Malaria and lymphatic filariasis: the case for integrated vector management

Henk van den Berg, Louise A Kelly-Hope, Steve W Lindsay

The global programmes to eliminate both malaria and lymphatic filariasis are facing operational and technical challenges. Available data show that the use of treated or untreated bednets and indoor residual spraying for malaria control concomitantly reduced filarial rates. In turn, mass drug administration campaigns against lymphatic filariasis can be combined with the distribution of insecticide-treated bednets. Combining these disease control efforts could lead to more efficient use of resources, more accurate attribution of effects, and more effective control of both diseases. Systematic integration requires coordination at all levels, mapping of coendemic areas, and comprehensive monitoring and evaluation.

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Laboratory of Entomology, Wageningen University, Wageningen, Netherlands (H van den Berg PhD); **Centre for Neglected Tropical Diseases, Liverpool School of Tropical Medicine, Liverpool, UK** (L A Kelly-Hope PhD); **and School of Biological and Biomedical Sciences, Durham University, Durham, UK** (Prof S W Lindsay PhD)

Correspondence to: Henk van den Berg, Laboratory of Entomology, Wageningen University, PO Box 8031, 6700 EH Wageningen, Netherlands **henk.vandenberg@wur.nl**

Introduction

Several groups have advocated combining control efforts for malaria with those for neglected tropical diseases, lymphatic filariasis in particular.[1–5] Malaria, caused by protozoa of the genus *Plasmodium*, and lymphatic filariasis, caused by the nematodes *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, overlap in their distribution in most of Africa, south and southeast Asia, and some parts of Latin America.[6,7] Similarities exist between malaria and lymphatic filariasis in relation to their transmission: both diseases may be transmitted by the same or related vector species, both are potentially controlled by the same vector-control interventions, both have no or almost no hosts other than human beings, and both prevail under conditions of poverty and poor environmental sanitation.

Malaria and lymphatic filariasis cause the highest global burdens of all vector-borne diseases, particularly in Africa and southeast Asia (table 1).[7–11] Malaria is transmitted by *Anopheles* species in all regions, whereas regional differences exist in the mosquito genera that transmit filarial parasites. In much of Africa and parts of the western Pacific (eg, Papua New Guinea), the anopheline vectors of malaria are also the principal vectors of lymphatic filariasis.[12] *Culex quinquefasciatus* is an important vector in urban areas of east Africa, but in west Africa this species is considered refractory to infection with *W bancrofti*.[13] Elsewhere, members of the *Culex pipiens* complex (predominantly *C quinquefasciatus*) and *Aedes* species are the principal vectors of lymphatic filariasis.[7,11]

Integrated vector management is promoted by WHO as the best approach to improve the efficacy, cost-effectiveness, ecological soundness, and sustainability of vector control.[14] To achieve integration, vector control should be based on local evidence, adopt a multidisease approach, and combine interventions wherever appropriate and feasible. In its implementation, integrated vector management depends on collaboration between health-sector programmes, other sectors, and communities.[15,16] Here we aim to substantiate a recent statement by WHO on integrated vector management to control malaria and lymphatic filariasis[17] by summarising available evidence and suggesting the way forward.

Two global programmes and their challenges

The history of global programmes for the control of malaria and filariasis shows that the emphasis on vector control or drugs changes over time. Vector control, primarily through indoor residual spraying with DDT (dichlorodiphenyltrichloroethane) and dieldrin, was central in the first malaria eradication campaign (1955–69), but lost its significance as financial and technical constraints put eradication out of reach; eradication of malaria was never attempted in sub-Saharan Africa.[18–20] Malaria control programmes have regained a strong emphasis on vector control in the past two decades, following evidence of the cost-effectiveness and general applicability of insecticide-treated bednets[21] and indoor residual spraying.[22] Both interventions, when used on a large scale, have resulted in major reductions in malaria in many countries.[23] Similarly for lymphatic filariasis, vector control once was the primary control strategy, but the emphasis switched to preventive chemotherapy; however, vector control is regaining recognition because of recent problems in mass drug administration programmes.[24,25]

The contemporary Global Malaria Programme[8] and Global Programme for Elimination of Lymphatic Filariasis[25] share the goals of local elimination and global eradication of disease by achieving universal coverage of populations at risk with appropriate interventions. These shared aims suggest that the two programmes are a good match.

Despite major progress in malaria control towards reaching targets for the distribution and use of long-lasting insecticidal nets (LLINs),[8] much more is needed to increase penetration within communities and to access hard-to-reach communities. The high coverage with insecticidal vector-control methods, however, will exert strong selective pressure for insecticide resistance in vector populations,[26,27] which emphasises the importance of surveillance, resistance management, and the need to diversify interventions. As such, both global programmes will face operational and technical challenges with regards to vector control in the future.

Regarding filariasis, the primary form of control remains preventive chemotherapy. A barrier to initiation

	Malaria			Lymphatic filariasis		
	At risk[8]	DALY[9]	Vectors[7]	At risk[10]	DALY[9]	Vectors[7,11]
Africa	705	30·9	*Anopheles*	432	2·3	*Anopheles, Culex*
Americas	160	0·1	*Anopheles*	12	0·0	Mainly *Culex*
Eastern Mediterranean	241	1·4	*Anopheles*	24	0·1	*Culex, Anopheles*
Europe	51	0·0	*Anopheles*	0	0·0	NA
Southeast Asia	1209	1·3	*Anopheles*	877	3·5	*Culex, Anopheles, Aedes, Mansonia*
Western Pacific	849	0·2	*Anopheles*	42	0·1	*Culex, Anopheles, Aedes, Mansonia*
All	3215	33·9	..	1386	5·9	..

At-risk populations are in millions; DALY=disability-adjusted life-years (millions).

Table 1: **Risk, burden, and vectors of malaria and lymphatic filariasis, by WHO region**

of programmes to eliminate lymphatic filariasis is the coendemicity of *Loa loa* in large parts of central Africa.[28,29] Patients with loiasis can develop serious neurological reactions to the drugs used in mass drug administration,[30] especially at high *L loa* microfilariae burdens.[31] Elsewhere, the challenge in lymphatic filariasis elimination is to reach minimum effective coverage of mass drug administration[25] in annual rounds through scale-up and promotion of compliance; however, there is uncertainty about the coverage level and the number of annual rounds needed to achieve elimination in the local context.[29] Field studies and mathematical models have shown that vector control can have an important complementary role in the elimination effort.[24,32,33] As such, where mass drug administration is supplemented by vector control, lower coverage levels and fewer annual rounds would be needed to achieve elimination.

Programme interactions

Vector control to prevent transmission of malaria parasites and mass drug administration to prevent transmission of microfilariae are two strategies that can affect several diseases. Vector control can reduce vector–human contact for more than one disease, particularly where malaria and lymphatic filariasis have the same principal vectors. Mass drug administration campaigns can facilitate the improvement of vector control if linked with the distribution of LLINs.[1] In central Nigeria, this linkage resulted in substantial improvement in both ownership and use of LLINs for malaria control, without an adverse effect on drug administration operations.[34]

Mass drug administration can have several effects: treatment substantially reduces the microfilariae load of *Wuchereria* sp and *Brugia* sp parasites in human hosts.[35] Additionally, the drugs albendazole and ivermectin have broad anthelmintic activity with benefits for the prevention and control of other widespread diseases, such as intestinal helminth infection and onchocerciasis.[36,37] An auxiliary result of mass drug administration is the known temporary effect of the drugs on the survival of mosquito vectors feeding on treated hosts in operational settings, thus contributing to control of malaria and lymphatic filariasis.[38–41] Interactions between malaria parasites and filariae in people with both are complex and largely unknown. Helminth infections might adversely affect the acquisition of immunity to malaria,[42,43] and so the treatment of lymphatic filariasis would indirectly relieve the burden of malaria. Direct effects of anthelmintic drugs on *Plasmodium* species have not been reported. More generally, as mass drug administration causes worm expulsion, it affects various morbidity outcomes, including those associated with malaria control: anaemia, growth retardation, and cognitive impairment.[44]

Evidence of combined effects

Several studies have documented the outcome of integrated control of malaria and lymphatic filariasis (table 2).[45–55] In some studies, the integration was deliberate; in others, vector control interventions intended for malaria control inadvertently affected lymphatic filariasis. In most reported instances, both diseases had the same anopheline vectors.

In the Solomon Islands, where both diseases had anopheline vectors, indoor residual spraying with DDT targeted at malaria inadvertently eliminated lymphatic filariasis, but did not eliminate malaria.[45,46]

In Papua New Guinea, two studies in the absence of mass drug administration showed that untreated bednets had a stronger effect on microfilariae burden than on malaria sporozoite antigen rates.[49,53] In the same country, insecticide-treated bednets in combination with weekly mass drug administration caused a decline in microfilariae but had no significant effect on malaria prevalence.[50] In Cambodia, treated bednets offered better protection against the morbidity of lymphatic filariasis than did untreated bednets.[54]

In Pondicherry, India, lymphatic filariasis is concentrated in urban and malaria in rural areas, and the diseases have separate vectors. Environmental management was implemented at large scale with the participation of communities and collaboration between sectors.[47,48] The microfilariae burden dropped substantially for young children, and malaria was locally eliminated. Other studies have confirmed the value of environmental management of lymphatic filariasis transmitted by *Culex* sp mosquitoes where breeding is confined to wells and pits,[32,56,57] but without the integration of malaria vector control.

On the Kenyan coast, insecticide-treated bednets aimed at control of malaria had a large effect on the vector potential of lymphatic filariasis, based on the human blood index and mosquito density.[51] In a follow-up study, although insecticide-treated bednets reduced the vector biting rate by just 22%, this resulted in the annual infected biting rate plummeting by 95% and the annual transmission potential (ie, the number of infective larvae

inoculated per person per year) by 92%.[52] Hence, despite a modest reduction in biting rate, the transmission of *W bancrofti* was strongly suppressed. A recent study from Uganda showed a substantial reduction in *W bancrofti* infection and infectivity in people where both mass drug administration and LLINs were used, but the contribution of LLINs remains unclear.[55]

The effect of insecticide-treated bednets on culex-transmitted lymphatic filariasis has not been systematically assessed. Bednets are used against nuisance biting from culex mosquitoes. Insecticide-treated bednets do not seem to kill culex mosquitoes, possibly because of tolerance or contact irritability to the insecticides,[58] although an irritant effect could cause mosquitoes to exit the homes of bednet users, reducing the number of bites received. Insecticide-treated bednets might also divert *C quinquefasciatus* from human to non-human hosts.[51]

In summary, in places where anophelines have been implicated as principal vectors for both lymphatic filariasis and malaria parasites, the use of untreated and treated bednets and indoor residual spraying have convincingly reduced filarial rates. In several instances, the effect was greater for *W bancrofti* than for malaria, which could be because of the density-dependent processes involved in anopheline transmission of filariae,[59,60] or because transmission of lymphatic filariasis is less efficient than that of malaria.[24,61] Integration of environmental management for malaria and lymphatic filariasis, including the construction of soakage pits, cleaning of drains, and improvement of sanitation, also merits attention in the context of integrated vector management, as suggested from the results from India, especially where vector breeding is focal and within human habitations. Consequently, integration requires inputs from various sectors, many of which lie outside the health sector.

Towards integration

Malaria and lymphatic filariasis have much in common in terms of their geographical distribution, transmission biology, and mutual interactions. Moreover, the global programmes to contain them have matching goals, strategies, and challenges.[8,25] Integration would be required at the level of communities, districts, ministries, and donors.[16] The prospects for integration are contingent

	Eco-epidemiologic setting	Principal vectors	Interventions	Design	Outcome
Solomon Islands, 1974–77[45,46]	Rural, humid coastal	*Anopheles punctulatus* group (as vector of malaria and *Wuchereria bancrofti*)	Indoor residual spraying with DDT for malaria eradication; no MDA	Yearly examination of a cohort of people during the malaria eradication programme	*W bancrofti*: infection reduction from 22% in 1974 to 0% in 1977 Plasmodia: not reported
India, 1979–86[47,48]	Rural and urban, dry coastal	*Anopheles subpictus* (vector of malaria); *Culex quinquefasciatus* (vector of *W bancrofti*)	Environmental management* through community participation and collaboration between sectors	Baseline and postintervention in rural and urban setting	*W bancrofti*: microfilariae rate dropped 29%, or 91% for children aged 0–4 years (urban setting) Plasmodia: local elimination (rural setting)
Papua New Guinea, 1986–87[49]	Rural, humid coastal	*A punctulatus* group (as vector of malaria and *W bancrofti*)	Untreated bednets; no MDA	Longitudinal comparison in one village	Reduction in human blood index of vectors *W bancrofti*: 50% decline in filarial infection rates Plasmodia: slight drop in sporozoite antigen rates
Papua New Guinea, 1987–88[50]	Rural, upland	*A punctulatus* group (as vector of malaria and *W bancrofti*)	Permethrin-treated bednets; weekly MDA with diethylcarbamazine citrate	Baseline survey in five villages, with postintervention survey after six months	*W bancrofti*: microfilariae rate dropped from 48% to 6% Plasmodia: decline in *Plasmodium falciparum* and *Plasmodium vivax* rate from 10% to 8%, but not significant
Kenya, 1994–95[51,52]	Rural, humid coastal	*Anopheles funestus, Anopheles gambiae* (vectors of malaria and *W bancrofti*); *C quinquefasciatus* (vector of *W bancrofti*)	Permethrin-treated bednets for malaria control; no MDA	Six treatment and six control villages	*W bancrofti*: annual infective biting rate reduced by 95%, annual transmission potential reduced by 92% Plasmodia: not reported
Papua New Guinea, period not indicated[53]	Rural, humid coastal	*Anopheles farauti* (*A punctulatus* group) (as vector of malaria and *W bancrofti*)	Habitual use of untreated bednets; no MDA	Community survey among 1073 persons to compare bednet users with non-users	*W bancrofti*: bednet users had significantly lower rates of microfilariae and antigenaemia Plasmodia: no effect on *P falciparum* and *P vivax* infections
Cambodia, 2001–02[54]	Rural, lowland	Vectors not identified	Treated or untreated bednets used for overnight stays in forest and rice fields	Case-control study using risk factor analysis	*W bancrofti*: use of untreated bednets offered protection but treated bednets offered superior protection against disease morbidity Plasmodia: not reported
Uganda, 2007–10[55]	Rural, upland	*A gambiae* sl and *A funestus* (as vector of malaria and *W bancrofti*)	Long-lasting insecticidal bednets; MDA with albendazole and ivermectin	Survey before and after intervention in seven villages, comparing bednet users with non-users	*W bancrofti*: clear reduction in infection where MDA and bednets were both present, but the contribution of bednets was equivocal Plasmodia: not reported

DDT=dichlorodiphenyltrichloroethane. MDA=mass drug administration. *For example, construction of soakage pits, emptying water tanks, sealing of wells and septic tanks, cleaning of drains.

Table 2: **Studies that show the effect of integrated control of malaria and lymphatic filariasis**

on the local context of disease epidemiology, vector ecology, and a country's operational capacity. Therefore, the initial focus for integration should be where the potential benefits are greatest, which seems to be in sub-Saharan Africa and parts of the Pacific where both diseases are transmitted by anopheline vectors.[7,62]

We propose four reasons for integration: more efficient use of resources; segregated programmes could have unintended consequences; more accurate attribution of effects; and increased effect on both diseases.

First, efficiency is improved when activities of geographical reconnaissance, planning, implementation, monitoring and evaluation, data management, and reporting for the two diseases are combined, and when expertise, training, logistics, and infrastructure are shared. Particularly, the distribution of LLINs or indoor residual spraying could be planned, implemented, and assessed in tandem with mass drug administration.[1,34] Entomological expertise generally available for malaria could be used to improve vector control of lymphatic filariasis[3]—eg, by establishing a core group on vector control with a cross-disease mandate.[16] Also, lymphatic filariasis programme staff could contribute to annual checks of the quality and use of bednets during mass drug administration campaigns, with benefits for control of both malaria and lymphatic filariasis. Broadening the remit of staff that have managed a single disease programme to one that covers several diseases can initially be challenging, since personnel can feel uncomfortable about moving into new areas. Careful training and mixing of staff can make this process more straightforward. Importantly, as the prevalence of either disease drops to extremely low, pre-elimination, levels, continued surveillance is essential to prevent disease resurgence. This detailed surveillance is long-term and expensive, but becomes less so if the surveillance system can be used for monitoring and evaluation of several diseases simultaneously. In many ways this is similar to how the smallpox eradication programme evolved into the expanded programme on immunisation.[63]

Second, in the absence of integration, a disease-specific programme could inadvertently increase risk for the other disease. Even though the available evidence suggests mostly complementary and synergistic effects between control of the two diseases, the interactions between filariae and malaria in co-infected vectors or hosts are dynamic and still largely unknown. Hence, uncertainty about the overall effect on malaria transmission could be circumvented by supplementary vector control.[64] Moreover, as countries approach elimination of either disease, whether removing one disease will lead to a change in prevalence of the other remains unclear.[65] This uncertainty emphasises the importance of national coordination between the two programmes throughout their elimination phases.

Third, integration of programmes would enable improvement of evaluation, with more accurate attribution of the observed effects to the resources used, with the recognition that interventions can affect both diseases. Hence, in an area covered by LLINs and mass drug administration, the malaria programme should consider the role of anthelmintic drugs in the reduction of plasmodia transmission,[40] and the lymphatic filariasis programme should account for the effect of malaria-control interventions on filarial transmission.

Fourth, the ultimate benefit of integration will be improved control of both diseases. Past studies have shown inadvertent benefits of malaria vector control on lymphatic filariasis.[45,46,49,52–54] The synergistic effects between the control of malaria and lymphatic filariasis are evident and should no longer be left to chance, but should be optimised through improvements in three areas: coordination, logistics, and use of existing infrastructure; microstratified mapping of coendemic areas and interventions; and monitoring and evaluation of the efficacy of approaches, including drug and insecticide resistance surveillance. Donors must support the unique requirements for programme integration—requirements that could be in addition to those of disease-specific programmes, but that will make those programmes more effective.

Between 2008 and 2010, an estimated 294 million insecticide-treated bednets were delivered to sub-Saharan Africa, aimed at malaria control.[8] If in the coming years the distribution of LLINs were coordinated between the national disease-control programmes and optimally targeted, while using the infrastructure of mass drug administration wherever feasible, this could benefit control of both diseases. Likewise, the mass administration of ivermectin could be optimised by scheduling at times of peak vector biting to reduce transmission,[66] or at low transmission levels with the aim of malaria elimination. Such strategies would be especially relevant in situations where insecticide resistance or outdoor biting reduce the effectiveness of LLINs and indoor residual spraying.[67,68] Perhaps the biggest advantage of the coordination of drug administration and LLINs will be their combined effect on anaemia, a major killer of young children, through the reduction of malaria and hookworm infections.[1]

The use of microstratified mapping of malaria and lymphatic filariasis endemic areas, overlaid with the distribution of LLINs and coverage of mass drug administration, is an important requirement.[37] These maps would help prioritise geographical areas for integrated control of malaria and lymphatic filariasis, along with operational research, and assist in prediction of the anticipated benefits from integration. Moreover, the recently developed maps for the rapid assessment procedure for loiasis provide valuable information that demarcates *L loa* endemic areas in Africa.[28] Where the endemicity of *L loa* and lymphatic filariasis overlap ivermectin is contraindicated, so interventions targeted at the vectors of lymphatic filariasis should be emphasised.[37]

Search strategy and selection criteria

We searched PubMed and Scopus for articles published from 1960 to May, 2012. Studies were identified using search terms "malaria" and "*Wuchereria*" or "*Brugia*". References from the retrieved articles were used to identify other relevant publications that were not identified from the database searches. Each article written in English was assessed for its methodological quality and the relevance of its results.

In the face of spreading resistance in anophelines against the pyrethroids used in LLINs,[27] a window of opportunity seems to exist in endemic countries to use LLINs in a so-called attack phase, to substantially reduce prevalence of malaria and lymphatic filariasis and so to reach more manageable or pre-elimination levels of both diseases.[27,69] From pre-elimination to postelimination, vector control will have a continuing role to reduce transmission risk and prevent a rebound of infection, with progressive use of additional methods within the context of integrated vector management.[70–73]

Contributors

HvdB did the reference review and drafted the report. LAK-H and SWL contributed to the further development of the report.

Conflicts of interests

HvdB has received consultancy fees from WHO's Department of Control of Neglected Tropical Diseases, though not for preparation of this report. LAK-H and SWL declare that that they have no conflicts of interest.

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