Malaria

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It's Not Neglected Any More

Public consciousness about malaria is rising in this country. Just a few years ago, many Americans thought that malaria was an ancient plague and were surprised to discover that it still plagues populations in Africa, Asia, and other tropical parts of the globe. Of course, people still have much to learn, but between the President and First Lady visiting malaria control programs in Africa and the Denver Nuggets raising money for bed nets treated with mosquito-zapping insecticide, malaria is harder to miss these days.

Here are the rote statistics: half a billion cases and one million dead each year—most of them African children. What's new—and startling, certainly for the global health community—is the fact that a billion dollars is now pouring into malaria control every year. Less than a decade ago, it was just a few tens of millions. With such an enormous financial commitment and the attention of the world, will this investment pay off? Will we finally be able to change the numbers on the malaria scoreboard? People are talking big: the "e word" is in play again. *Eradication*. Is it a pipe dream or can it be reality?

While scientific advances in the treatment of malaria are cause for optimism, the lack of a unified worldwide plan or vision for malaria control remains a serious concern. More people sleep under protective nets and have access to effective drugs than ever before but malaria-endemic countries tend to be among the world's poorest, which also means they have the weakest healthcare infrastructures. And while malaria may be the most important health problem historically, it is overshadowed by AIDS—which not only makes people vulnerable to other diseases, but also has soaked up the best and the brightest in the healthcare workforce.

Can we control malaria? Or will it continue to control the lives of the people affected? A lot depends on what happens over the next few years: if success can be documented, funding will probably continue to flow. But, if progress is not great enough, despite the large sums devoted to tackling malaria, the disease may win again.

Today's Control Measures Can Work

Clear evidence has emerged, from the places where the current wave of malaria control started earliest, that the tools we have do work. The big three interventions are effective drugs, insecticide-impregnated bednets, and the spraying of indoor walls with insecticide (referred to as indoor residual spraying). Take Kwazulu Natal (KZN), the state that had the highest malaria burden in South Africa up to the year 2000, when the KZN malaria control program conducted house-to-house campaigns of indoor spraying, and

(But It's Not Gone, Either)

switched to the best type of drug. Prior to that, some districts reported 5,000 cases each month during the high season. In 2001, the numbers fell to 1,000 per month. Since 2002, not more than a few hundred cases have been reported. Today, mothers no longer spend their days caring for children in crowded malaria wards. Both the annual number of cases and number of deaths in KZN have fallen 90 percent. Zanzibar, a large island off the Tanzanian coast, and other countries (Rwanda and Ethiopia, for instance) where insecticide-treated nets are integral to the mix, are beginning to yield similar stories.

We still need better drugs and insecticides, and the search continues for the holy grail: a vaccine against malaria. But we know that using current methods will lead to huge declines in the malaria burden. Whether or not they can lead to eradication is still an open question.

Funding Is at an All-Time High

The harsh reality is that the best science and the best intentions will have little impact without funding. That goes for implementing malaria control programs and for carrying out research needed to advance knowledge, both in the laboratory and in the field. Recent progress has been possible because of money. Current funding for malaria control is at an all-time high and still in crescendo mode. Since 2000, three major new funding sources have transformed the scene: the Global Fund for AIDS, Tuberculosis and Malaria (the Global Fund), the World Bank Booster Program for Malaria, and the President's Malaria Initiative (through the U.S. Agency for International Development, USAID). The Department for International Development, the British bilateral aid agency, is also a major donor to malaria efforts and, in smaller amounts, other countries have increased aid as well. The role of the Bill & Melinda Gates Foundation, in money and in visibility for malaria, cannot be overlooked. Overall, it adds up to a billion dollars per year.

The Global Fund has made the biggest financial contribution over the largest number of countries, and has the best chance of maintaining a long-term commitment. The President's initiative is billed as a five-year, $1.2 billion program, and like the President's Emergency Plan for AIDS, funding will likely be renewed if progress is being made. It is difficult to project what priorities may look like in the United States five years from now, however. Clearly, a different president will be in office who may want his or her stamp on some other cause.

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Better Tools on the Way

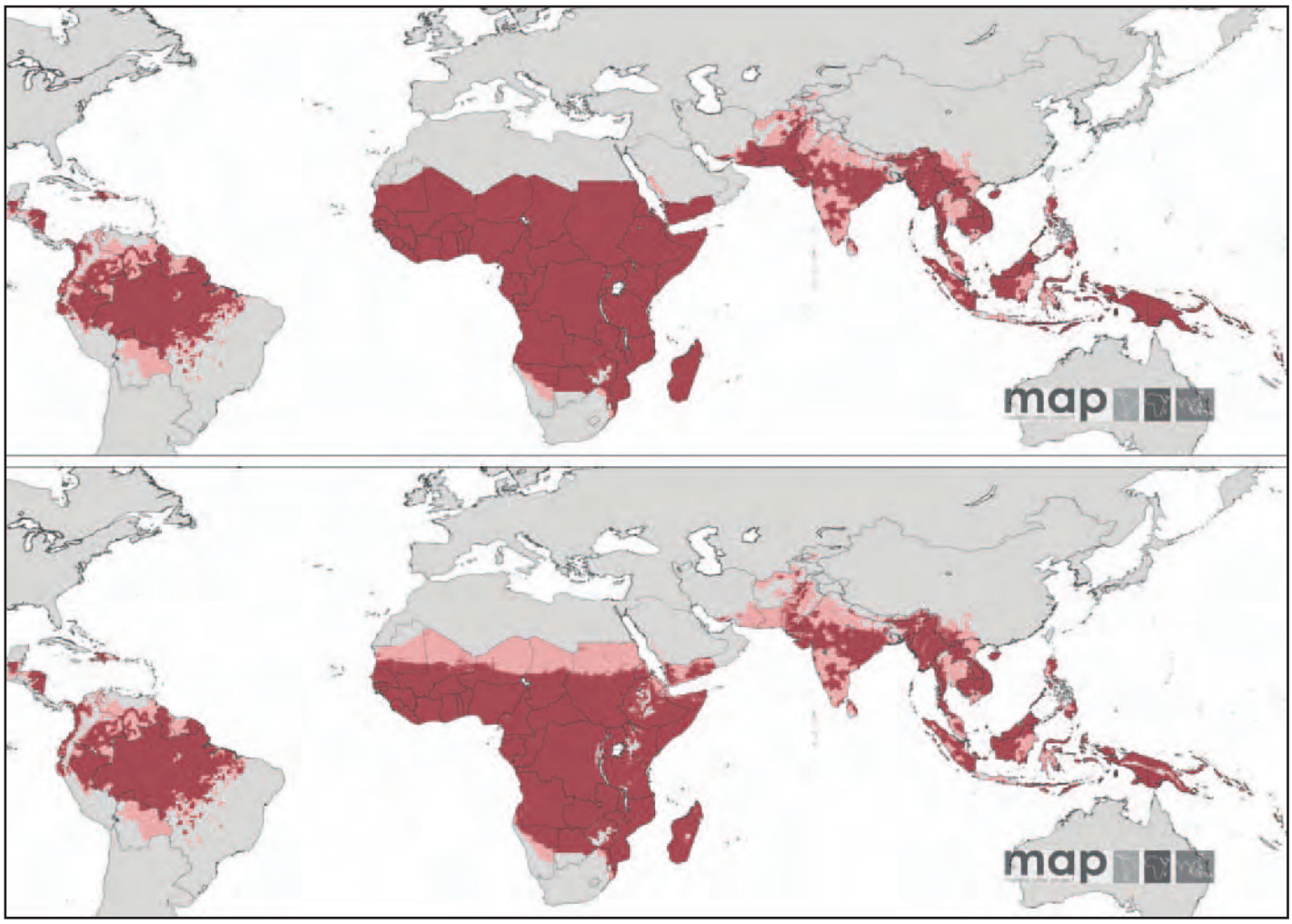
The first and only serious attempt to eradicate malaria globally, which began with much fanfare in 1955, succeeded in southern Europe and large parts of Asia and the Americas, but failed in sub-Saharan Africa. The World Health Organization's (WHO) malaria eradication campaign relied on a single tool—spraying of the then-remarkable insecticide DDT. By 1969, when a halt was called to the campaign, it was clear that DDT alone could not wipe out malaria in Africa, where intensity of transmission was higher (year-round in many areas) and infrastructure was poor. Most obviously, DDT-resistant mosquitoes took over well before the job was done. Where DDT had outlasted the species that spread malaria elsewhere, the African vector (*Anopheles gambiae*) was tougher, and in the end, mosquitoes triumphed. Some also believe that sub-Saharan Africa was written off as a lost cause for malaria, and that sufficient effort was not made.

It could be different this time. We have a bigger and better arsenal of tools and, equally important, a better understanding of how they work. We know from well planned and executed field trials that insecticide-treated bed nets reduce childhood deaths from malaria. Net technology itself has improved: an earlier generation required users to retreat them every three months with insecticide, but the current models incorporate insecticide into the fabric itself. And we have a new generation of drugs—artemisinin-combination therapies, or ACTs—that are even more effective than chloroquine, which was lost to resistant malaria parasites after a decades-long run. Even DDT has been rehabilitated. The years during which it was not used has winnowed out the resistant mosquitoes and DDT is now used more judiciously, by spraying only internal walls, as in KZN. A few other insecticides can also be used, but development of new insecticides has lagged.

For the long term, the malaria drug pipeline is fuller than it's ever been. Although novel drugs may come from a variety of sources, the Medicines for Malaria Venture, a non-profit "public-private partnership," has the deepest and broadest inventory of drugs in development of any organization. Over time, even the best new drugs will need replacement—not in crisis, but as a matter of course. That should now be possible, although it will likely be another decade before the partnership's R&D results in new forms of treatment.

Malaria Knowledge Is Advancing

The breadth and organization of knowledge are also advancing in important ways. Recently, the first results of the Malaria Atlas Project (MAP) were published, combining sophisticated data processing and old-fashioned, shoe-leather epidemiologic detective work. The international Kenya-based MAP team (including David Smith, an



***P. falciparum* Malaria Risk Defined by Annual Parasite Incidence (PfAPI; top), Temperature, and Aridity (bottom). Areas were defined as stable (dark-red areas), unstable (pink areas), or no risk (light grey). The few areas for which no PfAPI data could be obtained, mainly in India, are in dark grey. The borders of the 87 countries defined as *P. falciparum* endemic are shown. Highland areas where risk was excluded due to temperature appear in light grey. The aridity mask excluded risk in a stepwise fashion, reflected mainly in the larger extents of unstable (pink) areas compared to the top panel, particularly in the Sahel and southwest Asia (southern Iran and Pakistan).** Source: Guerra, CA, Gikandi, PW, Tatem, AJ, Noor, AM, Smith, DL, et al. (2008) "The limits and intensity of Plasmodium falciparum transmission: Implications for malaria control and elimination worldwide." PLoS Med 5(2): e38. doi:10.1371/journal.pmed.0050038

RFF visiting scholar) has produced the most detailed malaria map to date. Using records unearthed from around the globe, it shows not just how many people are at risk of malaria, but also their level of risk. MAP could be the basis of a global plan for malaria control, containment, and eventual eradication. Talk is now about "shrinking the map."

Drug Resistance: Liability and Opportunity

One of the biggest threats to malaria control is drug resistance. The world was lucky that chloroquine—the 20th century mainstay—was effective for decades. For reasons not well understood, very few malaria parasites ever maintained genetic mutations conferring true resistance to this drug. But over time, the progeny of a resistant strain from Southeast Asia finally spread throughout Asia and then Africa. In Asia, replacement drugs were used starting in the 1960s. By the 1990s, mortality rates in Africa were rising because chloroquine no longer worked, and African countries, by and large, did not have the resources to switch drugs. The exception was a switch to another remarkably inexpensive drug, sulfadoxine-pyrimethamine (SP). It was very effective initially but, unlike chloroquine, was rendered ineffective in a few short years by drug-resistant malaria.

Chloroquine and SP resistance were both global catastrophes and wake-up calls: malaria drugs are precious, shared resources that must be managed so that they do the most human good, but they also must be protected from loss to drug resistance for as long as possible. The fact that the world is now relying on one drug class—

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the artemisinins—as the backbone of malaria drug treatment for at least the next decade makes protection all the more imperative.

Continuing research at RFF is playing a key role in advancing both science and policy for better stewardship of antimalarial drugs. This spring, RFF researchers hosted scientists and policymakers from around the world at a first-of-a-kind conference on antimalarial treatment strategies, held in South Africa. A major theme was that malaria drugs are shared resources, and their effectiveness, a "global public good."

The conference was the culmination of 18 months of work that extended earlier epidemiologic modeling at RFF. The earlier work predicted large benefits from using malaria drugs in combination (rather than as monotherapy, which had been the norm), both in terms of saving lives and prolonging the effectiveness of drugs. The current combinations all include an artemisinin plus a companion drug (ACTs)—each of which should be effective malaria drugs for the locale.

Would using more than one combination in a given population give even greater protection to the drugs? Would they remain effective for years, maybe even decades, longer? That is just what the models developed at RFF predict: multiple first-line therapy should significantly delay the spread of resistant parasites. But can endemic countries implement such policies?

No one expects a clinic or doctor to randomly assign patients to one ACT or another when they come in needing treatment. So RFF has suggested practicable alternatives: children get one ACT and adults another, for example. Or the use of one ACT in the public sector and another in the private sector. Today, multiple drugs are sold from big-city pharmacies down to small village shops. Unfortunately, many are ineffective (people still buy chloroquine and SP because they are affordable and, currently, ACTs are not), substandard, or outright counterfeits. Both the affordability and the quality of drugs sold in the public sector are another focus of RFF work.

Financing Malaria Drugs Through "Radio Malaria"

"Radio Malaria" is the nickname for the Affordable Medicines Facility-malaria—AMFm. The AMFm strategy was born of the central idea in a 2004 study by an Institute of Medicine (IOM, part of the U.S. National Academy of Sciences) committee. RFF Senior Fellow Ramanan Laxminarayan was a member of the committee, and I served as the study director. The committee's idea for a global subsidy has developed into the outlines of an international organization, slated to begin operation in 2009. By the plan's outline, manufacturers of high-quality ACTs (judged, as currently, by the WHO or another international authority) will sell them at "chloroquine" prices to governments and to the wholesalers that supply the private markets in endemic countries. AMFm will then pay the manufacturer a supplemental amount for each dose sold, so that manufacturers will be paid a fair (but competitive) wholesale price.

By taking advantage of a chain of distribution that already exists through the private sector (where more than half of antimalarials are acquired currently), AMFm would expand access to these lifesaving drugs and delay their loss of effectiveness to resistant malaria parasites for years or decades. The title of the IOM report says it all: *Saving Lives, Buying Time*.

Money, effective control measures, knowledge, innovative financing mechanisms, the promise of even better interventions—all are on the increase where malaria is concerned. Thus far, interventions and plans have been approached in nearly all cases on a country-by-country basis. Some countries have seen greater success than others. The key to future worldwide control—possibly even eradication—will be a plan with global scope that can shrink the malaria map until it no longer exists. ■