Defining and Defeating the Intolerable Burden of Malaria

III. Progress and Perspectives

Summary

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INTRODUCTION

The past 10 years have brought unprecedented advances in malaria research, resulting in recommendations for front-line use of artemisinin-based combination treatments (ACTs) for patients exposed to drug-resistant malaria and long-lasting insecticide treated nets (LLINs) for personal protection. Sequencing of the genomes of Plasmodium falciparum, Anopheles gambiae, and humans offers great opportunity for better understanding of genetic susceptibility to infection and illness and development of improved and new diagnostics, drugs, vaccines, and insecticides. Research coalitions supported by the United States National Institutes of Health, Wellcome Trust, Bill & Melinda Gates Foundation, the Multilateral Initiative on Malaria (MIM), and the Special Programme for Research and Training at the World Health Organization (WHO) are spearheading these breakthroughs. The Global Fund for AIDS, Tuberculosis, and Malaria, the Global Malaria Programme and Roll Back Malaria Partnership (RBM) at WHO, the United States President’s Malaria Initiative (PMI), the Malaria Control Booster Program at the World Bank, the Bill & Melinda Gates Foundation, and other funding organizations are contributing hundreds of millions of dollars to malaria control based on the medical, public health, and economic burden of this disease. Most importantly, all endemic countries are developing and implementing malaria control policies, strategies, and plans: many countries are increasing coverage and use of drugs and nets and insecticides. Residual spraying (IRS) of homes is making a comeback. Increasing coverage and use of drugs and nets and insecticides control policies, strategies, and plans: many countries are increasing coverage and use of drugs and nets and insecticides residual spraying (IRS) of homes is making a comeback. Some countries are controlling malaria.1

The first two malaria burden supplements to the American Journal of Hygiene and Tropical Medicine quantified the morbidities, mortalities, and economic consequences of this scourge.2,3 The second supplement covered, in particular, the status of ACTs and vaccine research and the importance of using information for decision making. Underscored were the benefits of establishing modern communications, data management, and information sharing systems for colleagues working in malarious countries.4 This collection of 42 papers describes the new and the old in malaria research and its application: new ways of looking at old issues and new findings in clinical, epidemiologic, drug, vector, and genetic and vaccine research. Special attention is given to the diagnosis of malaria in individuals and communities and detailed planning for scaling up national and international control programs including clinical and epidemiologic evaluations of malaria vaccines.

MALARIA: THINKING IN THE BOX

The WHO definition of malaria is an infectious disease caused by protozoa of the genus Plasmodium; episodes of illness are “attacks of chills, fever, and sweating caused by Plasmodium infection.” Although the lack of asexual parasitemia eliminates malaria as a clinical diagnosis, Koram and Molyneux5 affirm that “the presence of organisms in the blood provides no proof of causality” of illness or disease. They present a schematic that underscores the importance of high-quality clinical and laboratory diagnosis of malaria and similar syndromes to assure the best use of resources. Without diagnostic acumen, there will be failure to treat life-threatening conditions, erroneous diagnoses and treatment, and dissipation of resources. Gwer and others6 report that 30% to 40% of comatose children in eastern Kenya with a negative blood smear for parasites have invasive bacterial infections amenable to anti-microbials. The arrival of several ACTs after extensive pharmacologic and clinical evaluation has been one of the most spectacular advances in malaria research and control. Making available water-soluble artesunate for treating patients with severe malaria, including pregnant women in the second and third trimester, is forwarded by Day and Dondorp.7 They describe why and how parenteral artesunate has become the treatment of choice for severe malaria and for severely ill pregnant women in their second and third trimesters. Malaria-infected cells in the placentas of pregnant women express variant surface antigens (VSAs), mainly the VAR2-chondroitin sulfate (CS) protein; lack of immunity to VSA results in placental pathology, low birth weight, and maternal anemia. Rogerson and others8 aver that interventions countering these threats to fetal development should relate to the timing of placental infections.

EPIDEMIOLOGY AND CONTROL

Up to 600 million cases and > 2 million deaths are caused by P. falciparum and 400 million cases of P. vivax malaria occur annually. Breman and Holloway9 attest that substantially < 10% of these cases are reported officially. In sub-Saharan Africa, where falciparum is pervasive and the major killer of under fives, children experience four or more febrile episodes yearly; this results in billions of febrile episodes merit- ing anti-malaria drug treatment if no precise diagnostic tool is available. Good surveillance should begin at hospitals, where high-quality diagnosis and clinical management are most likely to occur; strengthened surveillance would spread to peripheral health units with proper training, supplies of equipment and reagents, and supervision. Measuring progress in malaria control mandates having demographically defined denominators in communities whereby overall disease and mortality can be ascertained. Such surveillance requires stan-

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dard case definitions, sentinel reporting stations, modern information technology equipment and mechanisms, and staff trained and supervised in their use by knowledgeable surveillance experts. Such a system, to be useful, requires timely analysis of data and feedback to local staff. The INDEPTH network has contributed greatly to understanding the seasonality and age-specific attack rates of malaria and other diseases throughout the world. Using verbal autopsies, seasonally adjusted malaria mortality in children < 15 years of age was found by Abdulla and others to be similar at seven different sites in Africa.19

At the turn of this century, the economic burden of malaria for sub-Saharan Africa was estimated at $12 billion US dollars yearly; heavily malarious countries were impeded by 1.3% per year in development as measured by the gross domestic product. Makundi and others13 estimate that more than $240 million are lost yearly in Tanzania in gross domestic product because of malaria. Constraints to control are the meager human, financial, and material resources and “an inefficient health care system,” HIV/AIDS and other competing priorities, and inadequate surveillance; these greatly restrict the rational establishment of priorities, planning of control programs, and obtaining resources for them.

All-cause child mortality is now advised by the malaria Monitoring and Evaluation Resource Group as an indicator for measuring malaria control progress in Africa. Rowe and Steketee12 posit that a 50% reduction in malaria mortality will result in a 17% reduction in overall child mortality. They attest that a 25% reduction in overall mortality will occur when malaria interventions are scaled up from <5% coverage to >70% coverage; going from low to high coverage of interventions is now occurring, but the patient access, use, and quality of services delivered requires better definition and improvement.

Brooker and colleagues define the extensive geographic overlap between P. falciparum and the major human helminth infections in Africa.13 Hookworm is the most prevalent geohelminth, and school-aged children are at greatest risk for co-infection; these infections add to the already heavy malaria-induced anemia. It is recommended that school-aged children and pregnant women benefit from an integrated approach to malaria and helminth control with combined detection and treatment programs. Nonetheless, malarial anemia causes more deaths than any other manifestation. In western Kenya, Obonyo and collaborators report that 86% of 1,116 pediatric admissions had a hemoglobin of < 11 g/dL, and 21% were severely anemic (< 8 g/dL); 85% of patients with severe anemia were parasitemic.14 Children < 3 years of age made up 86% of admissions. Overall, 8% of the anemic children and 12% of those with severe anemia died, and two thirds of the deaths were “malaria related.” Women in their first or second pregnancy living in malarious areas are at special risk of developing clinical malaria (especially anemia) and enduring fetal wastage and having small newborns; low birth weight is a risk factor for heightened neonatal and infant mortality. Studies in Burkina Faso by Coulibaly and others15 have shown that the frequency of parasitemia in all pregnant women was 32% in December, after the heavy transmission season, and 12% in May, at the end of the dry season. They advise that all pregnant women have intermittent preventive treatment (IPTp) and access to other preventive measures.

Eritrea is susceptible to epidemics of malaria. Ceccato and others16 report on monthly clinical case data from 245 health units in 58 districts that were used to stratify priority areas and guide interventions from 1998 to 2003. The use of remotely sensed climate data for prediction and prevention of epidemics in Eritrea will require much wider coverage of reporting sites than was possible during this study.

India reports 2 million confirmed malaria cases and 1,000 deaths yearly, but Kumar and others17 state that 15 million cases and 20,000 to 50,000 deaths are occurring. The presence of nine Anopheline vectors, perserviveness of P. vivax and P. falciparum (the latter resistant to drugs), and diverse climates and cultures present formidable obstacles to malaria control in India. P. vivax threatens almost 40% of the world’s population; quantifying this neglected burden is challenging because vivax is a relapsing parasite. Price and others18 affirm that the severity and epidemiologic and economic burden of vivax malaria has been greatly underestimated—up to 400 million cases yearly—and merits intensified epidemiologic surveillance and attention to diagnosis, patient management, and control.

**EVALUATION AND IMPACT**

Microscopic examination of Giemsa-stained blood smears and the newly developed rapid diagnostic tests (RDTs) are crucial for diagnosing malaria. Close supervision and quality assurance is required for both approaches. Wongsrichanalai and others19 state that investments in drug development must be coupled with investments in diagnostics, particularly because these tests are the basis for determining efficacy, resistance, and changes in transmission and burden. Cost-effectiveness analysis of RDTs was done in a Tanzanian trial of ACTs. Lubell and others20 found, in low- and high-transmission seasons, that an increase of > 2% and 9% of patients would be treated, respectively, using RDTs compared with microscopy at an incremental cost of $25 and $7 per patient treated. The cost effectiveness would be worse if those ordering the tests and the patients do not comply with test results. The authors concluded that RDTs may be more expensive than many countries can afford without external assistance or lower prices.

Trends in malaria burden can be assessed by information collected by nationally representative household surveys, at demographic surveillance sites, and through routine health system reports. Each has its usefulness and limitations. Cibulskis and others21 suggest that all three approaches should be used and that a demographically defined population at risk should serve as the denominator base for following trends.

The biggest challenge in disease control is translating program plans deriving from the burden into human, material, and monetary requirements for implementing actions. Tekele-Raimon and others22 have used geographic information systems and epidemiologic data to estimate the needs in Africa for meeting the Millennium Development Goals, with scaled-up national malaria control programs by 2015. $2.5 billion or $3.29 per person per year will be needed. What results would occur with this level of investment? In Ghana, up to one third of deaths in a hyperendemic malarious rural area are caused by malaria. Using a detailed demographic approach, Bawah and Binka23 calculate that life expectancy at birth would increase by >6 years in northern Ghana if malaria were eliminated as a cause of death.
DRUGS

It is becoming increasingly necessary to monitor systematically the efficacy of anti-malaria drugs in each country. Although most countries are switching to ACTs, there will be an interval before adequate supplies are available at low cost to all populations. Vestergaard and Ringwald24 discuss the therapeutic efficacy (in vivo) test, in vitro testing, and molecular markers of resistance. The in vivo test, which considers patients’ immunity, is used for developing and changing national policies, whereas the other tests detect drug sensitivity changes early and specific parasite resistance genes. Laufer and others27 advise that in vitro or molecular methods be used for identifying resistance patterns early in areas where resistance is low to moderate; these tests will be critical for confirming and characterizing resistance to artemisinin and their partner drugs if that occurs. WHO has strongly recommended the abandonment of artemisinin monotherapy; regrettably, many of these compounds are still being sold. A study in east Africa by Talisuna and others26 found that falciparum resistance to chloroquine and sulfadoxine-pyrimethamine was highest where malaria transmission was most intense. Vector control, with presumed decrease in transmission, increased the efficacy of these drugs. Judicious use of drugs and an active vector control initiative offers a good opportunity to control malaria while suppressing drug resistance.

The efficacy of the ACTs (e.g., artesunate-mefloquine, artemether-lumefantrine, dihydroartemisinin-piperaquine and others) usually exceeds 95%. Nosten and White27 report that these drugs are safe, well tolerated, and generally accepted as the best treatments for uncomplicated falciparum malaria and for pregnant women in their second and third trimesters. Boman and Mendis28 state that, of the 61 endemic malarious countries that have shifted to ACTs, 41 of them are in Africa. Of the 31.3 million ACT courses procured through WHO in 2005 for public sector use, > 80% went to Africa, most to 21 countries where ACTs are being deployed; considering the urgent need for ACTs, this number is very low. As the production and consumption of ACTs increases, increased financing becomes necessary to assure market stability. Also needed is discouragement of use of and control over the distribution of artemisinins as monotherapies through the private sector; regrettably, this occurs in 47 endemic countries.

ACTs remain costly compared with other anti-malarial drugs because the active ingredients are derived from naturally growing plants. A coalition of public and private partners supported by the Bill & Melinda Gates Foundation is using synthetic biology to manufacture a low-cost, microbially derived artemisinin through a fermentation process described by Hale and others.29 Many traditional and modern drugs are sold in villages by unlicensed and untrained merchants—“vendeurs” or “vendeuses.” Goodman and others30 describe an innovative approach whereby 16 interventions were identified to improve the practices of sellers of malaria treatments: these involved training and capacity building, generating demand, quality assurance, and creating an enabling environment. The United States Institute of Medicine reported that a global high-level subsidy was needed to make anti-malarial drugs widely available at affordable prices. Gelband and Seiter31 state that the ACTs were identified as needing immediate support; use of ACTs would delay the emergence of parasite resistance to artemisinin monotherapy, which has lamentably been marketed actively by several companies.

VECTORS

Omlim and others32 present an important discovery on the habitat of malaria vectors. At six sites in Kisumu city, western Kenya, immature Anopheles were found in treeholes; An. gambiae larvae were found in 19 tree species, 13 of which were exotic (imported). The authors indicate that treeholes represent a hitherto unrecognized habitat for some malaria vectors.

Transgenic strains of mosquitoes have been developed and evaluated to (1) replace or suppress wild vector populations and (2) reduce transmission and deliver public health gains. Knols and others33 state that developments in modern biotechnology, in particular genetic modification of vectors, requires competencies beyond the field of biology; the future of transgenic mosquitoes will hinge on the ability to govern the process of their introduction into societies in which perceived risks may outweigh the rational and responsible involvement of citizens and policy makers.

In 2006, dichlorodiphenyltrichloroethylene (DDT) was reintroduced into the arsenal of vector control interventionists focused on malaria control. The WHO issued a statement promoting the use of indoor residual spraying (IRS) with DDT for malaria vector control in epidemic and endemic areas. Sadasivaiah and others34 conclude that, although DDT is a low-cost anti-malarial tool, the possible adverse human and environmental effects of exposure through IRS must be carefully weighed against the benefits. This article discusses the controversy surrounding the use of DDT for IRS; its effective implementation in Africa; recommendations for its deployment; training, monitoring, and research needs for effective and sustainable implementation; and other insecticide options and vector control approaches.

Smith and others35 collected 255 bed nets 38 months after distribution in Lawra District of northwest Ghana to examine their physical condition and residual insecticide levels. The condition of the nets varied from nearly pristine to torn and highly damaged. It was determined with a simple field adaptable chemical measuring device that only 14.9% of the nets had retained full insecticidal strength. These results highlight the value of field data on bed net condition and insecticide longevity to guide decisions regarding mosquito control strategies, bed net purchasing, frequency of bed net replacement, and product development. Periodic monitoring of the new LLINs’ use, efficacy, and effectiveness is essential.

The use of ITNs is universally accepted as a major component of all malaria control programs. WHO recommends LLINs, and these are being manufactured by two companies. Children and pregnant women have priority; however, it is recognized that the entire family and community should receive and use ITNs. This will protect all persons and prevent the taking of nets from priority groups. Protecting all populations with ITNs will also decrease the infective reservoir of gametocytes and get the maximum impact for decreasing transmission. Lengeler and others36 describe the tension between those who favor free distribution of ITNs—an approach that will quickly achieve high coverage rates—and
those who supported “targeted subsidies” through direct distribution of ITNs or through vouchers; for the latter, a competitive commercial sector for ITNs is proposed. More experience is needed to test these options.

In 2000, the African heads of state endorsed the removal of taxes and tariffs on ITNs at the African Summit of Roll Back Malaria in Abuja, Nigeria. However, in 2007, 24 of the 39 signatory countries continue to impose such taxes. Alilio and others contended that these burdensome taxes substantially increase the price of ITNs, reduce affordability, and discourage the commercial sector from importing ITN products. Urgent tax and tariff reforms are needed if the required 160 million nets are to be deployed in Africa to reach the goals agreed on in the Abuja declaration.

GENETICS, IMMUNOLOGY, AND VACCINES

Ntoumi and others discuss why the sequencing of the human genome provides new opportunities to determine the genetic traits that confer resistance to infection or disease. The identification of these traits can reveal immune responses or host–parasite interactions that may be useful for designing vaccines or new drugs. Similarly, knowing the parasite genome sequence will accelerate the development of new anti-malarial interventions, for example, by identifying parasite metabolic pathways that may be targeted by drugs. Genomic studies of human populations raise important ethical issues, such as the disposition and use of data related to disease susceptibility or paternity and the ability of communities to understand the nature of the research and participate appropriately.

Lessons have been learned about different approaches to the development of vaccine candidates, including the different clinical trial phases and endpoints and methods to conduct them. Guinovart and Alonso state that improved understanding of mechanisms underlying naturally acquired immunity, definitions of surrogate markers of protection, including improved in vitro assays and animal models, and strengthened capacity in malaria endemic countries to conduct clinical trials will accelerate the development of malaria vaccines. Kilama and others describe the mission of the African Malaria Network Trust (AMANET), which is to promote capacity strengthening of African malaria research institutions; AMANET was founded in 2002 and is currently focusing on malaria vaccine development. The organization has trained > 900 African malaria researchers at workshops relevant to clinical trials of candidate malaria vaccines that will meet scientific, ethical, and international Good Clinical Practice standards. GlaxoSmithKline Biologicals (GSK) is committed to the development of a safe and effective malaria vaccine. Balou and Cahill describe the GSK malaria vaccine research program that was initiated in 1984 and has been continuously active, making it unparalleled within the vaccine industry. Through GSK’s pioneering business model and working in partnership with global vaccine funding agencies, the company is committed to seeing that, once approved, a safe and effective malaria vaccine will be available to everyone who needs it. A recently completed study in young children in Mozambique showed safety and an efficacy of > 50% of a pre-erythrocytic vaccine developed by GSK as part of a public private partnership.

INTERNATIONAL COOPERATION

The Multilateral Initiative on Malaria (MIM) was founded in 1997 to combat the burden of malaria through strengthening research capacity in Africa, increasing international cooperation and communication, and using research findings to inform malaria prevention, treatment, and control. A review of MIM undertaken in 2002 showed that, through improved communication and science-focused institutional networks, MIM had brought African scientists together, opened up communication among malaria stakeholders, and provided Internet access to literature. The achievements were made through four autonomous constituents including the coordinating Secretariat, now hosted for the first time in Africa by the African Malaria Network Trust (AMANET) for the period 2006–2010. The other constituents are the MIM TDR providing funding for peer-reviewed research; MIMCom facilitating Internet connectivity, access to medical literature, and communication between scientists inside and outside of Africa; and MR4 providing scientists access to research tools, standardized reagents, and protocols. Rugemalia and others affir that the result of MIM Secretariat activities is reflected in the tremendous increase in the malaria profile globally and resources for research, control, prevention, and advocacy. Nantula and others report that the six research coalitions fostered by MIM have resulted in > 100 scientific articles and dozens of malaria leaders being trained and advanced in their careers. Close to 70 research projects have been undertaken in 17 countries by 56 principal investigators through a peer-reviewed competitive grant program coordinated and managed by MIM TDR/WHO. Most impressively, the research results have been used for national malaria control policy development and operational planning.

The global malaria agenda is now experiencing an unprecedented time of public recognition and political will and momentum. Bates and Herrington state that there is a nascent, but increasingly sophisticated, global advocacy effort that has contributed to new and expanded malaria funding, programs, and technology. They describe the principles of sound advocacy along with the mechanisms that are needed for sustained, pro-political momentum and support for malaria research, resources, and results.

As of December 2006, the Global Fund for HIV/AIDS, Tuberculosis, and Malaria has committed $2.6 billion over 5 years to support malaria prevention and control in 85 countries. The Global Fund has worked closely with RBM partners to develop consensus on a set of outcome and impact indicators that have been incorporated into malaria grant agreements. Nahlen and Low-Beer report that, although the Global Fund has recommended that 5% to 10% of grant funds be invested in improving the capacity of the national monitoring and evaluation systems, an average of only 3.9% is invested in these systems. Several countries are already showing reductions in the malaria burden. To sustain the scale-up in funding to support malaria interventions, countries must ensure that resources are used to show robust, systematic, and regular measurement of impact on the burden of malaria.

CONCLUSION

The medical and economic burden of malaria is staggering and intolerable. Malaria is the number one killer of children...
in nearly every endemic country. Pregnant women who contract malaria risk having low birth weight babies, maternal anemia, impaired fetal growth, spontaneous abortions, and stillbirths.

The scope of papers in this volume address the challenge of reducing the global malaria burden through research and control. Priorities are preventing infection and illness; promoting effective diagnosis and treatment and responding to the emergence and spread of drug-resistant malaria; protecting pregnant women through a combination of IPT treatment and LLINs; addressing the needs of populations in complex humanitarian emergencies; and developing new tools and approaches for malaria prevention and control, including vector control innovations and vaccines. Once transmission starts to decrease in all malarious countries, the total demise of malaria will follow.

There have been positive commitments by the developed countries to address the burden of malaria by helping endemic countries to build leadership capacity in science and public health to more effectively prevent and treat malaria. Recent support includes making ACTs, RDTs, LLINs, IRS, and technical assistance widely accessible to the poor countries.

Tracking the progress toward the goal of reducing malaria-related illness and mortality around the world will require additional research, monitoring, and evaluation investments. There are no adequate routine registrations of cases and deaths in most malaria-endemic counties. It is important that, as more research and information technology tools become available, they are used to improve malaria control interventions and strengthen malaria surveillance systems.

REFERENCES


