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

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 resurfaced 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 mosquitoicides, and in part because of the generalized collapse of public health services in Africa.
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.

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-
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 unrelenting 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...