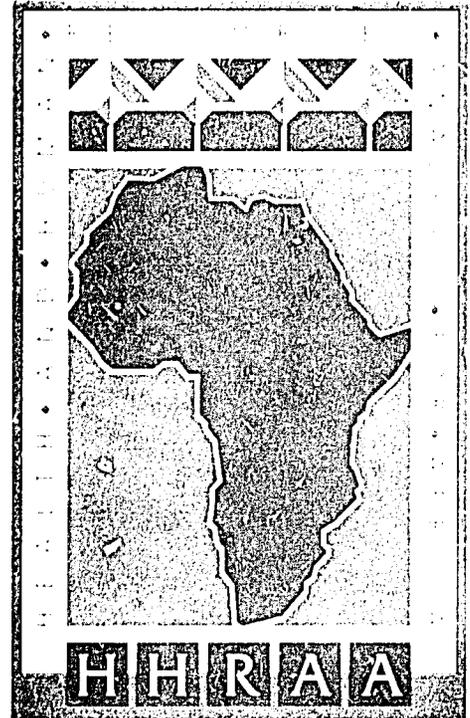


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Setting Priorities for Research, Analysis, and Information Dissemination on Malaria in Africa



**A Strategic Framework for
Setting Priorities for
Research, Analysis, and
Information Dissemination
on Malaria in Africa**

Prepared for the

Bureau for Africa

Office of Sustainable Development

by the

Health and Human Resources Analysis in Africa (HHRAA) Project

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Executive Summary

Malaria in Africa is an increasing problem, the dimensions of which are unlike those seen anywhere else in the world today. The World Health Organization estimates that 80 percent of the 267 million people infected with malaria are Africans and that 90 to 95 percent of malaria-related deaths in the world occur in Africa. Population, political, and economic pressures have been forcing Africans to leave non-malaria-endemic areas throughout the region (such as Ethiopia and Somalia) and to live and work in endemic areas without having acquired natural immunity. Long-term migrants, as well as seasonal laborers and nomadic populations, suffer some of the gravest consequences because of their transient status. Increased urbanization and attendant overcrowding and poor sanitary conditions have caused increases in human and vector pools. These population movements and various climatic factors have introduced malaria into areas that previously had been malaria-free. The extensive spread of drug-resistant malaria parasites throughout Africa, as well as the emergence of resistance to numerous previously effective insecticides, have significantly exacerbated the impact of malaria in Africa.

Reducing malaria morbidity and mortality and its impact on development should be the most important goal for malaria prevention and control in sub-Saharan Africa. USAID's Bureau for Africa has supported the combined effort involving experts at national, regional, and global levels to develop the Global Malaria Strategy. In the process of implementing the Global Strategy at national and regional levels in Africa, a certain number of issues will need to be addressed through analysis, research, and information dissemination to guide program managers in their efforts. The Office of Analysis, Research and Technical Support of USAID's Bureau for Africa hopes, under its Health and Human Research and Analysis in Africa (HHRAA) Project, to play a major role in this process.

This strategic framework summarizes available literature and other sources of information on priority issues related to malaria prevention and control in Africa, and indicates the policy-relevant information gaps that need to be addressed through research, analysis, and information dissemination activities. The strategic framework was drafted based on the outcomes of a consultative meeting and on previous consultations with African decision makers, a review of the literature, and the products of international expert bodies convened to discuss malaria prevention and control. It assesses, ana-

lyzes, and ranks the information needs and research priorities in the following areas:

- ◆ malaria epidemiology and national control programs,
- ◆ case management of malaria (diagnosis and treatment),
- ◆ malaria prevention, and
- ◆ monitoring and evaluation of malaria impacts on development.

Acronyms

ARTS	Office of Research, Analysis and Technical Support
CCCD	combatting communicable childhood diseases
CHW	community health worker
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
HHRAA	Health and Human Resources Analysis for Africa
IIMs	insecticide-impregnated materials
IIBN	insecticide-impregnated bed nets
NGO	non-governmental organization
PCR	polymerase chain reaction
PHC	primary health care
QBC	quantitative buffy coat
RIA	radioimmunoassay
SARA	Support for Analysis and Research in Africa
SSP2	sporozoite surface protein 2
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Introduction

Background

Malaria in Africa is an increasing problem, the dimensions of which are unlike those seen anywhere else in the world today. The World Health Organization estimates that 80 percent of the 267 million people infected with malaria are Africans and that 90 to 95 percent of malaria-related deaths in the world occur in Africa. In the late 1980s an upsurge in the incidence and case-fatality rates of malaria was reported throughout Africa. The increasing magnitude and severity of the malaria problem and its relationship to other diseases has heightened the urgency of addressing this problem in Africa.

Malaria particularly affects pregnant women and young children and is a major cause of low birth weight. Each year more than 1.5 million deaths in Africa, of which at least one million are among children, are attributed to malaria. Pediatric anaemia in Zaire due to malaria infection had increased in 1987 to three times its 1984 prevalence, resulting not only in significant increases in malaria-related morbidity and mortality but also in significant numbers of transfusion-induced HIV infection in children. Whether the number of children who die from *Plasmodium falciparum* malaria each year is one million, or two to three million, the totals are staggering and represent one of the most important child survival issues in the world.

Population, political, and economic pressures have been forcing Africans to leave non-malaria-endemic areas throughout the region (such as Ethiopia and Somalia) and to live and work in endemic areas without having acquired natural immunity. Long-term migrants, as well as seasonal laborers and nomadic populations, suffer some of the gravest consequences because of their transient status. Increased urbanization and attendant overcrowding and poor sanitary conditions have caused increases in human and vector pools. These population movements and various climatic factors have introduced malaria into areas that previously had been malaria-free. The extensive spread of drug-resistant malaria parasites throughout Africa, as well as the emergence of resistance to numerous previously effective insecticides, which have significantly exacerbated the impact of malaria in Africa.

Although effective treatment and prevention strategies have been field-tested in Africa, further work is needed to develop coherent, environmentally sound strategy for malaria control involving community participation, locally sustainable interventions, and innovative, cross-sectoral approaches that expand control efforts beyond the health sector.

The World Health Organization Regional Office for Africa (WHO/AFRO) has committed itself to support African countries in adapting and implementing the Global Malaria Strategy defined at the Ministerial Conference on Malaria held in Amsterdam (1992). WHO strategies for malaria prevention and control rely on anti-malarial drugs for case-management and prevention through personal protection such as the use of impregnated bednets and chemoprophylaxis for pregnant women.

During the next ten years, reducing malaria morbidity and mortality and its impact on development should be the most important and most realistic goal for malaria prevention and control in sub-Saharan Africa. Malaria eradication is not a realistic possibility, in part because an effective vaccine is unlikely to be available for at least another five to ten years (until about 2005–2010 or later).

USAID's Bureau for Africa has supported the combined effort involving experts at national, regional, and global levels to develop the Global Malaria Strategy. In the process of implementing the Global Strategy at national and regional levels in Africa, a certain number of issues will need to be addressed through analysis, research, and information dissemination to guide program managers in their efforts. The Office of Analysis, Research and Technical Support of USAID's Bureau for Africa hopes, under its Health and Human Research and Analysis in Africa (HHRAA) Project, to play a major role in this process.

Purpose of the Strategic Framework

The strategic framework provides a summary of available literature and other sources of information on priority issues-related to malaria prevention and control in Africa, and indicates the policy-relevant information gaps that need to be addressed through research, analysis, and information dissemination activities.

The purpose of the strategic framework is to present a synthesis of existing knowledge and information gaps and set research priorities relevant to decision-making toward reaching the following objective to sustain decreases in the adverse socioeconomic, demographic, and environmental impact of malaria by supporting:

- ◆ development of effective and efficient service delivery systems to prevent and control malaria, especially for the case management of malaria among vulnerable groups (children, pregnant women, and displaced persons);
- ◆ innovative approaches to monitor and evaluate the socioeconomic, demographic, and environmental impact of malaria; and
- ◆ development of better technology amenable to higher-impact interventions to prevent and control malaria.

The Process of Developing the Strategic Framework

As part of its support to the Office of Analysis, Research, and Technical Support within A.I.D.'s Africa Bureau (AFR/ARTS), the Support for Analysis and Research in Africa (SARA) Project organized at the Joint Meeting of the American Society for Tropical Medicine and Hygiene and the American Association of Parasitologists a consultative meeting on malaria and emerging health-related threats in sub-Saharan Africa. The consultative meeting participants were researchers and program managers from Africa and U.S.-based experts working on infectious and tropical diseases.

The purpose of the consultative meeting was to solicit expert advice in directing research, analysis, and dissemination priorities that USAID's Bureau for Africa should consider for its analytical agenda on malaria and emerging health-related threats in sub-Saharan Africa. The meeting brought together professionals knowledgeable about public health care programs in Africa, especially malaria control programs. Participants identified a number of priority program-relevant issues that could be addressed through research, analysis, and dissemination to improve malaria and related public health programs in Africa.

The strategic framework was drafted based on this consultative meeting and on previous consultations with African decision makers, a review of the literature, and the results of international expert bodies convened to discuss malaria prevention and control. It assesses, analyzes, and ranks the information needs and research priorities in the following areas:

- ◆ malaria epidemiology and national control programs,
- ◆ case management of malaria (diagnosis and treatment),
- ◆ malaria prevention, and
- ◆ monitoring and evaluation of malaria impacts on development.

Summary of Research and Information Dissemination Priorities

Malaria Epidemiology and National Control Programs

Malaria in Africa can be caused by any or all of the three distinct protozoan parasites, *Plasmodium falciparum*, *P. ovale*, and *P. malariae* (*P. vivax* rarely occurs in sub-Saharan Africa), with *P. falciparum* the dominant and cause of the most severe and lethal cases. There are several mosquito species of the genus *Anopheles* involved in transmitting the infection, with *Anopheles gambiae* being the most important.

Malaria exists in a range of African environments from coastal swamps through forests, savannahs, desert fringes, and the ever-expanding periurban slums around major African cities. Perennial or seasonal transmission can depend on yearly patterns of rainfall or the regular availability of water. The ethnic diversity of Africa create an array of life styles, habits, housing types, and concepts of malaria prevention, treatment, and control. All of these factors have to be taken into account when developing malaria control policies, strategies, and programs.

Studies in key areas with seasonal and year-round malaria transmission should be performed to use the results as models to develop and test malaria control strategies. The data obtained must distinguish between infection (parasitemia) and disease. It is important to develop a limited number of paradigms based on geography and transmission patterns and to conduct intensive study at a manageable number of sites. The results of these studies should help decision-makers to choose new approaches to prevention and control of malaria that are appropriate for the various regions and ecological zones of malaria transmission on the continent.

Case Management and Malaria (Diagnosis and Treatment)

Integrated Case Management of the Sick Child

Early diagnosis and prompt treatment—disease management—are fundamental to malaria control. Improving case management of malaria among children and pregnant women, on whom malaria has its greatest adverse impact, is a high priority. As malaria is mainly a problem of young children, health services should be receive guidelines and training for the diagnosis and treatment of malaria as part of WHO's "sick child" approach. The approach includes disease management of malaria, diarrheal disease, acute respiratory infections, measles, and malnutrition. Operations research should be conducted to assess health-seeking behavior as related to malaria and to test and evaluate the implementation of the "integrated case management of the sick child" approach. It is important to research different ways of strengthening and improving the quality of malaria case management at different levels of the district health system, including the household level.

Malaria Drugs

Availability and affordability to patients of effective antimalarial drugs is crucial for the control of malaria. Because chloroquine is an economical antimalarial that is still effective in most regions of Africa, it is essential to define the chloroquine-resistance prevalence and to develop strategies to prolong its useful life. To address the first objective, studies should be performed using modern methods to determine the prevalence of drug resistance. To address the second objective, different policies and strategies to control antimalarial use should be studied—to determine their impact on drug use and the prevalence of resistance.

Recognition and Diagnosis

The practical importance of diagnosis is that it is the initial step before treatment. To define the value of early diagnosis, it is essential to determine whether delay (time from onset of symptoms to intervention) is an important determinant of outcome. This question can be answered with available methods and is essential to set health priorities for local vs. regional health centers in sub-Saharan Africa. There is also a need to support the development of rapid and cost-effective tests for better biological diagnosis of malaria at all stages of the disease, from asymptomatic to severe malaria.

Malaria Prevention

Insecticide-Impregnated Materials (Bednets, Curtains)

Additional studies may be necessary to determine efficacy of the use of insecticide-impregnated mosquito nets on malaria morbidity and mortality. However, because several studies of the efficacy of bednets are in progress, substantial investment in studies of implementation and sustainability should be considered with caution until it is clear whether insecticide impregnated materials reduce malaria mortality.

Vaccine Development

Immunization against malaria may become possible in the future. Although some vaccines have been tested in the field, they are still at the early stages of development (WHO). Support for applied research on vaccine development will continue to receive a high priority, including development of field sites in sub-Saharan Africa, and studies of transmission-blocking vaccines based on gametocyte (sexual stage) antigens.

This priority should include development of screens/models to determine whether immunization with a candidate antigen prevents infection (parasitemia) or disease (e.g., cerebral malaria). This priority can also include development of appropriate primate models that provide systems for the study (relevant for vaccine research) of human complications, such as cerebral malaria and renal failure in *P. falciparum* malaria.

Monitoring Evaluation of the Impact of Malaria on Development

The potential impact of malaria on development, as well as the impact of development activities on the spread of the disease, should be carefully monitored and evaluated. Any malaria strategy adopted at the national or local level should be monitored to determine compliance with guidelines, and to determine its impact on morbidity and mortality. Process and health indicators should be used to assess the effectiveness of malaria control programs. Innovative and cross-sectoral approaches to include malaria prevention and control activities in other relevant development sectors should be designed, tested, and evaluated to control malaria.

Review of Issues and Information Gaps and Needs

Development of Malaria Control Programs

Epidemiology of Malaria in Sub-Saharan Africa

Malaria in Africa can be caused by any or all of the three distinct protozoan parasites, *Plasmodium falciparum*, *P. ovale*, and *P. malariae* (*P. vivax* rarely occurs in sub-Saharan Africa) with *P. falciparum* the dominant and cause of the most severe and lethal cases. There are several mosquito species of the genus *Anopheles* involved in transmitting the infection, with *Anopheles gambiae* the most important.

Malaria exists in a range of African environments from coastal swamps through forests, savannahs, desert fringes, and the ever-expanding periurban slums around major African cities. Perennial or seasonal transmission can depend on yearly patterns of rainfall or the regular availability of water. The ethnic diversity of Africa creates an array of life-styles, habits, housing types, and concepts of malaria prevention, treatment, and control.

Because the epidemiology of *Plasmodium falciparum* malaria in sub-Saharan Africa is a complex mosaic with shifting patterns as the seasons cycle, it provides few opportunities to generalize. For this reason, malaria control programs must be guided by local epidemiologic data. These data must be gathered where they are lacking and analyzed where they exist. It is equally important that they be collected on a manageable scale. Basic epidemiologic studies of morbidity and mortality need not be complex, highly technical, or expensive. In fact, they should use locally available resources so that they can be performed by indigenous persons, and thus simultaneously provide training opportunities. Only after this information has been obtained at the local level is it possible to plan and implement appropriate malaria control programs. Advantages of this strategy include its low cost, manageability, sustainability, and efficacy.

Development of Malaria Control Paradigms and Models

To be effective, malaria control programs must be based on local epidemiologic, environmental, social, and economic data. The development of a limited number of malaria control paradigms based on geography and transmission patterns offers the opportunity for intensive study at a manageable number of sites. This is necessary because neither the person-

nel nor the financial resources necessary to study all malaria-endemic areas are available in sub-Saharan Africa. This strategy is also consistent with the recommendations of WHO, and with the Institute of Medicine report on malaria. We recommend developing a set of paradigms for sub-Saharan Africa that considers the level of endemicity, intensity of transmission and geography for at least six settings: savannah, forest fringe, forest, agricultural (including irrigation), desert fringe and urban.

Once these paradigms have been developed, each should be used to develop model malaria control strategies. Although logical, this approach is novel because paradigms have rarely been used (or evaluated) as tools to develop or implement malaria control programs—even in pilot malaria control projects. Factors that must be considered in the use of paradigms to develop model control programs include endemicity (holo- vs. hyper- and meso-endemic transmission), intensity of transmission, vector(s), parasite species, host factors such as the prevalence of sickle cell anemia, drug resistance, and drug pressure.

When the paradigm and its model control program have been adapted to the local situation, that strategy should be implemented, using locally obtainable resources whenever possible. Additional factors that might affect the success of a control program include the availability (or absence) of health personnel, health centers, dispensaries, vehicles, and volunteer networks. Based on these considerations and on the desirability of integrating malaria treatment into primary health care (PHC), it is advisable to begin applying pilot control strategies in areas with established PHC programs. This approach should be carried out with the collaboration and support of public and private institutions, especially non-governmental organizations (NGOs).

It may be necessary to develop an epidemiologic cadre of African investigators capable of planning, performing, and analyzing health epidemiologic data to determine their own national health priorities. This critically important long-term investment cannot succeed without active national programs to which these trainees can apply their knowledge and skills.

Case Management of Malaria

Integrated Case Management of the Sick Child

Early diagnosis and prompt treatment—disease management—are fundamental to malaria control. Improving case management of malaria among children and pregnant women, on whom malaria has its greatest adverse impact, is a high priority.

Redd and coworkers (1992) found substantial overlap between clinical criteria for malaria and pneumonia; they therefore suggested that children meeting the criteria for pneumonia be treated with an antimicrobial such as pyrimethamine plus sulfadoxine, which was also effective against malaria (in the absence of laboratory facilities).

As malaria is mainly a problem of young children, health services should receive guidelines and training for the diagnosis and treatment of malaria as part of the WHO's "sick child" approach. The approach includes disease management of malaria, diarrheal disease, acute respiratory infections, measles, and malnutrition. Operations research should be conducted to assess health-seeking behavior as related to malaria and to test and evaluate the implementation of the "integrated case management of the sick child" approach. It is important to research different ways of strengthening and improving the quality of malaria case management at different levels of the district health system, including the household level.

Issues of Malaria Diagnosis

The availability of rapid malaria diagnosis lags behind the need. Although the blood smear remains the gold standard, the speed of microscopic diagnosis is often inadequate in areas with high caseloads because there are not enough skilled microscopists. In endemic areas, this question is further complicated because the presence of parasites on a blood smear does not establish that malaria is the cause of the patient's illness (Rougemont et al., 1991). The development of cheap, simple diagnostic methods to address this situation is an urgent need.

Molyneux et al. (1989) identified eight clinical and biological presenting features in malaria, each of which was individually associated with an adverse outcome (death or sequelae). High levels of TNF correlate with fatality in childhood cerebral malaria (Kwiatkowski et al. 1990). Although research suggests that early treatment prevents mortality from malaria (Rooth and Bjorkman 1992), it is not clear whether early treatment prevents severe malaria, including cerebral complications. Defining the impact of time (from onset to the time of intervention) on the risk of complications would greatly influence malaria control strategies. It would permit one to decide rationally whether the priority should be rapid local intervention at the primary health care level—if time is the critical determinant of outcome—or more sophisticated, even tertiary care centers (if complications are not directly related to the time from onset to interven-

tion (suggesting idiosyncratic, currently unpredictable, interactions between the parasite and the human host.) More research should be conducted on the clinical progression of, and the risk factors for, the disease itself (Oaks et al. 1991). For a proper conduct of such studies, one should subdivide the disease process into several steps: no infection, asymptomatic infection, non-complicated disease, severe disease, and death. Determinants for the progression from one step to the next can then be analyzed separately.

Clinical Diagnosis

Rougemont et al. (1991) have reported an association between fever and parasite count in West Africa during the wet season when there is high transmission. This association was further strengthened by the use of three simple clinical criteria. Similarly, Govardhini et al. (1991) reported from India that fever alone identifies about 75 percent of malaria cases. Conversely, during the dry season when there is low transmission, Redd and co-workers (1992) found substantial overlap between clinical criteria for malaria and pneumonia. Fever was among the criteria for presumptive treatment of malaria. Improving case management of malaria among children will require that clinical criteria for diagnosis be refined. Operations research should be conducted to assess health-seeking behavior as related to malaria, to determine the risk of true malaria attacks among children without fever (because current presumptive diagnosis is based on the presence of fever). The real impact of determining clinical and biological prognostic indicators in case-management in the reduction of mortality should be determined (Molynieux et al. 1989).

Laboratory (Microscopic) Diagnosis

Parasite counts lower than 10,000/ μ l have been reported to have no significant association with febrile episodes in some hyperendemic areas with seasonal transmission (Rougemont et al. 1991). In contrast, Rooth and Bjorkman (1992) suggested that 400/ μ l was a valid cut-off for one to nine year-old children with fever. To summarize the available evidence: it does not permit a consensus on an asymptomatic (cut-off) level of parasitemia.

Because these and other data suggest that the level of so-called asymptomatic parasitemia varies among individuals, it is likely that additional non-parasite factors such as the host response are also major determinants of whether *P. falciparum* infection is mild or severe. Studies to further

define correlates of clinical and biological prognostic indicators are recommended.

Alternatives to Conventional Microscopy

The following techniques are alternatives to classic microscopy to improve the biological diagnosis of malaria:

Quantitative Buffy Coat

The quantitative buffy coat (QBC) technique uses acridine orange to stain DNA and centrifugation in a capillary (hematocrit) tube to separate cells by density (specific gravity). With fluorescence microscopy, malaria parasites are visualized at the junction between the top of the red cell layer and the bottom of the buffy coat. Comparison of QBC with the thick smear indicates that the QBC is sensitive and specific (Spielman et al. 1988; Kumar et al. 1993). The QBC is also rapid: an experienced investigator can examine one specimen every 20 to 30 seconds (Anthony 1992; Kumar et al. 1993). However, the QBC is more expensive than conventional microscopy, and its performance may vary under different field conditions (Baird et al., 1992), and with inspection time (Anthony, 1992).

Immunoassays

Immunoassays have a detection limit similar to microscopy (10 to 20 parasites per microliter of blood), and may be useful for screening blood samples prior to transfusion or in epidemiologic studies (Namsiripongpun et al. 1993). Their major disadvantages are cost, short shelf life (RIA), and length of turn-around time (two to four hours for ELISA, longer for RIA). Assays that detect soluble parasite antigens may be able to diagnose malaria in smear-negative patients (i.e., in the absence of circulating parasitized red blood cells), a situation sometimes found in cerebral malaria (WHO 1990).

DNA Probes Polymerase Chain Reaction (PCR)

Two molecular strategies show promise for the diagnosis of *P. falciparum* infection: a DNA probe for a highly repetitive sequence, and a PCR based on a highly conserved sequence. Use of one DNA probe has been shown to be sensitive, specific, and economical (McLaughlin et al. 1993). It is a potentially interesting tool for patient management and for processing large numbers of samples (surveillance, blood banking). Barker et al. (1992) recently developed a simple method for treating blood samples that per-

mits direct detection of *P. falciparum* parasites using PCR. Sethabutr et al. (1992) have shown that PCR is more sensitive than microscopy (thick smear) for parasite detection.

Therapeutic Issues

Chloroquine remains the most important drug for the treatment of malaria due to susceptible parasites (*Plasmodium ovale*, *P. malariae*, most *P. vivax*, and some *P. falciparum*), and for chemoprophylaxis in pregnant women because it is inexpensive, safe, and effective. However, its value has decreased considerably because of chloroquine resistance in *P. falciparum*. Thus one of the central unsolved problems in malaria is the development of alternative antimalarial that are effective against chloroquine-resistant *P. falciparum*.

Development of Policies for Antimalarial Drug Use

Appropriate drug use requires correct diagnosis, followed by appropriate treatment. Treatment must be sufficiently aggressive to prevent (or reverse) potentially fatal complications such as hypoglycemia and cerebral malaria, but not so casual or widespread that it enhances development of resistance. Treatment must be targeted to persons with symptomatic infection (disease), not to those with asymptomatic parasitemia. What is needed are practical criteria—specific clinical symptoms or signs that are indications for therapy.

Treatment can be given by health professionals, community health workers, or parents who has been adequately trained. Uneven prescription practices by health care workers have been attributed to outdated textbooks and training, drug company promotions, patient preference for injections, irregular supplies of medicines, and a lack of guidance from public health officials. For example, the CCCC program in Togo found that two-thirds of health workers gave injections of quinine, even if patients could take the treatment orally, and the symptoms didn't warrant rapid administration of the drug (Bremner et al. 1988).

National policies on drug use must be developed and tested because excessive drug use may exacerbate drug resistance. For example, what are the effects of using a given drug for treatment of symptomatic *P. falciparum* infection on the subsequent development of resistance to that drug? This is a particularly important question for the sub-Saharan countries now using sulfadoxine-pyrimethamine (Fansidar[®]) because this combination selects rapidly for resistant parasites *in vitro*, and presumably will also do so *in vivo*. Similarly, at

what point are the benefits of chemoprophylaxis with chloroquine for pregnant women and children less than five years old counterbalanced by increasing chloroquine resistance?

National drug distribution policies should also develop criteria for approval of new antimalarials. Which, if any, of the newer more expensive antimalarials should be made available, and how should those decisions be related to (or driven by) national budgetary considerations, or by the prevalence of resistance?

Chemoprophylaxis

Drug use policies must consider the natural semi-immune state, which typically protects long-term residents against severe disease and death after years of exposure to malaria. Thus the semi-immune state obviates the need for chemoprophylaxis (to prevent severe complications and deaths) among life-long (non-pregnant) adult residents of malarious areas. (Note that semi-immune residents of endemic areas are often parasitemic; they are protected against disease, not against infection.)

Chemoprophylaxis for pregnant women should be examined using field (operations) research to identify the pregnancies at greatest risk and to assess the efficacy of chloroquine chemoprophylaxis. Malaria infection in primigravidas results in high parasite densities and is associated with low birth weight. Because the benefits of chemoprophylaxis are less clear than thought previously, and because community-wide chemoprophylaxis for pregnant women is difficult to implement and maintain, operations research is required to find better ways of managing malaria in pregnant women.

Monitoring of Antimalarial Drug Use

Antimalarial drug distribution is typically uncontrolled. In most malaria-endemic countries, antimalarials are available from street vendors, pharmacies, individuals who hoarded pills from their last treatment, and clinics. Particularly in areas where chloroquine resistance is present, excessive chloroquine use resulting from widespread availability may increase the prevalence of such resistance.

A practical surveillance system should be in place to identify treatment failures and their cause. This should be accompanied by development of tools

and protocols to monitor drug resistance and the use of alternative drugs when necessary.

Malaria Prevention

Vector Control: Insecticide-Impregnated Materials

Efficacy of Insecticide-Impregnated Materials (bednets, curtains...)

Bednets alone, when used correctly, protect against mosquito bites by creating a physical barrier between humans and the *Anopheles* mosquito. They are more effective when dipped in insecticides such as permethrin or deltamethrin; bednets (or curtains) dipped in such insecticides provide two additional anti-mosquito (killing and repellent) effects (Greenwood et al. 1993) and may markedly reduce indoor biting rates.

One important disadvantage of bednets and curtains is that they are effective only against mosquitoes that bite indoors when people are sleeping. Therefore, prior to implementing a wide-scale bednet (or curtain) program, it is essential to define vector behavior to determine landing and biting rates, resting behavior, and the times when bites occur. For these reasons, bednets (or curtains) represent only one component of a comprehensive malaria control program.

By reducing mosquito-biting rates, insecticide-impregnated bednets (IBNs) and curtains may reduce the incidence of malaria complications and deaths (Rozendale 1989, Chunge 1991). Although IBNs and curtains have been shown to reduce the prevalence of infection (parasitemia), their effects on serious complications and deaths are not clear. The general trend of the results thus far is that IBNs reduce the incidence of fever and the prevalence of anemia among young children, especially when combined with chloroquine (Greenwood et al. 1987; Rozendale 1989; personal communication C. Schiff 1993).

Interest in the effect of IBNs and curtains on mortality was stimulated initially by results from The Gambia showing an association between reduced childhood mortality and IBNs in an area with low malaria endemicity and low-intensity transmission. Because similar results have not yet been obtained in settings with more intense transmission, it is not clear whether IBNs were the sole factor responsible for the decreased mortality observed in The Gambia. As yet, no studies have demonstrated reduced childhood mortality in areas of high transmission. The potential link between the use

of IBNs (or curtains) and decreased childhood mortality is an exciting lead that warrants further research. In future studies it will be important to test whether impregnated bednet (or curtains) alone can reduce childhood mortality, or combinations of interventions such as early diagnosis and treatment plus IBNs are necessary to reduce childhood mortality.

Several investigators have argued that IBN strategies should be implemented in areas of high transmission despite the lack of information on their ability to reduce childhood mortality in such areas. These recommendations are based on studies demonstrating reductions in morbidity as measured by prevalence of parasitemia with fever, and—by inference—in the prevalence of symptomatic malaria. With the recognition that IBN programs are complex and require extensive resources (for initial procurement of nets and insecticide and for human resources in the field), WHO, other agencies, and the Atlanta consultative meeting participants have taken the position that a major commitment to implement IBN programs in areas of high-intensity transmission should not be made until data demonstrate that IBNs reduce mortality in such areas of transmission.

The efficacy of IBNs on malaria morbidity and mortality must be established. Because of variable vector behaviors, bednet strategies cannot stand alone in a malaria control program. Research is needed on the specific vector behaviors in the areas where bednets are used. There is evidence that IBNs can reduce morbidity related to malaria; the ability to reduce mortality is still uncertain. The highest priority should be given to studies on the effect of IBNs on childhood mortality in settings with high-intensity transmission. These studies will require extensive work with the community for full implementation of IBNs in the study villages or areas. This is an operational research question (not a question of implementation) and should be treated as such.

Cultural Acceptability and Sustainability of Insecticide-impregnated bednets

Cultural acceptability of bednets and curtains is a key issue in their effectiveness. Research on the community acceptance and use of insecticide-impregnated bednets in sub-Saharan Africa has shown that households in a wide variety of social and cultural settings are willing to use IBNs or curtains, although some beliefs and sleeping patterns may limit their use and effectiveness (Rozendale 1989; Chunge 1991; personal communications C. Schiff and J. Sexton 1993). Known barriers to IBN or curtain use include discomfort due to heat, and cultural reactions based on the resemblance of

IIBNs to death shrouds. In addition, specific skills are necessary use IIBNs or curtains effectively. These include tucking the IIBN in place when sleeping and hanging it properly during the day when it is not in use. The most important positive factor reinforcing the appropriate use of IIBNs is their ability to control nocturnal biting insects (pest value). Because there are many distinct cultures among the more than 40 nations of Africa, additional research is needed to define the most effective way to teach bednet use, identify cultural barriers to its use, and use the positive outcomes of bednets if they reduce mortality in areas with high-intensity transmission.

Social marketing of bednets depends on the promotion techniques and explanations given to the public, as well as availability and cost of nets and insecticide. An understanding of cultural barriers to net use must be in place before social marketing plans can be developed. Rates of use will vary depending on community participation, education, and political support.

If a bednet program is to work over the long term, it must be sustainable, based on community participation in bednet distribution, repair, and possibly manufacture. It has been argued that because bednets reduce some aspects of morbidity, they should be widely distributed with research focused on their acceptability to the target population, and whether bednet interventions can be made sustainable. While these issues should be investigated, they are secondary to the main issue, which is whether bednets reduce childhood mortality.

Development of national programs to implement bednet strategies should be delayed until the more fundamental questions related to bednet effectiveness have been answered. In addition to effectiveness, operations research is needed on local knowledge, beliefs, and perceptions of malaria and bednet use, and the economic implications of such a program.

Vaccine Development

Immunization against malaria may become possible in the future. Although some vaccines have been tested in the field, they are still at early stages of development (WHO). USAID has provided critically important support for vaccine development during the last 10 to 15 years, creating a program that would be difficult or impossible to sustain within either the National Institutes of Health or the World Health Organization. The USAID network of investigators and their studies provide the most important leadership worldwide in malaria vaccine development.

The natural immune response to plasmodial infection protects against severe disease and death: long-term (semi-immune) residents of highly endemic areas rarely have serious or potentially fatal complications. However, long-term residents of endemic areas are frequently parasitemic because the semi-immune state does not protect against infection. Different types of vaccines may be required for different populations. For example, vaccines that require boosting from natural infection make sense for children in sub-Saharan Africa, but not for expatriate tourists. Conversely, a vaccine that produced inadequate responses in malnourished children would be a particularly poor choice for sub-Saharan Africa. Because development of sporozoite and blood-stage vaccine antigens has encountered many unexpected problems, there is a real need to re-examine the immune mechanisms involved in protection, identify antigens that produce boosting as a result of natural infection, consider the possibility that some immune responses may increase the host's chance of severe disease, and identify new target parasite antigens.

Non-immune visitors need a vaccine that prevents infection because they have a limited ability to prevent infection from progressing to potentially life-threatening disease. This protection need last for only a few weeks or months in most cases, because repeat immunization is economically feasible. In contrast, long-term residents of endemic regions require a vaccine that protects against disease (not infection) and thus prevents complications and deaths. This protection must last for years, should be enhanced by repeated episodes of natural infection (boosting) (Oaks et al. 1991), and should be obtainable for children, who are at the greatest risk.

Although a vaccine may benefit the community as a whole by reducing transmission, the vaccinated individual may actually become more susceptible to severe malaria than the person was before immunization, as the semi-immune state wanes because of reduced transmission and the vaccine-induced response wanes from lack of boosting (i.e., if the vaccine alone does not protect for life). An analogous question raised by Molyneux in 1989 is whether an initially successful vaccination program could convert an area with holoendemic, stable malaria to an area at risk for epidemic, unstable malaria, where both vaccinated and unvaccinated persons would be at risk for severe disease.

Support for applied research on vaccine development will continue to receive a high priority, including the development of field sites in sub-Saharan Africa, and studies of transmission-blocking vaccines based on gametocyte (sexual stage) antigens. This priority should include development of screens/models

to determine whether immunization with a candidate antigen prevents infection (parasitemia) or disease (e.g., cerebral malaria). This priority should also include development of appropriate primate models that provide systems for the study (relevant for vaccine research) of human complications such as cerebral malaria and renal failure in *P. falciparum* malaria.

Monitoring and Evaluating the Impact of Malaria on Development

The potential impact of malaria on development, as well as the impact of development activities on the spread of the disease, should be carefully monitored and evaluated. A study conducted on the economic impacts of malaria in Kenya and Nigeria by the USAID-funded Health Financing and Sustainability Project has found that malaria is a major factor of school days lost. In Kenya each primary school student misses an estimated 20 school days per year due to malaria, 10.8 percent of Kenya's 186-day school year. Nigerian primary and secondary school students miss an estimated three to 12 school days per year, two to six percent of the school year.

Any malaria strategy adopted at the national or local level should be monitored to determine compliance with guidelines, and to determine its impact on morbidity and mortality. Process and health indicators should be used to assess the effectiveness of malaria control programs.

Studies to document the adverse impact of malaria on the community, families/households, agricultural sector, industrial sector, social sector, and political sector will provide important information for the formulation of future development strategies and the integration of malaria prevention and control activities into other development programs.

Innovative approaches should be designed and supported to strengthen local capacities in applied research to permit and promote regular assessment of African countries' malaria situation, in particular the ecological, social, and economic determinants of the disease.

USAID'S Bureau for Africa Approaches to Implementation of Analytical Activities

Malaria prevention and control is a high priority for the African region. To support policy formulation, strategies, and program development for malaria control in Africa, AFR/ARTS/EHR is committed to support analytical works in this area. AFR/ARTS count on the presence of USAID missions

and USAID-centrally funded large projects working on a long-term basis in African countries to implement its analytical agenda on malaria.

USAID cooperation with and support for a variety of African institutions at regional and national levels creates opportunities for conducting research, analysis, and dissemination activities in close collaboration with African individuals and organizations.

AFR/ARTS hopes to work in close collaboration and partnership with various agencies of the United Nations, especially WHO and UNICEF, to support analytical activities on malaria in Africa. USAID's cooperating agencies such as the Centers for Diseases Control and Prevention, National Institutes of Health, Tulane University School of Public Health, The Johns Hopkins University School of Hygiene and Public Health, and the Academy for Educational Development—which already have access to networks of African researchers and program managers dealing with malaria control—would be used to assist AFR/ARTS in implementing its analytical agenda on malaria.

Ongoing and wider consultation mechanisms will be organized to further discuss research priorities and develop analytical activities in support of implementation of the malaria strategy for Africa.

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