 billion packs of medicines and healthcare products every year. GSK claims a global community investment of $564.2 million for 2007 (3.8 percent of total profit before tax) with a focus on HIV/AIDS, TB, and malaria and supports voluntary licensing agreements. GSK contributes to health improvement of people living in the least developed countries (as defined by the United Nations) by setting a single nonprofit price for each of its drugs and vaccines for HIV/AIDS and malaria.

On the research side, GSK operated a dedicated drug discovery facility for neglected diseases in Tres Cantos, Spain, which is very active in malaria and TB. In addition, GSK works with PDPs by contributing R&D technology, manufacturing, and distribution expertise with MVI and MMV. GSK also developed an advocacy program called “Mobilizing for Malaria” through the GSK African Malaria Partnership and launched efforts in Belgium, Cameroon, Ethiopia, France, and the United Kingdom to increase awareness of malaria and to mobilize resources. Start-up funding totals $1.5 million over three years.

Novartis, a Swiss chemical and pharmaceutical company, achieved net global sales of $38.1 billion in 2007 and in partnership with other industry partners completed clinical trials for a pediatric

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5 March 18, 2008, exchange rate used to convert £282 million to $564.2 million.
formulation of Coartem®, a key antimalarial drug. To facilitate use of the original adult formulation, Novartis forged a relationship with the WHO to provide the drug at a nonprofit price to the public health systems in developing countries. During 2007, 66 million treatment courses were delivered in Africa (70 percent of which were intended for children). Although production capacity for Coartem® is 100 million treatments per year, lack of local infrastructure reduced sales far below expectations. In addition, a third-party audit of Novartis’ production and delivery of Coartem revealed that the company lost 80 cents on each adult dose—an unfortunate example of why Western countries sometimes hesitate to get involved in diseases affecting developing countries. Like GSK, Novartis collaborates extensively with PDPs on its neglected diseases activities.

Sanofi-Aventis, based in France, is a pharmaceutical company that generated global sales of $44.9 billion in 2006. The company’s research group collaborated with the Drugs for Neglected Diseases initiative (DNDi) to develop a co-formulation of artemesinin-derived artesunate and amodiaquine, known as Arsucam®, which is now prequalified by WHO and licensed in over 15 African countries. Although presented in co-blister format, this product meets clinicians’ requirements for formats suitable for adults, children, and infants. The company also recently signed an agreement with DNDi to co-develop a new formulation for single-tablet administration to reduce treatment from eight tablets to three tablets per day for three days.

Sanofi-Aventis also is working to bring several new antimalarial compounds through preclinical and clinical research.

Other For-Profit Companies

Sanaria (Latin for healthy air) is a biotechnology company exclusively dedicated to the production of a vaccine for malaria. Founded in 2002 by Stephen Hoffman and based in Maryland, Sanaria’s goal is to develop and commercialize a metabolically active, nonreplicating (attenuated or weakened) malaria sporozoite vaccine against P. falciparum. Sanaria partners with the U.S. government, biotechnology companies, and nonprofit research organizations. In 2006, Sanaria received $29.3 million from the Gates Foundation.

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6 April 9, 2008, exchange rate used to convert €28.4 to $44.9 billion.
7 Blister packs and co-blister packs are standard packaging for many pharmaceuticals; they are pre-formed plastic blisters with a printed paperboard card normally containing a heat-seal coating. They provide sealed and protective environments for drugs.
Nonprofit Players

Overview
In recent years, pharmaceutical companies, academic institutions, and research organizations have banded together to create nonprofit PDPs to drive product development in malaria drugs, vaccines, and diagnostics. PDPs are now the major developers of malaria drugs and vaccines. Research organizations, academic centers, and government agencies in both developed and developing countries, however, continue to play significant roles in malaria treatment and prevention research.

Product Development Partnerships (PDPs)

Drugs for Neglected Diseases initiative
www.dndi.org

Like other PDPs, the Drugs for Neglected Diseases initiative (DNDi) is a “virtual” pharmaceutical development organization capitalizing on existing fragmented R&D capacity in developing countries and complements it with the expertise necessary to conduct product development research. DNDi was founded by a group of seven organizations: five public sector institutions, the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, and France’s Pasteur Institute; one humanitarian organization, Médecins sans Frontières (MSF); and one international research organization, the U.N. Development Programme/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR), which acts as a permanent observer to the initiative. Since its inception, DNDi has conducted work on 20 products.

DNDi’s malaria activities have produced two new ACTs, ASAQ and ASMQ, that are now available in developing countries. Future activities on malaria are expected to focus on refining these products and assessing them through Phase 4 trials.

European Malaria Vaccine Initiative
www.emvi.org

The European Malaria Vaccine Initiative (EMVI) was established in 1998 by the European Commission and interested European Union Member States. It is run by Chairperson Renee Van Kessel under the auspices of the Statens Serum Institute (SSI) in Denmark, which acts as EMVI’s contracting institute. EMVI’s mission is to “address identified structural deficiencies in publicly funded malaria vaccine development.” EMVI facilitates and contributes financially and technically to nationally and internationally funded malaria vaccine R&D. EMVI also works with the African Malaria Network Trust (AMANET) to speed effective treatments through the production and clinical trials process. EMVI has a diverse vaccine portfolio composed of treatments developed by researchers worldwide. These projects are funded primarily by the governments of Denmark, Ireland, Sweden, and the Netherlands.
Foundation for Innovative Diagnostics
www.finddiagnostics.org

The Foundation for Innovative Diagnostics (FIND) was launched at the 2003 World Health Assembly to develop more accurate and cost-effective diagnostic technologies for developing world diseases. Based in Geneva, FIND is run by Chief Executive Officer Giorgio Roscigno. FIND’s work on malaria includes efforts to improve the accuracy of rapid diagnostics tests for use in the field, develop a new generation of malaria tests, and develop new assays for use in assessing potential diagnostics. Other FIND programs look at diagnostics for TB and sleeping sickness, as well as laboratory preparedness. The organization receives funding from the Gates Foundation, the Dutch Government, the European Union, USAID, Google, and Fondation André & Cyprien (Switzerland).

Institute for OneWorld Health
www.oneworldhealth.org

The Institute for OneWorld Health (iOWH) is an 8-year-old independent nonprofit pharmaceutical development organization founded by Victoria Hale. The organization focuses on drugs for visceral leishmaniasis, malaria, and diarrheal diseases. iOWH obtained grants of over $130 million, principally from the Gates Foundation, and is developing a microbial process for synthesizing artemisinin through a $42.6 million partnership with Amyris Biotechnologies, the University of California at Berkeley, and Sanofi-Aventis.

Malaria Vaccine Initiative
www.malariavaccine.org

The Malaria Vaccine Initiative (MVI) was created in 1999 by PATH (an international, nonprofit organization) through a grant from the Gates Foundation. The organization is currently run by Dr. Christian Loucq. MVI's mission is “to accelerate the development of promising malaria vaccines and ensure their availability and accessibility in the developing world.” To do so, MVI takes on projects with partners in Africa, Australia, Europe, the United States, and India. Currently, MVI has a diverse vaccine portfolio with three products in clinical development. The most advanced of these is RTS,S, which will begin Phase 2 studies in 2009.

Medicines for Malaria Venture
www.mmv.org

The Medicines for Malaria Venture (MMV) is a Switzerland-based PDP founded in 1999 and run by President and CEO Chris Hentschel. MMV’s main objective is “to bring public and private sector partners together to fund and provide managerial and logistical support for the discovery, development and delivery of new medicines to treat and prevent malaria.” In 2006, MMV spent $46.9 million on R&D. MMV’s top three funders are the Gates Foundation, the U.K. Department for International Development, and The Wellcome Trust. MMV’s portfolio encompasses drugs in varied stages from initial development to the clinical trials and is the largest with 37 projects currently in the pipeline.
Research Organizations

African Malaria Trust Network
amanet-trust.org

The African Malaria Trust Network (AMANET), led by Managing Trustee Wen L. Kilama, was established in 2000 as a reinvention of the 1995 African Malaria Vaccine Testing Network. Its mission is to “promote capacity strengthening and networking of malaria R&D in Africa.” Its accomplishments include the creation of the Afro–Immunoassay Network, a consortium of six African countries/institutions working on: developing standardized immunological assays to examine the association between malaria-specific antibody responses and subsequent protection from clinical malaria; product research and development including three candidate malaria vaccines; and, the development of infrastructure, education, and training in the countries of Burkina Faso Tanzania, Uganda, and Zambia. In 2003, AMANET’s Tanzanian branch became the host of the Multilateral Initiative on Malaria described above.

Infectious Disease Research Institute
www.idri.org

Founded in 2006 by Research and Development Head Steven Reed, the Infectious Disease Research Institute (IDRI) calls itself a “nonprofit biotech.” IDRI works closely with the Malaria Vaccine Initiative and other partners on development of malaria vaccine candidates. The Institute’s work on these projects capitalizes on its adjuvant and formulation capabilities. In addition to malaria, IDRI also works on projects relating to leishmaniasis, TB, leprosy, Chagas disease, Chlamydia, and Buruli Ulcer. Major funders of IDRI's work include American Leprosy Missions, the Gates Foundation, GlaxoSmithKline, The Global Alliance for TB Drug Development, Eli Lilly and Company, MJ Murdock Charitable Trust, NIH, and WHO.

Institut Pasteur
www.pasteur.fr

Institut Pasteur (IP) is a Paris-based private nonprofit foundation that contributes to the prevention and treatment of disease through research, education, and public health activities. Malaria research accounts for 60 percent of the work done by IP's Parasitology and Mycology Department, with the remainder focusing on leishmaniasis, trypanosomiasis, and toxoplasmosis. IP also has its own training courses, which are available to degree candidates from several universities. In 2007, IP had a budget of €233.2 M, of which 43 percent was revenue from its own activities, 30.3 percent was from donations (including legacies and patrimony incomes), and 26.7 percent was from government contributions.
Multilateral Initiative on Malaria
www.mimalaria.org

The Multilateral Initiative on Malaria (MIM) was founded in 1997. Its mission is “to strengthen and sustain through collaborative research and training, the capacity of malaria-endemic countries in Africa to carry out research that is required to develop and improve tools for malaria control and to strengthen the research-control ‘interphase’.” MIM is an alliance of individuals, funding partners and four autonomous constituents: MIM/TDR, MIMCom, MR4, and the MIM Secretariat. MIM/TDR is embedded in the UNICEF/United Nations Development Program/World Bank/WHO Special Program for Research and Training in Tropical Diseases. MIM/TDR evaluates research grant applications from African malaria scientists and awards funds via a competitive peer-review process. MIMCom is the Internet communication arm based at the U.S. National Library of Medicine whose aim is to improve access of the malaria research community in Africa to medical journals and important databases. MR4 is the Malaria Research Reference Reagent Resource Center, a biological resource center providing research reagents for free to malaria scientists. Finally, the MIM Secretariat is the governing body of MIM, and is currently housed in the Tanzania Branch of the AMANET.

Seattle Biomedical Research Institute
www.sbri.org

Since 1976, the Seattle Biomedical Research Institute (SBRI) has conducted research in support of new drugs, vaccines, and diagnostic technologies for developing world diseases. The Institute continues to be run Dr. Kenneth Stuart, one of its founders. SBRI’s malaria program, which is one of the largest U.S.-based malaria efforts, has over 70 scientists focused on three key areas: vaccine discovery for pregnancy malaria, severe malaria in children, and liver-stage malaria. Other projects within SBRI work on issues relating to African sleeping sickness, candidiasis, Chagas disease, HIV/AIDS, H. influenzae, leishmaniasis, listeriosis, toxoplasmosis, and TB. SBRI has numerous funding sources, including several U.S. government agencies, the Gates Foundation, and others.

Statens Serum Institut
www.ssi.dk

The Statens Serum Institut (SSI) is an enterprise of the Danish Ministry of Health and Prevention located in Copenhagen, Denmark, and has duties that are partly integrated in the national Danish health services. SSI’s research and development include work on improved TB diagnostics and development of new vaccines and vaccine technologies for both TB and malaria. In 2007, SSI had a budget of $192.7 M, of which approximately 86 percent came from its commercial activities (production of vaccines and other products for sale in Denmark and abroad), 9 percent came from government grants, and 5 percent came from public and private funding. It is worth noting that these numbers include funding for EMVI, which currently is housed within SSI.

8 The term “interphase” is used in MIM’s mission statement and refers to the continuum between research and application of research results in the field.
UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
www.who.int/tdr

The Special Programme for Research and Training in Tropical Diseases (TDR) was established in 1975 to “coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged.” TDR's work on malaria includes efforts to identify drug leads for development by other partners, to develop new and improved vector control methods, and to produce evidence that can support sound policymaking on the use of antimalarial drugs. TDR, has four main sponsors (UNICEF, UNDP, the World Bank, and WHO), and receives funding from 22 governments and 12 other groups.

Walter and Eliza Hall Institute of Medical Research
www.wehi.edu.au

The Walter and Eliza Hall Institute of Medical Research (WEHI) is an independent medical research institute located in Melbourne, Australia. The Institute covers cancer, genetics, malaria, autoimmune diseases, medicinal chemistry, drug discovery and translational research. Under Australian law, WEHI is a “benevolence” of the perpetual charitable Walter and Eliza Hall Trust and, as such, it can and does take individual donations. Malaria and leishmaniasis are the two focal points of the Institute's Infection and Immunity Division, which works on clinical and translational research, pathogenesis and immunity, parasite cell biology, and functional genomics and proteomics. WEHI also has an arrangement with the University of Melbourne where students enrolled at the university conduct their research in the Institute's laboratories. In 2007, WEHI had a budget of $35.2 million, of which 51 percent came from the Australian and Victoria governments, 23 percent came from the endowment's investment income, and about three percent came from bequests and donations.

Academic Centers

Academic centers and individual researchers are important contributors to global research and development efforts in the malaria field. Numerous dedicated centers have been established by universities in the United States, Australia, and Europe, as well as in endemic countries. Although not a focus of the Philanthropy Advisory Service, these centers, along with other academic researchers, are an important source of expertise and research capacity.

Government Research Agencies

Substantial malaria research continues to be conducted by government research centers in the developed and developing worlds. Groups like the Medical Research Council in South Africa and the Kenya Medical Research Institute are important partners in many of the clinical research efforts underway in Africa. Meanwhile, research being done at NIH, the Swiss Tropical Institute, and other government research groups in Europe and Australia provide important expertise and contribute to ongoing R&D efforts globally.
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based Combination Therapy</td>
</tr>
<tr>
<td>AMANET</td>
<td>African Malaria Network Trust</td>
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<td>AMC</td>
<td>Advanced Market Commitment</td>
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<td>ASCTP</td>
<td>Asia Clinical Trials Portal</td>
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<td>CANTAM</td>
<td>Central Africa Network on Tuberculosis, HIV/AIDS, and Malaria for the Conduct of Clinical Trials</td>
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<td>CM</td>
<td>Cerebral Malaria</td>
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<td>DNDi</td>
<td>Drugs for Neglected Diseases initiative</td>
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<tr>
<td>EDCTP</td>
<td>European and Developing Countries Clinical Trials Partnership</td>
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<td>EMVI</td>
<td>European Malaria Vaccine Initiative</td>
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<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<td>IDRI</td>
<td>Infectious Diseases Research Institute</td>
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<td>iOWH</td>
<td>Institute for OneWorld Health</td>
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<tr>
<td>IP</td>
<td>Intellectual Property</td>
</tr>
<tr>
<td>IPT</td>
<td>Intermittent Preventive Treatment</td>
</tr>
<tr>
<td>IRS</td>
<td>Indoor Residual Spraying</td>
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<td>Insecticide-treated Net</td>
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<tr>
<td>LLIN</td>
<td>Long-lasting Insecticide Treated Net</td>
</tr>
<tr>
<td>Malaria ERA</td>
<td>Malaria Eradication Research Agenda</td>
</tr>
<tr>
<td>MCTA</td>
<td>Malaria Clinical Trials Alliance</td>
</tr>
<tr>
<td>MIM</td>
<td>Multilateral Initiative on Malaria</td>
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<td>Medicines for Malaria Venture</td>
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<td>MR4</td>
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<td>NIAID</td>
<td>National Institute for Allergies and Infectious Disease</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<td>Product Development Partnership</td>
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<td>PMI</td>
<td>President's Malaria Initiative</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>PRV</td>
<td>Priority Review Voucher</td>
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<td>RBM</td>
<td>Roll Back Malaria Partnership</td>
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<tr>
<td>RDT</td>
<td>Rapid Diagnostic Test</td>
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<td>SBRI</td>
<td>Seattle Biomedical Research Institute</td>
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<td>SSI</td>
<td>Statens Serum Institute</td>
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<tr>
<td>TDR</td>
<td>UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases</td>
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<td>WEHI</td>
<td>Walter and Eliza Hall Institute</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
Glossary

Anopheles mosquito: Malaria parasites are transmitted by female Anopheles mosquitoes.

ACT: Artemisinin-based combination therapy is the current recommended first-line treatment for malaria.

Choroquine: Previously used as the standard medicine to treat and prevent malaria from vivax, ovale, and malariae; over and incorrect use rendered chloroquine ineffective against falciparum.

DALY: Disability adjusted life-years. This is a WHO and World Bank developed measure of the burden of disease and was designed to capture disability and pre-mature death in one indicator. Used more often in public health and health impact assessment, the indicator combines morbidity and mortality in one measure.

DEET: N,N-diethyl-m-toluamide, DEET is an insect repellent intended to be applied on the skin or clothing to prevent insect bites.

Erythrocytes: A cell that carries oxygen and contains hemoglobin; also called red blood cells.

GDP: gross domestic product; GDP = consumption + investment + (government spending) + (exports − imports).

GFATM: Global Fund for AIDS, Tuberculosis, and Malaria. The Global Fund was created as a finance mechanism to assist a turn around in the fight against AIDS, TB, and malaria. The Global Fund has committed over $10 billion to 136 countries in support of interventions against these three diseases.

Low birth weight: Weight that is below a defined limit at any gestational age.

Malaria-related anemia: In falciparum malaria, significant hemolysis (destruction of red blood cells) can cause anemia.

Mosquito coils: Coiled clay like material serve as pest repellent when lit. Each lasts up to two hours when lit.

Natural immunity: Through natural exposure to malaria parasites, people can develop immunity to malaria. Usually, children living in endemic and malaria-stable areas who become infected early in life experience more severe symptoms before the age of five years. As immunity develops however, the disease becomes less severe and the number of parasites circulating in the blood declines. This acquired immune response to malaria is strain specific and is lost if a person moves away from a malaria endemic area.

Placenta: Organ present in placental vertebrates during gestation (pregnancy).
**Plasmodium**: Genus of parasitic protozoa. There are four parasitic protozoa causing malaria: malariae; falciparum; ovale; and, vivax.

**Plasmodium falciparum**: The deadliest of the four species of parasite and is seldom fatal

**Plasmodium vivax**: the most frequent and widely distributed cause of benign, but recurring malaria

**SSA**: Sub-Saharan Africa; region of the African continent below the Saharan desert.

**Sickle cell trait**: A person can carry the sickle cell trait without developing the blood disorder. Sickle cell disease is a blood disorder in which the body produces an abnormal type of the oxygen-carrying substance hemoglobin in the red blood cells.

**SPf66**: The first malaria vaccine to undergo field trials. During Phase 1 trials a 75 percent efficacy rate was demonstrated and the vaccine was well tolerated by subjects and demonstrated immunogenicity. The Phase I2 billion and 3 trials were less promising, with the efficacy falling to between 38.8 percent and 60.2 percent. It remains unclear if the SPf66 vaccine confers immunity as recent studies in the Gambia illustrate no effect on the study population.

**Vaccine**: A medicinal preparation used to incite an immune response.

**Vector control**: Manipulation of mosquitoes carrying parasite.
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Data Sources