THE EARS OF THE HIPPOPOTAMUS: MANIFESTATIONS, DETERMINANTS, AND ESTIMATES OF THE MALARIA BURDEN

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Abstract. Malarial patients experience asymptomatic parasitemia; acute febrile illness (with cerebral damage, anemia, respiratory distress, hypoglycemia); chronic debilitation (anemia, malnutrition, nervous system–related sequelae); and complications of pregnancy (anemia, low birth weight, increased infant mortality). These manifestations in patients, communities, and countries reflect intrinsic (human, parasite, mosquito) and extrinsic (environmental, social, behavioral, political, and economic conditions as well as disease-control efforts) determinants. At a minimum, between 700,000 and 2.7 million persons die yearly from malaria, over 75% of them African children. Between 400 and 900 million acute febrile episodes occur yearly in African children under 5 yr of age living in endemic areas. Although about half of these children are parasiticemic, all merit consideration of malaria-specific therapy, which is becoming more problematic because of parasite resistance to drugs. These numbers will more than double over the next 20 yr without effective control. Fewer than 20% of these febrile episodes and deaths come to the attention of any formal health system. The relatively few ill patients who have any contact with the health services represent the “ears of the hippopotamus.” Greatly intensified research activities and control of the intolerable burden of malaria are mandatory if economic development is to accelerate in Africa. In particular, support should be targeted to understanding and preventing malaria-induced anemia, hypoglycemia, effects on pregnancy, and neurologic and developmental impairment. To decrease and stop transmission of this intolerable scourge, there is an urgent need for malaria vaccines, newer drugs, and better vector control methods as well as the ability to improve current technologies and use them more efficiently.

INTRODUCTION

The burden of malaria is a challenge to quantify because infection may be asymptomatic in partially immune persons, may manifest in acute catastrophic cerebral illness and death or permanent neurologic sequelae, or may appear in gradations between these clinical extremes. Many febrile illnesses in endemic areas mimic malaria, and confirmatory parasitologic diagnosis is not often available, reliable, or prompt, particularly in rural zones. Parasitemic patients can have other illnesses, complicating matters even more. Most important, case detection and reporting are woefully incomplete because of the poor state of surveillance in malarious countries. This situation, whereby very little disease is perceived or managed by health systems in the tropics, is analogous to a hippopotamus floating in deep water, with only the ears showing; the largest and most dangerous part of the beast rests below the water.

With the recent increased support for malaria research and control worldwide, particularly in Africa, it is urgent that there be more precise definition of malaria’s clinical, epidemiologic, and economic burden. A recent review has concluded once again that about 1 million deaths (range, 744,000–1,300,000) from the direct effects of malaria occur yearly in Africa, more than 75% of them in children. This burden is determined by a wide variety of factors and is expressed in several clinical and epidemiologic forms, many of which are not usually considered in calculations of the malaria toll. This article will give an overview of the manifestations, important determinants, and estimates of the burden that dominate thinking about malaria’s impact as we attempt to understand, control, and prevent this scourge early in the 21st century. It will preface a series of articles that address specific expressions of the malaria burden, many of which have been lamentably neglected.

MANIFESTATIONS OF MALARIA

Malaria is defined variably as acute febrile illness in endemic areas, with or without parasitemia, depending upon local capability for parasitologic confirmation. Malaria infection can result in asymptomatic parasitemia; clinical malaria (febrile episodes, parasitemia); severe malaria (anemia, neurologic syndromes); and mortality. The major manifestations of acute febrile illness, chronic effects, and pregnancy-related complications are shown in Figure 1. Acute severe illness can lead to cerebral malaria, with a high case fatality rate. Coma, severe anemia, and respiratory distress are ominous for children with acute malaria. One perilous but eminently treatable complication of malaria is hypoglycemia due to parasite metabolism in red blood cells (RBCs) and hyperinsulinemia secondary to use of quinine; pregnant women with malaria have a high risk of hypoglycemia. Even when patients get to a hospital, differing malaria treatment regimens result in different outcomes in the hospital and after discharge. The debilitating acute and chronic effects of anemia and neurologic, cognitive, and developmental impairment are not well quantified. Particularly devastating to development are the long-duration effects of malaria, manifested in learning and behavioral disorders and decreased capacity to work. The extent of the impact of malaria on the pregnant woman and her fetus, notable during the first and second pregnancies, have only recently been appreciated. In particular, low birth weight and subsequent increased infant and childhood mortality result from an infected placenta. The economic devastation caused by malaria reflects health care costs, lost workdays and school days by patients and family members, and other direct and indirect costs. Retardation of the rate of long-term national, regional, and continental economic growth as a consequence of malaria has been appreciated only recently.
mechanisms predisposing malarious patients to severe disease are beginning to be understood more completely. Tumor necrosis factor, cytoadhesion of parasitized RBCs (particularly in cerebral vessels), nitric oxide, lactic acidosis, and chondroitin sulfate A in the placenta are associated with adverse effects of malaria. The local epidemiologic profile of malaria and other diseases is very important for diagnosing and quantifying accurately the cause of febrile illness. In areas with unstable malaria, the predictive values (positive and negative) of fever will vary, depending upon season and other prevalent diseases. Hence, to manage patients properly, particularly ill febrile children, it is necessary to have a comprehensive understanding of the local pathology and epidemiology.

**DETERMINANTS OF THE MALARIA BURDEN**

The manifestations of malaria in patients and the toll in communities and countries reflect intrinsic and extrinsic determinants (Table 1). Of the intrinsic factors, host (human) immunity, parasite species, anopheline longevity, and avidity for humans have the greatest impact on the malaria burden. Among extrinsic factors, climate (mainly rainfall), economic conditions (poverty), political commitment, and effectiveness of control and prevention efforts are the most important determinants of malaria’s burden (Figure 2).

**Host factors.** Human populations exposed to malaria infection may vary in their susceptibility to infection and severity of illness. Sickle cell (AS) and other traits that alter RBC structure limit parasite multiplication within RBCs. The protection of populations by their genetic makeup is termed balanced polymorphism, a concept strengthened by the observation that the heterozygous (AS) trait is more prevalent in African populations and may protect against malaria, particularly cerebral malaria. The presence of the Duffy blood factor on the surface of RBCs is required for *Plasmodium vivax* to enter RBCs; because over 90% of sub-Saharan Africans lack the Duffy factor, *P. vivax* is essentially absent from most of this area. Hereditary ovalocytosis, β and α thalassemia, glucose-6-phosphate dehydrogenase deficiency, spectrin, Lewis and Kid Is (a) red cell type mutations in the gene for the red blood cell membrane protein and have also been associated with decreased susceptibility to severe malaria. A low frequency of the class I major histocompatibility complex molecule HLA-B53 has been associated with severe malaria in the Gambia, possibly associated with immunity to liver stages of the parasite. Other innate factors, such as ICAM-1, the putative receptor for infected RBCs binding to brain endothelium, and a polymorphism in the promoter region of tumor necrosis factor-α appear related to the frequency of severe disease. Although knowledge of host and parasite genetics has added greatly to our understanding of susceptibility to malaria, the use of genotype information for improved malaria treatments and prevention remains a challenge for the future.

The immune status of the individual and population plays the most important role in the clinical response to infection and transmission. Maternally derived antibody offers limited and short-duration protection to the newborn. In heavily endemic areas, over 30% of children acquire parasites by 3 months of age. Researchers have identified humoral antibodies to sporozoites, intrahepatic parasites, merozoites, malaria toxins, parasite antigens on infected RBCs, intraerythrocytic parasites, and, within the mosquito, to parasite fertilization; cell-mediated immunity plays a role in the liver and RBC invasion and parasite development. Even with repeated infection, protective immunity is incomplete; individuals in malarious areas frequently have premunition, i.e., parasitemia and antibodies without symptoms, and this is age dependent. There is recent evidence for a genetic basis for antibody and cellular responses to malaria proteins. Identification of specific immunologic determinants of protection will lead to development of the most promising vaccine candidates, including multistage vaccines.

**Figure 1.** Manifestations of the malaria burden.
### Table 1
Determinants of the Malaria Burden

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Genetic susceptibility</td>
<td></td>
</tr>
<tr>
<td>Sickle cell trait (AS), hereditary ovalocytosis</td>
<td>Limit parasite invasion/growth in red blood cells (RBCs)</td>
</tr>
<tr>
<td>β thalassemia, HbE, fetal Hb, glucose-6-phosphate dehydrogenase deficiency, major histocompatibility antigens HLA-B53</td>
<td>Protect against severe disease</td>
</tr>
<tr>
<td>Duffy blood factor</td>
<td>Surface receptor needed for <em>Plasmodium vivax</em> entry into RBC</td>
</tr>
<tr>
<td>Immunologic status</td>
<td></td>
</tr>
<tr>
<td>Major histocompatibility antigen</td>
<td>Absence on infected RBCs limits T-cell recognition</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Infected RBC receptor, binds to brain endothelium, cerebral malaria</td>
</tr>
<tr>
<td>Tumor necrosis factor polymorphism</td>
<td>Linked to severe disease</td>
</tr>
<tr>
<td>Naïve mother</td>
<td>Susceptible new born</td>
</tr>
<tr>
<td>Residence in area of no or unstable transmission</td>
<td>Naïve/incompletely protected population</td>
</tr>
<tr>
<td>Residence in area of stable transmission</td>
<td>Premunition, partial protection</td>
</tr>
<tr>
<td>Parasite</td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Severe illness</td>
</tr>
<tr>
<td><em>P. vivax</em>, <em>Plasmodium ovale</em></td>
<td>Relapses</td>
</tr>
<tr>
<td><em>Plasmodium malariae</em></td>
<td>Nephrotic syndrome, recrudescence</td>
</tr>
<tr>
<td>Antigenic diversity</td>
<td>New infections, not recrudescence</td>
</tr>
<tr>
<td>Resistance to drugs: <em>P. falciparum</em> (widespread); <em>P. vivax</em> (reports from Asia, South America)</td>
<td>Inadequate patient management and increased burden</td>
</tr>
<tr>
<td>Mosquito</td>
<td></td>
</tr>
<tr>
<td><em>Anopheles gambiae</em> complex</td>
<td>Most efficient vector, widespread in Africa</td>
</tr>
<tr>
<td>High entomologic inoculation rate</td>
<td>Stable intense transmission and severe disease in susceptibles</td>
</tr>
<tr>
<td>Resistance to insecticides</td>
<td>Transmission maintained and increased burden</td>
</tr>
<tr>
<td>Environmental</td>
<td></td>
</tr>
<tr>
<td>Warm temperatures, high rainfall and humidity</td>
<td>Increased mosquito longevity</td>
</tr>
<tr>
<td>Clear, still, sun-exposed water collections</td>
<td>Good vector breeding sites</td>
</tr>
<tr>
<td>Engineering projects: dams, roads</td>
<td>New breeding sites, “human-made malaria”</td>
</tr>
<tr>
<td>Education, social, behavioral, political, and economic</td>
<td>Uninformed, ineffective participation in control and prevention</td>
</tr>
<tr>
<td>Illiteracy and poor knowledge of disease cause, transmission, and control</td>
<td>Necessary for proper prevention and control</td>
</tr>
<tr>
<td>Community participation</td>
<td>Urban malaria</td>
</tr>
<tr>
<td>Urbanization, economic opportunity</td>
<td>Refugee movements to malarious areas</td>
</tr>
<tr>
<td>Natural disasters, civil and military disruption</td>
<td>Inability to obtain and deploy drugs, insecticides, bed nets, and other measures</td>
</tr>
<tr>
<td>Poverty</td>
<td>Reflects high priority, spirit of success</td>
</tr>
<tr>
<td>Political, economic commitment</td>
<td></td>
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### Table 1
Continued

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Interventions</td>
<td></td>
</tr>
<tr>
<td>Policies, strategies and tactics well-defined</td>
<td>Good program conception and implementation</td>
</tr>
<tr>
<td>Sufficient infrastructure</td>
<td>Ability to provide services</td>
</tr>
<tr>
<td>Good training, implementation and evaluation</td>
<td>Ability to maintain effective program</td>
</tr>
<tr>
<td>Drugs, insecticides and bed nets available and effective</td>
<td>Services effective</td>
</tr>
<tr>
<td>Adequate financing</td>
<td>Control and prevention</td>
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**Parasite.** Of the 4 species of plasmodia affecting humans, *Plasmodium falciparum*, the most recently evolved species, is the most virulent, for reasons incompletely understood. Although *P. vivax*, which can cause relapses months after an infection, is widespread in Central and South America and Asia, it causes substantial morbidity but fewer severe complications; recently, low birth weight was reported with placental infection by *P. vivax*; a well-established result of *P. falciparum* infection. If untreated, patients may remain parasitemic and asymptomatic for years. *Plasmodium ovale*, also a relapsing species, is a rare (<0.5%) cause of infection; it is found principally in Africa. Evidence is accruing that genetic diversity of parasites is frequent within species, patients, and localities, probably because of recombination and selection, and has an impact on clinical presentation in various age groups and on malaria transmission. This may account for the lack of protective immunity and the frequent repeat infections and clinical episodes of malaria in persons, particularly young children, living in areas of intense and stable transmission, and it must be considered in the development of vaccines.

The development of *P. falciparum* resistance to drugs over the past 20 yr has been a major cause of poor malaria pro-
gram performance and increasing burden; resistance to chloroquine is widespread, multidrug resistance is increasing, and new strategies are being developed for their use. Since 1980, following the demise of global malaria eradication, use of effective drugs to reduce mortality and morbidity has been the major strategy for malaria control, particularly in Africa. The increasing malaria burden reflects the inadequacy of this current strategy, which may become further compromised by the projected increasingly widespread use of sulfamethoxazole-trimethoprim as prophylaxis for patients with human immunodeficiency virus and acquired immune deficiency syndrome. Resistance to sulfamethoxazole-trimethoprim may cross-react with a major antimalarial drug and vice versa. This would have ominous implications, because sulfadoxine-pyrimethamine is becoming a cost-effective first-line therapy in eastern and southern Africa.

Mosquito. Although there are about 400 species of Anopheles, only 60 of them transmit malaria under natural conditions, and only 30 are of major importance. Of these, the Anopheles gambiae complex and Anopheles funestus are the most efficient vectors for P. falciparum transmission; the highest rates of sporozoite development are in An. gambiae, the species that is widespread throughout tropical Africa. Of all factors related to malaria transmission, apart from host immunity, the number (density), human-biting habits, and longevity of anopheline mosquito vectors are the most important. Transmission is directly proportional to the density of the vector, the square of the number of human bites per day per mosquito, and the 10th power of the probability of the mosquito’s surviving for 1 d. Mosquito longevity is particularly important, because the portion of the parasite’s life cycle that takes place within the mosquito—from gametocyte ingestion to subsequent inoculation—can take from 8 to 30 d, depending on ambient temperature. In general, sporogony within the mosquito is not completed at temperatures below 16–18°C, and transmission does not occur. The entomologic inoculation rate (EIR)—the number of sporozoite-positive mosquito bites per year—is the most common measure of malarial transmission; this varies from < 1 in some parts of Latin America and Southeast Asia to > 300 in parts of tropical Africa. The relation between level of exposure (the EIR) and the incidence of severe malaria and death remains controversial. A high EIR results in stable and intense transmission, with young children the most vulnerable for severe illness. Higher EIRs are, in general, associated with increased frequency and density of parasitemia, febrile episodes, anemia and cerebral malaria in heavily endemic areas. The lower the EIR, the greater the number of susceptible individuals who can develop severe infection and illness.

Because the health service delivery systems have been so poor for malaria control and other diseases, vector control has had limited success in heavily endemic countries, especially in Africa; indeed, outside of a few urban centers and research projects, vector control has not been a major strategy, with the exception of a few areas in southern Africa. There is increasing interest in attacking the mosquito both with classical vector control technologies to prevent and control epidemics and with insecticide-impregnated bed nets and other materials for personal protection. With the realization that the current drug-use strategy alone will have a minimal impact on transmission and limited success in decreasing the malaria burden, newer vector-focused approaches are needed.

Environmental. Tropical areas with warm temperatures, heavy rainfall, and high humidity are conducive to mosquito breeding and longevity and parasite sporogony. An. gambiae mosquitoes breed readily in large and small collections of sun-exposed still water, such as exist throughout tropical Africa. Human engineering projects, e.g., construction of dams, roads, and industrial and residential centers, can result in disruption of the terrain, allowing increased mosquito breeding. Geographic areas where populations are susceptible to epidemics are of particular importance; these zones are often inundated by unseasonal rains, influxes of migrants and ref-
ugees, and breakdowns of malaria and other disease control and prevention programs. Epidemics linked to rainfall, temperature, geography, and, above all, population susceptibility and unresponsiveness to incipient epidemics will become more frequent.76–78 Recent mapping of malarious zones by endemicity and epidemic risk can help prevent medically catastrophic and disruptive malaria epidemics if realistic program objectives and indicators for action are established, periodic monitoring and supervision occur, and corrective steps are taken promptly when gaps are found.79–82 The rapid trend toward urbanization in developing countries will bring more malaria to large cities and will expose susceptible populations to outbreaks.83 Measures to prevent malaria can be easier to implement and more cost-effective in urban and peri-urban areas than in rural zones.

Social, behavioral, political, and economic. Over the past 100 yr there has been a decrease in malaria transmission in northern countries, including those with tropical areas,
following an improvement in education and in social and economic conditions. The improvement of general hygiene and public health included the filling in of swamps, elimination of open drainage ditches and other mosquito breeding sites, screening of windows and doors, widespread use of air conditioning, and availability of rapid diagnosis and drugs for acute illness. Alleviation of poverty has been associated with a decrease in malaria endemicity. Economic and educational gains, along with the ability to manufacture, purchase, and deploy effectively DDT and other insecticides, may have had the greatest impact on the malaria burden in temperate zones.\textsuperscript{84,85} In some African countries, no association was seen recently between socioeconomic status (SES) and severe malaria, anemia, and reinfection.\textsuperscript{86,87} Here, the SES may not reflect access to or use of malarial control or prevention measures or may reflect the relative ineffectiveness of those employed. Knowledge of which malaria control strategies and interventions are most cost-effective is needed because of the huge economic and medical toll of malaria. Recent attention given to malaria by the presidents of several African countries and by the leaders of northern countries has been very gratifying and, one hopes, reflects the political, financial, and other support for research and operations that must continue to be forthcoming.\textsuperscript{88}
Interventions. The current malaria control and prevention measures include personal protection, drug use, and vector control strategies (Figure 3). The correct and timely application of these strategies can result in decreases in malaria-specific and overall mortality, but this is difficult to achieve and sustain. Experience in Sri Lanka during eradication activities in the 1960s and 1970s showed that malaria can resurge in epidemic form rapidly, even when transmission is almost interrupted, if priorities change, field operations falter, and maintenance activities and resources are inadequate or diverted. Because of the gaps in these strategies, difficulties in mounting and maintaining effective operational activities, and the peril of increasing parasite resistance to drugs and insect resistance to insecticides, establishment of a sound malaria research base, particularly in endemic countries, is essential; the focus is now on developing 1 or more vaccines against malaria and on developing genetically altered anophelines unable to complete the sporogonic cycle. Development of new prevention and control tools requires greatly increasing the research and capacity of institutions in malarious areas and of partner institutions in the North. It is expected that opportunities offered by, and collaboration between, the Multilateral Initiative on Malaria (MIM), the Tropical Diseases Research and Training Program (TDR)/World Health Organization (WHO), Wellcome Trust, Roll Back Malaria/WHO, and other agencies, coupled with increasing private-sector interest and commitment, will accelerate new discoveries, their translation into interventions, and their deployment operationally.

ESTIMATING THE BURDEN

Worldwide estimates of the number of patients with acute febrile illness due to malaria have varied from 10 to 500 million annually. These estimates are imprecise, misleading, and low because of inadequate diagnosis and incomplete reporting. Some authors have tried to approximate the number of febrile patients who might be parasitic, an exercise that is difficult and has limited operational importance in malarious areas without diagnostic capacity. Others have designated 5,000–10,000 parasites/μL, another threshold level for a malaria diagnosis in partially immune patients living in endemic areas, a criterion that has some epidemiological but no clinical relevance. It is paradoxical and regrettable that for many years Africa was not included in WHO reporting of malaria morbidity and mortality because of poor surveillance and lack of parasitologic diagnosis, yet there is universal agreement that close to 90% of cases globally occur in Africa (Figure 4), and virtually all cause of poor surveillance and lack of parasitologic diagnosis, yet there is universal agreement that close to 90% of malaria deaths were based on the autopsy study by Bruce-Chwatt in Lagos, Nigeria; malaria on the brain and their sequelae remain to be quantified fully. International and bilateral organizations (including WHO, the United Nations Children’s Fund [UNICEF], and the U.S. Agency for International Development [USAID]) and public health staff in malarious countries have advised that all febrile children under 5 yr of age in endemic areas be treated for malaria. Home treatment is encouraged initially because of the potential severe consequences of untreated illness, the lack of precise diagnosis, and the relative inaccessibility of secondary and tertiary health care facilities. Most febrile persons do not come to the attention of the formal health infrastructure. The “ears of the hippopotamus” represent the fewer than 20% of patients who have any contact with the formal health delivery service when they become ill and die (Figure 6). The number of the most potentially severe malaria episodes can be approximated using the number of young pediatric febrile episodes reported by parents during field surveys in rural and urban endemic areas: these vary generally from 4 to 9 per year in children under 5 yr of age. Using this information, between 400 and 900 million febrile episodes would have occurred annually in children less than 5 yr of age living in endemic areas in Africa at the end of the 20th century; without effective interventions, by 2020 these numbers will have at least doubled (Figure 7). If 30–60% of these children were parasitemic, as reported in some studies, about half would have true malaria (200–450 million annually). In many areas, the parasitemia rate for children is higher, particularly during and just after the rainy season. These numbers do not consider febrile episodes and malaria infections in older children and adults in Africa and in endemic areas of the Americas and Asia. These older groups in Africa have between 0.4 and 1 episode of malaria yearly and probably 2 or more febrile episodes. Taking these older age groups and other continents into consideration, it is highly likely that worldwide well over 2 billion febrile episodes resembling malaria occur annually and that a substantial portion are parasitemic, meriting effective treatment.

DISCUSSION

Malaria will be tamed only when its manifestations and determinants are understood more completely where the infection and disease have special epidemiologic and clinical profiles and when current and more efficacious control measures are applied more effectively. Study of the intrinsic factors—in particular the genetic profiles of the human host, parasite, and mosquito and their interrelationships—will open new avenues for development of improved and new interventions. Relatively little can be done now to enhance innate or acquired resistance to malaria, although more effective management of hospitalized patients susceptible to severe or cerebral malaria might occur by use of cytokines and, ultimately, vaccines. Parasites and mosquitoes are the main targets of current and future interventions. Recent discoveries that plasmodial infections are antigenically heterogeneous complicate at-
emts to develop an effective blood-stage vaccine, but at least 1 group has produced a multiantigenic construct. The geographic spread and intensity of multidrug-resistant \textit{P. falciparum} is ominous and mandates the development of newer drugs and trials of drug combinations. Improved understanding of the genetic and biologic basis of parasite resistance to antimalarial drugs is leading to newer diagnostic approaches.

An attack on the mosquito—by insecticide-impregnated personal protection material (bed nets)—is the main “new” approach to malaria control, one that results in decreasing overall mortality. This approach has the advantage of involving individuals, families, and communities in decision making and implementation. Whether long-term use of such materials will achieve the 50% decrease in malaria-related mortality and morbidity within 10 yr—the goal of the WHO Roll Back Malaria—remains to be seen. Re-NEWED effort in understanding \textit{Anopheles} biology and ecology may lead to an original intervention that will prevent parasite maturation in and transmission by the mosquito.

The recent sequencing of chromosome 2 of 1 isolate of \textit{P. falciparum} offers promise of increased understanding of the function of specific genes within the parasite and sites for newer drugs and vaccines; of note is the recent finding that a single gene in \textit{P. falciparum} confers chloroquine resistance. Awaited with urgency is the development and field testing of the more effective antimalaria drugs, vaccines, and vector control methods that will certainly follow these new discoveries. At the same time, more effective and efficient health care delivery systems need to be developed to uncover and treat more of the hippopotamus than is seen currently. Although falciparum malaria certainly merits our full and immediate preoccupation, the WHO Roll Back Malaria—remains to be seen.

Acknowledgments: I thank Drs. Louis Miller, Robert Snow, and Kenneth Bridbord for constructive comments; Mr. Sean Murphy and Ms. Kathleen Deren-Bernocchi for review of morbidity and mortality data; and Ms. Melanie Rouse for manuscript assistance.

**REFERENCES**


