

FOCUS ON RESEARCH

Malaria — Time to Act

Nicholas J. White, D.Sc., M.D.

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In the wealthier parts of the world, the death of a child from an infectious disease is a rare tragedy. In poor countries, it is commonplace. In rural sub-Saharan Africa, the majority of families have lost at least one child to a treatable infectious disease. Fortunately, with improvements in immunization coverage and public health in recent years, the death toll from killers such as pneumonia, diarrheal disease, measles, and tetanus has fallen. But deaths from AIDS and malaria have increased. It is estimated that 1 million children die each year from falciparum malaria, yet malaria is both preventable and treatable. The main reason why malaria-related mortality has increased while mortality associated with most other treatable and preventable infections has decreased is the continued deployment of ineffective antimalarial drugs in the face of increasing resistance.

Chloroquine has been our most important antimalarial drug for the past half-century. At the outset, it was simple to administer, was highly effective when given in a few doses, had few side effects, and was inexpensive (costing approximately 10 cents per treatment). Widespread deployment of both chloroquine and the insecticide dichlorodiphenyltrichloroethane (DDT) was remarkably effective in controlling and, in some places, eradicating malaria early in the global malaria eradication campaign of the 1950s. Chloroquine was widely

available in both public and private sectors, and it was used in industrial quantities; hundreds of metric tons were consumed each year.

But because chloroquine binds extensively to tissues and is very slowly eliminated (with a terminal elimination half-life of more than 1 month), a large proportion of the population in areas where malaria was endemic had detectable chloroquine concentrations in their blood at any given time. The selection pressure on malaria parasites was enormous, and resistance duly emerged in *Plasmodium falciparum* by the end of the 1950s. It arose almost simultaneously in low-transmission areas of South America and Southeast Asia and then spread relentlessly, arriving at the eastern seaboard of Africa in the late 1970s and marching steadily across the continent over the next decade.

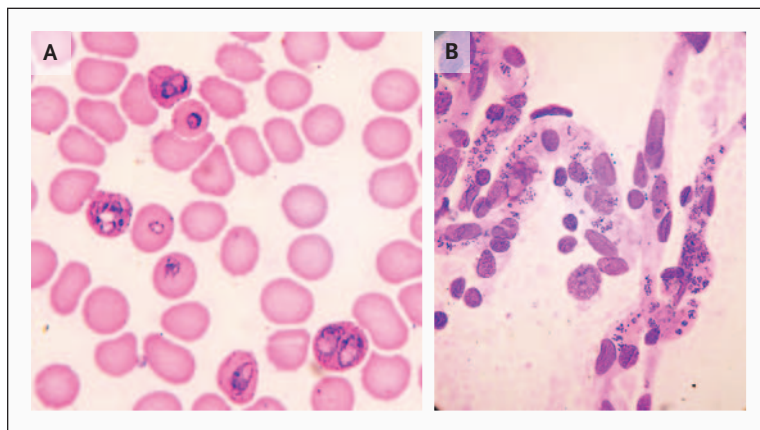
Chloroquine gave us 30 to 40 years of benefit. Unfortunately, its successor, sulfadoxine-pyrimethamine, often fell to resistance within 5 years of extensive use. But affected countries were reluctant to change their malaria-treatment policies, so as the rates of resistance increased, mortality also rose.

Artemisinin-based combination treatments are now considered the best therapy for falciparum malaria. Such treatments are effective, work rapidly, and have very few adverse effects; they combine unrelated compounds with different molecular targets (and thus different potential mechanisms of

resistance), thereby delaying the emergence of resistance. But they are more expensive than single-agent treatments. A cost per treatment of 50 cents to \$2.50 (sometimes more in the private sector) may not sound like a lot to pay for saving the life of a child, but it is often unaffordable to the rural poor, who are the most affected by malaria. Since 2005, most countries where malaria is endemic have adopted treatment policies based on these combination therapies, but only a small fraction of the population that needs these drugs actually receives them.

In 1993, Malawi became the first country in Africa to change its national policy on malaria treatment, shifting away from chloroquine therapy. In the subsequent years, while the selection pressure exerted on malaria parasites by chloroquine was lifted in Malawi, the molecular basis of chloroquine resistance was being elucidated. Mutations in *PfCRT*, a gene in the parasite that encodes a putative transporter, were shown to play a central role in chloroquine resistance. Early studies had suggested that chloroquine-resistant malaria parasites were actually more fit than their chloroquine-sensitive counterparts, even in the absence of selective pressure. Few, therefore, anticipated that chloroquine susceptibility would return if the drug was withdrawn.

But that is exactly what has happened in Malawi. Molecular epidemiologic studies from Ma-



Fatal Cerebral Malaria.

A thin film of blood obtained from a patient before death shows heavy parasitemia, with parasites mainly at mature stages (Panel A). A microscopic image of a brain specimen obtained from a patient after death shows capillaries and venules packed with erythrocytes infected with schizonts (Panel B).

lawi and parts of Asia where the use of chloroquine had been largely suspended showed a decline or disappearance of the K76T mutation in *PfCRT*. In this issue of the *Journal*, Laufer et al. (pages 1959–1966), who previously conducted such studies in Malawi, report the results of a clinical trial providing conclusive evidence that the disappearance of the K76T mutation has been associated with a return to chloroquine susceptibility.

How good is this news from a public health perspective? Can we now abandon these new, relatively expensive antimalarial agents and return to our old and trusted friend chloroquine? Laufer and her colleagues wisely counsel against doing so. Malawi is surrounded by a sea of chloroquine resistance. If chloroquine were reintroduced alone, resistant parasites would probably return rapidly, imported in people from neighboring areas. But the restored susceptibility is still good news: chloroquine resistance pre-

sumably confers a fitness disadvantage, and stable compensatory mutations sufficient to counter this disadvantage apparently have not occurred. Thus, chloroquine could reenter the increasingly promising queue of new candidate antimalarial agents — but it needs to leave before it can come back.

In most of Asia, South America, and the Horn of Africa, chloroquine is still needed for the treatment of vivax malaria. This situation could change, since most malaria infections are treated without any particular species having been diagnosed, and the artemisinin-based combination treatments (with the exception of artesunate–sulfadoxine–pyrimethamine) are reliably effective against all the malarias that affect humans.

In the remainder of Africa, where chloroquine has become ineffective against *P. falciparum*, the drug should be replaced as soon as possible by effective treatments. The World Health

Organization recommends artemisinin-based combination treatments as first-line therapy for falciparum malaria in all areas where it is endemic.

If these new, effective drugs are going to have an effect on malaria, they must be made affordable and available. To be affordable, they must cost 10 cents or less a day in both the public and private sectors, as chloroquine does. The Institute of Medicine recently recommended that an internationally funded scheme be instituted to reduce the cost to both the public and private sectors of obtaining antimalarial drugs whose quality is assured. Antimalarial drugs that are highly effective, have acceptable adverse-effect profiles, and are affordable should win out over ineffective medicines and thwart the burgeoning market in substandard and fake drugs. Richer countries will need to pay for this effort, but there are powerful humanitarian and economic arguments for ensuring ready access to effective antimalarial drugs.

With strong leadership and the singularity of purpose that characterized the successful campaign to eradicate smallpox, malaria can be rolled back. We already have the necessary tools: insecticides, insecticide-treated bed nets, and good drugs. An effective and affordable vaccine would be wonderful, but we do not need to wait for it. It is time to turn the tide on malaria. We can do it now, and it won't cost that much.

Dr. White is a professor in the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.