

Economic Access to Effective Drugs for Falciparum Malaria

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The increasing death toll from drug-resistant falciparum malaria is cause for international concern. In 2002, the US Agency for International Development commissioned the Institute of Medicine (IOM) to recommend global actions to ensure the broadest possible access to new, effective antimalarial treatments. In a report issued in 2004, the IOM Committee on Economics of Antimalarial Drugs recommended a global subsidy of \$300 million to \$500 million per year to replace increasingly ineffective drugs with coformulated artemisinin combination treatments to be distributed through public and private channels in affected areas. This approach allows the existing market to support the switch to new drugs and keeps treatment costs for consumers at levels similar to the current price of chloroquine. The leverage of an international subsidy of combination therapy can also discourage the distribution of monotherapies (such as solo artemisinins), the use of which might foster increasing resistance to antimalarial drugs in the future.

For more than 50 years, chloroquine silently saved millions of lives and cured billions of debilitating episodes of malaria. Falciparum malaria has always been a major cause of death and disability—particularly in Africa—but chloroquine offered a measure of control even in the worst-affected regions. At roughly 10 cents a course and readily available from drug peddlers, shops and clinics, it reached even those who had little contact with formal health care. Now chloroquine is increasingly impotent against falciparum malaria and malaria's death toll is rising. Yet desperate patients still turn to chloroquine and other failing, low-cost malaria medicines because they lack the few dollars needed to buy new, potentially life-saving treatments. Chief among these new treatments are the "artemisinins," paradoxically both an ancient and modern class of

drug that can still cure any form of human malaria. If falciparum malaria sufferers had the same broad access to artemisinins that currently exists for chloroquine, the rising burden of malaria in the world today would halt or reverse.

The crisis is both economic and biomedical. On the economic side, to state the obvious, the era of cheap and effective anti-malarial treatment may have ended, but poverty in sub-Saharan Africa and malarious countries elsewhere has not. Thus, although artemisinins at a dollar or two per course are both inexpensive by U.S. or European standards and highly cost-effective by any norm, neither national governments nor consumers in most malaria-endemic countries can afford them in quantities that remotely approach the world's current consumption of chloroquine—roughly 300–500 million courses of treatment per year.

Biomedically, today's malaria situation is also precarious. The artemisinins are the only first-line antimalarial drugs appropriate for widespread use that still work against all chloroquine-resistant malaria parasites. If resistance to artemisinins is allowed to develop and spread before replacement

drugs are at hand, malaria's toll could rise even higher.

The challenge, therefore, is two-fold: to facilitate widespread use of artemisinins while, at the same time, to preserve their effectiveness for as long as possible. [1, pp. 1–2]

Does the logic sound familiar? Infectious diseases specialists often strategize about how to forestall antibiotic resistance in individual patients, hospitals, communities, and beyond. Although we may not use the term, we also weigh positive and negative "externalities" of our treatment choices (an externality, in economic jargon, is a ripple effect on people who are not direct purchasers or recipients of the economic good in question). Is treatment for malaria any different?

In fact, almost all global discussions of malaria treatment policy reflect the same principles that guide any infectious diseases specialist who is managing an outbreak of antibiotic-resistant bacteria—that is, to save lives and prevent morbidity in the near term while protecting the efficacy of remaining treatments from further erosion. Implementing such principles in

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malarious settings is another matter, however. One major stumbling block is the severe burden that malaria places on people who have little access to health care and who often obtain self-prescribed treatment from the informal private sector. Treatment options are also limited, and market forces to develop new antimalarials are weak. Consequently, contemporary challenges in global malaria policy include stimulating research and development of new antimalarial drugs, changing national guidelines for first-line treatment, subsidizing production and purchase of new treatments, and harnessing market forces to allow such treatments to reach persons who need them most—namely, impoverished, rural populations in Africa, Asia, and other geographic pockets, where malaria still causes, in toto, >1 million deaths every year.

The Institute of Medicine (IOM) is a private, nonprofit institution that provides health policy advice under a US congressional charter granted to the National Academy of Sciences. The IOM Committee on the Economics of Antimalarial Drugs (hereafter, the IOM Committee) was constituted to perform the following 2 tasks: to recommend global actions to ensure the broadest possible access to effective antimalarial drugs, thus halting the rapidly increasing number of deaths due to malaria and eliminating attendant health and economic burdens as quickly as possible; and to consider some economic aspects of longer-term policy for antimalarial drugs. The US Agency for International Development was the IOM Committee's original study sponsor and was later joined by the Bill and Melinda Gates Foundation. The IOM Committee's work extended over 2 years, resulting in an ~350-page report entitled *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance* [1]. The table of contents of the report is outlined in table 1, and its recommendations are summarized in table 2. In keeping with current treatment strategies for HIV infection and tuberculosis, the report emphasizes com-

bination therapy, particularly artemisinin combination therapies (ACTs), for falciparum malaria. The recommended ACTs partner at least 2 effective antimalarial agents in a regimen that includes a natural derivative of *Artemisia annua*, a recently rediscovered source of potent antimalarial drugs.

In the following sections, I will briefly introduce relevant background information for and summarize conclusions of *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance*. For additional details, please consult the full text of the report, which is available on the World Wide Web (<http://books.nap.edu/openbook/0309092183/html/index.html>) and may also be purchased as a bound volume from the National Academies Press via telephone (1-202-334-3313 or 1-800-624-6242) or their Web site (<http://www.nap.edu>).

THE CENTRAL FACTS OF MALARIA RESISTANCE AND THE NEED FOR ACTs

Most readers know the >40-year history of chloroquine-resistant *Plasmodium falciparum* (CRPF). In brief, CRPF strains first emerged in South America and Southeast Asia in the late 1950s and early 1960s. Beginning in 1978, they entered and spread throughout Africa. In addition,

the past 2 decades have witnessed increasing resistance to folate inhibitor drugs among *P. falciparum* strains and focal outbreaks of multidrug-resistant falciparum malaria. Western-trained specialists routinely use this knowledge when treating patients with falciparum malaria in the emergency department or hospital ward and when prescribing preventive medication for travelers who will visit areas where falciparum malaria is endemic. Nonetheless, in many of those same areas (especially those in Africa), ineffective drugs such as chloroquine and sulfadoxine-pyrimethamine remain the first-line and frequently sole therapy for local residents. Although the drugs are cheap, the human cost of malaria is huge, both medically and otherwise. Children bear the lion's share of mortality, but the ~500 million annual attacks of malaria in all age groups also impede economic development. The overall economic burden of malaria in Africa, including lost productivity and investment revenues, was recently estimated to be 1%–4% of the gross domestic product of the continent, or \$3 billion to \$12 billion per year [2].

Ironically, when CRPF first gained a foothold in Southeast Asia during the early years of US involvement in the Vietnam War (i.e., mid to late 1960s), the need for new antimalarial treatments for local per-

Table 1. Table of contents for the Institute of Medicine malaria report *Saving Live, Buying Time: Economics of Malaria Drugs in an Age of Resistance* [1]

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| Part 1. A response to the current crisis |
| 1. Malaria today |
| 2. The cost and cost-effectiveness of antimalarial drugs |
| 3. The case for a global subsidy of antimalarial drugs |
| 4. An international system for procuring antimalarial drugs |
| Part 2. Malaria basics |
| 5. A brief history of malaria |
| 6. The parasite, the mosquito, and the disease |
| 7. The human and economic burden of malaria |
| 8. Malaria control |
| 9. Antimalarial drugs and drug resistance |
| Part 3. Advancing toward better malaria control |
| 10. Research and development for new antimalarial drugs |
| 11. Maximizing the effective use of antimalarial drugs |

Table 2. Recommendations of the Institute of Medicine for the treatment of malaria.

At the global level

Within 5 years, governments and international finance institutions should commit new funds of \$300 million to \$500 million per year to subsidize coformulated ACTs for the entire global market to achieve end-user prices in the range of \$0.10–\$0.20, the current cost of chloroquine.

Artemisinin production should be stimulated in the short term by assuring and stabilizing demand through funding of \$10 million to \$30 million per year from governments and international finance institutions.

A centralized process for organizing ACT procurement should be established.

Monotherapies for routine first-line treatment of falciparum malaria should be discouraged through a range of actions by the centralized procurement organization and governments of countries where malaria is endemic, assisted by Roll Back Malaria (Geneva, Switzerland) and other global partners.

At the country level

All countries receiving subsidized ACTs should facilitate access to the drugs, especially among the poorest segments of society, and improve their effective use. Countries and funding organizations should support research towards those ends.

Countries should be encouraged to perform intensive integrated control programs in areas of low transmission where transmission may be dramatically reduced or eliminated within a few years.

Monitoring, evaluation, and research

All countries should be encouraged to monitor public and private drug distribution systems to assure that subsidized antimalarials reach their intended targets with at least the same degree of success as chloroquine. Technical and financial assistance should be made available to perform these tasks.

The following monitoring and surveillance activities should be made a routine part of every national malaria control plan: monitoring the effectiveness of drug regimens, treatment failures, and the emergence of resistant strains; and surveillance for adverse effects of antimalarial drugs. Both should be required as a condition of access to subsidized antimalarials.

The global research and development investment should quickly increase from \$60 million to \$80 million per year to guarantee the ongoing development of new antimalarials.

One-half of this amount should go to Medicines for Malaria Venture (Geneva, Switzerland) from its regular funders, and the other half should be provided by the US government to the Walter Reed Army Institute of Research (Silver Spring, MD) and its public sector research partners.

NOTE. Data are in US dollars. ACT, artemisinin combination therapy.

sons with the disease was more dramatic than when CRPF later infiltrated Africa. This is because lower transmission rates in Asia (where residents of areas of high endemicity in this region experience far fewer infective mosquito bites per year than do most residents of Africa) result in lower rates of immunity. Communities in which there are lower transmission and immunity rates, in turn, experience a higher incidence of clinical disease and life-threatening complications involving people of all ages than do communities with high transmission rates, where children <5 years of age and pregnant women are most vulnerable.

The next part of the historical record may be new to some and familiar to oth-

ers. When drug-resistant malaria began to affect troops on both sides of the Vietnam conflict, Ho Chi Minh petitioned the Chinese leader at the time, Zhou en Lai, to find new antimalarial treatments. While US military researchers completed development of mefloquine, Chinese scientists examined their ancient herbal pharmacopeia and rediscovered a class of drugs derived from the sweet wormwood shrub (*Artemisia annua*), also known as qing-hao. Within a few years, Chinese scientists had studied qing-hao's antimalarial action from test tube to patient, identified its active structure, and refined its active derivatives. Currently, the following 3 types of derivatives are widely used: 2 closely related oil-soluble methyl ethers, artemether

and arteether; the water-soluble hemisuccinate artesunate; and dihydroartemisinin. Artesunate, artemether, and arteether are all synthesized from dihydroartemisinin and converted back to dihydroartemisinin within the body.

Today, a substantial amount of laboratory and clinical research suggests that artemisinin derivatives act more quickly against a broader range of asexual malaria-associated parasite stages than do any other available antimalarial drugs, including quinine [3, 4]. Artemisinin compounds also reduce gametocyte carriage, thus decreasing infectiousness after treatment, as evidenced by recent, dramatic decreases in malaria transmission on the Thailand-Burma border and elsewhere [5]. After >2 decades of use, artemisinins are standard treatment for *P. falciparum* infection in Thailand and Vietnam, where they have made great strides against the burden of drug-resistant malaria.

The recent experience in Southeast Asia has also yielded important lessons. The greatest practical drawback of the artemisinin class is its short half-life, which necessitates 5–7-day courses of monotherapy. When partnered with other, effective antimalarial agents, however, 3-day courses of artemisinins can quickly eradicate parasites and protect against the development of resistance to each component in the artemisinin-containing combination regimen [6]. Moreover, data from the largest series of randomized controlled trials ever conducted on antimalarial drugs in Africa mirror the results seen in Southeast Asia: in Africa, ACTs also improved cure rates, decreased gametocyte carriage, and were well tolerated with few side effects [7]. In 2001, the World Health Organization went on record to urge governments to rapidly adopt ACTs to provide more-effective malaria treatment and to slow the spread of drug resistance [8]. Current and future options for nonartemisinin partner drugs in ACT regimens include lumefantrine, mefloquine, amodiaquine, chlorproguanil-dapsone (also known as Lapdap [Glaxo-

SmithKline)), pyronaridine, piperaquine, and azithromycin. Additional nonartemisinin partner drugs, as well as synthetic artemisinins, are also in the pipeline.

THE ECONOMIC ISSUES ASSOCIATED WITH ACTs

By now, the advantages of ACTs are clear. However, at a cost of approximately \$2 per treatment (as opposed to 10 cents per treatment for chloroquine or sulfadoxine-pyrimethamine [SP]), they are, purely and simply, unaffordable for most persons with malaria in Africa and several other low-income regions where the disease continues to flourish. The IOM Committee concluded that subsidies of \$300 million to \$500 million per year were needed to substantially reduce ACT costs to end-users in these areas. The IOM Committee also recommended initial bridging investments by the global community to accelerate the production of artemisinins in quantities sufficient to treat all cases of malaria during the next decade (even if synthetic compounds eventually replace plant-derived artemisinins, in the most optimistic scenario, these agents will not enter clinical use for another 7–10 years).

A second, equally important question is the route by which any global subsidy of antimalarial agents enters the drug supply chain. To overcome the need for a new system of drug delivery, the IOM Committee recommended procurement by an international agency and parallel private and public market-driven distribution. In brief, the system was envisioned as follows. An international procurement agent (e.g., the United Nations Children's Fund) would buy ACTs from manufacturers at competitive, fair-market prices. The international agent would then sell the drugs to governments and private wholesalers on the condition that the drugs flow freely through all available public and private channels, just as chloroquine and SP do now. This approach would ensure that ACTs penetrate the farthest reaches of areas where malaria is endemic at a cost to consumers roughly equal to the current

price of chloroquine or SP. Although the IOM Committee's charge did not extend to other forms of malaria control, it strongly urged that an additional suite of separately financed interventions (e.g., expanded use of insecticide-treated bed nets, residual spraying where needed, and enhanced malaria education) accompany the flow of effective drugs.

The centralized purchase of ACTs offers other advantages. Because this approach guarantees a market, it encourages expanded artemisinin production. It can facilitate quality control. Most importantly, the IOM Committee saw that the international subsidy of coformulated combinations is a critical means by which to discourage the sale of solo artemisinins and other promising malaria drugs in the future, thus protecting all such monotherapies from premature demise due to drug resistance. In this way, the international subsidy of ACTs was seen by the IOM Committee as a global public good; in other words, as an investment that would benefit the entire world community by significantly slowing the development and spread of drug-resistant malaria parasites.

SELECTING THE BEST ACT FOR DIFFERENT SETTINGS AND PATIENTS

Admittedly, one ACT does not fit all (i.e., there is no single ACT which is appropriate for all patients and settings). Individual artemisinins have different pharmacologic properties (and, possibly, toxicities). Partner drugs effective at one site may be ineffective at another, because of local patterns of *P. falciparum* drug resistance. In selected circumstances, a solo artemisinin may even be appropriate (e.g., use of an artesunate suppository as an emergency stopgap for an African child with suspected cerebral malaria). Although the IOM Committee stopped short of recommending specific artemisinin derivatives and partner drugs, they did recommend that access to subsidized antimalarials be contingent on ongoing

monitoring of national and/or regional trends in drug resistance. Common methods for monitoring drug efficacy and resistance in current use include in vivo, in vitro, and molecular markers of resistance to chloroquine and SP. Despite drawbacks, in vivo tests (which involve clinical and parasitological monitoring of malaria-infected subjects after completion of supervised drug treatment) most closely predict the likelihood that parasites infecting a target population will respond to a particular treatment regimen.

Similarly, access to subsidized ACTs should be linked to ongoing surveillance for adverse drug effects in areas of high endemicity. A larger data base is needed to examine possible artemisinin-induced neurotoxicity in humans (originally observed in experimental animal models) and artemisinin effects during pregnancy and in young African children who might receive multiple courses of ACTs throughout their early childhood years.

DIAGNOSIS VERSUS EMPIRICAL TREATMENT OF FALCIPARUM MALARIA

Echoing Paul Ehrlich, the first medical scientist to envision pathogen-specific chemotherapy, infectious diseases physicians like to document causative organisms and treat them specifically. In addition to guaranteeing that patients receive correct diagnosis and treatment this scenario leads, over the long term, to fewer wasted drugs, fewer adverse side effects, and decreased pressure driving drug resistance. According to similar reasoning, in an ideal world, only those patients with proven cases of falciparum malaria would receive ACTs. In fact, in many parts of Asia, rapid diagnostic tests are now facilitating cost-effective delivery of ACTs.

Malaria in Africa poses different economic and biologic burdens, however. At this time, rapid diagnostic tests are still relatively expensive in Africa. Results of tests based on the histidine-rich protein 2 of *P. falciparum* may also remain positive for days to weeks after successful treat-

ment. In addition, in individuals with sub-clinical parasitemias, a positive rapid diagnostic test result may not correlate with acute clinical disease. These and other factors make rapid diagnostic tests less suitable for broad-based use in Africa today. Instead, the IOM Committee concluded that universal treatment of clinically suspected cases in individuals at high-risk for malaria is still the best immediate strategy in Africa, given the urgent need for swift administration of treatment in or near the home to stem the rapidly increasing mortality rate associated with drug-resistant falciparum malaria. After the introduction of ACTs in Africa, however, pilot programs and operational research that combine ACTs and rapid diagnostic tests in a variety of settings and at-risk populations were strongly encouraged.

CURRENT AVAILABILITY OF ARTEMISININS FOR TREATMENT OF FALCIPARUM MALARIA IN THE UNITED STATES

Although no artemisinin derivative is currently approved for use in the United

States, the Walter Reed Army Institute of Research (Silver Spring, MD), in partnership with Medicines for Malaria Venture (Geneva, Switzerland), has developed an intravenous formulation of artesunate for the treatment of severe and complicated malaria. An Investigational New Drug Application was filed with the US Food and Drug Administration in December 2004. If a commercial partner is identified, an approved product could be available in the United States within 2–3 years (A. Magill, personal communication).

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