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Perspective

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A New Attack on Malaria

Susan Okie, M.D.

This past October, at a scientific conference in Seattle, Bill and Melinda Gates issued a challenge that rocked the international health community. The leaders of the world's richest charitable

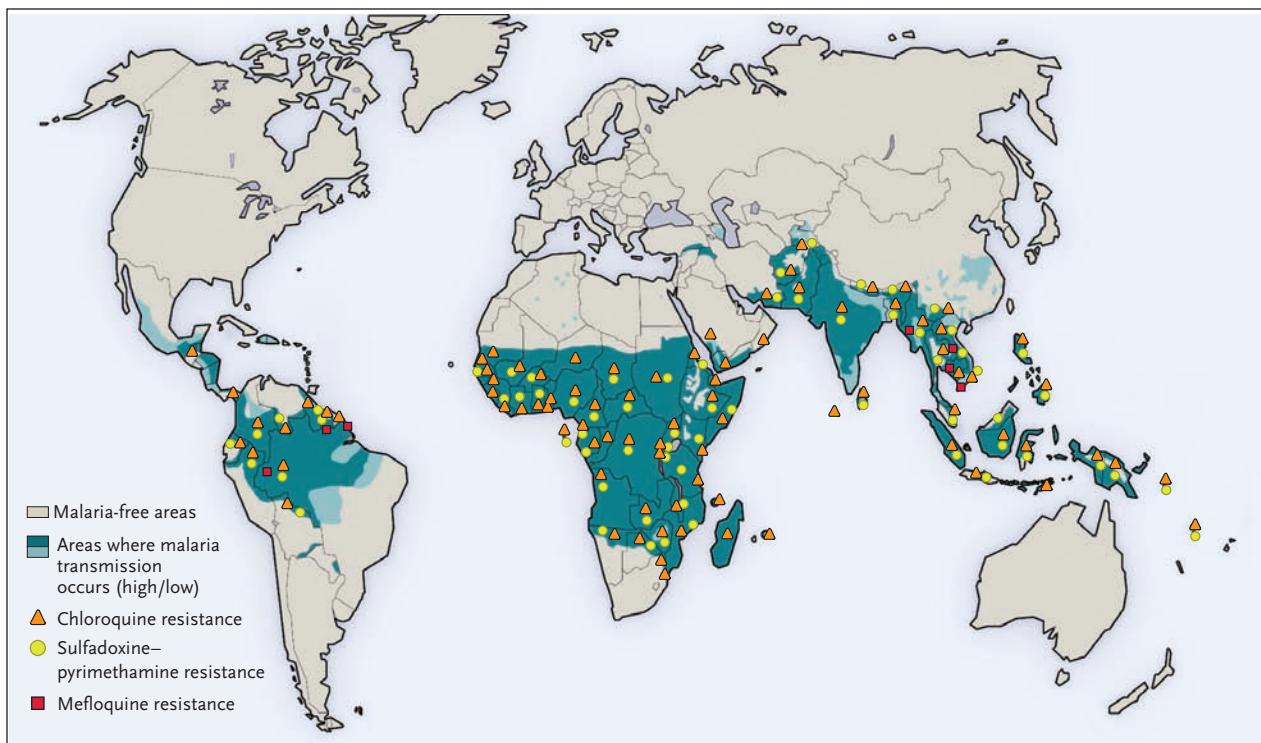
foundation called on scientists and health officials to join in a global effort to eradicate malaria, an infection that kills more than a million people each year, most of them infants and children.

Mention of the big "E word" has sparked a spirited debate about whether eradication will ever be possible, even as enthusiasm and funding build for a global drive to end malaria deaths in sub-Saharan Africa by focusing on prevention and treatment — an ambitious first step that would have an enormous impact on public health. That multibillion-dollar initiative, announced in April by United Nations Sec-

retary-General Ban Ki-Moon, was inspired by recent gains against malaria in countries such as Rwanda and Ethiopia, where national programs, funded largely by international donors, have reduced illness and deaths by about 60% over a period of 2 to 3 years with the use of insecticide-treated bed nets, rapid diagnosis, and combination-drug treatment. Yet *Plasmodium falciparum*, the parasite species that causes most malaria deaths, is a far more formidable foe than variola (smallpox) virus and poliovirus, which were targets of previous global eradication campaigns.

The World Health Organiza-

tion (WHO) defines eradication as permanent reduction to zero of the worldwide incidence of an infection by a specific agent, resulting from time-bound, deliberate efforts. Elimination is defined as reduction of the incidence of infection to zero within a defined geographic area. Since anopheles mosquito species with the potential to transmit malaria invariably remain present after the parasite has been eliminated in human hosts, countries must still use measures such as aggressive surveillance for cases in immigrants or arriving travelers, as well as provision of rapid diagnosis and treatment, to prevent reestablishment of the infection.¹ The malaria community is sharply divided over whether money and effort should be spent on shrinking the world malaria map by trying to eliminate infection in



Areas of Malaria Transmission and Antimalarial Drug Resistance.

Data on malaria transmission are for 2007 and are from the World Health Organization. Data on drug resistance are for 2004 and are from the Roll Back Malaria partnership.

areas where transmission is low or whether such projects will distract from reducing suffering in African countries where intense transmission renders elimination infeasible but where regional dissemination of prevention and treatment could reduce the incidence of clinical illness by 90% or more. Global eradication is judged to be impossible with the current tools. Yet “unless you think and worry” now about long-term eradication “and about what tools you would need, you can’t engage the scientific community about what those tools would look like,” said Regina Rabinovich, director of Infectious Disease Initiatives at the Bill and Melinda Gates Foundation.

History casts a shadow over any discussion of malaria eradi-

cation. Fifty years ago, in the world’s first coordinated disease-eradication effort, public health workers battled malaria for more than a decade with the insecticide dichlorodiphenyltrichloroethane (DDT) and the drug chloroquine. They eliminated the infection from 24 countries and freed 1 billion people from malaria risk, yet the emergence of mosquito resistance to DDT and parasite resistance to chloroquine led to epidemic resurgence of malaria in some countries where it had been nearly vanquished.¹ Moreover, the campaign never included the tropical African countries with the most intense transmission, where about 90% of malaria deaths occur. Widely viewed as a failure, it was followed by decades of inertia in the face of an increasing death

toll. “In international public health circles, that’s still a very potent memory,” said Donald Hopkins, vice president for health programs at the Carter Center.

Small wonder, then, that reaction to the call for a new global eradication campaign has been mixed. Even the choice of target organism is a matter of debate, because malaria infection in humans can be caused by four species of plasmodia, although only *P. falciparum* and *P. vivax* commonly produce clinically significant disease. The clinical spectrum is broad: of an estimated 500 million malaria cases annually, many are asymptomatic or cause relatively mild illness. “Even if you could not eradicate all the malaria species” that infect humans, “it still would be very, very

good to get rid of falciparum," the killer of African infants and children, said Hopkins. Some experts, including Rabinovich, favor targeting vivax, too, although that organism's ability to persist inside hepatocytes makes infections more difficult to cure. But Arata Kochi, chief of WHO's Global Program on Malaria, contends that "to move toward eradication at this moment is counterproductive." A better initial goal is, through prevention and treatment, "to make malaria a small problem" in countries where it is now a major scourge, said Kochi. In Zambia, for example, where the Gates Foundation and other donors began 3 years ago to fund a national effort to reach 80% of the population with preventive measures, "clinics literally are empty of malaria cases" during this year's rainy season, said Carlos C. (Kent) Campbell, director of the Malaria Control and Evaluation Partnership in Africa (MACEPA) at the Program for Appropriate Technology in Health (PATH). Kochi believes that with expected international funding, deaths from falciparum malaria in tropical Africa can soon be reduced by as much as 90%, even in countries such as Nigeria and the Democratic Republic of Congo, where political conditions or government instability have posed challenges to other public health efforts. A rapid, region-wide reduction in mortality "is a very likely scenario — it will happen in the next 3 to 5 years," Kochi predicted.

Besides promoting a reduction in mortality in the hardest-hit countries, WHO officials and many malaria experts support efforts to eliminate the infection

in countries where political motivation, available resources, and relatively low levels of disease transmission make such a goal feasible. Implementation of an elimination program is getting under way in Papua New Guinea, Vanuatu, and the Solomon Islands, and a joint program is being planned by South Africa, Namibia, Botswana, and Swaziland, said Richard Feachem, director of the Institute for Global Health at the University of California (San Francisco and Berkeley). China, which has endemic falciparum malaria and vivax malaria in some of its southern provinces and periodic outbreaks of vivax malaria elsewhere, is also considering an elimination program, Feachem said.

Some experts worry, however, that money spent on elimination may be wasted in countries with neighbors that have intense malaria transmission and ineffective health care systems. Earlier this year in Thailand, a country that has substantially reduced its malaria levels, I visited a frontier clinic where medics were treating a steady stream of malaria cases in workers emigrating from Burma, where public health programs are almost nonexistent. "It's indefensible" to attempt elimination in countries "where you have an enemy all round you," said Brian Greenwood, a professor of tropical medicine at the London School of Hygiene and Tropical Medicine. "It's not going to be easy to contain the infections" that cross borders, he said. Kochi noted that eliminating malaria from Southeast Asia would have global benefits because drug-resistant parasites usually evolve there first, but he added that because a mosquito vector there bites people who

sleep outdoors in the forest, it is difficult to control malaria with bed nets and indoor spraying of insecticide. "We don't know whether we can do it," he said.

International funding for malaria has risen dramatically — to about \$1 billion per year, from as little as \$84 million annually in the late 1990s² — but a global eradication campaign will require much bigger increases. Even achieving full coverage with prevention and treatment measures in the hardest-hit African countries would cost about \$2.2 billion per year for 5 years, according to a recent analysis.³ In 2005, the World Health Assembly urged member nations to establish operational plans to reduce the global malaria burden by at least 50% by 2010 and 75% by 2015; reaching these targets would cost an estimated \$3.8 billion to \$4.5 billion annually between now and 2015.⁴ A multidecade global eradication campaign would require additional investments for continued prevention and treatment of infection; research on new drugs, vaccines, diagnostics, and insecticides; and ongoing surveillance.

A crucial incentive for donors and health officials is that malaria's economic toll, in terms of treatment costs and lost productivity, will diminish if the disease is controlled, but Greenwood warns that political enthusiasm will be harder to sustain once the case rate drops. "The idea that you have a massive investment in elimination and then all the costs will go down — that's certainly not true until you get to eradication," he said. And the biggest operational challenge to global eradication is that malar-

ia is most entrenched in the region where the public health infrastructure is weakest, noted the Carter Center's Hopkins. A bitter lesson of previous disease-eradication campaigns, Hopkins said, is that "you need to start in the places where the problem is worst, because almost by definition it's going to take the longest time" to succeed there. "If you leave them till last, you cannot buy back that time."

There is broad consensus that global eradication of falciparum malaria is not possible with current weapons, which differ little from those of the 1950s: chiefly, an insecticide (the pyrethroid compounds used to treat bed nets) and a medicine (artemisinin, given as part of combination therapy), although DDT and a few other insecticides are sometimes used. Resistance to the pyrethroids has already appeared in some African mosquito populations, and artemisinin resistance may be emerging near the Thai-Cambodian border.⁵ If resistance to these compounds spreads faster than researchers discover new ones, gains achieved by malaria-control efforts could be short-lived. "This is one of my main concerns: how long we can keep existing tools effective," said WHO's Kochi, who criticized the nonprofit Medicines for Malaria Venture (MMV), funded by the Gates Foundation and others, for failing to aggressively pursue development

of alternatives to artemisinin. "The pipeline" for new drugs and insecticides "is very slow," he said. "Basically, there have been no new chemicals in the last 15 years."

Rabinovich of the Gates Foundation said that the MMV is investing in drug discovery and development. "There are easily 20 to 25 drugs in that pipeline right now," she said. "There is a gap in what's coming up for phase 2 and phase 3, but that's because there were no candidates to be pushed over that hump" when the initiative began. She added that the foundation is also funding research on insecticides, as well as on drugs and vaccines designed to block transmission of malaria from an infected person to additional hosts, by killing the sexual form of the parasite in the bloodstream or preventing maturation of the parasite within the mosquito.

Permanent elimination of malaria transmission from endemic regions may have to wait for new drugs and insecticides and, perhaps, for a highly effective vaccine. A vaccine developed by Glaxo-SmithKline Biologicals, currently being evaluated in trials in Africa, could be on the market by 2012 but appears to be less than 50% effective in preventing infection, although it may reduce the clinical severity of malaria. Researchers "are going to keep working on the next-generation" vaccine, said Christian Loucq, global program

leader of the Gates-funded PATH Malaria Vaccine Initiative. "We should be able to develop a vaccine with more than 80 or 85% efficacy — that is the tool that is going to be required," he said.

Even with effective new tools and successful regional elimination, experts estimate that global eradication of falciparum and vivax malaria could take 50 years or longer. Past eradication campaigns have taught us, said Hopkins, that "it's always going to be more difficult and take longer than you think." But Greenwood cites another lesson of the malaria-eradication campaign of a half century ago: "Don't give up."

Dr. Okie is a national correspondent for the *Journal*.

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