INTRODUCTION

When one looks over the global distribution of malaria in the 21st century, it is difficult to realize how widespread the disease has been and how its distribution has diminished during the past 150 years. This is important because in many places it may have the potential to return if appropriate climatic conditions prevail. Historically, malaria fever (ague) was reported in one form or another from parts of southern and eastern England and seasonally in Holland, Germany, across central and southeastern Europe, much of Asia, India, China, almost all the Americas, and of course most tropical regions (20). In North America the disease existed in large areas extending as far north as New York and even Montreal (15). During the U.S. Civil War, possession of quinine was vital for the warring forces to ensure that large numbers of the men were not incapacitated by the disease (107). During the mid-19th century, evidence of malaria became more sporadic and the disease receded from most of central Europe although it remained entrenched in the Mediterranean region and the Balkans (85). In the United States, major modifications of mosquito habitat through the Tennessee Valley Authority malaria control program, habitat degradation, deforestation, flooding, and other effects of development restricted the habitat of the malaria mosquito Anopheles quadrinaculatus and led to the local decline of malaria (33). Its eventual disappearance was probably due to improvements in life-style, screened housing, and the eventual absence of the reservoir within the human population. During that period, the prevalence of malaria in temperate areas of Europe was declining without spe-

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chial efforts (85), while in southern Europe and Turkey, where the disease was more endemic, elimination was achieved with the advent of DDT. Expanded mosquito control programs during the period from 1950 to 1970 finally brought success in many parts of the world through the concerted efforts of the World Health Organization (WHO) (47). (Table 1)

In spite of these successes, the fabric of many of these expanded control programs began to unravel during the early 1970s. The appearance of mosquitoes resistant to DDT and other residual insecticides (12), as well as the extreme difficulties involved in the supervision and financing of the various programs, led to problems which became overwhelming. This can be seen in Sri Lanka, a country with high levels of epidemic transmission in the past. During an epidemic in 1934, 60,000 new cases were being reported daily (19). Malaria eradication commenced in Sri Lanka in 1947, and in 1963, at the height of the eradication programs, only 17 cases were recorded throughout the country. Mass population movements into forested areas and the withdrawal of intradomiciliary spraying with DDT due to the advanced level of control achieved (i.e., transition from attack phase to consolidation phase) contributed to faltering control, and in 1969, over 500,000 cases were reported in the country (42). This situation was not unique. Numerous other problems arose because of inadequate field research and also because eradication was a concept dreamed up by over-enthusiastic authorities who showed little flexibility in their drive for completion of the plans (57).

Even in temperate countries from which malaria has disappeared, the vector mosquitoes still exist as a sort of biological time bomb. Particularly with the threat of global climate change, all that is required is the reintroduction of sufficient numbers of gametocyte carriers for the disease possibly to start up again in epidemic proportions (67).

At the advent of the new millennium, malaria continues to plague mankind as a burgeoning problem without any signs of abatement (47). The current world malaria situation is probably no better that it was 30 years ago, when the emphasis on eradication was replaced by a somewhat defeatist holding program (121). This new strategy allowed countries to adopt less than effective “control” programs, many which were based entirely on the distribution of the cheap, effective drug chloroquine. This has resulted, in part at least, in a series of problematic situations which eventually led to the breakdown in health services and the loss of skilled personnel dedicated to the study and control of malaria in areas of endemic infection. Additionally, there were biological problems which arose from widespread resistance of the parasite to the most effective and best-tolerated drugs and selection of vector mosquitoes which became resistant to many available insecticides.

WHO has attempted to address this deteriorating situation by holding a ministerial-level conference to develop a strategy to address malaria (123). This culminated in the global strategy for malaria control entitled “Roll Back Malaria,” which is now in the process of implementation. The strategy, which is not without critics (12) was developed mainly to address African conditions, where malaria is most serious. One of the arms of this approach calls for the use of antimalarial drugs in an almost unrestricted basis through clinics and health centers and even in the home following simple diagnosis. There is little emphasis on an integrated approach to malaria control (Table 2).

### GLOBAL STRATEGY FOR MALARIA CONTROL

#### Background

Attitudes regarding malaria during the past century have fluctuated between hope during periods when worldwide control seemed in reach, and despair as problems seemed to mount in spite of massive research efforts. For the most part, research thrusts have focused on the development of new drugs and vaccines (7), with decreasing emphasis on conditions in the field (124). Now, with the advent of the new century, we are faced with a situation which in many ways is far worse than in the 1950s, when the plans for eradication were first introduced (119). Countries where infection is endemic have lost much of the infrastructure which could be used to mount a systematic attack on the parasite and its transmission. Parasite resistance to available antimalarials is spreading and has rendered treatment increasingly difficult for most people exposed to infection (116). In some instances, the possibility of untreatable multidrug-resistant malaria looms precariously (12).
During the past 40 years or so, major decisions were made which guided the world body in its quest to attack malaria and to address the overall health programs in developing nations 

TABLE 2. Global strategy for malaria control

<table>
<thead>
<tr>
<th>Item</th>
<th>Technical elements (WHO 1993)</th>
<th>Implementation objectives</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Provide early diagnosis and prompt treatment</td>
<td>Develop paradigms for presumptive diagnosis by mothers or rural health workers; provide treatment in home and clinic (120)</td>
<td>Difficult to implement, particularly when second-line drugs are required. Many false positives (10, 35)</td>
</tr>
<tr>
<td>2</td>
<td>Plan and implement selective and sustainable preventive measures, including vector control</td>
<td>Expand use of ITN’s, encourage partnerships, train personnel</td>
<td>Lack of national implementation strategies may lead to disjointed programs; some partners have specific goals (e.g., UNICEF concentrates on pregnant women and children under 5 yr); this is not malaria control; regular change of personnel</td>
</tr>
<tr>
<td>3</td>
<td>Detect, contain or prevent epidemics</td>
<td>Develop epidemiological surveillance</td>
<td>Few training opportunities occur in countries with endemic infection also difficult to provide satisfactory career opportunities leading to a brain drain</td>
</tr>
<tr>
<td>4</td>
<td>Strengthen local capacities in basic and applied research to permit and promote the regular assessment of a country’s malaria situation, in particular the ecological, social, and economic determinants of the disease</td>
<td>Provide training opportunities for local scientists, regular planning on regional basis</td>
<td></td>
</tr>
</tbody>
</table>

Adopted by Ministerial Conference, October 1992 (120).

Points of discussion at the July meeting of the WHO-Southern African Malaria Control programme, Victoria Falls, Zimbabwe, 22 to 29 July 2001.

Decentralization of Health Services

In the meantime, the ability to control malaria has deteriorated in countries with endemic infection (106). Within these countries, major donors of aid have directed efforts toward promotion of decentralization of health programs, not specifically to handle malaria but to provide more services to the rural poor. The process of decentralization has had an insidious effect on the local infrastructure as the technical support for such developing nations to attack malaria, or even to develop rationally planned control interventions, has been eroded (48). Whereas the concept of decentralization is an appropriate basis for dispersing meager health services to the periphery, particularly in rural areas, when a professional scientific body of experts is somehow decentralized the result can be devastating. As with all scientific endeavour, a critical mass of experts is needed to facilitate the work. If these units are broken up and decentralized, the professional interaction is lost and the staff eventually will seek other, more stimulating activities, leading to a brain drain. Moreover, these staff cannot easily be replaced, particularly in the atmosphere of decreasing salaries and bureaucratic deterioration seen in these countries. The study of malaria and its epidemiology and control is a highly technical enterprise, requiring a body of experienced scientists to maintain oversight and efficient monitoring of the local situations. Without these personnel, ministries of health are not able to formulate rational malaria control strategies and hence become dependent on imported technical advisors who are usually unfamiliar with local conditions and whose advice may not be appropriate (103). It becomes difficult for the ministries to plan effectively for the efficient use of dwindling resources, and conditions then deteriorate to the crisis situation we now observe. In the light of this state of affairs, one needs to consider the various options available to malaria-endemic nations to control malaria in the most effective manner in their own ecological regions. Hopefully, it is for others to consider the hurdles that have been placed before these nations so that appropriate help may be given in the immediate future.

Past Achievements

Malaria control as propounded by various expert committees on malaria was a successful enterprise in many ways. It is frequently forgotten that by 1966 malaria eradication programs globally had freed some 525 million people (34% of the population living in previously malarious areas) from the threat of this disease (Table 1). In the Americas, concerted malaria control efforts, using both vector control and treatment, had achieved great success, with massive declines in infection being seen throughout the region (21). The successful attacks on malaria produced a strong infrastructure of personnel. Well-trained cadres of malaria control specialists were employed and carried out regular house spraying, treatment of cases detected by active surveillance, and collection of statistics for
assessments of the effects (50). In 1959, the Annual Parasite Index (the number of positive blood slides per 1,000 population) for the whole region of Latin America was 0.39. Sadly, by 1996 the Annual Parasite Index had increased eightfold and was 2.46 for the region; for people living in malarious areas, it was 12.5 (21).

Clouds on the Horizon

By 1966 the problem of anopheline resistance to DDT had become clear. There were 15 species resistant to DDT and 36 resistant to dieldrin (127); equally important, chloroquine resistance was reported in Southeast Asia and South America (120). Although eradication programs had achieved considerable success (Table 1), the WHO Expert Committee in 1968 adopted a definition that “Areas with technical problems are those where the planned single or combined attack measures correctly applied have failed to interrupt transmission.” By 1973, the changes in programs were extensive, with a totally new approach developed based on implementation of so-called tactical variants, which identified a series of levels under which control programs should operate. These ranges from a reliance on chemotherapy alone to reduce mortality (Tactical Variant 1) to a reliance mainly on chemotherapy and limited protection factors for reduction and prevention of mortality and morbidity, particularly in high-risk groups (Tactical Variant 2). Finally, with Tactical Variant 4, countrywide malaria control was the ultimate objective (120, 121). This change of strategy began the decline in many national malaria control programs. The effect of this on the control programs in the Americas has been disastrous—a profound decrease in house spraying and a depletion of trained operatives has resulted in an upsurge in malaria (21, 45) To illustrate, 1,500 cases were reported from Loreto Province in Peru in 1965 while 121,268 cases occurred in 1997 (44).

WHO surveillance has revealed that areas of western Asia, Armenia, Azerbaijan, and Tajikistan from which malaria had been eradicated in the 1960s had started to report cases of malaria, with several thousand cases occurring in 1994 (12, 126). Similar increases have been reported in Turkey (126) and Iraq (126); more recently, in South Korea there has been a logarithmic increase in vivax malaria between 1993 and 1997 (36). The reasons for this are difficult to summarize, but underlying the situation is a loss of international drive to consider the malaria problem holistically, and part of that is the design behind the Global Strategy for Malaria Control (12).

In a well-reasoned argument, Baird (12) supports the message of Butler and Roberts (21) and has delivered a warning to public health administrators. Both authors think that the two factors which contributed most significantly to the past control and reduction of malaria were (i) the use of DDT as an indoor spray to attack the vector mosquitoes and (ii) the widespread use of chloroquine as an effective chemotherapeutic. The emergence of chloroquine resistance and the deterioration of national control programs that applied DDT (and other insecticides) have been coincident with the upsurge of malaria. Currently, the Global Strategy for Malaria Control, which was designed as a lifeline for Africa (Table 2), emphasizes early diagnosis and prompt treatment as the major line of attack. While this is appropriate for immediate survival of severe cases, there is no evidence that it will effectively reduce the transmission of malaria. Lack of emphasis of the role of vector control as an intervention against malaria has restricted integrated approaches to malaria control (106). Authorities (12, 21) feel that this strategy is setting the stage for further spread and increase of malaria, not only because it deemphasizes vector control but also because it inevitably leads to misuse of drugs (home diagnosis and treatment), which will lead to an increase in parasite resistance and further escalation of the malaria problem (10, 35, 94).

In light of these warnings, it is pertinent now to examine the tools available for malaria control and consider how they may be used in an integrated approach to regulate this reemerging problem of malaria in the new millennium.

BASIC CONCEPTS OF MALARIA CONTROL

Biological Basis

Malaria is a focal disease with extremely varied epidemiology based largely on the reservoir, which may or may not be asymptomatic, and the biting patterns and vectorial capacity of the vector mosquitoes. Initially, this complex relationship was not well understood, and after the discoveries by Grassi and Ross of the role of mosquitoes in the parasite cycle (20), these insects became the main target of control efforts (85). In the absence of methods to kill adult mosquitoes, the strategy was to reduce breeding sites. Accordingly, a considerable effort was made to drain swamps and marshes and to somehow limit the populations of mosquitoes, whether vectors or not. The Pontine marshes near Rome and the Hula swamps in Israel are often used as examples of success in eliminating vector populations (33). However, as pointed out by White these examples were not necessarily applicable elsewhere (118). The Sardinian project (1946 to 1951) against Anopheles labranchiae confirmed that it was difficult to eradicate an endemic vector by systematic larvicide application or, even when insecticides were available, by targeting adults by house spraying (58, 85). The point is that if eliminating mosquito vectors is not an option, what then can be done?

Macdonald concentrated on mathematical models of malaria transmission and foresaw the importance of the prepatent period within the infected mosquito (61). Subsequently, by estimating the duration of prepatency in a mosquito after its infective blood meal and the variable life span of female anopheline mosquitoes, he reasoned that transmission could be interrupted by reducing mosquito survival to less than the duration of sporogony (the mosquito stage of the parasite leading to the production of infective sporozoites). He suggested that this would be more effective in controlling transmission than merely reducing the mosquito density (61). This is, in fact, the main reason why indoor spraying is far superior to larvicide application or space spraying to attack the mosquito populations. To explain this concept, it is necessary to understand vectorial capacity.

Vectorial capacity (C) defines the efficiency of a mosquito species to act as a vector of the malaria parasite. It is expressed by the formula $C = ma^2p^m - \log p$ (38, 39), where C is vectorial capacity, m is the relative density of female anopheline mosquitoes to humans, a is the probability that a mosquito will
feed on a human in a day, \( ma \) is the number of times a person is bitten per day, \( p^* \) is the proportion of the vector population that survives the incubation period of the parasite in the mosquito, and \( 1/\log_{10} p \) is the number of days that this proportion is expected to survive. The formula defines the critical role of the vector in determining the incidence of infection in any community and supports the theory behind indoor use of contact insecticides or insecticide-impregnated bed nets. It calculates the actual level of transmission as well as the epidemiology and pattern of illness seen in communities with endemic infection (89). In this expression, \( p^* \) greatly outweighs the importance of mosquito density in relation to humans (\( ma \)).

Thus, for the purpose of limiting transmission, it is more effective to reduce mosquito longevity than to reduce mosquito density (118).

This point needs to be reiterated continuously because it is forgotten frequently by those who recommend source reduction, “environmental management,” and other ill-defined concepts (93) which serve little purpose other than to deflect scarce resources to abating populations of nuisance mosquitoes. It is interesting that as early as 1931, systematic house spraying with pyrethrum was introduced (53). The concept was “not intended to destroy all Anopheles gambiae, but only those which are infected. . .largely to be found indoors” (118).

The duration of mosquito survival after an infective bite forms the fundamental basis for the use of indoor spraying or of insecticide-impregnated bed nets to control transmission. The duration of sporogony, the period following ingestion of infective gametocytes by a susceptible mosquito prior to the maturation of sporozoites and their migration to the salivary glands, is dependent on the prevailing temperature conditions. For Plasmodium falciparum, sporogony development in the mosquito is inhibited when the ambient temperature falls below about 20°C and lasts approximately 10 days at temperatures between 25 and 30°C. With P. vivax, development is more rapid at the higher temperature (approximately 6 days) but proceeds, although slowly, even at temperatures around 16°C (61). With all blood-fed mosquitoes, and particularly members of the genus Anopheles, the females become heavy and vulnerable after a feed, flying to a nearby surface, where they rest and commence digestion (40). Usually the meal is taken during the night, and the mosquitoes will seek a secluded corner or hard surface as a refuge. If this surface is treated with insecticide, the mosquito may acquire a lethal dose. However, even if only a partial (sublethal) dose is acquired, the mosquito may survive but must take a blood meal every 2 to 3 days in order to accomplish oviposition and ensure survival of the species. Thus, before a mosquito can transmit malaria parasites, it will very probably return to feed two or three times, and at each occasion it is vulnerable to exposure to insecticide. The role of the insecticide applied to the walls of a hut, room, or mosquito net is not necessarily to kill the mosquito immediately but to provide a sufficient dose to kill the mosquito before the infection becomes patent (41). In spite of the current high level of research into the biology of the malaria parasite, control of malaria transmission for the foreseeable future will continue to depend on these basic principles.

### Strategies for Control

Malaria control is too complex to be addressed by a single approach, and any attempt to do so is fraught with danger. It is important to tailor the strategy to the prevailing ecological and epidemiological conditions (78). To illustrate this, definitions of the four main patterns of epidemiology (Table 3) are based on indicators which can be measured in the community. Of significance, the immune status of the population and the patterns of malaria seen will be different in these four situations and will also affect the strategy for control. Therefore, these will be dictated by the prevailing transmission patterns and will be orientated to the following outcomes: (i) mortality control, (ii) transmission control, and (iii) eradication.

#### Mortality control

The major impact of malaria in any community is that of the death of individuals. To prevent a person dying from the disease, appropriate treatment is necessary. The strategy of mortality control involves detecting presumptive cases, determining which cases are parasite positive, and administering effective treatment. Such a strategy has little impact on morbidity due to malaria and has little or no effect on the overall transmission of the disease. In areas of hypoendemic infection, this morbidity results in a major burden on the population (66).

Mortality control is the main thrust of the current “Global Malaria Control Strategy” (Table 2) (123). Since it relies on chemotherapy, no particular program is required, nor is there any need for nationwide strategies and the development of local priorities. All that is required is some means for record keeping and a system for distribution of the drugs of choice to

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### Table 3. Classification of levels of endemicity of malaria transmission

<table>
<thead>
<tr>
<th>Endemicity level</th>
<th>Transmission</th>
<th>Parasite rate (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoendemic malaria</td>
<td>Low: subperiodic or sporadic</td>
<td>Usually &lt;10%</td>
<td>Mosquito populations unstable, usually difficult to detect; serious epidemics may occur</td>
</tr>
<tr>
<td>Mesoendemic malaria</td>
<td>Seasonal or periodic following good rains</td>
<td>11–50, depending on survey timing</td>
<td>Mosquito populations fluctuate, detectable seasonally; seasonal outbreaks occur; some detectable immunity in the population</td>
</tr>
<tr>
<td>Hyperendemic malaria</td>
<td>Intense transmission (seasonal) each year</td>
<td>51–75</td>
<td>Seasonal fluctuation in malaria cases; severe sequelae frequent in young children; some immunity in adults</td>
</tr>
<tr>
<td>Holoendemic malaria</td>
<td>Transmission may occur throughout the year with periods of high transmission</td>
<td>&gt;75</td>
<td>Mosquitoes detectable throughout the year although with seasonal peaks; high levels of anemia in very young children; immunity seen in adults</td>
</tr>
</tbody>
</table>

<sup>a</sup> Rate in children aged 5 to 10 years.
the peripheral clinics. Training is minimal and could also involve local commercial outlets for antimalarial drugs. It is an effective stopgap strategy to cope with epidemics of malaria when emergency situations arise (125). In crisis situations such as severe flooding or epidemic outbreaks, it is the strategy of choice because the tools can be mustered simply and quickly. The main problem is that chemotherapy alone is not a means of controlling malaria and is not sustainable in the long term. There are good data to indicate that treatments obtained from unskilled sources are frequently inappropriate and often ineffective and may promote drug resistance in the parasite population (18, 35, 76). The first-line drugs in current use, chloroquine and pyrimethamine-sulfadoxine, are becoming less effective due to increasing resistance. Replacement drugs are costly and may not be acceptable for use in understaffed clinics. Effective diagnosis would help with this problem. However, despite the availability of rapid diagnostics that are readily interpreted by unskilled clinic workers (71, 91), little effort is made to introduce them into widespread use. Persistence with chemotherapy alone will buy time but will create very serious problems in the future.

This global strategy was endorsed by the technical expertise present to advise Ministers at the Amsterdam Conference, but it was not without its critics. The Hon Timothy Stamps, Minister of Health for Zimbabwe, noted “If one considers the final tables in the Global Strategy, one can only presume these to be sterile impractical assumptions of a disintegrating scientific technology. No significant guidance was offered for countries like Zimbabwe which needs to protect her precious human resources.” As a result of the adoption of the Global Strategy, the Zimbabwe Ministry of Finance refused to continue with the old programs and reduced annual expenditure on malaria control from 3 million to 0.8 million U.S. dollars (106). Such concerns are currently expressed, perhaps with greater discretion but nevertheless with the same urgency, by Baird (12).

**Transmission control.** The transmission control strategy recognizes that malaria is an important cause of morbidity as well as mortality. The disease is extremely debilitating and extracts a high price from the communities affected. Children are anemic and unable to concentrate at school (90, 98), and society as a whole is debilitated. Whereas appropriate treatment is one aspect of the transmission control strategy, vector control is also a major player, and, properly applied, these aspects together have an impact on both the mortality and morbidity of malaria. This approach is effective in most epidemiological conditions (Table 3) and is an effective control strategy for a sustained attack on the malaria problem. It is adaptable to the use of insecticide-treated mosquito nets as well as indoor spraying of insecticide (26, 30, 50). It can be implemented in specific circumstances where malaria is a local priority or on a wide scale as part of a major program of intervention. Transmission control requires coordination and the development of strategic plans to intervene against malaria (50). A high level of expertise is needed with personnel trained in epidemiology and vector control as well as in planning, mapping, and communications to coordinate and supervise the operations. However, these would be the prerequisites in countries which have made commitments to controlling malaria.

Concerns have been raised by some health authorities (24, 66) that transmission control will eventually reduce local immunity acquired from longstanding infection in the population. This is true. Effective transmission control will reduce the incidence of infection and reinfection in the community, and eventually people will lose their acquired immunity. Therefore, such interventions should be planned in a sustainable manner. It is incumbent on the local government to recognize this when making commitments to malaria control. However, the technique can be incorporated into national malaria control schemes on a stage-structured basis in areas of high priority. It is even possible to create barriers to seasonal encroachment of vector populations and the potential for transmission to invade populated areas or towns (51).

**Eradication of malaria.** Eradication can be considered only in certain areas, e.g., in places where malaria has been eradicated and where it has been reintroduced and in areas of hyperendemic malaria where there are sufficient resources to undertake the process and where there is little likelihood of future introduction. The advantage of an eradication program is that it is time limited and, once it has achieved its objective, can be terminated with little further oversight (119). In Table 1 the relative successes of the various malaria control activities commenced in the mid-20th century period are outlined. Clearly, eradication programs were extremely successful, but eradication could not be achieved in many places and the technique must be considered not appropriate in most areas of endemic infection.

**TOOLS TO CARRY OUT MALARIA CONTROL**

**Personnel and Strategy Development**

Malaria control is a scientific, technical activity that requires skilled and dedicated staff with training in epidemiology, entomology, mapping and planning, and manpower management. Since much work is in the field, it requires personnel prepared to undertake field work. This is not an arena for pure clinicians or laboratory scientists, and although all play a role in the fight against malaria, the control operations are the realm of malarologists (45). The most important tools to control malaria consist of properly trained personnel with authority to coordinate and carry out their scientific work (94).

The rest of the tools to control malaria are still fundamentally similar to those used for eradication and control programs, i.e., the use of insecticides directed against adult mosquitoes to reduce the pressure of transmission in the human population and effective treatment to cure cases as they are diagnosed. In spite of years of research, there are no new techniques; in fact, with the advent of drug-resistant *P. falciparum*, we now have a less effective battery of drugs which can be applied safely in community-wide programs (37, 48).

What has been learned over the past several decades is that specific control strategies should be developed for specific country conditions and that there is not a “one set fits all” method available. We now understand the ecological conditions which affect and regulate the distribution and abundance of mosquito populations (41). Essentially, efforts to control malaria must be sustainable and rely on the double-pronged attack while the sustainability of programs will depend greatly on the local resources available and should not depend only on donor support. The extent of a sustainable control program
will, of necessity, depend mainly on local resources, which will then dictate local priorities. The simplest approach, therefore, is to rely on widespread chemotherapy in populations at risk. However, wherever possible (and even in areas of restricted priority) this should be combined with vector control (96). The use of vector control is not an ancillary factor that can be conveniently disregarded. It is essential not only to reduce transmission but also to prevent the development of drug resistance within the parasite population (76). There are good examples from Zimbabwe of the synergistic effects of the two methods where integrated malaria control has been in effect in selected areas for over 50 years (111; K. Day, personal communication). In a recent nationwide survey, chloroquine resistance has been found to occur with frequency in only three districts in spite of its use as the first-line drug for all that time and in spite of the advent of widespread chloroquine-resistant P. falciparum parasites in surrounding countries, e.g., Zambia (16, 69, 76). Additionally, combined vector control and prophylaxis using Deltaprim (pyramethine-dapsone) has been under way on a large sugar estate covering a resident population of 50,000 persons for over 40 years. The local Chief Medical Officer indicates that there is no transmission of malaria or breakthrough in prophylaxis on the estate, whereas transmission does occur in adjacent areas (A. Morar, 2001, personal communication).

Environmental Management

In a variety of texts, environmental management is proposed to reduce the number of breeding sites and overall populations of vector species (93, 96, 122). As mentioned above, there have been some situations where source reduction was effective (85). However, on the whole, anopheline mosquitoes are opportunistic breeders that favor open sunlit pools or small streams and rivulets (Table 4). In most cases it is impractical to suggest source reduction as an effective control effort for anophelines. Since anophelines are opportunists, their populations expand during rainy spells and they breed in such a variety of situations that any attempts to limit the extent of suitable habitat will not be very successful. Importantly, it is not the number of mosquitoes that is critical in the cycle but, rather, the length of mosquito survival which contributes to the efficient transmission of malaria (40, 60).

Controlling mosquito breeding sites by using spreading oils or by source reduction is often promoted by health authorities as a means of limiting nuisance mosquitoes. This is commendable since the pests are a considerable irritant to the human population as well as to domestic animals; however, most peri-domestic breeding mosquitoes are culicines, which are not involved in the transmission of human malaria. However, under certain conditions, e.g., in India, where important vectors (A. culicifacies and A. stephensi) are swamp or pool dwellers, drainage, the use of larvivorous fish (guppies), or even introduction of polystyrene beads into some habitats may effectively reduce some populations of mosquitoes by reducing the survival of larvae and pupae (97). However, the reduction is temporary if not properly managed, and even in India this strategy does not control an alternative vector, A. fluviatilis; hence, it has only limited effect on malaria transmission (108).

Any program to control malaria must be tailored to the species of vectors which are involved in transmission. Antimalaria interventions should be implemented in a coordinated manner by an authority which has the technical support and political power to carry out the programs. In several countries, particularly in Africa, numerous projects are operated through a number of agencies which are uncoordinated and which may have a variety of agendas. Each might provide some local effect, but none will be sustainable without a national program which is developed to meet the goals of the local people (government) and which will be sustained and supervised by governmental agencies. Sporadic, uncoordinated short-term interventions are not part of a goal-orientated integrated malaria control intervention. Even the Global Strategy acknowledges the coordinating role of government (123). This is necessary to set priorities which will benefit the nation and help develop a strategy and to fund and implement the control program (124).

Intradomicile Application of Residual Insecticides

Intradomicile application of residual insecticides, also referred to as indoor spraying, has been the mainstay of malaria control operations since the early parts of the last century. Because the rationale for this method is based on the feeding and resting habits of most malaria vectors, it is important first to understand these characteristics of the species of concern. While crepuscular (twilight) feeding patterns have been noted in a few instances, the majority of important vectors feed late at night, with peak biting activities between the hours of 20:00 and 05:00 nightly (117). Although some species prefer to feed outdoors, endophagy (indoor feeding) is most common (78, 117).

### TABLE 4. Larval breeding sites of Anopheles spp.

<table>
<thead>
<tr>
<th>Type of habitat</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent or semipermanent standing freshwater</td>
<td>Large open marshes or marshy margins to lakes and ponds</td>
</tr>
<tr>
<td></td>
<td>Small ponds, pools or borrow-pits; spring-fed pools and seepages</td>
</tr>
<tr>
<td></td>
<td>Standing water in fields, rice fields, open wells, forest pools or swamps</td>
</tr>
<tr>
<td>Transient freshwater collections</td>
<td>Open pools in fields, stagnant water in streambeds and cattle hoof-prints, pools in car tracks and road ruts</td>
</tr>
<tr>
<td>Permanent or semi-permanent running freshwater</td>
<td>Open streambeds with vegetation or running over gravel</td>
</tr>
<tr>
<td>Brackish water</td>
<td>Marshes, ponds and swamps (not tidal), ponds near salt pans and vleis (dambo)</td>
</tr>
<tr>
<td>Tidal swamps</td>
<td></td>
</tr>
<tr>
<td>Container habitats (seldom used by anophelines)</td>
<td>Rock holes, tree holes, plant axes and epiphytic water-bearing plants</td>
</tr>
<tr>
<td>Discarded containers (natural and artificial), tins, and tires</td>
<td></td>
</tr>
<tr>
<td>Crab holes and cracks in drying mud; water cisterns</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 5. Comparison of six insecticides used for house spraying* (WHOPES-approved products)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Organochlorine (DDT 75% WP)</th>
<th>Organophosphates</th>
<th>Carbamates</th>
<th>Pyrethroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application rate (g of ai/m²)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Residual efficacy duration (mo)</td>
<td>6–12</td>
<td>2–3</td>
<td>4</td>
<td>2–3</td>
</tr>
<tr>
<td>Cost (US$/kg (product)</td>
<td>3</td>
<td>7</td>
<td>8</td>
<td>2.5</td>
</tr>
<tr>
<td>Cost (US$/house (200 m²)</td>
<td>1.6</td>
<td>5.6</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Operational cost ratio²</td>
<td>1.1</td>
<td>5.6</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>Stains walls?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Controls other pests?</td>
<td>No</td>
<td>Some</td>
<td>Some</td>
<td>Yes</td>
</tr>
<tr>
<td>Odor?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Refusals?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

a Adapted from reference 118 with permission of the publisher. These insecticides are WHOPES-approved products.

b The operational cost ratio is defined as the cost per house/freight-saving factor and is given in U.S. dollars for 1996.

c ai, active ingredient.

Application. The proper application of insecticide is not trivial and, if incorrectly carried out, may be quite ineffective. Although applications can be done by unskilled personnel, a high level of supervision is necessary (50, 96). The work is difficult and usually involves hot and sometimes cramped conditions; people tire easily and need encouragement. Additionally, inefficient spraying and even misuse of the insecticide could occur if supervision is lacking or conniving. To prevent or control this, it is necessary for rigorous inspection to be carried out frequently.

Since spray operations are critical in regulating the actual treatment of the walls and eaves and around immovable furniture, a period of training is necessary (96). Wettable powder formulations cause abrasion of the spray nozzles, and so these need to be inspected regularly to ensure correct application of the spray (118). Ideally, spray solutions should be made up at a concentration which will treat a specific number of rooms (Table 5). Before application of insecticide, all furniture, hanging clothing, cooking utensils, food, and other items should be removed from the house and left covered outside. Indoor spraying is a very intrusive operation. Strangers are admitted into one’s private space, which is often a major problem to the homeowner. It also involves heavy lifting to remove items of furniture and personal effects prior to the spraying. If there are no real perceived benefits such as destruction of pests or nuisance insects, people soon object to the work, and so it is important to ensure an ongoing public-relations effort to explain procedures and motivate the community.

Selection of insecticides. A variety of insecticides are currently available, and the most appropriate for specific conditions must involve careful study by entomologists (Table 5) and support of local opinion. For example, the use of DDT or similar wettable powder may introduce transport costs, since the formulation is heavy and difficult to transport by bicycle. In the past, organophosphate insecticides such as malathion (Table 5) were substituted for the organochlorines DDT and BHC (118, 128). However, the cost and increased household disruption involved with the repeated applications needed for effective mosquito control have made these compounds unpopular. If these insecticides are replaced by Deltamethrin or Icon, much less material is required and a daily supply can be easily transported by bicycle (5, 110). Other features such as odor and wall staining are important and must be reviewed with the community. Finally, there is the element of cost; however, decisions about supply and expense are usually the subject of commercial tenders, and final selection is often done by independent sources.

Planning. Planning indoor spraying operations requires considerable effort on the part of the health authorities and involves careful mapping of all houses, location of the roads and routes of access, and generation of the daily work allocation to ensure that the community is appropriately warned before the arrival of the spray teams etc. There should be means for identification of houses so that the records of the spray teams can be checked on the ground. All the logistics, supplies, and transport needs must be delineated and budgeted so that the teams and supervisors all know their duties, allowing the daily schedule to be properly carried out (50, 111).

Insecticide-Treated Mosquito Nets

The development of synthetic pyrethroid insecticides which are stable and remain effective for long periods enabled entomologists to test the idea of impregnating mosquito nets of various textures and fabrics as a vehicle for residual insecticide. Much has been written about this technique, which is now well understood and has proven effective (26, 29, 52, 54) (Table 6). The initial seminal research was carried out in a series of huts in Tanzania (52). The well-designed experiments of Lines et al. answered several important questions before the rationale for the use of insecticide-treated mosquito nets (ITNs) could be established (56). In a series of trials with volunteers sleeping either under treated nets or under or adjacent to a treated net or in huts with no nets at all, the effects on the viability of exiting mosquitoes was discerned through the use of window and eave exit traps. Nets treated with permethrin were used for this work, and the excito-repellency of this insecticide was discernible in the results. Blood-fed mosquitoes were found in exit traps, but there was higher mortality among mosquitoes exiting rooms with treated nets than among mosquitoes exiting rooms where no treatment was used. This effect was seen with nets of various dimensions, nets with holes, or torn nets and even when nets were improperly tucked in or when people slept on wood frames without mattresses (56).

It is important to return to the basic concept of transmission control, i.e., reduction of vector life span. Conceptually, the
nets serve as a vehicle for the insecticide. Any ingressing mosquito must probe the protecting surface until either it is repelled or finds a hole to enter. This may happen with a treated net, and the mosquito can take a blood meal. When satiated, the insect must then probe again, trying to find an exit. During the process it will acquire a dose of insecticide. This may not be immediately lethal, but over several feeding excursions the insect will probably acquire sufficient insecticide to die and thus not transmit the infection (40).

The use of ITNs is a new and somewhat revolutionary tool for effective vector control. There is very little infringement on personal privacy, and the application of insecticide does not involve seasonal upheaval of furniture, clothing, etc. The method even provides effective protection from a major source of nuisance, that of nightly disturbance by mosquitoes (102), as well as destroying bed bugs and other pests (114). However, it is necessary to note that untreated or improperly treated nets alone do not provide effective protection from mosquito bites, and touting them as a means of personal protection may be misleading. Mosquitoes can feed through the net when body parts touch the netting, and access through small holes is well known.

Although ITNs are effective (52), there has to be extensive coverage and use of nets to achieve a substantial reduction in malaria transmission, in the same way that this needed for indoor spraying to be effective (17, 30). In a Tanzanian project, household coverage approached 75%, and contributed to a reduction in slide positivity (relative risk, 0.45) and febrile episodes (relative risk, 0.38) and improved weight gain in children younger than 5 years who slept under treated nets (90, 98). There was also a major impact on the density of infected mosquitoes in the protected areas (99, 113). There is little doubt about the efficacy of the system in reducing both child mortality and morbidity (3, 82). The use of ITNs could be integrated into any national malaria control strategy. Depending on the behavior patterns of the local vector species, ITNs could replace indoor spraying in many instances (74). The main problem to be addressed is the process of implementing and sustaining operations which are dependent on community support. Whereas indoor spraying can be carried out by government edict in a centrally planned, vertical-type program, ITNs can be introduced only in a systematic manner via a well-informed and committed community. Public information is a necessity and must be seen as an ongoing activity.

**TECHNIQUES FOR IMPLEMENTATION OF ITN PROGRAMS**

**Finance and Subsidy**

Any discussion about financing public health programs raises the important issue of subsidy, particularly when one section of society bears the impact. To what extent can the overall cost be shared? In developed countries, impoverished communities are seldom expected to bear the entire brunt of a public health intervention which in the long run will benefit the nation as a whole. This reviewer asks, should not those communities embracing malaria control activities for both personal and public good be entitled to some subsidy to defray their individual costs? One proceeds with an assumption of a response in the affirmative, even in light of certain agencies requiring full cost recovery. While such cost recovery may appease many economists, this is not the basis of public health.

There are several approaches for financing the distribution of ITNs as a means of vector control, ranging from outright gifts to sale of the items at commercial or subsidized prices. In the first situation, there is the hope that recipients will respect the items and use them for the purpose of malaria control. Alternatively, agencies are encouraging the sale of treated nets as a commercial activity promoted by advertising, together with some health education and some form of cost recovery (9). It is now accepted that the concept of sale and private ownership of mosquito nets is likely to be acceptable and result in their general use (9, 65, 105). Current information indicates that with the more active pyrethroids, e.g., deltamethrin, annual treatment will be sufficient (28). Merely handing out the nets does not mean they will be used, and there is considerable risk that many of the free nets will be sold on the open market by the recipients rather than used for protection against malaria. More importantly, if they are part of an overall strategy for malaria control, then the system will not achieve its overall

<table>
<thead>
<tr>
<th>Activity</th>
<th>Critical implementation conditions</th>
<th>Implementation process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td>Concept should be incorporated in a national malaria control program based on vector control</td>
<td>Nets and insecticide sold or distributed to target communities</td>
</tr>
<tr>
<td>Promotion (type 1)</td>
<td>Education to inform and convince population; supervision and coordination by community leaders (or malaria action committee)</td>
<td>Community involvement</td>
</tr>
<tr>
<td>Promotion (type 2)</td>
<td>Role for trained technical support staff; overall supervision and monitoring of all implementation activities</td>
<td>Strong, motivated support scientists; need overall authority for coordination and control</td>
</tr>
<tr>
<td>Affordability</td>
<td>Public are asked to bear some costs; need for marketing of commodities and subsidy to purchasers; arrangements for assisting impoverished persons</td>
<td>Honest and transparent financial transactions under coordinating authority</td>
</tr>
<tr>
<td>Insecticide use</td>
<td>Proper treatment and reimpregnation of nets is essential; education of target communities, careful supervision, and motivation needed</td>
<td>Supervision and control by dedicated technical personnel</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Trained epidemiologists, entomologists, and support staff must be employed by malaria control authority</td>
<td>Deployment of trained staff to collect data; adequate facilities including transport; computerized support</td>
</tr>
</tbody>
</table>
objective. With personal ownership in mind, there are two main approaches to consider.

The first is the sale of subsidized ITNs, with the proceeds or profits being converted into a community-held revolving fund that pays for sustaining community participation, purchase, and distribution of replacement nets as needed (79). If nets retail at approximately 75% of the street price, people are not inclined to sell or otherwise dispose of them (9, 102). These nets and additional insecticide can be obtained with some subsidy through the commercial sector, and the whole enterprise would be overseen by trained research and control officers who are retained by the Ministry of Health. Such a system was developed by the Bagamoyo Bednet Project (65).

The second is the promotion and sale of necessary items through a process of “social marketing” within the community. The nets and insecticide are packaged attractively and made available for sale through commercial outlets, although the promotional activities and some of the distribution costs are underwritten via large donor agencies (62, 105). A large project under the name KINET has reported success in southern Tanzania but with subsidies of 33 and 83% for the nets and insecticide, respectively (9). Reports available on these activities usually focus on the success of sales but omit anything about reimpregnation activities (105).

These systems both require an input of external financial support because the full commercial cost of both nets and insecticide will preclude ownership and use by large sections of the public. If ownership of ITNs is limited to those who can afford them or to a small section of the community such as pregnant women, these individuals may get some personal protection but the efforts will not contribute to malaria control and could not be considered an effective element of a public health intervention against malaria.

Reimpregnation

A key element in the ITN program is the need for nets to be retreated regularly with insecticide. Without reimpregnation, the nets will lose their function as vector control agents. It is essential that concerted efforts be made to ensure that people understand that the nets must be retreated regularly (annually) and that they should bring the nets to a center to have this done (or treat the nets themselves) (72, 73, 102). This task requires effort on behalf of the community and the supervisory staff. Also, logistics concerned with procurement, distribution, and use of insecticides must be put in place. Misuse of the insecticides must be scrutinized to ensure proper retreatment activities, and cash flow must be transparent and properly managed. In rural areas where community participation is an integral part of the program, financial remuneration for the workers may be necessary; this can best be done with a revolving fund where the interest accruing may be used for payment of services rendered by the committee (65, 102).

The issue of regular retreatment of nets has been the subject of much research and debate (9, 27, 29, 75). It is now considered that ITNs operate with similar efficiency to indoor spraying programs but with certain advantages (Table 6). Industry has developed single-dose tablets of deltamethrin (KO-Tabs) for individual use, but these packages are more expensive than group treatments. Large-scale treatments usually cost about 20 to 30 cents (U.S. currency) per net for the insecticide. Recently, nets produced under the name Permanet and treated with a proprietary formulation of deltamethrin have been claimed to remain insecticidal for up to 4 years. Curtis (C. F. Curtis, abstract from the Vector Control Workshop hosted by the London School of Hygiene and Tropical Medicine in September 2001, abstr. 2.2, 2001) has tested these pretreated polyester nets, but there has not been sufficient time to determine the duration of insecticidal efficacy. In comparative trials, the knockdown time for bioassay with mosquitoes (300 s) was similar for both Permanet and normal nets treated with the same dose of deltamethrin; even after 20 successive launderings, the knockdown time was similar (600 s), and data suggest that the Permanet polyester nets were more wash resistant than conventional nets treated with deltamethrin (28). This information does not disprove the efficacy claims of Permanet, but this is an area of critical research.

**Sustaining the Intervention**

Interested and motivated communities are important to sustain an intervention. For this to be effective, people should know what is expected of them and what they will receive in return. There should be a clear statement of activities, responsibilities, and rates of remuneration for people who provide time to do the work (65). This can be done if the scopes of work are defined and codified in a “constitution” that is agreed upon collectively. This was done in Bagamoyo, and the final document approved by the various communities contained details of membership, specifying the membership composition (i.e., the number of women, teachers, and medical personnel) and means of election. Each job category, the activities involved, the number of formal meetings to be held, their frequency, and the specific activities which were to be reviewed were described (65). To maintain a consistent level of remuneration, the interest accruing from the revolving fund was to be distributed among the personnel according to the number of hours worked and individual achievements. This program was to be reviewed by a medical official, e.g., the malaria officer, a member of the local Ministry of Health staff. Money could be removed from the fund established in the Bagamoyo district only with a cheque bearing three signatures, two from the committee and one from the malaria officer, thus ensuring that funds were, for the most part, used appropriately.

The alternative method proposed for sustaining interventions, that of social marketing, while popular with donor agencies, has also raised queries (9, 105). Despite considerable public relations work and initial advertising, there is no evidence as yet that it will be effective in controlling malaria in any national program or that the system will be sustained without continual financial input from the donors.

**STRATEGIES BASED ON BIOLOGICAL CHARACTERISTICS OF MALARIA TRANSMISSION**

**Barrier Spraying**

Under certain conditions, particularly when there are strong seasonal fluctuations in vector mosquito populations and the species survive the winter by seeking refuge in warmer, humid
areas, barriers to mosquito invasion can be created by limited but intense vector control operations. Properly designed, these will help prevent the periodic invasions of areas of hypoendemic infection or areas vulnerable to severe epidemics. Such areas are usually in proximity to regions where transmission is more seasonal and dependent on rainfall; in the green areas, transmission is unstable and seasonal; transmission in the yellow areas, above the 1,200-m contour, is hypoendemic or nonexistent. The districts between 900 and 1200 m (green) represent the area routinely sprayed in the past antimalaria program. In these areas, both vector control and chemotherapy were undertaken. In other areas, the Ministry of Health relied on chemotherapy alone that was provided through the rural clinic services to prevent outbreaks of malaria. The green zone acted as a barrier to prevent the encroachment of malaria onto the high plateau, which was the most heavily populated part of the country.

An example used in Zimbabwe was based on Leeson’s observations that A. gambiae sensu lato and A. funestus found winter refuges in the northeast of that country (51) (Fig. 1). In the spring, as conditions warmed in the areas above 900 m, vector species began to invade the upland areas and could be collected in pools along river valleys, progressively moving into more temperate areas. From these refuges, malaria spread into the adjacent farming and urban areas with devastating effects. A concerted system of intradomiciliary spraying across these lines of invasion just prior to the seasonal warming period served to protect invasions of high-density population areas, which were of economic importance to the country (5, 6). The importance of altitude and temperature in the seasonal ebb and flow of malaria under hypo- and mesoendemic conditions was stressed by Taylor and Mutambu (111). These data support the successful malaria control operations which guided the Ministry of Health in Zimbabwe for over 50 years and which have only recently been inadvertently dismantled. This dismantling is a result of the drive to decentralization required by international donors and has contributed to recent increases in transmission (1.8 million cases of clinical malaria recorded in 1998) (8).

The concept of barrier spraying can be applied in numerous epidemiological situations, provided that there is sufficient ex-
pertise to plan and execute the operations. Such methods could be implemented wherever there is a concern about seasonal encroachment into areas which are considered to be a high priority by local health authorities and politicians.

Structured Malaria Control

Situations occur where health authorities must attempt to protect defined communities from epidemics or reduce the overall intensity of malaria transmission. Under such circumstances, the area and community affected would be identified through specific local health priorities and may expand over wide stretches of country; however, the extent of the work would be limited by the availability of a sustained flow of financial resources. Examples would be large agricultural or industrial complexes, mines, and even cities or large population centers (115), as well as major areas which fall into the malaria control strategy of the country where the infection is endemic. In such instances it is feasible to design and plan interventions based on sustained vector control operations. These would commence just before the start of the main transmission seasons and would have to be maintained in a high state of coverage for the duration of the transmission period.

Such interventions require coordination and planning as well as the cooperation of the local communities involved. Because the programs involve and protect the overall community and even other population groups living in adjacent areas, it is important that all sectors of the community are kept informed and participate wherever possible. It is quite feasible for communities to select the type of vector control intervention which they feel is the most suitable, because in the long run, sustained success will depend on local interest and effort. Here again, levels of subsidy and remuneration must be negotiated, because it is essential that high levels of compliance are achieved in the vector control activities.

This structured approach would incorporate both vector control and chemotherapy. It would be feasible for the community to be protected with prophylaxis if the level of organization can cope with the logistics. In instances where effective vector control is in place, there should be little likelihood of breakthrough of resistant parasites. As mentioned above, the combination drug Deltaprim (pyrimethamine-dapsone) has been used in such circumstances in southeastern Zimbabwe for over 40 years with no discernible side effects and little evidence of failure in a community of approximately 50,000 persons (A. Morar, personal communication).

Evaluation of Efficacy

There is no need to review past results of the use of indoor spraying to control transmission of malaria; its efficacy is well known and accepted (47). However, the effect of ITNs remains a matter of debate, mainly because there has not been a major sustained national program in operation outside China (59) and because in the areas of holoendemic infection where most trials have been carried out, these trials have been of short duration, lasting at the most 5 years. However, the indications are good, and one can expect that sustained ITN programs will be successful. Original trials in The Gambia (32) and Tanzania (64) showed a decline in the number of infective mosquitoes and an improvement in indicators of both malaria infection and morbidity in the control area. Similar reports have come from elsewhere in Africa (68, 82, 89, 99) and from other sources quoted in Net Gain (52). It has been noted that ITNs may not reduce the overall population of mosquitoes; crepuscular (twilight-loving) forms and many culicine species are not always reduced in number (74). Even specimens of vector mosquitoes are still found in experimental traps, but since few of these are actually infected, the effect achieved is to reduce transmission (68, 113). An ITN program which will reduce the life expectancy of vector mosquitoes will thus achieve the effect predicted by the vectorial capacity model.

INSECTICIDES, INSECTICIDE RESISTANCE, AND MALARIA CONTROL

A list of some commonly used insecticides, together with cost-effective ratios, is given in Table 5. Although not exhaustive, it does cover the various classes of insecticides in use and enables comparisons to be made. Unfortunately, mention of DDT is contentious these days, and therefore some comments are appropriate. The advent of DDT and other chlorinated hydrocarbon insecticides provided the mainstay of malaria control after World War II. In fact, DDT was initially developed as a public health insecticide prior to its widespread use in agriculture and its identification as a major environmental pollutant (25). In spite of widespread use and exposure of humans across the globe, this insecticide has been relatively safe for use in public health programs as long as it is not spread into the environment. When used for indoor spraying, environmental contamination is greatly restricted, thus avoiding entry of the pesticide into the global food chain (10).

Resistance is also important. Widespread use of any insecticide will probably lead to the selection of resistant forms of the target organism. This has happened in several countries and with several vector species. However, in spite of its prolonged use over nearly 50 years, DDT is still effective in many parts of the world. Being a cost-effective insecticide for indoor spraying, DDT still plays an important role in some malaria control programs. More recently introduced (although developed for agriculture) pyrethroid insecticides have been extremely valuable in public health use. In spite of the widespread agricultural usage, Curtis (28) has reported little or no evidence of pyrethroid resistance among the important vectors in eastern Africa. In South Africa however, workers have demonstrated significant resistance of A. funestus to pyrethroids and have recommended reintroduction of DDT spraying in KwaZulu/Natal (46). In a recent symposium held under the auspices of the American Association for the Advancement of Science, the case was made not to ban DDT as a noxious pollutant because of its importance at a public health pesticide (94). Considerable debate has taken place about the role of DDT in public health. The reader is referred to a detailed summary of a recent discussion by Taverne (109). Properly used, the insecticide is applied in small quantities to indoor walls. As such, it is unlikely to contribute to the outdoor pollution problem, and it can help save many lives in the less advantaged, malaria-endemic regions of the world. However, indoor application of insecticides may impact the vector population in unexpected ways. In a recent review of malaria,
Phillips (89) quotes workers from Brazil who mention changes in the behavior of *A. darlingi*, which, although previously endophilic (indoor resting), now moves outdoor soon after feeding and thus is less exposed to insecticide than earlier in the control operations. Similarly, in Africa, indoor spraying has eliminated the endophilic *A. gambiense* in some areas, only to have it replaced by the more exophilic *A. arabiensis* (46). However, transmission by the latter species can still be controlled by indoor spraying of insecticide (47).

**DIAGNOSIS OF INFECTION**

As with all infections, rapid diagnosis must be integral to an appropriate treatment program. However, diagnosis of malarial infection is, for all practical purposes, the purview of village health workers, trained or untrained nurses, and some medical officers. Ideally, it should be done in a timely manner by trained medical laboratory technologists, but even then malaria parasites are difficult to see. This is often exacerbated when staining conditions are not optimal, a situation which often happens in rural settings. Even under hospital conditions where staff are usually under severe pressure, it is difficult to obtain results in a timely fashion; hence, most diagnoses in regions of endemic infection are based on clinical symptoms. When the patient is nonimmune, clinical indications are usually suggestive of malaria, but in areas of endemic infection these are extremely misleading and fraught with inaccuracies. Studies in northeastern Zimbabwe of 104,000 cases over a 12-month period showed that fewer than 30% of diagnoses made by trained nursing staff operating at rural clinics were slide positive (P. Taylor and A. Taputaira, Zimbabwe Sci. Assoc. First Natl. Symp. Sci. Technol., 1988). A similar result was noted in Madagascar, where only 12% of 6,884 presumptive diagnoses carried out in hospitals between 1997 and 1998 were found to be slide positive (2). This discrepancy is not always seen. In Ghana, malaria diagnosis at a health center was shown to be 62% slide positive (35). However, this was still three times more accurate than in home diagnoses (35). Unskilled home diagnosis is likely to be the most inaccurate means of diagnosing malaria and will result in high proportions of unnecessary and inappropriate treatments.

In response to the obvious need for rapid, easily interpreted diagnostics, a series of rapid malaria tests have been developed based on detecting parasite-specific circulating antigens such as HRP-2 (86). The dipstick tests use specific monoclonal antibodies to detect these antigens and reveal positive reactions with a colored line as in the *ParaSIGHT-F* test (91, 100). Over time, new products have been developed which use similar monoclonal antibodies. The ICT-PI/Pv test, which detects HRP-2 of *P. falciparum* and also a unique antigen expressed by *P. vivax* (49, 92), is thus able to discriminate between these two parasites. Both these antigen capture tests perform well with high sensitivity and specificity and have been extremely widely tested. Since they detect circulating antigen, these assays remain positive for about 10 days following treatment (100). These tests may also cross-react with rheumatoid factor (43), but that does not reduce their exceptional value for rapid and effective diagnosis of both important malaria parasites (71). An additional dipstick test which detects the enzyme lactate dehydrogenase and so also recognizes both parasite species has been tested in Central America (84) and India (104). This test has the advantage of turning from positive to negative in about 5 days after effective elimination of the parasites. Selection of the appropriate test is probably most dependent on cost, an issue which precludes the more widespread use of these important diagnostic procedures at this time.

Because of the importance of these tests in the overall Global Strategy of Malaria Control, there should be some drive to subsidise or reduce costs for the tests in countries where infection is endemic in order to make them economical and of greater value in malaria treatment programs. Perhaps this would be a role for Roll Back Malaria or WHO.

**TRAVEL MEDICINE AND PROBLEMS DUE TO GLOBAL CLIMATE CHANGE**

The problem of imported malaria is gaining notoriety in developed countries. *MMWR* Reports from CDC (www.cdc.gov) have shown gradually increasing numbers of cases detected in the United States, peaking at over 2,000 in 1980, but since then the case detection rate has remained around 1,600 annually. In the United States this presents a hazard of initiating so-called cryptic cases, which are probably mosquito borne. Several good vectors of malaria exist in the country, *A. heims* in California and *A. quadrimaculatus* in the south and much of the east; these species are capable of picking up gametocytes and initiating foci of transmission (45; *MMWR* Reports [www.cdc.gov]). Imported malaria is of increasing concern in Europe (83). In Aberdeen, over a 5-year period 110 cases of malaria were diagnosed; 60% of patients had *P. falciparum* infections, and the remainder were mainly *P. vivax* infections. The majority of infections were acquired due to lapse or absence of prophylaxis (63). A similar casual attitude has been reported from the United States, where records in San Francisco over a 10-year period ending in 1997 show that only 23% of travelers to areas of endemic infection had been compliant with antimalarial prophylaxis and none of these had developed infection (34).

Diagnosis of these imported cases is critical because of the life-threatening condition which may develop from a *P. falciparum* infection. A recent study in Italy comparing genus-specific PCR and Southern blot species-specific hybridization with rapid diagnostics and microscopy showed the advantage of both good-quality microscopy and the rapid diagnostic tests in securing a rapid and accurate diagnosis. PCR and microscopy had 100% agreement, while the rapid *ParaSIGHT-F* test showed a specificity and sensitivity of 94% (88).

With the impending changes in global climates, the problem of imported malaria will become more widespread because of the spread of malaria into new areas of endemicity and the cavalier attitude regarding prophylaxis among overseas travelers (63). In areas of endemicity, encroaching transmission has been reported in areas previously free of transmission. This is likely to be a response to warming conditions or else to periods of prolonged summer rains which occur as a result of extreme climatic episodes, which are becoming more frequent. Examples of this can be seen with the advent of malaria epidemics in the highlands of Madagascar (2); Kenya, where transmission may encroach on Nairobi and the Kenya highlands; and Uganda, where similar encroachment is happening (55) as well as in Lusaka, where malaria transmission occurs occasionally.
although the city was previously free of transmission (14). When conditions favor the extension of transmission into these previously malaria-free zones, increasing numbers of travelers are likely to return home with prepatent infections.

MALARIA VACCINES

Attempts to develop a malaria vaccine began early in the 20th century, and in spite of advances in biomedical technology and periodic bouts of unsubstantiated optimism in the field, no effective vaccine is available for use (95). It is not the purpose of this review to cover the current status of malaria vaccine development. However, mention of the various strategies pursued by research workers is in order so that we can develop a perspective of how vaccines may be utilized in controlling malaria.

The development of malaria vaccines has become the focus of considerable research. On the basis of research with rodents, scientists in the early 1970s demonstrated that irradiated sporozoites of P. falciparum and P. vivax inoculated into naive volunteers would provide protection against challenge from fully infective mosquitoes (7, 23). The main opportunity for this work to flourish occurred following the decisions to reduce emphasis on eradication programmes in the early 1970s (120). This was a period when discoveries in molecular techniques were incorporated into the studies of the malaria parasite. The fact that P. falciparum was amenable to in vitro cultivation prompted this species to become the main focus of study, an emphasis which has lasted until the present. The situation with P. vivax is more difficult because this species cannot yet be cultured in vitro. With P. falciparum the research effort has followed three main routes. The first has been to try and destroy circulating sporozoites before or during early stages of infection of hepatocytes to produce a sterile immunity. The second has been directed against the blood stage antigens of the parasite trophozoites in an attempt to reduce the virulence of infection and, by preventing further development of schizonts, to interrupt reproduction. Finally, there is an approach to prevent the development of sexual forms, and if they do develop, to attack the maturing forms when ingested by the vector mosquito. This last strategy is called transmission-blocking immunity. Cocktails of these vaccines are being contemplated (95).

Research has brought several candidate vaccines through phase 1 and in some cases phase 2 of vaccine development. The only vaccine to reach phase 3 was a multicomponent synthetic peptide, SPf66, which was claimed to have protective effects in trials in Columbia (87). The vaccine was tested in a series of trials in holoendemic situations in Africa (4, 31) and showed marginal, if any, protection. Finally, no protection was seen by senior administrators such as Gro Brundtland, Director General of WHO. In response, the Roll Back Malaria initiative has arisen with backing from the United Nations Development Program, World Bank, United Nations Children's Fund, and WHO (80). Philanthropic organizations such as the Gates Foundation, the National Institutes of Health, and others have added resources to this body, so that the enterprise has considerable opportunity to make an impact. The initiative is examining various strategies to do this. However, to any observing malarialogist, the main weakness globally is the dearth of trained, properly remunerated technical personnel prepared to work in the field (13).

Without local expertise to develop local strategies for the implementation of control programs, ministries of health will flounder in the process of implementation and their efforts will dissipate. The underlying necessity required to develop and sustain national programmes is to rebuild local infrastructure and expertise. This will require selection and training of local personnel from countries with endemic infection who have a commitment to learning about malaria and who will remain and develop their careers locally. There is a need for the local governments and also universities to offer such personnel the basic elements for career development (101, 103). This is the challenge for Roll Back Malaria, to help reestablish scientific civil services in areas of endemic infection since such organizations are the root of internal stability and drive. There is no easy solution, but one is essential otherwise we will have no real program for malaria control, neither this year nor in 10 years.

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