A Global Subsidy for Antimalarial Drugs

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Abstract. In 2004, the Institute of Medicine concluded that a global high-level subsidy was the best way to make effective antimalarial drugs—currently, artemisinin-combination therapies (ACTs)—widely available at affordable prices and at the same time substantially delay the emergence and spread of artemisinin-resistant strains of falciparum malaria. The subsidy would be available to manufacturers of all ACTs meeting pre-specified efficacy, safety, and quality criteria. Buyers would pay very low prices, allowing drugs to flow through existing channels, with the aim of reaching consumers at a similar price to chloroquine, the most frequently used (although no longer effective) malaria drug. Unsubsidized artemisinin monotherapies would be more expensive than subsidized ACTs (co-formulations), thereby largely eliminating their use through market forces. Conditions favoring the emergence of artemisinin-resistant malaria would be greatly reduced. The global high-level subsidy is a powerful idea that is moving from economic concept to pragmatic reality.

INTRODUCTION

The latter half of the 20th century brought significant changes in the way infectious diseases of global importance are treated. From the 1960s, the current multi-drug regimens for treating tuberculosis were tested and adopted as standard practice. AIDS appeared as a disease, and its long-term management developed with combinations of entirely new classes of drugs. The principle of using multiple drugs became established, and the search for more effective agents continues unabated. Over the same period, the treatment of malaria remained virtually unchanged. The malaria death toll has always been unacceptably high, but for a long time, the reasons were extreme poverty and inadequate health care systems rather than the lack of a cheap, effective drug. Chloroquine was that drug from the 1940s for five decades, at least in Africa (trouble with resistance had begun brewing in the late 1950s in Asia1).

The emergence and spread of chloroquine-resistant strains of falciparum malaria in Asia and eventually throughout Africa is now a familiar story.2 The loss of chloroquine has only compounded the still unresolved problems that have always existed, resulting in increasing malaria mortality rates.3,4 The back-story is one of what did not happen—no vigorous search for new drugs and no revisiting the idea of monotherapy until chloroquine and the other once-effective and inexpensive drug, sulfadoxine-pyrimethamine (SP), had lost ground in large swaths of Africa. One drug class—the artemisins—had been nurtured from its roots in Chinese herbal medicine and early pharmaceutical development by Chinese scientists and developed further both in China and separately under WHO’s Special Program on Research and Training for Tropical Diseases. The artemisinins emerged and stand as the single hope to replace chloroquine on malaria’s front lines for the near term. If their manufactured price was not 10 or more times more expensive than chloroquine, many products would be on the market, and the transition would be well under way. However, the cost of artemisinins put on the brakes.

That was the situation in 2001 when the Institute of Medicine (IOM) was asked by the United States Agency for International Development (USAID) to study the malaria drug situation. The core question the IOM committee deliberated on was this: how can effective drugs be made widely available when and where malaria strikes and at the same time protect effective drugs for as long as possible from being lost to drug resistance?

DISCUSSION

Six years is not a long time in medical history, but the years since 2001 have been particularly eventful in malaria. Still being debated in 2001 were the criteria for replacing chloroquine as the first-line drug in Asia and Africa, and more generally, whether resistance was widespread enough to consider wholesale replacement. The replacement drug was also unsettled: should countries switch to affordable and available SP, at least for a time, rather than move directly to an artemisinin compound at perhaps 20 times the cost? The timing of the inevitable move to ACTs was portrayed as a struggle between “go slow” and “go fast” camps. The idea of using drugs in combination for malaria is now so firmly rooted that it is easy to forget its novelty in 2001.5,6

Despite advances in policy and drug development, the drug situation has changed little for most of those with malaria in Africa. Chloroquine is still the most widely used drug—most likely, several hundred million courses of treatment in the last year. Artemisinin monotherapy is increasingly available, but still very expensive. In 2006, ~85 million courses of any type of artemisinin combination treatment (fixed-dose combinations and combinations involving loose tablets of partner drugs) were ordered (A Seiter, personal communications with manufacturers), most destined for the public sector or other organizations that serve the public in similar ways (e.g., religious health care institutions and relief organizations). In mid-2006, Sanofi-Aventis announced that it had 10 million unsold arte- sunate tablets that would either have to be destroyed or given away because of approaching expiration dates.7 In 2005, the supply of artemisinin-based drugs was a limiting factor, but in 2006, it is demand that lags behind the capacity of manufacturers. This is partially because of the relatively high cost of ACTs, but other factors limiting uptake include grant and procurement bureaucracy, supply chain logistics, delays and interruptions in donor funding, and lack of awareness of new treatment guidelines among health professionals.

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The glacial progress through 2006 is predictable based on the IOM committee’s analysis and recommendations, reinforcing the need to act on the solution proposed by the IOM committee in its 2004 report, *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance.* Although significantly more money is being spent on drugs for malaria by the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the President’s Malaria Initiative and others, the conditions for widespread use of ACTs and the elimination of monotherapy cannot develop without a fundamental change, such as the one proposed by IOM, which involves the private sector—including the “informal” private sector—and the organized health care system. Other solutions may be possible, but the IOM committee—which deliberated on alternatives—could not devise one, nor has one been proposed publicly by others since the IOM report appeared. Time is of the essence, certainly for those with malaria who cannot afford effective drugs and to eliminate monotherapy before resistance emerges.

The IOM committee’s central recommendation is as follows:

Within 5 years, governments and international finance institutions should commit new funds of US$300–500 million per year to subsidize co-formulated ACTs for the entire global market to achieve end-user prices in the range of $0.10–0.20, the current cost of chloroquine.

This recommendation describes a global subsidy that enters the system high in the drug distribution chain, meaning that highly subsidized drugs would be available to all high-level purchasers, both public and private sector. In this way, drugs would enter the existing public sector and commercial channels much as any other drug—including chloroquine. The aim is for the price to consumers at the end of the chain to be as low as the chloroquine consumer price.

The concept assumes that supplies of ACTs are adequate to meet all demand at low prices. If this condition is met, the attractiveness of price gouging, smuggling, and counterfeiting should be greatly reduced. Access would be at least as widespread as access to other common drugs, and ACTs would have a competitive advantage in the marketplace over monotherapies, which would be more expensive without the benefit of subsidization. Eliminating the use of monotherapies produces the “public good” of delaying the emergence of artemisinin-resistant malaria, but only to the extent that monotherapies for uncomplicated malaria are eliminated or severely limited everywhere. The effectiveness of the global subsidy would be enhanced by national policies limiting monotherapies, education campaigns about the effectiveness of ACTs, and other related activities.

The following sections dissect the IOM recommendation, explaining the reasons behind each key idea.

**...To achieve end-user prices in the range of $0.10–0.20, the current cost of chloroquine.** If a course of ACTs were to cost about as much as a course of chloroquine, a large proportion (it is impossible to be more precise) of malaria sufferers would be able to afford treatment. Efforts over and above the global subsidy would be needed to reach those still unable to afford any drugs.

Chloroquine-level prices are realistic. If chloroquine—as well as the next most popular inexpensive drug, SP—can reach consumers for 10–20 cents, another commodity using the same distribution channels also should be able to if it enters the supply chains at a low enough price.

**...For the entire global market...** A question that arises in the discussion of subsidies is how to spread the available money so that it does the most good. It is appealing to try concentrating the subsidy—“targeting”—on the groups or individuals who will benefit the most. “Untargeted” subsidies, by definition, benefit everyone, including some people who could easily afford the unsubsidized price. The IOM committee came down firmly on the side of an untargeted “global” subsidy, meaning the entire world’s supply of ACTs (and in the future, other effective combination antimalarials).

The key factors in coming to this conclusion are as follows: first, the population for which a subsidy is necessary for ACTs to be affordable is not a small minority. The IOM committee estimated that possibly one half of the potential consumers would be in this group. Getting drugs to them and keeping drugs from others would be a huge task, probably requiring new delivery streams and involving some (possibly considerable) expense. The issue of delivery relates back to where people acquire malaria drugs and the urgency with which they are needed. A wide variety of public and private outlets provide antimalarials in Africa and elsewhere, with the importance of different types of outlets varying from country to country. It is unrealistic to expect thousands of outlets—from clinics to pharmacies to general stores to street side peddlers—to have to take an active role in a subsidy program by somehow “signing up” or participating in a voucher program. To restrict subsidized products to a subset of outlets would deny access to some segment (possibly large) of the target population.

In the case of ACTs, a global subsidy has one enormous advantage over every other approach: the potential to eliminate the use of most monotherapies by making them substantially more expensive. By virtue of superior effectiveness at an equivalent price, ACTs should also eliminate chloroquine and SP through market forces, in places where it is not actively withdrawn.

Finally, a global subsidy means that these drugs are cheap everywhere, denying the profitability of parallel trade—buying them cheaply where they are subsidized and selling below market where they are not.

**...To subsidize co-formulated ACTs...** Co-formulated ACTs are the best available treatment of patients with uncomplicated malaria, and their availability at an affordable price means they will outcompete monotherapies. The next few years will see several new co-formulations enter the market at wholesale prices comparable to or lower than the current international choice, Coartem (Novartis, Basel, Switzerland). This should eliminate the need for continued use of combination therapy (two separate drugs), which risks people taking only one or the other, effectively monotherapy. One remaining hurdle is the WHO prequalification process, which poses significant technical or managerial hurdles for some ACT manufacturers.

**...New funds of US$300–500 million per year...** Estimating the price tag for the subsidy requires estimates of the average wholesale price, the target retail price, and the number of courses that would be demanded. During the IOM study, an adult course of ACTs was projected at about $1, once prices fell as a result of economies of scale. The committee assumed that the drugs would have to start through the
system at a cost close to zero to emerge at the chloroquine price, so a $1 per adult course subsidy was assumed.

It is generally accepted that at least half a billion cases of falciparum malaria occur each year worldwide. The IOM committee estimated that 300–500 adult-equivalent cases (i.e., including childhood cases, for which the drug cost would be about half) might be treated. More recent estimates, based on a phased-in subsidy, lower uptake, and lower per-course prices have pushed the estimate down to an estimated need of about US$200–250 million in the ramp-up years.

... Governments and international finance institutions should commit... Subsidizing the global supply of ACTs will require the collaboration of the global community and a substantial amount of "new" money. A potential difficulty is that a global subsidy would benefit all endemic countries, both friend and foe of funders. However, the "public good" anticipated—the extended useful life of artemisinins and other drugs—will be produced only with a truly global subsidy. Denying subsidized drugs in some countries creates the conditions for monotherapy to thrive and for drug-resistant malaria strains to survive and spread, without regard for national boundaries. An intrinsically positive feature of the subsidy model is that it rewards countries for implementing effective malaria control programs with good systems for drug supply and dispensing: Because the subsidy amount is proportional to the number of treatments consumed, countries that are able to ensure fast uptake will capture more of the subsidy money than the slow movers.

Within 5 years... The IOM report was released > 2 years ago. The target of 5 years for implementation was based on both realism and optimism and still seems to be realistic—if maddeningly slow, given the intensifying need. The good news is that the idea has caught hold, is being pursued, and has a good chance of becoming reality.

PROGRESS SINCE THE RELEASE OF SAVING LIVES, BUYING TIME

The global subsidy idea would not have moved forward simply through publication of a report. Fortunately, champions emerged. First were members of the committee itself, including the distinguished chairman, Nobel prize-winning economist, Kenneth Arrow. Because of Professor Arrow's endorsement, the economic community—including the World Bank—took the idea seriously. Interest early on by the Roll Back Malaria (RBM) Partnership Finance and Resources Working Group was key to what has happened since. A modeling study commissioned by the Working Group explored more fully the likely effects of a global subsidy, confirming that it should indeed "save lives" and "buy time." Since then, other key parties, notably the WHO Global Malaria Program, have been persuaded of the validity of the global subsidy concept and have endorsed its further development.

In mid-2006, the Bill & Melinda Gates Foundation provided a grant to the World Bank, on behalf of the RBM Working Group, to fund development of a detailed plan for the subsidy to take it from the economic concept to pragmatic reality. That work, to be completed in ~12 months, has begun as of late 2006. The three major objectives are as follows: 1) to develop a detailed architecture and operational plan for the global subsidy, including exit clauses to address situations in which the subsidy might no longer be needed or appropriate; 2) to build a coalition that has the critical mass to generate funding and political support so that the subsidy can become reality; and to address questions related to external effects of the subsidy or external risk factors that could jeopardize the initiative.

The Dutch government has taken a leading role in promoting the subsidy, including sponsorship of a January 2007 meeting in Amsterdam, which resulted in a strong affirmation of the idea and a resolve among most partners to move ahead as quickly as possible. One conclusion, about which no disagreement was voiced, was that the level of funding needed for the subsidy itself was not large in the context of global health and should not be a barrier to establishing the subsidy. Skepticism and opposition—sentiments that favor the status quo—have diminished over time, although they have not disappeared entirely.

In terms of what will be subsidized, the ACT supply also has been slow to develop but should be ready to meet the subsidized demand. In early 2007, two new ACTs are emerging from the not-for-profit research and development pipeline through the Drugs for Neglected Diseases initiative and another is due through the Medicines for Malaria Venture.

The global subsidy has proven a powerful idea that continues to gain currency. The next few years will determine its fate, and more importantly, the fate of those who would otherwise suffer or die for lack of affordable, effective malaria drugs. If entirely successful, the subsidy will make available a necessary tool for malaria control. Achieving the greatest benefits from this tool will require continued efforts and increased resources for all other malaria control interventions.

Received December 29, 2006. Accepted for publication March 5, 2007.

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