EXPERT REVIEWS

Current practices in the management of lymphatic filariasis

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Lymphatic filariasis is a major cause of acute and chronic morbidity in 81 countries. The availability of safe treatment regimens along with rapid diagnostic tools resulted in a global program to eliminate the disease. The two main objectives of the global elimination program are to interrupt transmission of the parasites and to provide care for those with the disease. The strategy for transmission interruption is preventive chemotherapy through mass drug administration. This article reviews the current treatment regimens for lymphatic filariasis and discusses the challenges posed by co-endemicity with other diseases. The role of integrated vector management as a supplementary strategy for mass drug administration and new strategies for treatment and morbidity control through antibiotic targeting of the *Wolbachia* endosymbionts are also discussed.

Keywords: albendazole • diethylcarbamazine • doxycycline • ivermectin • lymphatic filariasis • mass drug administration • morbidity control • neglected tropical disease • preventive chemotherapy • vector control • *Wolbachia*

Lymphatic filariasis (LF) is a major cause of acute and chronic morbidity in 81 countries in Asia–Pacific, Africa and the Americas [1]. Approximately 1.3 billion people living in these regions are at risk of infection with the mosquito-borne nematode parasites [1]. Of the estimated 120 million people harboring the parasites, 91% have *Wuchereria bancrofti*, while *Brugia malayi* and *Brugia timori* infections account for the other 9% [2,3]. *B. timori* is only known to be endemic in Timor and the Flores islands of the Indonesian archipelago [4]. These lymphatic-dwelling parasites cause damage to the lymphatic system, which leads to pathology in the form of elephantiasis, lympho-edema and hydrocoele. It is the second largest cause of permanent and long-term disability [5]. *W. bancrofti* seems to be exclusively a human parasite, whereas *Brugia* spp. are zoonotic in many situations. Many different species of mosquitoes act as carriers of these pathogens [4,6].

The principal carriers of nocturnally periodic *W. bancrofti* are *Culex* species in urban and semi-urban environments and *Anopheles* in most rural areas of Africa and elsewhere [4]. *Aedes* species are vectors of subperiodic *B. malayi* and *W. bancrofti*, *Mansonia* mosquitoes transmit both periodic and subperiodic *B. malayi* and *W. bancrofti*, and *Ochlerotatus* species are mainly carriers of nonperiodic *W. bancrofti* [6]. Infection is initiated when the host-seeking mosquito deposits an infective third-stage larva (L3) on the skin of the host during the process of obtaining a blood meal. The infective larvae penetrate the skin at the site of the bite and migrate to the lymphatic system of the host where they mature into fecund adult worms after 6–12 months. For *Brugia* spp., the life cycle from L3 to adult worm is 3 months. The reproductive lifespan of the adult worm is estimated at 4–6 years, during which millions of microfilariae (MF) are produced, each with a lifespan of approximately 12 months [4,7]. MF circulate in the host bloodstream and the life cycle is completed when they are ingested with the blood meal taken by female mosquitoes. Within susceptible vectors, MF penetrate the gut wall and migrate to the flight muscles, where they develop from L2 larvae into the infective-stage larva (L3).

Lymphatic filariasis is a disease targeted for elimination. The availability of safe, single-dose, two-drug treatment regimens capable of reducing microfilaremia to near-zero levels for 1 year or more, along with remarkable improvements in techniques for diagnosing the infection, resulted in advocacy for a global strategy to eliminate the disease through mass drug administration (MDA) [8]. Following the conclusion by an

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independent International Task Force for Disease Eradication that LF was one of only six infectious diseases considered to be 'eradicable' or 'potentially eradicable' [9], the World Health Assembly in 1997 adopted Resolution WHA50.29, calling for the elimination of LF as a public health problem globally. Out of the 81 countries afflicted with LF, 48 have launched national elimination programs. The WHO, in collaboration with other international agencies in public health and the private sector, formed a 'Global Alliance' and launched a Global Programme to Eliminate Lymphatic Filariasis (GPELF) by the year 2020 [10].

The GPELF has two major objectives: to interrupt transmission of the parasite (transmission control) and to provide care for those who suffer the devastating clinical manifestations of the disease (morbidity control) [8,11]. The WHO-recommended strategy for interrupting transmission is preventive chemotherapy and transmission control (PCT), mainly through MDA of albendazole in combination with either ivermectin or diethylcarbamazine citrate (DEC) [5]. This paper reviews the current global treatment strategies for transmission control of LF and discusses the challenges posed by co-endemicity with other diseases and the fragile primary healthcare system. The role of integrated vector management as a supplementary strategy for transmission control and new strategy for treatment and morbidity control through antibiotic targeting of the *Wolbachia* endosymbionts are also discussed.

Preventive chemotherapy & transmission control

The objective of the PCT strategy is to avert the morbidity that leads to disability associated with pathology in the form of lympho-edema, hydrocoele and elephantiasis. It is described in detail in a WHO manual intended to guide the coordinated implementation of regular, systematic, large-scale interventions that provide anthelminthic drug treatment as a core component of the joint and synergic control of neglected tropical diseases (NTDs), such as LF, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis [201]. Early and regular administration of the WHO-recommended drugs (albendazole and DEC or ivermectin) reduces the occurrence, extent, severity and long-term consequences of morbidity [12–17]. In practice, PCT for LF elimination requires the delivery of good-quality drugs, either alone or in combination, to as many people in need as possible, once yearly for 4–6 years. High priority is given to achieving full coverage of at-risk communities (endemic implementation units), which may be defined by state, province, district, subdistrict, town or village. Endemic communities are identified using rapid diagnostic tools, such as the immunochromagraphic card test for LF [18,19]. Improvement in techniques for diagnosing and rapid mapping of LF, and the availability of safe and effective medication for use in MDA is the cornerstone of this strategy. It is characterized by rapid low-cost diagnosis, easy implementation, pro-poor and nondiscriminatory practices that will result in a rapid impact. This health service delivery model has worked extremely well for the management of LF. In the first 8 years since GPELF was launched in 2000, 1.9 billion treatments with the antifilarial drugs (albendazole and ivermectin or DEC) were provided through MDA to approximately 570 million individuals living in 48 out of the 83 initially LF-endemic countries [1]. Some global health experts are now advocating for the recognition of PCT as a critical platform for upscaling malaria interventions, particularly bed nets and antimalarial drugs [20,21].

The approach for LF is a once-yearly, single-dose, two-drug regimen utilized by the target population, with the goal of reaching 80% population coverage yearly, for at least 5 years, in order to interrupt transmission of the parasite [5]. Community-wide treatment is achieved through MDA in target populations. Treatment can be administered from house to house by mobile teams or from a fixed station accessible to the community. MDA campaigns may be organized as a national day or over a short 2–4-day period. Preventive chemotherapy is a pro-poor approach that is built around the utilization of donated drugs. Many LF elimination programs in Africa have adopted the community-directed intervention (CDI) strategy for MDA, which was developed for ivermectin distribution for onchocerciasis control [22–26]. CDI is the principal strategy adopted by the African Programme for Onchocerciasis Control (APOC). In the CDI model, each community is expected to take the leading role in planning, implementing and assessing its local drug-delivery strategy. It is based on the principle of voluntary community participation by community drug distributors (CDDs).

Treatments for transmission control

Repeated once yearly, MDA dramatically reduces the reservoir of the transmissible MF stage available for uptake by vectors of LF [13,17,27,28]. There is a threshold for MF density in the human host and vector contact rates below which transmission will be interrupted [6,29–32]. In Africa and the Americas, LF is co-endemic with onchocerciasis over a wide range of its distribution [33]. Where onchocerciasis is co-endemic, the regimen is ivermectin 200–400 µg/kg plus albendazole 400 mg; elsewhere, the regimen should be DEC 6 mg/kg plus albendazole 400 mg [5,34]. The attributes, safety and efficacy of these drugs were recently described in a comprehensive review by Gyapong *et al.* [5]. Systematic reviews of the treatment options, including the relative efficacies of different drug combinations for transmission control, have been presented in detail elsewhere [5,34–36].

Diethylcarbamazine

Diethylcarbamazine is a drug that has been used exclusively to treat filarial nematodes since 1948 and has been administered to hundreds of millions of people. Its mode of action is different from any other class of anthelminthic and it appears to require host components from the arachidonic acid pathway, innate immune system and nitric oxide for its activity [37,38], accounting for its lack of activity *in vitro*. DEC is indicated for the treatment of individual patients infected with *W. bancrofti*, *B. malayi* or *B. timori* [4]. Administered as a single dose of 6 mg/kg, it is effective in reducing microfilaremia, both acutely and chronically over the course of at least 1 year [5,13,17,34,39]. The optimal dose of DEC does not clear all the MF in an infected person, and all adult worms are not killed, but this is unlikely to be attributed

to drug resistance [5]. In infected individuals, and particularly in those who are parasitemic, adverse reactions may occur following administration of DEC. Nevertheless, DEC continues to be the mainstay for the treatment of patients with LF.

Albendazole

Albendazole, a heterocyclic aromatic organic compound, is an inexpensive benzimidazole-type scolicidal anthelmintic with a broad range of antiparasitic activity against helminths (roundworms, cestodes and flatworms). It is also an effective antifilarial agent whose optimal dosage has yet to be determined [5]. Even at the single, low (400-mg) dose used for treating most intestinal helminth infections, it decreases *W. bancrofti* microfilaremia progressively over the course of 6–12 months [5,40]. However, two systematic reviews on the effect of albendazole on *W. bancroti* failed to demonstrate a significant effect of the drug against adult and larval filarial parasites, either alone or in combination with other antifilarial drugs [34,35].

Ivermectin

Ivermectin (22,23-dihydroavermectin B1a plus 22,23-dihydroavermectin B1b) is a broad-spectrum antiparasitic agent. At doses of less than 200 µg/kg, it is active against filarial infections, particularly onchocerciasis and LF [41,42], but is also effective against other NTDs (strongyloidiasis, ascariasis and trichuriasis) [42,43] and ectoparasites (lice and scabies) [44] . With these doses, side reactions to the drug are limited almost exclusively to the consequences of inflammatory reactions to dead parasites, particularly the MF, as ivermectin has no macrofilaricidal activity. Ivermectin is a highly effective, well-tolerated drug for decreasing microfilaremia in LF [5]. Although 400 µg/kg appears to be a more effective dose than either 200 or 100–150 µg/kg, choice of the dosage level and the dosing frequency in public-health programs against LF should be evidence-based.

Anti-wolbachial therapy

The development of a new treatment for LF has arisen through exploiting the mutualistic symbiosis between the nematode and *Wolbachia* bacteria. All species causing LF are host to the endosymbiont, which is essential for parasite growth, development, embryogenesis and survival [45]. Treatment of bancroftian filariasis with a 4-, 6- or 8-week course of a 200 mg/day dose of doxycycline results in long-term sterility and eventual death of adult worms [45–48]. In addition to the antiparasitic effects of treatment, individuals treated with anti-wolbachial therapy show significant improvements in lymphatic pathology and the severity of lymphoedema and hydrocoele [46]. A 3-week course of doxycycline is sufficient to render the parasites sterile and patients amicrofilaremic, but does not lead to significant macrofilaricidal activity [49]. In this trial, *Wolbachia* loads were reduced by only 80% compared with more than 90% in regimes with macrofilaricidal effects. This suggests there is a threshold of *Wolbachia* reduction necessary to result in the loss of adult worm viability (>90%), yet lower reductions can lead to sterilization through blockage of embryogenesis. A 6-week course of 100 mg/day doxycycline is also effective at reducing *Wolbachia* and microfilaremia in brugian filariasis [50]. It is not possible to directly assess macrofilaricidal activity in brugian filariasis, but the 98% reduction in *Wolbachia* load would be consistent with a macrofilaricidal outcome as observed with *W. bancrofti*. At 12 months post-treatment, microfilaremia prevalence was reduced by 77 and 88% in patients receiving doxycycline alone or doxycycline plus DEC–albendazole, respectively, compared with a 27% reduction in the group receiving placebo plus DEC–albendazole. An additional outcome of this trial was to show that prior treatment with doxycycline reduced the frequency and severity of adverse reactions to DEC–albendazole [50].

The slow-kill of adult worms, which occurs from 12 months after treatment, together with the lack of rapid microfilaricidal activity delivers a good safety profile through the avoidance of parasite- and/or *Wolbachia*-mediated inflammatory adverse reactions – a phenomena linked to the release of *Wolbachia* from drug-killed nematodes [51]. Importantly, the delivery of a rapid macrofilaricidal drug as would be predicted from drugs with direct anti-nematode activity would be accompanied by potentially severe and debilitating adverse reactions to both adult worms and MF. The slow-kill induced by anti-wolbachial therapy appears to be the only currently available solution to this problem.

Together, these trials show that sufficient reductions in *Wolbachia* result in long-term sterilization and amicrofilaremia, macrofilaricidal activity of between 78–92%, and clinical improvements or prevention in the progression of pathology, and avoidance of both microfilarial and macrofilaricidal side effects. This has led to these regimes being recommended as an alternative treatment for individual cases, with superior efficacy and morbidity prevention to current standard antifilarial treatment [52].

The minimum period of a 4–6-week course of doxycycline required to achieve these effects and its contraindication in children under 9 years of age and pregnancy precludes the widespread use of doxycycline-based anti-wolbachial chemotherapy in the context of current control strategies. A 2- or 4-week course of rifampicin, an alternative antibiotic with anti-wolbachial activity suitable for the treatment of children, is effective at depleting bacteria, and reducing in embryogenesis and microfilarial production in onchocerciasis [53], although a 1-week course alone or in combination with azithromycin is ineffective [54].

Attempts to resolve these issues has led to the establishment of an anti-wolbachial drug discovery and development program (A-WOL) [202], which aims to develop anti-wolbachial therapy that is compatible with MDA approaches. This program includes objectives to test combinations of antibiotics active against *Wolbachia* given for reduced periods of time to optimize anti-wolbachial treatment with existing tools. In addition, it provides a process by which to identify existing and novel antibiotics and drugs with improved activity over currently used antibiotics, and to discover key *Wolbachia* drug targets through bioinformatic and high-throughput screening approaches. The A-WOL program aims to provide a product pipeline and drug portfolio that will optimize anti-wolbachia therapy of existing drugs and prioritize the development of novel drugs and combinations for use in future control and the treatment of filariasis [55]. After

the first 2 years of A-WOL activity, approximately 3700 drugs have been screened, delivering 166 hits, of which several have progressed through *in vivo* screens to deliver improved activity over doxycycline.

The implementation of anti-wolbachial therapy into existing control program strategies will require a redesign of current approaches to take into account the macrofilariacidal outcome and the need to diagnose and treat infected individuals rather than all eligible groups in communities. As it stands, the use of anti-wolbachial therapy should be considered under restricted circumstances where existing programs have failed, such as in the Maupiti Attol in French Polynesia where, despite 34 years of massive DEC treatment, there was still residual infection [56], at the end point of successful programs where a residual populations require eradication, or in the event of the development of resistance to existing drugs [6]. The use of anti-wolbachial therapy might also provide an alternative to the treatment of LF in areas co-endemic with loiasis, which through targeting the endosybmoints of *W. bancrofti* would avoid severe host reactions induced by the rapid kill of *Loa loa* MF (a species of filariae without *Wolbachia*).

Community-directed treatment

The capability to eliminate microfilaremia for long periods with a single dose of two safe and effective drugs opened the possibility for treating whole communities in an effort to interrupt transmission and prevent LF infection (and consequent disease) [5]. Indeed, with the newly available, simplified diagnostic techniques and highly effective, single-dose, multidrug treatment regimens, LF has made a profound paradigm shift from the focus on infected individuals to an infection-prevention, public health focus on affected communities, and it was this technique-enabled paradigm shift that laid the groundwork for GPELF [11,57]. Treatment of the entire endemic population at annual intervals has been recommended as the principal strategy to achieve the goal of LF elimination [8,40]. The challenges are to achieve adequate treatment coverage and sustain annual delivery for sufficiently long periods. In most endemic countries, high coverage and sustained drug delivery to all high-risk communities are difficult to achieve by the health services alone, which are often overburdened with other responsibilities [58].

In 1994, the WHO, in collaboration with the Onchocerciasis Control Programme and a group of scientists working on a multicountry study on community-based treatment with ivermectin, developed the concept of community-directed treatment (ComDT) which is simple, effective and sustainable within the context of the socioeconomic constraints of endemic countries. With this approach, the basic tenets involve an initial sensitization of the endemic communities on the problems of the disease and its transmission, the benefits of controlling the infections by MDA, and education on the dosage, exclusion and inclusion criteria for receiving the treatment drugs, and possible side effects and their management. Members of the community select distributors from within the community who are trained by health personnel to undertake MDA. The community decides the mode of drug delivery – either house-to-house or collection from a central point. Thus, with this concept, the community itself has the responsibility for the organization and execution of the treatment of its members. This translates into community acceptance, with an attendant increase in coverage and compliance. The results of the large, multicountry study showed that ComDT was feasible and effective in onchocerciasis control [33], and such treatment is now the basic control strategy of the APOC [22,23].

The success story of ComDT for onchocerciasis was further tested for other MDA programs. In Ghana, ComDT of LF involving the regular public-health services (ComDT/HS) was compared with mass treatment in which only the health services participated (HST). The treatment coverage achieved by ComDT/HS (74.5%) was much higher than that of HST (43.5%) [59]. Unpublished data from a similar study conducted in Kenya showed similar results. A qualitative study in Tanzania compared ComDT with the school-based approach for the control of schistosomiasis and soil-transmitted helminthiasis among school-age children. Results of the study suggest that the ComDT approach was wel-accepted and can be implemented effectively to ensure better coverage, especially of nonenrolled school-age children. In a similar quantitative study, coverage of treatment in nonenrolled school-age children using ComDT was 80% compared with 59.2% for the school-based approach where nonenrolled children were invited for treatment [60]. ComDT strategy has, therefore, become the main drug-distribution strategy against LF in a number of endemic countries, particularly in sub-Saharan Africa where health services do not reach the most remote communities. The success of ComDT provides a sure way of achieving the set targets, not only for LF but also for other diseases targeted for mass treatment by the WHO, such as schistosomiasis and soil-transmitted helminthiasis [61]. The confidence in, and competence of CDDs has culminated in their being used for other health interventions. A preliminary assessment, funded by the APOC, has indicated that a large number of CDDs are already involved in other health and development activities (e.g., distribution of vitamin A, malaria treatment, polio immunization, Guinea worm eradication, nutrition, water protection and serving as community health workers, among others) [25].

Challenges to ComDT

Community-directed treatment has been proved to be an effective treatment delivery strategy in Africa [22]. However, the situation is different in Asia, particularly in India, a country with an estimated 450 million people at risk of LF infection. In a study of some rural areas in India, ComDT was implemented and its effectiveness was compared with that of the traditional health service-organized drug delivery. Under the ComDT, 68% of the population received DEC, compared with 74% with the health service treatment strategy. However, only approximately 53% of ComDT recipients and 59% of the health service recipients were reported to have taken the DEC. Although not statistically significant, the distribution and compliance rates were lower under the ComDT strategy, whereas health service-organized distribution was less cumbersome and found to be more acceptable by the

community [62]. In such areas, theimplementation of ComDT was constrained by various social and operational factors, including difficulties encountered by health personnel in the sensitization of communities where the knowledge of the disease is poor, poor response of community leadership to the concept of ComDT, people's reluctance to accept the drug from CDDs, whose knowledge of the drug is poor, and group and caste conflicts [62]. Other challenges were constraints in influencing the tasks of CDDs, such as the complex record-keeping demands that affected the schedule and work load of the distributor, resulting in a demand for incentives. The concept of the community contributing as partners to support (in 'kind' cash) distributors did not work in many areas. The health system and its partners, therefore, continue to look for options of incentivizing CDDs.

Notwithstanding, the already burdened and overstretched health systems of most endemic countries, ComDT cannot be entirely executed without the full cooperation and overarching supervision and surveillance by health systems of countries. This is even more imperative, especially for countries such as India where ComDT has not gained full acceptance, even though the country's health service's manpower alone is not sufficient for drug distribution per annual round. In all studies designed to test the efficiency and acceptability of ComDT, success appears to be dependent on the initial effective community entry process by health staff that is able to motivate enthusiasm, show recognition of respected traditional authorities and gain approval of community heads who play a pivotal role in the acceptance and sustenance of drug-delivery programs in communities. The need for health staff and community members to work in tandem cannot be overemphasized.

In integrating ComDT into existing health systems, governments of endemic countries need to be convinced of the effectiveness of such an integrated approach. Commitment is key in rolling out drug-delivery programs through health service structures to ensure community ownership of such programs. Health staff play a vital supervisory and technical role through the provision of professional expertise and conducting household and community surveys to ensure that technical program requirements are met. The success of this integrated approach can provide a solid structure for the delivery of other health interventions already in progress in some endemic countries and ensure that health services are delivered to remote and hard-to-reach communities with no or inadequate health facilities.

Drug distribution under the overall leadership of health services with active involvement of community members may be the best option to cover the target population. All studies clearly indicate that ComDT is a sure way to achieve the ultimate coverage required for interruption of transmission. However, community involvement must be undertaken in ways consistent with local norms, systems and structures acceptable to the community. Strategies that do not conform to local cultures are likely to be opposed or unsustainable for the number of rounds required. If adhered to, constraints including noncompliance, attrition of CDDs and requests for incentives, among others, can be handled at the community level by leaders within communities.

If elimination of LF as a public health problem is to occur in Africa, a solution has to found to the problem of *L. loa* co-endemicity in central Africa. Neurological serious adverse events (SAEs) following ivermectin treatment that occur in individuals harboring high *L. loa* microfilarial densities are of major concern in the context of mass ivermectin distributions organized in Africa for onchocerciasis and LF control. These SAEs are induced by the rapid and massive microfilaricidal effect of a standard dose of ivermectin (150 µg/kg). Kamgno and coworkers [63] performed a randomized, controlled, double-blind trial to determine whether ivermectin given as a single low dose of 1.5 mg (i.e., 25 µg/kg for a 60-kg person) or two doses of 1.5 mg given at a 2-week interval will lead to a more progressive decrease in *Loa* microfilarial loads compared with the standard dosage [12]. The low dose of ivermectin brought about a significantly smaller decrease in *Loa* microfilaremia than the standard dose. However, this decrease was not sufficiently different from that obtained after the standard dose acceptable to public health programs requiring a wide safety margin. A second low dose of ivermectin given 15 days after the first dose did not lead to a further decrease in *Loa* microfilaremia. Finally, the variability in the response observed in the group treated with 25 µg/kg suggests that even lower doses would have no effect on a significant number of patients. Ivermectin given at a low dose (~25 µg/kg) is probably not adequate to prevent the occurrence of post-treatment neurological SAEs [63]. Further clinical trials are currently underway exploring the utility of treating such population with albendazole to reduce the *L. loa* MF load before treating with ivermectin. The 3-day treatments with albendazole failed to lead to sufficient reductions that were safe enough for ivermectin treatment [64,65], and so alternative regimes are required.

Serious adverse events associated with MDA for NTDs have generally been kept to the minimum. However, in recent years, SAEs associated with the mass distribution of ivermectin in Cameroon have caused widespread concern. Many of these SAEs were characterized by progressive neurologic decline and encephalopathy within a few days of taking ivermectin [66–68]. This has warranted some careful programmatic reviews to improve program delivery. One of the major causes of SAEs is co-endemicty with *L. loa*. *L. loa* infection mainly occurs in parts of central Africa and is usually co-endemic with the major neglected diseases of concern such as onchocerciasis and LF. Treatment of onchocerciasis or LF with ivermectin can cause SAEs, but there is a significantly higher risk if the patients are co-infected with *L. loa*. Minor adverse drug events, such as fever, headache, pruritus, lymphadenopathy and myalgia, are usually associated with the rapid death of the MF of *Onchocerca volvulus* and typically occur upon first exposure to the ivermectin [69]. SAEs include life-threatening adverse drug experience, in-patient hospitalization including encephalopathy and even death. SAEs were found to occur rarely in large clinical and community trials of ivermectin conducted in West Africa in the 1980s [69–71].

A systematic review by the Mectizan Donation Program shows that the majority of *L. loa* SAEs have been reported from Cameroon [67,72]. Out of approximately 165 million reported

treatments delivered during the period 1989–2001, a total of 207 SAE cases were reported, giving rise to a cumulative incidence of one reported SAE per 800,000 reported treatments. Of these, 51% reported some form of altered consciousness. The mean age was 40 years and 70% of the cases were males. The mean time between ivermectin intake and onset of illness was 1 day, but patients came to medical attention approximately 4 days after the onset of symptoms. For 57% of the cases (n = 118), that was their first exposure to ivermectin. The majority of cases were reported from Cameroon (n = 176 [85%]), with peaks in the incidence of SAE reporting in 1989–1991 and 1994–1995 when the program expanded to ivermectin-naive populations. In total, 55% of the cases from Cameroon (i.e., 97 out of 176 cases) were encephalopathic and were reported from the central-southern region of the country; two-thirds of which were presumed to be associated with high-intensity *L. loa* infection. The clinical outcome of the SAEs was documented for 137 out of the 207 total cases (66%). For those whose outcome is known, there were 28 deaths (cumulative case–fatality rate of 20.4%). They concluded that further research was needed to understand the apparent clustering of encephalopathy cases in central-southern Cameroon since *L. loa* infection alone probably does not explain the increased incidence of this type of SAE from this region, and that a passive surveillance system for SAEs following ivermectin treatment is required of all ivermectin mass-treatment programs in Cameroon, the Central African Republic, the Democratic Republic of Congo and Sudan [67,72].

The occurrence of *L. loa* encephalopathy following mass-treatment of onchocerciasis or LF with ivermectin can therefore adversely affect NTD control efforts in central Africa [68]. There is, therefore, a need to know the geographic distribution of communities with very high densities of *L. loa* microfileremia and, therefore, an increased risk of encephalopathy. Mapping co-infection with *L. loa* (RAPLOA), a new technique that correlates the proportion of community members reporting a history of eyeworm with the prevalence of high-intensity *L. loa* microfileremia in that community, is for rapid assessment of areas at potential risk of treatment-related *L. loa* encephalopathy [72]. A pragmatic decision model aimed at minimizing sequelae of *L. loa* encephalopathy following mass-treatment with ivermectin in areas co-endemic for LF and loasis based on RAPLOA has been developed, which significantly reduce the risk of death and neurologic complications from *L. loa* encephalopathy [71,73,74].

Role of vector control

The challenges to the MDA approach have necessitated the need for alternative or supplementary community-based approaches to transmission control [6,75,76]. A nonhuman reservoir does not exist for *W. bancrofti* and high human–vector contact is required to maintain transmission, even for the very efficient *Culex* vectors. Hairston and De Meillon estimated that more than 15,000 infective bites of *Culex quinquefasciatus* were required to produce a new patient infection [77]. This suggests that transmission can be interrupted by reducing human–vector contact through vector control or an integrated approach combining vector control and MDA. Vector control is particularly attractive for LF because transmission of the parasite is very 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.

Several new and effective antimosquito tools are now available for integrated vector management to become an important component of the filariasis elimination strategy. Vector control alone may interrupt the transmission of LF in some epidemiological settings where *Anopheles* mosquitoes are the only vectors, as demonstrated by the elimination of *Anopheles*-transmitted LF from the Solomon Islands [32,78–81] and Togo [82,83] through indoor spraying of residual dichlorodiphenyltrichloroethane (DDT). However, in many endemic areas, this approach is unlikely to be sustainable because more than one vector species, with different feeding and breeding habits, may be involved in transmitting the same LF parasite [76].

Indoor spraying of residual areas led to reduction or interruption of the transmission of *W. bancrofti* by *Anopheles punctulatus* group in the Solomon Islands [80], Papua New Guinea [84] and Indonesia [85], and by the *Anopheles gambiae* complex and *Anopheles funestus* in Togo [82,83]. It has been suggested that in all these examples where vector control alone interrupted filariasis, facilitation was the vector–parasite relationship involved [30,32]. The threshold below which transmission will be interrupted in *Anopheles*-transmitted filariasis can be achieved either by reducing the density of parasites or the density of mosquitoes, or both.

Effective control of the urban vector, *Culex quinquefasciatus*, is hampered by the lack of appropriate tools for sustained interruption of breeding in the numerous polluted breeding sites, such as pit latrines, soakage pits, septic tanks and cess pits. The treatment of enclosed bodies of water with a floating layer of expanded polystyrene beads has been shown to prevent mosquito breeding for extended periods of time [86–90]. Expanded polystyrene beads are capable of preventing breeding in sanitation structures for at least 5 years [87], although the periodic emptying of these structures is likely to reduce the effective life of a single treatment. By applying polystyrene beads to all the wet, *Culex*-infested pit latrines in Makunduchi – a community of 12,000 people on Zanzibar island, Tanzania – Maxwell and coworkers reduced the number of mosquito bites per person per year from 25,000 to 440 (98%) and the number of infective bites per person per year went down by 99.7%.

Reuben and coworkers compared the impact of single-dose two-drug treatment (DEC plus ivermectin) alone versus its combination with vector control in India, and concluded that exposure to infective larvae was significantly reduced by the addition of vector control [91]. Vector control was carried out using polystyrene beads and larvivorous fish (*Tilapia* spp.) in the major breeding sites of *Cx. quinquefasciatus*. After the first round of treatment, chemotherapy alone brought about a 60% drop in annual transmission potential (ATP), while the integrated control method reduced ATP by 96%. However, when the drug pressure was removed 2 years later, transmission resumed in villages with no vector control but remained interrupted for 1 year in the vector-control villages.

Recent studies comparing the effect of permethrin-impregnated bed nets and DDT house-spraying against malaria transmission in the Solomon Islands showed the former to be more effective [92,93], suggesting that treated bed nets may be as effective against LF as house-spraying. The effect of untreated bed net usage on *W. bancrofti* microfilaremia and disease was investigated, without undertaking a specific intervention, in three coastal villages on Bagabag island, Papua New Guinea [94]. The majority (60.1%) of the 1057 villagers interviewed reported that they had used a bed net on the previous night. In general, bed net users had significantly lower rates ($p < 0.003$) and intensities ($p = 0.010$) of microfilaremia than non-users. These studies suggest that effective vector control would be an important supplementary approach to expedite interruption of transmission. The emerging evidence that pyrethroid-impregnated screening materials such as bed nets and curtains could be as effective as DDT in reducing transmission of filaria parasites by *Anopheles* and *Mansonia* mosquitoes is encouraging. However, the control of *Aedes* mosquitoes as vectors of *W. bancrofti* remains problematic, and chemotherapy seems to be the most appropriate way of reducing transmission [76]. However, one study has shown that *Aedes polynesiensis* feeding on people treated with ivermectin or DEC have a significant reduction in survival rate [95]. The participation of communities in the implementation of integrated control efforts is an essential component of control activities, especially 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.

Morbidity control

When transmission has been interrupted, the adult worms may continue to induce lymphatic pathology and consequent morbidity. Alleviating the suffering caused by the disease (morbidity control) is the secondary objective of GPELF [8,11]. This objective addresses three filariasis-related conditions: acute inflammatory episodes, lympho-edema and hydrocele [96] . There is increasing evidence for bacteria as a causative agent of acute inflammatory episodes in filariasis-endemic areas, known as acute dermatolymphangioadenitis (ADLA) [96–102]. Lympho-edema management strategies are based on the central role of ADLA as a trigger for lympho-edema progression. A regime of rigorous skin hygiene and simple self-help measures, such as limb elevation, exercise, use of topical antibiotics and anti-fungals aimed at minimizing episodes of ADLA attacks and lymph stasis, is the WHO strategy for the management of filarial lympho-edema [103]. These simple morbidity management tools have resulted in dramatic reductions in ADLA rates, a lower prevalence of chronic inflammatory cells in the dermis and subdermis, and improvements in quality of life [96]. Data on the impact of MDA on filarial morbidity are inconsistent. Several studies report reductions in acute inflammatory episodes, lympho-edema and/or hydrocele following MDA [14–17], but other studies report no such association [104,105]. The use of anti-wolbachial therapy has shown to improve upon standard hygiene treatment for the treatment of lympho-edema and lymphatic vessel pathology [46] and hydrocoele [55], and offers an additional tool for morbidity control.

Expert commentary & five-year view

Preventive chemotherapy for the management of LF has been discussed mainly within the framework of MDA with DEC, ivermectin and albendazole. This strategy has resulted in dramatic reductions in infection prevalence and transmission intensity at the community level. Within the next 5 years, the PCT platform will be adopted for upscaling other NTDs, including soil-transmitted helminths and schistosomiasis. It could also be adopted as the platform for bed net distribution for malaria control. With regard to LF, the regimes for these drugs do not fully cover the needs of individual patients who seek treatment owing to symptoms. New regimes for individual drug administration have been indicated using anti-wolbachial therapy with doxycycline [52]. Doxycycline 200 mg/day should be administered for 4 weeks plus IVM/ALB single dose, if:

- The patient is co-infected with onchocerciasis (and therefore unable to take DEC)
- The patient lives in an area with low or interrupted transmission
- The patient suffers from microfilarial-induced disease symptoms (e.g., tropical pulmonary eosinophilia), and so would benefit from long-term suppression of microfilaremia
- The patient is not pregnant and over the age of 9 years

Alternatively, doxcycline 200 mg/day for 6 weeks plus IVM/ALB single dose is the reccommended treatment if:

- Disease symptoms are prevalent or anticipated through family history
- The patient is not pregnant and over the age of 9 years

Individual treatment will also be essential for systematic non-compliers who can serve as reservoirs for initiating transmission in a community undergoing MDA. The question of whether or not anti-wolbachial therapy can be used to safely treat individuals co-infected with loaisis and onchocerciasis has been addressed in trials in Cameroon and there are currently undergoing analyses. The rationale of these trials was to determine the efficacy of doxycycline against *O. volvulus* without evoking the antiloiasis effects of ivermectin. One of the trials challenges the conventional wisdom that a 6-week course of treatment is beyond the capacity of CDI strategies by delivering such treatments through communities with onchocerciasis and loiasis co-infection. The outcomes of these trials should help determine whether this approach may offer an alternative to ivermectin-based treatments in areas of loaisis co-infection, which are currently excluded from onchocerciasis and LF control programs. Within 5 years, the development of optimized or alternative anti-wolbachial therapy will have been determined by A-WOL and, if successful, will offer an alternative approach to the control and treatment of filariasis. This approach should offer alternative control strategies to treat patients in areas of co-infection with *L. loa* or in the event of the development of resistance to existing drugs [6].

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Key issues

- The availability of safe treatment regimens along with rapid diagnostic tools resulted in the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000.
- The two main objectives of the GPELF are to interrupt transmission of the parasites and to provide care for those with the disease.
- The strategy for transmission interruption is preventive chemotherapy through mass drug administration (MDA).
- Where onchocerciasis is co-endemic with lymphatic filariasis (Africa and the Americas), the regimen is ivermectin 200–400 µg/kg plus albendazole 400 mg; elsewhere, the recommended regimen is diethylcarbamazine citrate 6 mg/kg plus albendazole 400 mg.
- There are systematic noncompliers who remain microfilaremic after several rounds of MDA, which does not fully cover the needs of individual patients.
- New regimens for individual drug administration have been indicated using anti-wolbachial therapy with doxycycline.
- The challenges of MDA to achieve adequate treatment coverage and sustain annual delivery for sufficiently long periods have necessitated the need for alternative or supplementary community-based approaches, such as integrated vector control.
- When transmission has been interrupted, the adult worms may continue to induce lymphatic pathology, and there should be plans to control the consequent morbidity.

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