Malaria among African Children

HOPE FOR PROGRESS AGAINST A GROWING MENACE

Ramanan Laxminarayan

Malaria is a silent killer that takes the lives of an estimated one million children under the age of five in sub-Saharan Africa each year. This disease, caused by a mosquito-borne parasite, kills as many as three million persons annually, according to the World Health Organization (WHO), with between 300 million and 500 million new malaria cases occurring every year. Some recent estimates suggest the worldwide total may be closer to 660 million cases annually, and again most of the deaths are in young children.

The rising toll among African children from malaria—as well as HIV/AIDS—runs counter to significant gains in children's health due to fewer deaths from diarrhea, measles, and other vaccine-preventable illnesses. An important reason for this rising death toll is that chloroquine and sulfadoxine-pyrimethamine (fansidar), the two drugs most commonly used to treat malaria in sub-Saharan Africa, are facing high levels of parasite resistance.

There are encouraging signs, however, that public health strategies based on new artemisinin drugs derived from Chinese herbal medicine could work to dramatically mitigate rising deaths from malaria in Africa, particularly among children. Recent research at RFF confirms recommendations from WHO and the U.S. Institute of Medicine (IOM) for new drug therapies that hold promise for malaria-endemic regions. The findings bolster the

argument that an annual international subsidy of roughly $300 million for antimalarials could ameliorate the threat of malaria and potentially save millions of lives.

The hope is that combined drug therapies can be implemented more widely in affected areas. Like the AIDS "cocktail" that has transformed that illness from an automatic death sentence to something that can be aggressively managed, at least in industrialized countries, the new malaria combination therapies are believed to be more effective at delaying the emergence of resistance when compared to single drugs used as stand-alone treatments, which are rapidly losing their effectiveness.

Malaria doesn't just kill its victims. It also places a colossal burden on the health and economic well-being of people who live in malaria-prone regions, regardless of whether they have the disease. Malaria causes the members of a household not to "specialize," because they have to be able to substitute for other family members who may be suffering from malaria; for example, a father who might otherwise earn a cash wage must take care of a sick mother or children. Also, households in malarious regions are less likely to grow high-yield crops that require labor inputs at critical periods during the growing or harvesting season, than households living in areas with low malaria risk.

Macroeconomic studies have shown that malaria could shave as much as 1.3 percent off annual economic growth rates even after controlling for other factors that affect growth. The effect of malaria on household well-being has also been examined. In one project, RFF researchers gauged the impact of reducing malaria on household economic prosperity

in Vietnam. Our analysis showed that reductions in malaria incidence through government-financed malaria control programs contributed to higher household income for all households living in endemic areas. Based on our estimates, the roughly 60-percent average reduction in malaria nationwide in Vietnam during the 1990s translated to a 1.8 percent increase in annual household consumption.

First-Line Treatments Failing

In spite of the strong evidence that reducing malaria can improve economic wealth, there is little to show in terms of progress on the ground. In fact, across much of sub-Saharan Africa, the disease is gaining momentum. Again, the increasing ineffectiveness of first-line antimalarials is believed to be an important contributing factor.

Since its introduction in the 1950s for malaria treatment, chloroquine has been the mainstay of malaria treatment throughout the world. Costing only a few pennies a dose, chloroquine was used widely, even for treatment of febrile illnesses that were unrelated to malaria. It was also mixed with common salt in some countries to provide a prophylactic impact. Despite widespread usage of the drug, mutations conferring resistance to chloroquine are believed to have arisen independently only a few times during its long history of use.

However, these mutations spread widely and with the "selection pressure" imposed by widespread chloroquine use,

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the drug became largely ineffective against the malaria parasite *Plasmodium falciparum,* except in pockets of South Asia and West Africa. In the face of resistance to chloroquine, many countries have turned to the drug sulfadoxine-pyrimethamine (SP), but parasite resistance to this drug has evolved rapidly, possibly because of its prolonged half-life, resulting in a higher probability of selecting resistant strains. The mutations that conferred resistance to SP were first reported in 1980s in Southeast Asia and are now prevalent in many regions of the world.

In recent years, with the availability of artemisinin derivatives, there has been new reason for hope. Artemisinin drugs, which have been known to Chinese medicine for many centuries, are derived from *Artemesia annua* (a common weed known as sweet wormwood) and are highly effective in treating *P. falciparum,* the most prevalent and deadly parasite in sub-Saharan Africa. Moreover, resistance to artemisinin has yet to be detected in clinical settings.

Recognizing the potential for resistance to curtail the useful life of this valuable drug, WHO has issued guidelines for artemisinin-based combination therapies (ACTs) that incorporate an antimalarial drug unrelated in mechanism of action and genetic bases of resistance to artemisinin, so that a single mutation cannot encode resistance to both components. However, these guidelines are difficult to enforce and are not always followed.

One reason for this is that artemisinin monotherapy is available for sale in many countries (and was even official treatment policy in Vietnam during the 1990s) and has the potential to negate the effectiveness of ACTs globally. Rec-

ognizing that artemisinin monotherapy could be discouraged only by a combination of official policy and economic incentives, an IOM panel composed of economists and public health professionals recently issued a report calling for a high-level, globally administered subsidy for ACTs. Panelists recommended that ACTs be made available to any public or private agency at a price that was comparable to that of antimalarial monotherapy at roughly 10 cents a treatment course—a global treatment plan that would cost between $300 million and $500 million each year. With the potential for malaria to decrease with ACT use, at least in low transmission settings, the cost of the subsidy could only decline over time.

The head of the WHO malaria program has gone a dramatic step further, recently calling on 18 pharmaceutical companies that produce artemisinin to stop selling the drug in its singular form or face public condemnation and possible efforts on the part of WHO to disrupt their sale.

Balancing Short- and Long-Term Costs

Some of the background research that informed the IOM committee's deliberations was conducted at RFF. This work analyzed different strategies that could be adopted to treat malaria where resistance was a concern. Countries could introduce the cheaper drug SP as a replacement for chloroquine and then move to ACTs when resistance emerged to compromise SP potency. The advantage of this strategy would be the significantly lower price and ease of dosing for SP (a

one-day treatment). An alternative strategy would be move directly to ACTs.

Switching first to SP was preferable when the proportion of patients who would get malaria treatment was either very low or very high. At very low levels of treatment coverage and low selection pressure, resistance to the less-expensive SP is not a problem and therefore is the preferred option. At extremely high levels of treatment coverage, however, resistance evolved so rapidly, regardless of whether SP or ACTs were used, that the difference between the two drugs was not as great. It was for intermediate (and the most plausible) levels of treatment coverage that introducing ACTs was always superior even though it was the more expensive drug.

Our research also showed that for shorter time horizons, it made sense to use SP first to delay the costs of ACTs. If one were only interested in the short term, using the less expensive drug makes better economic sense because the costs of resistance-related morbidity do not enter the policymaker's set of considerations. However, for longer planning horizons, a direct switch to ACTs made better economic sense given the costs of higher morbidity associated with increasing resistance to SP.

Overall, we found that introducing ACTs immediately was likely to be preferable, under most circumstances, to an alternative strategy of first using SP in countries where SP had yet to be introduced and then moving to ACTs. There were two reasons for this. First, introducing SP, a drug to which resistance was likely to emerge in the next few years, would result in deaths and morbidity that could be averted by moving to ACTs right away. Second, the continued use of artemisinin monotherapy and partner drugs alongside SP would greatly speed up resistance to ACTs when they were introduced.

More recent work at RFF, in collaboration with colleagues at the National Institutes of Health and the World Bank, has focused on the important question of whether a large subsidy for ACTs would increase their use so much as to excessively speed up the rate at which resistance emerges to the combination. Since the benefits of the subsidy in terms of driving out artemisinin and other potential partner drug monotherapy could be offset by the negative consequences of expedited resistance to ACTs, would subsidies help at all?

Using economic and epidemiological mathematical models of malaria transmission and drug resistance, we find that the answer turns out to be yes for a wide range of possible economic and epidemiological parameters. Subsidies are likely to prolong the life of artemisinin and partner drugs even if overall ACT were to go up significantly in response to the subsidy. However, this would happen only if subsidies were introduced without delay. A delay would permit contin-

ued use of monotherapy of both artemisinin and of likely partner drugs to artemisinin and emergence of low-level resistance. Resistance would then be magnified through intense selection pressure with the introduction of a full subsidy program.

This research also indicates that subsidizing one specific ACT throughout the world could result in much faster emergence of resistance than if two or three combinations were used that had unrelated partner drugs to artemisinin. The underlying intuition is simple. Using a single combination in all regions places greater selection pressure for parasites to become resistant to that combination. Use of different combinations relieves the selection pressure for resistance to evolve to any single combination. To take the thought experiment further, if we were able to treat every single malaria patient with a completely unique drug or combination, the likelihood of resistance developing to each of these drugs would be infinitesimal. In general, the idea of using the same ACT combination worldwide deserves serious reconsideration. Moreover, different ACT combinations may, if priced effectively, drive out monotherapies by offering consumers a choice of different antimalarials with different dosing schedules and other attributes.

The effectiveness of antimalarial drugs is a global public good, of particular value in malaria-prone regions that also are among the most economically impoverished parts of the world. Inappropriate drug use in neighboring countries reduces the incentive of any given country to deploy drug regimens that may be rapidly undermined by resistance originating outside their borders. Therefore, a case can be made for globally coordinated action and fiscal support to protect the effectiveness of these valuable drugs. If we are smart in how we deploy the ACT drugs, there is a real promise of making sure that millions of children in Africa will reach adulthood. ■

Further Reading

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