system, participants considered the use of inundative release of refractory mosquitoes as a strategy for limited field-testing of the performance of specific genetically engineered vector strains. Although considered suitable only for a small vector population with limited interpopulation gene flow (such as a real or ecological island setting), the ability to limit or quickly control unforeseen risks in the genetic manipulation of an island population will be important in early-stage trials designed to demonstrate the efficacy of particular genetic modifications of the vector population.

Although there was support for continued, intensive research in this area, a clear recommendation emerged that there should be no precipitous releases of transgenic arthropods. The malaria group was willing to recommend barring field trials of transgenic insects that were designed solely for research; others felt that initial field safety testing of the various individual elements of the engineered organism was crucial to development. The parallel processes of drug and vaccine development illustrate these two views. For either product, and indeed for engineered *Anopheles* mosquitoes, there is a requirement for preliminary studies of safety and efficacy in culture and in animal models before the first clinical trial is initiated. With many new drugs (other than cancer drugs), the first human trials are performed in small numbers of normal healthy volunteers, and safety is the end point examined. In these situations it would be inappropriate to endanger patients who are already sick by exposing them to a drug candidate of unknown toxicity. By contrast, when new vaccines are developed, they are most often combined with adjuvants that improve their potency or direct their effects to one or more segments of the human immune system. Under its current guidelines the U.S. Food and Drug Administration does not allow investigation of the adjuvants alone without the vaccine candidate being tested at the same time. The malaria working group requires tangible benefits at each phase of field testing. The other working groups—discussing symbionts, transducing viruses, and other mechanisms of driving traits into populations—decided to follow drug-development protocols. These differences may be appropriate given the different nature of the engineering tools and the different risks associated with each one.

Despite nearly universal recognition that enormous technical and sociological problems must be overcome before the implementation of genetic control strategies for malaria can be field tested, participants concluded that public health strategies incorporating transgenic vectors offer the potential of health benefits. Participants from disease-endemic areas, many of whom had limited prior exposure to transgenic arthropod research or policy discussions, were among the most supportive and optimistic about the public health goals such strategies hope to achieve. Participants also noted that the broad scope of biological research required for the development of genetic control strategies is likely to contribute both to the more efficient application of currently available control tools and to the development of new approaches.

References

1. C. M. Morel, Y. T. Touré, B. Dobrokhotov, A. M. J. Oduola, *Science* **298**, 79 (2002).
2. C. F. Curtis, *Nature* **218**, 368 (1968).
3. *Prospects for malaria control by genetic manipulation of its vectors* (TDR/BCV/MAL-ENT/91.3) (World Health Organization, Geneva, 1991).
4. C. J. Coates, N. Jasinskiene, L. Miyashiro, A. A. James,, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 3748 (1998).)
5. F. Caterrucia *et al.*, *Nature* **405**, 959 (2000).
6. G. L. Grossman *et al.*, *Insect Mol. Biol.* **10**, 597 (2001).
7. M. de Lara Capurro, *Am. J. Trop. Med. Hyg.* **62**, 427 (2000).
8. J. Ito *et al.*, *Nature* **417**, 452 (2002).
9. D. Y. Onyabe, J. E. Conn, *Heredity* **87**, 647 (2001).
10. M. J. Donnelly, M. C. Licht, T. Lehmann, *Mol. Biol. Evol.* **18**, 1353 (2001).
11. W. C. Black IV, G. C. Lanzaro, *Insect Mol. Biol.* **10**, 3 (2001).
12. C. Walton *et al.*, *Mol. Ecol.* **10,** 569 (2001).
13. R. Wang, F. C. Kafatos, L. Zheng, *Parasitol. Today* **15**, 33 (1999).
14. T. W. Scott, W. Takken, B. G. J. Knols, C. Boëte, *Science* **298**, 117 (2002).
15. D. D. Thomas, C. A. Donnelly, R. J. Wood, L. S. Alphey, *Science* **287**, 2474 (2000).

VIEWPOINT

Malaria—a Shadow over Africa

Louis H. Miller[1] and Brian Greenwood[2]

Reduction in severe disease and death from *falciparum* malaria in Africa requires new, more effective and inexpensive public health measures. The completed genomes of *Plasmodium falciparum* and its vector *Anopheles gambiae* represent a big step toward the discovery of these needed tools.

The current focus of malaria control programs in Africa is rightly on the management of sick children through early treatment with effective antimalarial drugs. However, this cannot be the final strategy. The two first-line drugs, chloroquine and sulfadoxine/pyrimethamine (Fansidar), are no longer effective in many parts of East Africa where chloroquine resistance (introduced from Asia) is rampant. Combinations of new drugs may help to slow the emergence and spread of resistant parasites (*1*), but control strategies based on early treatment mean a never-ending struggle to develop and deploy new drugs before the *Plasmodium* malaria parasites become resistant to existing drugs. Thus, the long-term control strategy must be to interrupt the transmission of this parasite. Unfortunately, this will be extremely difficult in parts of Africa where people may be bitten as many as 1000 times a year by infected mosquitoes. Insecticide-treated bed nets—now being vigorously promoted in many parts of Africa—reduce bites from infected mosquitoes by as much as 90% (*2*). However, their effectiveness is already under threat as a result of the emergence of pyrethroid resistance in *Anopheles funestus* in Mozambique and in *A. gambiae* in agricultural areas of West Africa (*3*). Household spraying with residual insecticides is highly effective in reducing malaria in some parts of Africa, but it is logistically demanding, costly, and may have adverse environmental effects.

There are many ways to reduce malaria transmission, but none can provide a complete block in transmission, particularly in the highly endemic areas of Africa (*4*), and new approaches are desperately needed (*5*). Publication of the *Plasmodium falciparum* (*6*) and *Anopheles gambiae* genomes (*7*) represents a big step forward in our search for new tools for controlling malaria. Combined deployment of three strategies that each have the potential to reduce malaria transmission by 90%—drug treatment, vaccination, and vector control—should be sufficient to stop transmission, even in highly endemic areas of Africa. We will need to first test such strategies in areas with a low intensity of transmission before attempting the challenging task of preventing malaria transmission in the highly endemic areas of Africa.

Anyone who has thought deeply about the problem of reducing severe disease and death from malaria in Africa realizes the crucial need for a malaria vaccine. Pre-erythrocytic, blood-stage, and transmission-blocking vaccines have recently been developed by a number of groups (*8*). Each type of vaccine has a part to play in the complex, highly diverse epidemiology of malaria and the associated variety of patterns of

[1]Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892, USA. [2]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1B 3DP, UK.

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.

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