

## INTRODUCTION AND SUMMARY

## THE INTOLERABLE BURDEN OF MALARIA: A NEW LOOK AT THE NUMBERS

JOEL G. BREMAN, ANDRÉA EGAN, AND GERALD T. KEUSCH

*Fogarty International Center, National Institutes of Health, Bethesda, Maryland; Multilateral Initiative on Malaria, Fogarty International Center, National Institutes of Health, Bethesda, Maryland*

*“When you cannot measure it, when you cannot express it in numbers, you have scarcely . . . advanced to the stage of Science, whatever the matter may be.”*

William Thomson, Lord Kelvin, 1824–1907

For more than 50 years the mantra of “one million deaths due to malaria” has been uttered annually by lay and scientific writers alike. This figure, until recently, had generally gone unexamined in regard to its overall accuracy, clinical components, and most importantly, economic implications. The most troubling aspect of the unexamined burden of malaria during the Twentieth Century was the frequent exclusion of Africa from any calculations because of incomplete case detection and diagnosis in that continent. Apart from a few urban centers, no country in Africa was included in the WHO-sponsored Malaria Eradication Program, which began in the 1950s and ended unsuccessfully in the early 1970s. As late as the 1980s, only 3–10 million cases were reported annually by countries in the WHO Africa region, a small fraction of the total.<sup>1</sup> Outside of Africa, blood smear differentiation of *Plasmodium vivax* from *Plasmodium falciparum* was occurring, but the burden of malaria due to *P. vivax* was not always quantified precisely, even during the eradication program.

There have been several attempts to quantify malaria’s importance epidemiologically during the last decade, with increasing interest in controlling malaria through strengthened national and local health care systems. Estimates have remained, for the most part, close to the original figure of one million deaths—and the number of “cases” and “infections” has varied from 90 to 500 million respectively.<sup>2,3</sup> Most importantly, there has been a general consensus that about 90 percent of all cases occur in Africa, although the basis for this assumption has not been clear. Relatively few reports of the economic toll due to malaria have been published.

This supplement aims to describe what is known about the burden of malaria by considering the major manifestations, determinants, and consequences of the disease. The goals are also to promote more research on malaria’s toll and to develop improved interventions to decrease these effects. The supplement is derived from a symposium, “The Intolerable Burden of Malaria: A New Look at the Numbers,” held in December 1999 during the 48<sup>th</sup> Annual Meeting of the American Society of Tropical Medicine and Hygiene. Data were presented at the meeting indicating that malaria’s endemicity and burden in Africa could be defined and monitored more precisely by looking at parasitologic, clinical, epidemiologic, and entomologic indices. The meeting highlighted the concern that the effects of malaria on anemia, pregnancy, and neurological sequelae were not well-defined and were grossly underestimated. The economic burden of malaria was shown to be a major deterrent to eco-

nomics development, with the clear implication that investments in effective malaria control would result in substantial economic gains. Indeed, malaria is a cause of poverty, not the reverse. With the widespread and growing interest in the burden of malaria-related research and accelerated control, several papers, in addition to those presented at the symposium, were solicited for this supplement.

The emergence of *Plasmodium falciparum* resistance to drugs, first documented in the 1950s–1960s in Asia and the Americas and in the 1970s in Africa, is considered one of the major impediments to successful control.<sup>4</sup> Despite the spread and increasing intensity of drug resistance and the progressive change of first-line drugs from chloroquine to pyrimethamine-sulfadoxine in many areas of the world, there are scant data showing that morbidity and mortality have increased during this time or that they are due to increasing parasite resistance to drugs. Trape demonstrates a two- to three-fold increase in hospital admissions and deaths, and a six-fold increase in pediatric malaria mortality from data collected prospectively when chloroquine resistance emerged in Senegal in the late 1980s and early 1990s.<sup>5</sup> Similar phenomena had been reported earlier from Malawi and the Democratic Republic of the Congo (formerly Zaire) by retrospective analysis of hospital-based data.<sup>6,7</sup> Western Africa, including Senegal, has had relatively low-level resistance compared to elsewhere in Africa, so questions remain as to the percent of the increasing morbidity and mortality actually due to malaria. The HIV/AIDS epidemic began to spread at about the same time as chloroquine resistance. Yet, the major segment of the mortality due to malaria observed in Senegal, as elsewhere, has been in pediatric populations, although young children are not the major group afflicted by HIV/AIDS in Africa.

McElroy and colleagues show that, in the 1990s, 26 percent of the more than 1,500 children born in rural western Kenya died over a four-year period.<sup>8</sup> Neonatal and infant mortality were 32 per 1,000 and 176 per 1,000 live births, respectively. In Africa, malaria-attributable death rates have been reported as high as 25–30 percent for children under the age of five years.<sup>2,3,9,10</sup> These rates, based often on the change in mortality following intervention projects, drop below five percent in children over five years age in areas of stable endemicity. If these figures can be generalized, up to five percent or more of all African children borne in malarious areas will die from malaria. True, malaria’s burden reflects the variability in the microepidemiology of the disease and the availability and effectiveness of control measures throughout the continent. Even so, the number of malaria-associated deaths in children under the age of one alone computed using McElroy’s data may be one to two million per birth cohort, a figure exceeding that reported by others.<sup>2</sup> Steketee and others and Murphy and Breman show that the

malaria-related effects on pregnant women, their fetuses, and newborns comprise an extremely large and often hidden burden.<sup>11,12</sup> The manifestations of these effects are maternal anemia, low birth weight, and consequent infant mortality. Understanding each manifestation is important because these conditions are preventable. The authors posit that between 75,000 and 400,000 infant deaths per year are associated with malaria infections during pregnancy.

In their review of studies from throughout Africa, Guyatt and Snow report severe anemia (hemoglobin < 8 gm percent; packed cell volume < 25 percent) in more than eight percent of pregnant women studied; 11 percent of primigravidae were anemic.<sup>13</sup> Using attributable fraction analysis, the authors conclude that more than seven percent of the severe anemia in pregnant women is due to malaria—hence in sub-Saharan Africa, over 400,000 women annually may develop severe anemia as a result of malaria. Goodman and others show that, for primigravidae, the pyrimethamine-sulfadoxine (SP) regimen is found to be more cost-effective than the chloroquine regimen due to lower costs and higher compliance.<sup>14</sup> Both intermittent (once monthly) SP therapy and chloroquine given weekly appear to be “good value for money in comparison with other methods of malaria control.”<sup>14</sup> Extending the preventive regimens to all gravidae, and increasing the number of doses per pregnant woman, would make the interventions slightly less cost-effective. A major caution is that the increasing chloroquine resistance will soon render this drug ineffective.<sup>15</sup>

Of all the manifestations of malaria, those affecting general cognition and behavior may be the most subtle and ill-defined, and have the most profound implications. Holding and Snow state that 5–20 percent of survivors of cerebral malaria may have gross neurologic sequelae.<sup>16</sup> Cerebral malaria, frequently associated with major metabolic and physiologic changes, particularly hypoglycemia, decreased cerebral perfusion/hypoxia, and cytokine induction, results in tissue damage, generalized seizures, paralysis, speech and behavior disorders, hearing impairment, blindness, epilepsy and cerebral palsy—syndromes that in Africa are poorly defined clinically, epidemiologically, and economically. While few studies have looked at long-term cognitive impairment due to malaria or any other infectious disease in Africa, tests developed in western countries showed that 14 percent of Kenyan children were impaired after more than three years, compared to five percent of controls; for those having severe malaria, the odds ratio association with cognitive impairment was 4.5. Decreased “executive functions,” (i.e., the ability to initiate, plan, and carry out tasks) were some of the other deficits found. The authors state that “impairment of these higher order functions is likely to be reflected in an increase in the difference between affected and unaffected children over time.” Up to 85 percent of cerebral malaria patients have status epilepticus and up to 22 percent of cases result in temporal lobe epilepsy. Status epilepticus is associated with diminished cognitive function in about 30 percent of cases; temporal lobe epilepsy results in language and memory deficits.

Retardation of cerebral development may result from low birth weight. Sub-optimal development of the brain during early maturation may result in specific impairments in high order functioning (planning, decision making, self awareness

and social sensitivity), rather than direct damage from parasites per se.<sup>17</sup> Low birth weight is a risk factor for poor neurosensory, cognitive, and behavioral development, for impaired immunologic maturation, and for limitations in school performance. According to Taylor, between two and four times more children born prematurely “will experience failure in school compared to normal birthweight children and will need specialist or educational services.”<sup>17</sup> Among school-aged children, up to half of all absences were due to medical reasons and up to eight percent were due directly to malaria.<sup>16</sup>

The various “syndromes” due to malaria are varied, complex, and frequently overlap.<sup>18</sup> Murphy and Breman quantify the major clinical manifestations of malaria by reviewing past studies, and applying estimates of disease rates to current demographic profiles of malarious African populations, focusing on children under five years of age.<sup>12</sup> They conclude that close to 600,000 persons contract cerebral malaria yearly, with a case fatality rate of about 20 percent. Neurologic complications lasting longer than six months may occur in up to 19,000 of these patients. Severe anemia due to malaria occurs in between 1.5–6.0 million African children; with a case fatality rate of nearly 15 percent, up to one million children may die every year from malaria-induced anemia. Respiratory distress, hypoglycemia, and overlapping conditions contribute another one to two million cases and, with a mortality nearing 20 percent, well over 200,000 deaths. In Africa, there may be up to one million malaria-associated low birth weight babies born each year and approximately 400,000 of these children will die. All of these “gaps” in the burden contribute up to 1.7 million deaths in African children yearly, with more than 50 percent due to anemia. The exact cause of death is unknown in reports of malaria deaths from countries and international agencies; hence, it is likely that deaths ascribed to acute febrile illness due to malaria may be grossly underestimated, particularly when malaria-induced anemia, low birth weight babies, hypoglycemia, and other adverse events may not be included in their calculations, because of an inability to diagnose these conditions in most of Africa.

The major reason for defining the burden of malaria is to take action to decrease its impact. One of the biggest challenges is to develop standardized case definitions and generally accepted measures of progress as interventions against malaria proceed.<sup>19</sup> Implementation of malaria control interventions has been accelerating slowly over the past two decades and is now expected to increase briskly with the recent initiation of the Roll Back Malaria Project (RBM). This laudable WHO-inspired and -coordinated program aims to halve the burden of malaria over a period of ten years via interventions adapted to local needs and the strengthening of the health sector. This will be achieved by applying currently efficacious technologies in malarious countries, mainly in Africa, and by “channel(ing) funds and supplies efficiently to local communities.”<sup>20,21</sup> Remme and others define the critical areas for monitoring RBM process (activity) indicators and, most importantly, the outcome indicators, morbidity and mortality. To address 1) impact, 2) prevention and treatment, 3) health sector development and 4) program support, a core group of four indicators is recommended.<sup>22</sup> One concern with the Roll Back Malaria monitoring scheme is

that each country is free to select its own indicators, making comparison difficult. It is important that programs have a common set of indicators so that comparisons can be made promptly and donors (including national and international partners) will have access to frequent updates of the progress being made as a result of their investments.

While humanitarian and medical reasons for investing in disease control efforts are justified, the arguments that garner the most resources for control and eradication programs are economic. Gallup and Sachs show that where malaria has been eliminated economic growth has increased substantially over the following five years, compared to growth in neighboring countries.<sup>23</sup> Countries with intensive malaria lagged in growth by 1.3 percent per person per year compared to neighboring countries; a ten percent decrease in malaria incidence was associated with a 0.3 percent increase in annual economic growth. It is incontestable that the control of malaria in Africa and elsewhere will increase economic indices, encourage international investment and foreign trade, and result in improved social and political stability.

*Plasmodium falciparum* causes the greatest toll from malaria, but *P. vivax* is more pervasive and treacherous than is generally believed. Mendis and others posit that, of the 80 million cases of *P. vivax* malaria that occur annually, up to 20 percent occur in sub-Saharan Africa, mainly in the east and south where genetically receptive populations reside.<sup>24</sup> The remainder of *P. vivax* occurs in the Middle East, Asia, and the Western Pacific, and to a lesser extent in Central and South America. Many of these areas have low transmission and little acquired immunity; therefore, all age groups are vulnerable to periodic epidemics. This parasite is thought to cause little mortality, but repeat infections can have major deleterious effects on growth and development, well-being, and economic prosperity.

The papers in this supplement, while illuminating, make it clear that much more precision is needed before a full understanding of malaria's burden will be available. The interface between parasite biology and immunology, the pathogenesis of infection, the clinical manifestations, the epidemiologic features, the impact of interventions, the economic consequences, and the relationship of malaria with other health problems—particularly HIV/AIDS, other febrile illnesses, and malnutrition—require more intense investigation by southern and northern scientists and public health workers. The Multilateral Initiative on Malaria (MIM) is a coalition of African malariologists and scientific, public health, and development institutions throughout Africa and of international non-African malariologists and research and funding agencies.<sup>25,26</sup> The MIM is dedicated to realizing the principle that progress to control malaria depends on the presence of a first-rate malaria research program run by African scientists working in Africa. The ongoing battle against malaria requires an intensified research program to improve current tools and develop new ones for malaria control and facilitate the more effective use of currently available strategies.

Thus, the MIM Secretariat (currently at the Fogarty International Center, National Institutes of Health), the TDR at the World Health Organization, and MIM partners support research by African scientists and training to strengthen African research capacity to improve malaria control. The pro-

gram is multi-faceted, focusing on vector biology, anti-malarial drugs, the clinical immunology and pathophysiology of malaria to develop vaccines and other interventions, and improvement in patient management and prevention tools. An important part of this process has been investing in the capacity of African malaria research centers and researchers to have reliable Internet communication among themselves and their international collaborators, and to be able to access information via the Internet. The 1999 symposium and this publication and its dissemination are another important MIM-supported effort to improve scientific communication in the field.

Authors' addresses: Joel G. Breman, Deputy Director, Division of International Training and Research, Fogarty International Center, National Institutes of Health; Senior Scientific Advisor, Secretariat, Multilateral Initiative on Malaria; Bldg. 31, Room B2C39, 31 Center Drive, MSC 2220, Bethesda, Maryland 20892-2220; Phone: (301) 496-1653, FAX: (301) 402-0779, E-mail: jbreman@nih.gov. Andréa Egan, Coordinator, Secretariat, Multilateral Initiative on Malaria, Fogarty International Center, National Institutes of Health, Bldg. 31, Room B2C39, 31 Center Drive, MSC 2220, Bethesda, Maryland 20892-2220; Phone: (301) 402-6680, FAX: (301) 402-2056, E-mail: egana@mail.nih.gov. Gerald T. Keusch, Director, Fogarty International Center, National Institutes of Health; Director, Secretariat, Multilateral Initiative on Malaria Bldg. 31, Room B2C07, 31 Center Drive, MSC 2220, Bethesda, Maryland 20892-2220; Phone: (301) 496-1415, FAX: (301) 402-2173, E-mail: keuschg@nih.gov.

#### REFERENCES

1. Breman JG, Campbell CC, 1988. Combating severe malaria in African children. *Bull World Health Org* 66: 611-620.
2. Snow RW, Craig M, Deichmann U, Marsh K, 1999. Estimating mortality, morbidity and disability due to malaria among America's non-pregnant population. *Bull World Health Org* 77: 624-640.
3. Breman JG, 2001. The ears of the hippopotamus: manifestations, determinants and estimates of the malaria burden. *Am J Trop Med Hyg* 64(suppl 1): 1-11.
4. Su X, Kirkman LA, Fujioka H, Wellems TE, 1997. Complex polymorphisms in an approximately 330 kDa protein are linked to chloroquine resistant *P. falciparum* in Southeast Asia and Africa. *Cell* 91: 593-603.
5. Trape JF, 2001. The public health impact of chloroquine resistance in Africa. *Am J Trop Med Hyg* 64(suppl 1): 12-17.
6. Khoromana CO, Campbell CC, Wirima JJ, Heymann DL, 1986. *In vivo* efficacy of chloroquine treatment for *Plasmodium falciparum* in Malawian children under five years of age. *Am J Trop Med Hyg* 35: 465-471.
7. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F, 1989. Hospital based surveillance of malaria-related paediatric morbidity and mortality. *Bull World Health Org* 67: 189-196.
8. McElroy PD, ter Kuile FO, Hightower AW, Hawley WA, Phillips-Howard PA, Oloo AJ, Lal AF, Nahlen BL, 2001. *Am J Trop Med Hyg* 64(suppl 1): 18-27.
9. Molineux L, 1985. The impact of parasitic diseases and their control, with an emphasis on malaria in Africa. Vallin J, Lopez A, eds. *Health Policy, Social Policy and Mortality Prospects*. Paris: Ordina Editions, 13-44.
10. Payne D, Grab B, Fontaine RE, Hempel JH, 1976. Impact of control measures on malaria transmission and general mortality. *Bull World Health Org* 54: 369-377.
11. Steketee RW, Nahlen BL, Parise ME, Menendez C, 2001. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg* 64(suppl 1): 28-35.
12. Murphy SC, Breman JG, 2001. Gaps in the childhood malaria burden in Africa: adding cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia and com-

- lications of pregnancy to the calculus. *Am J Trop Med Hyg* 64(suppl 1): 57–67.
13. Guyatt HL, Snow RW, 2001. The epidemiology and burden of *Plasmodium falciparum*-related anemia among pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg* 64(suppl 1): 36–44.
  14. Goodman CA, Coleman PG, Mills AJ, 2001. The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. *Am J Trop Med Hyg* 64(suppl 1): 45–56.
  15. Schultz LJ, Steketee RW, Chitsulo L, Macheso A, Kazembe P, Wirima JJ, 1996. Evaluation of maternal practices, efficacy, and cost-effectiveness of alternative antimalarial regimens for use in pregnancy: chloroquine and sulfadoxine-pyrimethamine. *Am J Trop Med Hyg* 55(suppl): 87–94.
  16. Holding PA, Snow RW, 2001. The impact of *Plasmodium falciparum* malaria on performance and learning: a review of the evidence. *Am J Trop Med Hyg* 64(suppl 1): 68–75.
  17. Taylor HG, 1984. Early brain injury and cognitive development. Almlı C, Fingers S, eds. *Early Brain Damage: Research Orientations and Clinical Observation*. New York: Academic Press, Inc., 325–345.
  18. Marsh K, Snow RW, 1999. Malaria transmission and morbidity. *Parassitologia* 41: 241–246.
  19. Bryce J, Rongou JB, Nguyen-Dinh P, Naimoli JF, Breman JG, 1994. Evaluation of national malaria control programmes in Africa. *Bull World Health Org* 72: 371–381.
  20. Nabarro D, Taylor E, 1998. “The Roll Back Malaria” campaign. *Science* 280: 2067–2068.
  21. Alnwick D, 2000. Roll Back Malaria—what are the prospects? *Bull World Health Org* 78(12): 1377.
  22. Remme JHF, Binka F, Nabarro D, 2001. A framework and indicators for monitoring Roll Back Malaria. *Am J Trop Med Hyg* 64(suppl 1): 76–84.
  23. Gallup JL, Sachs JD, 2001. The economic burden of malaria. *Am J Trop Med Hyg* 64(suppl 1): 85–96.
  24. Mendis K, Sina BJ, Marchesini P, Carter R, 2001. The neglected burden of *P. vivax* malaria. *Am J Trop Med Hyg* 64(suppl 1): 97–106.
  25. Bruno JM, Feachem R, Godal T, Nchinda T, Ogilvie B, Mons B, Mshana R, Radda G, Samba E, Schwartz M, Varmus H., Diallo S, Doumbo O, Greenwood B, Kilama W, Miller, LH, da Silva LP, 1997. The spirit of Dakar: a call for action on malaria. *Nature* 386: 541.
  26. Davies CS, 1999. The Multilateral Initiative on Malaria: co-ordination and co-operation in international malaria research. *Parassitologia* 41: 497–500.