MALARIA

VBC TROPICAL DISEASE PAPER NO. 1
MALARIA

by

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Life cycle illustrations: Taina Litwak
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The blue square shows an Anopheles mosquito, which transmits malaria. The other symbols depict essential components of vector-borne disease control: the environment, communities and research.
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Executive Summary

Malaria affects an estimated 270 million people and causes one to two million deaths every year, primarily among children and pregnant women. It is one of the leading causes of death, disability and illness in the world.

The disease is caused by infection with protozoan parasites of the genus *Plasmodium* and transmitted by the bite of a female *Anopheles* mosquito. Malaria is actually a group of four related diseases caused by infection with one of the four malaria parasites of man: *P. falciparum*, the most virulent form, *P. vivax*, *P. malariae* or *P. ovale*.

Intermittent high fevers, shivering chills, body pains, headaches, fatigue, nausea and vomiting, diarrhea and anemia are common malarial symptoms. More serious outcomes include spleen enlargement, liver and kidney failure, brain damage and death. The severity of these symptoms depends upon the parasite species as well as the age, previous health status and immunity of the infected person.

It is estimated that there are at least 15 unreported cases of malaria for every case reported in sub-Saharan Africa (Clyde 1987). In the Americas, the ratio of reported cases to infected persons is about 1:2.3 and in eastern Asia, it is about 1:6.2.

Approximately 110 million clinical cases occur every year and more than two billion people are at risk. About 474 million people live in areas where no specific malaria control measures are attempted and prevalence has not changed in recent years (WHO 1990).

In many areas of the developing world, intense economic development activities, driven by rapid population growth, have dramatically changed the incidence patterns of malaria. Deforestation, land exploitation, dam-building and irrigation have increased opportunities for transmission by creating vector habitats and bringing nonimmune people into malarious areas. This "man-made malaria" has contributed to a resurgence of the disease in many parts of the world.

South of the Sahara, an estimated 250 million people are chronically infected and approximately 90 million of them suffer acute manifestations of the disease during the year. The number of malaria cases reported in the LAC region rose from about 399,000 in 1977 to 1.1 million in 1988. In South and Southeast Asia, a resurgence of malaria that began during the 1970s continues today.

The World Health Organization (WHO) estimates that malaria is responsible for the deaths of one million African infants and young
children each year. The disease is the leading cause of mortality among children younger than five in several African countries. It also reduces children's resistance to other life-threatening infections.

Maternal malaria infections also are a serious threat to child survival. Malaria during pregnancy often causes premature births, stillbirths, spontaneous abortions or low birth weights.

Malaria is undoubtedly a serious impediment to development in highly endemic areas, but few studies have measured its full economic impact. A recent VBC study on the economic impact of the disease in sub-Saharan Africa estimates that the average direct cost of a case of malaria is $3.40, which is equal to the per capita health budget of many African countries. In other words, treatment of one case of malaria exhausts a person's entire share of his or her government's health resources.

A worldwide effort to eradicate malaria through insecticide spraying and chemotherapy made some progress in industrialized countries, but proved unsustainable in the developing world. In 1969, WHO adopted the more realistic goal of malaria control. Ten years later, four tactical variants, or control options, were designed to place control in the context of primary health care.

Indoor house spraying, chemotherapy and chemoprophylaxis are still the primary methods of malaria control, but the spread of drug and insecticide resistance has seriously hampered antimalarial efforts. Other constraints to successful control include a severe lack of trained manpower, rising costs, reduced support and the difficulties of integrating vertical malaria programs into national health services.

One of the most important lessons learned from past eradication and control efforts is that no single intervention can provide sustainable malaria control. Integrated control uses a combination of complementary interventions, including treatment with antimalarial drugs, environmental management, biological control and insecticide spraying targeted at high-risk areas.

Progress has been made in vaccine development, but an effective vaccine for use in the field is still years away. Other important areas of current research are the development of fast, accurate diagnostic technologies, research on new drugs and the use of drug combinations to counteract resistance, epidemiologic studies, and research on vector behavior. The effectiveness and acceptability of using insecticide-impregnated bed nets to control malaria in communities are being tested in several field trials.
1. Introduction

Malaria is one of the leading causes of illness, disability and death in the developing world. The disease is caused by infection with protozoan parasites of the genus *Plasmodium*, which are transmitted by *Anopheles* mosquitoes.

Although malaria is often considered a single disease, it is actually a group of four related diseases characterized by a wide variety of symptoms. Intermittent high fevers, shivering chills, general body pains, headaches, fatigue, nausea and vomiting, diarrhea and anemia are common malarial symptoms. More serious outcomes include spleen enlargement, liver and kidney failure, brain damage and death. The severity of these symptoms depends upon the parasite species as well as the age, previous health status, and immunity of the infected person.

In infants, young children, pregnant mothers and others with little or no immunity, malaria may be fatal. Every year, malaria results in between one and two million deaths. Most adults living in malarious areas have partial immunity and are at risk of chronic or repeated infections. Many are asymptomatic carriers of the disease.

a. Biogeography

Malaria probably originated in Africa and spread, following human migrations, to the Mediterranean, Mesopotamia, the Indian subcontinent and Southeast Asia. Indigenous malaria has been recorded from Archangel in the USSR (64°N latitude) to Cordoba, Argentina (32°S latitude), and from the Dead Sea (400 meters below sea level) to Cochabamba, Bolivia (2,800 meters above sea level). Transmission depends upon a number of factors related to the parasite, the human host, the vector's ecology and the social environment. As a result, malaria is a focal disease that can devastate some areas and leave others relatively untouched (Map 1).

Because environmental factors play such an important role in sustaining malaria transmission, the disease can be introduced or reintroduced into an area as a result of significant changes in the environment. Irrigation, road building, mining, forestry and other economic development activities increase opportunities for transmission by creating new vector habitats and bringing immunologically naive people into malarious areas. This "man-
Map 1. Global Distribution of Malaria, 1988

Prepared by the Vector Biology and Control Project
Source map: World Health Organization, 1990
made malaria," along with insecticide and drug resistance and the deterioration of malaria control efforts, has contributed to a resurgence of the disease in many parts of the world. Epidemics or unusual increases in malaria incidence have been reported from the Amazon region of South America, Ethiopia, Madagascar, Sri Lanka, the Solomon Islands and other areas. Once a primarily rural disease, malaria is a growing problem in cities and peri-urban areas as a result of the trend toward urbanization in the developing world.

b. Parasitic agent

The microorganisms that cause malaria are sporozoan parasites. There are four species of malaria parasites of man: P. malariae, P. vivax, P. falciparum and P. ovale. Many other genera and species of related sporozoan parasites infect mammals, birds and reptiles.

It is not always possible to differentiate clinically between the Plasmodia infections of man without a laboratory diagnosis. Epidemic conditions, acquired tolerance, additional infections with the same or other Plasmodium, previous treatment, and the strain of the parasite species may modify periodicity and host reaction.

Life cycle

The life cycle of Plasmodium is complex (p. 7), with asexual reproduction in human hosts and sexual reproduction in mosquito vectors.

The cycle begins when an infective female Anopheles mosquito bites a person, inoculating sporozoites into the blood stream. Within minutes, these sporozoites enter liver tissue. There they become spherical schizonts, which divide, enlarge, and form large numbers of merozoites, completely filling the interior of the enlarged liver cells. When the infected liver cells rupture, the merozoites enter the blood stream to invade red blood cells. Usually only one or two merozoites invade a single blood cell.

In the cycles of P. vivax and P. ovale, latent liver stages can begin development long after blood stages have disappeared. As a result, the disease may reoccur up to five years later even
though the host has not been bitten again by an infective mosquito. Such a case is called a relapse. In *P. falciparum*, many merozoites emerge from the liver simultaneously, causing an overwhelming and often fatal blood infection. *P. falciparum* does not relapse because no schizonts are retained in the liver.

Asexual parasites resemble signet rings at the earliest stage. In one or two days, each of these ring forms develops into a schizont, which forms six to 24 merozoites, depending on the species.

Fever symptoms appear when a large number of red blood cells rupture simultaneously and mature merozoites are released to invade other red blood cells. The periodicity of fever symptoms depends upon the length of the cycle within the red blood cells, which varies with each *Plasmodium* species. This erythrocytic cycle may be repeated many times in chronic infections. Reappearance of parasites from the red cell stage shortly after an apparent cure is called recrudescence.

A few days after symptoms first appear, some merozoites develop into gametocytes, which may be ingested by an *Anopheles* mosquito. The life cycle will be completed in a female mosquito, whose eggs need blood to mature.

Once they reach the gut of the mosquito, gametocytes mature into male and female gametes, which fuse to form zygotes. Zygotes penetrate the mosquito’s gut wall and form oocysts, which enlarge and mature, eventually containing thousands of sporozoites. After 10 to 14 days, depending upon the species and ambient temperature, these oocysts rupture, releasing sporozoites into the body cavity. The sporozoites move to the salivary glands, where they remain until the mosquito’s next feeding.

*Plasmodium falciparum*

*Plasmodium falciparum* is the most virulent species of human malaria and causes most malaria deaths. It is largely confined to tropical and subtropical regions because its development in the mosquito is greatly retarded when the mean temperature is lower than 20°C (68°F). Since it takes about three weeks for the sporozoites to develop in the mosquito at that temperature, the disease can maintain itself only in areas where the mean temperature is at least 20°C for long periods of time.
Life Cycle of Plasmodium

Anopheles mosquito ingests Plasmodium gametocytes in blood.

Gametocytes mature and reproduce, forming zygotes. After 10-14 days sporozoites are released.

Sporozoites are injected into human host with mosquito's saliva.

Sporozoites migrate to liver.

Invade liver cells.

Form merozoites.

Cells rupture, release merozoites into bloodstream.

Some merozoites develop into gametocytes in red blood cells.

Merozoites invade millions of red blood cells.

Blood cells rupture, causing fever and chills.

Merozoites multiply asexually.
The fever and chills, or paroxysms, associated with *P. falciparum* infections are likely to be more exhausting than those of either *P. vivax* or *P. malariae*. Paroxysms are irregular and may last 20 to 36 hours. Prostration and headache are more severe, vomiting more frequent, and mental confusion and physical incapacitation more common. Lower back pain and muscle aches often occur in people who are chronically infected.

*P. falciparum* is the most dangerous form of malaria because of its simultaneous production of large numbers of parasites and its effect on blood vessels. Infected red cells clump together, stick to white cells and cling to the walls of blood vessels, blocking and slowing the movement of blood. As a parasite continues to divide and invade other red blood cells, the infected cells clog the capillaries, depriving parts of the body of oxygen. When this happens in the brain, patients may go into a coma and frequently die. Most malaria deaths in the Allied armed forces during the Second World War resulted from such cerebral malaria attacks.

Severe forms of malaria under endemic conditions are almost always due to *P. falciparum*. In infants, children, expatriates and others who are immunologically naive, *P. falciparum* infection can cause death within 18 hours after the first symptoms appear if effective treatment is not initiated.

*Plasmodium vivax*

*Plasmodium vivax* is the most common form of malaria and has the widest distribution throughout most of the temperate zones and the tropics. It causes the so-called benign tertian malaria, with paroxysms occurring every third day.

Although fevers peaks every 48 hours in vivax infections, daily increases in temperature are common during first attacks. Cerebral symptoms are rare. Certain strains appear to induce relapses every six to eight months if left untreated. *P. vivax* is seldom fatal except during epidemics. Progressive anemia and marked enlargement of the spleen are common in untreated cases.

*Plasmodium malariae*

*Plasmodium malariae* is rare in most malarious regions. One reason for its relative rarity may be that *P. malariae*’s develop-
ment in the mosquito is usually slow. At 20°C, sporozoites are produced after four or five weeks.

A *P. malariae* infection is generally no more severe than a vivax infection. The paroxysms are more regularly spaced (72-hour cycle), but do not last as long as those of any other form of malaria.

This quartan malaria has a marked tendency to relapse. Clinical episodes may reoccur three, four or more years after the initial infection.

*Plasmodium ovale*

*Plasmodium ovale* is the least common of the human plasmodia. It causes a mild, tertian (48-hour cycle) malaria with a low frequency of relapse. It is found in tropical Africa on the Atlantic Coast and in Eastern Africa, the Philippines, New Guinea, and possibly in Asia.

c. Vectors

There are approximately 400 species of *Anopheles* throughout the world. Sixty of these species are vectors of malaria, but only about 30 of them are considered of major importance.

There is a broad range of vector efficiency between the species. This may be associated with their propensity to feed on man (anthropophily) or animals (zoophily), their breeding patterns, mean longevity, genetic factors and population densities.
2. Distribution and Severity

The World Health Organization (WHO) receives epidemiological reports from about half of the 100 countries where malaria is indigenous. Only five of these countries are in tropical Africa, where malaria is most prevalent. In 1988, five million cases were reported to the WHO (Table 1). Estimates of unreported cases range as high as 90 million.

Epidemiological reports to WHO are based on microscopically confirmed cases. Even in countries with good health infrastructures and well-established malaria control programs, limited detection and underreporting are the rule rather than the exception. Surveillance and treatment services often do not cover the entire population at risk.

According to Clyde (1987), there are at least 15 cases of malaria for every one that is reported in sub-Saharan Africa. In the Americas, the ratio of reported cases to infected persons is about 1:2.3 and in Eastern Asia, it is about 1:6.2.

WHO estimates that there are 270 million people infected with malaria parasites and 110 million clinical cases occur every year. More than two billion people are at risk. About 474 million people live in areas where no specific measures are undertaken to control malaria transmission and prevalence has remained unchanged in recent years. Another 1.6 million live in places where endemic malaria had been considerably reduced or eliminated, but transmission has been reinstated (WHO 1990).

a. Latin America and the Caribbean (LAC)

Since 1977, the number of malaria cases reported in the LAC region has risen from 399,000 to 1.1 million. It is estimated that about 40 percent of the region's inhabitants live in malarious zones.

Half of all malaria in the Americas occurs in Brazil, primarily in the Amazonian region. The disease is also a serious public health problem in the Dominican Republic, Haiti, Honduras, Nicaragua, El Salvador and the Andean countries.

In Haiti and the Dominican Republic, 99 percent of malaria cases are due to *P. falciparum*. Falciparum malaria rates, defined
as the percentage of malaria cases caused by *P. falciparum*, are very high in Brazil (51 percent), French Guyana (72 percent), Guyana (56 percent) and Surinam (85 percent). High falciparum rates also are reported in Colombia (33 percent), Venezuela (31 percent) and Ecuador (28 percent).

**b. Africa (AFR)**

Malaria is considered the most important parasitic disease in sub-Saharan Africa, with an estimated annual incidence of 90 million new cases. About 250 million people are chronically infected. WHO estimates that at least 80 percent of all malaria infections occur in Africans. Recent increases in the transmission of malaria in urban and peri-urban areas have exacerbated the problem.

Malaria is one of the five most important causes of mortality and morbidity in sub-Saharan Africa, particularly among infants, young children and pregnant women. Up to 50 percent of all cases are in infants and children younger than five and it is estimated that five percent of children die from the direct or indirect effects of malaria before reaching the age of five. The disease accounts for 15 to 20 percent of clinic attendances in the AFR region.

**c. Asia and the Near East (ANE)**

After almost 40 years of A.I.D. involvement, malaria continues to be the most important infectious disease in South and Southeast Asia. Significant gains were achieved during the eradication era; however, due to various economic, administrative and technical problems, a resurgence of malaria began during the seventies and continues today.

For example, in Sri Lanka, where the number of reported cases had been reduced to 17 in 1963, a severe outbreak began in 1982. By 1987, the annual number of cases had risen to 606,000. In Nepal, malaria incidence increased by 33 percent from 1980 to 1985. During the past decade, malaria incidence also began to increase in Pakistan, where the percentage of falciparum cases rose from 37 percent of all cases in 1988 to 53 percent in 1989.

Recent increases in malaria have been reported from Indonesia, Thailand and the Philippines. After rising by nearly 50
percent between 1986 and 1987, malaria incidence seems to have stabilized at about 155,000 cases a year in the Philippines.

In the Near East region, malaria transmission is limited and focal, placing approximately 175 million people at risk. According to the most recent available compiled data from WHO, there was no indigenous malaria in Bahrain, Cyprus, Israel, Jordan, Kuwait, Lebanon, Qatar and Tunisia in 1989. Malaria transmission has increased in Afghanistan and Iran, but has been greatly reduced in Iraq, Syria, Yemen and the United Arab Emirates.

**d. Child survival**

Malaria is most prevalent and severe among those who have acquired little or no immunity. These include infants and children who have lost the protection from maternal immunity and have not yet reached immunologic maturity, and pregnant women, who are in a mild immuno-suppressed state because of pregnancy.

WHO estimates that malaria is responsible for the deaths of one million African infants and young children each year. The disease is the leading cause of mortality among children younger than five in several African countries, including Ghana, Malawi and the Gambia. Various studies have found that malaria may account for 25 percent to 70 percent of child mortality rates in some areas.

The proportion of fever cases attributable to malaria in children is difficult to assess because its symptoms are similar to those of other diseases and because of the variety of fevers and the possibility of asymptomatic parasitemias. In some regions, nearly half of all fever cases can be attributed to malaria. A very high proportion of infants will develop the disease.

Anemia is one of the most important consequences of malaria in children because its long-term effects include stunting of growth, general debilitation and higher susceptibility to other diseases. Malaria contributes significantly to the number of anemia cases in the developing world.

Another important effect of malarial infection in children is reduced response to meningitis, typhoid and tetanus vaccines, which may increase a child's risk of contracting infectious diseases even in the presence of efficient immunization programs.
Maternal malaria infections also affect children's health. Higher rates of abortion, fetal death and premature delivery are observed during epidemics and in areas of unstable transmission. Cases of congenital malaria may also be seen. Congenital malaria is rare in areas of more stable transmission, but premature births, stillbirths, spontaneous abortions and low birth weights are common. These effects are most severe during first pregnancies.

WHO recommends chloroquine prophylaxis for pregnant women living in malarious areas beginning at least three months before delivery. Studies have found that pregnant women receiving prophylactic doses of chloroquine have fewer malarial attacks and a lower incidence of anemia than women who are not taking chloroquine. They also tend to deliver babies with higher birth weights.

An African child is almost assured of becoming infected with malaria before reaching the age of one year. The child's first malarial attack may not be fatal, but subsequent attacks carry a higher risk of mortality until protective immunity develops later in life. Until then, children face contracting severe febrile illness, often accompanied by seizures and loss of consciousness, and developing a debilitating anemia and poor response to vaccines for other diseases. These factors make malaria a major threat to child survival in Africa and other highly endemic areas.

e. Economic impact

Malaria has long been considered a constraint to economic development in endemic areas because attacks can incapacitate people for four to 10 days, but the extent of the disease's economic impact has proved difficult to document. Many studies that have attempted to assess malaria's effect on economic productivity have failed to satisfactorily measure the physical impairment caused by the disease or its indirect costs.

The direct costs of malaria include lost wages, the cost of treatment, and the expense of traveling to a clinic or hospital. A VBC study on the economic impact of the disease in sub-Saharan Africa estimates that the average direct cost of a case of malaria is $3.40, which is equal to the per capita health budget of many African countries. In other words, treatment of one case of malaria exhausts a person's entire share of his or her government's health resources.
Before large-scale control began in India during the 1930s, the annual cost of malaria treatment was US $60 million and annual wage losses were at least US $50 million (1988 dollars). In the Philippines, an estimated US $14 million in wages were lost every year and annual malaria treatment costs averaged US $25 million before malaria control efforts began (Wernsdorfer and McGregor, 1988).

The indirect costs of malaria are more difficult to quantify. They result from reduced productivity, pressure on health services, limitations on land use in malarious areas, damage to tourism, school absenteeism and lost investments in child health.

The VBC study found that the burden of malaria in Africa was equivalent to a loss of 2.4 days of work for each person. By 1995, it will be 4.7 days. The total direct and indirect cost of the disease averages 0.66 percent of a country's gross domestic product (GDP) and is projected to double to 1.28 percent by 1995. The current share may seem modest, but it is a higher share of GDP than the entire Ministry of Health budget in any African country. In many African countries, the cost of this one disease outstrips the public resources available for all diseases.

One of the most thorough studies of the economic impact of malaria examined the effects of an epidemic on farmers in a colonization program in eastern Paraguay (Conly 1975). The study found that malaria attacks greatly reduced efficiency among the farmers. Despite the additional help of hired workers and family members, total days worked fell seven percent below normal among the farmers most affected by malaria. Cash crops (tobacco, cotton, corn) were given preference, and total days per hectare spent on minor food crops dropped 35 percent. Harvesting coincided with the height of the malaria season, resulting in a 33 percent loss of efficiency in the harvesting of tobacco, a 28 percent loss for cotton, and a 10 percent loss for corn.
3. Control Measures

a. History of malaria control

Since malaria was first recognized as a disease, the history of its control has gone through three major phases.

Pre-eradication Era

Before World War II, when insecticides that could kill adult mosquitoes were not generally available for malaria control, three approaches were used in various combinations:

1. Chemotherapy/chemoprophylaxis: controlling transmission by treating or preventing infection in individuals.

2. Reducing human-vector contact: use of screens and mosquito nets in houses.

3. Environmental sanitation integrated into rural development: "source reduction" by draining and filling breeding sites; use of larvicides; biological control (larvivorous fish); and water management.

These measures were used primarily in Europe and North America. They were applied in tropical colonies when they were necessary for European settlements and in some agricultural areas. The lessons learned from the integrated approaches to rural development and malaria control used in the U.S. Tennessee Valley Authority, Italy and Israel have not been studied sufficiently to determine their applicability in developing countries.

Eradication Era

World War II boosted the development of new technologies. Two important tools developed during the war, DDT and chloroquine, radically changed the approach to malaria control.

DDT is a residual insecticide that is sprayed on walls, killing adult females when they rest after a blood meal. This insecticide provided four main advantages for malaria control: 1) it was highly effective and long-lasting; 2) it had low toxicity for human populations when used as a residual spray; 3) it could replace
more complex, expensive engineering and environmental measures; and 4) it could be produced at low cost.

Chloroquine was developed in 1934 and the first successful clinical trials were conducted during World War II. This drug was inexpensive and more effective than previous antimalarial compounds. It also had fewer important side effects than quinine and other compounds in use.

The combination of these new malaria control tools proved very effective in Italy, Greece and some parts of the Middle East, where widespread use of DDT permanently eliminated malaria transmission. These early successes led to the proposal that worldwide malaria eradication was possible. The strategy was to: 1) kill populations of female vectors by spraying the inside walls of houses with DDT and other insecticides that were being developed and 2) eliminate populations of malaria parasites by treating all infected individuals with a synthetic antimalarial drug.

WHO formally adopted the goal of eradication in 1955. Implementation began in 1957. The eradication effort excluded sub-Saharan Africa because it was decided that inadequate infrastructures and other logistical problems would make it too difficult to implement the strategy there.

The eradication approach proved partially successful. Malaria was eradicated in Europe, the United States, many Caribbean islands, the USSR, Australia and parts of Asia. About 700 million people, or more than half of the previously exposed population, were no longer at risk. Malaria incidence was markedly decreased in the Indian subcontinent, Venezuela and Colombia.

However, the success was not complete, primarily in the tropical countries, for several reasons, including the development of insecticide and drug resistance. Outdoor biting and resting and other differences in vector behavior also undermined the effectiveness of indoor residual spraying. In addition to these technical problems, the eradication strategy proved inappropriate for most developing countries, which were unable to maintain or afford these intensive interventions for long periods of time.

Control Era

By the late 1960s, it was clear that global eradication of malaria could not be achieved. In 1969, WHO set more realistic goals of reducing malaria incidence and maintaining it at "tolerable levels." Achieving these goals would require less intensive,
costly measures than eradication and would allow adaptation to local needs and capabilities. Instead of independent vertical campaigns, WHO advocated integration of malaria control into the general health systems.

A new approach to malaria control was not developed until 10 years later when the World Health Assembly adopted the "Health For All By The Year 2000" strategy, with its focus on primary health care (PHC). In 1979, WHO defined the following "tactical variants," or control options, to be applied in each country according to its situation and resources:

1. Reduction/prevention of mortality by administration of antimalarial drugs to all suffering from the disease.

2. Reduction/prevention of specific mortality and reduction in morbidity by providing drug treatment to all suffering from the disease and those in highly vulnerable groups (children, labor aggregations and other high-risk populations).

3. Prevention of mortality and reduction in morbidity and prevalence through drug administration and vector control.

4. Application of control measures on a countrywide basis with the ultimate objective of eradicating the disease.

Unlike the previous eradication policy, malaria control implies 1) a prolonged or even constant effort; 2) interventions aimed at disease control rather than transmission interruption; 3) targeting resources where they are needed most through epidemiological stratification; 4) integration of control programs into primary health care structures; 5) decentralization of activities; and 6) increased identification and use of appropriate technologies.

b. Current control measures

Chemotherapy

Antimalarial drugs may be used for three different purposes: 1) protective or prophylactic, when their continuous use prevents parasites from reaching a level high enough to induce symptoms; 2) curative or therapeutic, when they are used to treat the acute attack and suppress the infection; and 3) preventive, when they kill gametocytes, interrupting the parasite's life cycle in the mosquito and preventing transmission.
Several drugs are used for malaria chemotherapy and chemoprophylaxis. The choice of regimen depends upon the malaria species and strain and the geographic area where the infection originated because different strains do not always have the same sensitivities to drugs. The most commonly used therapeutic regimen is 1,500 mg of chloroquine for three days (900 mg the first day and 300 mg the two following days) to treat an acute infection. When malaria parasites are resistant to chloroquine, alternative compounds include mefloquine (Lariam®), quinine or a combination of sulfadoxine and pyrimethamine (Fansidar®). Vivax and ovale malaria require an additional drug, primaquine, for total eradication of latent tissue stages.

Chloroquine is used for chemoprophylaxis at the dose of 250 mg once a week. In areas of sub-Saharan Africa where chloroquine-resistant falciparum malaria has been reported, it is recommended that adults take a daily dose of proguanil (Paludrine®) in addition to the chloroquine. Limited data suggest that proguanil is effective for prophylaxis in tropical Africa, but there are no current data on its effectiveness in other areas where chloroquine resistance has developed.

Chemical control

Insecticide spraying against the adult female mosquito is still the primary method of malaria vector control. Long-acting, residual insecticides are applied to the interior walls and roofs of houses, storage sheds and domestic animal shelters. These measures reduce the longevity of susceptible mosquitoes that rest before or after blood feeding, diminishing the probability that they will survive through the maturation cycle of the malaria parasite and transmit the infection. When the vector is resistant to DDT, more expensive insecticides are used to control resistant mosquito populations. The classes of insecticides commonly used to replace DDT are organophosphates (malathion, fenitrothion) carbamates (propoxur, bendiocarb) and synthetic pyrethroids.

Environmental management

Concerns about cost and environmental safety have resulted in a renewed interest in alternatives to chemical control, particularly environmental management. The options for environmental management fall into three categories: environmental modification, environmental manipulation, and modification or manipulation of human habitation or behavior.
Environmental modification involves physical changes that are usually permanent. These include drainage, land filling and grading, and preventive measures built into the design of canals, reservoirs and other impoundments. Environmental manipulation refers to measures that produce temporary conditions unfavorable to larval production, including regulation of water levels, removal of vegetation, and stream flushing.

Modification or manipulation of human behavior or habitation can help reduce contact between humans and vector mosquitoes. Such measures include building houses away from vector sources, mosquito-proofing houses with screens, and using bed nets and other methods of personal protection. Behavioral research on local perceptions of malaria is essential to designing effective health education campaigns to encourage community participation in source reduction and personal protection.

**Biological control**

Certain species of fish, plants, bacteria and other natural enemies can be used to reduce mosquito populations in small areas. No single biological agent can provide sufficient control to reduce disease transmission, but natural predation can be exploited, enhanced and protected to increase the efficacy of biological control and reduce the cost of other methods.

*Gambusia affinis* and other larvivorous fish have been used as biological tools to control mosquitoes for almost 100 years. *Bacillus thuringiensis israelensis* (*Bti*), a spore-forming bacterium that acts as a larvicide against a broad spectrum of mosquito species, has been used for large-scale control of riceland mosquitoes in the United States. It allows selective control of mosquito larvae with little or no effect on other organisms. However, the cost of *Bti*, which must be applied frequently to control larvae, has precluded its use in many developing countries.

**Integrated control**

One of the most important lessons learned from past eradication and control efforts is that no single intervention can provide sustainable malaria control. Integrated control uses a combination of complementary interventions, including environmental management, biological control and insecticide spraying targeted at high-risk areas. Successful integrated control requires a thorough understanding of the epidemiology of the disease and the ecology of the vector in the control area.
c. **Constraints to control**

**Drug resistance**

Parasite drug resistance is the most severe impediment to successful malaria treatment. Drug resistance is defined as the ability of a strain of a parasite to survive and multiply after active drugs have been administered in standard or higher doses.

*In vivo* resistance to normal doses of chloroquine is graded following a system recommended by WHO:

RI: Parasitemia reappears one to three weeks after termination of treatment.

RII: Parasitemia decreases with treatment but does not disappear during the first week of treatment.

RIII: No decrease or increase in parasitemia during the first week of treatment.

Chloroquine resistance is the most common form of resistance and is limited to cases of falciparum malaria. The availability of effective alternative drugs is limited. They are usually more expensive often involve regimens that patients fail to complete.

The origin of and possible reasons for development of chloroquine resistance in an area are, in order of sequence: 1) drug pressure selects preexisting mutant strains; 2) intense transmission perpetuates and magnifies the problem; and 3) migration of nonimmune individuals spreads and maintains the problem.

Resistance tends to appear in foci before extending into large areas. The geographical distribution of chloroquine-resistant falciparum malaria has increased greatly since it was first suspected in Thailand in 1957 and confirmed in Colombia in 1959.

In the LAC region, chloroquine resistance has been reported in all malarious countries south of the Panama Canal, with the greatest prevalence is in Brazil, Colombia, Ecuador and Venezuela. Studies have also confirmed multi-drug resistance of *P. falciparum* to chloroquine, mepacrine, proguanil, Fansidar and combinations of diaphenilsulfone (DDS) and pyrimethamine in the region.
Drug resistance is considered a major problem in the countries of Southeast Asia. The spread of drug-resistant strains of *P. falciparum* through population movement is particularly serious in Thailand, where resistance of *P. falciparum* to mefloquine also has been reported.

Chloroquine-resistant *P. falciparum* malaria was originally confirmed in Africa at the RI level in apparently nonimmune travellers who had contracted the infection in Kenya in 1979. As of 1987, a total of 26 sub-Saharan African countries had reported *P. falciparum* resistance to chloroquine, including resistance at the RIII level in Mozambique, Ethiopia and Tanzania. Sulfadoxine/pyrimethamine resistance has been reported in Kenya and in the United Republic of Tanzania.

**Insecticide resistance**

The development of resistance to insecticides among *Anopheles* mosquitoes was first noted in the late 1940s after the extensive use of DDT. Currently more than 50 species show resistance to either organochlorine, organophosphate or carbamate insecticides, or cross resistance to two or more classes of insecticides.

In addition to genetically based physiological resistance, or the ability to biochemically detoxify otherwise lethal doses of insecticide, some species demonstrate behavioral resistance by avoiding contact with the applied insecticide. Both forms of resistance reduce or negate the efficiency of malaria control strategies primarily based on the assumption that *Anopheles* vectors feed indoors and rest on the surfaces of insecticide-treated walls after feeding.

A major factor contributing to widespread resistance of vectors to insecticides in the ANE and LAC regions is the overuse of agricultural pesticides in areas of intensive cultivation of cotton, rice, sugar cane and other crops. Resistance to DDT and Dieldrin has been observed in many countries in the AFR region.

More than any other factor, insecticide resistance has increased the cost of control programs that rely on indoor house spraying, making them less sustainable by developing country governments. Consequently, many control programs are more dependent on donor assistance to meet the increasing costs of insecticides and the labor needed to spray more frequently. Furthermore, because of the rising costs of research and development, few compounds are entering the market.
Limitations of alternative methods

There is an urgent need for innovative research on alternative methods of control and field testing to determine operational feasibility and cost-effectiveness. Many of these methods have inherent limitations. For example, bed nets are only effective when mosquitoes bite indoors while people are sleeping and biological control is only practical as a supplementary control measure. Although the importance of community involvement in control efforts is recognized, little is known about encouraging participation in source reduction and personal protection or integrating the efforts of community malaria volunteers into primary health care programs.

d. Institutional constraints

The global shift in strategy from malaria eradication to control requires a different approach. Unfortunately, many programs that were well-organized for eradication have not been able to make the necessary philosophical, programmatic or logistical changes.

Some efforts have been made to take a more focused approach to control by identifying populations at high risk of malaria transmission. Such "stratification" is an epidemiological tool for program management. When transmission was confirmed or suspected, eradication programs usually triggered "total coverage" of the affected areas with a single measure, most often indoor house spraying. The stratification approach requires a more refined diagnosis of the situation and the intervening factors. Therefore, stratified control programs need well-trained personnel with a high level of expertise from a variety of technical backgrounds.

Broad-scale vector control operations are not considered feasible in most parts of sub-Saharan Africa, where malaria control relies on the use of antimalarial drugs to prevent and reduce morbidity and mortality. Few countries have realistic plans of action for control, and there is an acute shortage of trained personnel.

The temporary gains in malaria control achieved during the eradication era are being reversed in many Asian countries. These countries have not been able to mount an adequate response to drug and insecticide resistance and the ecological and social changes exacerbating transmission throughout the region. Although there has been a general economic improvement in the ANE region, many malaria control programs are deteriorating. High commodity costs, lack of trained personnel, and weak organizational and management
structures hamper efforts to incorporate vertical malaria control programs into national primary health care systems.

LAC governments also are struggling to integrate malaria control into general health services as malaria rates continue to increase in most endemic areas. Most national malaria programs are using a modified eradication strategy to promote control goals. Countries often find it difficult to identify and adopt cost-effective, community-based control strategies and to reshape infrastructure and staff patterns to support such strategies.

e. Human resource constraints

Malaria programs can make satisfactory progress only in countries where proper training and supervision of staff takes place at all levels. The establishment of career structures for competent and adequately trained personnel, as well as good management and communication practices, are indispensable prerequisites for an effective program. Unfortunately, inadequate resources for salaries and training in malaria control are crippling formerly successful vertical malaria control programs in many countries. The multidisciplinary group of workers needed to perform the various tasks of malaria control are no longer available, leading to inadequate training, planning and much reduced supervision. This is one reason for the resurgence of malaria during the recent past in Sri Lanka, India and other countries.

f. Economic constraints

A malaria program’s economic resources should be sufficient to support the activities necessary to control malaria. Costs do not necessarily correlate with the level of malaria to be controlled. However, when malaria eradication programs were converted to control programs, funding by international and bilateral agencies was greatly reduced. In fact, international funds allocated to antimalarial activities are less than one-fifth of the amount available in the 1960s.

Reduced support at a time when the costs of insecticides, antimalarial drugs, staffing, transportation, equipment and buildings are rising may severely impede progress in malaria control. Obviously alternative malaria control measures that are affordable and sustainable must be developed and supported. In the end, however, malaria control costs must be balanced against the cost of treatment and losses in economic productivity because of malaria.
4. Current Research

Three technical advances have made important contributions to basic research in malaria: 1) development of a method for continuous cultivation of *P. falciparum*, which provided a laboratory source of parasite material, in 1976; 2) development of hybridoma technology for the production of monoclonal antibodies in 1977; and 3) recent developments in recombinant DNA technology and engineering techniques that provide a source of individual antigens for use in vaccine research and other studies. With these technologies, protective antigens have been identified at several phases of the parasite's life cycle and the genes encoding a number of these antigens have been cloned.

a. Diagnostic technologies

Epidemiologic studies are of increasing importance for both research and control operations. In recent years, great attention has been paid to developing technologies that allow fast, accurate mass screening to identify people who are infected.

DNA hybridization probes, a diagnostic technique based on the binding of a synthetically labeled DNA strand to a complementary one of a parasite in infected blood, have been established in the United States, Sweden and Israel. Yale and Harvard researchers have jointly developed a highly sensitive technique called Quantitative Buffy Coat (QBC). It has been evaluated successfully in Ethiopia, but further assessment and standardization will be necessary before QBC is available for routine use in those programs that can afford the necessary equipment.

Immunooassays based on the binding of synthetically labeled antibodies to an antigen have been improved and adapted to malaria research in recent years. They have already proved valuable in the detection of sporozoite-infected mosquitoes. Current research focuses on their use in diagnosing human infection.

b. Vaccine development

A better understanding of the molecular basis of the immune response to the malaria parasite has led to impressive progress
toward vaccine development, but there are still difficult obstacles to overcome before an effective vaccine can be developed.

Experimental vaccines are being developed against various stages in the parasite's life cycle: the sporozoite, the liver schizonts, the asexual erythrocytic parasites and the gametocytes. Researchers believe that the most effective vaccine will be polyvalent, or made up of antigenic determinants from several life stages and species.

The circumsporozoite (CS) protein of *P. falciparum* has been used to develop two candidate sporozoite vaccines. An anti-sporozoite vaccine against *P. falciparum*, produced by the National Institute of Health (NIH) and the Walter Reed Army Institute of Research (WRAIR), is being tested. Another anti-falciparum sporozoite vaccine has been produced by chemical polypeptide synthesis at the New York University with support from A.I.D. More recently, researchers at WRAIR in collaboration with the Smith, Kline and French Laboratories have reported experiments that suggest the possibility of an oral vaccine using the CS determinant as an immunogen.

Several laboratories in Australia, Europe, Latin America and the United States are trying to produce a vaccine against the asexual blood stages of *P. falciparum*, which would minimize clinical symptoms and prevent mortality. A synthetic vaccine developed in Colombia has been reported to provide partial protection of humans against challenge with asexual blood forms of *P. falciparum*. Trials are underway in several Latin American countries, but results have not yet been reported. To date, no other asexual blood stage candidate vaccine has been developed.

There are no candidate sexual phase or transmission-blocking vaccines, but experimental and epidemiological data indicate that such a vaccine is feasible. Antibodies that develop during natural infections in humans can block the transmission of the parasite to mosquitoes. A potential risk of transmission-blocking vaccines is that they could enhance transmission instead of blocking it.

Other targets for immunological intervention are being explored. Recent work by a group at Hoffman la Roche Laboratories in Basel and the University Cantonal Hospital in Geneva has demonstrated malarial aldolase as a potential site of immunological intervention. These findings are promising because aldolase's function is essential to the parasite. Therefore, it is unlikely that parasite mutants would evolve that could escape immune attack by protective antibodies against this enzyme.
c. Chemotherapy

The emergence and geographical spread of drug-resistant strains of *P. falciparum* has prompted research on new therapeutic tools and approaches. There are two important fields of research in this area: development of new drugs and the use of different drug combinations.

During the past years, WRAIR has screened several hundred thousand compounds in search of new candidate antimalarials. Mefloquine is one of the major results of this program. Others, such as halofantrine, have been developed or are under trial. Qinghaosu (artemisinine) and its derivatives, artemether and artesunate, originally developed in China, have shown promising results in preliminary trials. However, relapses have been recorded with these compounds at the dosages used.

Some malariologists are convinced that the most effective approach to overcoming drug resistance in many geographical areas is using combinations of existing drugs. This approach has met with some success in field trials. WRAIR is examining ways to reverse chloroquine resistance by administering it with non-antimalarial drugs that increase its chemotherapeutic action.

d. Epidemiologic research

In epidemiologic research, there has been increased attention to clinical manifestations, the prevalence of severe and complicated malaria, the effects of the disease in young children and pregnant women, long-term immunity, the therapeutic and side effects of drugs, and the use of serological tests to ascertain the immune status of populations. More recently, the study of socio-economic factors influencing disease transmission and control have been included in epidemiological approaches to identify groups at risk. During the past five years, longitudinal studies in Thailand, New Guinea and Kenya have elucidated the factors that maintain high levels of malaria transmission, including high vectorial capacity and population movements.

e. Vector control

Entomological studies have not kept pace with changing ecological conditions, largely produced by expanding human populations and concurrent expansion of land under cultivation,
increases in deforestation, mining operations, or ecological modifications caused by economic development projects.

Studies in Africa and Asia are elucidating the differences between anopheline siblings that were once believed to be separate species, such as the *Anopheles gambiae* complex and the *An. dirus* complex. Some research on vector behavior is being conducted in Latin America, but most progress has occurred in Thailand and other developing Asian countries.

A particularly promising area of research is the development of biochemical tests to determine the existence and nature of insecticide resistance in vector species. Further development and application of these techniques will help researchers design strategies to reduce or delay the development of resistance in vector populations.

**f. Bed net studies**

Bed nets or curtains impregnated with insecticides (generally permethrin, deltamethrin, or another pyrethroid) not only serve as a physical barrier to biting, but kill vector mosquitoes and may have a repellent effect that will protect the sleeper. Impregnating nets with insecticide also extends their life because even nets with holes or tears in them are still effective.

Impregnated bed nets have been tested in Asia, Africa and Latin America. The small-scale village trials conducted to date have been successful in reducing vector densities, but have not shown conclusively that impregnated bed nets reduce malaria incidence or severity. In China, however, more than two million treated bed nets have protected about five million people. The acceptability and affordability of these techniques among populations in affected areas are not well known. Their applicability in different settings depends on cultural factors, sleeping habits, and degree of compliance.
Malaria occurs in more than 60 A.I.D.-assisted countries. The disease is a serious threat to maternal and child health, particularly in Africa, where it is one of the three leading causes of death among children younger than five. Few comprehensive studies have documented malaria’s impact on productivity, but it is clear that the disease is a serious impediment to economic development in highly endemic areas.

Historically, A.I.D. has been the major donor to malaria control efforts, particularly in Asia, but support for such projects began to decline during the 1980s. The number of bilateral malaria control projects dropped from 12 in 1985 to six in 1990. The Agency continues to support malaria control programs through bilateral agreements with the governments of Pakistan, Belize, Ecuador, El Salvador and Honduras. Its principal malaria control assistance efforts in Africa are incorporated into primary health care projects through the CCCD project. Malaria control also has been a component of A.I.D.-supported primary health care projects in Haiti and El Salvador.

Technical assistance in malaria control is provided to the A.I.D. regional bureaus by the Office of Health, Bureau for Science and Technology (S&T/H). This bureau has provided direct overseas consultant assistance to malaria control projects in eight countries and, through the Vector Biology and Control Project, the services of short-term consultants in the fields of entomology, malariology, epidemiology, parasitology, management and operations research in about 40 countries. S&T/H also provides financial support to WHO’s malaria research and control efforts, including the Special Programme on Research and Training in Tropical Diseases (TDR).

Since 1966, A.I.D. has supported research on malaria immunity and the development of a malaria vaccine. Candidate vaccines were first produced and tested in the laboratory in 1984, and it was hoped that final development of a vaccine would be accomplished by 1989. Unfortunately, further research is needed to produce an effective malaria vaccine for field use in developing countries.

Although A.I.D. continues to provide substantial assistance to malaria control and research efforts, there has been a decided shift in program emphasis in recent years. The Agency has begun to support more research activities and to give increased attention to malaria control within the primary health care system. Such support is jus-
tified not only because of malaria's tremendous impact on public health, but because of its economic importance as a drain on scarce health resources and a serious constraint to development.

a. The Horizon

During the next 10 years, A.I.D.-funded research may lead to the development of a malaria vaccine, which probably will be tested first in New Guinea. In addition, many advances in malaria diagnosis treatment can be expected. Progress will be made in delineating the vectorial risk factors that contribute to malaria outbreaks in changing ecological situations, including urban environments, and in the effective use of insecticide-impregnated bed nets and other low-cost prevention methods. Better community-based health education programs will lead to more sustainable malaria control activities and reduced insecticide use. Emphasis will continue to be placed on preventing mortality from malaria in young children and pregnant women.

Significant progress in malaria control can be expected during the next decade if A.I.D. continues to support research in both the laboratory and the field and to provide technical expertise to developing countries.

A.I.D. has asked the National Academy of Sciences' Institute of Medicine to review malaria vaccine research and control efforts and to make recommendations to guide the Agency's future strategies for malaria. The IOM panel is scheduled to release its recommendations in 1991.

Recent Agency policy initiatives have begun to move A.I.D.-supported malaria programs in new directions. A.I.D. can be expected to increase its emphasis on developing cost-effective control strategies, improving management, and strengthening local institutions to enable them to develop control programs that can be sustained with national resources. Coordination between the various development sectors whose efforts often unwittingly encourage malaria transmission will be an important priority.

b. Priorities for future action

- Institutional strengthening, with an emphasis on sustainability and enhancing the abilities of national and local institutions to marshal their own financial and human resources for malaria control.
• Training of skilled malaria control specialists and additional training of general health personnel in disciplines needed to provide support to control efforts.

• Operations research on: insecticide resistance; changes in malaria epidemiology; new approaches to training non-technical people in malaria control and supervision of community-based control activities; and integration of malaria control into primary health care systems.

• Research on innovative methods of control, including community participation in source reduction, health education to encourage personal protection, and more effective insecticide application methods.

• Collaboration between specialists in vector-borne disease control and agriculture, forestry, water and sanitation, and other sectors during project planning stages to design economic development schemes that will not be impeded by increased malaria transmission.

• Research on the economic impact of malaria and the cost-effectiveness of different approaches to control.

• Studies to answer questions about the clinical and pathological aspects of malaria to improve treatment, particularly treatment of acute cases of cerebral malaria and malaria in pregnant women.

• Continued development and testing of malaria vaccines.

• Behavioral studies to identify the socio-cultural factors that constrain or facilitate malaria control efforts.

• Research toward a better understanding of vector species, their distribution, and ecological and behavioral characteristics to improve traditional control measures and enhance efforts to use alternative methods.

• Development of simple diagnostic tests for early diagnosis and prompt treatment of cases.

• Development of health and management information systems that permit appropriate information flow between policy makers, program managers, field staff and community workers to improve planning, monitoring and evaluation of control programs.
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### Annex 1

#### Table 1

Number of Malaria Cases Reported by WHO Region (in Thousands), 1981-1988

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<td>6,754</td>
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**Total (excluding Africa)**

|       | 7,935 | 6,543 | 5,777 | 5,691 | 4,921 | 5,081 | 5,191 | 5,059 |

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*aThe information provided does not cover the total population at risk in some instances.
*bMainly clinically diagnosed cases.
*cIncomplete figures.

Source: WHO Weekly Epidemiological Record, No. 25, June 22, 1990