MALARIA

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

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QUICK FACTS

INCIDENCE:

Worldwide: Up to 2.7 million people die each year from malaria, most of them African children. Between 400 million and 900 million cases of acute malaria occur annually in African children alone.

United States: According to the U.S. Centers for Disease Control and Prevention, more than 1,000 new cases are reported annually in travelers returning from malaria-endemic areas.

CAUSE:

One-celled parasite, genus *Plasmodium*
Four species infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*

TRANSMISSION:

Most commonly, from an infected *Anopheles* mosquito bite.

SYMPTOMS:

Flu-like, including chills, fever, and sweating accompanied by headache, nausea, and vomiting; attacks can recur. Life-threatening illnesses, such as severe anemia or cerebral malaria, may occur in some infected individuals.

DIAGNOSIS:

Based on symptoms and travel history; confirmed by blood smears that identify the parasite.

TREATMENT:

Chloroquine, where parasite is not resistant to it; combination of antimalarial drugs where chloroquine is ineffective; treatment of symptoms as required.

PREVENTION:

Chloroquine or other antimalarial drugs taken before and during travel to a malarious area and continued for several weeks after returning; mosquito repellants and sleeping under bed nets; no approved vaccine is currently available.

CONTENTS

WHAT *is Malaria?*

Malaria is a disease caused by a **parasite*** that lives part of its life in humans and part in mosquitoes. It remains one of the major killers of humans worldwide, threatening the lives of more than one-third of the world's population. Malaria thrives in the tropical areas of Asia, Africa, and South and Central America, where it strikes millions of people. Sadly, as many as 2.7 million of its victims, mostly infants and 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. In 2000, health care workers reported 1,400 cases of malaria to the U.S. Centers for Disease Control and Prevention (CDC). Malaria in the United States is typically acquired during trips to malaria-endemic areas of the world and therefore is often called travelers' malaria.

During the past 10 years, CDC has documented local cases of malaria in states as varied as California, Florida, Texas, Michigan, New Jersey, and New York. In the summer of 1999, one highly publicized case occurred at a Boy Scout camp on Long Island, New York, where two boys were infected by mosquitoes.

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 the 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, or, as the Italians were to say, "mal aria" or bad air. In 1880, scientists discovered the real cause of malaria, the one-celled ***Plasmodium*** parasite, and 18 years later, they attributed the transmission of malaria to the ***Anopheles*** mosquito.

Historically, the United States is no stranger to the tragedy of malaria. The toll that this disease, commonly known as "fever and ague," took on early settlers is vividly depicted in the popular children's book "Little House on the Prairie" by Laura Ingalls Wilder. Historians believe that the incidence of malaria in this country peaked around 1875, but they estimate that by 1914 more than 600,000

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

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

The malaria parasite typically is transmitted to humans 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. The **larval** stage of the *Anopheles* mosquito thrives in still waters, such as swamps. The discovery by scientists that mosquitoes carried the disease unleashed a flurry of ambitious public health measures designed to stamp out malaria. These measures were targeted at both the larval 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 cases, malaria was conquered completely, benefiting more than 600 million people, and it was sharply curbed in the homelands of 300 million others.

Difficulties soon developed, however. Some stumbling blocks were administrative, others financial. Even worse, nature had begun to intervene. More and more **strains** of *Anopheles* mosquitoes were developing **resistance** to DDT and other insecticides. Meanwhile, the *Plasmodium* parasite was becoming 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, these include such standbys as draining swampy areas and filling them with dirt, and 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 its development and spread

MALARIA *Parasite*

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

Four species of *Plasmodium* 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 can infect a single individual 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 treatment, however, it is almost always curable.

Plasmodium vivax, the most geographically widespread of the species and the cause of most malaria cases diagnosed in the United States, 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 they 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*

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.

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

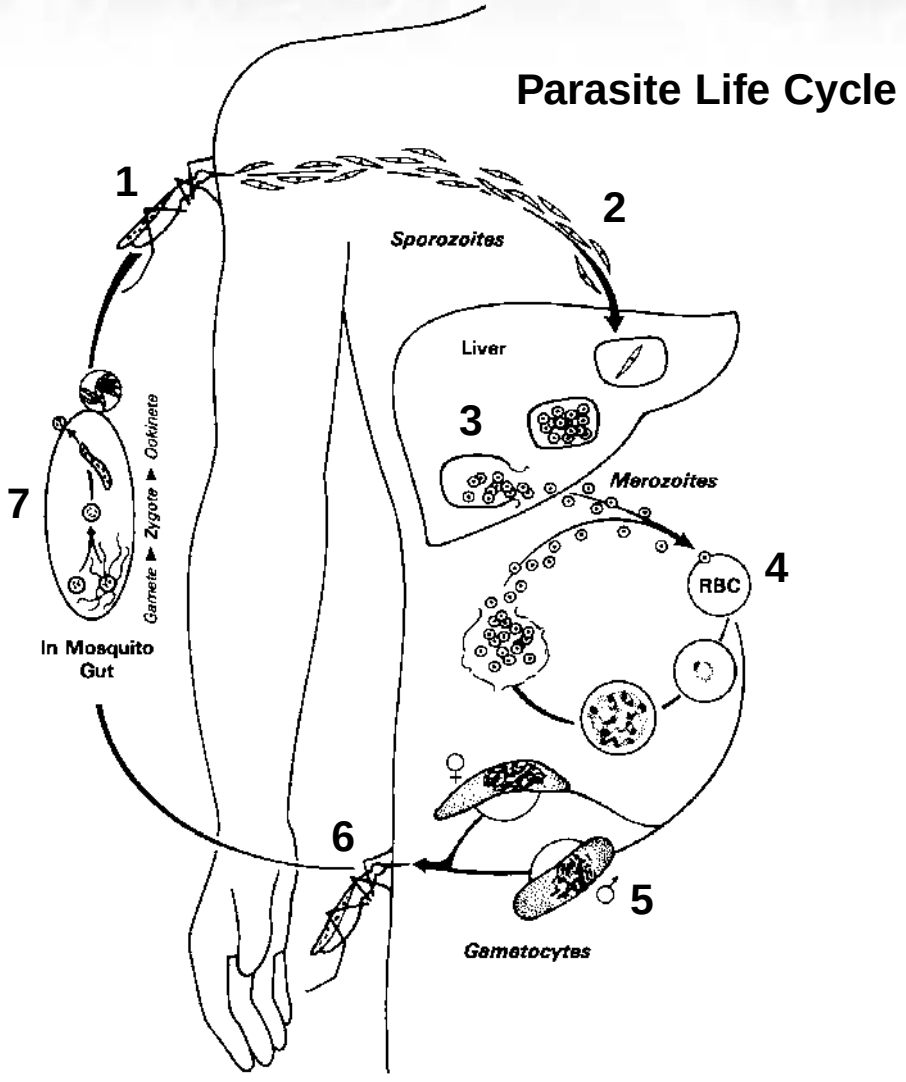
The thread-like sporozoite promptly invades a liver cell. There, during the next week or two (depending on the *Plasmodium* species), each sporozoite develops into a **schizont**, a structure that contains thousands of tiny rounded **merozoites** (another stage of the parasite). When the schizont matures,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

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 cause relapses in infected individuals.

Merozoites released from the liver rapidly invade red blood cells where they fuel their activities by consuming **hemoglobin**, the oxygen-carrying part of the blood. Within the red blood cell, 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 red blood cells, and the infection continues its cycle until it is brought under control, either by medicine or the body's immune defenses.

The *Plasmodium* parasite can complete its life cycle through the mosquito because some of the merozoites that penetrate red blood cells do not develop asexually into schizonts. Rather, they change into male and female sexual forms known as **gametocytes**. These circulate in the person's bloodstream, awaiting the arrival of a blood-seeking female *Anopheles*.



1. Female anopheline mosquito injects *Plasmodium* sporozoites into the bloodstream. 2. Sporozoites migrate to the liver and infect liver cells. 3. Sporozoites reproduce asexually to form thousands of merozoites, which ultimately rupture from the liver cells and re-enter the bloodstream. 4. Once in the bloodstream the merozoites invade red blood cells (RBCs). Parasites mature within those cells and are then released to infect even more RBCs. Disease and death in malaria is most commonly caused by this stage of infection. The common malaria drugs chloroquine and quinine also block the parasite's life cycle at this stage. 5. Some RBC parasites differentiate into male and female forms called gametocytes. 6. When a female mosquito feeds on an infected person, she ingests gametocytes from the blood. 7. Inside the mosquito midgut, the gametocytes differentiate into forms resembling sperm and eggs, allowing sexual reproduction to occur. The resulting parasites grow into sporozoites and migrate to the insect's salivary glands.

When she bites an infected person, the female mosquito 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. Fertilization produces an **oocyst** filled with infectious sporozoites. When the oocyst matures, it ruptures and the thread-like sporozoites migrate, by the thousands, to the mosquito's salivary (saliva-producing) glands. And the cycle starts over again when she bites her next victim.

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 suddenly increase.

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°F. *P. falciparum* stops at somewhat higher temperatures. This explains why parasites can be found in various parts of temperate areas.

Effect of Human Intervention

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

World Malaria Situation

Malaria is endemic to tropical and subtropical regions.

Malaria situation, 1999 (*source: WHO*)

Areas in which malaria has disappeared, been eradicated, or never existed

Areas with limited risk

Areas where malaria transmission occurs

City conditions can create new places for mosquito larvae to develop. Agricultural practices also can affect mosquito breeding areas. Although 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 between malaria-endemic and non-endemic regions.

Blood

Malaria is transmitted occasionally by transfusions of blood from infected individuals, sharing of needles to inject intravenous drugs, or 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, nausea, and vomiting. Within an hour or two, the person's 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 red blood cells. When many red blood cells 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 patient 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 red blood cells in all stages of development, leading to very high parasite levels in the blood. In contrast, *P. vivax* parasites infect only young

red blood cells, which means the number of parasites in the blood does not reach the same high levels as seen in *P. falciparum* infection.

DIAGNOSING *Malaria*

A doctor or other health care worker should suspect malaria whenever a person who has been in the tropics recently or received a blood transfusion develops a fever and other signs that resemble the flu. A doctor will examine blood smears, taken from a finger prick, under a microscope. If parasites are present, the diagnosis is confirmed. A "thick" smear makes it possible for the health care worker to examine a large amount of blood. Then, the species of parasite can be identified by looking at a corresponding "thin" smear. This is important for deciding on the best treatment.

Mixed infections are possible. 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 patient's condition and prior activities strongly suggest malaria, the doctor may decide to start treatment before being sure the patient has malaria.

TREATING *Malaria*

In most cases, malaria can be successfully treated, although the recuperating patient may find it takes several weeks to recover full strength. Before deciding on the best medicine to use, the doctor should try to identify the species of parasite responsible for the disease and where the patient got the infection. Up-to-date information on the geography of malaria, such as which species are present in which areas, whether chloroquine-resistant parasites are present, and which seasons of the year carry the greatest risk, is available at international travel clinics, CDC, and WHO.

In the United States, patients with *P. falciparum* malaria are usually hospitalized and treated as medical emergencies because their conditions may get worse quickly. Patients should talk with a doctor who specializes in infectious diseases and is knowledgeable about diagnosing and treating malaria and its complications.

Chloroquine, long considered the medicine of choice for treating malaria, is no longer considered the first-line antimalarial drug in many countries, and national malaria control programs are recommending alternatives. Because chloroquine-resistant parasites are becoming more widespread, doctors must carefully monitor patients who are treated with it.

If the number of parasites in the blood does not drop significantly during treatment, it may mean the parasites are resistant to the medicine. In addition, if a person develops any fever within a period of weeks to months after apparently successful treatment, the medicine may not have gotten rid of all the parasites. Additional treatment may then be required.

Health care workers should watch patients with *P. falciparum* malaria closely for potentially severe complications, including anemia, kidney failure, fluid imbalance, or respiratory distress. Brain damage can occur following cerebral malaria, which happens when large numbers of red blood cells containing parasites clog tiny blood vessels in the brain.

PREVENTING *Malaria*

Before leaving home, anyone traveling to a malarious area should consult CDC, WHO, a knowledgeable health care provider, an international travel clinic, or a local health department to get advice on what medicines to take before, during, and after the trip. Health risks for malaria vary with the destination and types of activities the traveler will undertake.

A traveler who spends even a single night in a malarious area risks getting infected. The first line of defense is to limit contact with mosquitoes by taking these measures.

- Use mosquito repellent
- Keep arms and legs covered
- Stay indoors beginning at dusk and throughout the night (when *Anopheles* mosquitoes like to feed)
- Sleep under mosquito netting

People traveling to malarious areas should also protect themselves by taking antimalarial medicines to prevent infection. CDC has current guidelines on antimalarial drugs.

Anyone who develops fever or other symptoms suggesting malaria, either while taking preventive medicines or after stopping them, should seek medical attention immediately.

MALARIA *and Pregnancy*

Malaria poses a serious threat to both the pregnant woman and her unborn child. Women who live in malarious areas are much more likely to develop acute *P. falciparum* malaria when they become pregnant. Infants born to mothers with malaria often will have low birth weights.

If possible, pregnant women from non-malarious areas should postpone travel to those regions until after their babies are born. Pregnant women who cannot postpone travel until after delivery should protect themselves from mosquito bites and take antimalarial medicines, if recommended by their doctors.

PROSPECTS *of Conquering Malaria*

Researchers in the fight against malaria have three major goals: new medicines, better methods of mosquito control, and a vaccine to prevent people from becoming infected.

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, and 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 are increasing in numbers. 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 devices that enable *Plasmodium* parasites to avoid the toxic effects of malaria drugs. Understanding how those devices work should enable scientists to develop new medicines or alter existing ones to make it more difficult for drug resistance to emerge. By knowing how the parasite survives and interacts with people during each distinct phase of its development, researchers also hope to develop drugs that attack the parasite at different stages.

Mosquito Control

The appearance and spread of insecticide-resistant mosquitoes, as well as stricter environmental regulations, now limit the effectiveness of the insecticide DDT, the mainstay of the 1950s and 1960s malaria eradication programs. More recently, researchers have found that mosquito netting soaked with other insecticides, which prevent mosquitoes from making contact with humans, significantly reduce malaria transmission. Therefore, as part of its Roll Back Malaria program, WHO is promoting widespread use of mosquito netting in endemic areas. Still, in some parts of Western Africa, mosquitoes have become resistant to the pyrethroid insecticide used to treat mosquito netting. Although scientists do not think this 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 commercialization. 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, the National Institute of Allergy and Infectious Diseases (NIAID) launched a 10-year Research Plan for Malaria Vaccine Development based on four cornerstones.

- Establishing a resource center to provide scientists worldwide with well-characterized 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

Under these and other programs, scientists are conducting research to understand the nature of protective immunity in humans and how 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* mosquito and the *P. falciparum* parasite were published in 2002. Researchers are sequencing other *Plasmodium* species. These advances mark a milestone in malaria research. Combined with the recently completed human genome sequence, scientists have the complete genetic blueprints for the malaria parasite and both of its animal 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.

M A L A R I A

The conquest of malaria is a top priority for many international and government organizations, philanthropic foundations, and research institutions. In 2001, the NIAID published the *Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. That plan highlighted the serious toll exacted by malaria and reinforced its position as one of the three biggest infectious global health problems. As the lessons of the past decades have so convincingly demonstrated, however, 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 the persistent and deadly parasites.

As with all 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 endemic regions. Therefore, strengthening the research capability of scientists in these areas is another major focus of these efforts. NIAID works closely with national and international organizations involved in malaria research and control. The Institute was also 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.

Antibody—Protein molecules that are produced and secreted by certain types of immune system cells in response to stimulation by an antigen.

Antigen—Any substance that provides an immune response when it is introduced into the body.

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, however, no longer effective against a growing number of strains of *P. falciparum* malaria.

Endemic—Malaria is constantly present.

Epidemic—A disease 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 the red blood cell.

Hypnozoite—A form of the parasite that remains inactive within the liver and can produce relapses.

Immunity—The protection generated by the body's immune system in response to invasion by "foreign" invaders, including bacteria and viruses as well as parasites.

Larvae—Immature wingless forms of insects such as mosquitoes.

Merozoite—The form of the malaria parasite that invades human red blood cells.

Oocyst—A parasite stage within the mosquito, produced by the union of male and female gametes.

Parasite—An animal (or plant) that must live on or in an organism of another species, from which it draws its nourishment.

GLOSSARY

Paroxysm—An attack of a disease that is likely to recur at periodic intervals.

Plasmodium—The genus of the parasite that causes malaria. The genus includes four species that infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale*.

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

Relapse—The recurrence of disease some time after it has been apparently cured.

Resistance—The ability of an organism to develop strains that are impervious to specific threats to their existence. The malaria parasite has developed strains that are resistant to drugs such as chloroquine. The *Anopheles* mosquito has developed strains that are resistant to DDT and other insecticides.

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 vector of the parasite are mosquitoes; the "carriers" or "hosts" are humans.

Virulent—Characterized by rapid, severe, and malignant course.

MORE INFORMATION

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NOTES

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RESEARCH

Selected Highlights of NIAID-Supported Malaria Research

Basic Research

Basic research is the key to developing new ways to prevent and treat malaria. By researching the underlying biology of malaria parasites and how they interact with people and mosquitoes, scientists can identify new molecular targets for malaria drugs and vaccines. Researchers are also conducting studies on the specific human, mosquito and parasite factors that contribute to malaria, including serious complications such as cerebral malaria and anemia. Additional basic research is ongoing to learn how a person's immune system responds to malaria infection and fights off the disease.

In October 2002, researchers reported a major advancement in all areas of basic malaria research when they announced the complete genetic blueprints of the major malaria vector, the *Anopheles* mosquito, and of *Plasmodium falciparum*, the deadliest malaria parasite. Combined with the recently completed human genome sequence, scientists now have the complete set of human, parasite, and mosquito genes involved in malaria transmission. These accomplishments provide an unprecedented look at the underlying genetics of malaria and will enable scientists to use that information to develop new ways to treat and prevent the disease.

By mining the genome information for *P. falciparum* alone, NIAID scientists recently showed the parasite to be more genetically diverse and much older—at least 100,000 years old—than previously thought. Their research also showed that resistance to the malaria drug chloroquine arose independently on multiple continents and spread across the globe from at least four points of origin.

In 1998, NIAID funded and formed the Malaria Research and Reference Reagent Resource Center (MR4), which is managed by the Centers for Disease Control and Prevention and the American Type Culture Collection. The MR4, founded in response to the needs of researchers, provides reagents, materials, and protocols necessary for malaria research. All resources are provided free-of-charge, and more than 270 researchers have received assistance from MR4 to date. In collaboration with the World Health Organization and other agencies, MR4 also organizes workshops and training programs to help move potential products from the laboratory into clinical trials. Recently, MR4 has provided key reagents for a study of antimalarial drug resistance in Uganda, sponsored a drug-resistance workshop in Benin, and provided malaria research training in India and Cameroon.

Collaborating with the World to Combat Malaria

Malaria is a global health problem and therefore requires a global research approach. NIAID participates in many collaborative projects with other U.S. agencies, international organizations and foreign governments. Within the United States, NIAID participates in the Federal Malaria Vaccine Coordinating committee, an interagency working group that provides for timely exchange of information and collaborative efforts to accelerate malaria vaccine research and development. The Institute also works with the U.S. Agency for International Development to support collaborative vaccine development research. NIAID also has joined with the Malaria Vaccine Initiative, administered by the Program for Appropriate Technology in Health (PATH), to support a promising vaccine candidate and to develop additional candidates for future testing. Within the National Institutes of Health (NIH), NIAID recently teamed with the National Institute of Child Health and Human Development and the Fogarty International Center (FIC) to fund research targeted at understanding malaria-associated anemia.

In 1997, NIAID joined with FIC, the World Health Organization, and other institutions to form the Multilateral Initiative on Malaria (MIM). MIM's mission is to increase and enhance worldwide research on malaria by facilitating

multinational research cooperation. The Institute also has established malaria research facilities in Mali and Ghana and has trained local scientists and physicians to conduct malaria research from within endemic countries. In addition to studies conducted by the Mali and Ghana laboratories, NIAID supports research on multiple aspects of malaria infection in Kenya, Cameroon, Indonesia, Malawi, The Gambia and Gabon.

Vaccine Research

An effective vaccine that will prevent malaria is a major goal of NIAID. In 2001, the Institute opened its Malaria Vaccine Development Unit (MVDU) at its Rockville, Maryland, research facility. The MVDU is an 8,000-square-foot, state-of-the-art biotechnology laboratory designed to develop and produce promising malaria vaccine candidate antigens. The facility is part of a joint effort by NIAID researchers and the Institute's administrative scientists who oversee NIAID-funded malaria research conducted at universities, private industries, and international research sites. The MVDU serves a vital function by moving potential vaccines through the pipeline for testing in people. The unit assists with production, scale-up, clinical-grade manufacturing, and clinical trials in the United States and malaria-endemic countries.

Scientists from the Institute's Laboratory of Parasitic Diseases are conducting exciting studies on malaria vaccines. Through the NIAID-sponsored Malaria Research and Training Center in Bamako, Mali, researchers are accelerating preparations and training for testing several vaccine candidates. Phase I clinical trials are expected to begin in early 2003. NIAID scientists also recently reported they could genetically modify mice to produce promising vaccine antigens in their milk. Once extracted from the milk, the experimental vaccine protected four out of five monkeys from an otherwise lethal dose of the malaria parasite. That research suggests that milk-giving animals such as goats may serve as inexpensive vaccine-manufacturing units.

NIAID also supports extensive research on malaria vaccines conducted by researchers from academia and industry. The Institute currently funds multiple studies aimed at developing vaccines against different stages of the malaria parasite and has conducted Phase I and Phase II clinical trials of several of the most promising candidates. Vaccines under study include those directed against the parasite both before and after it moves into red blood cells. Another promising approach under investigation is transmission-blocking vaccines. Those vaccines do not prevent a person from contracting malaria, but they prevent the malaria parasite from developing inside a mosquito that has bitten a vaccinated person. NIAID researchers and grantees from U.S. universities are working to develop such vaccines, which could reduce symptoms in infected people and slow the spread of malaria by breaking the cycle of mosquito transmission.

Research is also underway on combination vaccines derived from multiple parasite life stages, and early candidates are being prepared for use in Phase I human safety trials. DNA vaccines, one of the newest vaccine technologies, are an additional area under investigation by NIAID grantees, and several examples have been tested in animal models of malaria.

NIAID employs a number of mechanisms to generate corporate interest in malaria vaccines. Using grants, contracts, and other cooperative funding agreements, the Institute has enlisted the support of several pharmaceutical and biotechnology companies in producing an effective vaccine. Following the NIH lead, the European Union recently launched a small European Malaria Vaccine Initiative to try to develop links with industry and accelerate the movement of vaccine candidates through the development pipeline and into clinical trials.

Drug Research

New drugs to treat malaria, particularly those infections caused by forms of *Plasmodium* that are resistant to current medications, are greatly needed. Because the parasite has a complex life cycle, researchers are seeking to understand the molecular biology of the parasite and how it interacts with its human host at each stage in that cycle. Using that information, scientists hope to develop new drugs that block different molecular processes required for parasite survival.

NIAID researchers have made tremendous strides in elucidating *Plasmodium* biology, and they hope to use that information for developing new drugs. Scientists have identified key temperature-regulated genetic elements that switch on and off different phases of the parasite's life cycle. Other scientists have discovered additional genes or their regulatory elements that control the ability of the parasite to change its appearance and avoid immune detection, resist the effects of the malaria drug chloroquine, invade red blood cells via multiple ports of entry, bind to the human placenta, and invade the mosquito digestive tract. Scientists have also used studies of the three-dimensional structure and physical properties of human and mosquito cell membranes to learn more about how the parasites infect and grow inside red blood cells and the mosquito midgut. NIAID researchers have made seminal discoveries about how *Plasmodium* inserts a key channel in red blood cell membranes that enables the parasite to acquire nutrients and grow.

NIAID grantees are also hard at work identifying promising targets and compounds for new malaria drugs. Researchers have developed compounds that destroy a key reproductive stage of *Plasmodium* and others that appear to block the parasite's development within red blood cells. Other investigators are scanning the genes revealed by the *P. falciparum* genome project to identify new targets that exist in the malaria parasite but not in people. New drugs designed to attack those targets would therefore damage the parasite but not its human host.

Mosquito Research

Research on mosquito genetics, physiology, and ecology may lead to new ways to treat, prevent, or control malaria. NIAID funds many research projects at institutions in the United States and abroad aimed at developing a comprehensive understanding of the insect's biology.

One cutting-edge area of mosquito research is the development of genetically modified insects that are incapable of harboring and transmitting the malaria parasite. Researchers have identified small proteins that interfere with *Plasmodium* development within the mosquito; other scientists have shown that genes can be successfully introduced into the insects and maintained in future generations.

Because some mosquitoes support malaria parasites while others do not, researchers are attempting to understand the biological basis of that difference. Towards that end, some scientists are studying the fates of *Plasmodium* sexual stages in mosquitoes and the process by which the parasites may be encapsulated within the mosquito gut. Other grantees are studying the genetic basis behind an insect's susceptibility or refractoriness to *Plasmodium* infection.

One NIAID scientist also has developed a new tool for studying how mosquitoes and parasites interact with one another. He recently developed a model of *Plasmodium* infection in fruit flies, which are well-studied laboratory animals whose genetic blueprints are known. Although those insects are not natural hosts of the malaria parasite, the new laboratory model allows scientists to study how insect physiology can affect the survivability of *Plasmodium*.

Investigators also are looking at the ecology of mosquitoes to determine the distribution of different species, their preferred ecological niches, the factors that affect where individual species and subspecies live, and how the partitioning of those species affects malaria transmission. Specifically, NIAID grantees are studying the relationship between vegetation and mosquito abundance in Belize and mosquito behavior and larval ecology in Kenya; the effect of rice irrigation on malaria prevalence in Mali; and how mining and deforestation are leading to the emergence of important new malaria vectors in Brazil.

For more information on NIAID malaria research activities, please log on to our Web site at www.niaid.nih.gov.

M A L A R I A

NIAID is a component of the National Institutes of Health (NIH). NIAID supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma and allergies.

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