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Limitation and facilitation in the vectors and other aspects of the dynamics of filarial transmission: the need for vector control against *Anopheles*-transmitted filariasis*

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In certain filaria–mosquito combinations, the number of infective, third-stage larvae (L_3) that develop in a mosquito is not proportional to the number of microfilariae (mff) ingested by that mosquito. As the number of mff ingested increases, the yield of L_3 per microfilaria may either increase (in a process known as 'facilitation') or decrease (in a process known as 'limitation'). Each ingested microfilaria that is successful (in terms of reaching the haemocoel) increases (facilitation) or decreases (limitation) the 'permeability' of the stomach wall for the next microfilaria. Limitation is seen in some culicine mosquitoes, especially the *Aedes* spp. that transmit *Wuchereria bancrofti*, which, in consequence, become relatively more efficient as vectors as they ingest fewer mff. This phenomenon makes the interruption of filarial transmission by *Aedes* spp. particularly difficult.

As the survival of anopheline mosquitoes is adversely affected by filarial infection, the use of mass drug administrations (MDA) to reduce the prevalence and intensity of microfilaraemias may increase the mean life-span of some of the local *Anopheles* species. If these same species also act as vectors of malarial parasites, effective, drug-based control of *W. bancrofti* may worsen the problem posed by malaria. Therefore, wherever malaria and bancroftian filariasis are co-endemic and caused by parasites transmitted by the same species of mosquito, MDA should be augmented by interventions (use of bednets or house-spraying) against adult *Anopheles*.

Although there may be practical and economic reasons why the control of lymphatic filariasis (LF) using mass drug administrations (MDA) is to be preferred to control of the disease via vector control (VC), either intervention, if effective, could interrupt the transmission of the parasites that cause the disease. The choice of whether to use MDA, VC or both in a particular setting depends partly on the vector–parasite combinations involved and whether the filarial vectors also transmit any other human pathogens, such as *Plasmodium* spp.

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MODES OF PARASITE TRANSMISSION

In at least some of the mosquito vectors of the parasites causing LF, the parasitic yield — the number of human-infective, third-stage larvae (L_3) developing from each microfilaria ingested — is not constant. It may increase as the number of microfilariae (mff) ingested increases (in a phenomenon known as 'facilitation') or it may decrease (in a phenomenon known as 'limitation'; Bain, 1971; Brengues and Bain, 1972). Facilitation and limitation affect the epidemiology and control of LF, via the transmission dynamics of the filarial parasites causing the disease (Pichon, 1974*a*, *b*). Limitation (negative density-dependence) occurs in some culicine

vectors (Pichon, 1974*a*, *b*; Subramanian *et al.*, 1989, 1998) whereas facilitation (positive density-dependence) occurs in some of the anopheline vectors (Pichon, 1974*a*, *b*; Southgate and Bryan, 1992). Both phenomena can be described mathematically (Fig. 1), limitation as the equation:

$$y = Hx/(x + H)$$

and facilitation as:

$$y = x - [Hx/(x + H)]$$

where x is the number of mff ingested/mosquito, y the number of L_3 [or, in some analyses, of first-stage larvae (L_1)] developing/mosquito, and H is the inverse of the regression slope coefficient for yield (y/x), in the case of limitation, or for failure [$1 - (y/x)$], in the case of facilitation. The H parameter is a measure of the 'reciprocal adaptation' for a particular vector–parasite combination. The combinations giving high values of H, such as the 20 estimated for *Ae. polynesiensis* infected with *W. bancrofti* var. *pacifica*, probably represent very ancient adaptations (see Table). Pichon (1981) used this assumption, and the results of other studies on subperiodicity, to develop the hypothesis that *W. bancrofti* speciation might have accompanied the ethnogenesis of the Polynesians.

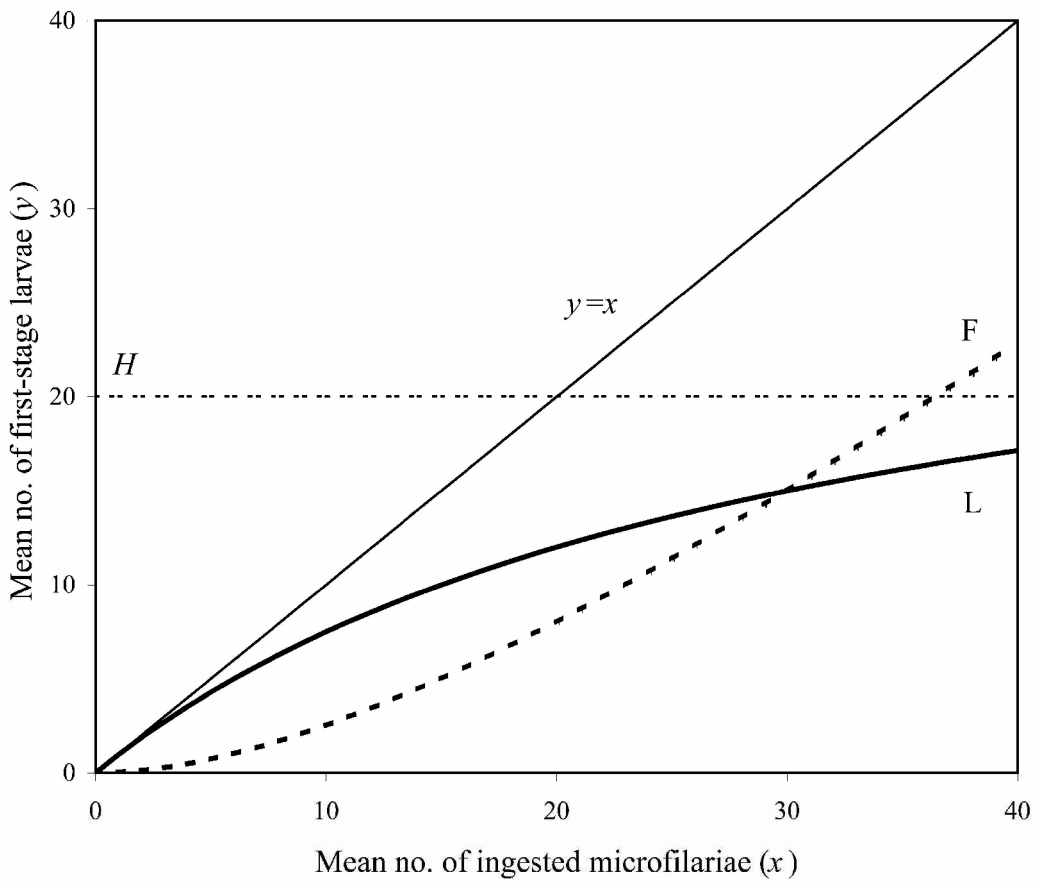

FIG. 1. A diagrammatic representation of limitation (L) and facilitation (F), here shown for the production of first-stage larvae (L_1) from ingested microfilariae. H, the inverse of the regression slope coefficient b, allows for measurement of the 'reciprocal adaptation' for a particular vector–parasite combination.

TABLE. *Quantification of the limitation (H) in some of the culicine vectors of filariae and of the facilitation (H′) in some of the anopheline vectors*

Vector	Parasite	Locality	Filarial larval stage	H/H'	Reference
LIMITATION					
Aedes polynesiensis	Sub-periodic *Wuchereria bancrofti*	Tahiti	L_1	$H=20$	Rosen (1955)
			L_3	$H=20$	Prod'hon *et al.* (1980)
Ae. aegypti⋆	Sub-periodic *W. bancrofti*	Tahiti	L_1	$H=10^{\dagger}$	Prod'hon *et al.* (1980)
			L_3	$H=0$	Prod'hon *et al.* (1980)
Ae. aegypti⋆	*Setaria labiato-papillosa*	Burkina Faso	L_1	$H=3.5^{\dagger}$	Brengues and Bain (1972)
Culex quinquefasciatus⋆	Sub-periodic *W. bancrofti*	Tahiti	L_1	$H=68^{\dagger}$	Prod'hon *et al.* (1980)
			L_3	$H=0.3$	Rosen (1955)
Cx. quinquefasciatus	Periodic *W. bancrofti*	Tanzania	L_3	$H=3$	Jordan and Goatly (1962)
Cx. quinquefasciatus	Periodic *W. bancrofti*	India	L_3	$H=7$	Subramanian *et al.* (1998)
Mansonia longipalpis	Sub-periodic *Brugia malayi*	Malaya	L_1	$H=35^{\dagger}$	Wharton (1957*b*)
FACILITATION					
Anopheles gambiae	Periodic *W. bancrofti*	Burkina Faso	L_1	$H'=78$	Brengues and Bain (1972)
			L_3	$H'=78$	Brengues and Bain (1972)
An. gambiae	Periodic *W. bancrofti*	Gambia	L_1	$H'=120$	Southgate and Bryan (1992)
An. arabiensis	Periodic *W. bancrofti*	Gambia	L_1	$H'=42$	Southgate and Bryan (1992)
An. melas	Periodic *W. bancrofti*	Gambia	L_1	$H'=3.6$	Southgate and Bryan(1992)

⋆Not a natural vector of the filaria.
†For the reduction in parasite numbers after the parasites leave the stomach of the vector.

Limitation

In filarial transmission, as in many physical systems, negative density-dependence (i.e. limitation) helps to produce stability. Where limitation occurs, such as in the transmission of *W. bancrofti* by *Aedes* in Polynesia or by *Culex* in India (Subramanian *et al.*, 1998), East Africa (Jordan and Goatly, 1962) and the Americas (WHO, 2002), the total interruption of transmission (the ultimate goal of LF-control programmes) is not only hard to reach but also unstable [Fig. 2(a)]. Despite the island distribution of *W. bancrofti* transmitted by *Ae. polynesiensis* in Polynesia, there appears to a surprising stability in the LF in this region. The rather homogeneous geographical distribution of LF endemicity in Polynesia contrasts markedly with the patchy endemicity of anopheline-transmitted *W. bancrofti* across West Africa. In Polynesia, sub-periodic *W. bancrofti* is present in every Polynesian island where humans and the vector species of mosquito co-exist, and intensive MDA using diethylcarbamazine (DEC) and some VC, all carried out by the Institut Louis Malardé (www.ilm.pf) in an exemplary fashion for more than 50 years, failed to eliminate LF from any island community. This failure is associated with the amazing efficiency of *Ae. polynesiensis* as a vector, itself a consequence, in part, of the limitation phenomenon. On the Polynesian islands of Moorea and Maupiti, the prevalence of LF was reduced from 30%–35% to 3%–6% within a few years but several more decades of control interventions then failed to reduce prevalence any further (Esterre *et al.*, 2001). The elimination of the residual infections appeared impossible and this could not be attributed to the resistance of the parasite or the reluctance of the population to participate in the MDA. Interruption of MDA in another island was followed by a return to the high prevalences observed pre-intervention within 5 years. As recently discussed by Burkot and Ichimori (2002), Burkot *et al.* (2002) and Lardeux *et al.* (2002), new tools are needed to control the diurnally active *Ae. polynesiensis* and the other efficient vectors of sub-periodic *W. bancrofti* in Polynesia.

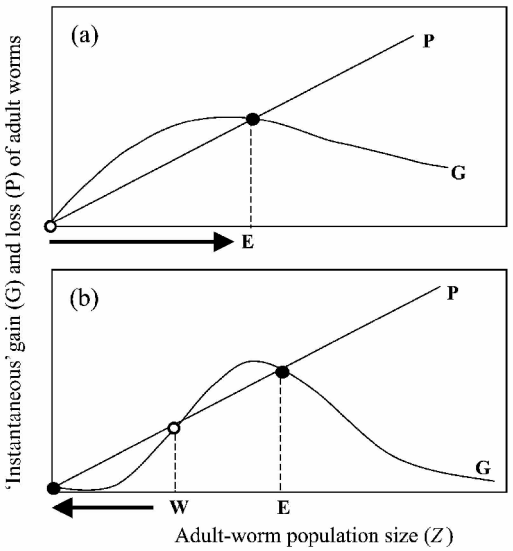

FIG. 2. Representation of limitation in culicine transmission (a) and of facilitation in anopheline transmission (b), assuming there is filaria-attributable mortality in the vectors. The curves run above or below the line of adult-worm mortality (P) — assumed to follow a negative-exponential — except at the points of stable equilibrium (E) or Webber's critical point (W). The arrows indicate the direction in which the size of the parasite population is likely to go, spontaneously, as the result of control interventions. After Pichon *et al.* (1974).

Limitation also occurs in the *W. bancrofti*–*Cx. quinquefasciatus* combination, within the mosquito's stomach (i.e. in the development of L_1 from mff) and also in the development of L_3 from L_1. In the study in Tahiti by Prod'hon *et al.* (1980), for example, the development of *W. bancrofti* L_1 from the mff ingested by *Cx. quinquefasciatus* was found to carry an *H*-value of >60, whereas the corresponding *H*-value for the development of the L_3 was only 0.3. Pichon *et al.* (1976) found that the same phenomenon seems to occur in the development of *Brugia malayi* in *Mansonia longipalpis* (=*Ma. dives*) (Wharton, 1957*a*, *b*). Although *Cx. quinquefasciatus* is fortunately not an efficient vector of the sub-periodic *W. bancrofti* found in Polynesia, it can transmit a Caribbean strain of periodic *W. bancrofti* (Rosen, 1955).

Facilitation and Thresholds

The transmission of *W. bancrofti* by anopheline mosquitoes is characterized by facilitation (Brengues and Bain, 1972). Pichon *et al.* (1974) suggested that this mechanism could cause instability in the parasite population, and explain the patchy distribution of LF endemicity in areas where *W. bancrofti* is transmitted by *Anopheles*. In this case, there is a threshold point — which, to honour Roger Webber (who was once confronted with the same questions about LF as the author, albeit at a different extremity of the Pacific Ocean), is here named Webber's critical point (*W*) — that is relatively far from eradication and close to the stable equilibrium [Fig. 2(b)]. Below this point, the parasite population dies out spontaneously. The re-establishment of a stable parasite population in an area in which transmission has been interrupted and infection eradicated would then necessitate the introduction of many parasites (in humans and/or mosquitoes). Local eradications could have occurred in historical or recent times, either spontaneously or following human intervention, such as the spraying of houses with DDT during the World Health Organization's Malaria Eradication Campaign in the 1950s. It now seems clear that house-spraying to control malaria inadvertently caused the first, well documented, local eradication of LF. This occurred in 1979 in Choiseul (one of the Solomon Islands), where *W. bancrofti* was transmitted by *An. farauti* (Webber, 1977, 1979, 1991). The results of a parasitological survey of Choiseul in 1996–1997 (J. Leafasia, unpubl. obs.) and an immunological survey in 1998–1999 (S. Randell, unpubl. obs.) indicated that, 20 years after the eradication, the island remained LF-free.

The evidence for a threshold in a model of host–parasite relationship is not only interesting theoretically. In operational terms, the quantification of a target threshold to break transmission should motivate the staff involved in control/eradication campaigns. Two thresholds have, in fact, already been estimated. For *An. farauti*-transmitted *W. bancrofti* in the Solomon Islands, Webber and Southgate (1981) showed that there was a critical biting rate (0.66/human-hour, or about eight bites per person each night) necessary for continued transmission. For *An. sinensis*-transmitted *B. malayi* in China, Zang *et al.* (1991) considered that, if no individual carried >200 mff/ml blood, human infection would invariably die out if its prevalence fell below a threshold of 1.55%–2.23%.

There may be no such threshold in areas such Polynesia, where limitation, not facilitation is the rule. Knowing why eradication is so difficult in these circumstances may be some comfort to those involved in the local control campaigns. In fact, even in vector–parasite combinations complicated by limitation, another threshold does exist. It occurs when the probability that two worms differing in sex meet in the same host is too low. Unfortunately, this threshold will be very much lower than Webber's point and close to zero. Whether it is attainable is still unknown.

Disease control (based on VC, MDA or both) should be relatively efficient in regions with anopheline transmission, such as West Africa. Once the interventions take the disease below Webber's point, the filarial population should steadily decrease to the point of stable eradication.

DIFFERENTIAL VECTOR MORTALITY CAUSED BY FILARIAL PARASITES

In the early, laboratory studies (Adams-Chapman, 1965; Brengues and Coz, 1972), heavy *W. bancrofti* infections were found to cause only slight additional mortality in a pool of *Ae. polynesiensis* and *An. gambiae* s.l. (and, curiously, the mortality of the non-infected controls was significantly higher than that of mosquitoes carrying light infections). In the field, however, Brengues *et al.* (1975) detected strong mortality among

An. gambiae s.l. and *An. funestus* caused by the first-stage and second-stage larvae (L_1 and L_2) of *W. bancrofti*. He found that the mean intensity of infection with the L_1 or L_2 was significantly higher in the mosquitoes coming to bite at night than in those captured, while resting (in the same houses), on the following morning. Since the parasite load in these vector species only reduces when parasites cross the stomach wall and enter the haemocoel, the observed decrease in filarial load from night to morning could only be attributed to differential mortality caused by the filariae in the infected mosquitoes.

Using a model of negative-exponential survival dependent on the parasite load (Dietz, 1975; May, 1977; Pichon *et al.*, 1976, 1980*b*), Pichon *et al.* (1980*b*) found that, if a mosquito contains one L_1, taking a new bloodmeal decreases its probability of survival to the next morning by a factor (θ) equal to 0.95. If the mosquito contains 10 L_1, its differential probability of survival during the next few hours is close to θ^{10} ($=0.5$). During the parasite's development from L_1 to L_2, the corresponding survival coefficient (θ) is 0.84 for a burden of one larva, and 0.17 for a burden of 10 larvae.

It is believed that the presence of filarial parasites in the thoracic muscles (which are used for locomotion) slows down the speed of take-off and of flight of the mosquito. In captivity, this phenomenon may be beneficial to the mosquitoes, as it may reduce the risk of being wounded against the netting of the cage or from drowning in the water of the oviposition container. However, under natural conditions, an inability to respond quickly to the threat of predation (by ants, spiders, lizards etc.) is a serious handicap to an infected mosquito. This could explain, at least in part, why the L_3 burdens observed in the field are generally much smaller than those seen after experimental infections in the laboratory. Most estimates of the filaria-attributable mortality in mosquitoes are probably under-estimates, as they take no account of any mortality caused while the parasites are L_3.

If there is significant filaria-attributable mortality in the potential vectors of *W. bancrofti*, filarial infection may limit the size of the population of these mosquitoes, especially in areas where bancroftian filariasis is hyperendemic. The reduction of the parasite population by MDA may thus produce an increase in the numbers of the vector species.

OTHER FACTORS

In many areas, an MDA-induced increase in the mosquito biting rate may be a 'price worth paying' to control LF. In some areas, however, filarial parasites are transmitted to the human population by the same *Anopheles* spp. that transmit malarial parasites. For example, malarial parasites can be transmitted to humans by the vectors of nocturnally periodic *W. bancrofti* in West Africa (*An. funestus* and the *An. gambiae* complex) and Papua New Guinea (*An. farauti* and other members of the *An. punctulatus* group) and the vectors of nocturnally periodic *B. malayi* in Malaysia (such as *An. campestris* and *An. donaldi*).

Many factors will have to be considered if a realistic estimate of the impact of anti-filarial MDA on malaria transmission is to be made: facilitation; differential vector mortality; frequency of bloodmeals; level of anthropophily; and the frequency distribution of infection intensities in the vectors biting an individual (Pichon *et al.*, 1980*a*). The theoretical distribution of the parasites in each vector species of mosquito is a zero-truncated negative binomial with parameter $k = 0.3$ (Pichon *et al.*, 1979; Grenfell *et al.*, 1990; www.bondy.ird.fr/~pichon). The potential impact of the MDA-based eradication of microfilaraemia on the survival of a cohort of 100,000 female *Anopheles* has been simulated (Fig. 3) using the ParaDis 'freeware' (www.bondy.ird.fr/~pichon/paradis/parad2.html). It is estimated that, in Tingrela, in Burkina Faso (a highly endemic

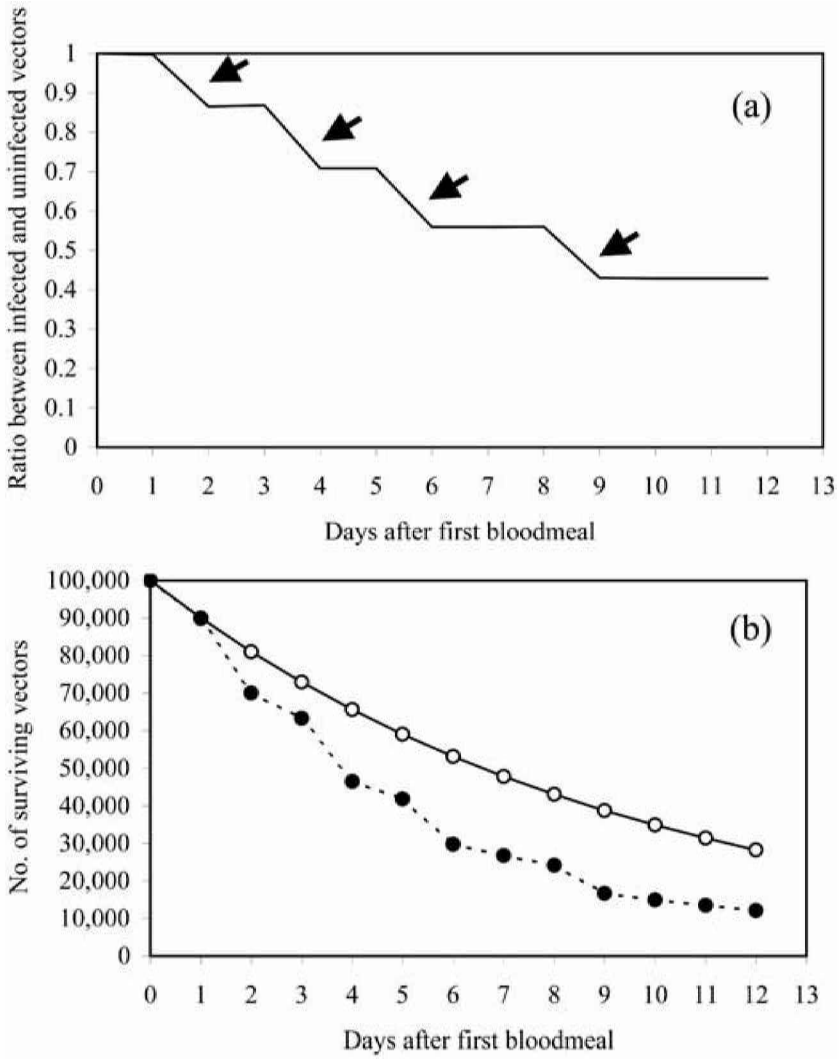

FIG. 3. Potential impact of the clearance of microfilaraemia (using mass drug administrations) on the survival of 100,000 potential vectors of human malaria. The two graphs indicate (a) the differential survival of a cohort of *Anopheles* exposed to high microfilaraemias, and (b) the survival of *An. gambiae* s.l. in the presence (●) or absence (○) of microfilaraemias. The arrows indicate periods of 'post-prandial' mortality attributable to the filarial development in the infected mosquitoes.

focus of LF; Brengues *et al.*, 1975), the suppression of microfilaraemia caused by MDA would result in 233 potentially malaria-infective mosquitoes for every 100 that there would have been in the absence of MDA. The value of 233 is almost certainly an underestimate as it takes no account of any filaria-attributable mortality that may occur more than 12 days after the ingestion of the mff. Even if the true value is slightly higher than 233, it would still be too low to indicate that antifilarial MDA (in areas where malaria and LF are co-endemic) would have an immense impact on the prevalence of malaria or the level of malaria-attributable morbidity. (The survival of most filaria-positive mosquitoes is not markedly affected by the infections because the intensity of the infections is

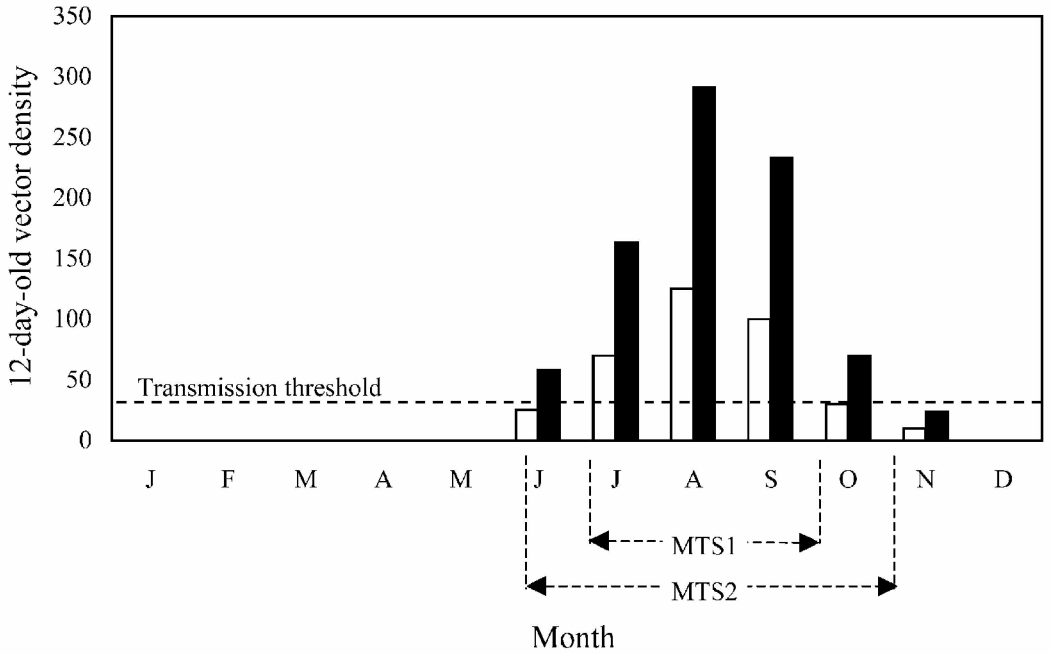

FIG. 4. The hypothetical relative durations of the malaria-transmission season (MTS) in areas where *Wuchereria bancrofti* is hyper-endemic (□) or absent (■). Only in the filaria-free area are the numbers of potential vectors of malaria [surviving long enough to be infective (i.e. 12 days)] high enough in June and October to support significant malaria transmission in these months.

generally low.) In a highly endemic focus of LF in which each resident is bitten 400 times a year by mosquitoes carrying *Plasmodium falciparum* sporozoites, elimination of the LF might increase the annual number of malaria-infective bites to 900/resident. Although the impact of the MDA on malaria may be slight, it may well be long lasting. Moreover, in climates with a short rainy season, the malaria-transmission period could be lengthened by antifilarial MDA (Fig. 4). Therefore it is recommended that, in highly endemic LF foci where the mosquitoes acting as the filarial vectors may also be malarial vectors, antifilarial MDA should be augmented with vector control (such as the use of insecticide-treated bednets) and adequate malaria surveillance. Similar observations to those of Brengues *et al.* (1975) should be made on other field populations of filarial vectors, so that the 'post-prandial parasitic over-mortality' (PPPOM), particularly of members of the *An. gambiae* complex, can be estimated. Such mortality will have to be considered if the prevalence of microfilaraemia is to be accurately estimated by xenomonitoring (Chadee *et al.*, 2002; Ramzy, 2002; WHO, 2002).

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