This work was supported and made possible
by the Africa Bureau, Office of Operations and New Initiatives (ONI)
and the Office of Analysis, Research and Technical Support (ARTS),
United States Agency for International Development (A.I.D.)
through the Africa Child Survival Initiative -
Combatting Childhood Communicable Diseases (ACSI-CCCD) Project,
Africa Regional Project (698-0421),
Washington, D.C.

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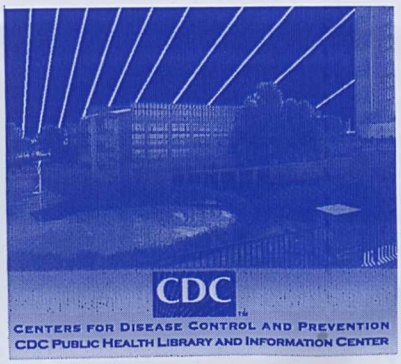
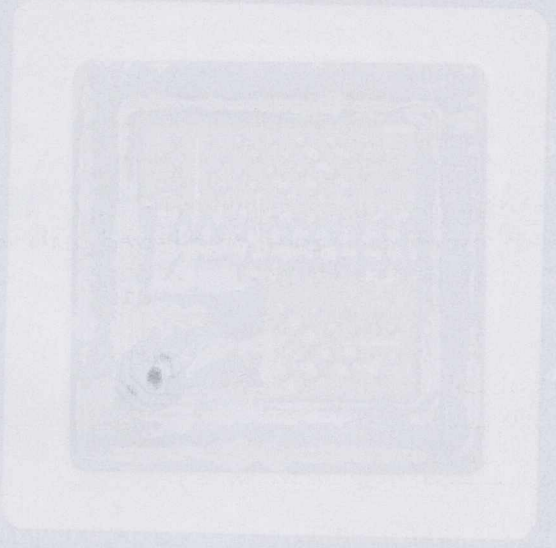
# Addressing the Challenges of Malaria Control in Africa






**UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT**
Africa Regional Project (698-0421)
Participating Agency Service Agreement (PASA) No. 0421 PHC 2233

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Public Health Service
Centers for Disease Control
and Prevention
International Health Program Office
Atlanta, Georgia 30333



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## ABBREVIATIONS USED

| | |
|---|---|
| ACSI-CCCD | Africa Child Survival Initiative-Combatting Childhood Communicable Diseases |
| CDC | Centers for Disease Control and Prevention |
| CQ | Chloroquine |
| CSF | Cerebrospinal fluid |
| EIR | Entomologic inoculation rate |
| HIV | Human immunodeficiency virus |
| IBN | Insecticide-impregnated bed net |
| IM | Intramuscular |
| IUGR | Intrauterine growth retardation |
| IV | Intravenous |
| LBW | Low birth weight |
| MOH | Ministry of Health |
| NMR | Neonatal mortality rate |
| RBC | Red blood cell |
| SP | Sulfadoxine-pyrimethamine |
| WHO | World Health Organization |

## EXECUTIVE SUMMARY

Malaria is an increasingly serious problem in sub-Saharan Africa. It exacts an enormous toll on the health of children, killing more than 1.5 million each year. It also presents an obstacle to national development because of its high human and economic costs. Malaria in Africa is again the focus of concern and commitment by national governments and international organizations after a period of neglect during the eradication program of the 1950s and 1960s. The largest, most notable, and most successful example of this renewed interest was the malaria component of Africa Child Survival Initiative-Combatting Childhood Communicable Diseases project (1982-1993), funded by the United States Agency for International Development to help African countries improve their children's health. The progress of the malaria component in policy and leadership development and in formulating effective interventions in the 12 malaria-endemic sub-Saharan African countries participating in the project provides the basis for the technical and programmatic recommendations outlined in this document, *Addressing the Challenges of Malaria Control in Africa*. The document is written especially for those involved in technical and programmatic aspects of public health programs in sub-Saharan Africa.

The document defines the problem of malaria, its impact, biology, and epidemiology; outlines interventions for malaria control; and describes requirements for an effective malaria control program.

*Plasmodium falciparum*, the parasite that is responsible for most of the malaria infections and almost all malaria-associated death in Africa, affects children in one of three ways: acute malaria illness, chronic or persistent malaria parasitemia with anemia, or perinatal malaria infection in the mother, which can cause low birth weight and early infant mortality. Groups at risk are identified, and interventions to manage and prevent these three classifications of disease are described in detail—diagnosis, patient management, and criteria for selecting antimalarial drugs. The appropriate use of chemoprophylaxis is discussed, and factors involved in embarking on a program using insecticide-impregnated bed nets are considered.

Of course, interventions can achieve their objectives only when implemented. Therefore, a malaria control program that can successfully conduct these activities is essential, and, in this document, the necessary components of a malaria control program are described. Ideally, the malaria control activities should be integrated with other disease control activities to capitalize on aspects of their shared implementation. The challenge ahead is to implement effective malaria control programs based on locally appropriate, efficacious interventions that will improve child survival in Africa.

# INTRODUCTION

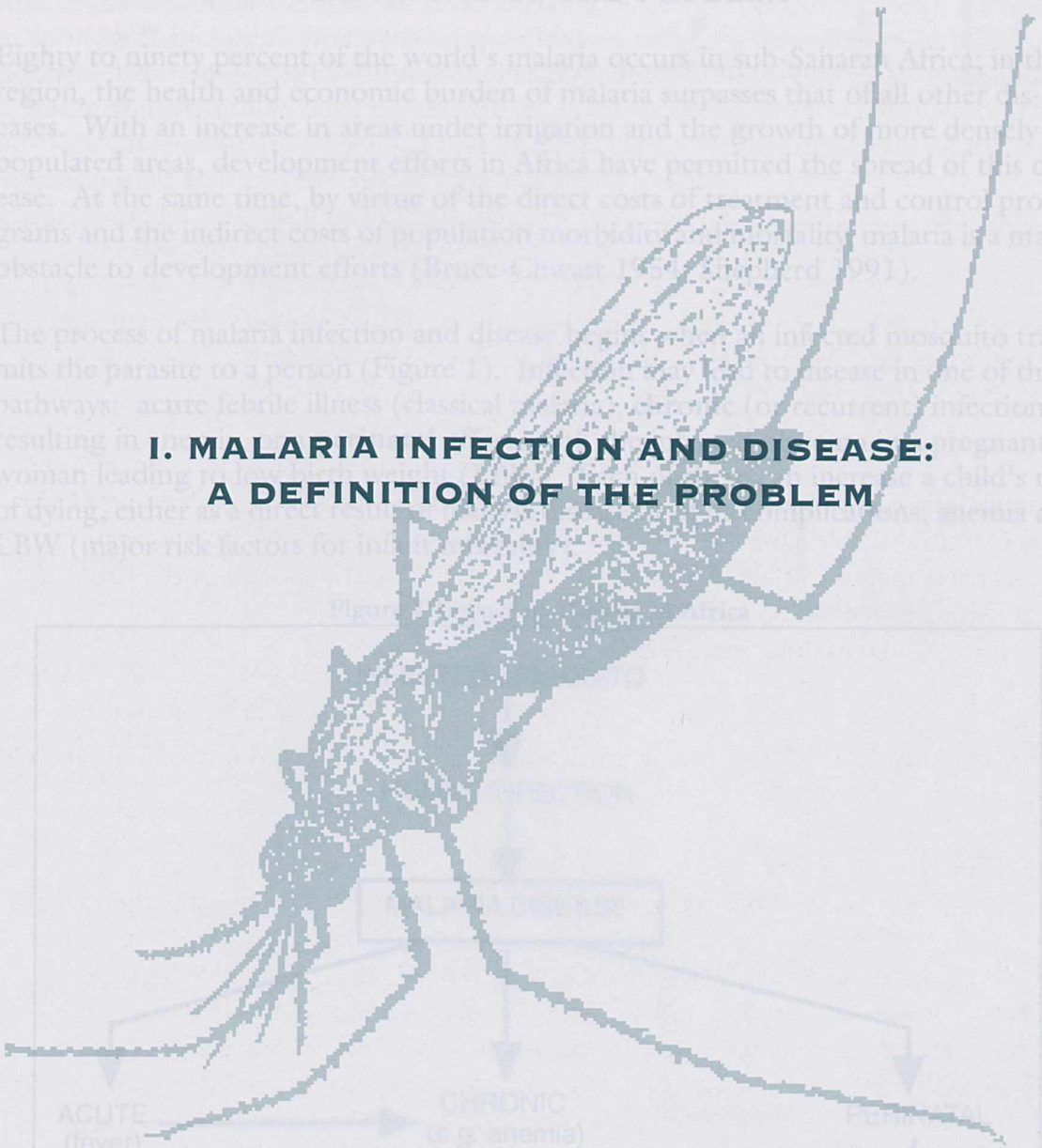
This document reviews the increasingly severe problem of malaria infection and disease in sub-Saharan Africa, describes interventions for managing and preventing the disease, and outlines requirements for a malaria control program. The document is designed to assist those involved in developing and implementing public health programs in this region.

The perception of malaria as a difficult disease that requires complex intervention strategies has been used to explain the failure of the global eradication program of the 1950s and 1960s. Although complexity exists in biologic, epidemiologic, and programmatic features, by examining the components of disease impact and formulating interventions that address these components, policy makers can develop successful malaria control programs based on realistic objectives.

The basis for the technical and programmatic recommendations is the experience of the malaria component of the Africa Child Survival Initiative-Combatting Childhood Communicable Diseases (ACSI-CCCD). Thirteen sub-Saharan African nations participated in this effort funded by the United States Agency for International Development. During the course of the 12-year project, all 12 countries with endemic malaria made important progress in developing malaria policies and programs and in implementing interventions to improve child survival. The recommendations in this document are based on the most effective interventions devised as a result of CCCD operational research and introduced in malaria control programs in CCCD countries.

In addition, the ACSI-CCCD work is the basis of two other documents. *Controlling Malaria in Africa: Progress and Priorities* reviews project accomplishments and activities in participating countries and highlights priorities for malaria control for the next decade. *Malaria prevention in pregnancy: the effects of treatment and prophylaxis on placental malaria infection, low birth weight, and fetal, infant, and child survival* presents the results of a major study conducted in Mangochi, Malawi, from 1987 to 1990. All three documents are available from the ACSI-CCCD Technical Coordinator, International Health Program Office, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia 30333, Fax (404) 639-0277.

# I. MALARIA INFECTION AND DISEASE: A DEFINITION OF THE PROBLEM



# INTRODUCTION

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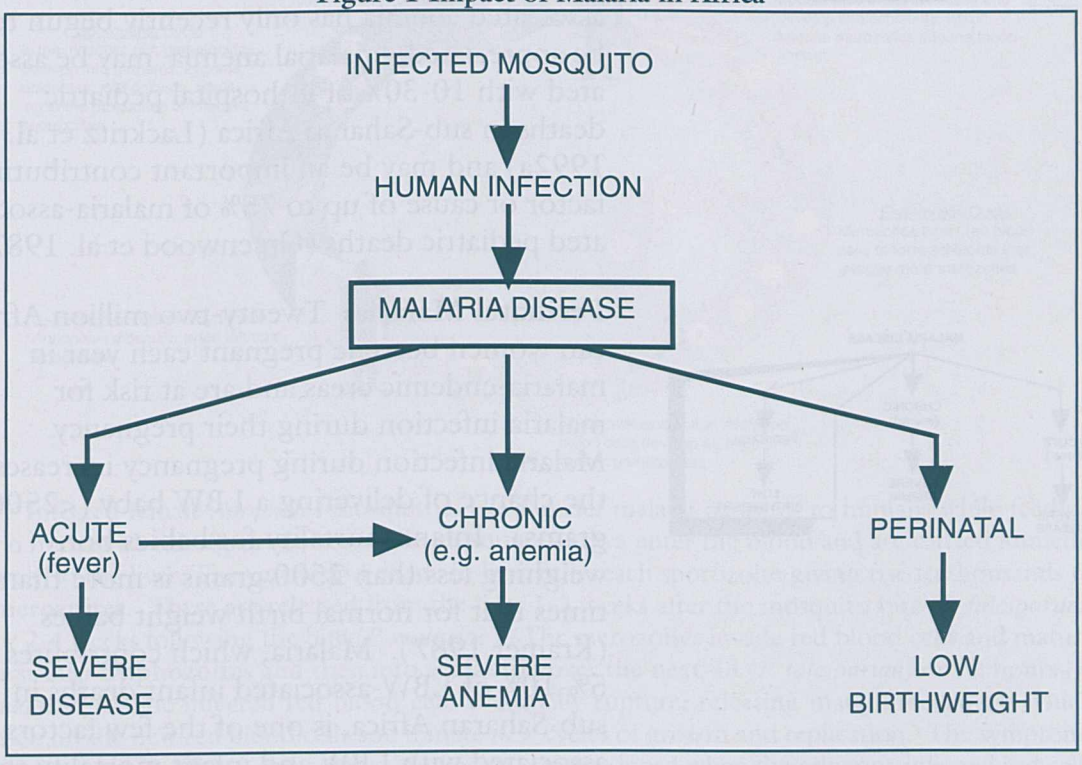
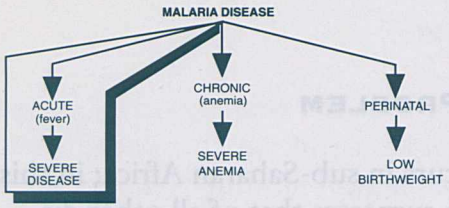
## THE IMPACT OF THE PROBLEM

Eighty to ninety percent of the world's malaria occurs in sub-Saharan Africa; in this region, the health and economic burden of malaria surpasses that of all other diseases. With an increase in areas under irrigation and the growth of more densely populated areas, development efforts in Africa have permitted the spread of this disease. At the same time, by virtue of the direct costs of treatment and control programs and the indirect costs of population morbidity and mortality, malaria is a major obstacle to development efforts (Bruce-Chwatt 1954; Shepherd 1991).

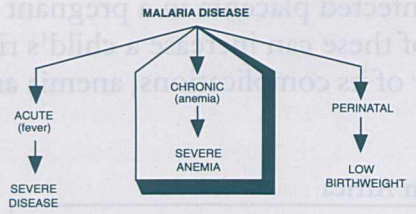
The process of malaria infection and disease begins when an infected mosquito transmits the parasite to a person (Figure 1). Infection may lead to disease in one of three pathways: **acute** febrile illness (classical malaria), **chronic** (or recurrent) infection resulting in anemia, or a **perinatal** effect, with the infected placenta in a pregnant woman leading to low birth weight (LBW). Each of these can increase a child's risk of dying, either as a direct result of malaria disease or of its complications, anemia and LBW (major risk factors for infant mortality).

**Figure 1 Impact of Malaria in Africa**

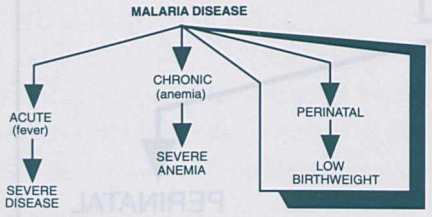





**Acute Malaria:** Each of the 125 million African children less than 5 years of age living in malaria-endemic areas may experience from 5-10 acute febrile episodes that resemble malaria each year (Breman and Campbell 1988). Between 25% and 50% of these episodes will be due to malaria parasites. Of these infections, approximately 0.5%-1% are severe and life-threatening (Marsh 1992). For these cases of severe and complicated malaria, the in-hospital case fatality rate is between 15% and 20% (World Health Organization [WHO] 1990). Roughly 1.5 million children die every year of malaria in sub-Saharan Africa.




**Chronic Malaria:** Red blood cells are destroyed during the course of a malaria infection, and bone marrow suppression during parasitemia limits the production of replacement red blood cells, causing many patients to become anemic. The death toll for malaria-associated anemia has only recently begun to be appreciated; malarial anemia may be associated with 10-30% of in-hospital pediatric deaths in sub-Saharan Africa (Lackritz et al. 1992a) and may be an important contributing factor or cause of up to 75% of malaria-associated pediatric deaths (Greenwood et al. 1987).




**Perinatal Malaria:** Twenty-two million African women become pregnant each year in malaria-endemic areas and are at risk for malaria infection during their pregnancy. Malaria infection during pregnancy increases the chance of delivering a LBW baby (<2500 grams). Infant mortality for babies born weighing less than 2500 grams is more than 4 times that for normal birth weight babies (Kramer 1987). Malaria, which contributes to 5%-10% of LBW-associated infant deaths in sub-Saharan Africa, is one of the few factors associated with LBW and infant mortality that can be managed or prevented during pregnancy.

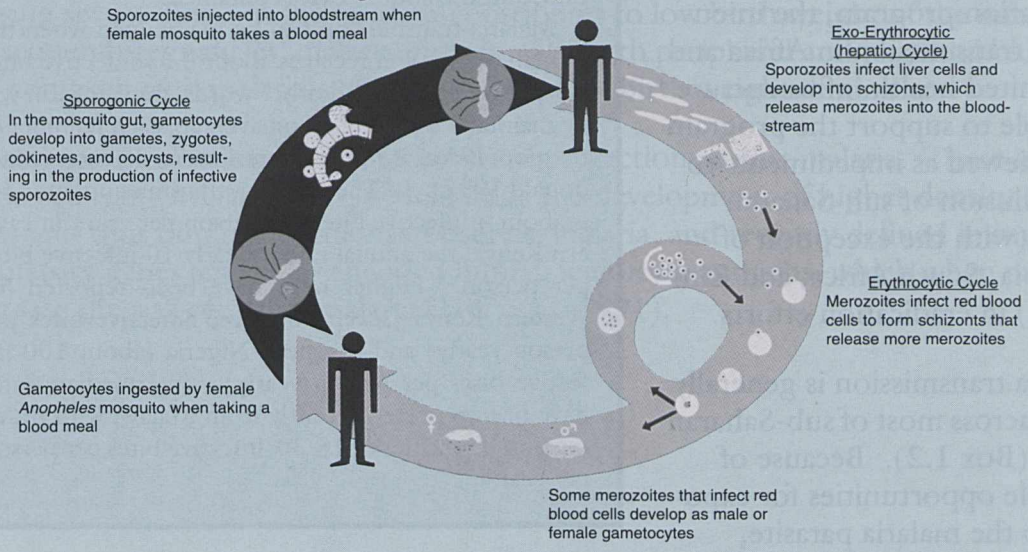
## THE BIOLOGY AND EPIDEMIOLOGY OF MALARIA

The biology of the life cycle of the parasite is summarized in Box 1.1. The proportion of persons affected by acute malaria (complicated or uncomplicated), chronic malaria (malarial anemia), or perinatal infections will vary from region to region, depending on the topography, altitude, temperature, humidity, rainfall, and the opportunity for human-vector contact. For these reasons, malaria control programs must be tailored to individual settings, and the particular manifestations of malaria infection in that setting must be taken into consideration.

### Box 1.1 Life Cycle of the Malaria Parasite in Humans

Four species of malaria parasite are capable of infecting humans. Only two species, *Plasmodium falciparum* and *Plasmodium malariae*, are important in Africa. *P. falciparum* is responsible for over 90% of the malaria infections and essentially all malaria mortality in sub-Saharan Africa. Infections with *P. malariae* generally are not serious, but may be associated with nephrotic syndrome. *Plasmodium vivax* is limited to North Africa, and *Plasmodium ovale* is responsible for <1% of infections; neither is associated with substantial morbidity and mortality.

**Box Figure 1.1 Life Cycle of the Parasite**




Infected female *Anopheles* mosquitoes can transfer malaria parasites to humans while feeding on human blood. **Sporozoites** in the mosquito's saliva enter the blood and are carried immediately to the liver. They grow and divide in liver cells, each sporozoite giving rise to thousands of **merozoites**. These are released from the liver 1-2 weeks after the mosquito bite (*P. falciparum)* or 2-4 weeks following the bite (*P. malariae*). The merozoites invade red blood cells and mature first into **trophozoites** and then into **schizonts** over the next 48 (*P. falciparum)* or 72 hours *(P. malariae*). The infected red blood cells eventually rupture, releasing many **merozoites** which then invade new red blood cells and initiate new cycles of growth and replication. The symptoms of acute malaria (fever, chills, aches, and pains) are produced when the schizont-infected red cells burst. Sexual forms of the parasite (**gametocytes**) develop in red blood cells after 7-10 days, but their union occurs in the mosquito gut, following a blood meal in which both male and female gametocytes are ingested by the mosquito. Following maturation and multiplication, the **sporozoites** migrate to the salivary glands of the mosquito and are available to be injected during a subsequent blood meal.

The epidemiology of malaria is determined by the efficiency of the mosquito vector (i.e., the capacity to transmit the malaria parasite), the intensity and the stability of malaria transmission, and human susceptibility and immune response.

In sub-Saharan Africa, the predominant species of anophelines, especially *Anopheles gambiae, Anopheles arabiensis,* and *Anopheles funestus,* are highly efficient vectors because their preferred sources for blood meals are humans. *A. gambiae* are especially efficient because they dwell and bite indoors at times when people are likely to be inside, and they support the development of the parasite well. The intensity of malaria transmission in Africa far exceeds that of other malaria-endemic areas in the world (Coluzzi 1992); this caused the international eradication effort to exclude the region from its program in the 1950s and 1960s. As mosquito control was the central strategy of the eradication program, the intensity of transmission in Africa and the limited health infrastructure available to support the program were viewed as impediments to the inclusion of sub-Saharan Africa (with the exception of Ethiopia, South Africa, and Zimbabwe) in eradication efforts.

**Box 1.2 Measuring Malaria Transmission**

The standard measure of malaria transmission may be expressed as the entomologic inoculation rate (EIR), or the number of infective bites per person per time interval (e.g., year). The EIR is calculated by determining the number of bites per person per night for a given species and then multiplying by the sporozoite rate (the proportion of *Anopheles* infected with malaria sporozoites). The result, the average number of infective bites per person per night, is multiplied by 365, and the annual EIR is obtained.

Malaria transmission can be maintained when the human population receives about 0.33 infective bites per person per year (in other words, transmission will be maintained as long as, on average, each member of the population is infected once every 3 years) (Macdonald 1957). In The Gambia, transmission intensity is about 4 infective bites per person per year; in eastern Kenya, the annual rate is nearly 10 infective bites per person. Higher rates have been reported for Western Kenya (several hundred infective bites per person yearly) and northern Nigeria (about 100 infective bites per person yearly). Intermediate rates have been reported recently from Malawi with transmission intensities of 15-30 infective bites per person per year.

Malaria transmission is generally stable across most of sub-Saharan Africa (Box 1.2). Because of multiple opportunities for exposure to the malaria parasite, adults (except for pregnant women) have developed immunity to malaria infection. Therefore, young children and pregnant women are the groups at highest risk for malaria disease. In areas where transmission is unstable (desert fringe areas, newly developed agricultural areas, areas where large population movements occur), residents will not have acquired adequate immunity to malaria infection or illness. In these settings, all age groups and persons are at risk, and the potential for malaria epidemics exists.

The risk of **malaria infection** is determined by exposure to infected mosquitoes. The risk of **malaria illness** is determined by the individual's immunologic response to infection, which in turn depends on the frequency and duration of previous malaria infections (Greenwood, Marsh, and Snow 1991). Therefore, in endemic areas, young

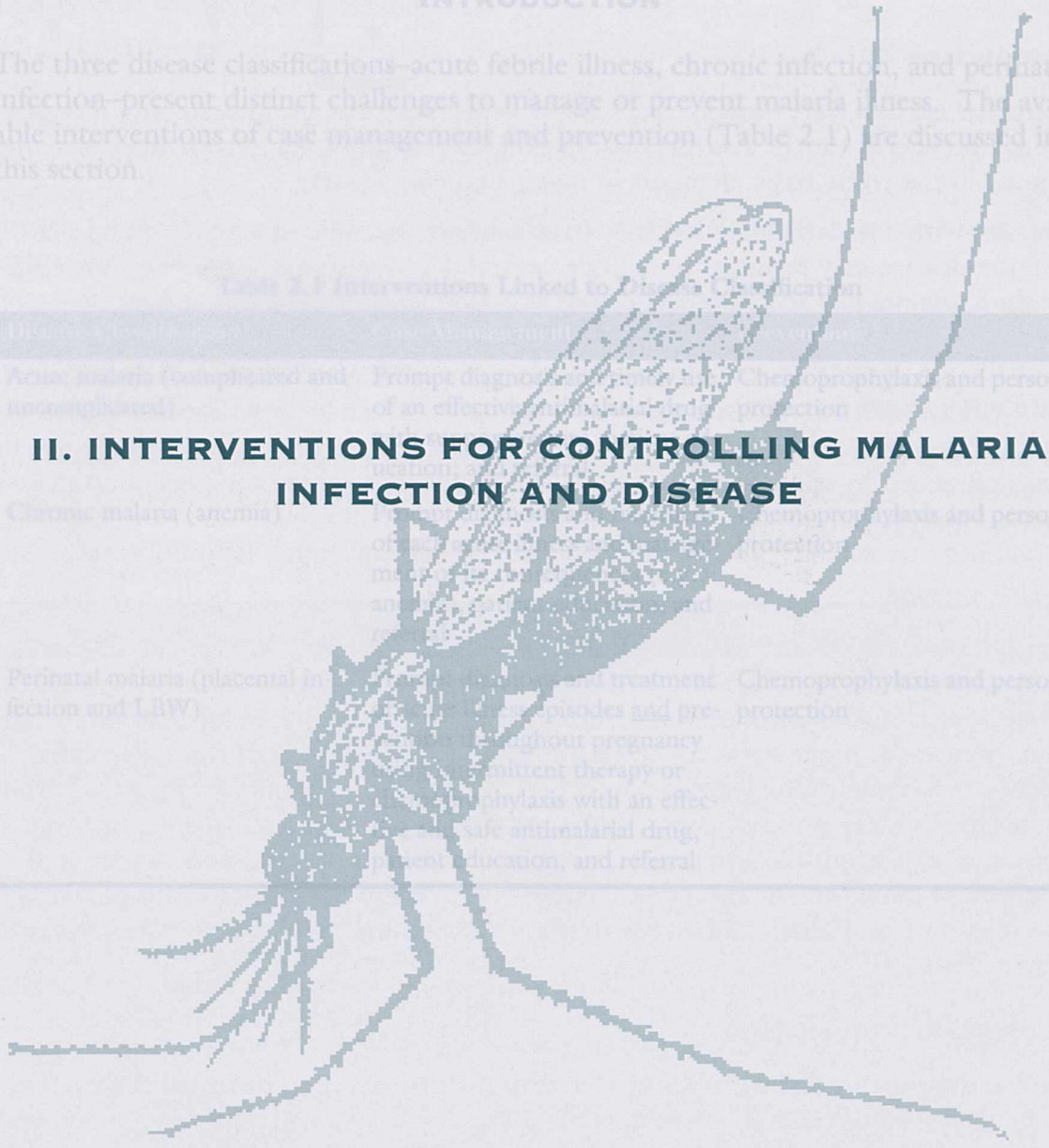
children and any individuals moving from nonendemic areas are at high risk for malaria illness if they become infected. The most important manifestation of malaria immunity is the capacity to suppress infection and to tolerate infection with few symptoms.

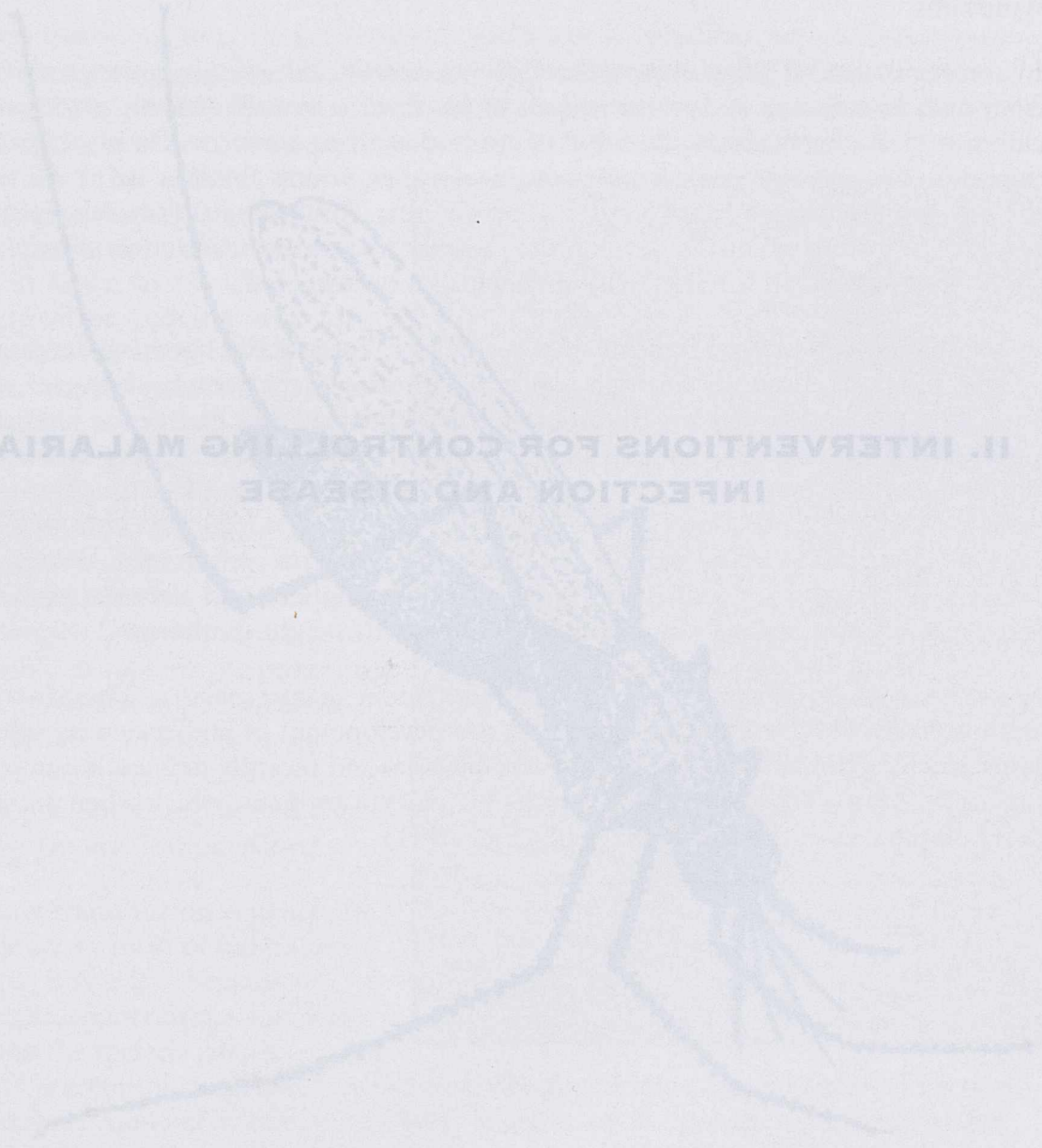
In areas of intense *P. falciparum* transmission, newborns have an apparent protection from malaria infection and severe malaria illness for 2-6 months (Marsh 1992), coinciding with the approximate duration of antibodies that pass across the placenta to the fetus. Once this transplacental protection wanes, young children are at risk for the full range of disease consequences of parasitemia. Children who survive repeated episodes of malaria gradually develop the capacity to contain infection at lower, nonlethal densities and to sustain parasitemia without becoming ill.

In settings of high malaria transmission, women of reproductive age have developed a high degree of immunity through repeated exposure to the parasite; however, during pregnancy, and particularly during the first pregnancy, they experience increased susceptibility to malaria. This may be due, in part, to the presence of the utero-placental space, which apparently provides an immunologically safe place for parasite development and replication (McGregor 1984). The malaria infection, although not causing severe illness in the mother, contributes to low birth weight of the infant. In subsequent pregnancies, malaria infection (of both peripheral and placental blood) is less common, and malaria's contribution to low birth weight diminishes.

Several genetically determined traits afford protection against malaria. These include sickle cell trait (Miller 1992), which limits the development of higher density infections and thus diminishes the risk of severe malaria, and recently defined immune regulatory genes and their encoded human leukocyte antigens, which when present, decrease the risk of severe malaria (Hill et al. 1991).

# II. INTERVENTIONS FOR CONTROLLING MALARIA INFECTION AND DISEASE





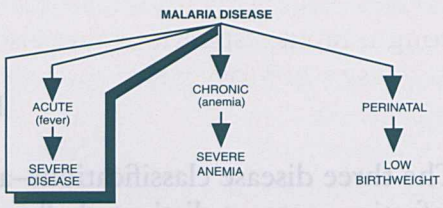
## INTRODUCTION

The three disease classifications–acute febrile illness, chronic infection, and perinatal infection–present distinct challenges to manage or prevent malaria illness. The available interventions of case management and prevention (Table 2.1) are discussed in this section.

**Table 2.1 Interventions Linked to Disease Classification**

| Disease Classification | Case Management | Prevention |
|---|---|---|
| Acute malaria (complicated and uncomplicated) | Prompt diagnosis and timely use of an effective antimalarial drug with supportive care, patient education, and referral | Chemoprophylaxis and personal protection |
| Chronic malaria (anemia) | Prompt diagnosis and treatment of each acute illness and management of its consequences (e.g., anemia), patient education, and referral | Chemoprophylaxis and personal protection |
| Perinatal malaria (placental infection and LBW) | Prompt diagnosis and treatment of acute illness episodes and prevention throughout pregnancy using intermittent therapy or chemoprophylaxis with an effective and safe antimalarial drug, patient education, and referral | Chemoprophylaxis and personal protection |

# RECOGNIZING AND MANAGING ACUTE MALARIA




## Introduction

Untreated malaria infections can rapidly progress to severe, life-threatening illnesses and death (WHO 1990). For this reason, prompt recognition and treatment of acute disease have become basic elements in malaria control efforts.

A person with a malaria infection may have acute symptoms, usually fever and malaise; the disease may progress to include central nervous system signs (e.g., encephalopathy), anemia due to red blood cell destruction, and other organ system involvement. Other diseases may be associated with similar clinical symptoms, and the challenge of treating acute malaria involves deciding when to provide antimalarial treatment in circumstances where it may not be possible to make a specific diagnosis.

The choice of a specific antimalarial drug depends on the species of parasite involved, the severity of clinical illness, local parasite drug sensitivities, and the facilities available for administering treatment.

## At-risk groups

In malaria-endemic areas, malaria should be considered in the differential diagnosis of virtually any febrile illness in a young child. Children less than 5 years of age are at particular risk of severe malaria-related morbidity and mortality; those between 6 and 36 months are at highest risk for dying of malaria. Others at high risk for malaria infection are nonimmune travelers, workers (including the military) transferred from nonmalarious areas, and refugees. When malaria is introduced to an area, or reintroduced as a result of changes in ecology or weakened malaria control practices, the entire population may be at risk. These nonimmune persons can suffer malaria morbidity and mortality comparable to that of the young sub-Saharan African child (Marsh 1992).

## Recognizing acute malaria

**Clinical diagnosis of acute malaria.** Fever or history of fever is the usual clinical basis for the diagnosis of malaria. Most patients, or their parents, will note fever as an early symptom. Because body temperature can rise and fall in conjunction with the parasite life cycle, patients with malaria may be afebrile (axillary temperature $\leq 37.5^{\circ}$ C) at the time of presentation to a health care facility. Among such patients, a history of recent (within 48 hours) fever may be the only basis for presumptive treatment of malaria.

Under ideal conditions, patients in malaria-endemic areas presenting with fever and malaise would receive comprehensive evaluations including a detailed history and physical examination, blood films for malaria parasites, and additional laboratory investigations (hemoglobin, blood glucose, blood culture, complete blood count, chest radiograph, lumbar puncture) as indicated to exclude other possible diagnoses. Even with these diagnostic tests, however, diagnosing acute malaria may be difficult

because the signs and symptoms (fever, headache, malaise, nausea and vomiting, cough, rapid respirations) are also seen in patients with other common infections, such as respiratory infections or diarrheal disease, and because malaria parasitemia may coexist with any of these diseases.

The laboratory diagnosis of malaria disease (in contrast to malaria infection) is hampered by the fact that, in endemic areas, a substantial portion of asymptomatic individuals may have malaria parasites circulating in their blood, and people with fever from another cause may also have incidental parasitemia, thus compromising the diagnostic significance of a positive blood film in febrile long-term residents of these areas. Thus, the presence of parasitemia should not preclude an aggressive search for other causes of fever.

The diagnosis of malaria based on fever or a history of fever is sensitive in identifying patients with parasitemia (Redd et al. 1992) (Box 2.1). This definition lacks specificity, however, because it inevitably includes persons (parasitemic as well as aparasitemic) with fever from some other cause. Seasonal or regional differences in malaria transmission patterns and seasonal fluctuations in other illnesses (meningitis, pneumonia, gastroenteritis) will alter the positive predictive value of this definition (Rougemont et al. 1991; Olivar et al. 1991). Efforts to improve the definition by including additional symptoms will increase specificity at the expense of sensitivity.

**Box 2.1 Sensitivity, Specificity, and Positive Predictive Value of Malaria Diagnosis**

The objective of the diagnostic process for malaria is to identify patients who need treatment for malaria. Because microscopic diagnosis is generally unavailable in Africa, fever or a recent history of fever is the usual clinical basis for diagnosing malaria.

Fever or history of fever is a **sensitive** case definition. In other words, fever is likely to identify most children with malaria parasitemia. However, since most children who are ill have fever, the disadvantage of this case definition is that its **specificity**, its capacity to exclude aparasitemic children, is low. If children are treated on the basis of this case definition, many of those receiving antimalarials will be aparasitemic.

The **positive predictive value** of fever as the case definition for malaria (the probability that a febrile child will be parasitemic) is not always high. When fever or history of fever was used as the clinical case definition for malaria in Zimbabwe, only 27% of children clinically diagnosed as having malaria were also parasitemic. In a study in Malawi, 37% of children with fever (according to mothers' histories) and 47% of children with measured axillary temperatures ≥37.5° C had malaria parasitemia.

A case-control study in Niger showed a seasonal effect on the case definition: during the wet season, children with fever were more likely to be parasitemic than those who were afebrile. This association was not observed during the dry season. The **positive predictive value** of the definition varies with season in this setting.

Results of these studies show that epidemiologic characteristics such as season, in addition to clinical characteristics, are important in identifying those at risk for the complications of malaria. Available data are inadequate to translate these factors into specific recommendations for national programs. Malaria programs should begin to collect local epidemiologic information, such as season- and age-specific rates of parasitemia, as a first step in refining recommendations for treatment of children with malaria. Equating all febrile illnesses with malaria is a sensible starting point, but national programs recognize the limitations of such an approach. Additional studies are needed to identify which children are at risk for complications of parasitemia, including severe mortality and death. Treatment and prevention efforts should then be focused on these children.

**Laboratory diagnosis of acute malaria.** The gold standard for the diagnosis of malaria infection remains the microscopic detection of parasitized red blood cells in properly stained peripheral blood films (Earle and Perez 1932). This method requires a microscope, slides, stains, and a trained microscopist. It is labor-intensive, taking 5-30 minutes to examine the blood film of one child. In addition, it requires long-term maintenance of equipment and skills of the microscopist (WHO 1988).

Methods to simplify and accelerate the process are being developed.

- The Quantitative Buffy Coat[1] method is commercially available (Becton Dickinson and Company, Franklin Park, New Jersey, USA) and is based on staining parasite DNA with a fluorescent dye. Parasites are detected after centrifuging blood collected in specially constructed hematocrit tubes (Rickman et al. 1989). This technique also requires long-term maintenance of equipment and a skilled microscopist.
- Parasite DNA or RNA can be isolated from whole blood or from fingerprick blood collected onto filter paper, and various approaches to identify malaria parasites by molecular probes are being developed (Draper et al. 1986; Lal et al. 1989).
- Some malaria parasite antigens can be recognized in enzymatic assays; diagnostic methods using ELISA or Dipstick are under investigation (Peyron et al. 1993).

Each of these methods has its own constraints, and none has replaced microscopy; some may prove useful for large-scale screening or epidemiologic research.

Because the clinical syndromes of fever, encephalopathy, and anemia may be caused by other diseases, no single diagnostic test can distinguish among the various causes of these conditions. If more information on fever (temperature, bacteriologic cultures), parasitemia (presence or density), anemia (hemoglobin or hematocrit measurement), and other possible sources of infection (chest radiographs) can be acquired, the specificity of the diagnosis will improve. More microscopy and perhaps more hemoglobin or hematocrit measurements are needed; these tests are much less costly than chest radiographs or bacteriologic cultures and can provide essential information.

With these tools, patients could be diagnosed more accurately, thus allowing more judicious administration of treatment. For instance, instead of providing antimalarials to all children with fever, those drugs could be provided only to febrile children who are parasitemic, and alternative diagnoses could be sought in aparasitemic febrile children.

Realistically, for the foreseeable future in Africa, more effective management of pediatric illness, including malaria, will come from the systematic application of clinical criteria in the absence of definitive laboratory confirmation.

[1]Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

## Definitions of uncomplicated and complicated malaria

It is important to distinguish between patients with uncomplicated malaria illness and those with complicated disease because the management of the two differs markedly. The former can be treated as outpatients, while the latter require more intensive care.

**Complicated** malaria refers to patients with *P. falciparum* parasitemia and any one or more of the following (WHO 1990):

- Altered consciousness
- Convulsions
- Inability to take food or medications by mouth
- Respiratory distress
- Severe anemia
- Hypoglycemia
- Shock

Because these patients generally require parenteral medications (intravenous [IV] infusions or intramuscular [IM] injections), their treatment must be supervised by trained health workers.

**Uncomplicated** malaria refers to malaria disease in the absence of any signs of complicated disease. In general, patients with uncomplicated malaria can be managed as outpatients, but parents or guardians should be alerted to the warning signs of complicated disease (above) and urged to return for further evaluation if the patient's clinical condition deteriorates.

Only a small proportion of children infected with malaria parasites develop severe or complicated malaria (Greenwood et al. 1987), and it is difficult to predict which children will develop life-threatening disease. For this reason, all young children with mild malaria should be treated as if they were at risk for developing more severe disease.

## Managing acute malaria: objectives

- To prevent mortality associated with malaria infection.
- To prevent patients with uncomplicated malaria infections from developing life-threatening illness and/or chronic malaria.
- To resolve the clinical symptoms and parasitemia associated with acute malaria infection rapidly and without sequelae.

## Managing acute malaria: strategy

- Promptly recognize acute malaria (complicated and uncomplicated); use effective antimalarial drugs at proper dosages in conjunction with supportive care, parental education, and referral when necessary.

## Managing patients with uncomplicated malaria

**Introduction.** As management of uncomplicated malaria has to date had the objective of minimizing the risk of progression to complicated disease, treatment decisions must often be based on a malaria case definition (fever or history of fever) that is sensitive, but not specific (Greenwood et al. 1991; Redd et al. 1992).

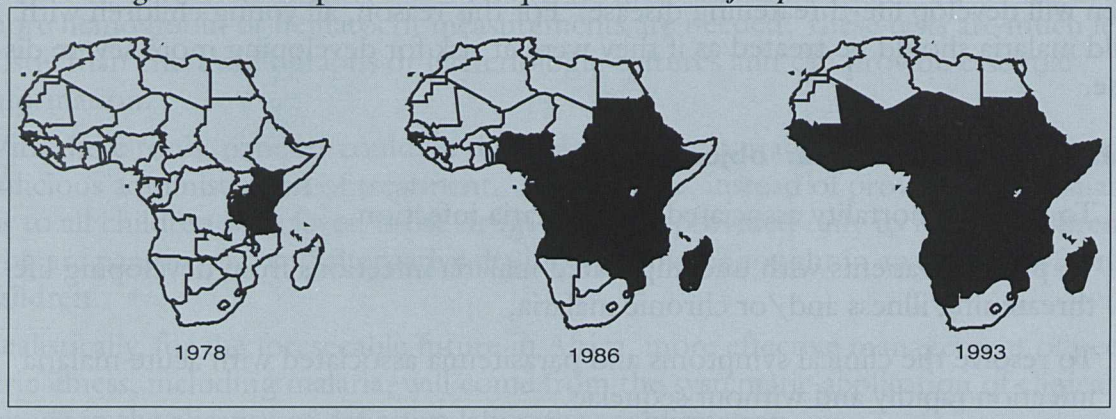
**Choice of an antimalarial drug.** The choice of an antimalarial drug or drug regimen for an individual patient or for use in a control program should be based on the following criteria: efficacy, cost, availability, ease of administration, likelihood of compliance, and tolerance of side effects.

### Box 2.2 The Chloroquine Story

The first antimalarial drug, quinine, was discovered in the 16th century. Quinine, a natural product derived from the bark of the cinchona tree, was the mainstay of treatment until world supplies were truncated during World War I. Effective drugs were needed to treat troops in malaria-endemic areas, and the first generation of synthetic drugs (pamaquine, mepacrine) emerged from a concerted research effort.

Chloroquine (CQ), a synthetic 4-aminoquinoline, was developed during World War II, one result of an intense search for safer, more affordable, more efficacious malaria chemotherapy. These qualities, combined with its ease of administration, made CQ the most widely used antimalarial in the world.

**Box Figure 2.2 The Spread of Chloroquine-resistant *P. falciparum* Malaria in Africa**




Parasite resistance to CQ was first recognized in South America in 1961, in Southeast Asia in 1962, and in Africa in 1978. Except for the Middle East, North Africa, Central America west of the Panama Canal, Haiti, the Dominican Republic, northern Argentina, and Paraguay, CQ-resistant parasites have been identified in all other malaria-endemic areas. Acceptable alternatives to CQ are few, and the inexorable spread of CQ resistance has been a major challenge for malaria control programs in endemic areas.

*Efficacy* Increasingly, it is understood that the efficacy of an antimalarial used to treat children less than 5 years of age (those at highest risk for severe illness and death due to malaria) can be judged by its ability to alleviate symptoms of the disease, clear parasites, and allow an adequate parasite-free interval for hematologic recovery (defined as the return to pre-illness level of hemoglobin concentration) (Bloland et al. 1993). As chloroquine (CQ) resistance has intensified, CQ's subsequent failure to clear peripheral parasitemia results in shortened duration of clinical improvement and inadequate recovery from the associated anemia (Box 2.2). It is time to change to a drug that will clear parasitemia when resistance to treatment exceeds the following dimensions: the mean sustained clinical recovery is less than 14 days and the mean hemoglobin concentration increase among children with anemia (<8 g/dL initially) fails to increase by 1 g/dL within 14-21 days. Experience suggests that these events occur in proportion to the frequency of high level resistance, mainly of the RIII type; the problem is of epidemiologic importance when RIII resistance exceeds 5%-10% (Box 2.3). In older individuals (those no longer at great risk for malaria mortality), the requirement for parasite clearance may be less critical.

*Cost* Several antimalarials are similar in terms of efficacy and safety. Consequently, price is an important determinant in selecting which agent(s) to include in a control program. Cost per treatment course should be compared for various choices; a relatively high per tablet cost may be offset by a lower number of tablets required per treatment (Table 2.2) (Foster 1991). The cost per case effectively treated should be examined: a more expensive drug may ultimately cost less than a cheaper drug which, because of its reduced efficacy, must be administered more frequently. Costs could be further reduced by targeting the use of the most effective antimalarials to those persons at greatest risk for malaria-associated mortality and severe disease.

**Table 2.2 Drugs Available for the Treatment of Malaria**

| Drug | Route of Administration | Oral Regimen[1] | Cost per Adult Treatment[2] (US$) |
|---|---|---|---|
| Chloroquine | PO[3], IM[4], IV[5] | 3 doses, over 3 days | 0.08 |
| Pyrimethamine/sulfadoxine | PO, IM | Single dose | 0.13 |
| Quinine or quinidine | PO, IM, IV | 3 times daily for 3-7 days | 0.99-1.51 |
| Tetracycline | PO | 4 times daily for 7 days | 0.25 |
| Mefloquine | PO | Single dose | 1.92 |
| Halofantrine | PO | 3 doses in 24 hrs | 5.31 |

[1] Oral regimen cited only
[2] Cost of drug only, excluding delivery
[3] PO = Oral
[4] IM = Intramuscular
[5] IV = Intravenous

## Box 2.3 Drug Resistance

Resistance to most other antimalarial drugs (mefloquine, quinine, sulfadoxine-pyrimethamine) has developed, and is especially severe in Southeast Asia. Multidrug resistant parasites will eventually spread to Africa, but have not yet been detected in significant numbers.

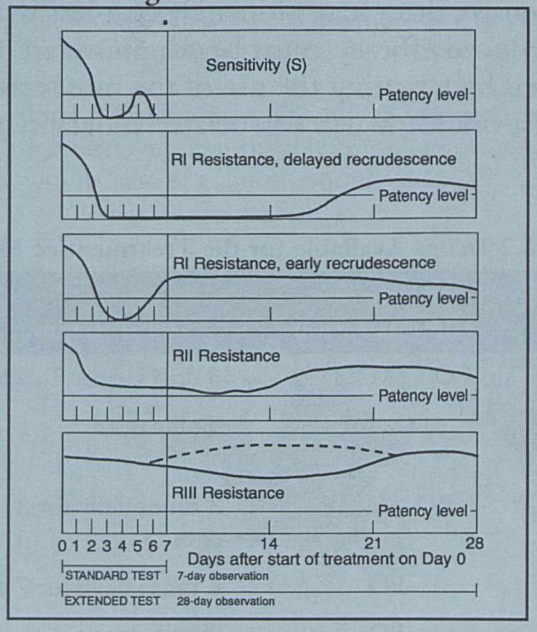
### Recognizing drug resistance

Drug resistance in malaria parasites is generally first noted by clinicians when patients fail to respond to the standard treatment regimen. For chloroquine, deterioration in drug efficacy is a gradual process; initially, only a few patients are affected. They may improve symptomatically, but parasitemia reappears within 3-4 weeks (RI, see chart below). In time, a substantial proportion of the patient population will be infected with chloroquine-resistant *P. falciparum*, and the resistance may be such that parasitemia does not diminish at all after treatment (RIII) (See Box Figure 2.3).

### Measuring drug resistance

The development of drug resistance in a population of malaria parasites can be measured in vivo (by noting inadequate responses to properly administered treatment) or in vitro (by measuring the effect of various concentrations of the drug on the growth of malaria parasites in culture). For operational purposes, in vivo testing is most useful. Recent data on the long-term effects of persistent parasitemia (Bloland et al. 1993) support the use of an expanded 28-day in vivo test of drug efficacy to include clinical and hematologic follow-up evaluation of study subjects when the 7-day in vivo test demonstrates moderate to high levels of RII and RIII resistance.

**Box Figure 2.3 Resistance Levels**

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### Staying ahead of drug resistance

The malaria parasites have the capacity to develop resistance to a wide range of drugs, and widespread use of any drug will contribute to the development of resistant parasites. Therefore, it is essential to continue to monitor antimalarial drug resistance and to develop new antimalarial drugs.

*Availability* Once drugs are chosen for a control program, a steady drug supply must be maintained, and the drug must be available at all places where malaria drugs are dispensed, e.g., hospitals, dispensaries, shops. A program predicated on the prompt and effective treatment of febrile illness will be undermined if the recommended drugs are not readily available.

*Compliance and ease of administration* As noted in Table 2.2, many of the drug regimens require repeated dosing, and their efficacy requires the patient to take the drug repeatedly. Poor compliance with the regimen will be the major determinant of poor effectiveness. As a consequence, single-dose regimens are much more likely to be effective in both an individual and a programmatic setting.

*Side effects* Side effects need to be considered when choosing an antimalarial regimen for a malaria control program. Common, but not severe, side effects may reduce compliance. For example, pruritus due to CQ has limited its role in some populations. The possibility of severe side effects from an antimalarial, even if rare, must be carefully weighed against its benefits.

In conclusion, the goal of treating young children at high risk is to clear both symptoms and parasitemia. In the rare settings where CQ remains efficacious, it should be the first-line treatment. However, the best alternatives in many settings of sub-Saharan Africa now are the combinations of sulfa drugs with dihydrofolate reductase inhibitors (e.g., sulfonamide + pyrimethamine). These drugs are still efficacious and have the advantage of being administered as a single oral dose. A single dose of sulfadoxine-pyrimethamine (SP) is only slightly more costly than CQ. Where the resistance to CQ surpasses 15% to 30% of RIII level, the cost per case effectively treated is actually lower because of the greater efficacy of SP (Sudre et al. 1992). Although malaria parasites will inevitably become resistant to SP, targeting its use to high-risk groups (children less than 5 years of age, nonimmunes, pregnant women) may slow the development of drug resistance. Meanwhile, research into new antimalarial agents must continue in the attempt to keep ahead of developing drug resistance.

**Drug administration.** *Prompt treatment of febrile illness* Cerebral malaria can develop within hours. In most cases, however, there is an antecedent history of fever. Therefore, effective treatment should be provided at the earliest possible opportunity (Box 2.4). Treatment for acute uncomplicated malaria should be readily and reliably available in hospitals, health centers, clinics, pharmacies, dispensaries, and if important parts of the population lack access to formal health care facilities, in shops and homes.

*Supervised administration* When possible, the first dose of an oral antimalarial agent should be given under supervision. The patient should be observed for 30 minutes; if the child vomits during that time, treatment options include repeating the initial treatment (again, under supervision and with observation) or switching to a parenteral drug.

*Use of antipyretics* Children who have a body temperature above 38° C and who are irritable or appear uncomfortable should receive an antipyretic. Paracetamol, both safe and inexpensive, is the preferred antipyretic for children. Mothers should understand that even though the antipyretic will relieve the fever temporarily, it will not cure the cause of malarial fever, and so the antimalarial drug is essential.

*Follow-up management* Patients or their guardians should be instructed to return immediately if the patient's clinical condition begins to deteriorate (e.g., clouded consciousness, convulsions, or inability to eat or drink) or if the patient does not show significant clinical improvement within 72 hours of starting treatment.

**Box 2.4 How Prompt Should "Prompt" Treatment Be?**

Uncomplicated malaria can become complicated very quickly. It is not uncommon for mothers to appear at a health clinic carrying an unconscious child and to relate the following history: "She's had a fever for a day. We gave her chloroquine tablets and she played well all morning. Then she had a fit and she hasn't woken up since." Of 131 comatose patients in Malawi, the mean duration of fever prior to admission was 47 hours, and the mean duration of coma before admission was only 8 hours.

Is it possible to intervene in such a rapidly progressive illness? A small proportion of those infected with malaria develop complicated disease and the determinants of this evolution are not known. Until the risk factors for severe disease are better defined, "prompt treatment" with an effective drug for all in whom malaria is a likely diagnosis is the best approach. Since little is known about the natural history of malaria infections, the safest assumption is that "prompt" means "now." This implies that antimalarial drugs should be available to people where they live, i.e., homes, shops, and local dispensaries, as well as in clinics and hospitals and that people must know how to use them.

Health care personnel should be trained to respond to patients who fail to improve after receiving any antimalarial treatment. It is important to distinguish between drug failure (represented by persistent parasitemia) and an inaccurate initial diagnosis in patients who remain symptomatic despite having received antimalarials. In fact, in most in vivo trials, very few children have both persistent parasitemia and fever unless RIII-resistant parasites exist. To make this distinction in patients with persistent or recrudescent fever, health care personnel should perform a thorough physical reexamination and a microscopic search for peripheral blood parasites. Subsequent treatment should be based upon these clinical and laboratory findings.

## Managing patients with complicated malaria

**Introduction.** In sub-Saharan Africa, the vast majority of severe and complicated malaria occurs in children less than 5 years of age who are infected with *P. falciparum*. Nonimmune individuals are also at risk of developing life-threatening falciparum malaria, but they represent a small fraction of patients in sub-Saharan Africa with life-threatening malaria.

The clinical spectrum of severe malaria in children is different from that in adults. Adults with severe falciparum infections may develop multiorgan system failure (adult respiratory distress syndrome, hemorrhagic diatheses, and hepatic and renal failure). Among children, complicated malaria is manifested as two clinical syndromes: cerebral malaria and severe anemia.

Cerebral malaria may evolve over the course of 24-36 hours, beginning with such nonspecific signs and symptoms as fever, malaise, and headache. Very often, however, children begin convulsing or lapse into coma without any discernible warning (Box 2.4). The deceptive calm of the earlier stages of the infection and the rapidity with which symptoms can develop require that interventions be delivered promptly (Molyneux et al. 1989).

Life-threatening anemia can develop rapidly in patients with heavy parasitemia, or it may develop more slowly, over the course of several incompletely treated or clinically undetected infections. The clinical picture is the same, regardless of the speed with which it evolves: patients are pale, breathless, easily fatigued, and often slightly confused (Lackritz et al. 1992a). Once cardiorespiratory compromise is evident, blood transfusion is required. For a more complete discussion of anemia, see pages 24-28.

**Differential diagnosis of complicated malaria**. Altered consciousness is the hallmark of cerebral malaria, although its clinical presentation can also include convulsions, frank coma, confusion, abnormal respiratory rate or rhythm, hypertonicity, and posturing (WHO 1990). As in uncomplicated malaria, the differential diagnosis of altered consciousness in an African child includes a variety of illnesses (Box 2.5). In patients with a clinical picture consistent with cerebral malaria, antimalarial treatment should be administered while sequential blood samples taken at 8-12 hour intervals are examined for malaria parasites. Parasitemia may be found in patients unconscious for reasons other than malaria. Therefore, the clinical decision to treat a given patient for cerebral malaria must include consideration of the local epidemiology of severe malaria and an aggressive search for other etiologies (e.g., meningitis). When there is doubt, treatment should be started promptly and continued until the diagnosis is clarified.

**Quantifying altered consciousness**. Describing altered consciousness in an operationally useful way has been made easier by the development and validation of a coma scale. The Blantyre (Malawi) Coma Score (Molyneux et al. 1989) is helpful both in recognizing and following pediatric patients with severe malaria (Table 2.3). It is easily taught and learned, can be easily performed at the bedside, requires no special equipment, and has very little interobserver variability.

**Table 2.3 Blantyre Coma Score**

| Best Motor Response* | | Best Verbal Response* | | Eye Movements | |
|---|---|---|---|---|---|
| Localization | 2 | Normal cry | 2 | | |
| Withdrawal | 1 | Abnormal cry | 1 | Follows** | 1 |
| None | 0 | None | 0 | Does not follow | 0 |

* Response to a painful stimulus (sternal rub, pressure on supraorbital ridge, or nailbed).
** Follows a bright object, mother, or examiner's face.

**Box 2.5 Differential Diagnosis of Altered Consciousness**

Care should be taken to exclude other causes of altered consciousness in children: **meningitis, hypoglycemia, bacteremia, severe anemia**. Each requires specific therapy and may be fatal if untreated.

The confirmatory diagnosis of meningitis is made when bacteria are identified in and cultured from the cerebrospinal fluid (CSF). The culture usually requires several days; antibiotic treatment is usually started on the basis of a cloudy appearance or gram stain of the CSF when the lumbar puncture is performed. Infected CSF is characteristically "cloudy" because of the increased number of white blood cells present.

Hypoglycemia (low blood sugar) can be caused by malaria, quinine treatment, any severe infection (sepsis), gastroenteritis, and starvation. Hypoglycemic individuals can become confused, lose consciousness, or have convulsions. There are no reliable clinical clues for hypoglycemia, but blood glucose levels can be estimated easily at the bedside using a glucosometer. This allows the treatment (50% dextrose, intravenous) to be given immediately.

Blood cultures are required to make the diagnosis of bacteremia. Sophisticated laboratory facilities (sterile culture systems, incubator) are required, so firm diagnoses may not be possible in certain settings. However, a recent study from western Kenya suggests that up to 25% of pediatric hospital deaths were associated with bacteremia (Lackritz et al. 1992b).

Cerebral oxygenation can be impaired in patients with severe anemia (<5 g/dL or 15% hematocrit), especially when the basal metabolic rate is increased as it is in patients with fever. Clinical examination and a hemoglobin or hematocrit measurement can confirm this diagnosis.

If a child is able to localize a painful stimulus (score 2), cries normally in response to painful stimuli (score 2), and can visually track an object (score 1), the child scores "5" and does not have significant cerebral impairment.

For research purposes, children with *P. falciparum* parasitemia and coma scores of 2 or less in the absence of other causes of altered consciousness are considered to have cerebral malaria. They require parenteral medication and careful clinical attention.

Any altered consciousness is cause for concern (regardless of parasitemia); in malaria-endemic areas, sick children who meet the local epidemiologic profile and who are unable to take medicines by mouth should be treated as if they have cerebral malaria.

**Specific antimalarial treatment**. Children with cerebral malaria are unable to swallow and require parenteral treatment. CQ resistance is now widespread among *P. falciparum* parasites (Box 2.2) and for this reason, patients with severe malaria, particularly with altered consciousness, should be treated with quinine dihydrochloride or its stereoisomer, quinidine gluconate, by slow IV drip. When possible, the drug should be administered intravenously; pharmacokinetic studies indicate that therapeutic concentrations and steady-state levels of drug are present shortly after the administration of a loading dose by slow IV infusion (Winstanley et al. 1992; Mansor et al. 1990). At least 3-4 doses of drug during at least 24 hours are required to attain a similar state in the absence of a loading dose. Rapid infusions of quinine stimulate pancreatic release of insulin and can precipitate hypoglycemia (Taylor et al. 1988). This complication can be avoided if the quinine is administered slowly (during 2-4

hours) and a continuous source of glucose is provided (5% dextrose, 80 ml/kg during 24 hours through IV or nasogastric routes). Parenteral treatment with quinine should be continued until the patient is alert enough to eat and drink at which point treatment can be continued with either quinine tablets (for 7 days) or with a single treatment dose of SP.

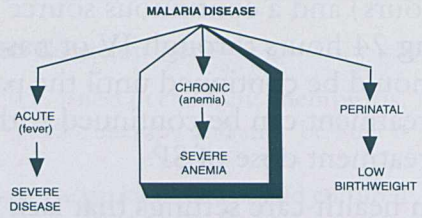
In health-care settings that lack the capacity to establish and maintain IV infusions, quinine can be administered as an IM injection (Mansor et al. 1990; Schapira et al. 1993). Patients with Blantyre Coma Scores of 3-4 can be treated with IM quinine entirely at peripheral health care facilities. Those with Coma Scores ≤2 should be referred to a center in which IV infusions and more intensive medical and nursing care are available. When a cerebral malaria patient is transferred from a remote site for more sophisticated care, treatment can be accelerated by giving the initial dose(s) of quinine via the IM route before or during the transfer. The loading dose of quinine (20 mg/kg) should be split into two 10 mg/kg doses given 4 hours apart to minimize the risk of precipitating hypoglycemia.

**Supportive care.** Cerebral malaria patients also require good supportive care to minimize the complications associated with coma. Patients should be nursed lying on their sides to decrease the chances of aspirating after vomiting. Regular assessments of the coma score are helpful; the most common causes of a decrease in coma score after the start of treatment are an unwitnessed convulsion, hypoglycemia, or the rapid development of life-threatening anemia. Each of these requires a specific therapeutic intervention (anticonvulsants, 50% dextrose, packed red blood cell or whole blood transfusion). A steady supply of fluids and glucose is essential; however, overhydration should not occur. These fluids can be administered by IV infusions or through nasogastric tubes, and they should be continued until patients are able to eat and drink.

## Acute malaria: the future

Even with the best available care, the in-hospital mortality rate for severe and complicated malaria in African children is about 20% (White et al. 1987; Molyneux et al. 1989). Quinine-resistant *P. falciparum* exists in Southeast Asia and is likely to spread to Africa. Efforts to develop and evaluate new drugs (e.g., halofantrine, artemisinine compounds) and to pursue novel approaches to the treatment of acute malaria (complicated and uncomplicated) should continue. However, to reduce overall (as opposed to in-hospital) mortality, it is critical to identify those at risk of developing severe disease and to take specific measures to prevent infection and illness. Efforts are under way to identify epidemiologic and host genetic factors that will predict which children are at risk for severe disease. Interventions designed to halt the progression to life-threatening disease can then be targeted to this group.

# RECOGNIZING AND MANAGING THE CHRONIC EFFECTS OF MALARIA: ANEMIA




## Introduction

Recurrent or chronic *P. falciparum* infections occur in areas where transmission is intense or resistance to commonly used drugs exists. The most common clinical presentation of chronic malaria is anemia, a decrease in the number of red blood cells (RBCs) in circulation. The destruction of parasitized blood cells is an inevitable consequence of malaria infection; in addition, malaria infection may impede RBC production by unknown mechanisms and may increase the destruction of unparasitized RBCs.

Blood transfusions are required to treat severe anemia. Largely for technical reasons (collecting, storing, and preparing blood for transfusion requires special equipment and expertise), patients requiring blood transfusions must be hospitalized. The spread of the human immunodeficiency virus (HIV) in sub-Saharan Africa has endangered the blood supply (Box 2.6) at the same time that the spread of CQ-resistant parasites, by increasing the number of inadequately treated patients, has created a larger population of anemic individuals. Against this backdrop, the issues of diagnosis, management, and prevention of chronic anemia assume greater urgency and importance (Box 2.7).

**Box 2.6 Transfusion-associated HIV Infection**

Studies in Zaire have shown that pediatric blood transfusions, given primarily for the treatment of malaria-associated anemia, account for an estimated 25% of pediatric HIV infections and for 40% of HIV infections among children older than 12 months of age (St. Louis et al. 1993).

## At-risk groups

As in acute malaria, the local epidemiology of malaria is a major determinant of risk groups for chronic malaria; the other contributing factor is drug efficacy. Individuals are unlikely to develop chronic malaria if treatment of the acute disease eliminates parasites from the peripheral blood.

**Box 2.7 Development of Anemia**

In areas of stable malaria transmission, younger children are more susceptible to developing anemia. Studies in western Kenya identified an age-specific population at risk for death from severe anemia. Among hospitalized patients, those less than 2 years of age were at greatest risk for severe anemia, blood transfusion, and anemia-associated mortality. Of all hospitalized children with hemoglobins <5 g/dL, 93% were under 2 years of age (<24 months old) (Lackritz et al. 1992a).

Among all blood transfusions given in three university hospitals in Côte d'Ivoire and in one district hospital in Kenya, two-thirds were given to children, and approximately 20% of all hospitalized children were given blood. Twenty-nine percent of all children admitted to a Kenyan district hospital had Hb <5.0 g/dL; they had a mortality rate of 18% (compared with an 8% mortality rate among children with Hb ≥5.0 g/dL). Children less than 36 months of age accounted for 92% of all children with Hb <5.0 g/dL, 92% of ali transfusions, and 87% of all in-hospital deaths.

Findings were similar in the communities surrounding the above-mentioned hospital in western Kenya: children less than 36 months of age had the highest prevalence of anemia and severe anemia and were the only age group in which malaria parasitemia was associated with anemia. Older children (70%) and women (30%) were often parasitemic, but there was no association between malaria parasitemia and anemia in these older age groups.

Among this very young age group, malaria and nutritional deficiencies are the two most important causes of anemia. Other causes, e.g., hookworm infestation, are not important until children are older. Sickle cell disease, when it occurs, may also cause anemia in children.

## Definition of anemia

The normal range for hemoglobin concentration is between 11-15 g/dL (Table 2.4) (WHO 1968).

**Table 2.4 World Health Organization Definitions of Anemia**

| Age | Hemoglobin (Hb) (g/dL) |
|---|---|
| Children 6 mos.-6 yrs. | <11 |
| Children 6-14 yrs. | <12 |
| Adult men | <13 |
| Adult women | <12 |
| Pregnant women | <11 |

Table 2.5 indicates widely accepted hemoglobin and hematocrit ranges for mild, moderate, and severe anemia.

**Table 2.5 Hemoglobin and Hematocrit Ranges for Anemia**

| Degree of Anemia | Hemoglobin (Hb)(g/dL) | Hematocrit (Hct) (%) |
|---|---|---|
| Mild | 8 - 11 | 25 - 34 |
| Moderate | 5 - 8 | 15 - 24 |
| Severe | <5 | <15 |

## Recognizing anemia

**Clinical diagnosis of anemia**. Patients with mild or moderate anemia are usually asymptomatic, and most diagnoses at this stage are made incidentally in the process of investigating other complaints.

Severe anemia can be detected on physical examination: patients have pale tongues, conjunctivae, nailbeds, and palmar creases. Patients with life-threatening anemia manifest signs and symptoms of cardiac failure. (Box 2.8).

The clinical syndrome of life-threatening anemia is not circumscribed by a fixed range of hemoglobin concentrations, but is determined by the hemoglobin concentration, the rapidity of the fall in hemoglobin, the patient's physical condition, and the patient's level of activity (Box 2.9).

**Laboratory diagnosis of anemia**. The laboratory determination of hemoglobin concentration can confirm and quantify the clinical impression of anemia. Hemoglobin concentration can be determined by several different methods, and reasonable estimates are possible even without electricity.

An alternative to hemoglobin concentration as a measure of anemia is the packed cell volume, or hematocrit. A small sample of blood is centrifuged, and the proportion of the total volume of red blood cells is determined (normal range 35%-45%). In general, the hematocrit (%) is approximately three times the hemoglobin concentration (g/dL); the two measurements are essentially interchangeable.

Inexpensive laboratory tests are urgently needed to detect anemia early and prevent the inappropriate use of blood transfusion.

**Box 2.8 The Pathogenesis of Life-threatening Anemia**

The function of hemoglobin is to carry oxygen to body tissues. When the supply of hemoglobin is diminished, as it is in anemic patients, the cardiovascular system compensates by delivering more blood to the tissues. To do this, the heart beats more rapidly. The patient breathes faster, increasing cardiac output. Eventually, if the hemoglobin concentration falls low enough, quickly enough, the heart cannot supply enough blood, and the entire cardiovascular system begins to fail. The level of hemoglobin concentration at which this occurs depends on tissue needs. These increase with exertion, for instance, and with fever. Therefore, patients who are asymptomatic at rest may develop the signs and symptoms of "high-output" cardiac failure if they become infected, or if they try to increase their activities.

**Box 2.9 Physical Findings in Anemia**

The degree of anemia in an individual can be estimated by inspecting areas of the body where blood circulates close to the surface: in nail beds, palmar creases, and conjunctivae. These areas become noticeably pale when the hemoglobin concentration falls to 5-6 g/dL.

When anemia is severe enough to cause cardiac failure, the usual signs and symptoms of this syndrome are evident: rapid heart rate, shortness of breath, and enlarged liver. Patients may often be drowsy and confused because of insufficient flow of oxygenated blood to the brain.

### Managing chronic malaria: objective

- To prevent anemia-associated mortality.

### Managing chronic malaria: strategies

- Recognize patients with mild/moderate malaria-associated anemia and provide effective antimalarial treatment.
- Recognize patients with life-threatening anemia and provide supportive care and transfusion with blood screened for HIV and hepatitis B and C.

### Managing patients with chronic malaria: anemia

**Mild and moderate anemia**. Patients with mild or moderate anemia are often asymptomatic, and the anemia is usually only recognized incidentally. When the anemia is associated with malaria, a significant improvement in hematologic status ensues from effective antimalarial treatment. Life-threatening anemia is less likely to develop if patients with malaria-associated anemia are recognized early and treated properly (Box 2.10).

**Box 2.10 Hematologic Recovery with Proper Treatment**

Studies in Zaire, Kenya, and Côte d'Ivoire have identified malaria as an important risk factor for severe anemia in both community and hospital studies. With the geographic extension and intensification of chloroquine (CQ) resistance, many areas have reported an increase in the proportion of children presenting to clinics with malaria and anemia. In Kenya and Malawi, children with malaria and anemia (Hb <8g/dL) were randomly assigned to treatment with either CQ or sulfadoxine/pyrimethamine (SP). Those who received SP demonstrated twice the level of hematologic recovery than those receiving standard CQ therapy. Persistent parasitemia is a major contributor to anemia; effective treatment can significantly improve pediatric hematologic status in areas of CQ resistance (Bloland et al. 1993).

**Severe anemia**. Treatment decisions for severe anemia are based on the clinical condition of the patient. When the anemia is not life-threatening (see below), it can be managed conservatively with rest as necessary, antimalarial drugs, nutrition, and micronutrient supplementation (iron, folate). Anemic children with signs of cardiac failure are at high risk for dying.

**Blood transfusion**. Laboratory capacities to group and cross-match blood from both donor and recipient and to screen donor blood for anti-HIV antibodies are prerequisites for safe blood transfusion (Box 2.11).

**Box 2.11 Transfusion and Survival**

Studies in Kenya compared survival of severely anemic children who were transfused with that of children who, because of shortages of supplies and banked blood, were not transfused (Lackritz et al. 1992a). Transfusion improved survival, but only among children with hemoglobins below 5.0 g/dL who also had clinical evidence of cardiorespiratory distress (grunting, intercostal retractions, or nasal flaring). Because of reliance on family donors for blood, transfusions were often delayed. Severely anemic children died early in the course of their hospitalization, and transfusions given 2 or more days after hospitalization were not associated with decreasing risk of death. Had transfusions been limited to children with hemoglobin <5.0 g/dL and evidence of distress and administered within 2 days of admission, the number of transfusions would have been reduced by nearly half without increasing mortality.

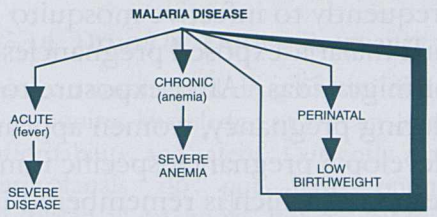
Children with life-threatening anemia should receive 10-15 ml/kg packed red cells. If it is not possible to administer packed cells, then 20 ml/kg whole blood should be given (WHO 1990).

Administering blood to patients in cardiac failure can be dangerous, because the extra fluid may overwhelm the cardiovascular system. Blood transfusions should be given slowly (6 hours). Diuretics will also help by removing excess fluids.

Other supportive measures are important to improve survival of severely anemic children. Patients receiving blood transfusions should be observed frequently so that complications can be recognized and treated promptly.

**Postdischarge follow-up**. Recent data from Kenya suggest that severely anemic patients who survive hospitalization (with or without blood transfusion) remain at greatly increased risk of dying within 2 months of discharge (Lackritz et al. 1992b). Further research is required, but these data suggest that in-hospital care may have a limited effect on longer-term survival and that management of severely anemic children may require more assiduous outpatient followup.

## CONTROLLING MALARIA IN PREGNANT WOMEN




### Introduction

In most of sub-Saharan Africa, malaria infection and higher density parasitemia are more common in pregnant women than in nonpregnant women of comparable age and from the same area (McGregor 1984). In areas with lower levels of malaria transmission, women have limited exposure to the parasite and lower levels of acquired immunity. In these areas, malaria infection causes maternal illness and fetal loss through abortion or stillbirth more often than LBW. However, because malaria transmission in most of sub-Saharan Africa is high, the main effect of malaria in pregnancy is LBW.

Low birth weight is the most important risk factor for neonatal and early infant mortality (Box 2.12). Malaria is one of several causes of LBW in populations of sub-Saharan Africa. Numerous maternal characteristics including short stature, low pre-pregnancy weight, low weight gain during pregnancy, and severe anemia are also associated with LBW. A malaria-specific intervention should be able to reduce the incidence of LBW, but the reduction will be proportional to the LBW attributable to malaria.

**Box 2.12 Low Birth Weight**

Low birth weight (LBW) is defined as birth weight of <2500 grams. LBW is the primary risk factor for neonatal and early infant mortality in both developed and developing countries. In developing countries, neonatal mortality rates (NMRs) in babies with birth weights of 2000-2499 grams and births weights of <2000 grams are approximately 2 and 11 times greater, respectively, than the NMR in normal birth weight babies.

Prematurity (gestation <37 weeks) and intrauterine growth retardation (IUGR [low weight for gestational age]) are the two contributors to LBW. Compared with NMRs in normal birth weight babies, NMRs in IUGR babies and premature babies are approximately 2 and 10 times greater, respectively.

Malaria has been recently shown to contribute to both IUGR and prematurity (Steketee et al. 1993).

Proper planning for a malaria control program for pregnant women requires certain country- or region-specific information: the prevalence of malaria in pregnant women by parity, the incidence of LBW by birth order, the incidence or prevalence of other adverse effects of malaria in pregnant women (e.g., febrile illness, anemia), and the efficacy of antimalarial drugs for use in pregnancy.

### At-risk groups

Women in their first malaria-exposed pregnancy are at highest risk for the adverse effects of malaria (Box 2.13). In areas of high endemicity where women are exposed

frequently to infective mosquito bites, most first malaria-exposed pregnancies are among primigravidas. After exposure to malaria during pregnancy, women appear to develop a pregnancy-specific immune response, which is remembered in subsequent pregnancies. Consequently, a woman in her second pregnancy has acquired some ability to control malaria infection, and she is less likely to develop high placental and peripheral parasitemia and thus to suffer their effects (anemia and LBW). By the time a woman has had several malaria-exposed pregnancies, she will have developed a relatively high degree of pregnancy-specific immunity and may be considered protected.

Malaria infection in primigravidas results in high parasite densities and is associated with LBW; malaria infections in subsequent pregnancies are of lower parasite density and contribute less to LBW (Steketee et al. 1987; Steketee et al. 1988). In addition, LBW is most common in firstborn babies, regardless of other factors such as malaria. Consequently, primigravidas and secundigravidas should be considered the groups at highest risk for adverse malaria-associated perinatal outcomes.

In settings where malaria transmission is highly seasonal, pregnant women are particularly at risk during and shortly after the high transmission season. In these locations, the interventions may be most effectively targeted to pregnant women only during these seasons.

**Box 2.13 Malaria During Pregnancy**

From work in The Gambia, McGregor (1984) has described malaria in pregnant women in the following way: Women of child-bearing age have developed a high degree of immunity to the malaria parasite through repeated exposure and are not generally susceptible to the effects of severe clinical malaria. However, pregnancy establishes within this immune host a highly vascular organ (placenta) that shields the parasite from destruction by extrauterine immune effector mechanisms and permits localized parasite replication. This shelter appears temporary and the presence of the parasite in uterine and placental vasculature induces local responses that effectively restrict parasite replication. These local responses are least effective in the 'naive' uterine-placental interface of primigravidas, but increase in subsequent malaria-exposed pregnancies.

Although the immunologic mechanisms necessary to establish and maintain the local response have not been further delineated, women in the first malaria-exposed pregnancy are at greatest risk and need targeted control programs.

Following delivery of the baby and placenta (the repository of parasites), the peripheral parasitemia in these women is rapidly cleared without further treatment with antimalarials (Nguyen-Dinh et al. 1988).

## Managing malaria in pregnant women: objectives

- To reduce malaria-associated LBW.
- To reduce maternal and fetal morbidity and mortality associated with malaria infection.

## Managing malaria in pregnant women: strategies

Specific strategies are determined by the baseline data that define the malaria epidemiologic setting and by the level of prenatal care available in the community. On the basis of these considerations, three strategies emerge:

- Treat acute episodes of malaria.
- Prevent asymptomatic malaria infection with regular treatment or with chemoprophylaxis using either therapeutic or suppressive doses of an antimalarial drug.
- Prevent infection by reducing the risk of infective mosquito bites.

## Managing pregnant women with malaria

**Early recognition and treatment of malarial illness**. Febrile illness in pregnant women should be treated with an antimalarial drug. The choice of antimalarial drug depends on efficacy, safety, availability, and affordability (Box 2.14). Chloroquine is the first choice in areas where it remains highly effective, but such settings are increasingly uncommon. In African settings with CQ-resistant parasites, SP combinations or quinine are effective alternatives. Because of the high risk associated with malaria illness in pregnant women, other antimalarials (mefloquine, halofantrine) could be used, even though less information on their safety is available.

**Preventing malaria infection**. Across sub-Saharan Africa, most pregnant women with peripheral parasitemia and placental malaria infection will be asymptomatic. There are no clinical indications of infection to alert the woman or health worker to proceed with treatment. Consequently, a management strategy cannot be based solely on fever recognition and treatment. Antimalarial drugs need to be administered on a regular schedule during pregnancy; they will have both therapeutic (for women who are parasitemic at the time of treatment) and prophylactic effects.

**Selecting antimalarial drugs for prevention during pregnancy**. Only a limited number of effective antimalarial

**Box 2.14 Drug Use During Pregnancy**

Selecting an antimalarial drug for use during pregnancy requires knowledge of efficacy, availability, affordability, and safety. Currently available antimalarials do not have optimal characteristics in all categories, but choices must be made. The following may be useful in the decision process:

**For treatment of an acute malaria attack:** This is a serious problem that threatens the life of both mother and fetus; therefore, the characteristics of efficacy and availability override safety and affordability. Quinine alone for 7 days, quinine treatment for 3 days, followed by sulfa-pyrimethamine (SP) combinations, SP alone, mefloquine, or halofantrine are likely to be highly effective. Chloroquine (CQ) can be used for *Plasmodium vivax, P. malariae,* and *P. ovale* infections where it remains highly effective and in the few areas where *P. falciparum* is fully CQ sensitive.

**For treatment or prevention of parasitemia (asymptomatic):** Efficacy, availability, safety, and affordability are all important characteristics to be considered in the decision process. An initial treatment dose is required to clear parasitemia from the high proportion of pregnant women who will have asymptomatic parasitemia. In settings where it remains highly effective, CQ can be used for this treatment (25 mg base/kg) and then continued as weekly prophylaxis (5 mg base/kg, equal to 300 mg base per week). With the increasing number of areas where CQ is no longer highly effective, alternatives include SP, biguanides (proguanil and chlorproguanil), and pyrimethamine. Resistance to pyrimethamine is widespread and its efficacy must be proven before choosing this alternative. The biguanides are not recommended as initial treatment and must be given daily for prophylaxis. Compliance is a problem, and efficacy must be monitored. Recent studies with SP suggest that single dose therapy at first antenatal clinic and again at the beginning of the third trimester was highly effective in a highly endemic area in treating and preventing malaria. This regimen would be affordable and easily deliverable in conjunction with tetanus toxoid administration, which should be given at approximately the same times.

Other drugs (e.g., mefloquine, halofantrine) are less available and more expensive; and less is known about their adverse effects during pregnancy.

drugs can be used during pregnancy because of pharmacologic characteristics and potential adverse effects. With spreading parasite resistance to CQ, the number of available alternative effective drugs is an important consideration (Box 2.14).

Before a drug is chosen, logistics issues, including availability and affordability, must be examined. If prenatal care is provided through clinic services, all clinics must have a ready supply of the drug; if care is provided in communities with local attendants, drugs must be made available in the community. Where women must purchase the drug themselves, it must be affordable, especially for the poorest women, who may need it most.

Finally, investigators have noted that acceptance and compliance by pregnant women are critical in establishing an effective program (Heymann et al. 1990). In Malawi, where local custom suggests that women avoid bitter food and medicine during pregnancy, bitter-tasting CQ, which had been recommended as the antimalarial for chemoprophylaxis in pregnancy, was met with poor acceptance and compliance by the women. Intermittent treatment that could be given at monthly (or less frequent) antenatal clinic visits or at similar intervals in a community-based care system would constitute a more effective intervention simply by eliminating the need for compliance at home with a weekly or daily dosing regimen.

The epidemiology of malaria, the parasite's response to antimalarial drugs, and the epidemiology of LBW affect the prevention program. If an evaluation demonstrates a high prevalence of LBW (>15%) in primigravidas and of malaria infection (>15%) in primigravidas at the time of enrollment in antenatal clinics, treatment with an effective antimalarial drug will reduce placental infection and lower the incidence of LBW. Intermittent therapy or regular chemoprophylaxis will then be necessary to keep the placenta parasite-free.

**Box 2.15 Sulfadoxine-pyrimethamine Use During Pregnancy**

In 1992, a study in Malawi investigated the use of sulfadoxine-pyrimethamine (SP) as an effective and practical drug in Africa for control of malaria during pregnancy. During the rainy and postrainy season, women (N=566) in their first or second pregnancies who were between 16-32 weeks gestation were enrolled and placed on one of three antimalarial regimens: chloroquine (CQ) treatment followed by CQ weekly prophylaxis; SP treatment followed by CQ weekly; SP treatment twice–at first visit and again in early third trimester. Outcomes measured were parasitemia and placental infection at delivery.

Placental infection was seen in 50% of women on CQ alone, 37% of women on SP-CQ, and only 9% of women on SP/SP. Women receiving the two-dose SP regimen had a significantly lower prevalence of placental infection than women on either CQ regimen, $p<0.05$. The two-dose regimen could be coupled with tetanus toxoid administration and would provide a simple, affordable, and effective malaria prevention regimen for pregnant women in areas of CQ-resistant *P. falciparum*.

Although few affordable, safe, and effective drugs are available for use during pregnancy, SP has recently been shown to be effective when given as intermittent therapy (Box 2.15). The administration of a prevention regimen should be limited to pregnant women in their first and second pregnancies if local epidemiologic studies confirm that these are the at-risk pregnancies. If malaria transmission is highly seasonal, these measures could be applied specifically during the high transmission season (beginning with the start of the increase in transmission and continuing for 2-3 months after transmission has returned to low levels).

## REDUCING MALARIA TRANSMISSION

### Introduction

By increasing malaria morbidity and mortality and adding a layer of complexity to the management of malaria illness, the extension of CQ-resistant *Plasmodium falciparum* has forced health professionals to broaden malaria control efforts. Older methods are being reconsidered; new measures are being sought.

A number of malaria control measures–environmental, barrier, chemical, and biologic–have the potential to reduce malaria transmission (Box 2.16). They can either reduce the vector population or interrupt the vector-human contact.

**Box 2.16 Transmission Prevention**

1. **Environmental measures** can decrease transmission by decreasing vector breeding sites through water management (drainage, ditching, filling, or weed removal).
2. **Barrier measures** impair transmission by limiting physical contact between vector and host. These personal protection methods include clothing, bed nets, and curtains. Recently, insecticides have been used to impregnate bed nets and curtains, resulting in a combination of the barrier and chemical control measures.
3. **Chemical measures** affect transmission by killing anopheline mosquitoes or their larvae with insecticides. Measures include indoor residual spraying with insecticides (e.g., DDT, malathion, fenitrothion, and bendiocarb); outdoor application of larvicides that attack the mosquito larvae in their breeding sites (e.g., temophos, methoprene); indoor and outside space spraying (malathion); and personal protection measures such as repellents and coils, which use chemicals such as DEET, pyrethrins, and pyrethroids.
4. **Biologic measures** interfere with transmission by increasing the number of anopheline predators, which include fish (e.g., top-feeding minnows), nematodes, and aquatic fungi that show promise as larvicidal agents, and a toxin of strains of the bacteria *Bacillus thuringiensis*. Many of these remain as research tools and have not been widely employed.

Although these various methods may be quite effective when properly applied, they are all costly; each has major technical or labor requirements and may be difficult to sustain.

- Environmental modification is appropriate where breeding sources are confined and easily identified and where a readily available, moderately skilled, labor force exists (e.g., in urban areas); thus, this method may be less practical in rural or semirural areas.
- Chemical control measures must be carried out within a vertical program and require trained staff and a continuous supply of insecticide and spray equipment. These measures have limited applicability for a primary health care program. Use of pesticides, like the use of antimalarial drugs, engenders resistance. Detecting resistance requires frequent monitoring and, once detected, newer, more expensive insecticides must be substituted.

- Biologic methods, although intriguing, have not been effective in large-scale field settings.

Environmental, chemical, and biologic methods have not been easily initiated or sustainable in African malaria control efforts. The expense involved and the requirement for sustained effort combine to compromise their potential efficacy.

However, among the barrier methods, insecticide-impregnated bed nets (IBNs), have generated much interest in recent years. Because some studies have suggested that IBNs have great potential for individuals and communities, their use is being examined in different epidemiologic settings in Africa.

## Reducing malaria transmission with insecticide-impregnated bed nets

Bed nets are an age-old technique for decreasing human contact with insects and increasing privacy. Recently, bed nets impregnated with an insecticide, commonly one of the nontoxic synthetic pyrethroids, have been evaluated for malaria prevention. Impregnation enhances protection by killing the insects on contact or by repelling them from the sleeping area. The anticipated effects of widespread use of IBNs are a decline in human-vector contact, a decrease in the density of infective vectors, and a reduction in malaria transmission, with a consequent decline in malaria-related morbidity and mortality (Greenwood and Baker 1993).

Several studies have indicated that IBNs are effective in reducing inoculation rates, in reducing the incidence of malaria disease, and in lowering malaria-related mortality (Box 2.17).

### Box 2.17 Efficacy of Insecticide-impregnated Bed Nets

The Centers for Disease Control and Prevention investigations of impregnated bed nets (and curtains), in collaboration with the Kenya Medical Research Institute, indicated significant decreases after 1 year of use in the presence of *Anopheles gambiae*, in entomologic inoculation rates (EIRs), in acquisition of *Plasmodium falciparum* infection (malaria incidence), in development of high parasitemia levels (>2,500 parasites/$mm^3$), and in the frequency of clinical malaria episodes. Transmission in the study area of western Kenya is approximately 100-200 infective bites per person per year (Beier et al. 1990).

Another widely cited recent study designed to measure the effect of permethrin-treated nets on child mortality was carried out in a population of over 20,000 in The Gambia, an area of moderate and seasonal transmission (EIR = 5-10) (Alonso et al. 1991). In 1 year among children between the ages of 1 and 4 years, overall mortality and malaria-related mortality were reduced by 63% and 70%, respectively.

However, although some studies show positive results, investigators generally agree that additional data are required to evaluate whether IBNs are effective in reducing malaria mortality in malarious areas with perennial heavy transmission. Issues requiring further study are outlined in Box 2.18.

### Target groups

Insecticide-impregnated bed nets can be targeted to two different groups:

- Individuals: While little evaluation of the effect of personal use of IBNs has been done, there is consensus that IBN use for individuals is advisable. If used correctly, bed nets reduce the person's chances of being bitten by infected mosquitoes. Families who can afford to purchase nets and keep them properly impregnated should be encouraged to do so. In the promotion of IBNs, emphasis should be placed on the value of protecting young children and women of reproductive age from sundown to sunrise.
- Communities: The use of IBNs by a high proportion of people in communities will lead to decreased malaria-related morbidity and mortality through community-wide reduction of transmission.

Mosquitoes that are diverted from biting persons sleeping under IBNs may seek others not sleeping under IBNs, thus increasing exposure to malaria parasites for the unprotected. Universal coverage is ideal, as the reservoir of gametocytes necessary to maintain malaria transmission would be greatly decreased. Therefore, efforts should be made to have as many persons as possible in a community use IBNs.

**Box 2.18 Research Issues for Insecticide-impregnated Bed Nets**

1. Studies need to be carried out in different epidemiologic milieus. To date, most studies have been carried out in areas of low transmission (entomologic inoculation rates [EIRs] in the range of 0.5-15 infective bites per person per year). Since malaria intensity and potential vector biting and resting habits differ in low and high transmission settings, evaluation of bed-net efficacy should be carried out in environments with different transmission patterns.
2. A standard methodology must be used. Many of the early studies focused on entomologic indices. Standard clinical, behavioral, operational, and economic issues should be examined.
3. Decreased sensitivity of *Anopheles* mosquitoes to permethrin-impregnated nets has been observed in Kenya. This finding identifies the need for insecticide sensitivity surveillance, efficacy studies of newer and alternate insecticidal products, and evaluation of bed-net material–insecticide-binding properties that determine the duration of insecticide effect.
4. The cumulative and long-term effects of insecticide-impregnated bed nets on parasitologic, entomologic, clinical, immunologic, behavioral, and economic indices need to be assessed over several transmission seasons. Estimating trends over time will allow an assessment of the proportional contribution of nets to health impact in light of such intervening events as local epidemics of nonmalaria illness, unusually heavy rainfall, movements of populations, and promotion of other public health interventions.

### Reducing malaria transmission: objective

- To reduce transmission of malaria infection.

### Reducing malaria transmission: strategy

- Use IBNs during nighttime sleeping hours in endemic areas.

### Factors affecting insecticide-impregnated bed-net use

Using impregnated bed nets on a community-wide basis necessitates overcoming a number of obstacles to implementing the strategy. Behavioral considerations; the

cost and financing of IBNs; the logistics involved in procuring, distributing, and impregnating IBNs; the technical training and management; and health education–all present challenges to the successful use of this intervention.

**Behavioral considerations**. The IBN intervention should be promoted in settings where *Anopheles* bite mostly indoors. The strategy will be more effective when the population involved sleeps inside during the hours of mosquito feeding and when the population is amenable to the nightly use of IBNs. Deviations from these behavioral patterns will favor continued malaria transmission.

**Cost and financing**. The cost of IBNs represents a substantial investment. A durable net costs between US$5-40, and each family, on average, requires two or more IBNs to cover adults and children. Each impregnation of the bed net, which is required every 4 to 6 months, costs about US$1. Average per capita annual income in some sub-Saharan African countries is estimated at US$300-500 per year, so the purchase and maintenance of an IBN could represent approximately 1%-10% of the annual household income.

There are also costs at the national level. Before a bed-net program is promoted, a vector assessment is advisable to determine if the mosquitoes transmitting malaria in that area are indoor-biting. This assessment is not inexpensive. If it is decided that IBNs are an appropriate strategy, and the entire population of a country is to sleep under IBNs, IBNs will need to be made or procured, purchased by households, impregnated, reimpregnated, and maintained properly. If the Ministry of Health (MOH) decides to promote IBNs as a public health intervention, a policy and a strategy for IBN-use must be established, specifying the required human and monetary resources and the role of the MOH in coordinating community participation and encouraging private enterprise and donor support.

Subsidies by organizations or the government to purchase IBNs or to impregnate them have had some success. Various organizations (e.g., UNICEF) have begun to provide nets to local health departments through cost recovery schemes. In western Kenya, over 200,000 impregnated nets have been purchased at a fixed price and then distributed in the community. In Burkina Faso, the national malaria program has established "impregnation centers" where persons can come to have their curtains and nets soaked for a modest fee. In The Gambia and Burkina Faso, programs to impregnate bed nets in all communities are receiving national and international support.

Insecticide-impregnated bed nets also have the potential to develop into a cottage industry with income-generating opportunities for members of the community. Relatively few data are available on the willingness of communities to employ bed nets as a public health measure and to make, impregnate, install, and maintain them as a business.

**Procurement and distribution**. Communities must decide whether they will manufacture or import bed nets, how they will be distributed to all households in the community, and how impregnation and regular reimpregnation can be accomplished.

**Training**. Nationals must be trained in the science and technology related to bed nets, as well as in the skills necessary to manage a bed-net program. A cadre of workers with experience in impregnating and hanging bed nets and with program management skills will be needed. Training should emphasize skills needed for the planning, management, logistics, and managerial monitoring of a bed-net program; entomology should also be included in training, although it is of lesser importance. Epidemiologic surveillance (perhaps in sentinel villages and health units) should be set up to allow continuous evaluation of the effort. Technical issues related to bed-net use are outlined in Box 2.19.

**Health education and marketing**. IBN-use must be promoted within the community and the message communicated to all households in an area. Although many of the villagers in African countries know of bed nets and have seen them in a home or marketplace, fewer than 5% use bed nets, virtually none of which are impregnated with insecticide. A recent study designed to measure the effectiveness of bed nets in areas of high transmission in Kenya found that bed-net coverage increased to 95% during the study. Bed nets were provided to village residents at no cost, and assistance was provided in impregnating and hanging them.

### Insecticide-impregnated bed nets: the future

Questions remain regarding the efficacy of IBNs in a variety of malaria transmission settings in sub-Saharan Africa. For countries interested in embarking on a local or a national program, two major questions must be answered: Will the IBNs be effective in the proposed setting? and Can the factors that affect the success of a program of IBN use be addressed satisfactorily?

As ongoing and anticipated research is completed, our understanding of the efficacy of IBNs will increase. Although the studies are time-consuming and costly, each country contemplating IBNs as an intervention should begin by evaluating local levels of transmission, i.e., measuring parasite prevalence and EIRs in representative transmission areas of the country. Results from studies evaluating IBNs in other settings with similar EIRs can then be used to predict the likely efficacy of IBNs in a particular environment.

### Box 2.19 Technical Issues for Insecticide-impregnated Bed Nets

**Bed-net models and sizes:** Bed nets can be rectangular, conical, or wedge-shaped. The rectangular model is recommended because the sleeper is less likely to touch it; thus, the mosquito cannot bite the sleeper through the net. Although nets can be made to order locally in some countries, many persons use the nets produced in Thailand because of their low cost.

**Bed-net materials:** The most common materials for bed nets are nylon, polyester, and cotton, alone or in combination. Polyethylene is also used for nets, although it is somewhat flammable and has been found unsuitable because holes develop readily. Nylon and polyester produce better results in killing and repelling mosquitos. Nylon, polyester, and polyethylene tend to be more durable than cotton. Strength of the material affects protection; nets of a lower denier (a measurement of weight of fabric) tear more easily than those made with a heavier, and therefore, stronger fabric.

**Mesh size**: Mesh (hole) size must not be so small that persons sleeping under the bed net become uncomfortable because of poor air flow and consequently do not use the net. On the other hand, the mesh size must not be so large that if the net is not properly impregnated, the mosquito is allowed to pass through. Recommended is a mesh size of 1.25 $mm^2$.

**Insecticides and dosages:** The most commonly used insecticides for impregnating bed nets are the pyrethroids, two of which are currently in use–permethrin and deltamethrin. Others are being tested. The amount needed to impregnate a bed net differs according to the insecticide used (Schreck and Self 1985).

**Impregnation procedures**: One standard approach is the following:

1. Use a clean net.
2. Calculate size of netting in meters squared.
3. Calculate amount of water necessary to soak the net to the point of saturation. The type of material used determines how much water will be needed (cotton absorbs approximately 3 times as much water as synthetic materials).
4. Calculate the total volume of insecticide needed to impregnate the net.
5. Mix the insecticide and water calculated from 3 and 4.
6. Soak the net with the solution, and then gently wring out any excess into a treatment container (plastic sack, large plastic wash tub, or vat).
7. Lay the net on a clean flat surface to dry. Drying the net on the user's mattress provides secondary benefits by controlling bed bugs and other pest insects.
8. When the net is almost dry, hang it in a shady place to finish drying.
9. Once the net is dry, hang it over the bed, using string to tie the corners of the net to the rafters or to nails. In some cases, nails may have to be provided to the homeowner. Make sure the net is low enough so that the bottom border can be securely tucked in around the bottom of the mattress, thereby preventing mosquito entry.

# PREVENTING MALARIA THROUGH CHEMOPROPHYLAXIS

## Introduction

Malaria infection and illness can be prevented with appropriate chemoprophylaxis, i.e., the regular administration of antimalarial drugs. Adequate blood levels of an effective drug will either prevent primary infection of liver cells (causal prophylaxis) or will interrupt the erythrocytic cycle (suppressive prophylaxis) once an individual has been infected. Few safe and effective causal prophylactics are available now.

Those at highest risk of developing life-threatening malaria illness (nonimmune children, travelers, immigrants) will benefit from chemoprophylaxis. The other primary target group for chemoprophylaxis is pregnant women living in malaria-endemic areas, especially those in their first and sometimes their second malaria-exposed pregnancies. The use of effective chemoprophylaxis in pregnancy has been shown to decrease the incidence of LBW infants in a population.

**Box 2.20 Experiments in Mass Chemoprophylaxis**

Greenwood and colleagues (1988) have demonstrated reductions in overall mortality, malaria-specific mortality, and number of episodes of fever associated with malaria parasitemia among children after initiation of chemoprophylaxis and treatment. In a reevaluation occurring 3 to 4 years after initiation of chemoprophylaxis in this area, children aged 3-59 months who had received chemoprophylaxis and treatment experienced a 49% reduction in mortality and a 73% reduction in clinical attacks of malaria compared with a randomly assigned placebo group (Menon et al. 1990). Studies conducted in Nigeria (Bradley-Moore et al. 1985) demonstrated improved hematologic status of persons in communities that received chemoprophylaxis with chloroquine; additional studies have demonstrated improved hemoglobin among those who received chemoprophylaxis with chloroquine. Other studies of chemoprophylaxis have demonstrated similar reductions in morbidity but have been too small to detect significant reductions in mortality.

## Chemoprophylaxis for children

A number of studies have established that chemoprophylaxis is effective in decreasing malaria morbidity and mortality among children (Box 2.20), yet mass chemoprophylaxis is not generally recommended as a malaria control strategy. One reason is that choice of drug is problematic: the most affordable drugs (CQ, proguanil) have limited use because of parasite resistance, the most effective drug (mefloquine) is currently very expensive, and other potentially useful drugs are limited by severe adverse reactions (Stevens-Johnson syndrome for SP, agranulocytosis for dapsone) or other restrictions (tetracycline is not advised for pregnant women and children <8 years of age because of the adverse staining effect on the fetus' developing teeth and because of the adverse effects on the mother's liver). In addition, there is a risk that the use of widespread chemoprophylaxis will favor the development and spread of drug-resistant parasites. Data differ on this point depending on the drug under consideration, its mode of action, and the intensity of the selection pressure exerted on the parasite. Finally, the economic and logistic demands of establishing and maintaining programs for

mass chemoprophylaxis are daunting (WHO 1992), and compliance on a population-wide basis has not been high (McCormack and Lwihula 1986).

**Targeted chemotherapy**. Certain subsets of children (those with sickle cell anemia, immune suppression, and a history of severe anemia or febrile convulsions) might benefit from chemoprophylaxis but supporting data do not exist. Are some children at higher risk for complicated malaria than others? Recently it has been shown that defined immune responses, such as tumor necrosis factor, mediate the pathology associated with severe malaria (Hill et al. 1991), but other risk factors have not been determined. If and when they are, it may be feasible to target chemoprophylaxis toward children who are known to be at increased risk of developing complicated malaria.

In an urban area of seasonal transmission in Malawi, the risks of developing severe anemia or cerebral malaria are highest during the rainy season (January-April). Children under the age of 4 years are at highest risk for these complications. The efficacy of chemoprophylaxis targeted toward this age group (or, more specifically toward children who are known to have had severe anemia or cerebral malaria) and administered only during the months of highest risk has not been studied but may well be a cost-effective approach to lowering malaria morbidity and mortality.

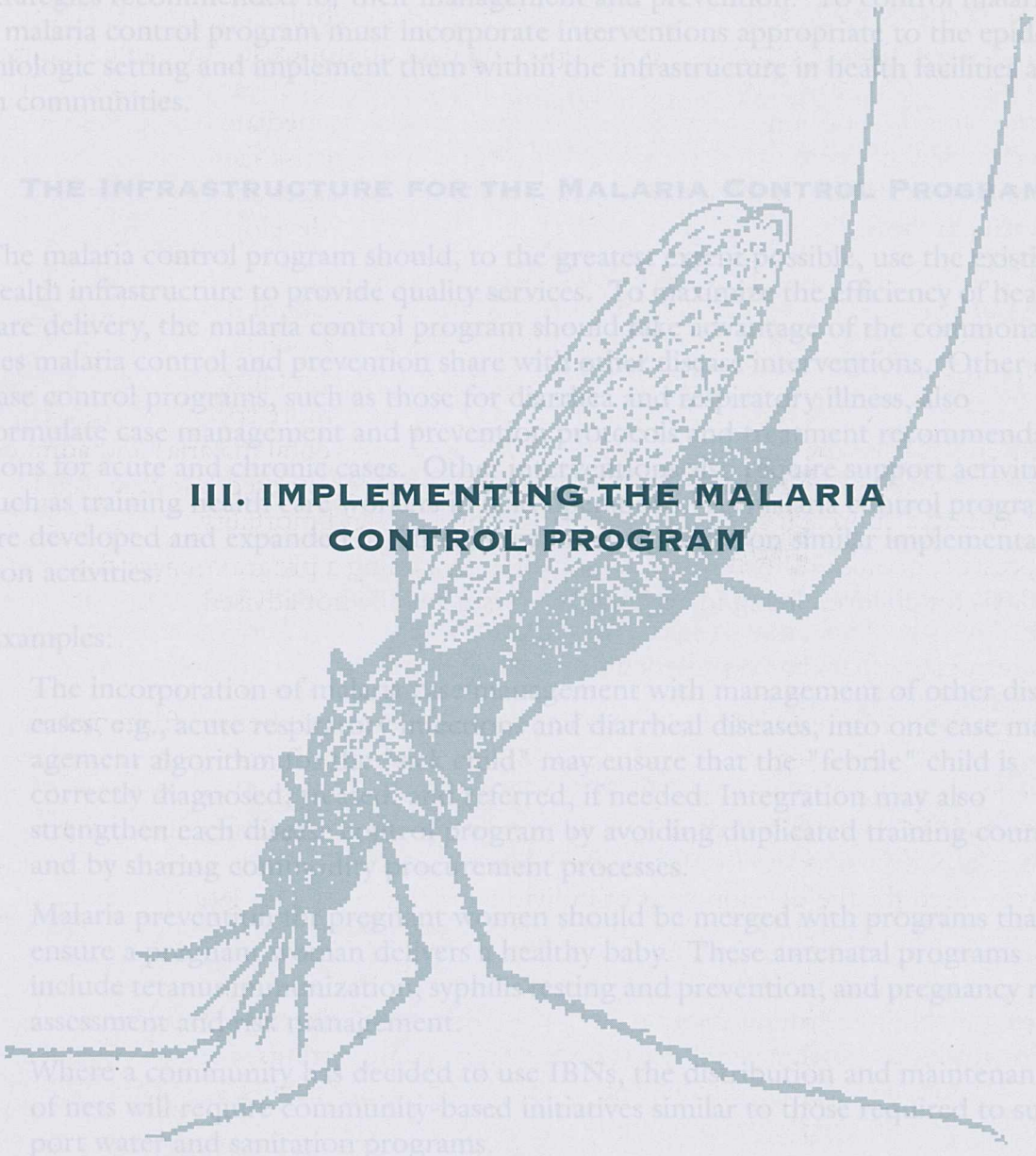
At present, because of the expense involved in sustaining a program, mass chemoprophylaxis for children living in endemic areas is generally not advised.

### Chemoprophylaxis for travelers and immigrants

Nonimmunes traveling into malarious areas for short periods benefit from malaria chemoprophylaxis. Optimal chemoprophylactic regimens will vary from area to area, depending on local drug sensitivities. The Centers for Disease Control and Prevention and WHO annually compile recommendations for short-term chemoprophylaxis; these booklets provide information for all malaria-endemic areas and should be consulted for the development of individual regimens (CDC 1993).

### Chemoprophylaxis for pregnant women

Chemoprophylaxis during pregnancy has been shown to decrease the incidence of LBW infants (Steketee et al. 1993). In the appropriate settings, a malaria-specific intervention can lower infant mortality rates. For further details, see pages 29-32.



# III. IMPLEMENTING THE MALARIA CONTROL PROGRAM

mass chemoprophylaxis are daunting (WHO 1992), and compliance on a population-wide basis has not been high (McCormack and Lwihula 1986).

**Targeted chemotherapy.** Certain subsets of children (those with sickle cell anemia, immune suppression, and a history of severe anemia or febrile convulsions) might benefit from chemoprophylaxis but supporting data do not exist. Are some children at higher risk for complicated malaria than others? Recently it has been shown that defined immune responses, such as tumor necrosis factor, mediate the pathology associated with severe malaria (Hill et al. 1991), but other risk factors have not been determined. If and when they are, it may be feasible to target chemoprophylaxis toward children who are known to be at increased risk of developing complicated malaria.

In an urban area of seasonal transmission in Malawi, the risks of developing severe anemia or cerebral malaria are highest during the rainy season (January-April). Children under the age of 4 years are at highest risk for these complications. The efficacy of chemoprophylaxis targeted toward this age group (or, more specifically toward children who are known to have had severe anemia or cerebral malaria) and administered only during the rainy season is unknown but may well be a cost-effective approach to reducing severe disease and mortality.

At present, because of the expense involved in sustaining a program, mass chemoprophylaxis for children living in endemic areas is generally not advised.

**Chemoprophylaxis for travelers and immigrants.**

Nonimmunes traveling into malarious areas for short periods benefit from malaria chemoprophylaxis. Optimal chemoprophylactic regimens will vary from area to area, depending on local drug sensitivities. The Centers for Disease Control and Prevention and WHO annually compile recommendations for short-term chemoprophylaxis; these booklets provide information for all malaria-endemic areas and should be consulted for the development of individual regimens (CDC 1993).

**Chemoprophylaxis for pregnant women.**

Chemoprophylaxis during pregnancy has been shown to decrease the incidence of LBW infants (Steketee et al. 1993). In the appropriate settings, a malaria-specific intervention can lower infant mortality rates. For further details, see pages 29-32.

## Introduction

The three facets of malaria infection and disease in Africa have been examined and strategies recommended for their management and prevention. To control malaria, a malaria control program must incorporate interventions appropriate to the epidemiologic setting and implement them within the infrastructure in health facilities and in communities.

## The Infrastructure for the Malaria Control Program

The malaria control program should, to the greatest extent possible, use the existing health infrastructure to provide quality services. To maximize the efficiency of health care delivery, the malaria control program should take advantage of the commonalities malaria control and prevention share with other disease interventions. Other disease control programs, such as those for diarrhea and respiratory illness, also formulate case management and prevention protocols and treatment recommendations for acute and chronic cases. Other interventions also require support activities, such as training health care workers in field operations. As malaria control programs are developed and expanded in Africa, they must capitalize on similar implementation activities.

Examples:

- The incorporation of malaria case management with management of other diseases, e.g., acute respiratory infections and diarrheal diseases, into one case management algorithm for the "sick child" may ensure that the "febrile" child is correctly diagnosed, treated, and referred, if needed. Integration may also strengthen each disease control program by avoiding duplicated training courses and by sharing commodity procurement processes.
- Malaria prevention for pregnant women should be merged with programs that ensure a pregnant woman delivers a healthy baby. These antenatal programs include tetanus immunization, syphilis testing and prevention, and pregnancy risk assessment and risk management.
- Where a community has decided to use IBNs, the distribution and maintenance of nets will require community-based initiatives similar to those required to support water and sanitation programs.

## Requirements for the Malaria Control Program

A malaria control program requires the following:

- Committed leadership
- A written policy
- A detailed plan for policy execution, often referred to as a "program plan"
- Successful implementation of the program plan
- A mechanism for monitoring program implementation and evaluating program effectiveness

### Leadership

Commitment must come from the leaders in the MOH–as witnessed by a written policy and by sufficient allocation of funds. A person or a clearly defined unit within the government must be given the responsibility and authority to plan and evaluate a malaria control program. If the responsibility becomes diffused or if the program lacks the necessary authority or resources to implement its plan, the malaria policy and plan are less likely to be implemented effectively.

Because the malaria control program may not be a distinct unit within the country's public health system, a malaria technical group is required. The leadership and technical expertise that can be provided by this group are essential for policy formulation and program evaluation.

### Policy

A malaria control policy provides guidelines to health care workers, program planners, and donor agencies on disease management and prevention.

**Box 3.1 Malaria Policy Contents**

- Preamble with statement of government approval
- Background
- Epidemiologic information
- Technical guidelines

The policy consists of a preamble (background information on the program), a brief analysis of the current situation, including epidemiologic information, and technical guidelines (Box 3.1). The technical guidelines state the goal of the program, identify the appropriate interventions (case management and prevention), and for each intervention, describe what health workers need to be able to do. For case management, guidelines should specify correct diagnosis, treatment, education and follow-up, and referral. For prevention interventions, guidelines should specify personal protection, chemoprophylaxis, and vector control methods. See Box 3.2 for aspects to consider when formulating technical guidelines for case management of malaria.

Policies are most useful when they are written as a brief statement (4-8 page) that is approved by government officials, and, for added advantage, by a high level technical

### Box 3.2 Technical Guideline Considerations

**Diagnosis**

*Acute:* The diagnostic tools (such as microscopy and the capability to measure hemoglobin concentration) available at peripheral health centers depend on the specific needs of that center (e.g., the number of patients seen with malaria) and its capacity to use the tools (e.g., the number of trained technicians). Referral centers should have the full range of diagnostic equipment, from thermometers to microscopes (WHO/AFRO 1992).

*Chronic:* Because managing severe anemia requires documenting the clearance of parasitemia in addition to monitoring the level of hematologic improvement, health facilities should have the capacity to perform hemoglobin or hematocrit and microscopic examination of blood smears. However, since peripheral clinics will probably not be able to have such tests available, improving clinical recognition of anemia is critical.

*Perinatal:* Health workers in antenatal clinics should be prepared to treat or provide chemoprophylaxis to pregnant women coming to the clinic. All pregnant women with malaria illness should be treated, and, depending on the local epidemiology of malaria, women in their first or second pregnancies need chemoprophylaxis.

**Treatment**

*Acute:* Because determination of an appropriate drug dose for an individual child depends on the child's age and weight, the health facility will need scales and charts that specify treatment according to age and weight. Drugs recommended in the national policy guidelines must be available. Additional supplies for treating severe malaria (IV fluids and administration sets) must also be available in facilities where parenteral therapy is given (WHO/AFRO 1992).

*Chronic:* Several malaria drugs must be available in health facilities: where there is resistance to the primary drug for malaria (e.g., CQ), a second drug(s) must also be available at the peripheral level so that children at greatest risk for the deleterious effects of chronic parasitemia can be treated to eliminate parasitemia. Once life-threatening anemia is detected, health care facilities must have either the capability of providing blood transfusions or have access to immediate referral for the patient. Capabilities include facilities for banking blood, performing typing and cross-matching, testing for HIV (and hepatitis B and C), having supplies (e.g., blood bags, administration sets) for blood administration, and having clinical proficiency for supportive care (e.g., fluid management).

*Perinatal:* Antimalarial drugs should be given under observation at the clinic to minimize the problems of low compliance that come with home administration. So that the complete treatment is given, antenatal cards should have a space for recording the treatment or prophylaxis provided (including drug dosage and timing).

**Patient education and follow-up**

*Acute:* Caretakers must be told the importance of the febrile child's completing the drug treatment schedule and returning if the fever is not cleared.

*Chronic:* As additional information is gained on the chronic complications of malaria, health facility activities may need to be modified.

*Perinatal:* Pregnant women must understand the importance of visiting the antenatal clinic once a month during pregnancy to receive antenatal care. The delivery of the malaria intervention should be coupled with other activities. For example, antenatal care should include provision of nutritional supplements and guidance and treatment with iron and folate tablets; and intermittent therapy with sulfa-pyrimethamine could be given in conjunction with tetanus toxoid administrations, which require a similar schedule during a woman's first or second pregnancy.

**Referral**

*Acute:* Appropriate management of malaria requires referral of patients with complicated illness and of patients who fail to respond to initial therapy and therefore need further diagnostic evaluation. Referral centers must be able to provide the additional diagnostic capability and the necessary treatment. If referral is not possible, malaria management at peripheral facilities must have guidelines and supplies in order to manage complicated cases. A policy of referring complicated malaria cases has the potential of centralizing life-saving medical care; the care would then be unavailable to the majority of those with life-threatening illnesses because of economic and logistic constraints.

*Chronic:* In the case of life-threatening anemia, facilities must have access to immediate referral for the patient.

advisory group. The policy must be disseminated to all levels of the government and private sector involved in its execution. The statement must be clear and comprehensive so that health workers and government officials can understand the goal of malaria control, the recommended interventions, and the strategies. The policy statement should be viewed as a dynamic document, to be revised as necessary on the basis of experience in implementing the national program.

## Program plan

A written program plan states measurable impact, outcome, and process objectives that are related to one another and to the national malaria control policy (Bryce et al. 1993) (Box 3.3).

**Box 3.3 Malaria Program Plan Contents**

- Impact, outcome, and process objectives and indicators
- Implementation plan for support activities
- Monitoring and evaluation plan

- **Impact objectives** correspond to the priority goal of the program (e.g., mortality reduction) as stated in the national policy. Time frame: 5-10 years.

  Example: By 2003, malaria-related morbidity in children under 5 years of age will be reduced by 25%.

- **Outcome objectives** correspond to the priority intervention (e.g., case management or prevention), priority target population (e.g., children under 5 years of age), and those charged with the care of the target population (health care workers, mothers, family members, etc.). Time frame: 2-5 years.

  Example: By 1998, 90% of children less than 5 years of age diagnosed with malaria in a health facility will receive the correct antimalarial treatment according to the national policy guidelines.

- **Process objectives** correspond to the various activities (training, supervision, commodity supply, surveillance, health education, operational research, etc.) necessary to achieve the intended outcomes and impact. Time frame: 1-2 years.

  Example: By 1995, 80% of health workers in a given district will be trained (or retrained) in case management protocols for malaria.

The implementation plan lists support activities and tasks to be conducted and specifies who will conduct them and when, where, and how they will be conducted. Support activities include health worker training, health worker supervision, establishment of diagnostic capabilities appropriate to the health facility level, procurement and distribution of antimalarial drugs and supplies, patient education, community education, and disease surveillance. These activities are needed to ensure that the patient receives the needed attention at the health care facility and that patients will continue appropriate care in the home. Only if the health worker is properly supported can a malaria program provide adequate case management of patients.

These support activities need to be prioritized. Resources, both human and financial, will probably be limited; clearly stating which activities have the highest priority is important so that existing resources will be used effectively.

Monitoring and evaluation plans need to be included. Monitoring plans describe how to monitor activities and tasks, who will perform the monitoring, what methods will be used, and how often monitoring will be conducted. Evaluation plans describe how to measure attainment of outcome and impact objectives, who is responsible for evaluations, what methods and data sources will be used, how often data will be collected, and to whom it will be reported. The plan should also specify how monitoring and evaluation results will be used to improve program activities and achieve objectives.

A program plan should include a detailed time line and budget for conducting activities. It may also describe the organizational structure of the malaria control program.

### Program implementation

To achieve the objectives, the program plan needs to be implemented fully. Therefore, the Malaria Control Program needs to maintain a technically capable staff that can develop and carry out the plan.

Program monitoring can assess whether the program plan is being implemented as designed–that health worker training is occurring as planned, supervision is being conducted, the necessary commodities are available in the facilities specified in the implementation plan, needed data are being collected by the health information system, and health education materials are being disseminated to the appropriate groups. If these activities are not being conducted as specified, leadership should determine why the activities are not being carried out and institute remedial actions to ensure that activities do occur as originally planned.

### Monitoring, evaluation, and operational research

To ensure the effectiveness of specific interventions and of the overall program, a Malaria Control Program must have monitoring, evaluation, and operational research systems, which are outlined in the program plan. Monitoring is the ongoing process of tracking program implementation, generally through process measures. Evaluation is the periodic measurement of indicators that show the success in attaining program objectives. Operational research is the use of periodic, focused research to improve program implementation.

The monitoring and evaluation system must be based either on indicators (i.e., measurements that can be repeated over time to track progress toward the achievement of objectives) or on a set of criteria, or technical standards. Criteria or technical standards, unlike indicators, may not be quantifiable variables. Criteria used to judge a program policy, for example, might include whether the policy is realistic given current resources or whether it reflects the national epidemiologic situation.

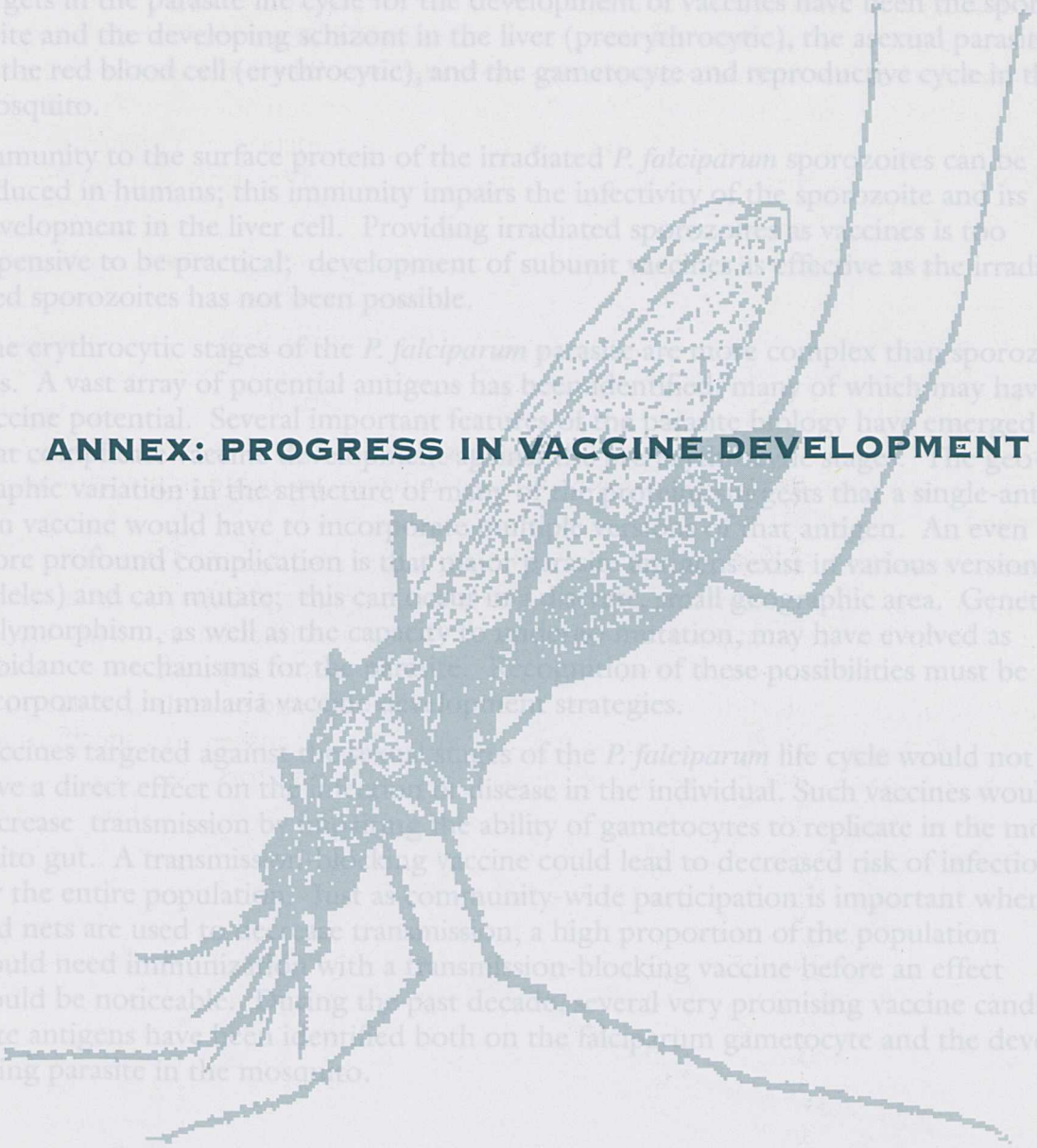
The goal of most malaria programs is to reduce malaria-related mortality, and this should be reflected in the impact objectives. Evaluation of mortality reduction is difficult for two reasons: most of the mortality due to malaria occurs not in the health facilities, where it can be reported, but in the community; and the opportunities for microscopic confirmation of malaria are limited. Therefore, with only fragmentary impact measurements for routine evaluation possible, more emphasis should be placed on assessing intermediate outcomes of program activities that have a proven relationship to morbidity and mortality (e.g., proportion of patients diagnosed as having malaria by the provider who are prescribed treatment in accordance with national policy).

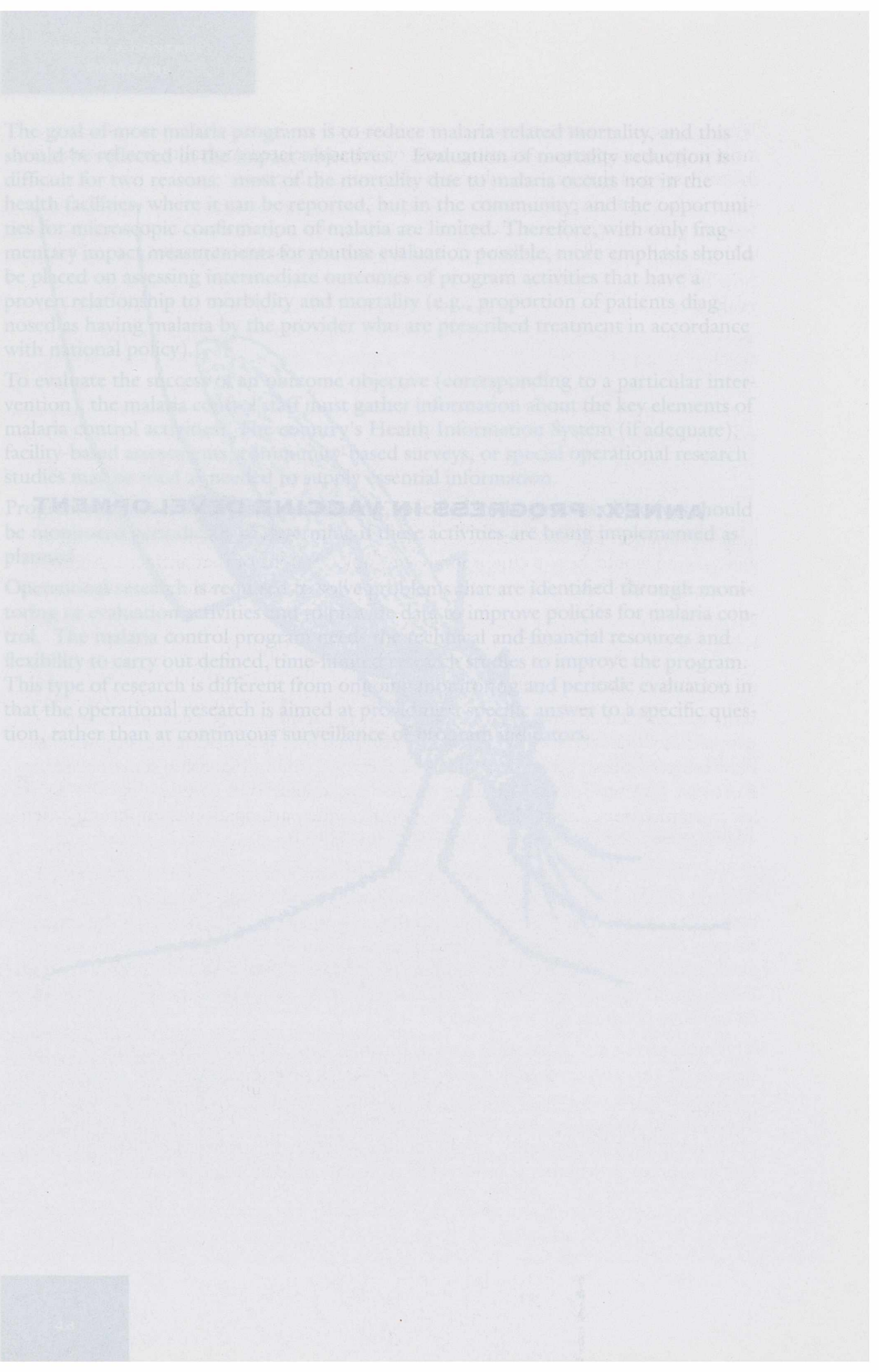
To evaluate the success of an outcome objective (corresponding to a particular intervention), the malaria control staff must gather information about the key elements of malaria control activities. The country's Health Information System (if adequate), facility-based assessments, community-based surveys, or special operational research studies may be used as needed to supply essential information.

Program support activities, such as training, specified in the process objectives should be monitored periodically to determine if these activities are being implemented as planned.

Operational research is required to solve problems that are identified through monitoring or evaluation activities and to provide data to improve policies for malaria control. The malaria control program needs the technical and financial resources and flexibility to carry out defined, time-limited research studies to improve the program. This type of research is different from ongoing monitoring and periodic evaluation in that the operational research is aimed at providing a specific answer to a specific question, rather than at continuous surveillance of program indicators.

# ANNEX: PROGRESS IN VACCINE DEVELOPMENT





Malaria vaccine research has to date concentrated on *P. falciparum* because it is the most important species in causing most of malaria-related mortality and because it is the only species that can be cultivated (Institute of Medicine 1991). The potential targets in the parasite life cycle for the development of vaccines have been the sporozoite and the developing schizont in the liver (preerythrocytic), the asexual parasites in the red blood cell (erythrocytic), and the gametocyte and reproductive cycle in the mosquito.

Immunity to the surface protein of the irradiated *P. falciparum* sporozoites can be induced in humans; this immunity impairs the infectivity of the sporozoite and its development in the liver cell. Providing irradiated sporozoites as vaccines is too expensive to be practical; development of subunit vaccines as effective as the irradiated sporozoites has not been possible.

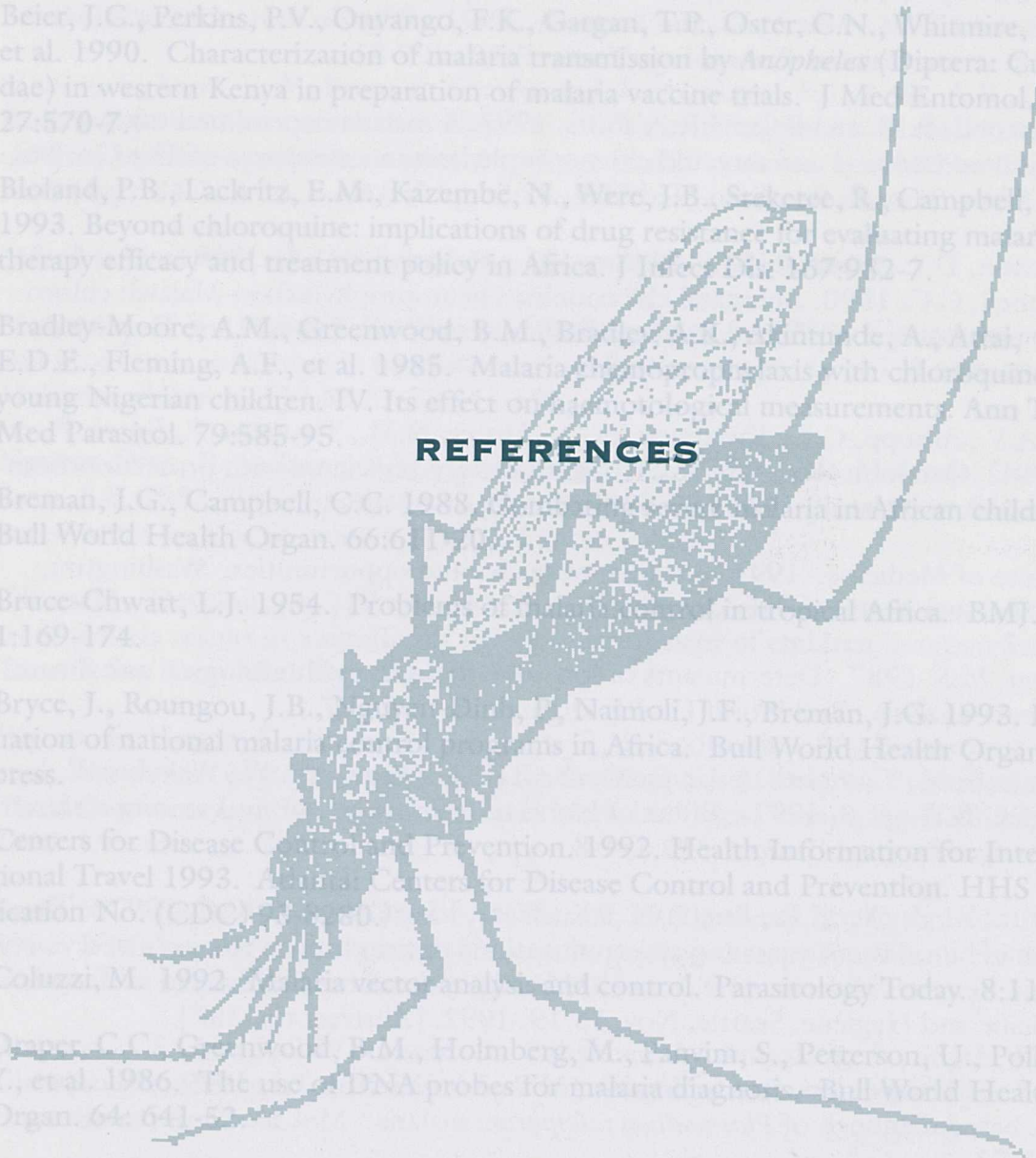
The erythrocytic stages of the *P. falciparum* parasite are more complex than sporozoites. A vast array of potential antigens has been identified, many of which may have vaccine potential. Several important features of the parasite biology have emerged that complicate vaccine development against the pre-erythrocytic stages. The geographic variation in the structure of many of the proteins suggests that a single-antigen vaccine would have to incorporate multiple versions of that antigen. An even more profound complication is that major parasite antigens exist in various versions (alleles) and can mutate; this can occur in a discrete, small geographic area. Genetic polymorphism, as well as the capacity to undergo mutation, may have evolved as avoidance mechanisms for the parasite. Recognition of these possibilities must be incorporated in malaria vaccine development strategies.

Vaccines targeted against the sexual stages of the *P. falciparum* life cycle would not have a direct effect on the infection or disease in the individual. Such vaccines would decrease transmission by impairing the ability of gametocytes to replicate in the mosquito gut. A transmission-blocking vaccine could lead to decreased risk of infection for the entire population. Just as community-wide participation is important when bed nets are used to decrease transmission, a high proportion of the population would need immunization with a transmission-blocking vaccine before an effect would be noticeable. During the past decade, several very promising vaccine candidate antigens have been identified both on the falciparum gametocyte and the developing parasite in the mosquito.

## THE PROMISE OF VACCINES FOR MALARIA CONTROL IN AFRICA

Eventually a series of malaria vaccines will be developed that will provide an array of protective immunity against malaria infection and disease. A great deal of basic research is required to unravel the mechanisms of naturally occurring immunity and to formulate effective vaccines. The time and resources required for the clinical testing of candidate vaccines alone make it seem unlikely that malaria vaccines will be available for use in Africa during the current decade. Investing in the study of malaria immunity must remain a priority, however, because immunity is the key factor determining the precarious balance between the human host and the falciparum

parasite. Current malaria control strategies must recognize the essential role of natural immunity in limiting the severity of malaria infection. In the future, control programs may be able to accelerate or enhance this natural immunity through the use of vaccines.



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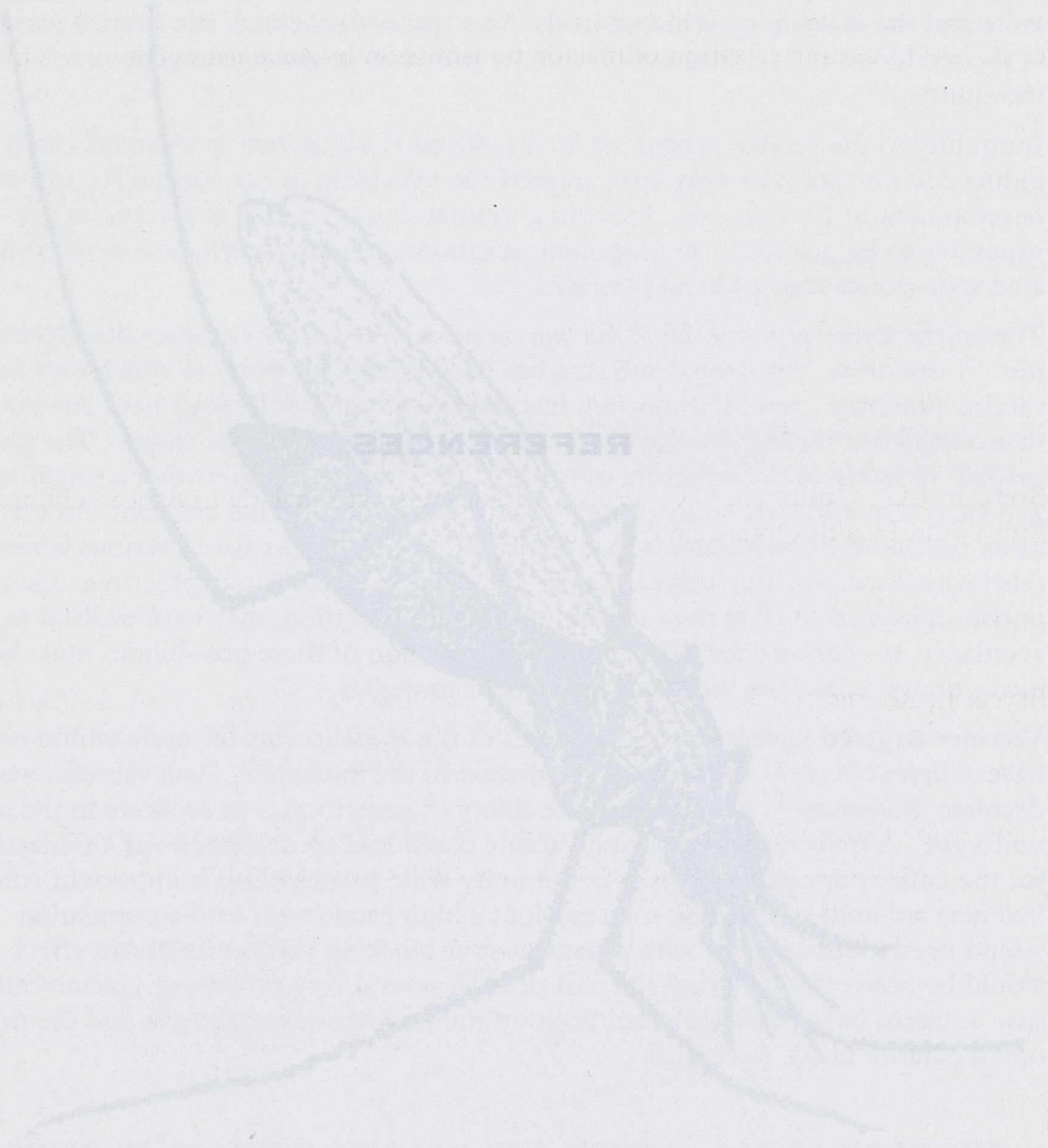

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