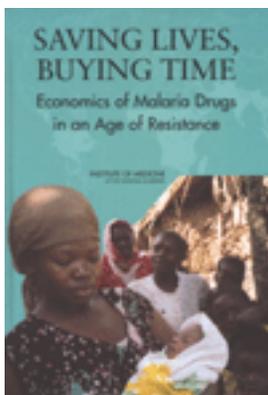


Free Executive Summary



Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance

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Drugs

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For more than 50 years, low-cost antimalarial drugs silently saved millions of lives and cured billions of debilitating infections. Today, however, these drugs no longer work against the deadliest form of malaria throughout the world. Malaria deaths in sub-Saharan Africa -- currently just over one million per year -- are rising because of increased resistance to the old, inexpensive drugs. Although new effective drugs called "artemisinins" are available, they are unaffordable for the majority of the affected population, even at a cost of one dollar per course.

Saving Lives, Buying Time: Economics of Malaria in an Age of Resistance examines the history of malaria treatments, provides an overview of the current drug crisis, and offers recommendations on maximizing access to and effectiveness of antimalarial drugs. To delay the development of resistance for as long as possible, first-line malaria treatment must be "combination" therapy, which should include an artemisinin, while the use of "monotherapies" must be minimized. The book finds that most people in endemic countries will not have access to currently effective combination treatments without financing from the global community. Without funding for effective treatment, malaria mortality could double over the next one or two decades and transmission will intensify.

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Executive Summary

INTRODUCTION

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 a 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 antimalarial 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.¹

Biomedically, today's malaria situation also is 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 twofold: to facilitate widespread use of artemisinins while, at the same time, to preserve their effectiveness for as long as possible. The central recommendation of this report—a *sustained global subsidy of artemisinins coformulated with other antimalarial drugs*—is the most economically and biomedically sound means to meet this challenge.

Two caveats must accompany this report and its recommendations. Even in the best of times when chloroquine was still effective, it did not reach everyone. As a result, at least one million people died each year from malaria, most of whom could have been saved by adequate treatment. Merely substituting artemisinin combination therapies (ACTs) for chloroquine is not the whole answer. *Expanded access* to effective treatment will also be needed if we are to gain ground against malaria.

Second, malaria control requires a suite of interventions to *prevent* disease: insecticide-treated bednets, environmental measures to limit mosquito breeding, and intermittent preventive treatment of high-risk asymptomatic individuals (eventually, malaria vaccines will join the armamentarium). If proven preventive interventions are combined with ACTs, we can expect even greater progress generally, while, in some areas, good drugs plus good control can actually reduce malaria transmission to near zero. Commitments of international funding substantially greater than the sums needed for an antimalarial drug subsidy but still modest in terms of their return on investment are therefore needed to advance malaria control overall.

However, this report does not address malaria control comprehensively; that is a task for others. This committee was asked to recommend economic mechanisms to make effective antimalarial drugs widely accessible in order to stem the deaths from drug-resistant malaria that now occur day in, day out. When it comes to saving lives, effective drugs will always be a mainstay while malaria continues to threaten humankind.

¹It should be noted that the price of artemisinins is based on the costs of production and not added premiums to recoup research and development costs, which were borne largely by the public sector.

THE CURRENT MALARIA SITUATION

Although malaria was once a global scourge, by the mid-20th century it was eliminated as a major health problem in much of the world. The hard core remained, however, and in many parts of sub-Saharan Africa, malaria still is the largest contributor to the burden of disease and premature death. To a lesser degree, malaria also remains an important health problem in parts of south Asia, South America and other tropical regions of the world.

Chloroquine began losing its effectiveness against falciparum malaria in Asia during the 1960s and 1970s. Looking back, we know that mutant parasite strains with genetically-mediated chloroquine resistance initially arose in areas of low malaria transmission (Asia and South America) and reached east Africa by the 1980s. Over the next 2 decades, sub-Saharan Africa—where real malaria control had never been achieved, yet chloroquine was effectively treating illness and preventing deaths, especially among children—was hard hit. After declining from post-World War II through the mid-1990s, death rates from malaria are now increasing in Africa. The failure of chloroquine, followed by the waning efficacy of other low-cost drugs such as sulfadoxine-pyrimethamine (SP), appears to be the main cause.

It was the original emergence of drug resistance in Asia that inspired development of the artemisinins, an extraordinarily effective family of antimalarials derived from a traditional Chinese medicinal herb. Although they are nonproprietary, artemisinin compounds still cost more to produce than chloroquine because plants must first be cultivated and harvested and the drugs then extracted and processed rather than simply synthesized from inexpensive chemicals.

Over the past 2 decades, the use of artemisinins in Asia has grown continuously, but demand in Africa has remained negligible. At first the reason was that chloroquine and SP were still effective in Africa, but now the reason is strictly economic: artemisinins cost about 20 times more than chloroquine, and African countries and their citizens cannot afford their higher price tag. The lack of global demand for artemisinins has, in turn, led to a desultory pace of production and impeded the economies of scale and improved production methods that would substantially reduce prices, were larger markets and competition in place.

This is the crux of the current crisis: African countries are increasingly adopting artemisinin combination therapies (ACTs) for first-line treatment of uncomplicated malaria; however, without external funding neither governments nor consumers—who bear most of the cost—can afford them.

The IOM committee took these realities into account in devising a concrete plan for reversing the trend of increased malaria morbidity and mortality while preserving effective drugs for the future. To understand the

reasoning behind the recommendations of the committee, it is important to appreciate certain biological aspects of malaria, particularly as they relate to the development and spread of drug resistance.

DRUG RESISTANCE AND THE NEED FOR COMBINATION THERAPY FOR MALARIA

The evolution of drug resistance is an inevitable consequence of genetics and natural selection when drugs are used against microbial pathogens, including the protozoan parasites that cause malaria. As effective and robust as the artemisinin drugs are today, it is only a matter of time before genetically resistant strains emerge and spread. However, practical steps can be taken to push that day further into the future. The logic is as follows.

In the case of any antimalarial drug, the new development of drug resistance is a rare event: a chance genetic change in a single parasite in a single patient.² But once that single malaria parasite generates multiple descendants, the math changes. Now, mosquitoes can acquire resistant parasites from a single individual and transmit them to other people. The subsequent spread of a *robust, resistant clone* would be similar to the spread of any malaria strain.

The way around this dismal scenario derives from the fact that a nascent resistant parasite will *not* survive and proliferate in an infected person's bloodstream if a *second* effective antimalarial drug *with a different mechanism of action* is simultaneously present. The key, therefore, to preserving the artemisinins is to eliminate their routine use as "monotherapies," and to treat patients with uncomplicated malaria (the vast majority of cases) with "artemisinin-based combination therapies" (ACTs) instead. ACTs equal an artemisinin derivative plus *another unrelated* anti-malarial drug, ideally coformulated in a single pill so that individual drugs cannot be knowingly or inadvertently used as monotherapies. Combining drugs in this way—already an accepted practice in the treatment of tuberculosis and HIV/AIDS infection—minimizes the likelihood that a single parasite with drug resistance will propagate and spread. Since all drug-resistant microbes are capable of crossing national borders, delaying the development of resistance through this strategy creates a benefit, otherwise

²This discussion is simplified to basic concepts. In fact, the rate at which resistant parasites emerge varies tremendously by drug, which explains why chloroquine remained effective for decades (the known instances of new chloroquine-resistant strains developing are fewer than 10), whereas resistance to SP arises much more quickly (SP-resistant strains have developed *de novo* dozens or hundreds of times).

known as a “global public good,” for people living both within and beyond malaria-endemic areas.

Although still relatively new to malaria, combination therapy is no longer controversial: within just the past few years, it has been endorsed by the World Health Organization, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and by malaria experts worldwide. In addition, combinations are not only good for preventing resistance, they also confer advantages to patients. In the case of the artemisinins, the treatment regimen is shortened from 7 days using monotherapy to 3 days using a combination.

In order for antimalarial combination treatment to keep drug resistance at bay over the long term, however, it must be used as first-line treatment for uncomplicated falciparum malaria as widely as possible. Should monotherapies persist in some locales and drug resistance result, there would be no way to contain the resistant parasites to one country or continent. Artemisinin monotherapy is, in fact, widely used in Asia today in the same areas where resistance to chloroquine and SP originally surfaced not that long ago. There is an urgent need for Asian-based production of artemisinin monotherapy to convert to ACT production, aided by a global subsidy. The window of opportunity to create a global public good—years of extended effective antimalarial drug life—is open now, but it may not remain open very long.

The equal urgency for change in Asia and Africa may seem counter-intuitive but antimalarial drug resistance historically has emerged in areas of low transmission—mainly Southeast Asia and South America—and then spread to high-transmission areas, mainly Africa. This pattern fits with current understanding of the biology of drug resistance in low- and high-transmission areas. As a practical matter, it is therefore essential that ACTs quickly dominate the market in low-transmission areas in Asia and Africa, as well as penetrate Africa’s most endemic locales.

“Market penetration” will occur in a meaningful way only if the brunt of the increased cost of the drug is not borne by consumers—many of whom earn less than \$1 per day. As the most practicable way to achieve this end, this report recommends a large subsidy near the top of the distribution chain, which will lower the price to consumers at all points of sale.

THE ECONOMICS OF ARTEMISININS AND ACTs

By Western standards, artemisinin derivatives are already inexpensive. They also are well within the bounds of what is internationally acknowledged as cost effective for health care interventions in low-income countries. With the incentive of a secure and large market, producers already are promising that wholesale prices for a course of ACTs will fall to US\$.50-1.00 (or possibly lower) within 2 years. However, that projected price is

still 5 to 10 times higher than the price of chloroquine or SP in Africa, making artemisinins essentially unaffordable for most sub-Saharan governments and individuals, especially the poor, rural families whose children are most likely to die from malaria.

Without substantial and sustained subsidies, in some countries well over half of all malaria patients needing treatment—including most who currently are able to acquire chloroquine and SP—will not have access to artemisinin-based drugs. Children will die and many more will suffer.

Priming the Market for ACTs

Once scaled up, the additional cost of ACTs versus currently failing drugs for the world is expected be US\$ 300-500 million per year (a closer approximation is difficult because estimates of malaria cases—or fevers assumed to be malaria—are imprecise). This cost estimate assumes that ACTs will be used to treat up to half a billion episodes per year, which roughly equals the number currently treated by chloroquine or SP. The estimate also assumes a competitive market in which ACT prices fall over time.

In the meantime, there is a chicken-and-egg dilemma surrounding ACT supply and demand. Without an assured market, potential manufacturers will not commit to adequate ACT production, nor will farmers expand the cultivation of *Artemisia annua*, the source plant.³ There is a critical need to jump-start ACT production. To do this, the global community must provide sufficient funds to encourage investments by manufacturers, guarantee purchases of ACTs and generally stimulate a robust world market. This must be done through a visible, centralized mechanism, ideally using existing national and international organizations (e.g., UNICEF, WHO), which can quickly take on the task.

THE CASE FOR A GLOBAL SUBSIDY FOR ANTIMALARIAL DRUGS: THE CORE RECOMMENDATION OF THIS REPORT

The global community can take definitive action by subsidizing the difference in cost between inexpensive but ineffective antimalarials, and effective ACTs. For ACTs to reach most consumers, the subsidy must first bring the price of ACTs down to about the price of chloroquine (even at those prices, the poorest in society will need assistance to make them af-

³On average, one hectare of *A. annua* produces enough raw material for about 25,000 adult courses of an ACT. This equates to 20,000 hectares (200 km²) for 500 million courses (Personal communication, J.M. Kindermans, Médecins Sans Frontières, June 8, 2004).

fordable). Then the subsidy must be sustained, at least over the medium term, until either economic conditions improve in the endemic countries, or the price of effective antimalarials comes down significantly. Furthermore, for consumers to *preferentially* choose ACTs over monotherapies, they must cost no more than the least expensive monotherapy available (whether an artemisinin or another drug). Otherwise, simple economics will dictate that a vulnerable monotherapy will be chosen over an ACT, and the global benefits of combination treatment in countering the emergence of resistance will not be achieved. (This report recommends specific measures to keep unneeded monotherapies off the market, as well.)

The subsidy must be applied in a way that does not diminish access to antimalarials. The routes through which people obtain antimalarials vary from place to place, but overall in Africa, upwards of 70 percent of these drugs reach consumers through the private sector, particularly small pharmacies, street side drug peddlers, and general store kiosks.

The importance of drug availability “close to home” cannot be overemphasized: if not treated, malaria can kill a small child within 24 hours of the onset of fever. Delayed consultations and referrals and correspondingly slow access to treatment can work for chronic infectious diseases such as tuberculosis, but not for malaria. Of course, public sector and nongovernmental organizations are important sources of health care, especially where they do reach populations as the village level, but frequently they are restricted to towns and cities.

Recognizing the many pathways by which antimalarials flow to consumers leads inevitably to the conclusion that external financing should be injected at a point very high in the purchasing chain—above the level of individual countries. It is widely recognized—including by this committee—that existing drug distribution is not optimal. As a result, overtreatment, undertreatment and other poor prescribing practices are rife, drugs (mainly chloroquine) have been wasted, malaria episodes left uncured, and other health conditions untreated. Clearly, public sector systems and regulatory oversight must be improved and sustained. *However, it is equally clear that private sector distribution systems reach millions of people with no other practical alternative.* Efforts to improve drug delivery—utilizing better information, technology (e.g., rapid diagnostic tests tailored to sub-Saharan Africa), and support for health systems generally—must continue. Such changes will realistically evolve over a longer time frame, however, than is currently available for the switch to ACTs, which is urgent.

A global subsidy near the top of the distribution chain will stabilize demand and create incentives for ACT production, resulting in lower prices. A global antimalarial subsidy also will accomplish the following for the global community:

- with the assent of individual countries, it will allow ACTs to flow through existing public- and private-sector channels even in remote places, without disrupting existing market structures;
- it will allow all countries to adopt the most appropriate malaria treatment policies, including ACTs as first-line treatment, without concern over the sustainability of external funding for their purchase and without forcing countries to choose between effective antimalarials and other malaria control measures;
- it will provide equity of access to inhabitants of all endemic countries, including those countries that, for whatever reason, may not receive sufficient external funds to purchase ACTs at market prices;
- it will give the global community leverage to dissuade artemisinin manufacturers who wish to sell through the subsidized system from producing artemisinin monotherapy;
- it will minimize administrative costs of applying the subsidy;
- it will minimize the incentives for counterfeit ACT production;
- it will minimize incentives for diversion and smuggling of ACTs, which would exist with differential subsidies and pricing; and
- as new drugs with appropriate characteristics to save lives and counter resistance are developed, it will provide a mechanism of integrating them into an existing distribution system.

Funding a Global Antimalarial Subsidy

Countries with the greatest malaria burdens are least able to cover the added cost of ACTs, either through public or private sector budgets. Governments and citizens of endemic countries will contribute something, but most of the shortfall must come from external sources. This does not mean altogether *new* funding, however. Substantial amounts of committed but unspent monies—especially from the World Bank’s International Development Association—could be tapped to support ACT purchases. Other likely sources are bilateral aid programs from the United States and other countries. The Global Fund to Fight AIDS, Tuberculosis and Malaria is in a good position to solicit contributions from around the world and earmark substantial amounts for this purpose.

One issue to be raised up front is historical precedent: in the past, major development institutions and aid agencies have allocated funding almost exclusively at the country level. Although this approach is appropriate for the majority of projects, it is not ideal for programs involving global public goods. Putting together a global subsidy for ACTs will require creativity and flexibility from these funders, but it is possible. Structuring an antimalarial subsidy supranationally is also consistent with recent efforts to increase global funding for the major diseases of poor countries.

Some may argue that a subsidy for ACTs can stop the current backslide, but it will do nothing to solve the many other problems that allow malaria to thrive. However, the availability of very effective drugs is likely to inspire increased country- and local-level malaria control efforts that previously may have seemed futile when programs were saddled with ineffective drugs. It is vitally important that funding for ACTs not be diverted from other malaria control measures.

How Much Money Is Needed?

If 300-500 million episodes are treated annually worldwide, and US\$1 is the incremental cost per ACT course, an adequate ACT global subsidy would be US\$300-500 million. This would constitute drug costs for the entire world. Although the sum is substantial, it is less than will be spent every year on antiretroviral drugs to treat a fraction of the people in Africa infected with HIV. And rather than continuing to increase each year, the demand for antimalarials should, in the worst case scenario, stay roughly stable. In the best case, demand will decline as better treatment and other control measures take effect.

The Need for a Centralized Procurement System

A mechanism for centralized procurement of antimalarial drugs (analogous to the process by which many nations now obtain subsidized tuberculosis drugs and childhood vaccines) should be established. This responsibility could reside with an existing organization or with a new one (for example, a program currently being explored by WHO, similar to the recently-established “Global Drug Facility” for tuberculosis). The functions of a centralized procurement agency would be: 1) to help keep prices low and production high through multiple producers; 2) to monitor quality control; and 3) to structure incentives to assure that individual countries follow the most prudent malaria treatment policies. The procurement agency must be empowered to make multiyear commitments toward the purchase of ACTs. The agency also could provide technical assistance to countries on internal regulatory matters, and surveillance and monitoring activities.

The Specifics of Procurement Nationally and Internationally

In effect, the procurement agency would buy ACTs directly from manufacturers at competitive prices, then resell them to countries at a lower, subsidized price (this process would ideally occur through a “virtual” rather than a physical warehousing system). Although decisions regarding the

allocation of ACTs within countries would remain under the control of national governments, ACTs must flow into both the public and private sectors in every country for the subsidy to achieve its goal. In addition, governments will need to oversee price controls in the private sector in order to assure that the subsidy truly reaches consumers and that profit margins are not excessive. Pricing rules do exist in most countries, but they can be difficult to enforce. Improved packaging and labeling (which could include a printed price), and consumer education will facilitate both price controls and the rational use of antimalarial drugs, and should be supported internationally and nationally.

The need for action is urgent, but optimal levels of financing and procurement will likely take 2 to 5 years to ramp up. During this “phasing-in” period imposed by limited financing or drug supply, priorities should reflect global humanitarian need. Currently, East and Southern Africa and parts of Southeast Asia are the regions with the highest burden of chloroquine-resistant malaria coupled with the least access to ACTs.

THE NEED TO MAINTAIN RESEARCH AND DEVELOPMENT FOR NEW ANTIMALARIAL DRUGS

Managed well, artemisinins could remain the first-line antimalarial for many decades. Resistance has not yet developed in Asia, even following extensive monotherapy use. Eventually, however, the artemisinins will begin to lose effectiveness and new drugs will be needed. Even before that happens, drugs that can be manufactured more cheaply, or are superior to artemisinins (e.g., effective in a single dose) could supplant or join artemisinins on the front line.

For the first time in decades, the R&D pipeline for antimalarials has been invigorated through the Medicines for Malaria Venture (MMV), a public-private partnership begun in 1998. MMV, the WHO Special Programme on Research and Training in Tropical Diseases (TDR) and the Walter Reed Army Institute of Research (WRAIR) are the main innovators in antimalarials. Current annual funding needs for these organizations total an estimated US\$60 million dollars, rising another US\$20 million per year as more drugs reach the stage of clinical and field trials. These projected investments represent only a small addition to the cost of supplying artemisinins globally, but are several times the current collective budgets. Agencies supporting malaria control should allocate sufficient funds to these organizations to meet the MMV goal of one new antimalarial drug every 5 years, and WRAIR’s similar target.

IMPROVING ACCESS AND THE PROMISE OF INTEGRATED MALARIA CONTROL

Additional themes that run through this report are *access* and *integrated malaria control*. Even during the decades when chloroquine was effective, about one million Africans—mainly children—died of malaria every year. Lack of access to health care and inadequate preventive measures in Sub-Saharan Africa remain ongoing challenges. With comparably priced *effective* antimalarials, the access problem will not worsen, but neither will the full benefits of effective combination treatments be realized. This will require strengthened health care systems, better patient education regarding combination antimalarial treatment, and further innovations in antimalarial tools and access to them.

On the positive side, there is every reason to believe that effective drugs combined with other control measures in well-designed, locally appropriate programs can lower the malaria burden close to zero in some places. Insecticide-treated bednets can reduce child mortality substantially, given sufficient coverage of households. Environmental measures—spraying interior walls and rafters with insecticide, reducing mosquito breeding sites near houses—also work. These measures alone are worthwhile, but partnered with effective treatment, they are synergistic, especially in areas of relatively low malaria transmission. Witness the transformation recently brought about in KwaZulu Natal province, South Africa. This program combined the first internationally available ACT (artemether-lumefantrine or Coartem™, prescribed after a positive rapid diagnostic test), indoor house spraying and insecticide-treated bed nets. The result was dramatically reduced malaria transmission within the space of 2 years. Despite the program's relatively high initial costs, South Africa is now reaping real cost *savings* that will continue to accrue indefinitely. Similar programs utilizing multiple tools are not immediately feasible in all locales, but by targeting areas where transmission has already decreased somewhat, packaged interventions can achieve additional progress and valuable lessons applicable to high-transmission areas in the future.

In summary, over time, malaria can be contained through strategic deployment of ACTs and other control measures, which should lead to improved economic opportunities for people held back by the disease for generations. Effective malaria control also frees up national health care to tackle other pressing problems, and global resources to counter the disease in yet more places. The prospect of new tools such as a malaria vaccine for endemic areas—although very unlikely within 10 years—is another reason for long-term optimism.

THE CURRENT CHOICE

What is the current choice? In the view of the IOM Committee, it is unacceptable that cheap, effective drugs with a single medical purpose are currently unavailable to people whose lives would be saved by them. Failure to prevent the premature loss of our relatively few effective drugs through the simple expedient of coformulated drugs (currently, ACTs) also is unacceptable. The strategy offered in this report is a way to preserve the effectiveness of antimalarials for all global citizens—a true global public good. With coordinated policies, funding, and implementation, progress can be made. Without rapid adoption of ACTs, we will only continue to lose lives and lose ground.

RECOMMENDATIONS

At the Global Level

1. Within 5 years, governments and international finance institutions should commit new funds of US \$300-\$500 million per year to subsidize coformulated ACTs for the entire global market to achieve end-user prices in the range of US\$0.10-.20, the current cost of chloroquine.

The subsidy must be applied high up in the ACT supply chain, above the level of individual countries. To assure the greatest international access, the public and private sectors of all endemic countries should be eligible to purchase ACTs at low, subsidized prices. In the future, subsidies could apply to other new combination antimalarials that meet technical criteria and are considered equivalent in their therapeutic promise to ACTs.

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

Funds must be committed toward the global purchase of artemisinins in the 2- to 5-year time frame to encourage new companies to begin and producing companies to ramp up production. Once funds are committed and the conditions of purchase developed, potential producer companies should be actively solicited and provided with information and, if needed, technical assistance. If upgraded production facilities are needed, the International Finance Corporation (a sister institution of the World Bank) could provide needed funds. WHO should be prepared to assist companies in making their products “pre-qualified” and eligible for purchase through an international procurement process.

3. A centralized process for organizing ACT procurement should be established.

In the short term, procurement should take place within an existing organization with the capacity to manage the task. This organization must have the authority to make multiyear commitments to purchase ACTs from manufacturers. In the medium term, procurement could remain with the original organization or it could move. The aim is to maintain a healthy, competitive market with adequate production capacity and low prices. The organization also could monitor quality control of ACT manufacture and provide technical assistance on regulatory matters. Access to the procurement organization should be available to all countries, subject to conditions related to rational drug use. Conditions of participation for both countries and manufacturers would be aimed at assuring access to high-quality ACTs and minimizing the availability of unnecessary monotherapies.

4. 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 malaria-endemic countries, assisted by Roll Back Malaria and other global partners.

Monotherapy with oral drugs as first-line treatment will be discouraged by the availability of lower-priced ACTs, but this should be reinforced by other disincentives. Countries that obtain subsidized ACTs through the centralized procurement organization should neither register nor allow domestic production of artemisinin monotherapies or other drugs that are or would be effective partners to artemisinins. Companies selling through the subsidized system could be required to forgo producing these same monotherapies. Exceptions may be necessary, e.g., if particular monotherapies are needed to treat or prevent malaria in pregnant women. Artemisinins are not recommended during the first trimester of pregnancy, but are under evaluation. The current standard for preventive therapy during pregnancy is SP, which will not be used as a partner drug in an ACT. There is also a case for producing and distributing artesunate suppositories as an emergency stopgap treatment for children with severe malaria who cannot take oral drugs.

At the Country Level

5. 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 toward these ends.

Countries should build on the malaria control impetus that widespread access to ACTs will create by:

- expanding access to ACTs (including treatment in or near the home) by decreasing geographic and financial barriers to drugs; and
- improving adherence to treatment schedules through public education, provider training, labeling, packaging, and dispensing.

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

Successful programs integrating household spraying with insecticides or insecticide-treated bednets, environmental management, and treatment with effective drugs, such as in KwaZulu Natal and Vietnam, should be encouraged in other low-transmission areas.

Monitoring, Evaluation, and Research

7. All countries should be encouraged to monitor public and private drug distribution systems to assure that subsidized antimalarials reach their intended targets at least as well as chloroquine has. Technical and financial assistance should be made available to carry out these tasks.

The procurement organization (in consultation with national and international bodies) should specify the monitoring information to be collected and help to ensure the availability of funds and technical assistance to accomplish this activity. Information should be collected, e.g., on the state of antimalarial packaging when drugs reach end users (whether the drugs are in their original packaging or have been repackaged in single doses, for example) and end-user prices. The availability of monotherapies also should be tracked.

8. Two different types of monitoring and surveillance should be made a routine part of every national malaria control plan: 1) monitoring the effectiveness of drug regimens, treatment failures and the emergence of resistant strains; and 2) surveillance for adverse antimalarial drug effects. Both should be required as a condition of access to subsidized antimalarials.

The best antimalarials for a country or region—in particular, partner drugs for artemisinins—must be selected based on accurate surveillance of individual drug efficacy, as close as possible to real time. Early warning systems that identify drug resistance, if acted upon in a timely way, could lead to the replacement of a failing ACT partner drug. This action, in turn, could protect the artemisinin component of a given ACT *and* save lives. Models for resistance monitoring exist in the multicountry networks already operating in various parts of Africa. Regarding safety, no major problems associated with ACT use have yet appeared, but widespread use

in Africa is still pending. Surveillance, particularly in the early years, will be needed to quickly identify potential problems. The requirement for monitoring and surveillance cannot be absolute, however, in cases where it would impede access to effective, combination antimalarials. Countries in or just emerging from conflicts, or those dealing with natural or manmade disasters, for example, may not have the administrative capacity to monitor drug resistance. The enforcement of this recommendation will necessarily lie in the hands of the international organization in charge of procurement.

9. The global R&D investment should quickly rise to \$60-80 million per year to guarantee the ongoing development of new antimalarials. Half of this amount should go to MMV from its regular funders, and half should be provided by the U.S. government to WRAIR and its public sector research partners.

Governments and other organizations that support malaria control activities should assure sufficient levels of funding to the major organizations behind antimalarial R&D, namely, MMV and WRAIR, to achieve the MMV target of one new antimalarial every 5 years, with similar progress expected from WRAIR.

SAVING LIVES, BUYING TIME

Economics of Malaria Drugs
in an Age of Resistance

Committee on the Economics of Antimalarial Drugs
Board on Global Health

Kenneth J. Arrow, Claire B. Panosian, and Hellen Gelband, *Editors*

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Cover photograph by Claire B. Panosian. Mkuranga, Tanzania, November 2002. Family and neighbors of Amina Selemani, including her daughter and newborn grandchild. Another grandchild, Zulfa Mshamu (not shown) received ACT treatment for malaria through a clinical research trial co-sponsored by the Ifakara Health Research and Development Centre and the U.S. Centers for Disease Control and Prevention.

*“Knowing is not enough; we must apply.
Willing is not enough; we must do.”*

—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Preface

Let me use this preface to share some of my own learning experience over the course of this study. At first blush, recommending appropriate therapy for malaria, as for other diseases, might seem a matter for medicine, pharmacology, and other branches of biology. Indeed, as this report will show, while biological and pharmacological details are of utmost importance, malaria policy also requires the best economic understanding we can muster. Anyone conscientiously engaged in practical policy making is painfully aware of the limitations of our understanding of the economic system. In the course of developing this report, I also became increasingly aware of our limited understanding of natural systems, a fact of life that my biological and medical colleagues on our committee candidly acknowledged.

Economics is the study of the allocation of scarce resources among competing ends. It is not surprising, therefore, that economic considerations should loom large in health policy, including the provision of effective pharmaceuticals. Today, the richer countries of the world are devoting an ever-growing proportion of resources to health care. In the United States, how to finance therapeutic drugs for the elderly is an ongoing political debate. If countries in which scarcity is least felt must still devote major attention to medical economics, how much more is this likely to be true of those countries, especially in Africa, where per capita incomes are 5 percent or less of the U.S. level?

It was clear before this IOM Committee met that the existing antimalarial drug supply was starting to fail. For more than 40 years, the system

had been largely based on a single agent—chloroquine—which was at one time very effective and remarkably cheap. Even in the poorest countries, at 10 cents per retail course, most people can still afford it. Moreover, the drug is familiar to the populace, and has been used—both within and outside of organized health care systems—well enough to prevent many malaria deaths and suppress (if not completely cure) acute attacks of the disease. For lack of an affordable alternative, chloroquine remains the most frequently used antimalarial in Africa. Chloroquine is distributed mainly through private economic channels, eventually reaching consumers via the local stores and drug sellers that are ubiquitous in poor countries. The private sector has, in this case, filled a niche left open by public and private health care systems that are neither sufficiently accessible nor affordable to serve much of the population—particularly, the rural poor.

Over time, however, resistance to chloroquine emerged worldwide, first leading to treatment failures in Southeast Asia, then to treatment failures in large parts of east Africa. It is now believed that chloroquine will be useless against most life-threatening falciparum malaria infections in fairly short order. In the meantime, replacement drugs have been introduced, but they too have quickly lost ground. The main exception is a family of antimalarials derived from sweet wormwood (*Artemisia annua*). Over the last 25 years, artemisinin derivatives have proved highly effective in Thailand, Vietnam, and other Asian countries while no artemisinin resistance has surfaced. Partnering artemisinins with a second drug confers even greater protection against the development of drug-resistant mutants. Two- or three-drug treatments—now commonly called artemisinin combination therapy, or ACT—also offer therapeutic advantages over single antimalarial drugs.

In short, the occurrence of a medical difficulty is offset by an opportunity. An economist does not expect a free lunch, as the cliché goes, and this lunch is not free. In fact, it is relatively, though not absolutely, expensive. At present, ACTs cost about US\$2 a treatment, roughly twenty times the price of chloroquine. By any reasonable standards, their cost per individual course is not large and will decline even further with competition and economies of scale. As best we can estimate, the total drug cost of ACTs for worldwide treatment of falciparum malaria is likely to be about \$500 million a year—barely noticeable on the scale of the budget of any major developed country. Nevertheless, this is an unmanageable cost for countries with per capita incomes of \$2,000 a year or less. Subsidies are needed.

Having said this, multiple economic issues arise. What is the justification for subsidies targeted to specific kinds of expenditures? Why is there not a whole series of new antimalarial drugs coming on line (as there is, for example, for HIV/AIDS or depression)? How do we measure the benefits of curing a case of malaria against the increased costs of treatment? If we

agree on the necessity of subsidies, how can we maintain an efficient system of distribution?

We discuss all of these issues in one way or another in the report, but I will make a few brief comments here. ACTs (compared with monotherapies) serve to avoid the emergence of resistance worldwide. This equals, in economists' jargon, the avoidance of negative externalities, or the creation of global and intertemporal public goods. Preventing or delaying the emergence of resistance will save lives in future generations. Even if artemisinin resistance eventually emerges, slowing down its appearance increases the chance that high-risk individuals will have access to new and improved drugs when that time arrives.

The historical slowness in producing new antimalarials reflects the way in which new drugs are developed in a market system. Research, development, and testing of drugs engender a large upfront cost. In a private enterprise system, the incentive to make this expenditure is the monopoly mark-up over the relatively low manufacturing costs, a monopoly conferred by intellectual property rights. This incentive, however, depends on the economic strength of the market. When a large market exists in rich countries, drugs are developed. When the market mainly consists of poor people, however, the incentive is weak and drug development usually founders.

In fact, the original development of artemisinins did exemplify an alternative path to pharmaceutical innovation. The first artemisinins were developed by Chinese medical researchers who claimed no intellectual property rights. Not even fame, the scientist's alternative motivation to money, was involved; the original paper was published under the name of a collective. However, today, if artemisinin production is to expand and ACTs are to become the global norm, the international community must take the initiative and fuel a series of actions to ensure this outcome.

Economic evaluation of a new antimalarial treatment requires an analysis of its respective costs and benefits, or at least a comparison of its reduction of malaria morbidity and mortality vis-à-vis other therapies. In the case of ACTs, the costs were so low and the relative efficacy so high that inquiring into the benefits in greater detail was hardly worthwhile.

Perhaps the knottiest issue we faced was how an ACT subsidy might be administered. It was hard to conceive that subsidizing ACTs at a local level, say through vouchers, would be compatible with a market-driven distribution system. Although public health systems have succeeded in distributing antimalarials in Thailand and Vietnam, the consensus of our experts was that such systems would not work equally well in Africa. We want to disturb the existing market system as little as possible. Therefore, we urge that the subsidies enter at a high international level.

Another lesson of medical economics is the importance of recognizing

the specific character of the disease under consideration. The policy challenges that arise in treating malaria are simply very different from those attached to other major infectious scourges. For example, speed of treatment is much more important in malaria than in TB or HIV/AIDS, and reliance on sophisticated diagnosis necessarily reduced. Malaria's distinctive mode of transmission (via mosquitoes) suggests additional environmental control measures. High mosquito breeding rates and the special "homophilia" of the major vector species in Africa also carry important policy implications.

In the course of the study, I learned that the challenge of controlling malaria involves far more than identifying and treating individual victims one at a time. Malaria exists as an entire ecology for which real control requires a complement of measures, chief among them, effective antimalarial drugs. Our charge was the study of the economics of drugs; we could not have done justice to other antimalarial measures. But I came away with the clear understanding that interventions such as insecticide-treated bednets and other, broad environmental strategies offer great potential for synergy when effective drug therapies are available.

Finally, this report consciously refrains from the frequent recommendation by committees such as ours for more research. Nonetheless, it must be said that resources devoted to gathering malaria data are grossly inadequate. For one thing, we were not able to determine clearly the number of malaria deaths worldwide, where the error may be 25 percent either way. Such an elementary fact as the current number of treatments taken per year (a very important figure when estimating the cost of changing the drug of choice) seems not to be known within a factor of three. One could go on, but these examples are illustrative. The information gaps and vast uncertainties made this committee's task more difficult, but not impossible. The scientists, physicians, and economists who compose the committee are unanimous about the correctness of the solutions proposed in our recommendations. We need not—and cannot—wait for better information to meet the current crisis.

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SAVING LIVES, BUYING TIME

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