



# New Antimalarial Drugs:

**M**ALARIA has been and remains one of the greatest scourges of humanity. Its geographical range is wide, even today. It is a particularly devastating health problem in Africa, especially between the Sahara Desert and South Africa. At one time, malaria was a major illness in the southern United States and southern Europe and was much more widespread in Latin America. Although figures are far from reliable, malaria deaths are estimated at over one million children a year—about 9 percent of all childhood deaths. However, with malaria more than many other killer diseases, mortality is a small fraction of morbidity. In the highly epidemic regions of Africa, the approximately 650,000,000 inhabitants are infected, on average, more than once a year.

The economic implications of a frequently sick population are evident. To some observers, the economic retardation of sub-Saharan Africa can be substantially explained by the prevalence of malaria. In addition to its direct effects on productivity, the presence of this devastating disease scares off foreign investors and traders.

There are several strategies other than drugs for controlling and reducing the incidence of malaria: draining standing water, spraying pesticides on potential breeding grounds for mosquitoes and on houses, and using netting to protect people from mosquito bites at night. Vaccine development continues but offers no medium-term prospects. These strategies are all important, but none is likely to eliminate malaria, especially in sub-Saharan Africa. Drugs remain our best hope. In this article, I focus on the use of drugs to combat malaria and the need for those currently in use in Africa to be replaced by new and much more expensive ones—the subject of a study by a committee, which I chair, of the Institute of Medicine of the U.S. National Academy of Sciences.

## Alternative drugs

A synthetic variation of quinine, called chloroquine, was introduced into general usage around 1950. It was effective and, at about 10 cents a treatment, remarkably cheap. Cost was no obstacle to its use, even in the poorest countries. Chloroquine was and still is widely used in Africa, Southeast Asia, and India, where it has contributed greatly to the control of malaria. But as a result of mutation, the malaria parasite has become resistant to chloroquine in Southeast Asia and most parts of East Africa. The resistant strains will soon undoubtedly take over elsewhere, such as in West Africa. An alternative inexpensive drug, sulfadoxine-pyremethamine, which replaced chloro-

quine in some places, has also been effective. But resistance to it developed even more rapidly than to chloroquine.

Faced with malaria in its southern areas, Chinese researchers reexamined traditional herbal medicine—specifically the claim that *Artemisia annua* (sweet wormwood) was useful against fevers and particularly periodic fevers (presumably malaria). Researchers were able to verify that claim and identify the active antimalarial elements in *Artemisia*. These derivatives, artemisinins, are the standard and highly effective treatment in Vietnam and Thailand and are increasingly being used in India. So far, despite intense use of artemisinins in Southeast

Asia, the malaria parasite does not appear to have developed resistance. Their only immediate drawback is cost—about \$2 a treatment. In moderate- and high-income countries, this amount would be of no consequence. But in low-income countries, which have the greatest malaria incidence and where individuals may be infected a few times a year, the cost would be prohibitive—even though costs per death averted are remarkably low.

One other consideration is the knowledge that resistance to artemisinins will develop. For this reason, it is widely

agreed that artemisinins should be given in combination with some other medication (artemisinin combination therapy, or ACT). The emergence of resistance would thus require two simultaneous mutations, a most unlikely event. And the combination conveys therapeutic advantages while raising the cost only slightly, if at all, over artemisinin monotherapy.

## Drug production and distribution

What are the critical economic aspects of antimalarials? First, because malaria affects only poor nations—those with highly restricted purchasing power—biology collides with economics. The creation of new pharmaceuticals involves high fixed expenses for research, development, and testing. These expenses are recovered, and profits made, in the markup of the price charged for a drug over the costs of producing it. Government imposition of temporary monopolies—patents—allows this markup in what would otherwise be competitive markets. But poor countries cannot afford the markup.

When the demand for a drug is worldwide, it is possible to charge more in richer countries than in poor countries. Such price discrimination is clearly emerging for antiretroviral drugs to treat AIDS and the drugs needed for tuberculosis, and it has characterized other drugs. But, with malaria, there is no scope to recover the fixed costs in the countries most

**A global public goods commission looks at ways to stop or slow the spread of drug-resistant strains of malaria.**

*Kenneth J. Arrow*

# Biology and Economics Meet

affected. Development of new antimalarials has consequently been confined to a dwindling number of private companies, the U.S. military, and public-private partnerships.

Second, the distribution of antimalarials in Africa is, for the most part, private. Governments, of course, set standards and impose tariffs, but drugs are largely imported, distributed, and sold at retail through purely market transactions. Although there are exceptions, public health systems are geographically less dense than retail stores, drugs in these facilities are frequently out of stock, and their operation is unpredictable. There seems no reason to expect their operation to improve enough to handle the proposed ACTs. Hence, it is important to ensure that private distribution continues for the time being.

Third, the costs of producing artemisinins and ACTs should, according to all precedents, decline because of larger scales of production, experience, and innovation (for example, artemisinins and chemically related drugs will probably be produced through synthesis instead of extraction from plants). But increasing supplies in the near future will take time—it takes about 18 months to plant and bring *Artemisia* to maturity—as will increasing productive capacity. Moreover, there must be ways to encourage competition, particularly through modifications of the drugs or of their manufacturing processes.

## A possible new direction

For a large and expanding part of the world, avoiding deaths from malaria will require much greater use of artemisinins. Protecting artemisinins from resistance will require combination therapy. How can the international public sector create financial and other incentives for countries and individuals to use artemisinins and to use them in combinations? Suppose, for the moment, we assume that ACTs must be subsidized because of their cost relative to African incomes. The case for doing so is strong. How is this best accomplished? Policymakers will need to find a way to provide a reliable and predictable demand for ACTs to encourage planting of *Artemisia* and a building up of capacity. They must not interfere with the functioning of the existing private distribution system and must prevent the diversion of funds to other purposes by governments or other agencies. Policymakers will also need to implement mechanisms for maintaining quality control over the manufacturers—internationally subsidized centralized-purchasing and quality-control mechanisms are one possible approach, particularly if allowed to supply private sector distribution systems.

What is the justification for subsidizing a particular good (antimalarial drugs or ACTs, in particular) rather than making general income transfers to poor countries? A standard economic argument says that imposing constraints on an individ-

ual's spending is bound to reduce his or her welfare. Therefore, it is usually concluded, income transfers should take the form of purchasing power and not of specific goods. For this reason, most advanced countries have largely abandoned housing subsidies. The counterarguments take three forms: the recipient does not know his or her welfare as well as the giver; the direct recipient is the local government, whose interests may conflict with those of the people; and spending has spillover effects (externalities). There is also the idea that antimalarials are an international public good. If a country does not use ACTs—in particular if it uses artemisinins as monotherapy—resistance is more likely to develop. With international travel, the spread of resistance is inevitable, and currently no other effective drug is available for widespread use. Another kind of externality is that donor nations are clearly more willing to give to overcome disease than for other reasons.

Finally, how can we, in the longer run, encourage the further development of antimalarial drugs and related strategies? Even better therapies are clearly possible, such as a single-dose drug that is as effective as artemisinins. Malaria vaccines have been researched but still need extensive exploration. Given the lack of research by major pharmaceutical companies (because there is no profitable market), there must be a lot of unexplored potential. What incentives can be created to encourage private and public research of these issues? Something beyond ordinary intellectual property rights seems to be necessary: public sector investment in research and development. ■

*Kenneth J. Arrow is Professor of Economics Emeritus at Stanford University.*

*This paper draws on the author's experience as Chair of the Committee on the Economics of Anti-Malarial Drugs of the Institute of Medicine. The opinions expressed are strictly his and are not to be attributed to the institute or the committee. The committee will publish its report in the spring of 2004.*

