disease in Africa, Asia, and Latin America. Soon these vaccines will undergo testing for efficacy in one target group, young African children. Trials of pre-erythrocytic vaccines developed by the Walter Reed Army Institute of Research, USA, in collaboration with GlaxoSmithKline and the Oxford group (A. V. Hill and collaborators), are now being tested for safety and efficacy in Mozambique and East Africa. Vaccines against blood stages of the parasite will soon be tested for efficacy in Africa by various groups. These initial studies will give us a better measure of the challenge before us. It is important to realize that, even if these vaccine trials are successful, it will be 10 to 15 years before they have undergone sufficient safety and efficacy trials to enable their broad distribution to African children.

Drug resistance in *P. falciparum* blood stages to the two most effective, inexpensive, and safe antimalarials—chloroquine and Fansidar—has driven the search for new drugs (*9, 10*). The artemisinins, derived from the plant *Artemisia annua*, are highly effective antimalarials that have the added advantage that they reduce gametocyte levels. Artemisinins combined with Fansidar are being tested for efficacy and safety in African children. Targets unique to *Plasmodium* parasites—such as the hemoglobin digestive vacuole and a plastid-like organelle called the apicoplast—are attractive targets for new antimalarial drugs. The recently described anion-selective channel found only in the membranes of parasite-infected red blood cells, which transports nutrients into erythrocytes (*11*), is also a potential therapeutic target. Development of drugs and vaccines is expensive and will require large public-sector investment (*12*).

The main vectors of malaria in Africa, *A. gambiae* and *A. funestus*, are extremely efficient transmitters of this disease (i.e., they have high vectorial capacity). One of the most important variables in the formula devised by Macdonald (*13*) to define vectorial capacity is the mosquito life-span, an exponential term. If the mosquito has a long life-span, then each human blood

meal (after parasite development in the blood) can transmit the infection. Thus, average mosquito life-span is a major determinant of vectorial capacity. For example, in Mopti, Mali, where people may be bitten by 300 or more *A. gambiae* per night, the malaria infection rate is extremely low, largely because of the low survival of mosquitoes in this region. A low environmental temperature (the temperature of the mosquito gut is ambient temperature) results in a longer development time for the parasite in the mosquito; below 22°C, *P. falciparum* is unable to develop. Thus, in mountainous areas of East Africa above 2000 m, there is little malaria transmission because it is too cold. Development of *P. vivax* in the mosquito is less dependent on temperature, so *P. vivax* transmission is found in some areas (for example, the former Soviet Union) where the average temperature is too low to allow *P. falciparum* transmission. Another important variable in determining the efficacy of a mosquito as a malaria vector is the human biting rate, because the mosquito must feed twice on humans: once to be infected and once to transmit the disease.

Mosquitoes of the *A. gambiae* and *A. funestus* population complex combine characteristics of longevity and a preference for human over animal blood. These vectors pose a huge challenge, as evidenced by the malaria epidemic that ensued when *A. gambiae* was accidentally introduced into Brazil from Africa in 1930 by trading ships (*14*). A group of scientists working on *Aedes aegypti* eradication to eliminate urban yellow fever identified *A. gambiae*, and luckily they were able to eradicate this intruder by treating water around dwellings with larvicides. In Africa today, other vector control approaches will be required. Information from the *Anopheles* genome should make it possible to genetically alter the characteristics of *A. gambiae* and *A. funestus* that make them such excellent vectors. For example, the vectorial capacity of these mosquitoes could be reduced by decreasing their susceptibility to malaria infection, decreasing their affinity for feeding on humans, or decreasing their longevity.

Combining new antimalarials and vaccines with vector control measures will be essential for halting transmission of malaria in Africa and other endemic areas of the world. The complete genome sequences of *P. falciparum* and *A. gambiae* will be essential to this endeavor.

References

1. N. J. White, *Drug Resist. Updates* **1**, 3 (1998).
2. S. W. Lindsay *et al.*, *Med. Vet. Entomol.* **3**, 263 (1989).
3. F. Chandre *et al.*, *Bull. WHO* **77**, 230 (1999).
4. L. Molineaux, G. Gramiccia, *The Garki Project* (World Health Organization, Geneva, Switzerland, 1980).
5. B. Greenwood, T. Mutabingwa, *Nature* **415**, 670 (2002).
6. M. J. Gardner *et al.*, *Nature* **419**, 498 (2002).
7. R. A. Holt *et al.*, *Science* **298**, 129 (2002).
8. T. L. Richie, A. Saul, *Nature* **415**, 694 (2002).
9. R. G. Ridley, *Nature* **415**, 686 (2002).
10. P. Rosenthal, *Antimalarial Chemotherapy, Mechanisms of Action, Resistance and New Directions in Drug Discovery* (Humana, Totowa, NJ, 2001).
11. S. Desai *et al.*, *Nature* **406**, 1001 (2001).
12. J. D. Sachs, *Science* **298**, 122 (2002).
13. G. Macdonald, *The Epidemiology and Control of Malaria* (Oxford Univ. Press, London, 1957).
14. R. M. Packard, P. Gadelha, *Parassitologia* **36**, 197 (1994).

VIEWPOINT

A New Global Effort to Control Malaria

Jeffrey D. Sachs*

The time has come to resurrect a worldwide effort to control malaria, following decades of neglect during which the disease has resurged in many parts of sub-Saharan Africa and other endemic regions.

The global campaign to eradicate malaria, launched in 1955 and phased out by the end of the 1960s, has been dubbed a misguided failure. Although the campaign did not come close to achieving its headline objective of eradicating malaria, it did lead to enormous and sustained reductions in the burden of malaria in dozens of countries around the world. Unfortunately, the world failed to heed the right lesson: Global eradication is not feasible, but sustained malaria control restricting transmission to low levels is. The time has come to resurrect a worldwide effort to control malaria, albeit one not predicated on complete eradication of the disease.

There are four reasons to launch a renewed global campaign against malaria. First, the abandonment of control efforts has led to a marked resurgence in disease and deaths due to malaria in Africa and parts of Asia, in part because of the spread of drug resistance to first-line drugs and mosquitocides, and in part because of the generalized collapse of public health services in Africa.

CREDIT: DONNY BLISS/NIH

The human and economic toll is horrendous, particularly in sub-Saharan Africa where malaria costs more than 1 million lives annually and 1 percentage point of economic growth per year (*1*). Second, substantial malaria control is possible by extending the coverage of existing technologies to impoverished households and communities. Third, advances in genomics including the completed genome sequences of the mosquito *Anopheles gambiae* (*2*) and the malaria parasite *Plasmodium falciparum* (*3*) offer promising new targets for drug and vaccine development (*4*). Fourth, many new programs to support a global control effort have been established recently, although a dire lack of funds prevents them from operating effectively and at a sufficiently broad scale.

Global control efforts from the 1940s to the 1970s virtually eliminated malaria transmission in the subtropics (Fig. 1). Malaria became almost wholly a disease of the tropics, particularly in Africa, where 90% of the malaria deaths now occur. The reasons for this are that the eradication campaign largely bypassed Africa and that malaria in the subtropics is easier to control because the intensity of transmission is much lower (*5*, *6*). Still, successes in the sub-tropics and various sites in tropical regions (*7*, *8*) demonstrated that intensive vector control measures combined with stepped-up coverage of medical treatment of infected individuals could bring transmission down sharply, and in some settings completely.[1]

The eradication effort was abandoned when it became apparent that eradication was not possible. Resistance to DDT, the cornerstone of indoor residual spraying, appeared in mosquito vector species; meanwhile, the malaria parasite was becoming resistant to chloroquine and other first-line drugs. Yet, even when cases of malaria rebounded dramatically in some places (such as Sri Lanka) because of DDT resistance, malaria death rates rarely reverted to earlier levels. And even with DDT resistance, the pesticide still proved effective in limiting transmission (*9*). In short, the eradication effort made real and sustained strides, and much more could have been accomplished. A deeper reason for abandoning the campaign may have been geopolitical. Malaria control had already been achieved in the southern United States, southern Europe, southern regions of the Soviet Union, much of Latin America, and large parts of Asia, especially China. Moreover, by the mid-1970s, the United States had withdrawn from Vietnam, so that the U.S. military evinced a sharply reduced concern for malaria control. Impoverished Africans were not on the geopolitical radar screen.

The end of the global malaria eradication campaign coincided with a general downturn in foreign aid. Africa fell into a significant debt crisis in the early 1980s, from which it has not yet recovered. Creditor governments and international institutions such as the International Monetary Fund and World Bank pushed for budget cuts in poor countries to make room for foreign debt servicing. Public health spending collapsed throughout Africa and with it the limited malaria control efforts that were in place. Spending cuts coincided with three other adverse trends in Africa, and parts of India, Southeast Asia and Latin America: (i) population growth that pushed human settlements into new ecological regions supporting malaria transmission; (ii) the growth of a "septic fringe" around Africa's sprawling urban settlements where urban transmission could thrive; and (iii) the continuing spread of drug and pesticide resistance.

Donor fatalism also took hold in the shadow of the "failed" eradication efforts. The World Bank made only two loans in the 1990s specifically designated as malaria-control loans, to India and Laos, and not a single loan to sub-Saharan Africa (*10*). Research programs of the U.S. military and U.S. Agency for International Development directed at a malaria vaccine or new drug development were cut back. The major pharmaceutical companies neglected malaria drug discovery or vaccine research because the travelers' market (visitors from the United States and Europe to malarious regions) was small and still handled by existing medicines.

By the late 1990s, much of the African political leadership had become desperate, and made a renewed malaria control campaign a pivotal demand during the election of the World Health Organization (WHO) director-general in 1998. Roll Back Malaria (RBM) was launched by a consortium of the WHO, World Bank, United Nations Development Program, and United Nations Children's Fund in November 1998. Other initiatives for drug discovery, vaccine development, and increased financing of control efforts were launched, including the research-oriented Multilateral Initiative on Malaria (MIM, in 1997), Medicines for Malaria Venture (MMV, in 1999), and the Malaria Vaccine Initiative (MVI, in 1999). The Global Fund to Fight AIDS, TB, and Malaria (GFATM, launched in January 2002) supports the implementation of prevention and treatment programs. All remain woefully underfunded, and an effective international effort has not yet begun.

An effective campaign will need to operate on four principles. First, it should focus on the most afflicted regions, mainly sub-Saharan Africa. Second, it should recognize that among the major epidemic diseases, malaria control is uniquely site specific, dependent on climate patterns, vector ecology and biology, and human activity. Third, the campaign should pursue two tracks: increased malaria control (both prevention and treatment) with existing technologies, together with a major investment in R&D for new technologies. Fourth, and above all, it should be funded adequately and consistently for at least two to three decades if it is to have a chance of success. Current worldwide donor spending for prevention and treatment programs is $100 to $200 million per year (and it is symptomatic of the laxity of global control efforts that up-to-date worldwide data have not been compiled). Actual needs exceed $2 billion dollars per year, and probably more, to fund replacements for chloroquine and other drugs to which resistance has developed (*11*).

Promising new drugs already available but not yet in widespread use include the artemisinin-based compounds, developed in the 1970s by Chinese scientists from deriva-

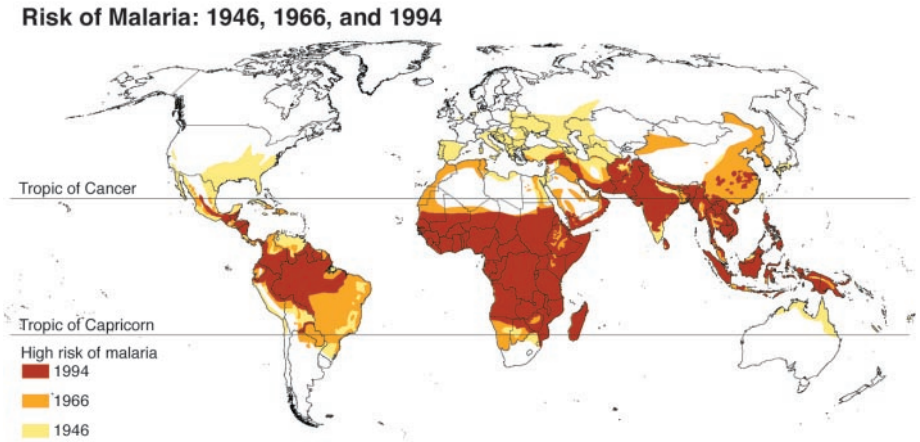

Fig. 1. The shrinking range of malaria is depicted by overlaying WHO maps for malaria risk for the years 1946 (pink), 1966 (red), and 1994 (brown). [Reproduced from (*15*)]

Earth Institute, Columbia University, New York, NY 10027, USA.

*The author is chairman of the WHO Commission on Macroeconomics and Health and Special Advisor to UN Secretary General Kofi Annan.

tives of the traditional Chinese herbal treatment Qinghaosu. Donors have been reluctant to support the introduction of artemisinin into Africa, both because of its high unit cost relative to chloroquine and other first-line drugs—chloroquine costs ~10 cents for a curative regimen whereas artemisinin costs $1—and out of fear that artemisinin too will rapidly generate resistance. To counteract this risk, artemisinin-based compounds should be introduced in combination with other antimalarial drugs. Ironically, the delay in sponsoring such an approach is leading to the indiscriminate spread of artemisinin-based monotherapies through informal drug supply networks in Africa.

Encouragingly, in regions of Africa containing intensive economic activity (mines, oil fields, rubber plantations, urban zones, tourist sites), corporate malaria control efforts bolstered by public support are making a big difference (*12*). Successful corporate efforts generally rely on an intensive mix of environmental vector-control measures, individual protection of workers through household residual spraying, and case management. Recent initiatives by the world economic forum and other business groups plan to link these corporate efforts to broader international malaria control programs, particularly through formal public-private partnerships (*13*).

Longer term, more sweeping solutions will come from new drug discovery and especially vaccine-development efforts based on recent genomic advances. No major pharmaceutical company reports a concerted malaria research effort. The Gates Foundation has valiantly aimed to spearhead new research by supporting the drug-development MMV and the MVI. MMV has the declared goal of developing one new antimalarial drug every 5 years at a cost of $150 million, or $30 million per year, plus significant "in-kind" industry support. These numbers are below most estimates of drug-development costs, and are very unlikely to cover the high expenses of drug trials. A reasonable estimate of total worldwide public and private annual spending on malaria drug and vaccine research is less than $100 million, or less than one-seventh of 1% of the $70 billion or more of annual worldwide biomedical R&D, for a disease that accounts for about 3% of the worldwide disease burden as measured by disability-adjusted life years (*14*). R&D donor needs for drugs and vaccines are around $1 billion per year on a sustained basis, compared with current annual spending of less than $150 million.

The RBM consortium, headquartered at WHO, should serve as the nerve center of a renewed global effort to fight malaria. This consortium should immediately prepare a comprehensive strategy that includes an operational multiyear plan of action together with a full assessment of donor funding needs. The proposed budget should clearly delineate the separate needs for current prevention and treatment programs, largely funded through the GFATM and the World Bank; the rapid development, clinical testing, and procurement of artemisinin-based and other drug combinations; and the outlays for R&D for new drug discovery and vaccine development, including effective systems for high-cost clinical trials. Annual outlays by donors must reach several billion dollars per year for a generation or so to get malaria under control in endemic areas of Africa and Southeast Asia. But this will be a very small price to pay for millions of lives saved per year and for hundreds of millions of people to be given the chance to escape from the vicious cycle of poverty and disease.

References and Notes

1. J. Sachs *et al.*, *Nature* **415**, 680 (2002).
2. R. Holt *et al.*, *Science* **298**, 129 (2002)
3. M. J. Gardner *et al.*, *Nature* **419**, 498 (2002).
4. C. A. Hoffman, S. L. Hoffman, *Science* **297**, 345 (2002).
5. The basic reproduction rate increases with temperature (and thus is higher in the tropics) and depends on the human biting rate of the vector, which is particularly high for the dominant African vectors *Anopheles gambiae*, *A. arabiensis,* and *A. funestus*.
6. K. Dietz, in *Malaria: Principles and Practice of Malariology*, W. H. Wernsdorfer, I. McGregor, Eds. (Churchill Livingstone, New York, 1988), vol. 2, pp. 1091–1133.
7. J. Utzinger *et al.*, *Trop. Med. Int. Health* **6**, 677 (2001).
8. J. Utzinger *et al.*, *Trop. Med. Int. Health* **7**, 657 (2002).
9. DDT still reduces the longevity of DDT-resistant mosquitoes, thereby reducing the force of transmission. DDT's use for indoor residual spraying poses no known ecological dangers, as opposed to its use in much greater volumes for agriculture.
10. Some health-sector loans included small amounts for malaria control. See the "Project Database" on the Malaria Home Page of the World Bank, www.worldbank.org.
11. The WHO commission on Macroeconomics and Health (2001) estimated that the direct costs of malaria prevention and treatment would require an additional $2.5 billion per year by 2007, but that estimate does not fully account for the increased overhead costs of an expanded health system, nor the costs of introducing new drugs to overcome drug resistance.
12. A. Spielman *et al.*, *Industrial Anti-Malaria Policies* (Center for International Development, Harvard University, 2002).
13. World Economic Forum, *Global Health Initiative: Resource Paper* (Geneva, February 2002.)
14. World Health Organization, *Commission on Macroeconomics and Health: Investing in Health for Economic Development* (Geneva, 2001).
15. J. L. Gallup, J. D. Sachs, *Am. J. Trop. Med. Hyg.* **64**, 85 (2001).

VIEWPOINT

Plasmodium Chloroquine Resistance and the Search for a Replacement Antimalarial Drug

Thomas E. Wellems

Genetic and biochemical research is providing new information on the mechanism of chloroquine resistance. Drug discovery initiatives are finding new leads that have favorable pharmaceutical properties and efficacy against chloroquine-resistant malaria.

The discovery of chloroquine and its subsequent worldwide use against malaria in the 20th century produced one of the greatest public health advances ever achieved by a drug against an infectious disease. Chloroquine's efficacy, affordability, easy administration, and low toxicity led to marked reductions in morbidity and mortality across the Americas, Africa, Asia, and Oceania. Chloroquine remained effective for decades. Despite its distribution in massive quantities (including distribution in the salt supplies of some countries), many years passed before chloroquine resistance (CQR) began to spread. *Plasmodium falciparum*, the most malignant of the four human malaria parasite species, showed foci of CQR in Southeast Asia and South America in the late 1950s, Papua New Guinea in the 1960s, and East Africa in the late 1970s. The steady and unremitting spread of CQR from these foci could only be met by a few alternative drugs, all of which were more expensive, encountered resistance problems of their own, or were less safe and more difficult to use than chloroquine itself. Morbidity and mortality from *P. falciparum* malaria consequently resurged, especially among children in Africa (*1*). Malaria caused by *Plasmodium vivax*, second only to *P. falciparum* malaria in its impact on health and economic development, remained responsive to chloroquine everywhere until a little over a decade ago, when

Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892, USA. E-mail: tew@helix.nih.gov