

# *Understanding* **Malaria**



*Fighting an  
Ancient Scourge*

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**Malaria**

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Ancient Scourge*



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
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# What is Malaria?

Malaria is a disease caused by a **parasite\*** that lives part of its life in humans and part in mosquitoes. Malaria remains one of the major killers of humans worldwide, threatening the lives of more than one-third of the world's population. It thrives in the tropical areas of Asia, Africa, and Central and South America, where it strikes millions of people. Each year 350 to 500 million cases of malaria occur worldwide. Sadly, more than 1 million of its victims, mostly young children, die yearly.

Although malaria has been virtually eradicated in the United States and other regions with temperate climates, it continues to affect hundreds of people in this country every year. The Centers for Disease Control and Prevention (CDC) estimates 1,200 cases of malaria are diagnosed each year in the United States. People who live in the United States typically get malaria during trips to malaria-**endemic** areas of the world.

*\*Note: Words in bold are defined in the glossary at the end of this booklet.*



# History of Malaria

Malaria has been around since ancient times. The early Egyptians wrote about it on papyrus, and the famous Greek physician Hippocrates described it in detail. It devastated invaders of the Roman Empire. In ancient Rome, as in other temperate climates, malaria lurked in marshes and swamps. People blamed the unhealthiness in these areas on rot and decay that wafted out on the foul air. Hence, the name is derived from the Italian, “*mal aria*,” or bad air. In 1880, the French scientist Alphonse Laveran discovered the real cause of malaria, the single-celled ***Plasmodium*** parasite. Almost 20 years later, scientists working in India and Italy discovered that ***Anopheles*** mosquitoes are responsible for transmitting malaria.

Historically, the United States is no stranger to the tragedy of malaria. This disease, then commonly known as “fever and ague,” took a toll on early settlers. Historians believe that the incidence of malaria in this country peaked around 1875, but they estimate that by 1914 more than 600,000 new cases still occurred every year.

Malaria has been a significant factor in virtually all of the military campaigns involving the United States. In World War II and the Vietnam War, more personnel time was lost due to malaria than to bullets.

The discovery that malaria was transmitted by mosquitoes unleashed a flurry of ambitious public



health measures designed to stamp out malaria. These measures were targeted at both the larval stages (which thrive in still waters, such as swamps) and adult stages of the insect. In some areas, such as the southern United States, draining swamps and changing the way land was used was somewhat successful in eliminating mosquitoes.

The pace of the battle accelerated rapidly when the insecticide DDT and the drug **chloroquine** were introduced during World War II. DDT was remarkably effective and could be sprayed on the walls of houses where adult *Anopheles* mosquitoes rested after feeding. Chloroquine has been a highly effective medicine for preventing and treating malaria.

In the mid-1950s, the World Health Organization (WHO) launched a massive worldwide campaign to eliminate malaria. At the beginning, the WHO program, which combined insecticide spraying and drug treatment, had many successes, some spectacular. In some areas, malaria was conquered completely, benefiting more than 600 million people, and was sharply curbed in the homelands of 300 million others.





Difficulties soon developed, however. Some stumbling blocks were administrative, others financial. Even worse, nature intervened. More and more **strains** of *Anopheles* mosquitoes developed **resistance** to DDT and other insecticides, and the environmental impact of DDT was recognized. Meanwhile, the *Plasmodium* parasite became resistant to chloroquine, the mainstay of antimalarial drug treatment in humans.

Researchers estimate that infection rates increased by 40 percent between 1970 and 1997 in sub-Saharan Africa. To cope with this dangerous resurgence, public health workers carefully select prevention methods best suited to a particular environment or area. In addition to medicines and insecticides, they are making efforts to control mosquitoes, by draining swampy areas and filling them with dirt, as well as using window screens, mosquito netting, and insect repellents.



At the same time, scientists are intensively researching ways to develop better weapons against malaria, including

- Sophisticated techniques for tracking disease transmission worldwide
- More effective ways of treating malaria
- New ways, some quite ingenious, to control transmission of malaria by mosquitoes
- A vaccine for blocking malaria's development and spread





# Cause of Malaria

Malaria is caused by a single-celled parasite from the **genus** *Plasmodium*. More than 100 different **species** of *Plasmodium* exist. They produce malaria in many types of animals and birds, as well as in humans.

Four species of *Plasmodium* commonly infect humans. Each one has a distinctive appearance under the microscope, and each one produces a somewhat different pattern of symptoms. Two or more species can live in the same area and infect a single person at the same time.

*Plasmodium falciparum* is responsible for most malaria deaths, especially in Africa. The infection can develop suddenly and produce several life-threatening complications. With prompt, effective treatment, however, it is almost always curable.

*Plasmodium vivax*, the most geographically widespread of the species, produces less severe symptoms. **Relapses**, however, can occur for up to 3 years, and chronic disease is debilitating. Once common in temperate climates, *P. vivax* is now found mostly in the tropics, especially throughout Asia.

*Plasmodium malariae* infections not only produce typical malaria symptoms but also can persist in the blood for very long periods, possibly decades, without ever producing symptoms. A person with



asymptomatic (no symptoms) *P. malariae*, however, can infect others, either through blood donation or mosquito bites. *P. malariae* has been wiped out from temperate climates, but it persists in Africa.

*Plasmodium ovale* is rare, can cause relapses, and generally occurs in West Africa.





## Life Cycle of the Malaria Parasite

The human malaria parasite has a complex life cycle that requires both a human host and an insect host. In *Anopheles* mosquitoes, *Plasmodium* reproduces sexually (by merging the parasite's sex cells). In people, the parasite reproduces asexually (by cell division), first in liver cells and then, repeatedly, in red blood cells (RBCs).

When an infected female *Anopheles* mosquito bites a human, it takes in blood. At the same time, it injects saliva that contains the infectious form of the parasite, the **sporozoite**, into a person's bloodstream [1].

The thread-like sporozoite then invades a liver cell [2]. There, during the next week or two (depending on the *Plasmodium* species), each sporozoite develops into a **schizont**, a structure that contains thousands of tiny rounded **merozoites** (another stage of the parasite). When the schizont matures, it ruptures and releases the merozoites into the bloodstream [3].

Alternatively, some *P. vivax* and *P. ovale* sporozoites turn into **hypnozoites**, a form that can remain dormant in the liver for months or years. If they become active again, the hypnozoites develop into schizonts that then cause relapses in infected people.

[Numbers in brackets refer to Parasite Life Cycle diagram on pages 10–11.]

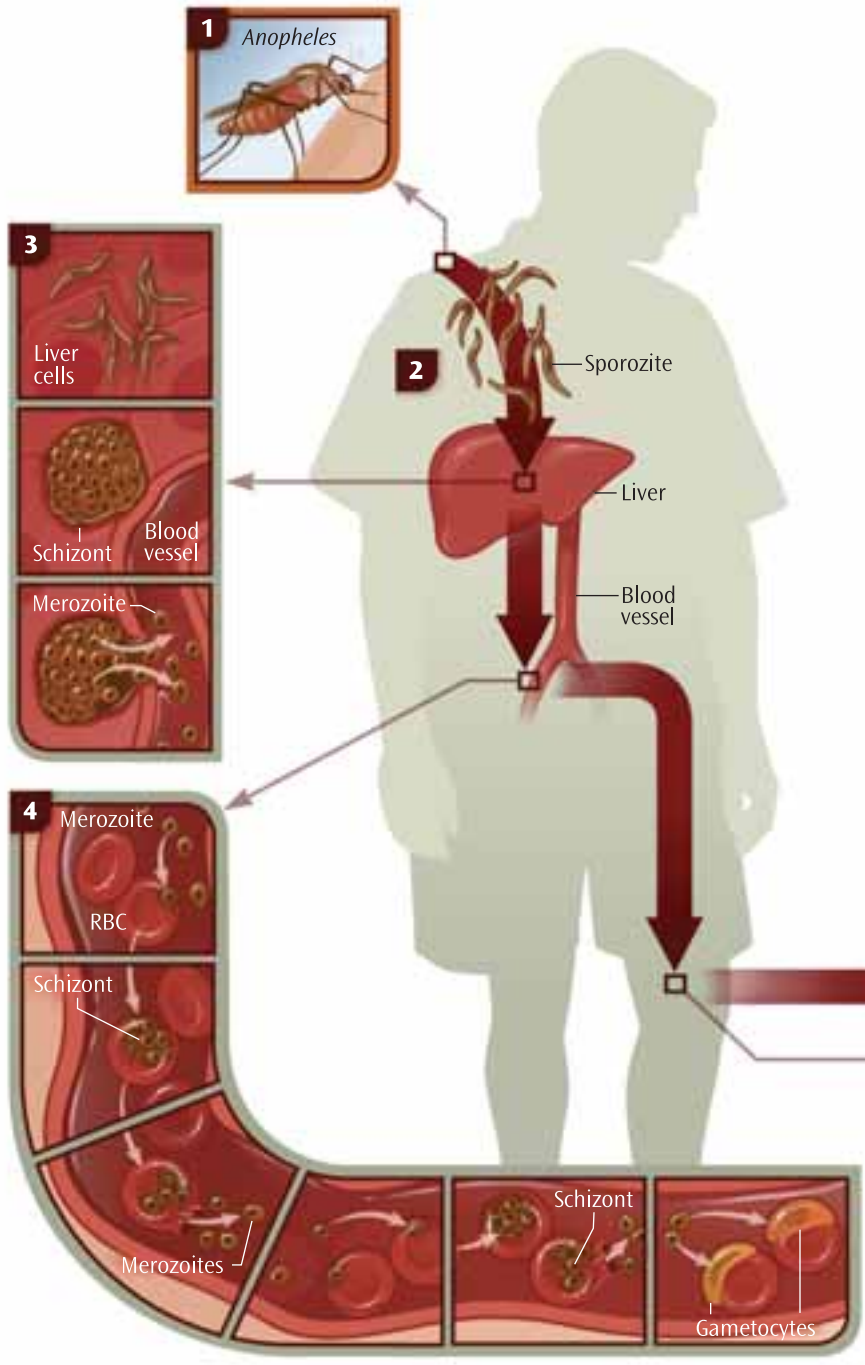


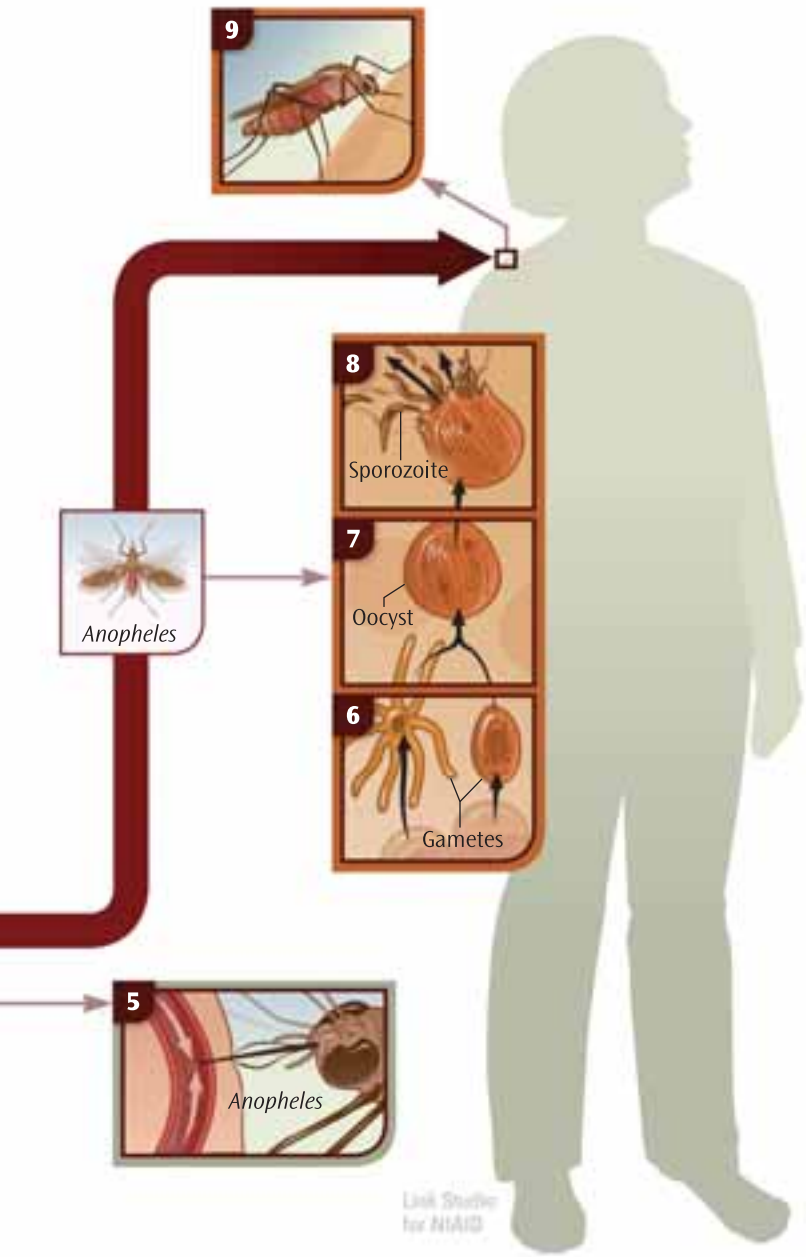
Merozoites released from the liver upon rupture of schizonts rapidly invade RBCs, where they grow by consuming **hemoglobin** [4]. Within the RBC, most merozoites go through another round of asexual reproduction, again forming schizonts filled with yet more merozoites. When the schizont matures, the cell ruptures and merozoites burst out. The newly released merozoites invade other RBCs, and the infection continues its cycle until it is brought under control, either by medicine or the body's **immune system** defenses.

The *Plasmodium* parasite completes its life cycle through the mosquito when some of the merozoites that penetrate RBCs do not develop asexually into schizonts, but instead change into male and female sexual forms known as **gametocytes** [4]. These circulate in the person's bloodstream, awaiting the arrival of a blood-seeking female *Anopheles* mosquito [5].

When a female mosquito bites an infected person, it sucks up gametocytes along with blood. Once in the mosquito's stomach, the gametocytes develop into sperm-like male **gametes** or large, egg-like female gametes [6]. Fertilization produces an **oozyst** filled with infectious sporozoites [7]. When the oocyst matures, it ruptures and the thread-like sporozoites migrate, by the thousands, to the mosquito's salivary (saliva-producing) glands [8]. The cycle starts over again when the mosquito bites its next victim [9].







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# Transmission of Malaria

The malaria parasite typically is transmitted to people by mosquitoes belonging to the genus *Anopheles*. In rare cases, a person may contract malaria through contaminated blood, or a fetus may become infected by its mother during pregnancy.

Because the malaria parasite is found in RBCs, malaria can also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood. Malaria also may be transmitted from a mother to her fetus before or during delivery (“congenital” malaria).



# Spread of Malaria

Many biological and environmental factors shape the character of malaria in a given location. Nearly all the people who live in endemic areas are exposed to infection repeatedly. Those who survive malaria in childhood gradually build up some **immunity**. They may carry the infection, serving as reservoirs for transmission by mosquitoes without developing severe disease. In other areas, where the infection rate is low, people do not develop immunity because they rarely are exposed to the disease. This makes them more susceptible to the ravages of an **epidemic**. An epidemic can occur when conditions, such as those discussed below, allow the mosquito population to increase suddenly.

## Effects of Climate

Climate affects both parasites and mosquitoes. Mosquitoes cannot survive in low humidity. Rainfall expands breeding grounds, and in many tropical areas, malaria cases increase during the rainy season. Mosquitoes must live long enough for the parasite to complete its development within them. Therefore, environmental factors that affect mosquito survival can influence malaria incidence.

*Plasmodium* parasites are affected by temperature—their development slows as the temperature drops. *P. vivax* stops developing altogether when the temperature falls below 60 degrees Fahrenheit. *P. falciparum* stops at somewhat higher temperatures. This effect explains why parasites can be found in temperate areas.





## Effect of Human Intervention

People have worked for centuries to control malaria and were successful in eradicating it from most of North America early in the 20th century. Certain human activities, however, have inadvertently worsened the spread of malaria.

City conditions, for example, can create new places for mosquito **larvae** to develop. Agricultural practices also can affect mosquito breeding areas. Although the draining and drying of swamps gets rid of larval breeding sites, water-filled irrigation ditches may give mosquitoes another area to breed. In addition, because farmers use the same pesticides on their crops as those used against malaria **vector** mosquitoes, the problem of insecticide-resistant mosquitoes is growing. Modern transportation also contributes to the spread of the disease, moving travelers and occasionally mosquitoes between malaria-endemic and non-endemic regions.



## Blood

Malaria is transmitted occasionally through transfusions of blood from infected individuals or sharing of needles to inject intravenous drugs, and can be transmitted from an infected pregnant woman to her unborn child. In the United States, however, transmission rarely occurs through blood transfusions, because blood donors are not allowed to donate for specified periods of time after traveling to or living in a malarious area.



## Symptoms of Malaria



Malaria typically produces a string of recurrent attacks, or **paroxysms**, each of which has three stages—chills, followed by fever, and then sweating. Along with chills, the person is likely to have headache, malaise, fatigue, and muscular pains, and occasionally nausea, vomiting, and diarrhea. Within an hour or two, the body temperature rises, and the skin feels hot and dry. Then, as the body temperature falls, a drenching sweat begins. The person, feeling tired and weak, is likely to fall asleep.

The symptoms first appear some 10 to 16 days after the infectious mosquito bite and coincide with the bursting of infected RBCs. When many RBCs are infected and break at the same time, malaria attacks can recur at regular time periods—every 2 days for *P. vivax* malaria and *P. ovale*, and every 3 days for *P. malariae*.



With *P. vivax* malaria, the person may feel fine between attacks. Even without treatment, the paroxysms subside in a few weeks. A person with *P. falciparum* malaria, however, is likely to feel miserable even between attacks and, without treatment, may die. One reason *P. falciparum* malaria is so **virulent** is that the parasite can infect RBCs in all stages of development, leading to very high parasite levels in the blood. In contrast, *P. vivax* parasites infect only young RBCs, which means the number of parasites in the blood does not reach the same high levels as seen in *P. falciparum* infection.



# Diagnosing Malaria



Health care providers should suspect malaria in anyone who has been in the tropics recently or received a blood transfusion, and who develops a fever and other signs that resemble the flu. They examine blood smears taken from a finger prick under a microscope to confirm the diagnosis. A “thick” smear makes it possible to examine a large amount of blood. Then, the species of parasite can be identified by looking at a corresponding “thin” smear. Because mixed infections are possible, these techniques are important for deciding the best treatment. For example, a person can be infected with *P. vivax* as well as the more dangerous *P. falciparum*. In the unusual event that parasites cannot be seen immediately in a blood smear, but the person’s condition and prior activities strongly suggest malaria, a health care provider may decide to start treatment before being sure the person has malaria.



# Treating and Preventing Malaria

In most cases, health care providers can successfully treat people with malaria. To decide which medicine to use, they should try to identify the species of parasite responsible and the geographical location where the person was infected. Up-to-date information on the geography of malaria is available from international travel clinics, CDC, and WHO, including

- Which species are present in which areas
- Whether chloroquine-resistant parasites are present
- Which seasons of the year carry the greatest risk

Before leaving home, anyone traveling to an area with malaria should consult a knowledgeable health care provider, an international travel clinic, a local health department, CDC, or WHO to obtain advice on what medicines to take before, during, and after the trip.

Health risks for malaria vary with the destination, conditions of travel, and types of activities the traveler will undertake. A traveler who spends even a single night in a malaria-endemic area risks getting infected.

CDC and WHO have information on how to limit contact with mosquitoes, as well as current guidelines on antimalarial drugs.



# Research on Malaria

As the lessons of the past decades have convincingly demonstrated, conquering malaria is difficult. No one anticipates a quick victory even if new malaria drugs hit the market, or a vaccine proves highly successful. Rather, researchers and health planners expect their best chances lie in a many-sided attack, drawing upon a variety of weapons suited to local environments. Skillfully combining several approaches, both old and new, may at last make it possible to outmaneuver these persistent and deadly parasites.

## Medicines

Medicines to treat malaria have been around for thousands of years. Perhaps the best known of the traditional remedies is **quinine**, which is derived from the bark of the cinchona tree. The Spanish learned about quinine from Peruvian Indians in the 1600s. Export of quinine to Europe, and later the United States, was a lucrative business until World War II cut off access to the world supply of cinchona bark. In the 1940s, an intensive research program to find alternatives to quinine gave rise to the manufacture of chloroquine and numerous other chemical compounds that became the forerunners of modern antimalarial drugs.

Chloroquine was the third most widely used drug in the world until the mid-1990s. It is cheap to manufacture, easy to give, and does not cause problems for most people. Unfortunately, chloroquine-resistant malaria parasites have developed and have spread to most



areas of the world. From the 1950s to the present, chloroquine resistance gradually spread to nearly all *P. falciparum* malaria-endemic regions.

In the 1960s, the U.S. Government, WHO, and other agencies launched a massive search for new antimalarial drugs. In addition, many doctors treating people in Asia are using yet another new family of drugs based on the parent drug artemisinin, an extract of the Chinese herbal remedy qinghaosu.

Unfortunately, malaria parasites in many geographic regions have become resistant to alternative drugs, many of which were discovered only in the last 30 years. Even quinine, the long-lived mainstay of malaria treatment, is losing its effectiveness in certain areas.

To address the problem of drug-resistant malaria, scientists are conducting research on the genetic mechanisms that enable *Plasmodium* parasites to avoid the toxic effects of malaria drugs. Understanding how those mechanisms work should enable scientists to develop new medicines or alter existing ones to make drug resistance more difficult. By knowing how the parasite survives and interacts with the human host during each distinct phase of its development, researchers also hope to develop drugs that attack the parasite at different stages.

For example, National Institute of Allergy and Infectious Diseases (NIAID) scientists are studying the **molecules** on host cells that malaria parasites use to attach to and enter the cells. Malaria parasites invade various tissues such as skin, blood, liver, gut, and salivary glands of human and mosquito hosts, which means the parasites





must be able to attach to a diverse array of molecules (called receptors) on the outside of host cells. By determining the three-dimensional structures of these receptors, scientists hope to determine exactly how the parasites target particular types of cells, which may reveal new targets for antimalarial drugs.

NIAID scientists are also working to understand how *P. falciparum* has adapted to survive and grow within RBCs. An important category of these adaptations involves the trafficking of nutrients across various membranes of the infected RBC. To this end, researchers have identified two nutrient channels unique to the infected cell and plan to study these further to identify their genetic bases and to develop detailed mechanistic models of nutrient transport. With these models, they may be able to design channel blockers that interfere with the parasite's ability to acquire needed nutrients. These blockers may prove to be novel and useful drugs for treating malaria.

Finally, NIAID scientists are unraveling the mechanisms of natural resistance to malaria infection, which is yielding valuable information for new antimalarial drug development. For example, in regions of West Africa, up to one-fourth of children carry hemoglobin C, a variant of hemoglobin that can reduce the risk of severe and fatal malaria by as much as 80 percent. The way hemoglobin C protects people, however, had been puzzling.

NIAID scientists and their team of international collaborators discovered that hemoglobin C protects against malaria by affecting a key parasite protein, called PfEMP 1, that malaria parasites normally place



on host RBCs in knoblike protrusions. The protruding proteins then make the infected RBCs stick to the lining of blood vessels in the brain and other critical tissues, which causes inflammation and circulatory obstruction. Hemoglobin C alters the membrane of RBCs so that the parasites cannot place PfEMP 1 normally at the cell surface. Thus, these RBCs are less able to adhere to vessel walls, which reduces disease severity. Other hemoglobin variants, such as the sickle-cell mutation, may protect against malaria by a similar mechanism. These findings suggest that interventions affecting the display of PfEMP 1 may reduce the impact of malaria.

## Mosquito Control

The appearance and spread of insecticide-resistant mosquitoes, as well as stricter environmental regulations, now limit the effectiveness and use of the insecticide DDT, the mainstay of 1950s and 1960s malaria eradication programs.

More recently, researchers have found that mosquito netting soaked with pyrethroid insecticides, which prevent mosquitoes from making contact with humans, significantly reduces malaria transmission. Therefore, as part of its Roll Back



Malaria program, WHO is promoting widespread use of insecticide-treated mosquito netting in malaria-endemic areas. Still, in some parts of Western Africa, mosquitoes have become resistant to pyrethroid insecticide used to treat the nets. Although scientists do not think this development is a serious limitation yet, it points out the need to continue research to identify new tools for mosquito control.

## Vaccines

Research studies conducted in the 1960s and 1970s showed that experimental vaccination of people with **attenuated** malaria parasites can effectively immunize



them against getting another malaria infection. Current methods to develop vaccines based on weakened or killed malaria parasites are technically difficult and do not readily lend themselves to being produced commercially. Therefore, much of the research on vaccines has focused

on identifying specific components or **antigens** of the malaria parasite that can stimulate protective immunity.



In 1997, NIAID launched a Plan for Research to Accelerate Development of Malaria Vaccines based on four cornerstones.

- Establishing a resource center to provide scientists worldwide with well-characterized reference and research reagents
- Increasing support for discovery of new vaccine candidates
- Increasing capacity to produce vaccine candidates at the quality and quantity that will be required for clinical trials
- Establishing research and training centers in endemic areas where potential vaccines may undergo clinical trials.

The NIAID Malaria Vaccine Development Branch (MVDB) is part of the institute's initiative to respond to the global need for malaria vaccines. MVDB has developed and produced several proteins on parasite antigens sequences to include in candidate malaria vaccines. This work involves collaborations with colleagues from other Federal agencies, the private sector, and academia in the United States and throughout the world, as well as assistance from a variety of partners, such as the U.S. Agency for International Development and the Malaria Vaccine Initiative.

Researchers are evaluating six potential vaccine antigens in human Phase I vaccine trials, either alone or in combinations, using three adjuvants, or vaccine boosters. The trials are under way both in the United States and in an endemic population in Mali in collaboration with the



University of Bamako, Mali. These vaccine trials form part of a clinical development plan working towards Phase II trials in an endemic area that will determine if these vaccines are able to make a substantial impact on parasite growth or transmission.

Under these and other programs, scientists are conducting research to understand the nature of protective immunity in humans and methods to induce protective immune responses with malaria antigens.

## Genome Sequencing

Genome sequencing, the process that allows scientists to determine an **organism's** genetic blueprint, is accelerating the discovery of new targets for drugs, vaccines, and diagnostic tests for malaria and other infectious diseases. By examining those blueprints, researchers can determine the genes that control a broad range of an organism's biological properties, such as feeding, reproducing, and adapting to its environment.

The complete genome sequences for the *Anopheles gambiae* mosquito and the *P. falciparum* parasite were published in 2002. Researchers are currently sequencing the genomes of other *Plasmodium* species. These advances mark a milestone in malaria research. Combined with the completed human genome sequence, scientists have the complete genetic blueprints for the malaria parasite and both of its hosts. Researchers are now using that information to learn more about how *Plasmodium* survives within people and mosquitoes, and to discover new ways to diagnose, prevent, and treat the disease.



## Other Research Efforts

As with other diseases of worldwide importance, a critical aspect of our future ability to control malaria will depend on the skills and expertise of scientists, health care providers, and public health specialists working in malaria-endemic regions. Therefore, strengthening the research capabilities of scientists in these areas is another major focus of these efforts.

Through its support of the Malaria Research and Reference Reagent Resource Center (MR4), NIAID provides well-characterized research materials to scientists in malaria-endemic areas. NIAID also works closely with national and international organizations involved in malaria research and control. In addition, NIAID was a founding member of the Multilateral Initiative on Malaria, which emphasizes strengthening research capacity in Africa.



# Glossary

**Anopheles**—the genus of mosquito that transmits malaria. This genus includes many species that are vectors for malaria transmission.

**antigen**—a molecule on a microbe that identifies it as foreign to the immune system and stimulates the immune system to attack it.

**attenuated**—treated in such a way as to decrease the ability of the parasite to cause infection or disease.

**chloroquine**—the primary drug used to treat malaria since 1945. It is no longer effective against a growing number of strains of *P. falciparum* malaria.

**endemic**—area where malaria is constantly present.

**epidemic**—a disease outbreak that affects many people in a region at the same time.

**gametes**—reproductive elements, male and female.

**gametocytes**—precursors of the sexual forms of the malaria parasite, which release either male or female gametes within the stomach of the mosquito.

**genus**—a category of organisms.

**hemoglobin**—the oxygen-carrying part of red blood cells.

**hypnozoite**—a form of the malaria parasite that remains inactive within the liver and can produce relapses of malaria.

**immune system**—a complex network of specialized cells, tissues, and organs that defends the body against attacks by disease-causing microbes.



**immunity**—the protection generated by the body’s immune system in response to invasion by “foreign” invaders, including bacteria, parasites, and viruses.

**larvae**—immature wingless forms of insects such as mosquitoes.

**merozoite**—the form of the malaria parasite that invades human red blood cells.

**molecules**—building blocks of a cell. Some examples are proteins, fats, and carbohydrates.

**oocyst**—a parasite stage within the mosquito, produced by the union of male and female gametes.

**organism**—an individual living thing.

**parasite**—plants or animals that live, grow, and feed on or within another living organism.

**paroxysm**—an attack of a disease that is likely to recur at periodic intervals.

***Plasmodium***—the genus of the parasite that causes malaria.

**quinine**—a drug, originally extracted from tree bark, which was the only available antimalarial treatment for nearly 300 years.

**relapses**—recurrences of a disease some time after it apparently has been controlled or cured.

**resistance**—the ability of an organism to develop strains that are impervious to specific threats to their existence.

**schizont**—a developmental form of the parasite that contains many merozoites.





**species**—organisms in the same genus that have similar characteristics.

**sporozoite**—the infectious form of the parasite, which is injected into people by a feeding mosquito.

**strain**—a genetic variant within a species.

**vector**—the organism, typically an insect, that transmits an infectious agent to its alternate host, typically a vertebrate. In human malaria, the vectors of the parasite are mosquitoes; the “carriers” or “hosts” are humans.

**virulent**—toxic, causing disease.



# More Information

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## **National Library of Medicine MedlinePlus**

8600 Rockville Pike

Bethesda, MD 20894

1-888-FIND-NLM (1-888-346-3656) or 301-594-5983

[www.medlineplus.gov](http://www.medlineplus.gov)

## **Centers for Disease Control and Prevention**

1600 Clifton Road

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