

Lots of money and new scientific tools have invigorated the fight against malaria. But the disease is unyielding, and the current weapons are losing their effectiveness

# A Renewed Assault on an Old And Deadly Foe

## MALARIA

The following articles look at the various tools and strategies being enlisted in the renewed fight against malaria, which kills more than 1 million people per year.

### POLICY

### AFRICAN RESEARCH VACCINES

### DRUGS

### GENOME SEQUENCING

### MOSQUITO ENGINEERING

After languishing for decades in the scientific backwaters, malaria research is suddenly being swept into the mainstream. International finance and aid organizations have declared malaria a global health priority, and money is beginning to pour in. Researchers who have been doggedly pursuing an intractable foe with limited resources now have the means to follow new leads—just as some promising avenues are opening up.

And funding agencies are finally beginning to plug a critical gap: a lack of research and medical capacity in developing countries where malaria exacts its deadly toll.

powerful mandate to be involved: Fighting malaria is precisely what CDC was created for in 1946. But basic research funding grew slowly: When the AIDS budget at the U.S. National Institutes of Health (NIH) broke the \$1 billion mark in 1991, for example, NIH's investment in malaria was just over \$10 million.

Now, signs of change are everywhere. The World Bank is pledging \$300 million to \$500 million in interest-free loans to fight the disease, especially in Africa. The World Health Organization (WHO) has set an ambitious goal of cutting malaria deaths in half by 2010 (see sidebar on p. 430). In major speeches, President Clinton has thrown his support behind efforts to develop a malaria vaccine. Indeed, the finance chiefs of the world's wealthiest nations, the G-8, have promised billions of dollars to fight malaria, AIDS, and TB. The Bill & Melinda Gates Foundation is donating \$115 million for antimalaria research, education, drugs, and vaccines. And at the National Institute of Allergy and Infectious Diseases (NIAID), still the largest single contributor to malaria research, the budget is expected to rise above

\$52 million in 2001. "There is a momentum we didn't have before," says NIAID director Anthony Fauci. "All of a sudden things are happening that were unimaginable a few years ago."

What changed? No single force, but a confluence of events has opened pocket-books. As Western economies have boomed, charities have become flush with stock earnings, for instance, and the U.S. Congress has promised NIH a 5-year budget doubling by 2003—all of which makes it easier to deliver on humanitarian urges. Self-interest plays a role as well, as politicians come to view countries wracked by poverty, disease, and war as a threat to national security. Says Fauci: "The important policy-makers in government are now talking about making this [alleviating the disease burden in poor countries] part of our foreign policy."

### Rising toll

Whatever the logic, the malaria research community welcomes the support. And the need has never been greater. More than 400 million people, WHO estimates, fall ill with malaria each year, and between 1 million and 3 million die—mostly children younger than 5 years, and most of them in Africa.



It's quite a turnaround. Despite malaria's horrific handiwork—it kills more people each year than any other infectious disease except AIDS and tuberculosis (TB)—it has been hard to muster support for a disease that "doesn't happen here." True, malaria has long received funding from a few deep-pocketed organizations, like the U.S. Army and Navy, which in many places lost more soldiers and sailors to parasites than to gunfire. The U.S. Centers for Disease Control and Prevention (CDC) in Atlanta also had a



**The face of malaria.** Most deaths occur among children under 5 years old, many of whom succumb to anemia or coma following infection by parasites carried by the *Anopheles* mosquito.

CREDITS: (LEFT TO RIGHT) A. CRUMP/WHO/TDR; COURTESY OF ED ROWTON/WRAIR



Public health experts believe the toll has actually been increasing in recent years, although numbers are impossible to verify. But no one disputes that the drug-resistant strains of the parasite are spreading, rendering cheap and effective drugs ineffective.

Scientifically, too, the time is ripe for a fresh attack. New resources are coming on line, such as data from the malaria genome project, which is deciphering the genetic code of the most deadly parasite, *Plasmodium falciparum* (see p. 439). Tom Wellems, a molecular biologist at NIAID, is ecstatic. The genome is a "tremendous" tool for zeroing in on how the parasite wreaks its havoc, he says, and for finding new drug targets. Equally important, says Fauci, young people are entering the field again.

These scientists will need all the new tools they can get. In the 1950s, WHO optimistically targeted malaria for eradication. After all, the United States and other Western countries had wiped out the disease, and Latin American countries were making progress. But today—with billions of people at risk of malaria in a swath that extends from Central and South America through Africa to South Asia—thoughts of eradication have disappeared. Indeed, even control seems like a distant dream. Not only is the disease notoriously difficult to fight, given the cunning strategies employed by the parasites that cause it, *P. falciparum* and *P. vivax*. But malaria is also exacerbated by poverty, malnutrition, inadequate housing, and ill-funded public health systems.

Pesticides and other barriers against mosquitoes help. The use of pesticide-soaked bed nets, for instance, has produced "a substantial reduction in child mortality" in western Kenya, where children may be exposed to 300 infective mosquito bites a year, says Richard Steketee, chief of CDC's malaria branch. "Few other interventions" have produced such credible evidence of effectiveness, he adds.

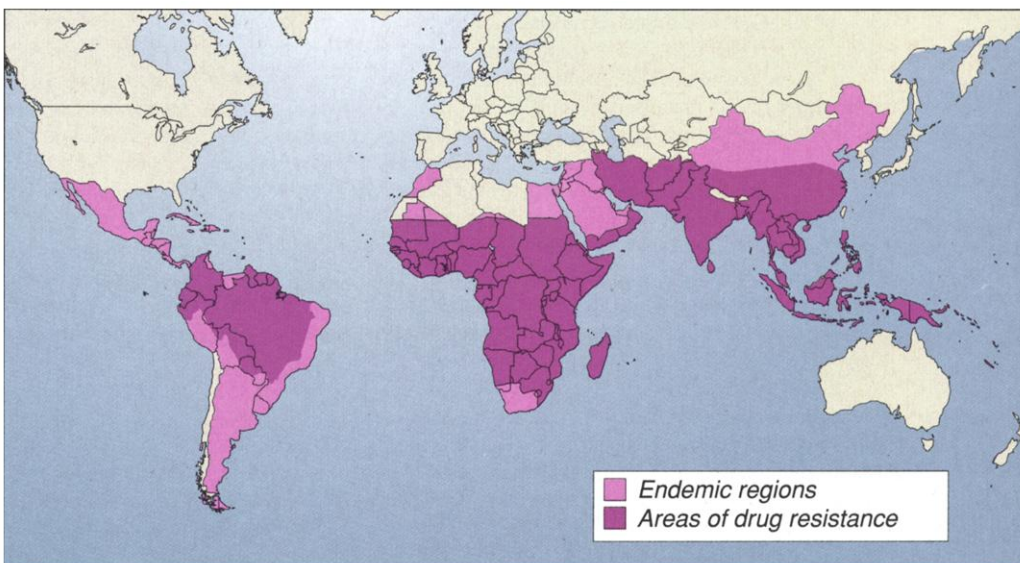
A malaria vaccine would be the ultimate weapon; most experts believe the disease cannot be controlled without one. But despite encouraging advances, a vaccine isn't likely soon (see p. 434). Antimalarial drugs are the last certain defense, and even they are failing as resistant strains of parasites spread across the globe (see map). First established in Asia, resistant strains have now spread into Africa. Chloroquine, the mainstay, is no longer useful in most of these endemic areas. Even later generation drugs like mefloquine and sulfadoxine-pyrimethamine can no longer be relied upon in much of Southeast Asia and are beginning to fail in Africa, as parasites acquire resistance to multiple drugs. A handful of new drugs are under development, but they are years from being approved (*Science*, 17 March, p. 1956).

Alarmed, WHO in 1993 called for a renewed global effort.

#### A turning point

WHO's plea didn't produce an immediate response. But in 1996, Britain's Wellcome Trust, the largest biomedical charity in the world, echoed the appeal with its own audit of the world's investment in malaria research. Worldwide, the trust said, just \$84 million was being spent annually on malaria research. But the economic cost of the disease in Africa

Dakar, Senegal, in January 1997. "Maxime insisted that the meeting should be in Dakar," says Louis Miller, a leader of NIAID's malaria effort, to ensure participation of African scientists. It worked. Some 50 African scientists from 22 countries, many of whom had not met before, attended along with 75 outside scientists. This "extraordinary" gathering, as Varmus called it, produced bold declarations—most notably, a push for a new multilateral fund to support African research. The various funding agencies also planned to



**Unstoppable?** Billions of people in tropical countries are at risk of being infected by malaria. More than 400 million become ill with it each year, and 1 million to 3 million die. Starting in Asia in the 1960s, the parasite became immune to an old and reliable drug, chloroquine; that resistance spread rapidly across the globe, and now newer drugs are beginning to fail.

alone was probably more than \$2 billion a year. The meager research investment, it continued, "is very low compared with other disease areas ... and appears to be declining further." Since then, the annual investment has climbed to more than \$100 million.

At about the same time, public health leaders began to focus on sub-Saharan Africa. After AIDS, malaria was still the most threatening disease on the continent. Harold Varmus, then director of NIH, argued that his agency should be doing more to address global health issues—and that malaria was one where you get a big bang for the buck. Maxime Schwartz, director of the Pasteur Institute in Paris, was equally committed but had no comparable budget to contribute. Varmus, Schwartz, and representatives of Britain's Medical Research Council and the Wellcome Trust met on the NIH campus in Bethesda, Maryland, in 1995 and 1996 to chart a new strategy for malaria. A key goal, they agreed, should be to build technical infrastructure in Africa and encourage Africans to take the lead in research.

They also laid the groundwork for an unprecedented meeting of African scientists in

enlist the help of reluctant pharmaceutical companies, concerned about a lack of profit, in developing badly needed new drugs. Varmus said that funding would be worked out at a session in The Hague in July 1997.

At The Hague, the Americans "were met with some skepticism" when they sought commitments from people who could write big checks, says one U.S. participant who asked to remain anonymous. "Some of the Europeans greeted our enthusiasm ... as our trying to take over." The joint research fund never materialized. Nor did pharmaceutical company executives offer to bankroll drug development projects. But the two meetings did create a new outfit: the Multilateral Initiative on Malaria (MIM), "a loose confederation" supporting African research (*Science*, 18 July 1997, p. 309).

#### New promises

With funding from NIH, WHO, and the Rockefeller Foundation, among others, MIM has awarded 23 grants, ranging in value from \$92,000 to \$250,000 per year, to collaborations that include African principal investigators at 18 sites in Africa (see p. 431). As part



## Can WHO Roll Back Malaria?

GENEVA—Ask malaria experts around the globe to rate the World Health Organization's (WHO's) performance in the fight against malaria, and you'll probably get an earful. Yet if you ask the same experts whether WHO is the right organization to lead a renewed onslaught against the disease, you are likely to get an unequivocal "yes." "We have to criticize WHO" for its past performance, says tropical medicine researcher Nicholas White of Mahidol University in Bangkok, Thailand. But if malaria is to be brought under control, he says, WHO's technical know-how and moral authority will be crucial. "We have to enthusiastically support them."

WHO Director-General Gro Harlem Brundtland needs that support. In October 1998, just 3 months after she took office, Brundtland announced Roll Back Malaria (RBM), a multiagency crusade that aims to cut malaria mortality in half over the next 10 years. Brundtland might just be the one to pull it off, say numerous public health experts. But "it will take an absolutely stupendous effort of leadership, coordination, and investment," cautions Kevin Marsh, coordinator of a collaborative research program in Kenya run by the Kenya Medical Research Institute (KEMRI), Britain's Wellcome Trust, and Oxford University. Although some researchers question whether the goal is realistic, most agree that RBM has already achieved an important political end: putting malaria higher on the agenda of political leaders, especially in Africa.

Malaria was high on the agenda once: In the 1950s and 1960s, WHO spearheaded an effort to eradicate the disease. But by several accounts, the organization began to fumble in the late 1960s, when it became clear that eradication efforts had failed in most parts of the world. "This failure seems to have knocked all the stuffing out of [WHO staff]," says Marsh. WHO drastically scaled back its technical staff in afflicted countries, largely leaving local health workers to treat the sick. "Malaria control programs collapsed," says Brian Greenwood, a malaria researcher at the London School of Hygiene and Tropical Medicine. "Since they couldn't eradicate malaria, they eradicated the [malaria researchers]." In creating RBM, Brundtland has made malaria again one of WHO's top priorities. RBM focuses on four goals: rapid treatment of children with life-threatening malaria; treatment of pregnant women infected with the malaria parasite; increased use of insecticide-

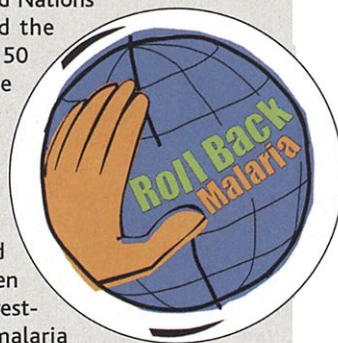
impregnated bed nets; and emergency control of malaria in areas afflicted with warfare or natural disasters.

WHO will carry out these tasks in tandem with the three other "founding partners" of RBM: the United Nations Development Program, UNICEF, and the World Bank. In addition, more than 50 other organizations, ranging from the Nigerian health ministry to non-governmental organizations such as Médecins Sans Frontières, are participating in this loose coalition. While some partners are donating personnel, others are contributing cash. The World Bank, for example, has pledged between \$300 million and \$500 million in interest-free loans to African countries for malaria prevention and control.

Even with the renewed energy and extra resources, cutting malaria deaths in half by 2010 will be a formidable challenge. For instance, RBM last April convened a malaria summit in Abuja, Nigeria, where nearly two dozen African heads of state pledged to take concrete steps to combat the disease. But if this "Abuja declaration" is to have any effect, it must be translated into real action on the ground, says entomologist John Vulule, acting director of the KEMRI field station in Kisumu, Kenya. "This may be an uphill task given the levels of poverty in sub-Saharan Africa," Vulule adds.

Already, some experts complain that the RBM campaign has been slow to reach areas most affected by malaria. In India, says Neeru Singh, a deputy director of the Indian Council of Medical Research, "there is no RBM activity in the Madhya Pradesh district," a hard-to-reach region where serious malaria outbreaks occur each year. RBM officials counter that their job is not to micromanage what goes on in each country but to help foster political commitment and technical support. And they also deflect concerns that by participating in a broad-based coalition, WHO is diluting its own leadership role. "WHO is trying to facilitate a partnership but not control it," says David Heymann, director of the agency's division of emerging and communicable diseases. Clearly, in its renewed war on malaria, WHO will need all the allies it can muster.

—MICHAEL BALTER



of MIM, NIAID is also helping to ensure that African scientists have adequate resources. Malaria researchers "are not short on concepts," explains Fauci; "what they are short on is ... materials." In 1998 the agency began building a repository of research reagents to be distributed for free. It provides antibodies, cell libraries, and DNA clones with oligonucleotide primers to "all legitimate malaria researchers," says project manager Yimin Wu. So far, 85% of its users are still American or European. But Wu plans to promote the repository to African scientists with training sessions. NIAID also plans to extend Internet connections to Africa. NIH's National Library of Medicine (NLM) has already established electronic

beachheads at seven African research sites, setting up satellite dishes, receiving stations, and small local networks. "We've tried to do that in a big way in Bamako, Mali," says Fauci. "It's like having an NIH lab in the mid-

dle of the jungle." The NLM group, along with the Africa Program of the American Association for the Advancement of Science (*Science's* publisher), is urging 11 biomedical publishers to subsidize free online access to their journals for African scientists during a 3-year trial.

Enthusiasm breeds yet more enthusiasm. Almost weekly, it seems, organizations are pledging more funds to fight malaria and other infectious diseases. But now comes the hard part: transforming that enthusiasm and basic science into treatments that can be used in rural villages. In some ways, Miller concedes, "we're worse off than we were in the 1950s," because effective pesticides like DDT are less available and the cheap anti-malarial drugs have lost their potency. But with malaria now high on the political agenda and researchers armed with new tools, it may not be so crazy to think again about bringing malaria under control.

—ELIOT MARSHALL



**Fearful vision.** English cartoonist Thomas Rowlandson imagined malaria fever haunting a victim in this 19th-century scene.

CREDITS: (TOP TO BOTTOM) WHO; 19TH-CENTURY CARTOON BY THOMAS ROWLANDSON, COURTESY OF THE WELLCOME TRUST