

solution to the short-term problem. Third, the proposed mechanism for the delivery of foreign aid — as a subsidy through the existing antimalarial-supply chains — is relatively undemanding of institutional capacity on the part of governments. In many of the poorest countries, the scarcest resource is not funding but, rather, the administrative capacity for procurement, financial management, and delivery logistics. This mechanism would bypass those potential bottlenecks.

As simple as the Institute of Medicine's concept appears to be, it requires management of a type

that acts. The great need is fortitude on the part of leading development-aid organizations; they have to depart from standard operating procedures. The Institute of Medicine's recommendation has gained some currency as a centerpiece in the highest levels of discussions about the financing of malaria treatment (with more meetings planned), but no commitments have been made to adopt it.

The need for the general use of artemisinin-based combination therapies is by now universally accepted. The international community must recognize the need

to finance and organize this use, through relatively uncomplicated steps and relatively modest expenditures.

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An interview with Dr. Arrow can be heard at www.nejm.org.

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Making Antimalarial Agents Available in the United States

Alan Magill, M.D., and Claire Panosian, M.D.

*"Shooting pains in my head were just one hint that my antimalarial medication couldn't stand up to the mosquitoes of Sierra Leone. The pains weren't bad at first, just faraway flashes like heat lightning. There were other signs, such as dizziness, but I thought I was just reacting to the stifling humidity. The muscle spasms in my right calf must be lack of exercise. I'd been in Freetown a month. After a 9-year civil war, the capital city of the West African country barely has electricity, much less Pilates. It does however have a malaria rate among the highest in the world."*¹

Tales of malaria abound among travelers to Africa, and this account is typical. Someone who is far away from reliable health care is suddenly flattened by heat and a raging headache. Even after receiving antimalarial prophylaxis, the visitor may envision his or her bloodstream swarming with the parasite that causes 9 percent of all deaths in Africa. Without

laboratory tests, there is no way to be certain of the diagnosis. The next step for some travelers, including the op-ed writer quoted above, is to locate a pharmacy, buy a blister pack of artemisinin-type tablets (artesunate or artemether-lumefantrine, typically), and take the drugs over the course of several days.

As *Plasmodium falciparum* becomes increasingly resistant to first-line agents such as chloroquine and sulfadoxine-pyrimethamine, artemisinin pills and rectal suppositories (ideally taken in combination with a second antimalarial drug) are the best presumptive treatment in areas in which the organism is highly endemic. The empirical algorithm may not appeal to medical purists, but for travelers it beats the worst-case alternative — death or at least hospitalization with malaria that is severe or complicated, typically with cerebral involvement.

For hospitalized patients with life-threatening malaria in Africa and most other areas where *falciparum* is endemic, the drug of choice is either intravenous quinine or intravenous artesunate.

Now consider another scenario. A traveler or a U.S. soldier recently returned from Africa has fever, chills, and a raging headache and goes to an emergency room in the United States. A blood smear shows anemia, thrombocytopenia, and multiple, intraerythrocytic rings of *P. falciparum*. Moreover, the patient has labored breathing, acidosis, and an altered mental status — danger signs warranting immediate parenteral treatment. You are the attending physician. Neither intravenous quinine nor oral, rectal, or intravenous artemisinins have been approved by the Food and Drug Administration (FDA) or are available in the United States. How quickly can you lay

your hands on intravenous quinidine gluconate, the single parenteral antimalarial agent that is available in this country?

In many hospitals, the answer is not very quickly. Over the past 10 to 15 years, most cardiologists in North America have stopped using intravenous quinidine as an antiarrhythmic agent. At a university medical center in Los Angeles with approximately 600 beds, for example, the only vials of quinidine gluconate purchased during the past five years were replacements for older, expired vials. Other hospitals no longer stock this preparation at all. The drug's manufacturer, Eli Lilly, has continued to maintain supplies despite the lack of a commercial market and ships the drug rapidly whenever a patient at a U.S. health care facility needs intravenous antimalarial treatment. Nonetheless, as quinidine gluconate slowly disappears from hospital formularies, there have been published² and anecdotal reports describing adverse patient outcomes attributable to its limited availability.

It is important to note that the side effects of intravenous quinidine — QT-segment prolongation, hypotension, and hypoglycemia, in particular — also restrict its use to hospitalized patients in cardiac-monitored beds. Although it is potentially lifesaving in a critically ill patient with malaria, the drug can also complicate an already precarious situation unless the patient is closely monitored. An antimalarial drug that did not require cardiac monitoring for safe use would be of great benefit, especially to U.S. military forces deployed overseas.

Almost 15 years have passed since the Centers for Disease Control (CDC) stopped disbursing

parenteral quinine under an investigational-new-drug (IND) application. Patients with a suspected or confirmed case of severe malaria need immediate antimalarial drug treatment, and the CDC found it difficult to ensure the prompt availability of intravenous quinine under the IND application; switching to intravenous quinidine made sense in 1991 because the agent was much more widely available in hospitals for the treatment of cardiac dysrhythmias. Further development of intravenous artesunate is uncertain as the Walter Reed Army Institute of Research seeks a commercial codevelopment partner. The institute's formulation, produced according to current good-manufacturing practices, began phase 1 clinical trials under U.S. IND status in May of this year. If and when a pharmaceutical company joins the Walter Reed effort, another 24 to 48 months might easily pass before an approved product becomes available for use in U.S. civilian and military patients.

The question is, can we wait that long? Malaria currently causes up to 500 million febrile illnesses and approximately 1 million deaths each year. If new global strategies do not allow oral artemisinin-based combination treatments to flow quickly to communities in Africa and elsewhere where malaria is endemic,³ some experts predict that the death toll from drug-resistant *P. falciparum* will double in the next 10 years. Supplying artemisinin-based combinations in these settings is a necessity. Over the next decade, however, infections acquired by U.S. citizens traveling abroad, expatriate workers, and overseas military personnel could also climb. On the basis of infection rates

recorded in Somalia in 1993⁴ and Liberia in 2003, we know that U.S. troops sent to Africa as peacekeepers are highly vulnerable to malaria. FDA-approved and currently available oral drugs such as quinine, mefloquine, and atovaquone-proguanil (Malarone), sometimes paired with adjunct antibiotics, will successfully treat some infected persons in the future, but we know from experience that parenteral treatments will make the difference between life and death for others.

Today, scientists interested in the development of antimalarial drugs are most focused on new drug treatments for the developing world, and understandably so. On the other hand, there is little support from major funding sources for the identification of better preventive medications that would facilitate compliance by civilians and military personnel who are at risk for malaria infection — this despite the fact that most of the roughly 1400 malaria cases reported to the CDC annually, half of which are due to *P. falciparum*, could have been foiled outright with appropriate chemoprophylaxis. If travelers do not use prophylactic medications correctly and subsequently become severely ill with falciparum infection, a safety net of easy, effective parenteral treatment is required. Such patients can surface any time, anywhere.

The economics of developing new drugs for severe malaria in the United States do not make sense for the major pharmaceutical companies that have the expertise to do the job. If such companies are unwilling to develop intravenous artesunate or intravenous quinine because of market realities, then appropriate incentives (such as those outlined in

the current “BioShield” legislation that is meant to foster the development of new products to counteract biologic and chemical terrorism) should be offered to induce them to participate. Alternatively, perhaps it is time to consider the formation of a government-sponsored company that would manufacture these orphan drugs and shepherd their applications through the FDA.

No one wants to lose a patient to falciparum malaria. In 2005, there are simply too many proven and promising tools available for the prevention and treatment of this ancient foe. Happily, June was a month of renewed resolve in terms of the global attack. On June 27, 2005, the Bill and Melinda Gates Foundation, which had already donated \$150 million toward the development of a malaria vaccine, announced a new round of global health grants totaling \$437 million, roughly 20 percent of which was earmarked for innovative malaria research. On June 30, President George W. Bush pledged more than \$1.2 billion over five years to fight malaria in Africa by expanding access to mosquito nets treated with

long-lasting insecticides and to indoor spraying, as well as by distributing new, effective drug regimens — primarily artemisinin-based combination therapies — through public- and private-sector outlets in target countries. To be launched in 2006 with an initial \$30 million outlay for programs in Tanzania, Uganda, and Angola, the U.S. government investment could eventually reach more than 175 million people in 15 or more African nations.

Coming one week before the Group of Eight summit in Gleneagles, Scotland, the timing of the White House announcement was hardly accidental. Statements released earlier in June by G8 finance ministers underscored the commitment this year to tackling diseases that undermine growth and worsen poverty. With its \$12 billion annual price tag in economic loss for Africa, malaria certainly qualifies. The Bush initiative aims to inspire other G8 countries and private foundations to contribute to a multifaceted campaign that could halve malaria deaths within five years among Africa’s poorest and most vulnerable citizens.

This is all very good news, except for one ironic fact. Although tens of millions of dollars are now destined to bring much-needed artemisinin-based combination treatments to malaria-plagued residents of Africa, the U.S. government still has no plan to ensure that potentially lifesaving, FDA-approved treatments (intravenous artesunate, intravenous quinine, or oral artemisinins) are available to its own citizens.

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Studying Herbal Remedies

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How plausible are claims that echinacea, or purple coneflower, a perennial that is native to North America, is an effective treatment for viral respiratory disease? Tracing the evolution of views about the benefits of echinacea from the traditions of indigenous populations to modern claims, one finds little rationale

for studying the effects of this herbal remedy on colds. Indigenous populations — who used echinacea in various forms, including teas, local applications, and inhaled smoke — had no concept of disease states or their causes, nor could they distinguish medicinal effects from the natural course of an illness. Herb-

al texts list the use of echinacea by at least 13 tribes of Native Americans for the treatment of such widely diverse conditions as sore mouth and gums, cough, dyspepsia, toothache, bowel complaints, hydrophobia, and snakebite.

The potential for distortion of information about this herb arose between the late 1600s and the

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