Malaria Management: Past, Present, and Future

A. Enayati[1,2] and J. Hemingway[2]

[1]School of Public Health and Environmental Health Research Centre, Mazandaran University of Medical Sciences, Sari, 48175-1553 Iran; email: A.Enayati@liverpool.ac.uk

[2]Liverpool School of Tropical Medicine, Liverpool L3 5QA, United Kingdom; email: hemingway@liverpool.ac.uk

Annu. Rev. Entomol. 2010. 55:569–91

First published online as a Review in Advance on September 15, 2009

The *Annual Review of Entomology* is online at ento.annualreviews.org

This article's doi: 10.1146/annurev-ento-112408-085423

0066-4170/10/0107-0569$20.00

Key Words

elimination, mosquito, pyrethroid, insecticide, monitoring

Abstract

The prospect of malaria eradication has been raised recently by the Bill and Melinda Gates Foundation with support from the international community. There are significant lessons to be learned from the major successes and failures of the eradication campaign of the 1960s, but cessation of transmission in the malaria heartlands of Africa will depend on a vaccine and better drugs and insecticides. Insect control is an essential part of reducing transmission. To date, two operational scale interventions, indoor residual spraying and deployment of long-lasting insecticide-treated nets (LLINs), are effective at reducing transmission. Our ability to monitor and evaluate these interventions needs to be improved so that scarce resources can be sensibly deployed, and new interventions that reduce transmission in a cost-effective and efficient manner need to be developed. New interventions could include using transgenic mosquitoes, larviciding in urban areas, or utilizing cost-effective consumer products. Alongside this innovative development agenda, the potential negative impact of insecticide resistance, particularly on LLINs, for which only pyrethroids are available, needs to be monitored.

DISTRIBUTION OF MALARIA AND ITS MAJOR VECTORS

Plasmodium falciparum originated in Africa and spread worldwide 10,000 years ago (74, 87, 118). Malaria distribution and transmission, with latitudinal extremes of 64 degrees north and 32 degrees south, are restricted to altitudes below 2000 meters and limited by the minimum temperature required to complete development of another malaria parasite, *Plasmodium vivax* (73, 74).

There were an estimated 247 million malaria cases among 3.3 billion people at risk in 2006, with around 881,000 deaths, most of whom were under five years of age, 91% of which occur in Africa (211). Endemicity of the disease is defined by the parasite rate, i.e., the proportion of a given population carrying asexual parasites in the blood, with hypoendemic defined as <0.1; mesoendemic defined as 0.11–0.5; hyperendemic defined as 0.51–0.75, and holoendemic defined as >0.75. Malaria is hypoendemic in the Mediterranean littoral areas and northern parts of South Africa, epidemic to hyper- and holoendemic in the Horn of Africa, and hyper- or holoendemic in tropical Africa.

Only a subset of *Anopheles* mosquitoes transmits malaria. Two international mapping projects are currently underway aimed at spatial modeling of the geographical distribution of 52 primary malaria vectors. The results from at least one of these projects should be in the public domain by 2010. Malaria was eradicated from North America and most of Europe in the 1970s, although the vectors are still present (73). The main malaria vectors in North Africa and the Mediterranean littoral areas are *An. atroparvus*, *An. labranchiae*, *An. gambiae* complex, *An. pharoensis*, and *An. sergentii*. In tropical Africa mosquitoes of the *An. gambiae* and *An. funestus* complexes are the main vectors accompanied by several secondary vectors (4, 23, 43, 56, 73, 172). In the Americas the major vectors are *An. albimanus* and *An. darlingi*. Transmission occurs in nine countries of the region that share the Amazon rainforest and in eight countries in Central America and the Caribbean (207). In South America, forest and forest fringe malaria vectors are *An. darlingi*, *An. aquasalis*, *An. albitarsis*, *An. bellator*, and *An. cruzii* (73, 172, 207).

Although most malaria morbidity and mortality occur in Africa, the largest population at risk of malaria is in Asia (74). Malaria is limited to the west of Asia and parts of the Middle East. The main vectors in the Middle East are *An. sacharovi*, *An. superpictus*, *An. stephensi*, *An. arabiensis*, and *An. culicifacies* (1, 5, 38, 92, 95, 141, 167). In central Asia malaria is endemic and the main vectors are *An. superpictus*, *An. pulcherrimus*, *An. hyrcanus*, and *An. sacharovi* (173, 188). In South Asia (India, Nepal, Bhutan, Bangladesh, Maldives, Sri Lanka, and Indonesia) the main vectors are *An. stephensi*, *An. culicifacies*, *An. fluviatilis*, *An. minimus*, *An. dirus*, *An. aconitus*, and *An. maculatus* (93, 174, 179, 193). In East and Southeast Asia (Myanmar, Laos, Vietnam, Malaysia, Cambodia, Singapore, Brunei, and Philippines) the main vectors are *An. minimus*, *An. dirus*, *An. sundaicus*, *An. maculatus*, *An. subpictus*, and *An. flavirostris* (18, 47, 52, 94, 132, 178, 186, 189, 199). In China malaria is endemic in Yunnan Province, which borders Laos and Myanmar. The main vectors are *An. sinensis*, *An. messeae*, and *An. minimus* (73, 124, 172, 195). In Oceania (Papua New Guinea, Solomon Islands, and Vanuatu) the main vectors are *An. farauti* and *An. punctulatus* (45, 107, 108, 127, 216).

THE BURDEN OF MALARIA

In 1900, more than 77% of the world population in 140 countries was at risk of malaria, with more than 25% in hyper- or holoendemic areas (74). Malaria mortality rates changed dramatically in the twentieth century. In 1900, more than 3.1 million deaths occurred among a total population of ~1.6 billion, a death rate of 19.4 per 10,000 people. Approximately 90% of this mortality occurred outside sub-Saharan Africa (14). In Africa the infant malaria-specific mortality rate was ~9.5 per 1000 people prior to 1960 (185).

In the first half of the twentieth century, the sanitation era of malaria control interventions

focused on reducing mosquito breeding sites. Mosquito control was successful in the Panama Canal, Indonesia, Malaysia, the mines of the Zambian copper belt, and in the eradication of the recently introduced *An. gambiae* in Brazil and Egypt (74).

THE 1960s MALARIA ERADICATION CAMPAIGN AND THE ROLE OF DDT

The terms "eradication" and "elimination" have been used interchangeably in the literature. Here, eradication is defined as a permanent reduction to zero of the worldwide incidence of an infectious organism as a result of deliberate efforts (210). For malaria, this definition means the parasite no longer exists. It does not mean the eradication of the mosquitoes that transmit malaria. Elimination is defined as a reduction to zero of the local incidence of a specified disease in a defined geographical area (210). Elimination campaigns require sustained vigilance to monitor and maintain transmission interruption, with a rapid response to small foci of transmission triggered by imported cases (210).

DDT was introduced in the 1940s and used by many national malaria control programs for indoor residual spraying (IRS) in the "global" malaria eradication program from 1957 to 1969, which excluded tropical Africa. These programs reduced the population at risk of malaria to approximately 50% by 1975 compared with 77% in 1900 (74). The mortality rate was reduced to 1.61 per 10,000 by 1970, a massive reduction from the 1900 baseline of 19.4 (14). Despite the successes, several technical, operational, economic, and political problems halted the malaria eradication campaign. Local malaria control interventions then gradually reduced the areas of active transmission to just under 50% of the world population at risk of malaria by 2000 (74). By 2004, 107 countries, with a total population of 3.2 billion people, were at risk of malaria transmission. Today, approximately three billion people (40% of the world's population) are at risk of malaria exposure. Sixty percent of all malaria cases, 75% of all *Plasmodium falciparum* malaria cases, and more than 80% of malaria deaths occur in Africa (184). Malaria is also a major cause of low birth weight, premature birth, infant mortality, and anemia in children and pregnant women (207).

Malaria eradication was never systematically attempted in Africa, as transmission was an order of magnitude more intense than in other continents. However, control interventions pre-1960 resulted in more than 4.4 million people in South Africa, Swaziland, Zimbabwe, and Mauritius living in areas where the malaria elimination efforts had reached consolidation phase, and transmission in forest areas of southern Cameroon and Liberia and highland savanna areas in Madagascar and Uganda was almost interrupted (97).

Elsewhere the question was whether malaria transmission could be interrupted on a local scale. Pilot interventions occurred in five eco-epidemiological zones in Africa (125). In these, malaria was reduced to low endemicity or even eliminated in semidesert areas, remote islands, and highland savanna with tropical and temperate climates. In hyperendemic areas, malaria was reduced from hyperendemicity to hypoendemicity in tropical areas in the forest zone, in the islands located near the mainland, and in parts of the highland savanna zone. Malaria was reduced from high endemicity to low mesoendemicity in the lowland savanna zone. In the Pare-Taveta area on the Kenya/Tanzanian border, malaria prevalence was reduced (7, 33) and all-cause mortality rates were halved after five years of IRS. *An. funestus* disappeared and the density of *An. gambiae* declined rapidly. However, complete interruption of transmission was not achieved.

The Nigerian Garki project is the most-cited African attempt at transmission interruption. High propoxur IRS coverage was supplemented with mass antimalarial drug administration (125). Transmission continued and modelers argued that this transmission was due likely to persistent outdoor-resting mosquitoes. It was concluded that, in holoendemic areas of West Africa, the elimination of transmission using IRS was not technically feasible (215, 217).

DDT was a major factor in the early successes. It had a central role in the elimination of malaria from Venezuela, Cyprus, Greece, and much of Italy and coastal British Guiana (63). When financial constraints led to a reduction in its use in 1951, it was apparent that transmission did not resume (130). The availability of effective antimalarial drugs and detection of insecticide resistance in *An. sacharovi* from Greece, which could have jeopardized sustained malaria control, increased the push for a malaria eradication campaign (63, 130, 215).

The rate of malaria rebound after local elimination was estimated three years after the Taveta intervention. *An. funestus* was still absent, but *An. gambiae* returned to preintervention densities and 20–90% of the population received one malaria infective bite per annum during 1961 compared with all the population receiving 2–26 infective bites per annum before the intervention. This sustained reduction was due both to the continued absence of *An. funestus* and to the increased drug administration (180). Five years after the cessation of IRS, *An. funestus* had returned (181), and after eight years, entomological indices returned to preintervention levels (182).

Despite their impressive health benefits, the African trials were universally considered failures because elimination was not achieved. Why was it not possible to sustain these benefits by continuing to spray indefinitely? There were two major issues: first, the intensity of effort required to sustain IRS indefinitely throughout entire countries, and second, insecticide resistance. Resistance was seen as a threat to sustainability, and the more frequent and complete the spraying operation, the more likely resistance would evolve (61).

MODELS OF MALARIA CONTROL

Mathematical models were developed to determine whether eradication was possible under a given set of constraints. Macdonald's early model of malaria control (110) suggested that the most vulnerable element in the malaria cycle was survivorship of adult female *Anopheles*. He suggested that the worst malaria transmission conditions known in Africa could be overcome by an increase in the daily mortality of the mosquitoes from 5% to about 45% (110).

Quantitative aspects of transmission were stressed, in which the basic reproduction rate of malaria (R_0) is an essential concept, as a measure of the intensity of transmission. R_0 is the expected number of secondary cases produced by a single infection in a completely susceptible population for the entire infective period (110). If R_0 is less than 1, the disease will be eliminated (110, 142). Successful vector control should reduce vectorial capacity to less than 0.01, producing an R_0 of less than 1. To be of practical use, the malaria models must be robust. Early models did not consider human population dynamics, seasonal *Anopheles* population dynamics, vector characteristics, human immunity, parasite diversity, insecticide and drug resistance dynamics, spatial heterogeneity, or environmental changes (120). Smith et al. (183) recently revised R_0 calculations and their implications for malaria control. Originally, R_0 was based on a quantitative description of the *P. falciparum* life cycle that assumes that human populations are effectively infinite and that all humans are bitten at the same rate. However, human populations are finite and biting is heterogeneous (i.e., mosquitoes do not bite different age groups, sexes, and races equally), which increases R_0, because those who are bitten most are more likely to become infected and will subsequently infect a large number of mosquitoes, amplifying transmission. The spatial scale of malaria transmission is also affected by vector ecology, especially the distribution of larval habitat and host-seeking behavior, and by human population density, movement, and distribution (183).

THE COMPONENTS OF VECTORIAL CAPACITY

Vectorial capacity is the average number of infectious bites, with a given parasite, that originates from one case of malaria in unit time, assuming that all the female mosquitoes

biting the case individual become infected (58). Vectorial capacity can be used to evaluate different interventions, and in nonendemic areas it is the best measure of receptivity (the probability that an infectious case, having arrived in the eliminated area, will cause an outbreak of local transmission, and the rapidity with which such an outbreak will expand). Vectorial capacity varies with time, vector, and parasite species. A number of simplifying assumptions are involved, for example, that the mosquito transmits the infection but is not affected by it, that its death rate is independent of age, and that a single value for human feeding and mosquito survival applies to all *Anopheles* females (126). In the Garki project (125) vectorial capacity preintervention was reduced 100-fold post-intervention but was still ~45 times higher than the critical level of 0.01.

THE STABILITY INDEX

Although the intensity of malaria transmission is sensitive to adult mosquito mortality, control interventions such as long-lasting insecticide impregnated nets (LLINs) and IRS that target this parameter are inefficient. Maximizing the benefits depends on the fraction of mosquitoes that are killed or repelled and on the stability index, the average number of bites by an average mosquito during a normal lifetime. An index of >2.5 indicates stable malaria; between 2.5 and 0.5 indicates intermediate stability; and <0.5 indicates unstable malaria (110, 142). Stable malaria is transmitted by a vector with a frequent human-biting habit (the probability of a mosquito feeding on human in a day), with moderate to high longevity, living at a temperature favorable to rapid completion of the extrinsic cycle (the period necessary for a mosquito to become infective to people after it has ingested the sexual forms of the parasite from an initial blood meal).

Stable malaria is difficult to control. Larviciding is not effective unless near perfection is achieved (49). Low bites per person per night (0.025 or less) are required to maintain transmission. Endemicity is high with little seasonal fluctuation. Unstable malaria is transmitted by a vector that bites humans relatively infrequently, the vectors are short-lived, and the temperature is unfavorable to rapid completion of the extrinsic cycle. A high density of the vector is required to maintain transmission. Anophelism without malaria is possible and vector control is effective. Intermediate stability involves a short-lived vector and a temperature unfavorable to rapid completion of the extrinsic cycle together with a high human-biting rate.

MODERN MALARIA ELIMINATION AND ERADICATION

Roll Back Malaria was established in 1998 (129) with the aim of halving the burden of malaria by 2010 (207). In most African locations where elimination remains out of reach, the program includes guiding questions such as, If transmission cannot be interrupted completely, and maximally intense vector control has great health benefits, but is not sustainable and cannot be extended to everyone, what are the less intense strategies of vector control that would be more sustainable and equitable? What level and mode of transmission suppression should control programs aim for to maximize long-term health benefits for the population as a whole? The goal of eradicating malaria was championed more ambitiously by the Bill & Melinda Gates Foundation (BMGF) in 2007 (54). They are calling for a massive directed research effort to produce a malaria vaccine, and better drug and insecticides, coupled with a coherent delivery strategy to provide access to these new technologies in the poorest quartile of the populations in malaria-endemic countries with the highest burden of disease. Although this effort had been well supported by the international community, it will be a long-term process and requires socioeconomic and infrastructural development, as well as new tools and techniques.

Malaria elimination consists of four phases: preparatory, attack, consolidation, and maintenance (210). In the preparatory phase,

legal, logistical, and financial preparations are instigated. Information on malaria foci are collected, analyzed, disseminated, and evaluated. The information is used to plan vector control activities and to classify infections. In the 1960s, during surveillance for malaria eradication, every malaria case was classified according to the origin of infection as indigenous, imported, introduced, or relapsing. Today these case classifications can be assigned using molecular techniques to track the parasite back to its geographical origin (120).

The attack phase parameters to be considered in selecting vector control interventions are their efficacy, cost, operational applicability and feasibility; ecological acceptability; acceptability to the population; and administrative applicability, including availability of infrastructure, trained personnel, financing, transport, legislative support, technical direction, public information and participation. Vectorial capacity and R_0 should be calculated to monitor the effectiveness of the attack phase interventions, and redirect resources (46, 120).

Early in the consolidation phase, surveillance needs to be instigated to identify hotspots of transmission and insecticide resistance. Active implementation of vector control measures may be required to clear any remaining foci and to drive R_0 below 1 (203, 210). The consolidation phase is a lengthy end game in which vigilance against reintroduction of malaria is needed. Vector control interventions, such as larviciding (200) and environmental management (89), which have a relatively modest impact, may be useful to reduce the length of the consolidation phase. A robust surveillance system that covers the whole population, especially areas that are hard to reach, where outbreaks are most likely, is needed along with a rapid response plan. Intense focal vector control will need to be directed using surveillance systems capable of tracking this moving target. In practice, in this phase it is likely that transmission will be low ($R_0 < 1$) in the general population with foci of higher transmission. Until all these foci are identified and controlled, elimination cannot occur.

The risk that the parasite might reinvade an area in the maintenance phase, when elimination has been achieved, depends on vulnerability and receptivity. Vulnerability is the probability of reintroduction, via the arrival of infectious gametocyte carriers (75, 142). It depends on the distance of the eliminated territory from malaria-endemic areas, the existence of natural barriers (e.g., oceans), the amount of human population movement, and the infection rate among the migrants. Reducing receptivity (142) is important when parts of the target area are largely free of transmission and continues to be important after elimination. For this purpose, the desirable features for vector control are low intensity, coupled with high long-term coverage, and low cost.

Other than state-delivered insecticide-based vector control, there are three important and interrelated elements to receptivity reduction: first, promoting personal responsibility for protection against mosquitoes, such as continued use of mosquito nets or house screening (69); second, taking deliberate measures to reduce the creation of human-made mosquito breeding sites, e.g., producing rice without producing mosquitoes. This effort is distinct from the often promoted cost-inefficient organized use of environmental measures to attack natural breeding sites. The third element is supporting social, economic, and environmental developments that have indirect beneficial effects on malaria transmission. For example, in Tanzania the switch from thatched to corrugated iron roofs profoundly reduced mosquito entry and biting in houses (105, 170).

MALARIA MANAGEMENT METHODOLOGIES

There are two main strategic approaches for malaria management: (*a*) malaria prevention (vector control, drug prophylaxis, and potential use of a vaccine) and (*b*) treatment (drugs and blood transfusions, among others).

Drugs

Several generations of drugs have been effective in malaria treatment. The earliest was

synthesized chloroquine, which saved millions of lives (191). These drugs target particular life stages of the malaria parasites and are subject to problems of drug resistance. Resistance has now made chloroquine widely ineffective for *P. falciparum* treatment.

- Drugs that treat clinical malaria. These drugs destroy asexual parasites in the blood. Most classic antimalarial drugs, such as chloroquine and amodiaquine, have blood schizontocidal effects. Some of these drugs also have some degrees of gametocidal effects, although only primaquine is effective against gametocytes of *P. falciparum* and *P. vivax* hypnozoites (34, 213).
- Drugs that kill gametocytes. These refer to drugs that destroy or reduce gametocytes in the blood, making the treated person less or noninfectious to mosquitoes. Most classic antimalarial drugs with gametocytocidal activities affect several malaria parasites (34). Gametocytes of *P. falciparum* may persist even after combination therapy with sulfadoxine-pyrimethamine plus artesunate, and contribute considerably to malaria transmission (162). An additional dose of primaquine clears gametocytemia (176).
- Drugs that kill the hypnozoites of *P. vivax* malaria. The hypnozoites of *P. vivax* malaria lie dormant and then cause several relapses months or even years after a primary infection. Among classic antimalarials, only primaquine is effective against hypnozoites (34, 212). Primaquine has adverse effects in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and there are issues with compliance, as it should be given for 14 days (99, 162).
- New Drug Development Initiatives. The pharmaceutical industry has been re-engaged in antimalarial drug development over the past decade with the establishment of Product Development Partnerships, such as the BMGF-supported Medicines for Malaria Venture (MMV) and the E.U.-funded Anti-Mal program, providing a pipeline for new drug discovery and development. Artemisinin-derivative drugs such as artemether, arteether, and artesunate have recently been commercialized (194) and used in malaria management in China and Southeast Asia (212). They are highly effective against the multiplicative blood stages as well as the gametocytes of the parasites. They produce rapid clearance of parasitemia (41, 68, 128, 138). The World Health Organization strongly supports administration of these drugs as artemisinin-based combination therapies (ACTs) (208).

Unlike filariasis elimination, mass drug administration (MDA) is not considered a major tool for malaria elimination. However, in low-transmission areas, MDA with drugs that both treat and provide prophylactic effects to prevent reinfection for a period may prove effective at reducing transmission (66).

Vaccines

Development of an effective malaria vaccine has been a longstanding but difficult objective. None of the vaccine candidates to date has made it through to commercial production, although one vaccine is in large-scale clinical trials and may subsequently be produced (131). Three parasite stages are targeted by the following malaria vaccine development programs:

- Pre-erythrocytic vaccines (PEVs) target the sporozoites to prevent them from invading hepatocytes (neutralizing antibody) or to destroy them once inside the hepatocytes (44). PEVs are designed to protect against infection, not to prevent transmission. There is a significant risk associated with a short-lived vaccine that completely prevents infection, as it may shift the occurrence of severe disease to older age groups (164). Such vaccines can only decrease transmission linearly and thus are not useful in hyperendemic areas in tropical Africa. However, in

settings with lower endemicities or in terminal stages of elimination, they may be useful.

- Blood stage vaccines inactivate the merozoites during the relatively short time that they are in the bloodstream, or target malaria antigens expressed on the surface of erythrocytes. This type of vaccine should reduce disease (62), mimicking naturally acquired immunity (44, 187).
- Transmission-blocking vaccines require the mosquito to ingest the parasite along with antibody and complement during a blood meal. The antigens of the parasite become exposed to the antibody in the mosquito's stomach, preventing its sexual stage. This type of vaccine should prevent further spread of the disease (102, 169). As they reduce transmission by attacking the gametocytes, their effect is through community protection and reduction of malaria transmission. As with anti-infection vaccines, their effect would be approximately linear.
- There has been little research into vaccines against *P. vivax* malaria. Two *P. vivax* vaccine candidates are being tested in preliminary clinical trials (82).

In theory, if a 100% effective vaccine is given to a population at risk with 100% coverage, it will eliminate malaria; however, these levels of efficacy and coverage are unobtainable, and hence any vaccine that is developed will need to be used in a coordinated manner with drug and vector control interventions (13).

Vector Control

Two forms of vector control, IRS and LLINs, are generally applicable for reducing disease transmission (49).

Insecticide-treated nets. The use of insecticide-treated nets (ITNs), especially pyrethroid, has been widely promoted not because they are more powerful, but because they are simpler and operationally less demanding than IRS (205). Initial ITN technology was dramatically improved with the development of LLINs that do not require retreatment. LLINs in several African trials reduced malaria morbidity and mortality. They influence several entomological indices of malaria, including vector deterency, vector blood feeding and vector mortality (12, 103, 104, 119, 122). They are less effective at reducing the entomological indices than IRS, although LLINs distributed in large numbers exert a mass mosquito killing effect (27, 83, 111, 112). They are potentially more vulnerable to insecticide resistance, as only pyrethroid insecticides are recommended for use on ITNs, owing to toxicity and efficacy concerns (218).

Indoor residual spraying. IRS is the application of stable formulations of insecticides to the inside of houses to kill resting adult female mosquitoes. The primary contributions of IRS in reducing malaria transmission are reducing the life span of female mosquitoes, so that they can no longer transmit malaria parasites, and reducing the density of the vector mosquitoes (209). Current IRS insecticide formulations last from 2 to 6 months. Although formulations have improved, with the exception of DDT, which itself is intrinsically stable, most IRS formulations last less than 4 months. To be effective, IRS should be used at maximum possible coverage to produce a mosquito vector mortality rate of ~45% (209). Both IRS and LLINs affect vectorial capacity and help to drive it below 0.01 during the attack phase (49). IRS affects the mosquito density per person and the probability of vector survival. Combining this intervention with MDA should reduce the sporozoite rates, increase the recovery rates of infected people, and reduce the reproductive rate. LLINs reduce human-mosquito contact, which results in lower sporozoite and parasite rates. When heterogeneous biting is considered and if coverage with these two measures could be directed toward those who are bitten the most (i.e., children), then theoretically local elimination seems more practical (183).

It is evident that LLINs alone, even with complete coverage, will not eliminate malaria in

high-transmission areas (19, 67). If the LLINs are deployed alongside IRS, the overall impact on vectorial capacity and R_0 in high-transmission villages would be to drive R_0 to <1, a critical point below which infection dies out.

Additional Vector Control Methods

Theoretically larval control measures could contribute toward malaria elimination; however, high coverage of breeding sites is required to achieve significant impact, which is a major operational and logistical challenge in many ecological settings (142). There are a few examples, e.g., in Brazil, of effective vector control through larval control (91). However, as larval control affects only the density of the vector population, its impact on vectorial capacity and R_0 is limited. Nevertheless, it may be of operational importance where attack on adult mosquitoes is difficult, for instance, owing to ecological (exophilic species) or social (community resistance to residual spraying) considerations (65). Several biological agents, such as fish, fungi, bacteria, viruses, and nematodes, have been proposed for many years for the control of mosquito larvae or adults; however, these approaches are technically demanding and have not been widely used in operational settings (55, 165).

INNOVATION IN VECTOR CONTROL FOR MALARIA

New Insecticides, Attractants, and Repellents

The main classes of insecticides used for vector control are organophosphorus insecticides (OPs), carbamates, organochlorines, and pyrethroids. All these classes target the mosquito nervous system. Efforts are being made to expand the number of available classes (25, 109). One initiative, the Innovative Vector Control Consortium (IVCC), a Product Development Partnership, aims to reduce peridomestic transmission of mosquito-borne pathogens through improved insect vector control with innovative products. Specifically, the IVCC facilitates the production of improved public health pesticides and formulations, and works with the disease endemic country stakeholders and industry to establish target product profiles for new paradigms in vector control (76).

The sequencing of the *An. gambiae* genome has also been exploited by several groups to identify the range and function of olfactory receptors in the mosquito, with the longer-term aim of developing new attractants and repellents that could play an operational role in vector control (84, 85). These could be deployed independently or may be combined with insecticidal treatments (136, 145, 190). Indeed, many insecticides have repellent properties and there is substantial debate on the relative importance of the killing and repellency properties of such molecules (11, 12, 112).

Transgenic Mosquitoes

The development of transgenic mosquitoes that are refractory to malaria infection and could be released using different gene drive systems is ongoing (116). Technological advances have been made to facilitate DNA introduction and delivery, and stability of the transformed lines, using different transposable elements. Insertional mutagenesis, functional studies of the inserted genes, enhancer trapping, and promoter-receptor gene fusion transformation technologies have been explored (22). Transgenics released into the wild could enhance the naturally occurring defense mechanisms against malaria parasites in mosquitoes, or introduce monoclonal antibodies or artificial peptides to interfere with the parasite's development within the mosquito (16, 88). However, even if refractoriness is introduced against all genotypes of the malaria parasite, and mosquitoes can be stably transformed with these genes, the success of genetic manipulation within an operational control program is by no means certain. Developing transgenic variants of all the important vector species would be extremely challenging, and a bigger

obstacle may be the means to spread these transgenes through wild populations (6, 100).

Another area of interest might be using certain *Wolbachia* strains to shorten the life span of mosquitoes, which in turn, considering the formula for the vectorial capacity, dramatically decreases the potential of a vector species to transmit disease. Such approaches have been successfully implemented on *Aedes* vectors of dengue (121) and may well be good candidates for research on malaria vectors (158).

CHALLENGES FACING MALARIA ELIMINATION

Informed by the global malaria eradication campaigns of the 1960s, researchers are aware of the constraints to implementing any new program, including political, administrative, financial, operational, social, ecological, and technical considerations (140). Some important technical constraints facing malaria eradication are discussed below.

Drug Resistance

For decades, chloroquine has been the medicine of choice in malaria case management. Although the first cases of *P. falciparum* resistance to chloroquine were reported from Colombia and Thailand in 1960 (202), since the 1980s chloroquine has lost its effectiveness in many high-transmission areas in the treatment of *P. falciparum*. Chloroquine resistance is of high operational significance in malaria management, especially in resource-constrained countries (212). However, as drug use is lower in the early stages of an elimination program, resistance may occur in the near-elimination phase of the disease (72).

The global policy for introduction of artemisinin derivatives is to introduce these in combinations to reduce the potential for resistance. Policing this policy is difficult, though, and the first cases of artemisinin resistance have already been reported in Cambodia, where efforts are now scaling up to contain the resistance spread (42, 137).

Insecticide Resistance

Although high coverage with IRS and LLINs should reduce malaria transmission, they may select for and be adversely affected by insecticide resistance. Pyrethroid resistance has different effects on the personal protection provided by ITNs (17, 20, 26, 28, 29, 40, 133, 134), but, where insecticide resistance rendered ITNs less effective, some degree of impact on entomological indices remained. A major question that remains largely unanswered is what combinations of mechanisms of insecticide resistance produce operationally significant levels of resistance that will affect the different vector control interventions.

All the insecticides used for IRS and LLINs have been used for many decades. DDT resistance occurred less than 2 years after its introduction and is now common. However, DDT use for several decades has not selected for resistance in some areas for some major vectors, e.g., *An. funestus* in southern Africa (80, 90). Resistance can involve both metabolic and target site-based mechanisms in a single population, as in *An. gambiae* from Kenya (155, 198). Cross-resistance can occur through shared target sites or shared metabolic detoxification routes. At least three major enzyme groups are responsible for metabolic resistance to all four insecticide classes.

Metabolic resistance to DDT and pyrethroids. Glutathione S-transferases (GSTs) dehydrochlorinate DDT and are often overexpressed in resistant mosquitoes (147). There are more than 30 insect GSTs and many have a role in insecticide resistance. In *An. gambiae* several GSTs are elevated and responsible for DDT resistance (37, 154, 157, 163). These GSTs also act as a secondary detoxification route for organophosphates, resulting in cross-resistance to insecticides such as fenitrothion. GSTs reduce oxidative damage from pyrethroids to produce resistance (197).

Monooxygenases are involved in the metabolism of pyrethroids, the activation and/or detoxification of organophosphorus

insecticides and, to a much lesser extent, carbamate resistance in many anopheline mosquitoes, including *An. gambiae* and *An. funestus* (80). They often confer high levels of pyrethroid resistance, which is likely to be operationally significant. Prior to the release of the *An. gambiae* genome (86), 34 P450 genes had been identified (153). Subsequent analysis of genome data revealed 111 P450 monooxygenases (156). To date, upregulated insect P450s have been assigned to six families (78, 80, 153).

DDT and dieldrin resistance was evident in *An. albimanus* from the Pacific coastal plains of several South American countries (168). Esterase-based deltamethrin resistance in adults and larvae of *An. albimanus* in Guatemala with cross-resistance to fenitrothion occurred (8, 9). Resistance to pyrethroids in *An. albimanus* from Mexico was monooxygenase based (144) and DDT resistance was GST based (143).

Target site resistance. The organophosphorus, carbamate, organochlorine, and pyrethroid insecticides all target the nervous system. The molecular target of DDT and pyrethroid insecticides is the sodium channel and that of organophosphates and carbamates is acetylcholinesterase (AChE) (24, 60). Single base point mutations change the properties of theses target sites, reducing their susceptibility to insecticide binding, and the insects become resistant. However, in isolation some of these mutations produce less than threefold resistance, which is unlikely to be operationally significant (166).

Mutations in the sodium channel that confer DDT and pyrethroid resistance are referred to as kdr (78, 80). Screening of populations of *An. gambiae* for the common kdr point mutations by PCR has led to a plethora of recent publications, although the common mutations in both East and West Africa were originally selected several decades ago by DDT (155). Two common mutations, L1014F kdr/w and L1014S kdr/e, occur. The kdr/w mutation was first detected in the Mopti (M) form of *An. gambiae* in the Ivory Coast and in the Savanna (S) molecular form in the Bamako chromosomal form (117, 192). kdr is less common in *An. arabiensis*. Both African kdr mutations primarily confer high DDT and low pyrethroid resistance (155). In West Africa, where kdr/w is widely distributed, resistant allele frequencies can reach more than 90% (17, 206). The gene has moved between the different chromosomal and molecular forms of *An. gambiae* in West Africa, although frequencies within the S form are higher and distribution more widespread than within the M form (206). Mutations in the AChE gene result in a decreased sensitivity to inhibition of the enzyme by organophosphate and carbamate insecticides (77). Broad-spectrum resistance of up to 1000-fold can be conferred, which is likely to be operationally significant.

With increased resistance to DDT and pyrethroids, bendiocarb has been used more frequently for IRS. *An. gambiae* in the Ivory Coast and Benin is resistant to organophosphate and carbamate insecticides, with allelic frequencies of up to 40% (135). This resistance is currently spreading within the *An. gambiae* s.s. populations in West Africa (39), but its operational significance has yet to be established. Pyrethroid (71, 214) and carbamate resistance in *An. funestus* (10) in southern Mozambique occurred with elevated monooxygenases and insensitive AChE as the mechanisms (15). Similarly, metabolic DDT and pyrethroid resistance and an altered AChE-based carbamate resistance mechanism occurred in *An. funestus* in Ghana (139).

Temporal changes in resistance. DDT resistance in *An. stephensi* was detected in Saudi Arabia (31), Iraq (32), and Iran (64), followed by dieldrin resistance in 1959 (36) and malathion resistance in the 1970s (53, 159), owing to a malathion-specific carboxylesterase (160, 171). kdr occurred in the Dubai strain (50) and in India (59, 98), which was operationally significant when coupled with monooxygenase-, esterase-, and GST-based mechanisms (48, 57, 177).

In *An. culicifacies*, DDT and dieldrin resistance occurred in the late 1950s in India and

Pakistan (106, 161), followed by malathion resistance in 1977 in India (113, 124, 151, 196). Deltamethrin was successfully used to control triple [DDT, dieldrin/HCH (hexachlorocyclohexane), and malathion] resistant *An. culicifacies* (2, 30) for more than 10 years, until resistance was detected in 1997 in Tamil Nadu (123). A similar pattern has emerged in Sri Lanka (21).

GST-based DDT resistance was detected in *An. dirus* s.l. in Thailand in the 1990s (148–150, 195) but had reverted to susceptibility to DDT or permethrin in Western Thailand in 2008 (195). In India, Bangladesh, and Bhutan *An. dirus* remains fully susceptible. *An. sacharovi* was detected DDT resistant in Greece in 1951, in Turkey in 1958 (35), which was GST-based (79), and in Iran in 1959 (114). This was followed by dieldrin resistance in 1970 (152) and altered AChE-based malathion resistance in 1974 in Turkey (79, 81). *An. maculipennis* was detected DDT resistant in Iran in 1954, (115), in Italy in 1957 (35), and in Turkey in 1960 (152). This species is DDT resistant throughout most of Central Asia (204, 219).

Impact of insecticide resistance on malaria vector control measures. Insecticide resistance may differentially jeopardize the effectiveness of IRS- and LLINs-based malaria control operations. In two separate studies on Bioko Island, Equatorial Guinea, and Benin, IRS-based malaria control with deltamethrin and with lambdacyhalothrin was adversely affected by kdr and by kdr plus metabolic resistance in *An. gambiae*, respectively (133, 175).

In an area with >90% kdr *An. gambiae* in the Ivory Coast, permethrin- and deltamethrin-treated bednets showed relatively good efficacy and provided some personal protection (28). An explanation for this apparent paradox is that resistant mosquitoes are less repelled by the insecticide, remain on the treated material for longer periods, and receive a higher insecticide dose (29). PermaNet and Olyset nets were tested in a rice-growing area of Burkina Faso where the vectors were pyrethroid resistant still, and provided some personal protection against malaria. However, mosquito entrance and blood-feeding rates were almost halved by pyrethroid resistance (26). In contrast, in the Ivory Coast, Olyset nets did not reduce the human biting rate and the entomological inoculation rate (40).

Forest Malaria

Forest malaria may be more difficult to control than nonforest malaria in many parts of Southeast Asia, Africa, and South America. The vectors are often partially or wholly exophilic and exophagic and do not normally enter houses protected by IRS or LLINs. In India, 54 million tribals of various ethnic origins are estimated to reside in forest areas. They account for 8% of the total population of India but contribute 30% of malaria cases and 50–60% of total *P. falciparum* cases and malaria deaths (174). In Cambodia, a major reduction of malaria morbidity and mortality has occurred over the past 20 years. However, population movements into forests and forest-fringe areas where the vector is *An. dirus* make implementing effective control measures difficult. As *An. dirus* is exophagic, exophilic, and an early biter (i.e., bites early in the night), LLINs and IRS are not effective control measures (47).

In Vietnam, forest malaria occurs in the central part of the country, in 16 of 64 provinces. The National Malaria Control Program reports that approximately 50% of total malaria cases, more than 90% of the severe cases, and approximately 95% of malaria deaths occur in these 16 forested provinces. Again, the main vector is *An. dirus* (51).

Malaria cases are increasing in some areas. For example, in Belém, Pará, a forest fringe area of Brazil, the total number of malaria cases has increased significantly since the late 1970s and has increased rapidly from 1993 to 1999, coinciding with the reappearance of *An. darlingi* as a result of the continued expansion of Belém into the surrounding forest in the 1990s (146). In the forested areas of equatorial Africa, where malaria transmission occurs

year-round, mosquitoes such as *An. moucheti* can sustain malaria transmission intensities as high as 100–300 infected bites per person per year in villages located close to large rivers and slow moving streams where its larvae develop (3).

Although Thailand, Cambodia, and Vietnam have not achieved nationwide elimination, malaria is now a major problem only in the highland forest areas. In contrast, African malaria vectors are much better adapted to open savanna conditions. Nevertheless, the build-out of malaria is happening in Africa, both through encroaching urbanization and through changes in house design and housing materials.

SUSTAINABILITY OF MALARIA ELIMINATION IN AFRICA

Theoretically if IRS and/or LLINs are implemented with maximum coverage, malaria elimination is possible (49). It requires political commitment, sound management, increased funding, and the work of many thousands of individuals worldwide (54). However, realistically with current control tools and much higher levels of insecticide and drug resistance than were faced by the eradication programs of the 1960s (89), coupled with low or deteriorating socioeconomic status in some countries (70, 96), bringing vectorial capacity and R_0 below critical levels is operationally close to impossible.

A prerequisite for malaria elimination in tropical Africa is strengthening the health systems. The activities of the attack phase can be delivered through vertical structures without heavy reliance on local health systems; however, the consolidation phase will require, in many African countries, substantial strengthening of the health, medical, and diagnostic services if they are to shoulder the burden of extensive follow-ups, active case detection and surveillance, and focal spraying. In this process, key weaknesses of the health system, such as service delivery, information systems, a system for distributing commodities and supplies, health workforce, health care finance, and governance, should be addressed. The current weak infrastructure in most tropical African countries, where R_0 is in the thousands and the level of insecticide-resistance is increasing in the vectors, makes it inadvisable to embark on malaria elimination in sub-Saharan Africa until radically new interventions emerge (101).

CONCLUSION AND RECOMMENDATIONS

Several attempts have been made to control malaria in the last century. The sanitation era relied on environmental and larviciding approaches, and the global malaria eradication campaigns followed the discovery of DDT and chloroquine. A renewed attempt proposed by the BMGF is underway to eliminate malaria starting with countries on the spatial fringes of malaria transmission and working inward to the most difficult settings. To be successful, elimination programs will need to combine lessons learned from previous attempts with advances in science and technology and improved political will and resources. The following are key recommendations for elimination programs:

- Draw lessons from the past, specifically the global malaria eradication campaigns.
- Carefully study the success or failure of countries embarking on elimination and draw lessons for other countries.
- Seek help and hard data to make proper technical, practical, and economic decisions on malaria control or elimination.
- Collaborate with research efforts on new tools, such as vaccines, new drugs, transgenic mosquitoes, new insecticides, attractants and repellents, and alternative interventions.
- Develop coherent implementation plans for the operational aspects of current and new tools.
- Develop capacity building and infrastructural investments, especially in the public health sector, to support elimination efforts.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Al-Taiar A, Assabri A, Al-Habori M, Azazy A, Algabri A, et al. 2009. Socioeconomic and environmental factors important for acquiring non-severe malaria in children in Yemen: a case-control study. *Trans. R. Soc. Trop. Med. Hyg.* 103:72–78
2. Ansari MA, Sharma VP, Razdan RK, Mittal PK. 1990. Field evaluation of deltamethrin against resistant *Anopheles culicifacies* in Distt. Ghaziabad (U.P.) India. *Indian J. Malariol.* 27:1–13
3. Antonio-Nkondjio C, Simard F, Awono-Ambene P, Ngassam P, Toto J-C, et al. 2005. Malaria vectors and urbanization in the equatorial forest region of south Cameroon. *Trans. R. Soc. Trop. Med. Hyg.* 99:347–54
4. Awolola TS, Oyewole IO, Amajoh CN, Idowu ET, Ajayi MB, et al. 2005. Distribution of the molecular forms of *Anopheles gambiae* and pyrethroid knock down resistance gene in Nigeria. *Acta Trop.* 95:204–9
5. Baomar A, Mohamed A. 2000. Malaria outbreak in a malaria-free region in Oman 1998: unknown impact of civil war in Africa. *Public Health* 114:480–83
6. Boëte C, Koella JC. 2003. Evolutionary ideas about genetically manipulated mosquitoes and malaria control. *Trends Parasitol.* 19:32–38
7. Bradley DJ. 1991. Morbidity and mortality at Pare-Taveta, Kenya and Tanzania, 1954–66: the effects of a period of malaria control. In *Disease and Mortality in Sub-Saharan Africa*, ed. RG Feachem, DT Jamison, pp. 248–63. Oxford: Oxford Univ. Press
8. Brogdon WG, Barber AM. 1990. Fenitrothion-deltamethrin cross-resistance conferred by esterases in Guatemalan *Anopheles albimanus*. *Pest. Biochem. Physiol.* 37:130–39
9. Brogdon WG, McAllister JC, Corwin AM. 1999. Independent selection of multiple mechanisms for pyrethroid resistance in Guatemalan *Anopheles albimanus* (Diptera: Culicidae). *J. Econ. Entomol.* 92:298–302
10. Brooke BD, Kloke G, Hunt RH, Koekemoer LL, Temu EA, et al. 2001. Bioassay and biochemical analyses of insecticide resistance in southern African *Anopheles funestus* (Diptera: Culicidae). *Bull. Entomol. Res.* 91:265–72
11. Brown M, Hebert AA. 1997. Insect repellents: an overview. *J. Am. Acad. Dermatol.* 36:243–49
12. Carnevale P, Bitsindou P, Diomandé L, Robert V. 1992. Insecticide impregnation can restore the efficiency of torn bed nets and reduce man-vector contact in malaria endemic areas. *Trans. R. Soc. Trop. Med. Hyg.* 86:362–64
13. Carter R. 2001. Transmission blocking malaria vaccines. *Vaccine* 19:2309–14
14. Carter R, Mendis KN. 2002. Evolutionary and historical aspects of the burden of malaria. *Clin. Microbiol. Rev.* 15:564–94
15. Casimiro S, Coleman M, Mohloai P, Hemingway J, Sharp B. 2006. Insecticide resistance in *Anopheles funestus* (Diptera: Culicidae) from Mozambique. *J. Med. Entomol.* 43:267–75
16. Catteruccia F, Nolan T, Loukeris TG, Blass C, Savakis C, et al. 2000. Stable germline transformation of the malaria mosquito *Anopheles stephensi*. *Nature* 405:959–62
17. Chandre F, Darriet F, Duchon S, Finot L, Manguin S, et al. 2000. Modifications of pyrethroid effects associated with kdr mutation in *Anopheles gambiae*. *Med. Vet. Entomol.* 14:81–88
18. Chatterjee P. 2005. Cambodia's fight against malaria. *Lancet* 366:191–92
19. Chiyaka C, Garira W, Dube S. 2007. Transmission model of endemic human malaria in a partially immune population. *Math. Comput. Model.* 46:806–22
20. Chouaibou M, Simard F, Chandre F, Etang J, Darriet F, Hougard J-M. 2006. Efficacy of bifenthrin-impregnated bednets against *Anopheles funestus* and pyrethroid-resistant *Anopheles gambiae* in North Cameroon. *Malaria J.* 5:77–82
21. Clarke JL, Herath PR, Wickramasinghe MB. 1974. Studies on DDT resistance in *Anopheles culicifacies* in Sri Lanka. *WHO/MAL/822–883*

22. Coates CJ. 2005. Stable transformation of vector species. In *Biology of Disease Vectors*, ed. WC Marquardt, WC Black, S Higgs, JE Freier, AA James, et al, pp. 613–24. Burlington, MA: Elsevier Acad.
23. Coetzee M, Craig M, le Sueur D. 2000. Distribution of African malaria mosquitoes belonging to the *Anopheles gambiae* complex. *Parasitol. Today* 16:74–77
24. Corbett JR, Wright K, Baillie AC. 1984. *The Biochemical Mode of Action of Pesticides*. London: Academic. 382 pp.
25. Cordova D, Benner EA, Sacher MD, Rauh JJ, Sopa JS, et al. 2006. Anthranilic diamides: a new class of insecticides with a novel mode of action, ryanodine receptor activation. *Pest. Biochem. Physiol.* 84:196–214
26. Dabiré RK, Diabaté A, Baldet T, Paré-Toé L, Guiguemdé RT, et al. 2006. Personal protection of long lasting insecticide-treated nets in areas of *Anopheles gambiae* s.s. resistance to pyrethroids. *Malaria J.* 5:8
27. Dapeng L, Deling L, Renguo Y, Peng L, Xueguang H, et al. 1994. Alphamethrin-impregnated bed nets for malaria and mosquito control in China. *Trans. R. Soc. Trop. Med. Hyg.* 88:625–28
28. Darriet F, Guillet P, N'Guessan R, Doannio JM, Koffi A, et al. 1998. Impact of resistance of *Anopheles gambiae* s.s. to permethrin and deltamethrin on the efficacy of impregnated mosquito nets. *Med. Trop.* 58:349–54
29. Darriet F, N'Guessan R, Koffi AA, Konan L, Doannio JM, et al. 2000. Impact of pyrethrin resistance on the efficacity of impregnated mosquito nets in the prevention of malaria: results of tests in experimental cases with deltamethrin SC. *Bull. Soc. Pathol. Exot.* 93:131–34
30. Das M, Srivastava SP, Khamre JS, Deshpande LB. 1986. Susceptibility of DDT, dieldrin and malathion resistant *Anopheles culicifacies* populations to deltamethrin. *J. Am. Mosq. Control Assoc.* 2:553–55
31. Davidson G. 1958. Studies on insecticide resistance in *Anopheles* mosquitoes. *Bull. WHO* 18:579–621
32. Davidson G, Jackson CE. 1961. DDT-resistance in *Anopheles stephensi*. *Bull. WHO* 25:209–17
33. Delfini LF. 1969. Final report on the malaria eradication programme in Zanzibar and Pemba. *WHO/AFR/MAL104*
34. Desjardins RE, Doberstyn EB, Wernsdorfer WH. 1988. The treatment and prophylaxis of malaria. See Ref. 201, pp. 827–64
35. de Zulueta J. 1959. Insecticide resistance in *Anopheles sacharovi*. *Bull. WHO* 20:797–22
36. de Zulueta J, Chang TL, Cullen JR, Davidson G. 1968. Insecticide resistance in *Anopheles stephensi* in Iraq: at the end of 1967. *WHO/MAL/68.655*
37. Ding Y, Ortelli F, Rossiter LC, Hemingway J, Ranson H. 2003. The *Anopheles gambiae* glutathione transferase supergene family: annotation, phylogeny and expression profiles. *BMC Genomics* 4:35
38. Djadid ND, Gholizadeh S, Aghajari M, Zehi AH, Raeisi A, Zakeri S. 2006. Genetic analysis of rDNA-ITS2 and RAPD loci in field populations of the malaria vector, *Anopheles stephensi* (Diptera: Culicidae): implications for the control program in Iran. *Acta Trop.* 97:65–74
39. Djogbénou L, Dabiré R, Diabaté A, Kengne P, Akogbéto M, et al. 2008. Identification and geographic distribution of the ACE-1R mutation in the malaria vector *Anopheles gambiae* in south-western Burkina Faso, West Africa. *Am. J. Trop. Med. Hyg.* 78:298–302
40. Doannio JM, Dossou-Yovo J, Diarrassouba S, Chauvancy G, Darriet F, et al. 1999. Efficacy of permethrin-impregnated Olyset Net mosquito nets in a zone with pyrethroid resistant vectors. I–Entomologic evaluation. *Med. Trop.* 59:349–54
41. Dondorp AM, Day NPJ. 2007. The treatment of severe malaria. *Trans. R. Soc. Trop. Med. Hyg.* 101:633–34
42. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, et al. 2009. Artemisinin resistance in *Plasmodium falciparum* malaria. *N. Engl. J. Med.* 361:455–67
43. Dube S, Ismail N, Hoosen AA. 2008. A retrospective review of malaria cases seen in a non-endemic area of South Africa. *Travel Med. Infect. Dis.* 6:296–300
44. Dubovsky F, Rabinovich NR. 2004. Malaria vaccines. In *Vaccines*, ed. SA Plotkin, WA Orenstein, pp. 1283–89. Philadelphia: Saunders
45. Dulhunty JM, Yohannes K, Kourleoutov C, Manuopangai VT, Polyn MK, et al. 2000. Malaria control in central Malaita, Solomon Islands 2. Local perceptions of the disease and practices for its treatment and prevention. *Acta Trop.* 75:185–96
46. Dye C. 1986. Vectorial capacity: Must we measure all its components? *Parasitol. Today* 2:203–9
47. Dysoley L, Kaneko A, Eto H, Mita T, Socheat D, et al. 2008. Changing patterns of forest malaria among the mobile adult male population in Chumkiri District, Cambodia. *Acta Trop.* 106:207–12

48. Enayati AA, Hemingway J. 2006. Pyrethroid insecticide resistance and treated bednets efficacy in malaria control. *Pest. Biochem. Physiol.* 84:116–26
49. Enayati AA, Lines J, Maharaj R, Hemingway J. 2009. Suppressing the vector. In *Shrinking the Malaria Map a Prospectus on Malaria Elimination*, ed. RGM Feachem, AA Phillips, GA Targett, pp. 140–54. San Francisco: Global Health Group
50. Enayati AA, Vatandoost H, Ladonni H, Townson H, Hemingway J. 2003. Molecular evidence for a kdr-like pyrethroid resistance mechanism in the malaria vector mosquito *Anopheles stephensi*. *Med. Vet. Entomol.* 17:138–44
51. Erhart A, Thang ND, Ky PV, Tinh TT, Overmeir CV, et al. 2005. Epidemiology of forest malaria in central Vietnam: a large scale cross-sectional survey. *Malaria J.* 4:58
52. Erhart A, Thang ND, Xa NX, Thieu NQ, Hung LX, et al. 2007. Accuracy of the health information system on malaria surveillance in Vietnam. *Trans. R. Soc. Trop. Med. Hyg.* 101:216–25
53. Eshgy N. 1978. Tolerance of *Anopheles stephensi* to malathion in the province of Fars, Southern Iran 1977. *Mosq. News* 38:580–83
54. Feachem R, Sabot O. 2008. A new global malaria eradication strategy. *Lancet* 371:1633–35
55. ffrench-Constant RH. 2005. Something old, something transgenic, or something fungal for mosquito control? *Trends Ecol. Evol.* 20:577–79
56. Fontenille D, Simard F. 2004. Unravelling complexities in human malaria transmission dynamics in Africa through a comprehensive knowledge of vector populations. *Comp. Immunol. Microbiol. Infect. Dis.* 27:357–75
57. Ganesh KN, Vijayan VA, Urmila J, Gopalan N, Prakash S. 2002. Role of esterases and monooxygenase in the deltamethrin resistance in *Anopheles stephensi* Giles (1908), at Mysore. *Indian J. Exp. Biol.* 40:583–88
58. Garrett-Jones C, Grab B. 1964. The assessment of insecticidal impact on the malaria mosquito's vectorial capacity, from data on the proportion of parous females. *Bull. WHO* 31:71–78
59. Gayathri V, Murthy PB. 2006. Reduced susceptibility to deltamethrin and kdr mutation in *Anopheles stephensi* Liston, a malaria vector in India. *J. Am. Mosq. Control Assoc.* 22:678–88
60. Georghiou GP, Saito T. 1983. *Pest Resistance to Pesticides*. New York: Plenum. 809 pp.
61. Georghiou GP, Taylor CE. 1977. Genetic and biological influences in the evolution of insecticide resistance. *J. Econ. Entomol.* 70:319–23
62. Good MF. 2001. Towards a blood-stage vaccine for malaria: Are we following all the leads? *Nat. Rev. Immunol.* 1:117–25
63. Gramiccia G, Beales PF. 1988. The recent history of malaria control and eradication. See Ref. 201, pp. 1335–78
64. Gramiccia G, de Meillon B, Ulrich AM. 1958. Resistance to DDT in *Anopheles stephensi*. *Bull. WHO* 19:1102–5
65. Gratz NG, Pal R. 1988. Malaria vector control: larviciding. See Ref. 201, pp. 1213–26
66. Greenwood BM. 2008. Control to elimination: implications for malaria research. *Trends Parasitol.* 24:449–54
67. Gu W, Killeen GF, Mbogo CM, Regens JL, Githure JI, Beier JC. 2003. An individual-based model of *Plasmodium falciparum* malaria transmission on the coast of Kenya. *Trans. R. Soc. Trop. Med. Hyg.* 97:43–50
68. Guerin PJ, Olliaro P, Nosten F, Druilhe P, Laxminarayan R, et al. 2002. Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. *Lancet Infect. Dis.* 2:564–73
69. Guyatt H, Snow RW. 2002. The cost of not treating bednets. *Trends Parasitol.* 18:12–16
70. Hales S, Woodward A. 2003. Climate change will increase demands on malaria control in Africa. *Lancet* 362:1775–76
71. Hargreaves K, Koekemoer LL, Brooke BD, Hunt RH, Mthembu J, Coetzee M. 2000. *Anopheles funestus* resistant to pyrethroid insecticides in South Africa. *Med. Vet. Entomol.* 14:181–89
72. Hastings IM. 2003. Malaria control and the evolution of drug resistance: an intriguing link. *Trends Parasitol.* 19:70–73
73. Haworth J. 1988. The global distribution of malaria and the present control effort. See Ref. 201, pp. 1379–420

74. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. 2004. The global distribution and population at risk of malaria: past, present, and future. *Lancet Infect. Dis.* 4:327–36
75. Hay SI, Smith DL, Snow RW. 2008. Measuring malaria endemicity from intense to interrupted transmission. *Lancet Infect. Dis.* 8:369–78
76. Hemingway J, Beaty BJ, Rowland M, Scott TW, Sharp BL. 2006. The Innovative Vector Control Consortium: improved control of mosquito-borne diseases. *Trends Parasitol.* 22:308–12
77. Hemingway J, Georghiou GP. 1983. Studies on the acetylcholinesterase of *Anopheles albimanus* resistant and susceptible to organophosphate and carbamate insecticides. *Pest. Biochem. Physiol.* 19:167–71
78. Hemingway J, Hawkes NJ, McCarroll L, Ranson H. 2004. The molecular basis of insecticide resistance in mosquitoes. *Insect Biochem. Mol. Biol.* 34:653–65
79. Hemingway J, Malcolm CA, Kissoon KE, Boddington RG, Curtis CF, Hill N. 1985. The biochemistry of insecticide resistance in *Anopheles sacharovi*: comparative studies with a range of insecticide susceptible and resistant *Anopheles* and *Culex* species. *Pest. Biochem. Physiol.* 24:68–76
80. Hemingway J, Ranson H. 2000. Insecticide resistance in insect vectors of human disease. *Annu. Rev. Entomol.* 45:369–89
81. Hemingway J, Small GJ, Monro A, Sawyer BV, Kasap H. 1992. Insecticide resistance gene frequencies in *Anopheles sacharovi* populations of the Cukurova Plain, Adana province, Turkey. *Med. Vet. Entomol.* 6:342–48
82. Herrera S, Corradin G, Arévalo-Herrera M. 2007. An update on the search for a *Plasmodium vivax* vaccine. *Trends Parasitol.* 23:122–28
83. Hii JL, Birley MH, Kanai L, Foligeli A, Wagner J. 1995. Comparative effects of permethrin-impregnated bednets and DDT house spraying on survival rates and oviposition interval of *Anopheles farauti* No. 1 (Diptera: Culicidae) in Solomon Islands. *Ann. Trop. Med. Parasitol.* 89:521–29
84. Hill CA, Fox AN, Pitts RJ, Kent LB, Tan PL, et al. 2002. G protein-coupled receptors in *Anopheles gambiae*. *Science* 298:176–78
85. Hill N, Lenglet A, Arnez AM, Carneiro I. 2007. Plant based insect repellent and insecticide treated bed nets to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon. *Br. Med. J.* 335:1023
86. Holt RA, Subramanian GM, Halpern A, Sutton GG, Charlab R, et al. 2002. The genome sequence of the malaria mosquito *Anopheles gambiae*. *Science* 298:129–49
87. Hume JCC, Lyons EJ, Day KP. 2003. Human migration, mosquitoes and the evolution of *Plasmodium falciparum*. *Trends Parasitol.* 19:144–49
88. Ito J, Ghosh A, Moreira LA, Wimmer EA, Jacobs-Lorena M. 2002. Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite. *Nature* 417:452–55
89. Keiser J, Singer BH, Utzinger J. 2005. Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review. *Lancet* 5:695–708
90. Kelly-Hope L, Ranson H, Hemingway J. 2008. Lessons from the past: managing insecticide resistance in malaria control and eradication programmes. *Lancet Infect. Dis.* 8:387–89
91. Killeen GF, Fillinger U, Kiche I, Gouagna LC, Knols BG. 2002. Eradication of *Anopheles gambiae* from Brazil: lessons for malaria control in Africa? *Lancet Infect. Dis.* 2:618–27
92. Klinkenberg E, Konradsen F, Herrel N, Mukhtar M, Van Der Hoek W, Amerasinghe FP. 2004. Malaria vectors in the changing environment of the southern Punjab, Pakistan. *Trans. R. Soc. Trop. Med. Hyg.* 98:442–49
93. Klinkenberg E, van der Hoek W, Amerasinghe FP. 2004. A malaria risk analysis in an irrigated area in Sri Lanka. *Acta Trop.* 89:215–25
94. Kobayashi J, Phompida S, Toma T, Looareensuwan S, Toma H, Miyagi I. 2004. The effectiveness of impregnated bed net in malaria control in Laos. *Acta Trop.* 89:299–308
95. Kolaczinski J, Graham K, Fahim A, Brooker S, Rowland M. 2005. Malaria control in Afghanistan: progress and challenges. *Lancet* 365:1506–12
96. Konradsen F, van der Hoek W, Amerasinghe FP, Mutero C, Boelee E. 2004. Engineering and malaria control: learning from the past 100 years. *Acta Trop.* 89:99–108
97. Kouznetsov RL. 1977. Malaria control by application of indoor spraying of residual insecticides in tropical Africa and its impact on community health. *Trop. Dr.* 7:81–91

98. Kumar S, Thomas A, Sahgal A, Verma A, Samuel T, Pillai MK. 2004. Variations in the insecticide-resistance spectrum of *Anopheles stephensi* after selection with deltamethrin or a deltamethrin-piperonyl-butoxide combination. *Ann. Trop. Med. Parasitol.* 98:861–71
99. Lalloo DG, Shingadia D, Pasvol G, Chiodini PL, Whitty CJ, et al. 2007. UK malaria treatment guidelines. *J. Infect.* 54:111–21
100. Lambrechts L, Koella JC, Boëte C. 2008. Can transgenic mosquitoes afford the fitness cost? *Trends Parasitol.* 24:4–7
101. *Lancet*. 2007. Is malaria eradication possible? *Lancet* 370:1459
102. Lavazec C, Bourgouin C. 2008. Mosquito-based transmission blocking vaccines for interrupting *Plasmodium* development. *Microb. Infect.* 10:845–49
103. Lindsay SW, Adiamah JH, Armstrong JRM. 1992. The effect of permethrin-impregnated bednets on house entry mosquitoes (Diptera: Culicidae) in the Gambia. *Bull. Entomol. Res.* 82:49–55
104. Lindsay SW, Adiamah JH, Miller JE, Armstrong JRM. 1991. Pyrethroid-treated bednet effects on mosquitoes of the *Anopheles gambiae* complex in the Gambia. *Med. Vet. Entomol.* 5:477–83
105. Lindsay SW, Jawara M, Paine K, Pinder M, Walraven GE, Emerson PM. 2003. Changes in house design reduce exposure to malaria mosquitoes. *Trop. Med. Int. Health* 8:512–17
106. Luen SC, Shalaby AM. 1961. Preliminary note on the development of DDT resistance in *A. culicifacies* Giles in Panchmahals District of Gujerat State (formerly part of Bombay State) India. *WHO/MAL/297-313*
107. Lum JK, Kaneko A, Taleo G, Amos M, Reiff DM. 2007. Genetic diversity and gene flow of humans, *Plasmodium falciparum*, and *Anopheles farauti* s.s. of Vanuatu: inferred malaria dispersal and implications for malaria control. *Acta Trop.* 103:102–7
108. Lum JK, Kaneko A, Tanabe K, Takahashi N, Björkman A, Kobayakawa T. 2004. Malaria dispersal among islands: human mediated *Plasmodium falciparum* gene flow in Vanuatu, Melanesia. *Acta Trop.* 90:181–85
109. Luo Y-P, Yang G-F. 2007. Discovery of a new insecticide lead by optimizing a target-diverse scaffold: tetrazolinone derivatives. *Bioorg. Med. Chem.* 15:1716–24
110. Macdonald G. 1957. *The Epidemiology and Control of Malaria*. Oxford: Oxford Univ. Press
111. Magbity EB, Marbiah NT, Maude G, Curtis CF, Bradley DJ, et al. 1997. Effects of community-wide use of lambdacyhalothrin-impregnated bednets on malaria vectors in rural Sierra Leone. *Med. Vet. Entomol.* 11:79–86
112. Magesa SM, Wilkes TJ, Mnzava AEP, Njunwa KJ, Myamba J, et al. 1991. Trial of pyrethroid impregnated bednets in an area of Tanzania holoendemic for malaria. Part 2. Effects on the malaria vector population. *Acta Trop.* 49:97–108
113. Malcolm CA, Boddington RG. 1989. Malathion resistance conferred by a carboxylesterase in *Anopheles culicifacies* Giles (Species B) (Diptera: Culicidae). *Bull. Entomol. Res.* 79:193–99
114. Manouchehri AV, Zaini A, Javadian E, Saebi E. 1974. Resistance of *Anopheles sacharovi* Favre to DDT in Iran, 1973. *Iran. J. Public Health* 4:204–11
115. Manouchehri AV, Zaini A, Motaghi M. 1976. Resistance of *Anopheles maculipennis* to insecticides in northern Iran. *Mosq. News* 36:51–53
116. Marshall JM. 2009. The effect of gene drive on containment of transgenic mosquitoes. *J. Theor. Biol.* 258:250–65
117. Martinez-Torres D, Chandre F, Williamson MS, Darriet F, Berge JB, et al. 1998. Molecular characterization of pyrethroid knockdown resistance (kdr) in the major malaria vector *Anopheles gambiae* s.s. *Insect Mol. Biol.* 7:179–84
118. Martinsen ES, Perkins SL, Schall JJ. 2008. A three-genome phylogeny of malaria parasites (*Plasmodium* and closely related genera): evolution of life-history traits and host switches. *Mol. Phylogenet. Evol.* 47:261–73
119. Maxwell CA, Myamba J, Njunwa KJ, Greenwood BM, Curtis CF. 1999. Comparison of bednets impregnated with different pyrethroids for their impact on mosquitoes and on re-infection with malaria after clearance of pre-existing infections with chlorproguanil-dapsone. *Trans. R. Soc. Trop. Med. Hyg.* 93:4–11
120. McKenzie FE. 2000. Why model malaria? *Parasitol. Today* 16:511–16
121. McMeniman CJ, Lane RV, Cass BN, Fong AWC, Sidhu M, et al. 2009. Stable introduction of a life-shortening *Wolbachia* infection into the mosquito *Aedes aegypti*. *Science* 323:141–44

122. Miller JE, Lindsay SW, Armstrong JR. 1991. Experimental hut trials of bednets impregnated with synthetic pyrethroid or organophosphate insecticide for mosquito control in The Gambia. *Med. Vet. Entomol.* 5:465–76
123. Mittal PK, Adak T, Singh OP, Raghavendra K, Subbarao SK. 2002. Reduced susceptibility to deltamethrin in *Anopheles culicifacies* sensu lato, in Ramnathapuram district, Tamil Nadu—selection of a pyrethroid-resistant strain. *Curr. Sci.* 82:185–88
124. Mittal PK, Wijeyaratne P, Pandey S. 2004. *Status of insecticide resistance of malaria, kala-azar and Japanese Encephalitis vectors in Bangladesh, Bhutan, India and Nepal (BBIN)*. **http://www.ehproject.org/PDF/Activity_Reports/AR-129%20Status%20Insect%20Format.pdf**
125. Molineaux L, Gramiccia G. 1980. *The Garki Project. Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa*. Geneva: WHO. 311 pp.
126. Molineaux L, Muir DA, Spencer HC, Wernsdorfer WH. 1988. The epidemiology of malaria and its measurement. See Ref. 201, pp. 999–1089
127. Müller I, Bockarie M, Alpers M, Smith T. 2003. The epidemiology of malaria in Papua New Guinea. *Trends Parasitol.* 19:253–59
128. Mutabingwa TK. 2005. Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccessible to the needy! *Acta Trop.* 95:305–15
129. Nabarro DN, Tayler EM. 1998. Global health: the "roll back malaria" campaign. *Science* 280:2067–68
130. Najera JA. 1999. *Malaria Control. Achievements Problems and Strategies*. Geneva: WHO. 126 pp.
131. Nayar A. 2009. Malaria vaccine enters phase III clinical trials. *Nature* 459:627
132. Ngo GL, Truong VC, Tran TH, Pham DN. 2008. Multiplex PCR assay for some malaria vector species in the Myzomyia series from Vietnam and Southeast Asia. *Int. J. Infect. Dis.* 12:e309
133. N'Guessan R, Corbel V, Akogbéto M, Rowland M. 2007. Reduced efficacy of insecticide-treated nets and indoor residual spraying for malaria control in pyrethroid resistance area, Benin. *Emerg. Infect. Dis.* 13:199–206
134. N'Guessan R, Darriet F, Doannio JM, Chandre F, Carnevale P. 2001. Olyset Net efficacy against pyrethroid-resistant *Anopheles gambiae* and *Culex quinquefasciatus* after three years' field use in Côte d'Ivoire. *Med. Vet. Entomol.* 15:97–104
135. N'Guessan R, Darriet F, Guillet P, Carnevale P, Traore-Lamizana M, et al. 2003. Resistance to carbosulfan in *Anopheles gambiae* from Ivory Coast, based on reduced sensitivity of acetylcholinesterase. *Med. Vet. Entomol.* 17:19–25
136. N'Guessan R, Rowland M, Moumouni T-L, Kesse NB, Carnevale P. 2006. Evaluation of synthetic repellents on mosquito nets in experimental huts against insecticide-resistant *Anopheles gambiae* and *Culex quinquefasciatus* mosquitoes. *Trans. R. Soc. Trop. Med. Hyg.* 100:1091–97
137. Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, et al. 2008. Evidence of artemisinin-resistant malaria in Western Cambodia. *N. Engl. J. Med.* 359:2619–20
138. Okell LC, Drakeley CJ, Ghani AC, Bousema T, Sutherland CJ. 2008. Reduction of transmission from malaria patients by artemisinin combination therapies: a pooled analysis of six randomized trials. *Malaria J.* 7:125
139. Okoye PN, Brooke BD, Koekemoer LL, Hunt RH, Coetzee M. 2008. Characterisation of DDT, pyrethroid and carbamate resistance in *Anopheles funestus* from Obuasi, Ghana. *Trans. R. Soc. Trop. Med. Hyg.* 102:591–98
140. Onori E. 1988. Malaria control constraints. See Ref. 201, pp. 1721–39
141. Oshaghi MA, Shemshad K, Yaghobi-Ershadi MR, Pedram M, Vatandoost H, et al. 2007. Genetic structure of the malaria vector *Anopheles superpictus* in Iran using mitochondrial cytochrome oxidase (COI and COII) and morphologic markers: a new species complex? *Acta Trop.* 101:241–48
142. Pampana E. 1969. *A Textbook of Malaria Eradication*. London: Oxford Univ. Press. 593 pp.
143. Penilla RP, Rodríguez AD, Hemingway J, Torres JL, Solis F, Rodríguez MH. 2006. Changes in glutathione *S*-transferase activity in DDT resistant natural Mexican populations of *Anopheles albimanus* under different insecticide resistance management strategies. *Pest. Biochem. Physiol.* 86:63–71
144. Penilla RP, Rodríguez AD, Hemingway J, Trejo A, Lopez AD, Rodríguez MH. 2007. Cytochrome P450-based resistance mechanism and pyrethroid resistance in the field *Anopheles albimanus* resistance management trial. *Pest. Biochem. Physiol.* 89:111–17

145. Pennetier C, Corbel V, Hougard JM. 2005. Combination of a non-pyrethroid insecticide and a repellent: a new approach for controlling knockdown-resistant mosquitoes. *Am. J. Trop. Med. Hyg.* 72:739–44
146. Póvoa MM, Conn JE, Schlichting CD, Amaral JCOF, Nazaré M, et al. 2003. Malaria vectors, epidemiology, and the re-emergence of *Anopheles darlingi* in Belém, Pará, Brazil. *J. Med. Entomol.* 40:379–86
147. Prapanthadara L, Hemingway J, Ketterman AJ. 1995. DDT-resistance in *Anopheles gambiae* Giles from Zanzibar Tanzania, based on increased DDT-dehydrochlorinase activity of glutathione *S*-transferases. *Bull. Entomol. Res.* 85:267–74
148. Prapanthadara L, Promtet N, Koottathep S, Somboon P, Ketterman AJ. 2000. Isoenzymes of glutathione *S*-transferase from the mosquito *Anopheles dirus* species B: the purification, partial characterization and interaction with various insecticides. *Insect Biochem. Mol. Biol.* 30:395–403
149. Prapanthadara L, Ranson H, Somboon P, Hemingway J. 1998. Cloning, expression and characterization of an insect class I glutathione *S*-transferase from *Anopheles dirus* species B. *Insect Biochem. Mol. Biol.* 28:321–29
150. Prapanthadara L-A, Koottathep S, Promtet N, Hemingway J, Ketterman AJ. 1996. Purification and characterization of a major glutathione *S*-transferase from the mosquito *Anopheles dirus* (species B). *Insect Biochem. Mol. Biol.* 26:277–85
151. Raghavendra K, Vasantha K, Subbarao SK, Pillai MKK, Sharma VP. 1991. Resistance in *Anopheles culicifacies* sibling species B and C to malathion in Andhra Pradesh and Gujarat states, India. *J. Am. Mosq. Control Assoc.* 7:255–59
152. Ramsdale CD. 1975. Insecticide resistance in the *Anopheles* of Turkey. *Trans. R. Soc. Trop. Med. Hyg.* 69:226–35
153. Ranson H, Claudianos C, Ortelli F, Abgrall C, Hemingway J, et al. 2002. Evolution of supergene families associated with insecticide resistance. *Science* 298:179–81
154. Ranson H, Cornel AJ, Fournier D, Vaughan A, Collins FH, Hemingway J. 1997. Cloning and localization of a glutathione *S*-transferase class I gene from *Anopheles gambiae*. *J. Biol. Chem.* 272:5464–68
155. Ranson H, Jensen B, Vulule JM, Wang X, Hemingway J, Collins FH. 2000. Identification of a point mutation in the voltage-gated sodium channel gene of Kenyan *Anopheles gambiae* associated with resistance to DDT and pyrethroids. *Insect Mol. Biol.* 9:491–97
156. Ranson H, Nikou N, Hutchinson M, Wang X, Roth CW, et al. 2002. Molecular analysis of multiple cytochrome P450 from the malaria vector, *Anopheles gambiae*. *Insect Mol. Biol.* 11:409–18
157. Ranson H, Prapanthadara L, Hemingway J. 1997. Cloning and characterisation of two glutathione *S*-transferases from a DDT resistant strain of *Anopheles gambiae*. *Biochem. J.* 324:97–102
158. Rasgon JL. 2008. *Wolbachia* and *Anopheles* mosquitoes. In *Insect Symbiosis*, ed. K Bourtzis, TA Miller, pp. 321–27. London: CRC Press. 384 pp.
159. Rathor HR, Toqir G. 1980. Malathion resistance in *Anopheles stephensi* Liston in Lahore, Pakistan. *Mosq. News* 40:526–31
160. Rathor HR, Toqir G. 1981. Mode of inheritance of malathion resistance in *Anopheles stephensi* Liston. *Mosq. News* 41:359–67
161. Rathor HR, Toqir G, Reisen WK. 1980. Status of insecticide resistance in anopheline mosquitoes of Punjab Province, Pakistan. *Southeast Asian J. Trop. Med. Public Health* 11:332–40
162. Reeder JC, Targett GA, Shanks GD, Greenwood BM. 2009. Killing the parasite. In *Shrinking the Malaria Map a Prospectus on Malaria Elimination*, ed. RGM Feachem, AA Phillips, GA Targett, pp. 127–39. San Francisco: Global Health Group
163. Reiss RA, James AA. 1993. A glutathione *S*-transferase gene of the vector mosquito, *Anopheles gambiae*. *Insect Mol. Biol.* 2:25–32
164. Ripley Ballou W. 2007. Obstacles to the development of a safe and effective attenuated pre-erythrocytic stage malaria vaccine. *Microb. Infect.* 9:761–66
165. Rishikesh N, Dubitiskij AM, Moreau CM. 1988. Malaria vector control: biological control. See Ref. 201, pp. 1227–49

166. Roman MS, Andrew WF, Ian D, Valerie JC. 1986. Potentiation of super-kdr resistance to deltamethrin and other pyrethroids by an intensifier (factor 161) on autosome 2 in the housefly (*Musca domestica* L.). *Pestic. Sci.* 17:483–88
167. Rowland M, Mohammed N, Rehman H, Hewitt S, Mendis C, et al. 2002. Anopheline vectors and malaria transmission in eastern Afghanistan. *Trans. R. Soc. Trop. Med. Hyg.* 96:620–26
168. Rozeboom LE, Johnson R. 1961. Inheritance of resistance to dieldrin in *Anopheles albimanus* Wiedemann. *Am. J. Trop. Med. Hyg.* 10:775–81
169. Sauerwein RW. 2007. Malaria transmission-blocking vaccines: the bonus of effective malaria control. *Microb. Infect.* 9:792–95
170. Schofield CJ, White GB. 1984. House design and domestic vectors of disease. *Trans. R. Soc. Trop. Med. Hyg.* 78:285–92
171. Scott JG, Georghiou GP. 1986. Malathion-specific resistance in *Anopheles stephensi* from Pakistan. *J. Am. Mosq. Control Assoc.* 2:29–32
172. Service MW. 2008. *Medical Entomology for Students*. Cambridge, NY: Cambridge Univ. Press. 289 pp.
173. Severini C, Menegon M, Di Luca M, Abdullaev I, Majori G, et al. 2004. Risk of *Plasmodium vivax* malaria reintroduction in Uzbekistan: genetic characterization of parasites and status of potential malaria vectors in the Surkhandarya region. *Trans. R. Soc. Trop. Med. Hyg.* 98:585–92
174. Sharma SK, Tyagi PK, Padhan K, Upadhyay AK, Haque MA, et al. 2006. Epidemiology of malaria transmission in forest and plain ecotype villages in Sundargarh District, Orissa, India. *Trans. R. Soc. Trop. Med. Hyg.* 100:917–25
175. Sharp BL, Ridl FC, Govender D, Kuklinski J, Kleinschmidt I. 2007. Malaria vector control by indoor residual insecticide spraying on the tropical island of Bioko, Equatorial Guinea. *Malar. J.* 6:52
176. Shekalaghe S, Drakeley C, Gosling R, Ndaro A, van Meegeren M, et al. 2007. Primaquine clears submicroscopic *Plasmodium falciparum* gametocytes that persist after treatment with sulphadoxine-primethamine and artesunate. *PLoS ONE* 10:1023
177. Shetty NJ, Rajasree BH. 1998. Genetic and biochemical studies on deltamethrin (a synthetic pyrethroid) resistance in *Anopheles stephensi*—a malaria mosquito. *Toxicol. Lett.* 95:149
178. Shirayama Y, Phompida S, Kuroiwa C. 2008. Monitoring malaria control in Khammouane province, Laos: an active case detection survey of *Plasmodium falciparum* malaria using the Paracheck rapid diagnostic test. *Trans. R. Soc. Trop. Med. Hyg.* 102:743–50
179. Singh N, Shukla MM, Dash AP. 2009. Control of malaria in Central India (Madhya Pradesh): hope or hype? *Trans. R. Soc. Trop. Med. Hyg.* 103:209–10
180. Smith A. 1962. Malaria in the Taveta area of Kenya and Tanganyika. *East Afr. Med. J.* 39:553–64
181. Smith A. 1965. Malaria in the Taveta area of Kenya and Tanzania. *East Afr. Med. J.* 43:7–18
182. Smith A, Pringle G. 1967. Malaria in the Taveta area of Kenya and Tanzania. *East Afr. Med. J.* 44:469–74
183. Smith DL, McKenzie FE, Snow RW, Hay S. 2007. Revisiting the basic reproductive number for malaria and its implications for malaria control. *PLoS Biol.* 5:42
184. Smith DL, Smith TA, Hay SI. 2009. Measuring malaria for elimination. In *Shrinking the Malaria Map a Prospectus on Malaria Elimination*, ed. RGM Feachem, AA Phillips, GA Targett, pp. 108–26. San Francisco: Global Health Group
185. Snow RW, Trape J-F, Marsh K. 2001. The past, present and future of childhood malaria mortality in Africa. *Trends Parasitol.* 17:593–97
186. Soe-Soe, Khin-Saw-Aye, Htay-Aung, Nay-Win, Tin-Aung, et al. 2001. Premunition against *Plasmodium falciparum* in a malaria hyperendemic village in Myanmar. *Trans. R. Soc. Trop. Med. Hyg.* 95:81–84
187. Sutherland C. 2007. A challenge for the development of malaria vaccines: polymorphic target antigens. *PLoS Med.* 4:0413–14
188. Temel T. 2004. Malaria from the gap: need for cross-sector co-operation in Azerbaijan. *Acta Trop.* 89:249–59
189. Torres EP, Salazar NP, Belizario VY, Saul A. 1997. Vector abundance and behaviour in an area of low malaria endemicity in Bataan, the Philippines. *Acta Trop.* 63:209–20
190. Touré YT, Oduola AMJ, Morel CM. 2004. The *Anopheles gambiae* genome: next steps for malaria vector control. *Trends Parasitol.* 20:142–49

191. Trape J-F. 2001. The public health impact of chloroquine resistance in Africa. *Am. J. Trop. Med. Hyg.* 64:12–17
192. Tripet F, Wright J, Cornel A, Fofana A, McAbee R, et al. 2007. Longitudinal survey of knockdown resistance to pyrethroid (kdr) in Mali, West Africa, and evidence of its emergence in the Bamako form of *Anopheles gambiae* s.s. *Am. J. Trop. Med. Hyg.* 76:81–87
193. Utarini A, Winkvist A, Ulfa FM. 2003. Rapid assessment procedures of malaria in low endemic countries: community perceptions in Jepara district, Indonesia. *Soc. Sci. Med.* 56:701–12
194. van Agtmael MA, Eggelte TA, van Boxtel CJ. 1999. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. *Trends Pharmacol. Sci.* 20:199–205
195. Van Bortel W, Trung HD, Thuan LK, Sochantha T, Socheat D, et al. 2008. The insecticide resistance status of malaria vectors in the Mekong region. *Malaria J.* 7:102
196. Vittal M, Deshpande LB. 1983. Development of malathion resistance in a DDT, HCH resistant *Anopheles culicifacies* population in Thane district (Maharashtra). *J. Commun. Dis.* 15:144–45
197. Vontas JG, Small GJ, Hemingway J. 2001. Glutathione *S*-transferases as antioxidant defence agents confer pyrethroid resistance in Nilaparvata lugens. *Biochem. J.* 357:65–72
198. Vulule JM, Beach RF, Atieli FK, McAllister JC, Brogdon WG, et al. 1999. Elevated oxidase and esterase levels associated with permethrin tolerance in *Anopheles gambiae* from Kenyan villages using permethrin-impregnated bednets. *Med. Vet. Entomol.* 13:239–44
199. Vythilingam I, Chan ST, Shanmugratnam C, Tanrang H, Chooi KH. 2005. The impact of development and malaria control activities on its vectors in the Kinabatangan area of Sabah, East Malaysia. *Acta Trop.* 96:24–30
200. Walker K, Lynch M. 2007. Contributions of *Anopheles* larval control to malaria suppression in tropical Africa: review of achievements and potential. *Med. Vet. Entomol.* 21:2–21
201. Wernsdorfer WH, McGregor SI, eds. 1988. *Malaria Principles and Practice of Malariology.* New York: Churchill Livingstone
202. Wernsdorfer WH, Payne D. 1988. Drug sensitivity tests in malaria parasites. See Ref. 201, pp. 1765–800
203. WHO. 1957. *WHO Expert Committee on Malaria, sixth report (WHO Tech. Rep. Ser. No. 123)*. Geneva: WHO. **http://whqlibdoc.who.int/trs/WHO_TRS_123.pdf**
204. WHO. 2001. Malaria vectors and approaches to their control in malaria affected countries of the WHO European Region. The Proc. Reg. Meet. Vector Biol. Control. *EUR/01/5027499*
205. WHO. 2004. *RBM partnership consensus statement on insecticide treated netting and indoor residual spraying*. **http://www.rollbackmalaria.org/partnership/wg/wg_itn/docs/RBMWINStatementVector.pdf**
206. WHO. 2005. *Atlas of Insecticide Resistance in Malaria Vectors of the WHO African Region*. Geneva: WHO
207. WHO. 2005. World malaria report. *WHO/HTM/MAL/2005.1102*
208. WHO. 2006. Guidelines for the treatment of malaria. *WHO/HTM/MAL/2006.1108*
209. WHO. 2006. Indoor residual spraying, use of indoor residual spraying for scaling up global malaria control and elimination. *WHO/HTM/MAL/2006.1112*
210. WHO. 2006. Informal consultation on malaria elimination: setting up the WHO agenda. *WHO/HTM/MAL/2006.1114*
211. WHO. 2008. World malaria report 2008. *WHO/HTM/GMP/2008.1*
212. Winstanley P, Ward S. 2007. Malaria chemotherapy. In *Control of Human Parasitic Diseases*, ed. DH Molineux, pp. 47–76. London: Academic
213. Winstanley PA. 2000. Chemotherapy for *falciparum* malaria: the armoury, the problems and the prospects. *Parasitol. Today* 16:146–53
214. Wondji CS, Morgan J, Coetzee M, Hunt RH, Steen K, et al. 2007. Mapping a quantitative trait locus (QTL) conferring pyrethroid resistance in the African malaria vector *Anopheles funestus*. *BMC Genomics* 8:34
215. Wright JW, Fritz RF, Haworth J. 1972. Changing concepts of vector control in malaria eradication. *Annu. Rev. Entomol.* 17:75–102
216. Yohannes K, Dulhunty JM, Kourleoutov C, Manuopangai VT, Polyn MK, et al. 2000. Malaria control in central Malaita, Solomon Islands: 1. The use of insecticide-impregnated bed nets. *Acta Trop.* 75:173–83

217. Zahar AR. 1984. Vector control operations in the African context. *Bull. WHO* 62(Suppl.):89–100
218. Zaim M, Aitio A, Nakashima N. 2000. Safety of pyrethroid-treated mosquito nets. *Med. Vet. Entomol.* 14:1–5
219. Zhakhongirov SM, Abdullayev IT, Ponomarev IM, Muminov MS. 2004. Monitoring the insecticidal resistance of main malaria carriers in Uzbekistan. *Meditsomskaia Parazitol. Parazit. Bolezni* 2004(Pt. 1):29–32

Annual Review of Entomology
Volume 55, 2010

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Entomology* articles may be found at http://ento.annualreviews.org/errata.shtml