Role of Vector Control in the Global Program to Eliminate Lymphatic Filariasis

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Abstract

Lymphatic filariasis (LF) is a major cause of acute and chronic morbidity in the tropical and subtropical parts of the world. The availability of safe, single-dose, drug treatment regimens capable of suppressing microfilaremia to very low levels, along with improvements in techniques for diagnosing infection, has resulted in the targeting of this major mosquito-borne disease for global elimination. The Global Program to Eliminate Lymphatic Filariasis (GPELF) was launched in 2000 with the principal objective of breaking the cycles of transmission of *Wuchereria bancrofti* and *Brugia* spp. through the application of annual mass drug administrations (MDAs) to entire at-risk populations. Although significant progress in initiating MDA programs in endemic countries has been made, emerging challenges to this approach have raised questions regarding the effectiveness of using MDA alone to eliminate LF without the inclusion of supplementary vector control. Here, we review advances in knowledge of vector ecology, vector-parasite relationships, and both empirical and theoretical evidence regarding vector management to assess the feasibility and strategic value of including vector control in the GPELF initiative to achieve the global elimination of LF.

LF: lymphatic filariasis

Mf: microfilaremia

Mass drug administration (MDA): community-wide treatment of individuals with antiparasitic drugs regardless of the infection status of each individual

GPELF: Global Program to Eliminate Lymphatic Filariasis

ALB: albendazole

DEC: diethylcarbamazine citrate

Limitation: a negative feedback process in which a parasite (at any stage) compromises the success of parasites at the same or another stage

LYMPHATIC FILARIASIS

Lymphatic filariasis (LF) is a major cause of acute and chronic morbidity affecting humans in tropical and subtropical areas of Asia, Africa, the Western Pacific, and some parts of the Americas. More than 1.2 billion people are estimated to live in areas where they are at risk for the disease (86), and of the 120 million actual cases of LF currently thought to occur in 83 endemic countries, 91% are caused by *Wuchereria bancrofti* while *Brugia malayi* and *B. timori* infections account for the other 9% (42, 43, 66). These lymphatic-dwelling parasites can cause severe damage to the lymphatic system, resulting in the development of lymphedema, genital pathology (especially hydroceles), and elephantiasis in some 41 million men, women, and children (85). A further 76 million have hidden internal damage to their lymphatic and renal systems. The filarial parasites have biphasic life cycles involving the definitive mammalian host and various genera of mosquito vectors, including *Anopheles*, *Aedes*, *Culex*, *Mansonia*, and *Ochlerotatus*. *W. bancrofti* appears to be exclusively a human parasite, whereas *Brugia* spp. are zoonotic in limited situations. Parasite transmission is indirect and occurs through the bite of an infective mosquito containing third-stage infective larvae (L3) that have developed through two intermediate stages (L1 and L2) from microfilaremia (Mf) ingested with the blood meal taken by female mosquitoes on an infected human.

GLOBAL PROGRAM TO ELIMINATE LYMPHATIC FILARIASIS: EVOLUTION AND CURRENT STATUS

The absence of a nonhuman reservoir for *W. bancrofti* and only minor animal hosts for *B. malayi* means that transmission can be interrupted by reducing the Mf stage through mass drug administration (MDA) alone. This, along with the emergence of safe, single-dose, two-drug treatment regimens capable of reducing Mf to very low levels for one year or more and remarkable improvements in techniques for diagnosing infection, resulted in advocacy for a global strategy to eliminate the disease through MDA (16, 49). This led in 1997 to the landmark adoption by the World Health Assembly of Resolution WHA50.29 calling for the elimination of LF as a public health problem globally. As a result, in 2000 the World Health Organization, in collaboration with other international agencies from the public health and private sectors, formed a global alliance (84) and launched a global campaign to eliminate LF by the year 2020 (87). The main goal of the Global Program to Eliminate Lymphatic Filariasis (GPELF) is to break the cycle of transmission of the parasites between mosquitoes and humans, mainly through MDA with albendazole (ALB) in combination with either ivermectin (IVR) or diethylcarbamazine citrate (DEC) (53, 83, 84). The Ministries of Health of all 83 countries afflicted with LF are now committed to taking action by setting up their own national elimination programs. By the end of 2006, 44 of the 83 endemic countries had implemented MDA (86).

CHALLENGES TO MDA CAMPAIGNS

Despite the progress made in initiating MDA programs, a number of challenges to these programs have begun to appear. First, many countries initiating MDA have not reached national scale even after 5–6 years and some countries face major challenges in sustaining MDA, principally as a result of significant resource constraints (86). Resource limitations and availability of rapid diagnostic tests have hampered progress in mapping implementation units for MDA. Delivering MDA in urban areas has also posed operational challenges. Second, the exact level and duration of treatments to achieve LF elimination in different endemic regions remain unknown (44, 45), such that it is difficult to predict or decide when to stop ongoing MDA programs. Third, a major challenge to implementing MDA at a level required to meet elimination targets within a reasonable

time frame has been the difficulty of achieving the required high drug coverages in endemic communities (57). Fourth, there has been a shift recently toward linking MDA for LF control with programs for controlling other neglected tropical diseases, such as schistosomiasis, soil-transmitted helminthiasis, and onchocerciasis (31, 48). This integrated approach is proving to be an attractive alternative to an individual programmatic approach, because it is perceived to remove duplication of effort and costs in programs that share common activities. However, with different objectives (e.g., parasite control versus parasite elimination) and the potential increased complexity in drug delivery (e.g., move from school-based programs to community treatment in the case of soil-transmitted helminthiasis and schistosomiasis), it is unclear if this approach will result in enhancing or hampering the goal of LF elimination. Finally, concerns of the potential for filarial parasites under mass chemotherapeutic pressure to develop drug resistance raise questions regarding the effectiveness of using MDA alone to achieve successful LF elimination (46, 68).

GROWING RECOGNITION OF THE POTENTIAL AND NEED TO INCLUDE VECTOR CONTROL

The challenges to MDA programs have led to growing concerns regarding the effectiveness of using MDA alone to eliminate LF without the inclusion of vector control (12, 13). This is especially pertinent given that vector control was once advocated as the primary tool to control filariasis (66), and the approach was feasible in some epidemiological settings, as demonstrated by the elimination of *Anopheles*-transmitted filariasis from Solomon Islands (75, 77, 78) and Togo (9, 67) by indoor spraying with dichloro-diphenyl-trichloroethane (DDT). Control of mosquito-borne diseases through residual house spraying and community-wide distribution of long-lasting insecticide-treated netting materials (LLITNs) is also currently occurring in many countries where malaria and LF are coendemic and transmitted by the same mosquitoes (58). Similarly, vector intervention measures to control dengue are in place in many parts of the world where *Aedes* mosquitoes transmit LF (13). Thus, an integrated strategy involving vector control is now thought to have great potential to become an important supplementary component of the filariasis elimination strategy. Here, we review advances in knowledge of vector ecology, vector-parasite relationships, population dynamics of vector-based interventions, and integrated control involving antimosquito measures such as residual house spraying and distribution of LLITNs to evaluate the feasibility and strategic value of including vector control in the GPELF initiative to achieve the global elimination of LF.

Parasite control: reduction of infection incidence, prevalence, or morbidity to a locally acceptable level at which the parasitic infection is no longer considered a public health problem

Parasite elimination: reduction of the incidence of infection to zero in a defined geographic area

Dichloro-diphenyl-trichloroethane (DDT): one of the best known synthetic pesticides long used to control vectors

LLITNs: long-lasting insecticide-treated netting materials

VECTOR SPECIES DISTRIBUTION AND ECOLOGY

W. bancrofti and *B. malayi* are unique among the various mosquito-transmitted parasites in that larval development can take place in several genera of mosquitoes. Three main zones of transmission are recognized: the South Pacific islands and some limited areas of Southeast Asia, where *Aedes* vectors predominate; West Africa, Papua New Guinea, Vanuatu, and Solomon Islands, where *Anopheles* mosquitoes are principal vectors; and China, Southeast Asia, Egypt, East Africa, the Caribbean, and Latin America, where the infection is transmitted mainly by *Culex quinquefasciatus* and other members of the *Cx. pipiens* complex (81).

Culex Species

Mosquitoes of the *Cx. pipiens* complex, especially *Cx. quinquefasciatus*, are urban vectors of nocturnally periodic *W. bancrofti* in Asia, Africa, the West Indies, South America, and Micronesia. *Cx. quinquefasciatus* breeds in a wide variety of stagnant water habitats, including water barrels, wells, tanks, privies, fresh pools, ponds, and canals near houses, provided that the water has been sufficiently polluted. It is mainly a night-biting mosquito, although it occasionally

bites freely in darkened rooms during the daytime. Feeding is both indoors (endophagic) and outdoors (exophagic). The distribution of *Cx. quinquefasciatus* is increasing with urbanization and human activity, and many rural pockets that were relatively free of this mosquito are now increasingly colonized (20).

Aedes and *Ochlerotatus* Species (Tribe Aedini)

Aedes mosquitoes are involved in the transmission of *W. bancrofti* and *B. malayi* in South Asia and the Pacific regions. Chow (21) lists 15 species of *Aedes* as vectors of LF. The diurnal subperiodic form of *W. bancrofti*, in which the microfilariae are present in the blood during the day as well as in the night, occurs only in the South Pacific region and the most important vector is *Ae. polynesiensis*. Other important *Aedes* vectors are *Ae. niveus*, *Ae. poecilus*, *Ae. samoanus*, *Ae. scutellaris* group, and *Ochlerotatus togoi* (formerly called *Ae. togoi*). *Ae. polynesiensis* is the most important vector of the subperiodic form of *W. bancrofti* in the Polynesian region wherever it occurs (12, 14). It breeds in artificial and natural containers of rainwater, such as coconut shells, fallen coconut leaf bracts, discarded tins, old automobile tires, and drums, as well as in tree holes, canoes, and crab holes made in sandy beaches. It also breeds in the leaf axils of *Pandanus*. The females are generally exophilic and exophagic day-biting mosquitoes that feed mainly on humans outdoors, with a minor peak at 08:00 hours and a minor peak at 17:00–18:00 hours (12, 14).

Mansonia Species

Six species of *Mansonia* transmit Brugian filariasis. The nocturnal subperiodic form is known to occur only in Brunei, Malaysia, and the Philippines, where it is transmitted mainly by *M. annulata*, *M. bonneae*, *M. dives*, and *M. uniformis*. *M. uniformis* is the most widely distributed species of the *Mansonia* mosquitoes. It is a vector of periodic *B. malayi* in Sri Lanka, India, and Thailand (61). *M. annulifera* and *M. indiana* are minor vectors in Malaysia. *M. annulata* is also a vector of periodic *B. malayi* in Indonesia and Thailand (61). *Mansonia* mosquitoes generally breed in swamps and tend to be exophagic and exophilic. Biting occurs mostly during the day, with peak activity soon after sunset. They are predominantly zoophilic and, although primarily exophagic, readily enter houses to feed on humans.

Anopheles Species

In many rural areas, especially in Africa, LF is transmitted by *Anopheles* mosquitoes. Nelson (51) lists 26 *Anopheles* species as vectors of Bancroftian and Brugian filariasis. Eighteen species are vectors of *W. bancrofti*, three of *B. malayi*, and five species transmit both parasites. *An. barbirostris* is the only known vector of *B. timori*. In Africa, where no *Brugia* parasites of humans occur, the most important vectors of *W. bancrofti* are the *An. funestus* group and members of the *An. gambiae* complex—including the freshwater-breeding *An. gambiae* s.s. and *An. arabiensis*, as well as *An. melas* and *An. merus*, which breed mainly in saltwater (81). The ecology and behavior of the *An. gambiae* complex have been reviewed by Gillies and Coetzee (28). *Anopheles* vectors of *W. bancrofti* in Asia include *An. jeyporiensis candidiensis* and *An. minimus* in China; *An. flavirostris* in the Philippines; and *An. balabacensis*, *An. maculatus*, *An. letifer*, and *An. whartoni* in Malaysia (81). The *An. punctulatus* group of mosquitoes, including *An. punctulatus*, *An. koliensis*, and *An farauti*, are the principal vectors of periodic *W. bancrofti* in Papua New Guinea, West Papua (Indonesia), Solomon Islands, and Vanuatu (5, 6, 10, 12, 14). Charlwood et al. (18) have written a comprehensive review of the ecology and behavior of the *An. punctulatus* group. Most *Anopheles* mosquitoes are active at dusk or dawn or are nocturnal. Some *Anopheles* mosquitoes feed indoors whereas others feed outdoors. After blood-feeding, some *Anopheles* mosquitoes prefer to rest indoors whereas others prefer to rest outdoors. Similarly, most *Anopheles* mosquitoes are also not exclusively anthropophilic or zoophilic.

VECTOR GENERA-PARASITE RELATIONSHIPS AND LYMPHATIC FILARIASIS ELIMINATION

Understanding the quantitative aspects of transmission of filarial parasites by mosquitoes is essential for the rational planning of control measures. An important determinant of transmission efficiency is the relationship between parasite yield, the success rate of ingested microfilariae becoming infective L3 larvae in the mosquito vector, and the density of microfilaremia in the human host. For filariasis transmission to be interrupted, vector density or microfilaria intensity needs to be driven below a threshold that ensures no new infection occurs. Two types of vector-parasite relationships, limitation and facilitation, are epidemiologically important. The relevance of these different relationships to filariasis elimination lies in the predicted importance of low-density microfilaremia in sustaining transmission in different epidemiological settings. The impact that vector genera differences can have on filariasis transmission and control was first pointed out by Pichon et al. (55, 56), who showed that this heterogeneous effect may arise primarily from variations in the form of density-dependent processes acting on parasite uptake and development in the different filaria-transmitting vector genera. The notable findings from this work, subsequently commented upon by other workers (26, 70, 72, 74), are that parasite infection dynamics in culicines, and to some extent in *Aedes* mosquitoes (70), may be of the negative density-dependent or limitation form. In the case of anopheline species, a critical Mf threshold exists at low-uptake burdens beyond which L3 output increases or is facilitated with further Mf uptakes but below which development of this larval stage is hampered (70).

More recent work, which also considers regulatory processes affecting the filarial parasite in the human host (25, 44), however, has shown that this analysis may be somewhat premature. Two key results arise from these fuller analyses. First, they showed that, as in other vector-borne infections, two types of eradication thresholds are also most likely to exist for LF: one related to the infection transmission process from the vectors and the other to worm infection levels in the human host. The theoretical threshold occurring in the vector-to-host transmission process is the vector biting threshold and defines the critical vector biting density, below which host-vector contacts are insufficient to sustain infection establishment and transmission (i.e., parasite replacement) in the population. The parasite eradication threshold occurring in the host-to-vector transmission process, on the other hand, is the breakpoint worm burden and defines the critical unstable parasite level in the host population, below which the parasite population spontaneously moves to the stable zero-parasite state and above which infection can establish and be sustained at stable steady states.

The second important finding to emerge from this new work is that, owing to the likely occurrence of inverse density-dependent mechanisms in the host, chief among which is the worm mating probability function, wherein the probability of finding mates for sexual reproduction becomes vanishingly small at low burdens (25, 41, 44), unstable breakpoint worm burdens may also occur in culicine-transmitted filariasis (44). This result therefore suggests improved prospects for the eradicability of culicine filariasis by MDA, compared with the conclusion of the earlier studies. However, because multiple inverse density-dependent factors may occur in anopheline-transmitted filariasis (e.g., the facilitation function regulating larval infection in vectors and the inverse worm mating probability function regulating parasite reproduction in the human host), the magnitudes of the two eradication thresholds are also likely to be higher for anopheline filariasis compared to the respective values that may occur for culicine and possibly *Aedes*-transmitted filariasis (25, 44). The multiple inverse density-dependent factors would again enhance the eradicability of anopheline filariasis compared to filariasis transmitted by culicines and *Aedes* mosquitoes. However, as pointed out by Michael et al. (44), the ultimate values of both thresholds in reality depend crucially on the

Facilitation: a positive feedback process in which a parasite (at any stage) promotes the success of parasites at the same or another stage

Density-dependent processes: regulatory mechanisms that govern parasite transmission that depend in a nonlinear manner on the parasite density

Parasite eradication: permanent reduction to zero of the worldwide incidence of infection

magnitude of the density-dependent processes operating in vectors and hosts as well as the degree of infection aggregation occurring in the host populations. As these thresholds are likely to vary among endemic communities, the value of either threshold is also likely to be variable among communities. Thus, it is extremely unlikely that single global threshold values exist for LF signifying infection eradication. This conclusion has important relevance for the design of LF elimination programs and the role of vector control in such programs.

EMPIRICAL FIELD EVIDENCE FOR THE IMPACT OF VECTOR CONTROL ON LYMPHATIC FILARIASIS TRANSMISSION

The incrimination of mosquitoes as vectors of *W. bancrofti* by Patrick Manson in India in 1877 was the first time that an insect was associated with the active transmission of an agent of any animal disease (69). This finding gave rise to renewed hopes about a new, possibly easy way of eradicating the mosquito-borne diseases by extermination of the vectors. Vector control is particularly attractive for LF because transmission of the parasite is inefficient. There is no multiplication of the parasite in the mosquito vector and only continuous exposure to bites of many infected mosquitoes maintains the infection in humans. Having evaluated the dynamics of transmission in Rangoon, Burma, Hairston & Meillon (29) calculated that approximately 15,500 infective bites of *Cx. quinquefasciatus* are required to produce a new patent infection. Subsequently, a number of studies involving *Culex*, *Anopheles*, and *Aedes* vectors in different parts of the world have provided data that allow estimates of this parameter, ranging from 2700 to over 100,000 infective bites per new human case (71).

For many years, control of *Cx. quinquefasciatus* was based on the use of organophosphorus insecticides, which gave excellent results in some tropical cities, such as Dar es Salaam, Tanzania, and Rangoon. However, resistance to chlorpyrifos, fenthion, and temephos were observed in larval populations from areas of Brazil, Burma, Kenya, Liberia, Sri Lanka, and Tanzania (82). More recently, resistance to malathion and pyrethroids has been reported in Cuba (65) and Cameroon (3). The greatest barrier to the effective control of *Cx. quinquefasciatus* is the lack of appropriate tools for sustained interruption of breeding in the innumerable polluted breeding sites such as pit latrines, soakage pits, septic tanks, and cesspits. A survey of sanitation structures in a section of Zanzibar Town, Tanzania, revealed 3075 pits that were potential *Cx. quinquefasciatus* breeding sites (39). Finding those ~25% of pits that contain water and therefore produce the *Culex* problem was routinely carried out by a team of about 10 people. Even with the best insecticides or biological agents, persistence is at best three months (32), making the required frequent retreatment of each pit costly and labor intensive.

The treatment of enclosed bodies of water with a floating layer of expanded polystyrene beads can prevent mosquito breeding for extended periods (23, 38, 47, 63). Layers of polystyrene beads in pit latrines persist if the pit does not flood. In a survey of *Cx. quinquefasciatus* breeding sites conducted in a section of Dar es Salaam, sanitation structures were the most prolific breeding places, totaling 2324 (20). When all the enclosed breeding sites were treated with polystyrene beads and checked seven months later, only one site (from which the polystyrene had been removed during emptying) contained immature stages of *Cx. quinquefasciatus*. Expanded polystyrene beads are capable of preventing breeding in sanitation structures for at least five years (23), although the periodic emptying of these structures is likely to reduce the effective life of a single treatment. Nathan et al. (50) used shredded waste polystyrene (discarded packaging material shredded to irregular particles 2–5 mm in diameter) in the same way to achieve several months of control of *Cx. quinquefasciatus* breeding in pit latrines.

Maxwell et al. (38) applied polystyrene beads to all the wet, *Culex*-infested pit latrines in Makunduchi—a community of 12,000 people

on Zanzibar, Tanzania. This treatment reduced the number of bites per person per year from ~25,000 to 440 (98%). Mass treatment of the community with DEC rapidly reduced the Mf rate from 49% to 10%, which had the effect of reducing the proportion of L3 infective mosquitoes from 2.4% to 0.4%, so that the number of infective bites per person per year went down by 99.7%. After this single campaign of DEC treatment plus sustained vector control, follow-up surveys showed continued decline to a Mf rate of 3% after five years (39). Evidence that vector control had contributed to this long-term decline was obtained by comparison with another town where DEC was used without vector control. Treatment with DEC without vector control resulted in a resurgence of Mf three to six years after the drug campaign. Whereas long-term prevention of resurgence of infection could probably have been achieved by annual rounds of drug treatment, the 98% reduction in the biting nuisance achieved by the vector control greatly increased public appreciation of the benefit of this integrated program.

In Zanzibar Town, treatment of 3075 pit latrines and cracked cesspits with polystyrene beads reduced the resultant *Cx. quinquefasciatus* biting rate by about 65%. Additional treatment of the drains and marshes in one sector of the town with *Bacillus sphaericus* did not produce a significant improvement in this reduction of mosquito biting rate compared to another sector where only the pit treatment with polystyrene beads was carried out (39).

In 1981 the Vector Control Research Center in Pondicherry, India, initiated a five-year integrated vector control program to reduce the transmission of *W. bancrofti* by *Cx. quinquefasciatus* (24, 59). Measures taken to prevent or eliminate the breeding of mosquitoes in their natural or human-made habitats included closing of wells and the application of expanded polystyrene beads in overhead tanks and sanitation structures such as cesspits and septic tanks. Biological control methods included the release of larvivorous fish such as *Gambusia* and *Tilapia* in suitable habitats. In the few areas where chemical larvicides were required, fenthion was chosen in addition to synthetic pyrethroids and juvenile hormone analogues. After five years of vector control activities, the indoor resting density of *Cx. quinquefasciatus* was reduced by 90% and the prevalence of Mf decreased by 60%. An analysis of the costs showed that integrated control methods compared favorably with control methods using conventional insecticides.

Reuben et al. (64), working in nine villages in southern India between 1995 and 1999, compared the impact of single-dose two-drug treatment (DEC plus IVR) alone with its combination with vector control. The nine villages were randomly allocated to three groups; one group of three villages received MDA in 1995 and 1996; a second group of three villages received MDA with vector control in 1995 and 1996; and a third group of three villages was not treated until 1999. Vector control was carried out using polystyrene beads and larvivorous fish (*Tilapia* spp.) in the major breeding sites of *Cx. quinquefasciatus.* Breeding sites where fish did not survive were treated with *B. sphaericus*. After the first round of treatment, chemotherapy alone brought about a 60% drop in the Annual Transmission Potential (ATP), and the integrated control method reduced ATP by 96%. However, when the drug pressure was removed two years later, transmission resumed in villages with no vector control but remained interrupted for one year in the villages with supplemental vector control. In 2001, the three villages that previously received MDA alone and the three that received MDA plus vector control were included in the GPELF program and treated with DEC plus ALB. Vector control continued in the three villages where it was previously carried out. Analysis in 2006 (73) showed that vector density decreased significantly in villages where vector control was used as an adjunct to MDA, and no infective mosquitoes were found in the small numbers caught during 2003–2005. Filarial antigenemia was low and continued to decrease significantly in 15- to 25-year-olds in villages receiving MDA with vector control in contrast to villages receiving only MDA. The authors concluded that the gains of MDA were

sustained only with the integration of vector control measures. They advocated the incorporation of vector control into the GPELF because it can potentially decrease the time required for eliminating LF.

Open breeding sites such as areas of flooded land and blocked drains can be treated with modern insecticides such as pyriproxyfen, an insect growth regulator, or the biological agent *B. sphaericus*. Pyriproxyfen treatment of open breeding sites in Dar es Salaam (19) inhibited the emergence of adult *Cx. quinquefasciatus* from these sites for up to 11 weeks during the dry season. The problem of mosquito breeding sites caused by bathroom sewage water can be effectively addressed through health education involving local community leaders. Households responsible for creating such breeding sites can be encouraged to eliminate them by diverting the water into an enclosed drainage structure, usually a latrine. Chavasse et al. (19) reported a 93% compliance from households in Dar es Salaam after five visits.

In Sarawak, Malaysia, Chang et al. (17) compared the impact of mass treatment alone (DEC) versus its combination with residual house spraying of pirimiphos-methyl when a control program against subperiodic Brugian filariasis was implemented in three villages: Kampong Ampungan, Kampong Sebangkoi, and Kampong Sebamban. In Kampong Ampungan, the mass administration of DEC combined with residual house spraying of pirimiphos-methyl reduced the Mf rate to 8% of the pretreatment level and the Mf density (MfD50) to 44% of the pretreatment level over a period of four years. In Kampong Sebangkoi and Kampong Sebamban, where only mass DEC therapy was applied, the Mf rate and MfD50 declined distinctly in the second blood survey but increased gradually in two subsequent follow-up blood surveys. In Kampong Ampungan, a significant reduction of infective biting rate (88.3%), infection rate (62.5%), and transmission potential (88.1%) of *Mansonia bonneae* was observed at the fourth spray round. The corresponding reduction rates in Kampong Sebangkoi and Kampong Sebamban were 35.3%, 26.7%, and 42.2% and 24%, 30.8%, and 15.4%, respectively. The biting density of the vector was reduced by 79.8% indoors and 31.8% outdoors in the sprayed village, whereas only a slight decrease in densities (17.9% indoors and 12.4% outdoors) was observed in the unsprayed village.

Indoor spraying of residual DDT was widely used and highly effective in most malaria control programs. House spraying with this insecticide led to reduction or interruption of the transmission of *W. bancrofti* by the *An. punctulatus* group in Solomon Islands (78), Papua New Guinea (5), and Indonesia (33), and by the *An. gambiae* complex and *An. funestus* in Togo (9, 67). Similarly, where malaria control operations were maintained at adequate levels, *W. bancrofti* transmission was reduced in parts of Central America where *An. darlingi* is the vector and in Southeast Asian countries where *B. malayi* was transmitted by *An. sinensis*, *An. barbirostris*, and other endophilic vectors (82). In the areas where vector control alone interrupted filariasis, facilitation was the vector-parasite relationship involved (72, 79).

Vector control dramatically reduced the transmission rates of Brugian filariasis by *Mansonia* species in Sri Lanka, where the prevalence rate of *B. malayi* was 6.8% in 1939, before DDT house spraying was implemented to control malaria (66). However, during a survey conducted between 1959 and 1965, after DDT house spraying had commenced countrywide to control malaria, microfilaremic individuals had completely disappeared from the country (1). The dramatic reduction in Mf rates was attributed to vector control by DDT spraying.

Rajagopalan et al. (60) compared infection and disease rates in Kerala state, India, reported in earlier studies conducted in 1934, 1955, and 1976 with a 1986 survey and concluded that prevalence of clinical Brugian filariasis can be reduced by integrated vector control alone. Vector control measures were initiated as early as 1933 by the state Filariasis Control Works, an organization engaged in physical removal of *Pistia* plants. In some areas, vector density was reduced by replacing *Pistia* with *Salvinia*, a weed that is less suitable for *Mansonia* breeding

(34). Indoor residual spraying of DDT was introduced in 1959 under the malaria control program, and pilot studies conducted in Kerala in 1959 showed that indoor application of residual insecticides reduced the density of *M. annulifera* to practically zero for at least six months (66). The impact of vector control in Kerala over the years led the WHO Expert Committee on Filariasis to conclude that transmission of *B. malayi* could be greatly reduced by vector control with or without chemotherapy (82). It was also pointed out that *B. malayi* had disappeared from some Indian villages, in the states of Madhya Pradesh, Orissa, and Tamil Nadu, while new foci of *W. bancrofti* were being established.

Recent studies comparing the effect of permethrin-impregnated bednets and DDT house spraying against malaria transmission in the Solomon Islands showed the former to be more effective (30, 36), suggesting that treated bednets may be as effective against LF as house spraying. Introduction of permethrin-impregnated bednets in a filariasis-endemic area of Kenya significantly reduced the indoor resting densities of *An. gambiae* s.l. by 94.6% and *An. funestus* by 96.7%, but there was no change in the number of *Cx. quinquefasciatus* collected indoors (8). However, the human blood index for *Cx. quinquefasciatus* was reduced from 93.1% to 14.4%.

The effect of untreated bednet usage on *W. bancrofti* Mf and disease was investigated, without undertaking a specific intervention, in three coastal villages on Bagabag Island, Papua New Guinea (7). The majority (60.1%) of the 1057 villagers interviewed reported that they had used a bednet the previous night. In general, bednet users had significantly lower rates ($P < 0.003$) and intensities ($P = 0.010$) of Mf than nonusers. Users were similar to nonusers in prevalence of lymphedema but hydrocele prevalence was 2.8 times higher in nonusers than users. The impacts of untreated bednets accumulate only slowly and cumulative effects of changes in human-vector contact are more likely to affect the prevalence of filariasis than malaria because the transmission of filariasis is less efficient than malaria. Similarly, a modest reduction in the number of mosquitoes biting humans, attributable to the use of insecticide-treated nets, strongly suppressed the risk of infection of *W. bancrofti* in the Kwale District of Kenya (54).

Chemical control and the use of impregnated materials is not effective when the vector is exophilic and diurnal. This is the case in most Pacific Island countries where *Ae. scutellaris* and *Ae. polynesiensis* are vectors of the diurnal subperiodic *W. bancrofti*. Larval control of these mosquitoes is also difficult because they breed in a wide range of small containers, which are too numerous to locate and deal with individually. In such situations mass chemotherapy offers the best prospect of control. However, the use of the systemic drug IVR in mass chemotherapy may have an effect on the survival of *Ae. polynesiensis*. Cartel et al. (15), working with this species in French Polynesia, observed significant reductions in mosquito survival up to three months after feeding on people treated with IVR and DEC.

New pyrethroids as well as biological agents such as insect growth regulators (pyriproxyfen) and bacterial toxins (*Bacillus sphaericus and Bacillus thuringiensis*) are now in operational use. Photostable pyrethroids (e.g., permethrin, deltamethrin, and lambdacyhalothrin) with residual insecticidal activity on impregnated curtains and bednets have proved to be effective against mosquito populations resistant to organophosphorus compounds (8, 80), although resistance to pyrethroids also is becoming a problem in many vector species. Note that the persistence of polystyrene beads is an order of magnitude greater than the longest persistence ever claimed for any chemical or microbial larvicide (**Table 1**).

Several new and effective antimosquito tools are now available for integrated vector management (IVM) to become an important component of the filariasis elimination strategy. In particular, the approach is likely to play an important role in endemic areas where more than one vector species, with different feeding and breeding habits, may be involved in

Integrated vector management (IVM): a vector control strategy that involves using more than one control method and that targets each method to the settings in which it is most appropriate

Table 1 World Health Organization recommended insecticides for indoor residual spraying for *Anopheles* mosquito control[a]

Insecticide compounds and formulations	Class group	Dosage (g/m^2)	Mode of action	Duration of effective action (months)
DDT WP	OC	1–2	Contact	>6
Malathion WP	OP	2	Contact	2–3
Fenitrothion WP	OP	2	Contact and airborne	3–6
Pirimiphos-methyl WP and EC	OP	1–2	Contact and airborne	2–3
Bendiocarb WP	C	0.1–0.4	Contact and airborne	2–6
Propoxur WP	C	1–2	Contact and airborne	3–6
Alpha-cypermethrin WP and SC	P	0.02–0.03	Contact	4–6
Cyfluthrin WP	P	0.02–0.05	Contact	3–6
Deltamethrin WP	P	0.01–0.025	Contact	2–3
Etofenprox WP	P	0.1–0.3	Contact	3–6
Lambda-cyhalothrin WP	P	0.02–0.03	Contact	3–6

[a]Reproduced with permission from the World Health Organization (**http://www.who.int/malaria/cmc_upload/0/000/012/604/IRSInsecticides.htm**). Abbreviations: C, carbamates; EC, emulsifiable concentrate; OC, organochlorines; OP, organophosphates; P, pyrethroids; WP, wettable powder.

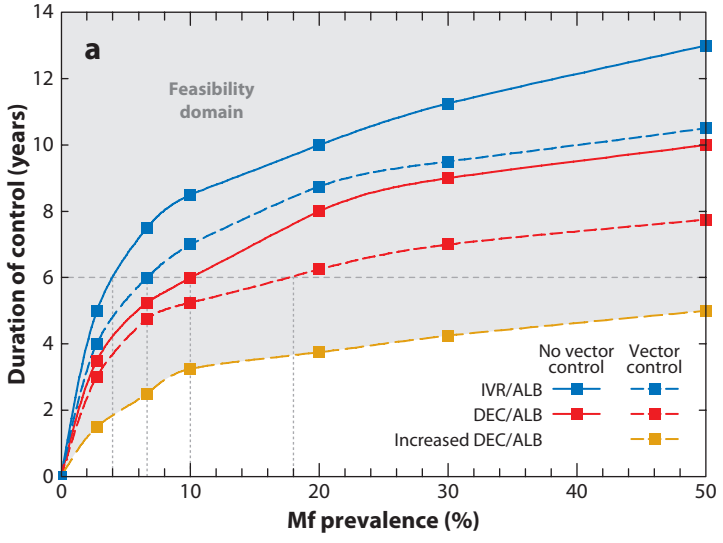
Figure 1

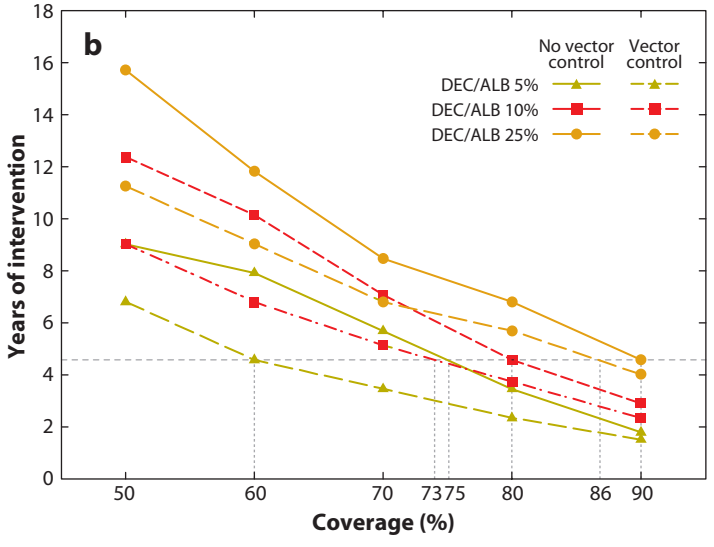
(*a*) Deterministic filariasis transmission model predictions of the number of years of intervention required by various annual MDA and combined annual MDA plus vector control options to achieve the target elimination threshold of 0.5% Mf prevalence (44) for a range of precontrol community endemicity (Mf%) levels. Solid curves give predictions for IVR/ALB and DEC/ALB annual MDA regimens, while dashed curves portray the corresponding results for each of these regimens combined with vector control. Drug efficacy values: DEC/ALB, 55% worm kill, 95% Mf cured, and six months Mf suppression; IVR/ALB, 35% worm kill, 99% Mf cured, and nine months Mf suppression. Vector control is assumed to be 90% effective in reducing vector biting. The orange dashed curve with orange squares denotes the effects of increasing the frequency of mass treatment to the DEC/ALB plus vector control regimen (mass treatment given once every six months). The vertical gray-dotted droplines indicate the maximum endemicity level at which it would be feasible to achieve the set target threshold of 0.5% Mf prevalence within the prescribed six years of control by each intervention. The shaded region represents the feasibility domain of the various filarial interventions examined and indicates simply that for each intervention-endemicity combination studied and for the given effectiveness and MDA coverage values, it will not be possible to reach the endpoint target of 0.5% Mf prevalence before the respective estimated years of intervention indicated in the figure (see Reference 44). All results at 1 ml blood sampling volume. (*b*) Model simulations of the number of years of intervention required by the mass annual DEC/ALB regimen either administered alone (*solid lines*) or with vector control (*dashed lines*) to achieve the 0.5% Mf prevalence threshold for a mix of precontrol community Mf prevalences (5%, 10%, and 25%) and drug coverage values. Ninety percent vector control efficacy assumed. Vertical gray-dotted droplines show the optimal drug coverage required at each endemicity level by each of these options to meet the control criterion of achieving the 0.5% Mf prevalence threshold in six years (modified after Reference 44). (*c*) The existence of bistable infection states and hysteresis loops in the Mf prevalence/vector biting rate plane for filariasis transmitted by culicine intermediate hosts. Bistable states (the endemic positive infection and the trivial zero-parasite states) (*solid purple lines*) may occur in filariasis as a result of the operation of inverse density-dependent regulatory processes, such as the mating probability function (44). These states emerge at the threshold vector biting rate and are separated by an unstable worm breakpoint boundary (*dashed purple curve*). The system is attracted to the stable zero-parasite state even if infection is introduced until the threshold vector biting rate is reached. Above this biting threshold the introduced infection is attracted either to the endemic stable state or to the zero-parasite state depending on whether the introduced infection values are above or below the unstable worm breakpoint threshold. The graph shows the two asymmetrical ways by which a shift between these alternative Mf stable states can occur with varying vector biting rates. If the parasite system is on the lower zero state but at high vector biting rates and thus close to the worm breakpoint bifurcation boundary, a slight incremental change in Mf levels may bring it beyond the bifurcation (e.g., at 0.1% Mf prevalence) and induce a drastic shift of the system to its endemic equilibrium (*rightmost red arrow*). If one attempts to restore the parasite-free equilibrium state by reducing the vector biting rate (*leftward black arrow*), the system shows hysteresis. A backward shift to the parasite-free equilibrium (*leftmost red arrow*) will occur only if the vector biting rate is reduced far enough to reach the threshold biting-rate bifurcation point. The hysteresis loop is wider for the anopheline model than for culicine-transmitted filariasis (data not shown), suggesting the vector control will be more effective in the case of eliminating culicine-mediated filariasis because it would more rapidly raise the worm breakpoint threshold value, thus enhancing both the prospects of parasite elimination and prevention of re-emergence following control.

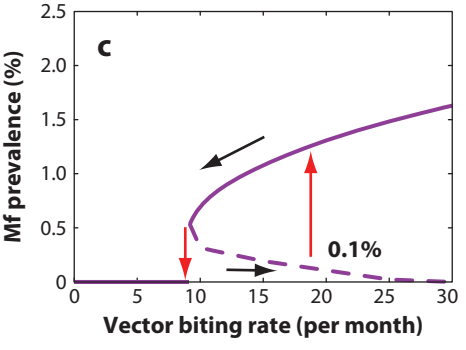
transmitting the same LF parasite. Similarly, concerns about insecticide resistance, safety, and environmental impact, as well as the high cost and sustainability of programs based predominantly on conventional insecticides, have stimulated increased interest in IVM. An IVM approach combines, in a feasible way, two or more of the antimosquito measures so that they can achieve a greater impact. This approach is evidence-based and an essential feature of it is the development of the capacity to generate local data on disease epidemiology and vector ecology. IVM activities thus promise to offer a new potentially highly effective approach for successfully incorporating vector control into LF elimination programs.

MODELING THE STRATEGIC IMPORTANCE OF VECTOR CONTROL IN LYMPHATIC FILARIASIS ELIMINATION

Recent modeling work has focused on quantifying the precise strategic roles that including vector control can play in LF elimination programs (44, 46). First, as portrayed in **Figure 1*a***,







Equilibrium: a parasite density (of any stage) that remains sufficiently constant over a long period of time

inclusion of vector control incorporating a 90% reduction in vector biting (7, 22, 39) in MDA programs with either IVR/ALB or DEC/ALB drug combinations (given at 80% drug coverage) not only enables extension of the range of baseline community infection endemicities (Mf prevalences) that can be feasibly brought under elimination (i.e., reducing below the 0.5% Mf prevalence elimination target threshold within the six-year period recommended by WHO). For a given baseline endemicity level, vector control also accelerates the effects of MDA in bringing about parasite elimination (i.e., reducing the number of years of MDA required to meet the elimination target of 0.5% Mf prevalence).

The results in **Figure 1*a*** show that addition of vector control to the IVR/ALB MDA regimen allows the achievement of the target threshold Mf prevalence in communities with up to 6.65% precontrol Mf prevalence at the 1 ml blood sampling volume (from only the 3.75% eradicable Mf prevalence possible with MDA alone), whereas in the case of the more effective DEC/ALB regimen, the added benefit would be to increase the controllable precontrol infection limit from 10% for MDA alone to 18% Mf prevalence for MDA plus vector control. Similarly, the number of control years saved by the inclusion of vector control to drug treatment indicates that, on average between 6 months to 1 year at low (<10%) and 1.5 to 2 years at moderate-high (>20%), precontrol community infection levels may be saved by adding vector control to each of the DEC/ALB and IVR/ALB regimens (**Figure 1*a***). These findings abundantly underscore the crucial role that including vector control in MDA programs will play in areas of high endemicity and in areas, such as Africa, where MDA using IVR/ALB is to be implemented.

The second important strategic role of including vector control in MDA programs is highlighted by the results in **Figure 1*b***. The key finding here is that all precontrol infection situations, including vector control, will lower the optimal MDA coverage required to meet a set control criterion compared with MDA alone. The gains, however, will be significantly larger for lower precontrol infection prevalence communities (e.g., whereas MDA with the DEC/ALB regimen would require an optimal drug coverage of 75% to achieve the target Mf threshold of <0.5% in six years at a precontrol Mf prevalence of 5%, the corresponding optimal coverage with the inclusion of vector control will need to be only 60% at this precontrol infection level compared to reductions observed in optimal drug coverages with vector control at higher precontrol infection levels) (**Figure 1*b***). Consequently, the effect of combining vector control with MDA in reducing the number of years required to achieve the infection elimination target will also be greater than using MDA alone at lower treatment coverages (**Figure 1*b***). Given that typical coverages achieved in large-scale community treatment programs are normally ~65% (57), this result affirms not only the strategic importance of including integrated vector management options in areas where obtaining high drug coverages may prove problematic, but also the ameliorative role that this measure can play in those situations in which program managers discover during MDA implementation declines from initial high coverages that could threaten program success (12, 23, 39, 46).

Better understanding regarding the third important strategic role of including vector control in LF MDA programs has come from stability analyses of filarial transmission models (25, 52). The most notable result is the likely existence of multistable parasite states separated by an unstable worm breakpoint boundary when the vector threshold biting-rate has been exceeded, which introduces the possibility of the occurrence of hysteresis in the transmission dynamics of LF (40). **Figure 1*c*** illustrates this phenomenon in terms of the equilibrium Mf prevalence versus vector biting-rate relationship for the model in which the vector is culicine.

The significance of the occurrence of this nonlinear phenomenon in transmission dynamics for including vector control in LF elimination programs is twofold. The first point is

related to the finding that the unstable worm breakpoint boundary separating the two parasite stable states (i.e., the zero and endemic infection states) is a dynamic function of the vector biting rates above the threshold biting rate. Thus, although the worm breakpoint prevalence is highest at the threshold biting rate, this declines markedly as vector biting rates above the threshold biting value increase (**Figure 1*c***). This inverse relationship readily highlights a strategic role for vector control in filariasis elimination, as reducing vector biting rates toward the threshold biting rate value will shift the values of worm breakpoints upward, thus making achievement of elimination easier.

Figure 1*c* further illustrates the significance of the occurrence of system hysteresis in filariasis control. If community vector biting is not reduced, then following parasite reduction in humans (by chemotherapy), a small fluctuation or input of parasites into a community can cause the ready re-emergence of the stable filarial endemic state. On the other hand, including vector control would essentially, by reducing the hysteresis loop, increase the re-emergence Mf prevalence threshold. This result supports empirical evidence (73) that vector control will be crucial to the long-term sustenance of parasite elimination from treated endemic communities.

CONCLUSIONS

The current principal strategy of GPELF for interrupting the transmission of LF is to treat the entire at-risk population through community-wide MDA programs. The data suggest that this strategy may indeed serve as a more effective approach to stop transmission where LF is anopheline-transmitted than where *Culex* is responsible, essentially owing to the intrinsically greater efficiency of the latter in transmitting LF. Even so, this review shows that including vector control would represent an important strategic tool to expedite and sustain the achieved interruption of filariasis transmission by both of these vectors. In addition, the results show that it could also serve as a major tool to overcome deficiencies in obtaining and maintaining the high drug coverages required by MDA programs alone for achieving LF elimination. With regard to methods, the emerging evidence that pyrethroid-impregnated screening materials such as bednets and curtains could be as effective as DDT in reducing transmission of filaria parasites by *Anopheles* and *Mansonia* mosquitoes is encouraging. The control of *Aedes* mosquitoes as vectors of *W. bancrofti*, however, remains problematic, and chemotherapy seems the most appropriate way to reduce transmission. This is further supported by the results of one study (15), which has shown that *Ae. polynesiensis* feeding on people treated with IVR or DEC may suffer a significant reduction in survival rate.

Successful vector control requires adequate resources and well-trained personnel. In reviewing decades of filariasis vector control activities in India and Myanmar, MacDonald (37) recognized that results were good when well-trained staff with substantial resources were employed and that results were much poorer when less well-equipped general health workers took over the programs. Many LF-endemic countries are resource constrained and therefore vector control is given low priority. However, strategic planning can make vector control cost effective. For instance, it may be cheaper to apply polystyrene beads to the limited number of *Cx. quinquefasciatus* larval habitat categories that commonly contribute a large proportion of the adult population. However, insecticides and biological control agents should be used as supplements, not as alternatives to environmental management (15). The participation of local communities in the implementation of integrated control measures is especially important in resource-poor countries. In many communities where filariasis mosquitoes are a biting nuisance, the noticeable impact of vector control might help to gain community support for integrated control programs involving chemotherapy. We suggest that priority now be urgently given to the formulation and evaluation of the impact that such targeted IVM strategies can

have on LF elimination in different endemic regions.

LF elimination will also be easier to achieve if MDA and vector control can be integrated into other public health programs (11, 48). Filariasis and malaria are coendemic in many parts of Africa (2, 4, 27, 35), Asia (62), and some Pacific Island countries including Papua New Guinea (6) and the Solomon Islands (76), where disease agents are transmitted by the same *Anopheles* mosquitoes. In such settings GPELF can synergize its activities with malaria vector control efforts using LLITNs. Forging such links would also present opportunities for support by the Global Fund to fight AIDS, Tuberculosis and Malaria, which will increase the overall prospects for the successful control of both of these parasites in afflicted populations.

SUMMARY POINTS

1. LF, also known as elephantiasis, is a leading cause of permanent and long-term disability in many parts of the tropical world.
2. The filarial parasites have biphasic life cycles involving the definitive mammalian host and various genera of mosquito vectors.
3. The parasites responsible for over 90% of global infections, *W. bancrofti* and *B. malayi*, have no animal reservoirs, suggesting that transmission can be eliminated by reducing the parasite load in human populations through mass drug treatments.
4. A global alliance was initiated in 2000 to eliminate LF through mass treatment alone.
5. Owing to emerging problems with mass treatment programs, vector control is increasingly recognized as a potential supplemental strategy for tackling the disease.
6. Empirical evidence and the availability of diverse vector management measures that take account of different vector ecologies and biting behaviors show that it may now be feasible to include integrated vector control activities in LF mass drug campaigns.
7. Mathematical modeling indicates three major strategic roles for including vector control in LF elimination programs: First, transmission elimination will be accelerated by raising worm breakpoint thresholds and by reducing the number of years of required drug intervention. Second, the drug coverages required will be lowered. Third, long-term parasite elimination from treated communities will be sustained by raising the infection thresholds to prevent the re-emergence of stable transmission.
8. The different population ecologies of parasite transmission in *Anopheles* versus *Culex* and *Aedes* mosquitoes suggest that it may be theoretically easier to eradicate LF from areas where the parasite is transmitted primarily by the first vector than from areas where the parasite is transmitted via the last two vectors. Inclusion of vector control is thus particularly important in areas with culicine and *Aedes* transmission.

FUTURE ISSUES

1. Making vector control a part of the global strategy for eliminating LF is predicted to reduce the number of treatment cycles required to interrupt transmission and to prevent re-emergence where interruption has been achieved. Field studies are now required to empirically test these predictions.

2. Comparison of the field effectiveness of combined MDA and vector control in reducing and even eliminating LF transmission between communities with *Anopheles* and *Culex/Aedes* are urgently required. The cost effectiveness and feasibility of using this approach versus using MDA alone also needs to be quantified.
3. More detailed evaluation of the effectiveness and sustainability of using available vector control measures is required, including assessing the formulation and effectiveness of the optimal IVM measures for controlling the major vector genera implicated in LF transmission.
4. More effective mosquito sampling and improved parasite diagnostic methods are required to accurately quantify the dynamics of LF control, including determination of when the goal of elimination has been attained.
5. Better integration of mathematical models with human infection and mosquito surveillance data is required to improve predictions and decision making with regard to both optimal design and assessment of the impact of interventions.
6. A greater understanding of vector-parasite relationships and spatial and temporal variations in exposure to infection will improve the estimation of elimination thresholds.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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39. Control of culicines by application of polystyrene beads to breeding sites can lead to long-term decline in filarial infection.

44. Mathematical models of filariasis transmission can allow determination of vector biting and worm breakpoint threshold values.

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