

no pain, no change in muscle function, and no migration of the chip. I have exposed myself to extremes of temperature, wind, water, and several physical impacts while rock and ice climbing; the chip is working fine. If I want to “upgrade” my chip — replace it with a future version that uses more advanced and detailed industry standards or enhancements — removing it will require only minor surgery.

As I researched implantable identifiers, I found substantial controversy about the notion of being “chipped.” A Google search for “RFID implant” yields thou-

sands of pages about Big Brother and 1984 as well as *The X-Files* and the idea of alien abduction. It is clear that there are philosophical consequences to having a lifelong implanted identifier. Friends and associates have commented that I am now “marked” and have lost my anonymity. Several colleagues find the notion of a device implanted under the skin to be dehumanizing. I have not investigated these or other moral, religious, or political implications of having an implanted identifier. I was chipped in order to evaluate the technologic, privacy-related, and medical issues

as they affect the provision of patient care. On the basis of my unscientific study with a sample of one, I conclude that there may be appropriate uses, that there are privacy implications that must be accepted by the implantee, and that we need to establish standards that permit seamless, secure access to information.

Dr. Halamka is the chief information officer at the CareGroup Healthcare System and an emergency physician at the Beth Israel Deaconess Medical Center, Boston.

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Making Antimalarial Agents Available in Africa

Kenneth J. Arrow, Ph.D., Hellen Gelband, M.H.S., and Dean T. Jamison, Ph.D.

An infant in rural Africa has fever. Acetaminophen does not work. The fever spikes, and the father makes his way to the local kiosk and buys malaria medicine — chloroquine — that seems to help but then fails. A day later, the baby is dead.

The outcome has little to do with the curability of the disease and everything to do with economics — the economics of poverty and the economics of antimalarial drugs. It was this aspect of the malaria crisis that the U.S. Agency for International Development asked the Institute of Medicine to examine in 2001.¹

The Africa Malaria Report 2003 prepared by UNICEF² paints a grim portrait of the continent that bears most of malaria's burden at the beginning of the 21st century. Despite “intensified efforts to control the disease,” the report states, “the number of children dying of malaria rose substantially in eastern and southern Africa

during the first half of the past decade. . . . In West Africa . . . there was little change.” No country in sub-Saharan Africa had a “substantial decline” in the disease. The culprit: the slow but imperturbable advance of chloroquine-resistant malaria across Africa. After decades of silently saving millions of lives, chloroquine — inexpensive, safe, and effective — is becoming impotent. One new class of antimalarial drugs, the artemisinins, could take its place.

The artemisinins are widely used in Asia, where resistance to chloroquine first emerged in the 1960s. After Chinese government scientists confirmed the antimalarial properties of compounds extracted from *Artemisia annua* (a plant known for centuries for its medicinal properties), companies in China and Vietnam began producing artemisinin-based drugs. But the African market did not develop, even when

chloroquine's days were indisputably numbered.

A major barrier was cost. At their cheapest, artemisinins cost at least 10 times as much as chloroquine. Cost was not the only factor, though. No global alarm had been sounded about the looming crisis because until the creation of the fledgling Roll Back Malaria Partnership at the end of the 1990s, the malaria-control community consisted of a cadre of scattered technical experts. Few heard the warnings of lone voices. In addition, the acknowledged failure of the market to produce drugs for “neglected” diseases meant that there was no trodden path for bringing the Asian production of artemisinins into the international drug arena. (That dynamic has since changed somewhat, with the creation of the Medicines for Malaria Venture, a partnership of public and private agencies for the development of new antimalarial drugs.)

To add to the complexity of the situation, by the late 1990s, the leading authorities on malaria had endorsed the concept of combination therapy as the new standard. The prime motivation was to preserve the effectiveness of the artemisinins and other still-effective antimalarial partner drugs in artemisinin-based combination therapies. As in the treatment of AIDS and tuberculosis, two effective drugs with different mechanisms of action can protect each other from the survival of resistant pathogens. Malaria knows no political boundaries, so for combination therapy to delay the emergence of resistance, it must be used in preference to artemisinin monotherapy as widely as possible. If monotherapies persist in some places, resistant strains will develop and spread globally.

The realities of how malaria is recognized and treated must be considered in the facilitation of widespread access to artemisinin-based combination therapies. There is general agreement (though little hard evidence) that in Africa, the majority of malaria treatments are purchased directly by patients or their surrogates and are used without input from the health care system. Improvement in the overall functioning of health care systems is an obvious long-term goal, but we cannot wait until such systems exist to supply artemisinin-based combination therapies while more and more children die of malaria. Either such therapies must be made available at an affordable price, through the same system that distributes chloroquine, or most people will not get effective treatment for malaria.

One artemisinin-based combination therapy, artemether-lume-

fantrine (Coartem, Novartis), is currently being produced and has a wholesale price of \$2.40 per adult course (reportedly with little or no profit margin), as compared with 10 cents retail for chloroquine. Other formulations should enter the market soon,



Artemisia annua.

with an expected decline in price to less than \$1 for an adult course. At the lower level, the global cost of the drugs in artemisinin-based combination therapies would be on the order of \$500 million per year — barely noticeable in the budget of any major developed country. Nevertheless, this is an unmanageable cost for countries with per capita incomes of \$2,000 per year or less. Subsidies are needed, but how can they best be applied?

There are few options. President George W. Bush, in his statement of June 30, has now made the treatment of malaria an official commitment of the United States. But if the U.S. initiative and others like it operate on a country-by-country basis instead of identifying a mechanism that would permit global subsidies and the global distribution of drugs, they will miss the opportunity to optimize both distribution and the useful lifespan of combination therapies.

It is hard to conceive that sub-

sidizing artemisinin-based combination therapies at a local level — say, through vouchers — would be compatible with the current market-driven distribution system. It is not realistic to invent a new distribution system for antimalarial drugs, particularly when the existing one works reasonably well under the circumstances.

The solution is to allow subsidies to enter at a high international level — at the top of the distribution chain. This requires that the producers of artemisinin-based combination therapies sell directly to some international agency. Then the agency, in turn, can resell to distributors — governments and private wholesalers — at very low prices, the difference being the subsidy. The drugs would then flow down to the end users through the same pathways as chloroquine now does, with the requisite profit margins being taken where the private sector now operates. If these drugs start at a very low price when they enter the supply chain and if their supply is adequate, the price to consumers should be about the same as the current price of chloroquine. This is the heart of the recommendation of the Institute of Medicine.¹

Centralized procurement from producers will have some important additional advantages. First, it will make it easier to enforce quality standards. Second, the procurement facility will guarantee the purchase of qualifying products for several years without waiting for orders from individual countries, providing an incentive for the drug manufacturers and the farmers who grow *A. annua* to enter the market. Currently, there is an artemisinin shortage. In this case, the long-run commitment is the

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.

Dr. Arrow is a professor emeritus of economics at Stanford University, Palo Alto, Calif. Ms. Gelband is senior program officer at the Institute of Medicine, Washington, D.C. Dr. Jamison is a professor of public health and of education at the University of California, Los Angeles.

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

1. Arrow KJ, Panosian CB, Gelband H. Saving lives, buying time: economics of malaria drugs in an age of resistance. Washington, D.C.: National Academies Press, 2004.
2. UNICEF. The Africa malaria report 2003. Geneva: World Health Organization, 2003.

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