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Review

Review on global co-transmission of human *Plasmodium* species and *Wuchereria bancrofti* by *Anopheles* mosquitoes

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ABSTRACT

Malaria and lymphatic filariasis are two of the most common mosquito-borne parasitic diseases worldwide which can occur as concomitant human infections while also sharing common mosquito vectors. This review presents the most recent available information on the co-transmission of human *Plasmodium* species and *Wuchereria bancrofti* by *Anopheles* mosquitoes. Important biological and epidemiological aspects are also described including the lifecycle of each parasite species and their specificities, the geographical biodiversity of each pathogen and their vectors where the parasites are co-endemic, and biological, environmental and climatic determinants influencing transmission. The co-transmission of each disease is illustrated from both a global perspective and a country level using Thailand as a study case. Different diagnostic methods are provided for the detection of the parasites in biological samples ranging from traditional to more recent molecular methods, including methodologies employing concomitant detection assays of *W. bancrofti* and *Plasmodium* spp. parasites. The relevant issues of combined malaria and Bancroftian filariasis control strategies are reviewed and discussed.

Contents

Abbreviations: ACT, artemisinin-combination therapies; DEC, diethylcarbamazine; DSP, diurnal subperiodic form; ELISA, enzyme-linked immunosorbent assay; GPELF, global programme to eliminate lymphatic filariasis; ICT, immuno-chromatographic test; IRS, indoor residual spraying; ITN, insecticide-treated net; ITS-1, internal transcribed spacer 1; IVM, integrated vector management; L1, L2, L3, first, second and third instar larva; LF, lymphatic filariasis; LLIN, long-lasting insecticidal net; MDA, mass drug administration; Mf, microfilariae; NP, nocturnal periodic form; NSP, nocturnal subperiodic form; PacELF, Pacific programme for the elimination of lymphatic filariasis; PCR, polymerase chain reaction; PNG, Papua New Guinea; PRG, Southeast Asia programme review group; RBM, Roll Back Malaria; RFLP, restriction fragment length polymorphism; WHO, World Health Organization.

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1. Introduction

Among the approximately 4000 known mosquito species, less than 10% are regarded as efficient vectors of pathogenic agents of infectious diseases having high impact, both direct and indirect, on human welfare and health. Malaria and lymphatic filariasis (LF) are two of the most common and identifiable mosquito-borne parasitic diseases worldwide (Fig. 1A, B). The overall prevalence and health significance of malaria and LF have made them top priorities for global elimination and control programmes (Kyelem et al., 2008; Molyneux and Zagaria, 2002; WHO-SEARO, 2006; WHO, 2007b, 2008b).

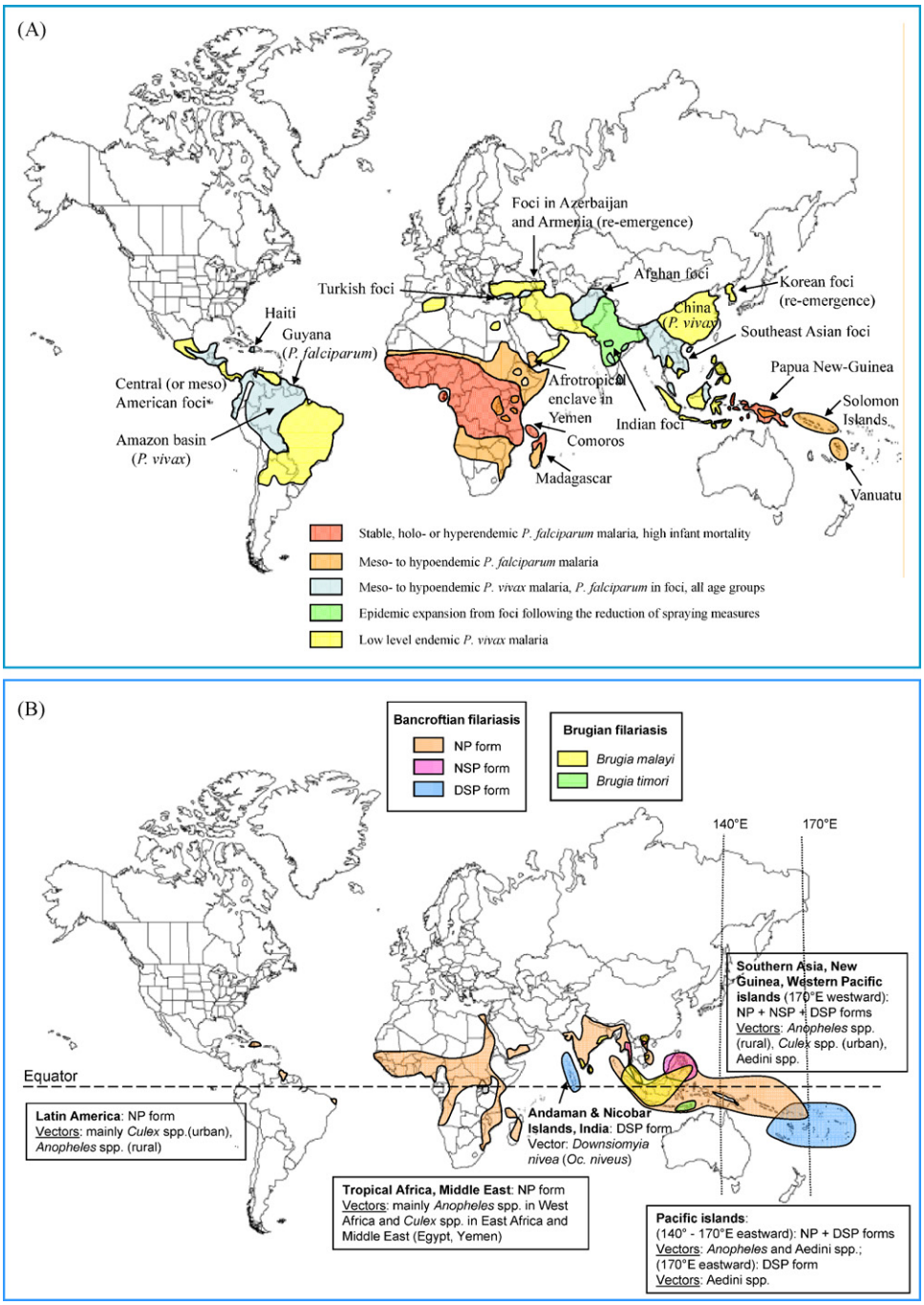

Fig. 1. Global distribution of human *Plasmodium* spp. and lymphatic filarial species; (A) malaria (Manguin et al., 2008a); and (B) lymphatic filariasis based on Mak (1981), Michael and Bundy (1997), Service (1993), and WHO (2008b).

Table 1
Number of endemic countries, estimated population at-risk and human cases annually by region, respectively, for malaria and lymphatic filariasis (LF); data for 2006 (WHO, 2008a, 2008b).

	Endemic countries (and territories)		Estimated population at-risk in millions (%)		Estimated cases in millions (%)	
	Malaria	LF	Malaria	LF	Malaria	LF
Africa	45	39	647 (20%)	382 (29%)	212 (86%)	51 (40%)
Americas	22	4[a]	137 (4%)	11 (1%)	2.7 (1%)	0.4
Asia[b]	17	15	2200 (67%)	891 (68%)	22 (9%)	75 (59%)
Middle East	13	3	295 (9%)	13 (1%)	8.1 (3%)	No data available
Europe	9	0	22 (<1%)	0	0.004	0
Pacific Islands	3	17	7 (<0.5%)	6 (<0.5%)	2.2 (1%)	1.8 (1%)
Total	109	78	3308	1303	247	128

[a] The latest WHO report presents only four countries, Brazil, Dominican Republic, Guyana and Haiti, with current active transmission of LF (WHO, 2008b).
[b] Asia from India to Southeast Asia, China, Indonesia.

These two diseases can occur as concomitant human infections in many tropical regions while also sharing common vectors (Buck et al., 1978). Half of entire human population, an estimated 3.3 billion people, lives in malaria risk areas around the world with about 250 million people infected annually. Malaria is believed responsible for approximately one million deaths per year, particularly among children under five years old and pregnant women (WHO, 2008a). Malaria is endemic in 109 countries, the majority located in the intertropical belt of Africa, Asia and Latin America (Fig. 1A). The highest malaria burden is found in Africa with an estimation of 212 million cases (86% globally) distributed in 45 countries (Table 1). The other continents contribute the remainder of the 35 million cases (WHO, 2008a). Effective control of malaria in many countries is aggravated by inadequate health infrastructure and overall poor socioeconomic conditions. The situation has become more complicated during the last 50 years with the increase in resistance to anti-malarial drugs used to combat the infections and development of insecticide resistance in *Anopheles* mosquitoes that serve as vectors (Manguin et al., 2008a; Mouchet et al., 2004).

After malaria, LF is regarded the second most common global arthropod-borne infectious disease with an estimated burden of 128 million people infected distributed over 78 endemic countries (Table 1) (WHO, 2008b). Like malaria, the predominance of LF infections are found in humid tropical areas of Asia, Africa, the western Pacific and scattered areas of the Americas (Fig. 1B, Table 1) with an estimated 1.3 billion people at-risk for developing new active LF infection annually (WHO, 2008b). Southern and southeast Asian regions have by far the greatest number of people (891 million) at-risk for LF (68% globally), with 454 million people at-risk in India alone (WHO, 2008b). Tropical Africa represents the second largest number of people at-risk, estimated at 382 million in 2007 (30% globally) and 51 million cases which for most of them are deemed seriously afflicted with disabilities and disfigurement (Lindsay and Thomas, 2000; Michael and Bundy, 1997; Muturi et al., 2008; WHO, 2008b). In 2005, countries under the Southeast Asia Programme Review Group (PRG) for LF elimination targeted nearly 543 million (~61%) of their at-risk population, while 44 million (~12%) were the focus of African countries (WHO, 2008b).

Among the three human LF parasites, *Wuchereria bancrofti* (Cobbald, 1877) Seurat, 1921 is by far the most prevalent. The parasite in its various 'periodic' forms is cosmopolitan occurring in tropical, subtropical and temperate regions of South Asia, East Asia, Africa, the western Pacific, and more restricted locations in the Americas (Michael and Bundy, 1997; Sasa, 1976). Infection from *W. bancrofti*, although not fatal, is considered a leading cause of infirmity, permanent disability and chronic morbidity, often resulting in societal stigma of disfigured victims (Fig. 2).

The four human Plasmodia are exclusively transmitted by *Anopheles* mosquitoes, of which approximately 70 species (~15% of all known anophelines) are considered to be of epidemiological significance (Manguin et al., 2008a; Service and Townson, 2002; WHO, 1989). *W. bancrofti* is mainly transmitted by *Culex* and *Anopheles* mosquito species for the nocturnally periodic form or by select members in the genera *Aedes*, *Downsiomyia* and *Ochlerotatus* for the two subperiodic forms (nocturnal and diurnal) occurring in southeastern Asia and the western Pacific.

The World Health Organization (WHO) have established two global initiatives, one for reducing malaria and the other for eliminating LF; Roll Back Malaria (RBM) and Global Programme to Eliminate Lymphatic Filariasis (GPELF), respectively. The ambitious aim of these programs is to relegate these two diseases as non-public health priorities by years 2025 and 2020, respectively. One advantage in favour of combating these two diseases is that both human Plasmodia and *W. bancrofti* lack epidemiologically significant non-human reservoir hosts. Being anthroponotic infections eliminates a major complicating factor when attempting to control or eradicate these two diseases. In fact, LF is one of the six infectious diseases considered 'eradicable' by WHO. Since 1997, the

Fig. 2. Elephantiasis (lymphoedema) of lower limb due to *Wuchereria bancrofti* infection. ftp://ftp.cdc.gov/pub/infectious_diseases/iceid/2002/pdf/ottesen.pdf.

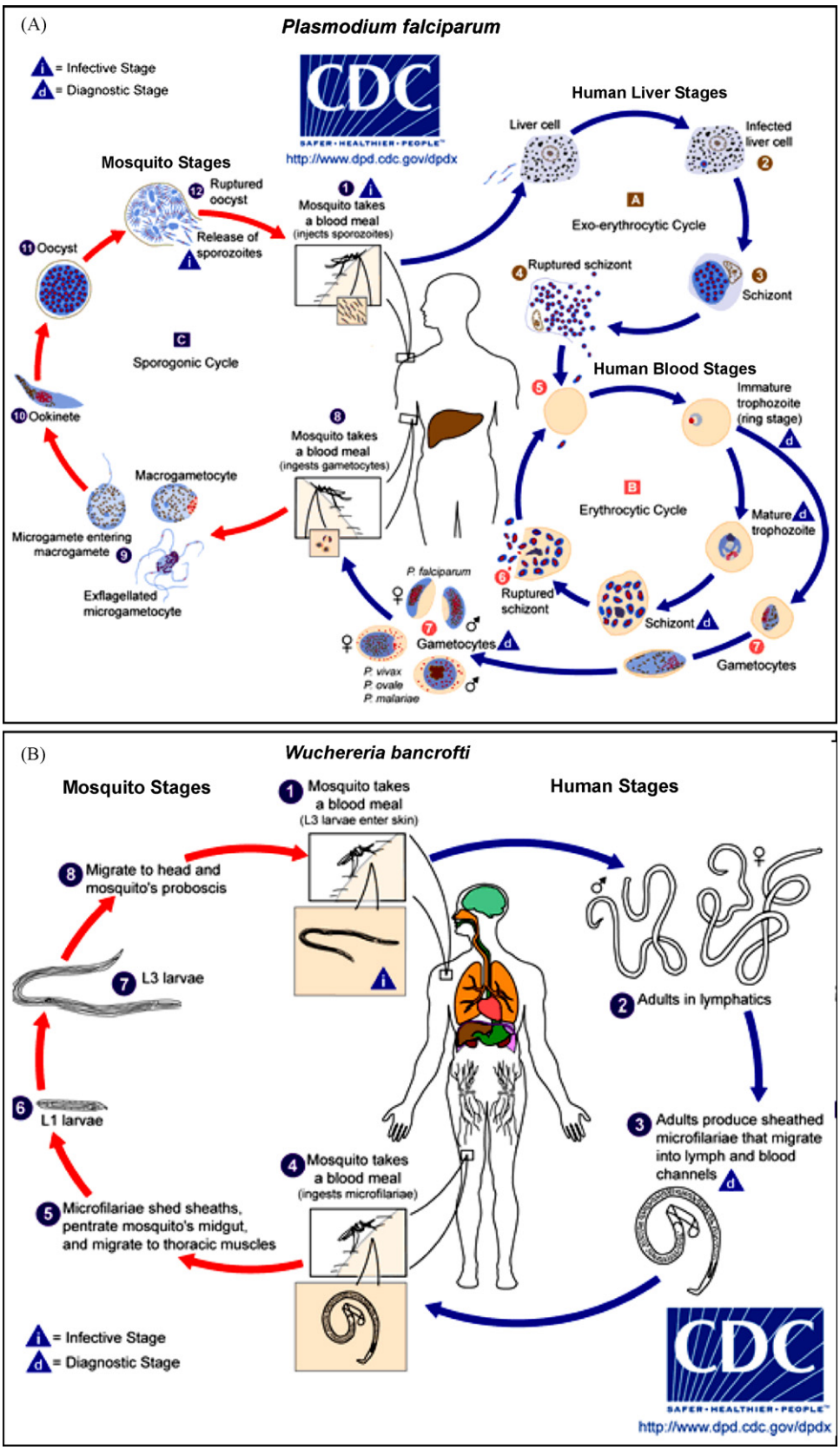

Fig. 3. Life cycle of the two diseases; (A) *Plasmodium falciparum*; and (B) *Wuchereria bancrofti*, with a note on terminology. http://www.dpd.cdc.gov/dpdx. *Note on terminology*:**-.** *Microfilaria rate* (mf rate): percentage of population found carrying microfilariae in their blood at the time of the survey, synonymous with infection rate.**-.** *Disease rate*: percentage of the population which has been reported as suffering from disease thought to be attributable to filarial infection.**-.** *Infection rate of vectors*: proportion of vectors examined and found infected with filarial larvae at any stage of development and belonging to a determined species.**-.** *Infectivity rate*: same as above but with vectors harbouring infective stage (third) larvae.**-.** *Elephantiasis*: disabling and disfiguring chronic lymphoedema of the limbs, breasts or genitals, accompanied by marked thickening of the skin.**-.** *Lymphoedema*: abnormal accumulation of lymph fluid in the tissues, causing swelling of a limb or other parts of the body which are then more

Table 2
Characteristics of the three human lymphatic filarial species.

Lymphatic filarial species	Form	Prevalence (Estimation of global burden)[a]	Vectors (mosquito genera or species)	Reservoir	Parasite incubation period[b]
Wuchereria bancrofti	Nocturnal periodic (NP) and subperiodic (NSP), diurnal subperiodic (DSP)	Worldwide tropical regions (115 million – 90%)	*Anopheles, Aedes, Culex, Ochlerotatus, Downsiomyia, Mansonia*	Human	4–15 months
Brugia malayi	Nocturnal periodic (NP) and subperiodic (NSP)	Asia: Southern Asia and scattered areas in southern and western India, Sri Lanka and Southeast Asia (13 million – 10%)	*Anopheles, Ochlerotatus, Mansonia, Coquillettidia*	Human, domestic cat, monkeys, feral carnivores	3–5 months
Brugia timori	Nocturnal periodic (NP)	Lesser Sunda Islands (Timor, Flores, Rote, Sumba, Alor) and Timor-Leste (500,000–800,000)[c]	*Anopheles barbirostris*	Human	3–5 months
		Total estimated cases: 128 million at-risk population >1 billion			

[a] Estimations of the global burden of each LF species are given in Fischer et al. (2004), Michael and Bundy (1997), and WHO (2006).
[b] Pre-patent period variable depending on intensity of infection and ability of adult worms to mate and produce microfilariae.
[c] Estimation between 500,000 and 800,000 cases depending on the source (Bangs MJ, unpublished data; Fischer et al., 2004).

GPELF program has been directed to all persons living in at-risk communities by providing once annual oral treatment, using a two-drug combination, either albendazole + ivermectin, or albendazole + diethylcarbamazine (DEC) for the elimination of microfilariae (mf) in the blood and disruption of adult female reproductive capacity (WHO, 2008b). However, there is a concern that mass drug administration (MDA) campaigns may fail to maintain adequate treatment coverage to achieve complete LF elimination. Many challenges to a LF elimination strategy remain including uncertainty of the threshold and duration of mf suppression required to achieve elimination, the uncontrolled mobility of infected individuals (i.e., loss to follow-up), non-participation of some infected individuals, and the possible development of resistance to the aforementioned anti-filarial drugs (Crompton and Savioli, 2007). An integrated approach using both vector control to prevent infection from mosquito bites and MDA to suppress microfilaremia in human populations, thus reducing potential of infecting susceptible mosquito vectors, may likely be the best strategy to overcome some of these challenges (Burkot et al., 2006). The potential benefits of vector control would include: (1) the ability to suppress filariasis transmission without the need to identify all individual reservoirs of disease ('foci of infection'); (2) minimizing the risk of reestablishment of transmission from imported microfilaremic individuals; and (3) decreasing the risk of dengue (in the western Pacific) and malaria transmission where *Aedes* or *Anopheles* species serve as vectors for both LF and either dengue or malaria, respectively.

For a better understanding of the co-transmission of malaria and Bancroftian filariasis by *Anopheles* mosquitoes, this review compares the two diseases biologically and the biodiversity that define the various, and sometimes unique epidemiologic situations in each region, the environmental and climatic factors that influence transmission, and the current understanding on their co-transmission globally. We focus on Thailand as an excellent case study of a national control strategy based on integrated RBM and GPELF principles.

2. Disease and lifecycle

2.1. Malaria

Protozoan parasites of the genus *Plasmodium* are responsible for human malaria, of which four species are primarily involved, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*. Recent reports have suggested the possibility of a fifth species, *Plasmodium knowlesi*, as an important and common emerging zoonotic pathogen responsible for human infections in Southeast Asia (Cox-Singh et al., 2008). Globally, *P. falciparum* is the most common cause of malarial infection, responsible for approximately 80% of all cases and 90% of the deaths. *Plasmodium* transmission from *Anopheles* vector to human is accomplished through direct injection of the parasite contained in salivary gland fluid during blood feeding (Fig. 3A). Of the 484 recognized species of *Anopheles* (Harbach, 2004), only about 20% or less are generally involved in malaria transmission (Bruce-Chwatt, 1980; Manguin et al., 2008a). In the lifecycle, the *Anopheles* mosquito is the definitive host for the parasite, where sexual reproduction between male and female gametes occurs, whereas the human technically serves as the intermediate host where only asexual multiplication takes place. *Anopheles* females become infected by imbibing sexually mature gametocytes present in the peripheral blood of the host. In the mosquito midgut fertilization produces the ookinete which traverses the mosquito gut and forms an oocyst under the outer most layer of the gut wall. After repeated multiplication, each oocyst eventually ruptures releasing hundreds of sporozoites into the mosquito body cavity, a proportion of which will invade the salivary glands awaiting the opportunity to infect another human upon the next blood feeding by the mosquito. This sporogonic cycle (ookinete–oocyst–sporozoite) within the mosquito takes on average 10–14 days depending on the ambient temperature and *Plasmodium* species. Infective female mosquitoes will generally remain infectious during their entire life which is spent repeating a cycle of blood feeding, developing and laying eggs every two to three days per gonotrophic cycle.

2.2. Lymphatic filariasis

This disease is caused by macroscopic nematode pathogens, of which *W. bancrofti* is responsible for 90% of all human LF infections. The remaining 10% are due to two species of the genus *Brugia* and occur only in Asia (Fig. 1B, Table 2). In some localities (e.g., Indonesia) dual *Wuchereria* and *Brugia* parasitism can be present in the same person. There are three variants of *W. bancrofti* recognized on periodicity patterns of circulating mf found in peripheral blood of humans; namely, the nocturnally periodic (NP), nocturnal subperiodic (NSP) and diurnal subperiodic (DSP) forms

susceptible to repeated bacterial infections.-. *Lymphangitis*: inflammation of a lymphatic vessel or vessels.-. *Lymphadenitis*: inflammation of the lymph nodes.-. *Lymphangiectasia*: dilatation of the lymphatic vessels.-. *Hydrocoele*: fluid-filled balloon-like enlargement of the scrotal sac around the testes which, if left untreated, can destroy the testicles.-. *Chyluria*: presence of lymph (chyle) in the urine, giving it a milky appearance.

(Table 2). Periodicity is based on the prevailing circadian distribution of mf in the peripheral blood, e.g., the nocturnally periodic form presents the majority of mf by night (peak periodicity 2200–0300 h) with very few observable by day as they sequester in the lungs. This striking pattern of periodicity is the apparent biological adaptation to the nocturnal biting habits of the primary vectors, either *Anopheles* species in rural areas or *Culex quinquefasciatus* in typical urban settings (Buck, 1991). The NP variant is responsible for the vast majority of infections occurring worldwide but with patchy distributions within the tropical and subtropical belt (Fig. 1B). NP probably represents the most highly evolved variant, able to utilize a wide variety of mosquito genera (six) and occurs in both urbanized and rural areas (Mak, 1987). The two subperiodic forms (also called 'non-periodic' types), are far more restricted in distribution (Fig. 1B). The NSP form is mainly seen in southern Asia, especially in Thailand along the border with Myanmar, northern Vietnam, Sabah (Malaysian Borneo), and the Philippines (Harinasuta et al., 1970; Mak, 1981; Meyrowitsch et al., 1998; Pothikasikorn et al., 2008). The DSP form appears restricted to island groups in the south-western Pacific and the Indian Ocean islands of Nicobar and Andaman (Fig. 1B). Microfilariae of the two subperiodic forms are present in the peripheral blood 24 h a day with peak densities typically seen in the late afternoon and early evening hours (1800–2000) (Gould et al., 1982). The presence of subperiodic mf is strongly correlated with the preferred hours of blood feeding of its primary vectors belonging to the genera *Aedes* and *Ochlerotatus* (Mak, 1987), many of which are diurnally active species.

More than 70 species of mosquitoes within six different genera are known vectors of *W. bancrofti* (Table 3), including *Anopheles* (43 spp.), *Aedes*/*Ochlerotatus*/*Downsiomyia* (approximately 20 spp.), *Culex* (6 spp.), and *Mansonia* (3 spp.) (Rao, 1984; Service, 1993; Suvannadabba, 1993; WHO, 1989; Zagaria and Savioli, 2002). Among the anophelines, 36 species are capable of both malaria and LF transmission, 26 of which are regarded as major LF vector species (Table 3) (WHO, 1989). Bancroftian filariasis and *Brugia malayi* are unique among the vector-borne parasitic diseases in that larval development can take place in several genera of mosquitoes (Table 2). As modified from Bockarie et al. (2009), three main zones of LF transmission are recognized herein: (i) West Africa, Southeast Asia (rural areas), New Guinea Island, Vanuatu and Solomon Islands, where *Anopheles* mosquitoes are the principal vectors; (ii) East Africa, Middle East (Egypt, Yemen), Southeast Asia (urban zones), and the Latin American region where the infection is transmitted mainly by *C. quinquefasciatus* and *Culex pipiens* group; and (iii) the south-western Pacific islands and limited areas of Southeast Asia where aedine (*Aedes*, *Ochlerotatus*, *Downsiomyia* spp.) vectors play a dominant role.

After microfilaria (mf) are imbibed with the blood meal by the female mosquito, they reach and penetrate the abdominal midgut (stomach) wall into the hemocoele to migrate to the insect's thoracic flight muscles to begin development (Fig. 3B). Microfilariae do not reproduce in the vector but rather each worm completes two intermediate larval stages (L1 and L2) molts to become a third-stage (L3) infective parasite; the L3 eventually breaks free from the flight muscles into the hemocoele and ultimately end up in the insect's head lodged in or near the labium of the proboscis. As for malaria parasite, the filarial development cycle within the mosquito takes approximately 10–14 days and is also temperature dependent. When the mosquito returns to blood feed, the 1.2–1.6 mm long L3 infective larvae will break through the cuticle or emerge from the tip (labellum) of the labium onto the skin. The parasite is thus 'indirectly' transmitted and must enter the host body via an open portal (e.g., the mosquito bite wound or a nearby break in the skin) (Fig. 3B). In contrast to malaria, the vector's salivary glands play no direct role in transmission, whereas high ambient humidity and skin moisture favour successful transmission.

After entering the host body, the L3 is transported via the lymphatic vessels to lymph nodes to begin development (following two intermediate molts) into mature adult male or female worms (0.2 mm wide and up to 10 cm long). For *W. bancrofti* it takes a period of four to 15 months (possibly longer) before the appearance of mf in the peripheral blood. Contrary to *Plasmodium*, the mosquito acts as the intermediate host and humans serve as the definitive host for *Wuchereria* and *Brugia* spp., wherein mature male and female worms mate and females produce copious numbers of microscopic mf (250–300 μm long, 8 μm wide). The adult worms are usually present in the lymphatic system, with mated females producing up to 50,000 mf per day, most of them finding their way into the blood circulation. Adult worms live for an estimated four to six years, but may survive up to 15 years or more with each producing ten of millions of mf in their lifetime. Microfilariae are believed to survive and circulate freely in the blood of the human host for many months, possibly longer, while awaiting an opportunity of being picked up by mosquitoes.

The reliance on mosquito-borne transmission can translate to marked geographical heterogeneity in parasite prevalence in the human population based on local transmission efficiency and biting intensity of local vectors, i.e., limited transmission in one locality, yet only a few kilometers distance, transmission might be magnitudes more intense. A number of biological and physical factors can play a significant role in the distribution and prevalence of *W. bancrofti*. It is noteworthy that the parasite is inefficiently transmitted, it is estimated to require many repeated exposure, between 2700 and one million infective mosquito bites to produce one new human case presenting with patent microfilaremia (Hairston and de Meillon, 1968; Southgate, 1984). Furthermore, many anopheline mosquitoes are not particularly competent vectors for successfully developing parasites when microfilarial intensity is low (Bockarie et al., 1998).

Depending on the transmission intensity, the LF infection is usually acquired early in childhood, although a period of 10–20 years of exposure may be required before presenting characteristic morbid manifestations visible at adolescence and adulthood. Although the chronic physical phase of the disease afflicts only a small percentage of those infected, in its most apparent forms, LF morbidity can result in temporary or permanent infirmity. The most obvious condition, elephantiasis, is the result of lymphoedema of the extremities, and frequently associated with lymphadenopathy, lymphangitis, hydrocoele (in males) and chyluria (Crompton and Savioli, 2007). The result is often painful and gross enlargement of the legs (Fig. 2) and arms, the genitals, vulva and mammary glands. The complex pathology was once attributed to physical lymphatic duct obstruction and worm calcification. Some evidence has shown that the pro-inflammatory response is actually directed at *Wolbachia* symbionts of the parasites (Taylor and Hoerauf, 1999). However, the best explanation appears to be a combination of host reactions to molecules released by living adult worms causing dilatation of the affected lymphatic vessels (lymphangiectasia) thereby disrupting the flow of lymph. Taken together with a variety of associated co-factors (e.g., long-term recurrent bacterial infections) and other host immune responses promoting acute inflammatory attacks in response to infection, the progression of lymphoedema appears magnified over time (Dreyer et al., 2000). Additionally, adult worms and mf can also cause internal damage and disease to other organs such as kidneys and lungs. The psychological and social stigmas associated with the disease are immense and it has a major social and economic impact in countries where 10–50% of men and up to 10% of women can be adversely affected due to permanent damage to the lymphatic system.

Table 3
List of the main and secondary vectors of Bancroftian filariasis, and *Anopheles* vectors susceptible to co-transmit both *Plasmodium* and *W. bancrofti* by alphabetic order with references in relation to the geographic region.

Regions	Main vectors of Bancroftian filariasis[a] (secondary or incidental vectors)	*Anopheles* vector species co-transmitting *Plasmodium* and *W. bancrofti* (primary and secondary)[b]	References
Asia[c]	*An. baimaii* (former *An. dirus* D) *An. balabacensis* *An. culicifacies* s.l. *An. dirus* (former *An. dirus* A) *An. donaldi* *An. flavirostris* *An. jeyporiensis*[d] *An. lesteri*[e] *An. letifer* *An. leucosphyrus* (former *An. leucosphyrus* B) *An. maculatus* *An. minimus* *An. sinensis* *An. subpictus* *An. tessellatus*[f] *An. vagus* *An. whartoni* *Downsiomyia harinasutai* *Downsiomyia nivea*[g] *Ochlerotatus harveyi* *Ochlerotatus poicilius* *Aedes annandalei* *Aedes desmotes* *Culex pipiens pallens* *Culex quinquefasciatus* *Mansonia dives* *Mansonia uniformis* (*An. aconitus*) (*An. barbirostris*) (*An. jamesii*) (*An. kweiyangensis*) (*An. latens*, former *An. leucosphyrus* A) (*An. nigerrimus*) (*An. philippinensis*) (*Culex bitaeniorhynchus*) (*Culex sitiens* spp. complex) (*Ochlerotatus togoi*)	*An. aconitus* *An. baimaii* (former *An. dirus* D) *An. balabacensis* *An. barbirostris* *An. culicifacies* s.l. *An. dirus* (former *An. dirus* A) *An. donaldi* *An. flavirostris* *An. latens* (former *An. leucosphyrus* A) *An. lesteri*[e] *An. letifer* *An. leucosphyrus* (former *An. leucosphyrus* B) *An. maculatus* *An. minimus* (former *An. minimus* A) *An. philippinensis* *An. sinensis* *An. subpictus* *An. tessellatus* *An. vagus*	Rattanarithikul et al. (2005, 2006) Sallum et al. (2005) Harinasuta et al. (1970) Chang et al. (1995) Hii et al. (1985) Ministry of Public Health (1998) Gould et al. (1982) Ravindran et al. (1998) Chow (1973) Jinjiang (1985) Rozeboom and Cabrera (1964) WHO (1987, 1989) Service (1993) Zagaria and Savioli (2002) Manguin et al. (2008a, 2008b) Kettle (1995)
	Total potential LF vectors: 36 (6 genera)	Total potential malaria-LF vectors: 19	
Middle East[h]	*Culex pipiens*[i] *Culex quinquefasciatus* (*Culex antennatus*)		WHO (1987)
	Total potential LF vectors: 3 (*Culex* spp.)	Total potential malaria-LF vectors: 0	
New Guinea	*An. farauti* s.l. *An. koliensis* *An. punctulatus* *Culex quinquefasciatus* (*Ochlerotatus kochi*) (*An. bancroftii*) (*Culex annulirostris*) (*Culex bitaeniorhynchus*) (*Mansonia uniformis*)	*An. bancroftii* *An. farauti* s.l. *An. koliensis* *An. punctulatus*	Hawking and Denham (1976) Alexander et al. (2003) Burkot et al. (1990b) Attenborough et al. (1997) Bockarie et al. (2002) Chow (1973) WHO (1987)
	Total potential LF vectors: 9 (4 genera)	Total potential malaria-LF vectors: 4	
Polynesia	*Aedes polynesiensis* *Aedes*, *Ochlerotatus* (10+ species)		WHO (1989)
	Total potential LF vectors: 10+ (2 genera)	Total potential malaria-LF vectors: 0	
Tropical Africa	*An. arabiensis* *An. funestus* *An. gambiae* *An. melas* *An. merus* *Culex quinquefasciatus* (*An. bwambae*) (*An. hancocki*) (*An. nili*) (*An. pauliani*) (*An. pharoensis*) (*An. wellcomei*)	*An. arabiensis* *An. bwambae* *An. funestus* *An. gambiae* (Mopti, Savanna forms) *An. melas* *An. merus* *An. nili* *An. pharoensis* *An. wellcomei*	Dzodzomenyo et al. (1999) Lok et al. (2000) Appawu et al. (2001) Dunyo et al. (1996) Kelly-Hope et al. (2006) Manguin et al. (2008a) Zagaria and Savioli (2002) Brengues et al. (1968) WHO (1987, 1989) Service (1993)

Table 3 (*Continued*)

Regions	Main vectors of Bancroftian filariasis[a] (secondary or incidental vectors)	*Anopheles* vector species co-transmitting *Plasmodium* and *W. bancrofti* (primary and secondary)[b]	References
	(*Culex antennatus*)		
	Total potential LF vectors: 13 (2 genera)	Total potential malaria-LF vectors: 9	
Tropical Americas	*An. darlingi* *Culex quinquefasciatus* (*Aedes scapularis*) (*Aedes taeniorhynchus*) (*An. albimanus*) (*An. aquasalis*) (*An. bellator*) (*Mansonia titillans*)	*An. albimanus* *An. aquasalis* *An. bellator* *An. darlingi*	Chadee et al. (2003) Hawking (1979) Zagaria and Savioli (2002) Manguin et al. (2008a) WHO (1987, 1989)
	Total potential LF vectors: 8 (4 genera)	Total potential malaria-LF vectors: 4	

[a] Bancroftian filariasis forms = nocturnal periodic (NP): worldwide with patchy distribution in tropical to subtropical regions; nocturnal subperiodic (NSP): Southeast and southern Asia (predominant in Thailand, also reported in Vietnam, Sabah – Malaysia, and Philippines) (Mak, 1981); and diurnal subperiodic (DSP): Australasia, W. Pacific, Andaman and Nicobar islands – India (Shriram et al., 2002, 2008).
[b] *Wuchereria bancrofti* of the NP form (worldwide).
[c] Asia: South, Southeast and Far eastern regions.
[d] *An. jeyporiensis*: also cited in the literature as variant candidiensis (Knight and Stone, 1977).
[e] *An. lesteri*: synonymy with former *An. anthropophagus* (Harbach, 2004).
[f] *An. tessellatus*: considered a secondary *W. bancrofti* vector in WHO (1987) and a primary one in Service (1993).
[g] Possible involvements of other *Downsiomyia* species (Finlaya Niveus group) (Reinert and Harbach, 2006).
[h] Middle East: Egypt, Yemen.
[i] *Culex pipiens*: synonymy with former variant *Culex molestus* (Ward, 1992).

3. Co-transmission of both diseases and diagnosis techniques

3.1. Co-transmission of both diseases

Interaction of co-infection between parasites and effects on the fitness and survival of vectors is poorly known or incomplete and based on only a handful of studies. Interspecies competition exists between *W. bancrofti* and *Plasmodium* within *Anopheles* mosquitoes and the human host, whereby one parasite entity appears to influence the development of the other, or vice versa, while sharing the same *Anopheles* vectors (Kelly-Hope et al., 2006). For instance, the physical disruption of the midgut by migrating mf may facilitate the penetration of parasites into the hemocoele, which may be responsible for the high number of *W. bancrofti* larvae observed in *Plasmodium*-infected *Anopheles punctulatus* (Burkot et al., 1990b), as well as the significantly higher sporozoite rates in *Wuchereria*-infected *Anopheles gambiae* than in non-infected mosquitoes (Muturi et al., 2006a). The natural defense mechanisms of a dual-infected vector may also be influenced to the benefit or determent of one or both parasites. There are a number of potential physical, cellular and humoral defense mechanisms an infected mosquito can mount against the invading and developing parasites, some of which can prevent infection or effectively arrest development in the mosquito host (Christensen, 1986; Nelson, 1964). Well described mechanisms such as the influence of physical damage on mf caused by pharyngeal and/or cibarial armature (Shoukry and Soliman, 1995) and melanotic encapsulation of larval stages (Christensen et al., 2005) have joined new knowledge on specific molecules involved in cellular signalling, proteolysis, stress response, transcriptional regulation and repair (Erickson et al., 2009). Other factors may also have an impact on parasite development in mosquitoes, such as resistance to insecticides that appears to inhibit normal development of mf in the vector (McCarroll et al., 2000). The vectorial capacity of mosquito vectors may be influenced by interaction between the two pathogens, thus affecting susceptibility (competence) and transmission (capacity) of one or both. Mixed malaria and filarial infections can affect vector survival and flight behaviour resulting to reduced transmission of both parasites simultaneously (Bryan, 1986; Klein et al., 1986; Kutz and Dobson, 1974; Townson, 1970). Therefore, multiple infections in mosquitoes are of no apparent advantage to parasite transmission (Bryan, 1986); consequently, simultaneous transmission of the two parasites is considered rare. This has been documented in Tanzania (Muirhead-Thomson, 1953) and along the Kenyan coast where a very low percentage of *An. gambiae* (0.06% and 0.4%) have been found harbouring the infective stages of both parasites, respectively (Kubasu, 1997; Muturi et al., 2006a).

Although little information is available on the interactions between both parasites during concomitant infection in humans, some studies have revealed that the intensity of *P. falciparum* is generally lower in microfilaremic individuals than in amicrofilaremic ones (Ghosh and Yadav, 1995) and filarial infections may have either benign or suppressive effects on malaria development (Schmidt and Esslinger, 1981; Yan et al., 1997). Therefore, there are probably interactions between malaria and filarial parasites that may influence the clinical presentation, pathogenicity, and even epidemiology of the disease (Ghosh and Yadav, 1995). Although potential vectors may be plentiful, the actual number of simultaneous infections in humans appears lower than expectations; for example in Orissa, India, only 0.3% of the blood smears examined harboured both parasites (Ravindran et al., 1998). Environmental factors may influence the duration of transmission of parasites, for instance a higher prevalence of *W. bancrofti* in Burkina Faso coincides with a shorter malaria transmission season, suggesting that periodic seasonal malaria incidence may affect the transmission success of filariasis in an area; while, perennial, high-intensity malaria may inhibit filarial development in the human host (Schmidt and Esslinger, 1981).

3.2. Application of diagnosis techniques, from traditional to molecular methods

For estimating the co-transmission of both diseases and for evaluating the impact of malaria or filariasis control programmes, it is quite important to monitor infection in mosquitoes (Gage et al., 2008). For filarial and malaria parasites, traditional methods of diagnosis based on Giemsa-stained peripheral blood films, phosphatase detection of mf, the Knott concentration procedure, and membrane filtration techniques, are often tedious and labour-

intensive that require expertise to detect, and when possible, identify the species (Ash and Orihel, 1987). The same applies for standard mosquito dissection techniques for observing sporozoites in salivary glands (WHO, 1975) and detection of filarial worms in thoracic flight muscles and hemocoele (Ramachandran, 1970). Consequently, well-trained microscopists are often required but in short supply in many countries where these infectious diseases are endemic. To overcome some of these difficulties, a number of immunologic techniques, e.g., enzyme-linked immunosorbent assays (ELISAs) and immuno-chromatographic (ICT) tests, have been developed as alternatives for accurate assessment of the prevalence of these pathogens in human and vector populations (Nuchprayoon et al., 2003; Wirtz et al., 1985). Recently, even simpler to use, more sensitive diagnostic assays, based on more advanced ICT technology or polymerase chain reaction (PCR), are being used for facilitating parasite detection and better apprehending the epidemiological and clinical course of malaria and LF infections. Highly sensitive species-specific ICTs that have useful applications where there is no evidence (host is apparently amicrofilaremic) of mf in the blood have been developed for the rapid detection of *W. bancrofti* infection (Weil et al., 1997). Similar wicking assay technology has been developed using either antigen or antibody detection formats for the diagnosis of malaria in humans and sporozoites in infected mosquitoes (Bangs et al., 2002; Wirtz et al., 1985; Wongsrichanalai, 2001).

Essential to the success of control programmes is the availability of simple and accurate tools to monitor presence or absence of parasites in mosquitoes and humans, thereby better assessing the effectiveness of control interventions. For instance, LF prevalence can be greatly underestimated when using a standard microscopic method compared to immunological tests (6% compared to 22% or 54% based on LF antigens or antibody detection tests, respectively) (Nuchprayoon et al., 2003). The use of advanced techniques with higher assay sensitivity and specificity, such as PCR assays, may be necessary to obtain a truer measure of disease prevalence. Molecular 'xenomonitoring' by detection of parasite DNA in host-seeking (non-blooded) and blood-fed vectors as a means of indirectly measuring human infectious diseases has been developed using several sensitive PCR assays for detecting filarial or *Plasmodium* DNA in mosquitoes (Bockarie et al., 2000; Chanteau et al., 1994; Goodman et al., 2003; Ramzy et al., 1997; Rao et al., 2006; Rougemont et al., 2004; Vasuki et al., 2008; Williams et al., 2002). Although a PCR-based method for the detection of filarial larvae in mosquitoes was developed in the early 1990s (Chanteau et al., 1994; Ramzy et al., 1997), the technique has been improved to become a more practical tool for routine monitoring (Chadee et al., 2002). As a result, a more sensitive restriction fragment length polymorphism (RFLP)-PCR assay (detection of as little as 0.1 pg of *W. bancrofti* genomic DNA) based on SspI enzyme restriction of a highly repeated 188 bp DNA sequence of *W. bancrofti*, has been standardized and validated (Chansiri and Phantana, 2002; Farid et al., 2001; Williams et al., 2002). Another RFLP-PCR assay, based on the amplification and digestion by Ase I of the internal transcribed spacer 1 (ITS-1) sequence, has been developed for the detection of a broad range of filarial species (Nuchprayoon et al., 2005). PCR becomes highly advantageous in hypoendemic LF areas seeking disease elimination and requiring sensitive monitoring and many wild-caught mosquitoes be tested. An algorithm has been developed using a PCR-based method and up to 50 pooled mosquitoes per assay for parasite detection. A software program, Poolscreen 2.0 (trunnasch@geomed.dom.uab.edu), allows the calculation of the estimated prevalence of infection in the vector population based on the size of the pool and proportion of negative pools screened (Chadee et al., 2002). These PCR-based assays would prove particularly useful for widespread application and xenomonitoring of transmission during the implementation of large-scale control programmes.

3.3. Concomitant detection of W. bancrofti and malaria parasites

Two PCR-based assays have been developed for simultaneously detecting both parasites, *W. bancrofti* and *Plasmodium* spp. in a single vector. One is a multiplex assay that uses a set of four primers amplifying the 400 and 450 bp fragments for *W. bancrofti* and the 208 bp fragment for *P. falciparum* (Chansiri et al., 2001). The other is a real-time multiplex quantitative PCR that can simultaneously detect *W. bancrofti*, *P. falciparum* and *P. vivax* in mosquitoes with higher sensitivity than conventional PCR assays by allowing the detection of lower levels of initial parasite DNA (Rao et al., 2009). It is envisaged that continuing advances in molecular detection technology will result in development of simpler and quicker testing methods that can be more easily deployed in the field.

4. Vectors in different world regions

4.1. Asia

Although this region has an estimated total at-risk population of 67% and 68% for malaria and LF, respectively, it is by far the most important region globally in terms of number of active filarial infections, contributing approximately 59% of the world's burden distributed over 15 countries[1] (Table 1). More than 70% of the LF cases occur on the Indian subcontinent, particularly India, Bangladesh, Maldives, Nepal, and Sri Lanka. Recent surveys carried out in China and Korea indicate that these two countries may no longer have active foci (WHO, 2008b) and only the southern region of Laos may still have LF transmission (WHO, 2007a). There are two types of LF in Asia, Bancroftian (*W. bancrofti*) and *Brugian* (*Brugia malayi* and *Brugia timori*) filariases (Table 2, Fig. 1B). Bancroftian filariae in their various forms are transmitted by *C. quinquefasciatus* (85%), *Anopheles* spp. (9%), and *Aedes*/*Ochlerotatus*/*Downsiomyia* (1%) and *Mansonia* spp. (5%) (Zagaria and Savioli, 2002); Brugian filariae are predominately found in rural locations and are vectored by *Anopheles* and *Mansonia* species mosquitoes for *B. malayi*, and by *Anopheles barbirostris* for *B. timori*. *Brugia malayi* occurs from scattered areas of India (south and north-east) and Sri Lanka to Southeast Asia (northern Cambodia, Vietnam, Indonesia, Malaysia, and the Philippines (Chhotray et al., 2005; Leang et al., 2004; Mak, 1981; Meyrowitsch et al., 1998; Schweinfurth, 1983). *B. timori* is restricted to a small group of islands of the Lesser Sunda Archipelago, primarily Timor, Flores, Rote, Alor, and Sumba (Joesoef and Cross, 1978; Mak, 1987). On Flores and nearby islands (e.g., Alor), *B. timori* has been found co-endemic with *W. bancrofti* (Fischer et al., 2004). Given the geographical extent and prevalence of LF, the presence of all three periodicity forms of *W. bancrofti* in the Asian region, together with the two human-infecting *Brugia* species (Fig. 1B), suggests Southeast Asia as the likely ancestral habitat for these parasites and from which *W. bancrofti* eventually disseminated to the other continents (Hawking, 1976).

The bionomics, ecology and epidemiological importance of *Anopheles* vectors involved in the transmission of both malaria and filariasis remain poorly understood in Southeast Asia (Muturi et al., 2008). In Asia (Table 3), at least 36 mosquito species belonging to six genera have been incriminated as either primary or secondary vectors of *W. bancrofti*, with a majority being *Anopheles* species (24

[1] 15 countries in Asia: Bangladesh, Brunei, Cambodia, India, Indonesia, Laos, Malaysia, Maldives, Myanmar, Nepal, Philippines, Sri Lanka, Thailand, Timor-Leste, Vietnam.

spp.) followed by aedine mosquitoes (7 spp.), *Culex* (4 spp.), and two *Mansonia* (*M. dives*, *M. uniformis*) (Pothikasikorn et al., 2008; Service, 1993; WHO, 1989). Based on our review, at least 19 *Anopheles* species have been implicated in the transmission of both malaria and LF parasites in Asia.

Malaria and LF parasites can and do naturally share the same vectors, in particular species of the *Anopheles dirus* and *Anopheles minimus* complexes, the *Anopheles maculatus* group, *Anopheles aconitus* and *Anopheles vagus* (Chareonviriyaphap et al., 2000; Harinasuta et al., 1970, 1971; Pothikasikorn et al., 2008; Prakash et al., 2004; Sallum et al., 2005). In Banggi Island (northeastern Sabah, Malaysia), *Anopheles balabacensis* and *Anopheles flavirostris* have been reported as vectors of malaria and Bancroftian filariasis and responsible for maintaining holo- to hyper-endemic levels of both diseases (Hii et al., 1985). In Sarawak (Malaysian Borneo), *An. barbirostris*, *Anopheles donaldi*, *Anopheles letifer*, and *Anopheles latens* (formerly *Anopheles leucosphyrus* A), are considered vectors for malaria and Bancroftian filariasis (Chang et al., 1995; Rahman et al., 1997). Eastern Indonesia presents a unique situation in which malaria, together with *W. bancrofti* and *B. timori* co-circulate and are transmitted by *Anopheles subpictus* and *An. barbirostris*, respectively (Fischer et al., 2004; Hoedojo et al., 1980; Lee et al., 1983). In Orissa, India, *Anopheles culicifacies* s.l. has been incriminated as the vector of *P. falciparum* and *W. bancrofti* with a human disease prevalence of 9.6% and 8.5%, respectively, and approximately 0.3% of the population with concurrent dual infections (Ravindran et al., 1998). In southern China, at least four *Anopheles* species, *An. dirus* s.l., *Anopheles lesteri*, *An. minimus* s.l., and *Anopheles sinensis* appear involved in the natural transmission of both malaria and *W. bancrofti* (Chen et al., 2002; Jinjiang, 1985). Expanded and more exhaustive entomological surveys and a greater use of molecular-level identification methods of *Anopheles* mosquitoes to differentiate members in species complexes is needed to define the precise role of each species in co-parasite transmission in different eco-epidemiological settings.

4.2. Africa

The two vector-borne diseases causing the most suffering in Africa are malaria and Bancroftian filariasis (Manga, 2002) with an estimated 212 million and 51 million people affected, respectively (Table 1) (Michael and Bundy, 1997; WHO, 2008a). Of the estimated one million deaths annually by malaria worldwide, approximately 91% are believed to occur in Africa (WHO, 2008a). Bancroftian filariasis, the only human lymphatic filariid present in Africa, is endemic in 39 countries and co-endemic with malaria across much of sub-Saharan Africa (Molyneux and Zagaria, 2002; WHO, 2008b). LF in Africa represents nearly one third of the global burden of the disease (Table 1). Nigeria, the most populous country in Africa, bears the greatest potential burden with 80 million (19% of total population) at-risk (Lindsay and Thomas, 2000; Ramzy, 2002; WHO, 2006). In 1993, 17 countries had LF prevalence rates exceeding 10% including four countries with rates over 20% [Guinea Bissau (37%), Comoros (27%), Seychelles (24%), Nigeria (22%)] (Michael and Bundy, 1997).

Approximately 90% of the LF transmission is attributable to *Anopheles*, the remaining 10% being maintained primarily by *C. quinquefasciatus*, a species utilizing polluted, foul-water (latrine pits, stagnant drains) as larval habitats. In many rural areas, both *Plasmodium* spp. and *W. bancrofti* are transmitted by a set of remarkably efficient mosquito vectors which includes the *An. gambiae* complex (both cytogenetic forms: Mopti and Savanna) and *Anopheles funestus* species group (Boakye et al., 2004). *Anopheles melas* and *Anopheles merus* appear the main vectors along the western and eastern coastal zones of Africa, respectively, while *Anopheles arabiensis*, *Anopheles pharoensis*, and *Anopheles wellcomei* are more focally involved in transmission on the continent (Appawu et al., 2001; Dunyo et al., 1996; Dzodzomenyo et al., 1999; Ramzy, 2002). *An. gambiae* (Mopti form), a species intrinsically linked to seasonal dry periods and irrigated agriculture, appears an important vector in southern Ghana (Dzodzomenyo et al., 1999). In West Africa, three discrete periods of transmission intensity have been described: Period 1, from May to July (early rainy season) with low LF transmission due to relatively focal and reduced densities of *An. gambiae*; Period 2, from August to September (end of rainy season) with more intense LF transmission due to the presence of higher densities of the two main vectors, *An. gambiae* and *An. funestus*; and Period 3, from October to November (early dry season) defined as more moderate LF transmission primarily involving *An. funestus* (Brengues et al., 1968).

Along the Kenyan and Tanzanian coastal zones, malaria and LF are co-endemic with a marked high prevalence in many areas (Muirhead-Thomson, 1953; Snow et al., 1994) with both parasites typically sharing the same vector species, *An. gambiae* s.l. and *An. funestus* (Muturi et al., 2006b; Rwegoshora et al., 2005, 2007). In more coastal East Africa and Egypt, *Culex* spp., particularly *C. quinquefasciatus* and in some areas *C. pipiens* (Egypt), are also important vectors (Lindsay and Thomas, 2000; Ramzy, 2002).

4.3. Western Pacific

Around 2% of the world's malaria and LF burden occur in this region, a percentage reflective of the relatively low human population (Table 1). The approximately six million people at-risk for LF are distributed over 17 countries or territories[2] with the majority (93%) of cases found in Papua New Guinea (PNG) (Burkot et al., 2002). Only *W. bancrofti* is present, however the epidemiology of LF in the Australasian/Pacific region is complicated with the presence of both nocturnal periodic (NP) and diurnal subperiodic forms of the parasite and also due to the greater diversity of the vector species involved. The distribution of LF is typically focal and normally endemic at least up to 400 m elevation above sea level (asl) (and at times up to 1000 m in New Guinea), confined mainly in the lowland and coastal zones with between 20% and 60% of the population having a patent microfilaremia (Chanteau and Roux, 2008; Hawking and Denham, 1976). Regionally, the highest prevalence for filariasis worldwide occurs in the western Pacific region with rates of up to 48% in Tonga and 39% in PNG and the Cook Islands (Michael and Bundy, 1997). Bancroftian filariae are transmitted primarily by *Culex* species (90%), followed by *Anopheles* (6%) and *Aedes*/*Ochlerotatus* (3%) (Zagaria and Savioli, 2002). The varying epidemiology of LF is reflective of the different vector species involved and distribution, and thus divided into four zones accordingly: *Anopheles* spp. in PNG, the Solomon Islands and Vanuatu; *C. quinquefasciatus* in Micronesia; *Aedes polynesiensis* in Polynesia; and *Ochlerotatus vigilax* in New Caledonia (Hawking and Denham, 1976). East of the 170° E longitude line marks the approximate transition zone from anopheline involvement to exclusively aedine species (approximately 10 or more species involved) in the transmission of *W. bancrofti* (Fig. 1B) *Anopheles* species are absent on all islands eastward of this line until reaching the western coast of the Americas. As most aedine vectors in the Pacific area are day or crepuscular-biting species, *W. bancrofti* has had to co-evolve its mf periodicity patterns (diurnal subperiodic) to better match vector peak feeding patterns to successfully propagate.

[2] American Samoa, Cook Islands, Federate States of Micronesia, Fiji, French Polynesia, Kiribati, Marshall Islands, Nauru, New Caledonia, Niue, Palau, Papua New Guinea, Samoa, Tonga, Tuvalu, Vanuatu, Wallis & Futuna.

In those areas, where *Anopheles* mosquitoes are the main vectors for malaria and Bancroftian filariasis, the members of the *An. punctulatus* group are by far the most efficient. This group is composed of at least 12 species, among which the three primary vectors are *Anopheles koliensis*, *An. punctulatus* and *Anopheles farauti*, the latter being a member of seven species identified within the Farauti complex. *An. koliensis* is considered the predominant malaria and LF vector below 650 m asl with infection rates up to 4% and 5%, respectively (Hawking and Denham, 1976). *An. punctulatus* is an anthropophilic mosquito, typically occurring in greatest density at elevations above 1000–2000 m asl. The vector infective rates for *W. bancrofti* at lower elevations can be high with values ranging from 4% to 15% (Bockarie et al., 1998; Hawking and Denham, 1976). *An. farauti* s.l. can occur up to 1500 m asl, however *An. farauti* is a predominately a lowland, coastal, brackish water species and has been found with infection rates varying from 3% to 25% for all filarial larval stages and 0.5% for infective L3 (Bockarie et al., 2002; Hawking and Denham, 1976). *Anopheles bancroftii*, a lowland, forest-dwelling species, is also reported to play a focal role as a malaria and LF vector.

Elevation is a clear limiting factor for malaria and LF transmission as the probability that a mosquito will be infective is inversely related to increasing altitude (Attenborough et al., 1997). Cooler mean ambient temperatures found at higher elevations can either arrest or preclude development of plasmodia and L3 in the mosquito within the normal lifespan of the vector. This is in agreement with findings from Papua (formerly Irian Jaya), Indonesia, where medical transect surveys along elevation lines found the cutoff point for *W. bancrofti* infections in the human population to be below 1000 m asl, while all four malaria parasites and vectors were capable of transmission up to a cutoff point of 1400–1600 m (Bangs MJ, unpublished data). Although development times in the mosquito are very similar, it would appear that lower temperatures have a greater impact on *W. bancrofti* transmission than malaria.

4.4. Americas

Malaria and LF have an estimated 2.7 million and 400,000 active cases, respectively (Molyneux and Zagaria, 2002; WHO, 2008b). Nocturnal periodic *W. bancrofti* is responsible for LF along the coastal plains of Central and South America, especially along the Atlantic seaboard and the Caribbean island of Hispaniola. The nematode parasite was most likely introduced by the African slave trade in the 1700s (Hawking, 1979). Seven countries in the Americas were considered LF-endemic, including Brazil, Dominican Republic, Guyana, Haiti, Costa Rica, Suriname, and Trinidad and Tobago, although the last three countries no longer report active transmission and, in Brazil, transmission continues only in metropolitan Recife (Pernambuco State) (Fig. 1B) (WHO, 2008b). Regionally, LF prevalence rates range from lows of 0.03% in Brazil to 7.3% in Guyana (Michael and Bundy, 1997). Haiti is the most heavily affected nation in the region with 80% of its population considered at-risk of infection, and representing 70% of the entire population at-risk in the Americas (WHO, 2006). Malaria transmission is more widespread (Table 1) and occurs in most countries of the tropical Americas ranging from Brazil reporting 59% of all cases (region's most populous country) to 3% in Haiti (PAHO, 2008). Concomitant transmission of both plasmodia and filarial parasites is most likely occurring in areas where both co-exist. However, mixed malaria and filariasis infections have only been reported in Guyana (Chadee et al., 2003). LF is mainly an urban infection and relatively rare in rural areas, except Guyana. *C. quinquefasciatus* is the main vector in urban foci; whereas *Anopheles* species, primarily *Anopheles darlingi*, and also *Anopheles albimanus* and *Anopheles aquasalis* are vectors involved in both malaria and LF transmission in rural areas (Table 3). *C. pipiens* is the principal vector in more temperate zones of Americas.

5. Impact of changing environmental determinants and conditions on transmission dynamics

Deforestation for logging and agricultural development is taking place at an accelerating pace worldwide and there is a widespread concern these rapid ecological changes might have significant impact on the spread of vector-borne diseases and human health (Gratz, 1999; Patz et al., 2000; Sutherst, 2004). However, with increases agricultural development and associated chemical and insecticide use, crop changes, deforestation, and human incursions, there have been relatively few investigations on how these changes on biodiversity and habitat have or could impact malaria or filariasis transmission. The consequences of human-modified environments have not been carefully assessed for most disease vectors. In Southeast Asia, the improvement of the malaria situation during the past decade appears to be partially due to environmental changes such as deforestation that reduced the habitats of one of the main vector, *An. dirus* s.l. (Delacollette et al., 2009). However, studies have shown that normal secondary or minor malaria vectors can contribute considerably to malaria transmission following environmental changes (e.g., irrigation, land development, deforestation), which could shift their feeding preference more towards humans and further favour their survival, hence increasing their vectorial status (Amerasinghe and Ariyasena, 1990; Maheswary et al., 1992). In Southeast Asia, the two species of the Minimus complex exhibit clear ecological differences highlighted by responses to deforestation that have changed the continuity of the landscape and the local microclimate (Matola et al., 1987). Agricultural practices have influenced the distribution of closely related species. In Thailand, *An. minimus* is associated with wider habitat preference, from dense canopy forest to agricultural fields, compared to its sibling species, *Anopheles harrisoni*, which has a more narrow habitat range (Rongnoparut et al., 2005). In northern Vietnam, *An. minimus* was found in more stable or undisturbed environments such as intact forested hills and rice agrosystems, whereas *An. harrisoni* was associated to maize agrosystems that typically require significant deforestation (Garros, 2005).

Environmental changes, either due to natural processes or direct human activity, are expected to exert a marked influence on the emergence or resurgence and proliferation of new and existing parasitic diseases. Improved surveillance and monitoring of climatic and landscape changes and possible impact on malaria and filarial transmission is urgently needed as a mean for timely identification of problems and control response and serving as the basis for developing better predictive models. Additionally, physical factors like ambient air temperature and humidity play an important role in malaria and filariasis transmission. The transmission efficiency (i.e., 'vectorial capacity') of vectors is generally enhanced with higher temperatures and relative humidity (e.g., shorter development time, increased vector longevity) that are also vital to the success of pathogen propagation and survival (e.g., reduced extrinsic incubation time and enhanced transmission). The warmer months of the tropical wet season, and summer months of more subtropical and temperate areas, are more conducive for filarial transmission and contributing to higher infection and infectivity rates and a shorter development period of the parasite in the vector (Chandra, 2008). Therefore, the epidemiological dynamics of malaria and LF must be viewed as closely interconnected which includes close interactions of mosquito (vector) populations, humans (reservoir), and parasites (pathogen) responding and adapting to environmental determinants of transmission. Disease epidemiology

involving landscape ecology, accurate measurements, quantitative detection, and analytical capabilities provided by geographic information system (GIS) technology, remote sensing and spatial statistics provides a means to gather, integrate, and better comprehend the complexity of many vector-borne pathogens at a site-specific level so that only appropriate, timely and targeted control measures be applied.

6. Thailand as an example

Thailand provides an excellent model to review the co-transmission of malaria and Bancroftian filariasis because the burden of these two endemic diseases remains high in certain segments of the Thai population (Fig. 4). Despite years of nation-wide success, malaria remains a public health priority, particularly in many rural and forested areas along the national borders with Myanmar and Peninsular Malaysia (Fig. 4A). These two areas alone represent 90% (55% and 35%, respectively) of the malaria cases nationally (Ministry of Public Health, 2008a). The annual parasite incidence (API, malaria cases per 1000 population) varies widely along the borders, exceeding 500‰ near the Myanmar–Thai border (Chareonviriyaphap et al., 2000). In 1947, the national malaria API was estimated at 286‰ but gradually fell to only 2.2‰ by 1975 following decades of intensive anti-malaria campaigns. In 1981, malaria resurged in prevalence to 10.6‰ and remained elevated at 6.8‰ in 1988. This was followed by a gradual decline of API reaching 2‰ in 1998, and then only 0.4‰ in 2008 (Chareonviriyaphap et al., 2000; Ministry of Public Health, 2008a). In terms of confirmed number of cases and deaths due to malaria since 1999, when the last epidemics were reported, a similar decline has been shown ranging from 125,359 cases and 740 deaths to 33,178 cases and 97 deaths in 2007 (Delacollette et al., 2009).

The remarkable success in reducing malaria rates across most of the country has been attributed to effective and well-organized vector control programs in rural areas based on routine indoor insecticide spraying and a nationwide campaign of distribution of pyrethroid-impregnated bednets, ready access to accurate diagnosis and prompt treatment, intensification of cross-border collaborations, and consistent funding to maintain program infrastucture and staffing due to the political will of the Thai government to make national malaria control a priority (Chareonviriyaphap et al., 2000; Delacollette et al., 2009). Malaria still represents a public health problem and, in recent years, up to 60,000–70,000 cases have been reported in Thai and non-Thai populations, with nearly 70% of the Thai population still at-risk of infection due to renewed or increased transmission. This is particularly true for those living along the western and southern international borders where a regular influx of malaria-infected migrants or refugees from neighboring countries can facilitate intense malaria transmission to continue (Chareonviriyaphap et al., 2000; Delacollette et al., 2009). Moreover, areas experiencing dramatic changes in land use and land cover have a potential to increase transmission risk (Petney et al., 2009). Since 1997, *P. falciparum* and *P. vivax* have shown a nearly equal proportion in Thailand; hovewer, along the Myanmar–Thai border the clinical epidemiology of the two malaria parasites has been very different in the ethnic Karen population located in a large, permanent refugee camp in Mae Sot District (Tak Province). While *P. vivax* was the most common infection seen in young children, with a decline in incidence with increasing age, *P. falciparum* incidence rates actually rose between 20 and 29 years of age, although the risk of developing a severe malaria decreased with increasing age as attributed to increased acquired partial immunity (Luxemburger et al., 1996). Besides extensive population movement across the international border, other sources of infection can occur in isolated forest villages (Singhanetra-Renard, 1986) where the exposed inhabitants often spend part of the year in rudimentary huts in order to draw agricultural products and other resources from the land (Somboon et al., 1998). Near the borders, rubber plantations and native fruit orchards are also conducive to transmission and high disease rates due to the presence of efficient malaria vectors within the Dirus complex, and exposure of workers and residents near these transmission foci (Singhasivanon et al., 1999).

Bancroftian filariasis is also endemic in rural, hilly, mostly forested areas along the Myanmar–Thai border (Fig. 4B) where an estimated three million people are exposed to infection (Pothikasikorn et al., 2008). Two LF forms occur in Thailand, the nocturnal

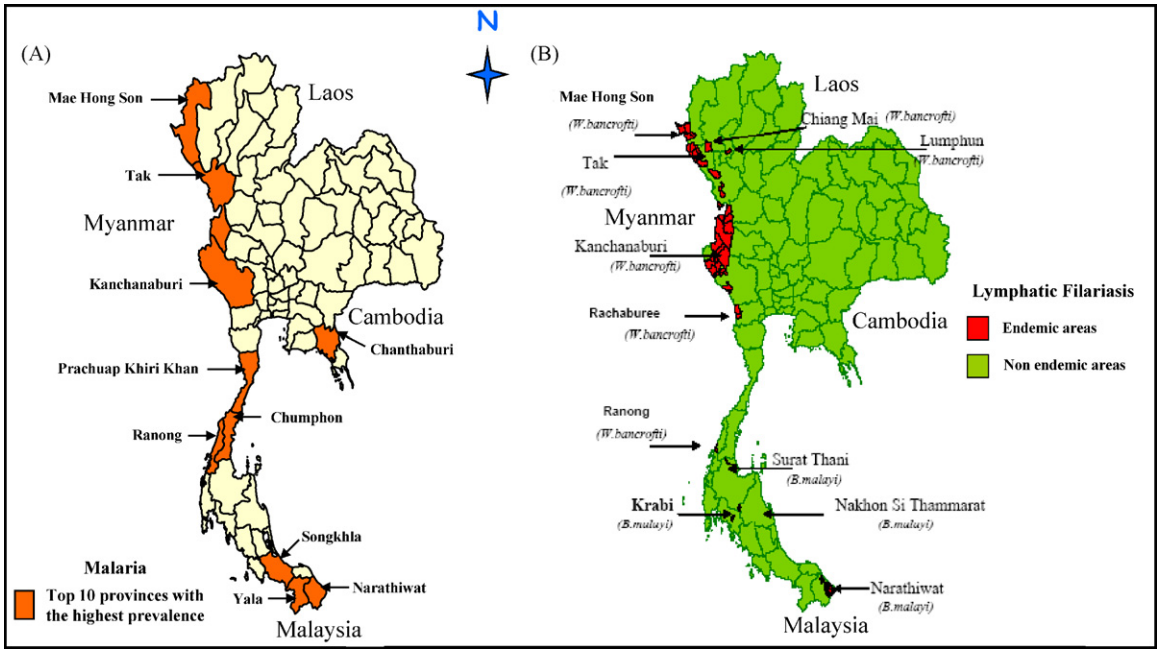

Fig. 4. Distribution of the two parasitic diseases in Thailand; (A) top 10 provinces with the highest malaria prevalence (Ministry of Public Health, 2008a); and (B) endemic areas of Lymphatic Filariasis (*W. bancrofti* and *B. malayi*) by subdistrict (Ministry of Public Health, 2008b).

subperiodic showing peak microfilaremia between 1800 and 2000 h (Gould et al., 1982; Harinasuta et al., 1974) and the more recently reported periodic (NP) form that is believed to have been introduced into western Thailand by Myanmar-migrant workers (Triteeraprapab et al., 2000). The NP parasites are primarily transmitted by *C. quinquefasciatus*, and typically in urban settings, therefore the possible establishment of a cycle of transmission in Thailand has raised concern (Triteeraprapab et al., 2000). Only limited data are available on the prevalence of LF in Thailand and its epidemiology remains poorly understood (Nuchprayoon et al., 2003). The high prevalence of LF along the western border region is reflected in one study showing up to 54% of Thai–Karen blood samples with anti-filarial IgG4 antibodies (Nuchprayoon et al., 2003). Another study revealed *W. bancrofti* in sentinel populations living inside Thailand having a high prevalence among cross-border migrants of Karen (36.8%) and Myanmar (24%) descent (Bhumiratana et al., 2005). Earlier surveys found the prevalence of filariasis reached 4.4% among Myanmar-migrant workers in Tak Province and 2.4% in Prachuab Khiri Khan Province, south-western Thailand (Triteeraprapab and Songtrus, 1999; Wiwanitkit, 2001). These cross-border populations have been considered as a source for transmission to local schoolchildren and exposed high-risk groups in the area.

Transmission of malaria and Bancroftian filariasis in forested areas along the Myanmar–Thai border is considered high risk and intense for another reason; the presence of highly efficient vectors. In these areas, *Plasmodium* spp. and rural strains of *W. bancrofti* share the same *Anopheles* vector species, in particular selected members of the Dirus and Minimus complexes and the Maculatus group (Chareonviriyaphap et al., 2000; Pothikasikorn et al., 2008). The Dirus complex (within the larger Leucosphyrus group) in Asia includes seven known species of which five are present in Thailand; four of them, *An. dirus* (former *An. dirus* A), *Anopheles cracens* (*An. dirus* B), *Anopheles scanloni* (*An. dirus* C), and *Anopheles baimaii* (*An. dirus* D), are regarded as efficient malaria vectors with sporozoite rates of up to 10% (Peyton, 1989; Sallum et al., 2005). The Minimus complex has three described sibling species; two are present in Thailand, *An. minimus* (former *An. minimus* A) and *An. harrisoni* (*An. minimus* C). Unlike *An. minimus*, the precise distribution of *An. harrisoni* remains unclear, as well as its true vectorial capacity and role in transmission on a large scale, because molecular identification assays have not been applied until very recently as a means of separating the two isomorphic species (Chen et al., 2002; Garros et al., 2006; Manguin et al., 2008b; Sungvornyothin et al., 2006; Trung et al., 2004; Vythilingam et al., 2003). The Maculatus group, which includes at least eight sibling species (Harbach, 2004) is distributed throughout southern Asia, and occurring in Thailand with five species represented along the Myanmar–Thai border (*An. maculatus*, *Anopheles sawadwongporni*, *Anopheles pseudowillmori*, *Anopheles dravidicus*, *Anopheles notanandai*) (Manguin et al., 2008b; Rattanarithikul et al., 2006). Some members of the group, especially *An. maculatus*, are known vectors of malaria (sporozoite rates of 5–10%) and *W. bancrofti* (Green et al., 1991; Pothikasikorn et al., 2008; Rattanarithikul et al., 1996). A potential vector, *An. vagus* has also been reported naturally infected with *W. bancrofti* (Harinasuta et al., 1970), yet this species has generally greater zoophilic blood feeding habits which probably limits its importance in parasite transmission compared to the other species.

Most members within a species complex cannot normally be distinguished accurately using morphology due to an absence of specific characters or overlapping ones, yet these sibling species may show very different host-seeking behaviour and vectorial capacity. Uncertain species identification is further complicated by the varying ability within species to effectively transmit pathogens depending upon local epidemiological conditions. Therefore, it is crucial to apply systematically the molecular techniques that have been developed to precisely identify sibling species in all future investigations for determining with more certainty the vectorial role of each species in relation to disease transmission (Manguin et al., 2008b).

In Thailand, beside anophelines, *W. bancrofti* can also be transmitted by mosquito species within five other genera; these include *Aedes* (*Ae. desmotes*, *Ae. annandalei*), *Culex* (*C. quinquefasciatus*), *Ochlerotatus* (*O. harveyi*), *Downsiomyia* (*D. harinasutai*, *D. nivea*), and *Mansonia* (*M. dives*) (Gould et al., 1982; Harinasuta et al., 1970; Ministry of Public Health, 1998; Rattanarithikul et al., 2005). A recent laboratory study on the susceptibility of Thai mosquitoes to develop NSP *W. bancrofti* L3 showed that *An. maculatus* and *An. minimus* had significantly higher infection rates with 73% and 61%, respectively, followed by *Downsiomyia* sp. (27.3%), *An. dirus* (24.7%), *Ae. desmotes* (24.2%), *C. quinquefasciatus* (19.2%), *Mansonia uniformis* (9.2%), and *Ae. albopictus* (0.01%). Other species, including *Ae. aegypti* and *Armigeres subalbatus* were found completely refractory to this parasite (Pothikasikorn et al., 2008).

Recently, filariasis control activities in Thailand have been effectively integrated with other vector-borne diseases control programs. In LF-endemic areas, asymptomatic microfilaremia plays an important role in the persistence of disease and transmission. The primary method of LF control has been periodic mass treatment with DEC and albendazole. In 2007, the MDA campaign achieved a drug coverage rate of approximately 83% of the at-risk Thai and migrant populations (WHO, 2008b). It would be of interest to simultaneously investigate malaria and LF regarding the natural vectorial capacity of *Anopheles* mosquitoes that transmit both pathogens, evaluating the interactions between parasites and primary vectors, and the influence of land cover and climatic factors on disease and vector distibution by developing accurate GIS-based mapping with data management and analysis to improve the simultaneous and integrated control of both diseases.

7. Arguments for combined malaria and lymphatic filariasis control strategies

This review has shown malaria and LF as co-endemic infections utilizing the same *Anopheles* vectors in many parts of Africa, Asia, South America and Hispaniola Island, and a number of widely scattered western Pacific Islands, including PNG and the Solomon Islands. The efficacy of anopheline mosquitoes as LF vectors depends on a number of contributing factors, some species-dependent, others influenced by environmental parameters, demography and disease prevalence and infection intensity in the human population. For example, when low microfilaremia is encountered in the population due to mass chemotherapy (and presumably excellent diagnosis and treatment programs), complete abatement of anopheline-transmitted *W. bancrofti* can be achieved (Bockarie et al., 1998). While the risk of acquiring *W. bancrofti* infection per infective mosquito bite is magnitudes less than malaria (Southgate, 1992), it is partly offset in that LF infection can persist for much longer (adult worm lifespan up to 15 years or more) than *P. falciparum* and most other typical malaria infections. However, similarities can exist with use of the same vector species. Therefore, a working synergy between the two primary control programmes, RBM and GPELF, has been proposed as not only possible, but also preferable in terms of cost-effectiveness when attacking the same vector species for the two diseases (Manga, 2002). In particular, standard vector-control methods, such as indoor residual spraying (IRS), insecticide-treated nets (ITNs), use of other personal-protection measures, mosquito larval habitat reduction and environmental management, can have the same dramatic impact on the reduction of LF,

malaria and other mosquito-borne diseases when the epidemiological circumstances and vectors favour such an approach. As only continuous and repeated exposure to infective mosquito bites can maintain LF in human populations, among the vector control measures available, physical protection from mosquito bites by use of ITNs or untreated bednets has received much attention as it has been proven to be both effective and simple to implement (Bockarie et al., 2002).

There are currently two major interventions for controlling *Anopheles* mosquitoes that transmit human pathogens: the use of ITN and IRS (Manga, 2002). In PNG, the impact of bednet usage on control of filarial transmission has been shown significant suggesting that even use of untreated bednets over time can provide significant protection against *W. bancrofti* infection (Bockarie et al., 2002; Burkot et al., 1990a). Bednets have also been found to reduce the risk of malaria transmitted by members of the Punctulatus group, even when human population coverage is incomplete (Smith et al., 2001). In PNG, ITN use was found to drastically decrease sporozoite rates in vector mosquitoes and result in a significant decrease in *P. falciparum* incidence in young children (Graves et al., 1987). Studies comparing the impact of permethrin-impregnated bednets and DDT house-spraying in the Solomon Islands showed the former to be more effective in preventing malaria (Hii et al., 1993), although IRS campaigns eventually lead to the eradication of anopheline-transmitted LF in the island group (Webber, 1979), again illustrating the greater vulnerability of filarial parasites to control efforts compared to plasmodia.

In Africa, the use of ITNs in a filariasis endemic area of Kenya significantly reduced the indoor resting and biting densities of *An. gambiae* s.l. (94.6%) and *An. funestus* (96.7%) (Bøgh et al., 1998). For non-commercially treated ITNs, better protection is afforded when they are re-treated with a pyrethroid at least once a year (Manga, 2002). In recent years, the expanded availability of affordable commercially treated, long-lasting insecticidal nets (LLINs), i.e., those with five years or more chemical effectiveness that would include the average life span of a standard bednet, have replaced the need to periodically re-treat nets in communities (WHO, 2008a).

The control of either disease depends on sufficient epidemiological knowledge before being able to propose and implement a sound intervention strategy. In many instances, the geographic distribution and endemicity of malaria has been relatively well described, while that of LF remains imprecise. Accurate mapping of the two diseases would greatly enhance monitoring and control (Alexander et al., 2003). Additionally, in areas where transmission of both diseases occurs but information on the main vectors remains incomplete, entomological studies are needed to better target disease control efforts and therefore provide better cost-effectiveness (Manga, 2002). For purposes of control monitoring there is a need for investigating some of the most crucial epidemiological aspects of transmission potential, such as (1) vectorial capacity of mosquitoes infected by one or both parasites; (2) immunobiology of host–parasite interactions in the relative exclusivity of one parasite versus the other, especially the host (both vector and human) response to one parasite which may facilitate or protect against the other parasite; and (3) assessing the possibility that the control of one parasite may inadvertently lead to a change (better or worst) in the incidence of the other (Kelly-Hope et al., 2006).

The current recommended treatments for malaria, namely artemisinin-combination therapies (ACT), together with vector control using primarily ITNs, remain effective methods for controlling malaria and LF when used properly (Fenwick, 2006). However, malaria parasites continue a ceaseless process of adaptation and genetic selection against our most potent chemotherapeutic tools. Because of a number of human-related factors that promote the more rapid development of resistance, there is disturbing evidence of declining treatment efficacy to ACT (the beginnings of resistance) against *P. falciparum* in Southeast Asia (Wongsrichanalai and Meshnick, 2008). On the other hand, the control of LF in communities has relied mostly on combination chemotherapy for both treatment and more broad-based MDA programs, with secondary measures being directed at vector control and reduction of human–vector contact (Mak, 1987). The GPELF recommendations for LF control, primarily combination therapy MDA, have defined those communities at-risk and targeted mass treatment once annually for four to six consecutive years (the estimated duration of the average reproductive life of adult female worms) (WHO, 2008b). A two-drug combination, albendazole combined either with diethylcarbamazine citrate (DEC) or ivermectin, has been proven to provide longer lasting suppression of mf in the blood than treatment with either drug alone (Molyneux and Zagaria, 2002). Currently, there appears to be no evidence that *W. bancrofti* has developed a reduced sensitivity to the combination therapy. The Ministries of Health of all 83 countries afflicted with LF have committed to implementing their own elimination program and more than half have already started organizing national-level MDA activities (Bockarie et al., 2009). MDA has provided excellent results on the control of LF showing either dramatic reductions in prevalence of microfilaremia (areas of Brazil, Brunei, Comoros, Dominica Republic, Indonesia, Laos, Malaysia, Thailand, Togo, Yemen, and Zanzibar); or the complete interruption of transmission (Cape Verde, China, Costa Rica, Korea, Solomon Islands, Suriname, Trinidad and Tobago) (Molyneux and Zagaria, 2002; WHO, 2008b). In PNG, where unchecked transmission is considered intense, the country has witnessed an almost complete interruption of new infections in areas organizing MDA (Bockarie et al., 1998). Despite the progress made in many countries having begun MDA, major obstacles remain. These include resource and logistic limitations, constraints on availability of rapid diagnostic tests, and the cross-border migration of infected persons from areas not under a LF control program; for instance, along the Myanmar–Thailand, Indonesian–Malaysian (Borneo) international borders (Bockarie et al., 2009). In many situations, the timed goals of the GPELF might be achieved more rapidly by combining targeted vector control strategies with MDA (Bockarie et al., 2009; Burkot et al., 2006).

Transmission intensity is a function of both the prevalence and intensity of microfilaremia in humans and the vector capacity of mosquito vectors (Southgate, 1992). In *Anopheles*, there is a positive correlation between the proportion of *W. bancrofti* mf that successfully develops and the density of ingested mf, a process termed "facilitation" that has been shown in *Aedes* and *Anopheles* mosquitoes (Southgate and Bryan, 1992). One mechanism that may be responsible is density-dependent physical damage of mf by the cibarial armature of the vector during blood feeding (Shoukry and Soliman, 1995). Facilitation suggests that low density microfilaremia infection thresholds might apply for *Anopheles* and *Aedes* vectors (Snow et al., 2006). However, modelling analysis has also suggested that facilitation may not play a role in natural reductions in mf prevalence and intensity, but rather by reductions in vector density by either natural processes or by vector control (Wada et al., 1995; Webber and Southgate, 1981).

The obvious potential benefit of vector control is particularly important because transmission of LF is relatively inefficient. Therefore, even a modest reduction in the number of infective mosquitoes can significantly suppress the overall risk of patent infection. The use of untreated bednets to disrupt human–vector contact is more likely to impact the incidence of filariasis compared to malaria (Bockarie et al., 2002; Burkot and Ichimori, 2002). For interrupting LF transmission, the simultaneous reduction of vector density and microfilarial intensity in humans taken

below a certain threshold (i.e., basic reproductive rate) can help ensure no new infections (Anderson and May, 1991; Bockarie et al., 2009). For instance, where MDA coverage or follow-up are compromised, the added impact of a selective vector control program can make up the shortfall, especially in areas where more efficient vector populations might readily sustain transmission or contribute to its resurgence (Zagaria and Savioli, 2002).

It is generally assumed that LF elimination, in areas where *Anopheles* species are transmitting NP strains of *W. bancrofti*, will be relatively easy to achieve (Burkot and Ichimori, 2002). Several countries and territories of the South Pacific are participating in the Pacific Programme for the Elimination of Lymphatic Filariasis (PacELF) based on five annual rounds of MDA using albendazole + DEC. Vector control has been relegated to a secondary role in most countries (Burkot and Ichimori, 2002), although bednets, insecticide-impregnated (Charlwood and Dagoro, 1987) or untreated (Burkot et al., 1990a) and indoor residual insecticide (DDT) campaigns (Webber, 1979) have proven effective in reducing malaria and filarial transmission. In the Solomon Islands and coastal areas of PNG, the eradication of filariasis succeeded using only vector control measures to interrupt transmission (Burkot et al., 2002). On the other hand, for LF transmission by *Aedes polynesiensis*, MDA must be accompanied by vector control as this mosquito species exhibits a biological response called "limitation" in which the efficiency of the vector for developing L3 worms actually increases with declining microfilarial densities in humans (Esterre et al., 2001; WHO, 1992), as also well demonstrated in *Culex* mosquitoes (Snow et al., 2006).

Despite these examples of success, vector control in malaria and LF abatement is largely considered a complementary activity linked to other disease-control methods such as the promotion and use of ITNs (Prasittisuk, 2002). Implementing synchronous and multifaceted strategies, with LF-MDA and comprehensive vector control as central components, can more aggressively stop filarial and malaria transmission. Success is more likely when direct vector control and personal-protection measures, namely, ITN, IRS (especially when using long-lasting residual compounds like DDT), larval monitoring and control, are combined into an integrated vector management (IVM) program. The accurate identification and assessment of the bionomics (i.e., life history and ecology) of mosquito species responsible for filarial and/or malaria transmission in specific endemic areas is of critical importance in selecting the most appropriate methods for sampling and control of real and potential vectors (Ramzy, 2002). This is particularly true with filariasis as more than one vector species, sometimes more than one genus, may be involved in transmission.

Table 3 lists mosquito species that have been implicated as vectors of *W. bancrofti*. We presume that those species listed as vectors are correct; however, it is important not to overlook the existence of at least 14 other genera of filarial parasites representing at least 34 different species that are also transmitted by mosquitoes to other vertebrate hosts (Anderson, 1992; Lok et al., 2000). Moreover, many more filarial species transmitted by mosquitoes are likely awaiting description. Without careful morphological examination, infective stage larvae of these other species (a number of which are poorly described as developing stages in mosquitoes) might be easily mistaken for those filariids responsible for human disease (Ramachandran, 1970) and must be excluded before implicating a mosquito species as relevant in the transmission of human disease.

New biological and epidemiological information can also bring to light better control strategies against both the vector(s) and the diseases they transmit. For example, in India, control strategies would vary depending on the location. Along the south coast (Pondicherry) the vectors of malaria and LF are of different genera, *Anopheles* and *Culex* spp., respectively (Rajagopalan et al., 1987), whereas in Orissa (northeast coast), both parasites primarily share the same anopheline vector species (Ravindran et al., 1998). The evaluation of the efficacy of interventions against mosquitoes also requires a sufficient level of expertise in mosquito identification, vector biology, mosquito surveillance and control methods as minimum prerequisites to implement effective mosquito control campaigns (Burkot et al., 2002). It is essential to retain both longitudinal data and collect current and site-specific information on the occurrence, distribution, and prevalence of co-infections, and determine the status and role of each vector species to improve the control of both diseases in line with global RBM and the GPELF objectives.

Vector abatement strategies for the simultaneous control of malaria and Bancroftian filariasis are still at the early stages of implementation. In future, a concerted synthesis between RBM and GPELF program activities should be developed with focus on designing and implementing IVM activities that promote the use of insecticide-treated materials (bednets and curtains), species-specific vector control compatible with local bionomics and environmental parameters, and sustainable long-term bio-environmental control methods in mind. Integrated vector control, combined with accurate infection diagnostics and effective treatment, along with community-wide anti-filarial MDA would appear the best strategy to move forward (Bockarie et al., 2009; Manga, 2002; Muturi et al., 2006a; Prasittisuk, 2002). Greater emphasis will need to be placed on LF morbidity reduction and vector control activities as these two elements of control will likely extend beyond 2020, the target year for global elimination of lymphatic filariasis (Gyapong and Twum-Danso, 2006).

8. Conclusion

Malaria and LF controls would greatly improve poverty alleviation programs and enhance economic development. However, these laudable control goals will only be possible with a better knowledge of the interaction between vector, parasite, and environment. In particular, there is an urgent need for a better understanding on how these pathogens are transmitted, not only the mosquitoes and their respective vectorial capacities, but also the impact of natural and changing environmental and climatic factors on the transmission and distribution of the diseases. Such studies have become even more important with the apparent increase of newly emerging and re-emerging diseases, including malaria, for which the situation continues to worsen as a result of the rapid global changes generated by human activities and population growth and movement (Manguin et al., 2008a; Roberts et al., 2000).

Concomitant infections of malaria and LF in *Anopheles* vectors and humans are more likely to occur when the prevalence of both parasites is high. Foremost to any control program is a reduction of parasite burden in the human population. As such, integrated control strategies targeting both diseases in areas sharing the same vector species are highly recommended as the most cost-effective approach to achieving simultaneous malaria and LF reduction or outright elimination. From this review, we conclude that much more information is needed in the area of entomological assessment of malaria and LF transmission under both field and laboratory conditions. Such information will help in the design and implementation of appropriate and coordinated control strategies against both diseases.

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