system, participants considered the use of inudative 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 strategists 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

**Malaria—a Shadow over Africa**

Louis H. Miller1 and Brian Greenwood2

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 forward in 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
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.