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REVIEW

Are coinfections of malaria and filariasis of any epidemiological significance?

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Abstract Africa accounts for about 33 and 90% of the world's burden of lymphatic filariasis (LF) and malaria, respectively. Despite tremendous progress in the approach to their diagnosis, epidemiology, and treatment, and global campaigns for their control and/or elimination, their global burden and economic costs have continued to rise. In most rural areas of the tropics, both diseases co-occur in the same human population and share common mosquito vectors. It is therefore conceived that control of the two diseases can be integrated using tools that have been proven effective recently or in the past. Before implementation of control programs in areas co-endemic for both diseases, it is deemed necessary to understand how the two diseases interact in the vector and human hosts. Here, we summarize available knowledge on coinfections of malaria and LF and provide an insight on how they can be managed.

Introduction

Malaria and lymphatic filariasis (LF) are the world's most important parasitic diseases transmitted by mosquitoes. They are significant causes of morbidity and mortality wherever they occur, making them priorities for elimination and control programs (Nabarro and Tayler 1998; Ottesen 2000). Both diseases are co-endemic in many areas of the tropics and are transmitted by a number of common vectors (Muirhead-Thomson 1953; Burkot et al. 1990; Chadee et al. 2003). It is therefore common to find coinfections of malaria and LF in a single mosquito vector and in human populations living in these areas. Because interaction among parasites is known to alter disease severity (Buck et al. 1978) and that the nature of interaction is not always predictable, knowledge of interactions among parasites is important in designing effective disease management programs. This paper demonstrates the epidemiological significance of concomitant infections of malaria and LF and highlights the strategies of managing coinfections with the two diseases.

Global burden of malaria and lymphatic filariasis

With half a billion annual infections and a death toll of 1–3 million deaths per year, malaria remains the most important parasitic disease transmitted by mosquitoes (World Health Organization 2005a). The greatest illness and death from malaria results from *Plasmodium falciparum*, the predominant malaria parasite in Africa, and the remaining proportion is accounted for by *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* (Adl et al. 2005). Like many other parasitic diseases, human mortality and morbidity resulting from malaria is mainly concentrated in sub-Saharan Africa, where 90% of global malaria burden occurs. Although numerous multinational research projects have attempted to decrease malaria incidence through improved health care, personal protection, and adult vector control since the 1950s (World Health Organization 1996), the direct and indirect costs of malaria estimated at $800

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million (US) per year in 1987, doubled in less than 10 years to an estimated $1.5–2.0 billion (US) in 1995 (Metcalf 1998).

The escalating burden of malaria has not only slowed economic development in many parts of sub-Saharan Africa but also has posed a global concern because of increased travel and trade. Many areas that were once considered malaria-free have witnessed severe malaria epidemics within the past two decades, and the situation continues to worsen (Roberts et al. 2000). The spread of insecticide and drug resistance, human population growth and movement, socioeconomic conditions, changes in climate, land use, and adaptability of vector mosquitoes to the changing environment has led to serious setbacks in global malaria control (Roberts 1964; Robert et al. 1998; Ghebreyesus et al. 1999; Githeko et al. 2000; Patz et al. 2000; Keating et al. 2004).

To exacerbate the intolerable burden of malaria is the reality that some tropical regions endemic for malaria also have a high prevalence of lymphatic filariasis (LF); another mosquito-borne disease that has continued to degrade human life despite being considered eradicable (Anon 1993). Currently, at least 1 billion people (240 million in Africa) are at risk of infection with LF, more than 120 million people in Africa, Asia, West Pacific, and South America are already infected, 44 million of which are seriously disfigured (Michael and Bundy 1997; World Health Organization 2001). It is estimated that some 4.6 million cases of lymphodema and more than 10 million cases of hydrocele occur in Africa (World Health Organization 2004). The psychosocial consequences associated with LF are enormous, and the disease is ranked the second most important cause of disability after emotional disorders (World Health Organization 1995).

More than 90% of LF cases are caused by *Wuchereria bancrofti*, the only known cause of LF in Africa, with *Brugia malayi* and *Brugia timori* accounting for the remaining 10% (Otessen et al. 1997). LF is responsible for an annual loss of 1 billion US dollars in Africa (Haddix et al. 1999), a figure similar to that incurred in India (Ramaiah et al. 2000). The great morbidity associated with LF provided the impetus for a global elimination program sponsored by the WHO, nongovernment organizations, the drug manufacturers Merck and GlaxoSmithKline, and numerous government health departments (Colatrella 2003). The program is based upon mass community treatment with diethylcarbamazine citrate (DEC) and albendazole in areas where there is no coendemicity with onchocerciasis and ivermectin (Mectizan®) and albendazole in areas where onchocerciasis and LF coexist (World Health Organization 1999; World Health Organization 2001). The goal of the program is to eliminate the disease globally by the year 2020 (Otessen et al. 1997). The program is now active in 20 African countries, nine of which are at mass drug administration (MDA) stage, and 11 have either completed disease mapping and waiting to start MDA, or mapping is still ongoing (WHO 2004). The therapeutic coverage rate is, on average, more than 70% and has shown a continued improvement over the years. However, less than 10% of at risk population is covered by MDA, and the implementation of disease management and vector control components have been delayed due to financial constraints, lack of personnel, technical difficulties with tools for endemicity mapping, and the co-endemicity of loiasis with LF in many endemic countries (Malacela-Lazaro and Twum-Danso 2004; World Health Organization 2004; World Health Organization 2005b; Gyapong and Twum-Danso 2006).

Despite the challenges in the global campaign to eliminate LF, there has been significant progress. For instance, substantial information is available on the vectors of LF and knowledge concerning the site-specific disease transmission and prevalence of human infection (Appawu et al. 2001; Ngwira et al. 2002; Muturi et al. 2006a; Muturi et al. 2006b). Information on the impact of various drug regimens (Kazura 1993; Ramzy et al. 2002; Alleman et al. 2006) and vector control (Maxwell et al. 1990; Maxwell 1999) in disease management is also available.

Anopheles vectors of malaria and filariasis

The major *Anopheles* species that transmit malaria are also important vectors of Bancroftian filariasis. The actual *Anopheles* species involved in transmission of the two parasites varies among geographical regions. In much of sub-Saharan Africa, *Anopheles funestus* and members of the *Anopheles gambiae* complex, mainly, *A. gambiae*, *Anopheles arabiensis*, *Anopheles merus*, and *Anopheles melas* are involved in transmission of malaria and Bancroftian filariasis (McMahon et al. 1981; Trape and Rogier 1996; Muturi et al. 2006b). Other examples of known *Anopheles* vectors of malaria and filariasis include *Anopheles philipinensis* and *Anopheles barbirostris* in India, *Anopheles leucosphyrus*, *Anopheles barbirostris*, and *Anopheles donaldi* in Malaysia (Webber 1991; Chang et al. 1995), *Anopheles darlingi* and *Anopheles aquasalis* in South America (Giglioli 1948; Validum 1998), and *Anopheles farauti* and *Anopheles punctulatus* in Papua New Guinea (Burkot et al. 1990). A comprehensive list of the various *Anopheles* species involved in malaria and filariasis transmission in different regions of the world is shown in Table 1.

Concomitant malaria and filarial infections in mosquitoes

Although the role of *Anopheles* mosquitoes as vectors of both human malaria and LF has long been established, little

Table 1 *Anopheles* vectors involved in malaria and filariasis transmission in various parts of the world

Geographic area	*Anopheles* species
Africa	*A. gambiae*, *A. arabiensis*, *A. merus*, *A. merus*, *A. funestus,*
India and Bangladesh	*A. philippinensis*, *A. barbirostris*
Malaysia	*A. leucosphyrus*, *A. barbirostris*, *A. donaldi*, *A. letifer*, *A. whartoni*, *A. macualtus*, *A campestris*
Philippines	*A. minimus*
Indonesia	*A. balabacensis*
Papua New Guinea	*A. farauti, A. punctulatus*
Solomons island	*A. koriensis*
South America	*A. darlingi*, *A. aquasalis*
China and Korea	*A. sinensis*

Sources: Burkot et al. 1990, Webber 1991, Chang et al. 1995, Validum 1998, Muturi et al. 2006a, and other sources

is known about the occurrence and prevalence of concomitant infections of the two diseases and how they interact within the vector. Earlier reports on occurrence of concomitant infections of the two parasites in the vector were coincidental and were observed during routine dissection of wild caught mosquitoes for either malaria or filarial infections. Muirhead-Thomson (1953) reported high infection rates of malaria and filarial parasites in *A. gambiae s.l.* in Dar-es-Salaam, Tanzania (then Tanganyika) and Accra, Ghana (then Gold Coast), but it was only on rare occasions that a single mosquito could carry malaria sporozoites and mature filaria larvae. Subsequent studies confirmed that concurrent transmission of malaria and filarial parasites by a single mosquito vector was rare in nature (Burkot et al. 1990; Muturi et al. 2006b).

Studies using *Aedes taeniorhynchus* indicated that mosquitoes infected with filarial nematode *B. malayi* were more susceptible to Rift Valley Fever virus because migration of microfilariae in mosquito midgut facilitated virus penetration into the hemocel (Turrell 1984). Further studies revealed that mosquito midgut was a significant barrier to malaria infection (Ponnudurai 1988), suggesting that concurrent ingestion of microfilariae and malaria gametocytes could be mutually synergistic. Burkot and colleagues (1990) conducted a field study using wild populations of *A. punctulatus* and observed significantly higher numbers of *W. bancrofti* in *Plasmodium*-infected mosquitoes compared with uninfected mosquitoes. However, there was a greater mortality of mosquitoes carrying both infections when the worms reached the third stage making concurrent transmission of such infections rare. Along the Kenyan coast, *Wuchereria*-infected *A. gambiae s.l.* had significantly higher *P. falciparum* sporozoite rates than uninfected mosquitoes suggesting that filarial parasites may enhance malaria infections (Muturi et al. 2006b). Nonetheless, simultaneous occurrence of mature worms and malaria sporozoites was very rare. Alberquerque and Ham (1995) used *Aedes aegypti* to investigate the immune responses invoked by mosquitoes when simultaneously infected with *Plasmodium gallinaceum* and *Brugia pahangi* under laboratory conditions. They found that intrathoracic inoculation of secondary infection of *B. pahangi* reduced the development rate of preexisting infection of *P. gallinaceum* by 9.5–49% in susceptible strains and 50–90% in refractory strain. In both strains, individuals carrying double infections defended themselves against oocytes by causing a reduction in their size and also by melanization in the *B. pahangi* refractory strain. They concluded that activation of phenoloxidase cascade in response to microfilariae in the hemolymph could also be used against oocyts in the midgut. Recent studies in endemic areas of Africa have shown that despite the two diseases sharing common *Anopheles* vectors and environmental factors necessary for replication, one disease tends to dominate the other probably as a result of interspecies competition between microfilaria and *Plasmodium* within the vector or human host (Kelly-Hope et al. 2006; Muturi et al. 2006a). The exact mechanisms of this competition remain a conjecture in the scientific community.

Concomitant infections of malaria and filariasis in humans and other vertebrates

Co-occurrence of malaria and filarial parasites in a single human has been known for a long time (Muirhead-Thomson 1953). However, information on the occurrence, prevalence, and interaction of the two diseases in humans is scant. Three studies conducted in India demonstrated natural occurrence of coinfections of malaria and filariasis in humans but in prevalence lower than 1% (Prasad et al. 1990; Ghosh and Yadav 1995; Ravindran 1998). In Guyana, South America, 0.4 and 3.3% of individuals examined for filariasis and malaria parasites, respectively, were positive for both infections (Chadee et al. 2003). Muturi et al. (2006b) found 4.3% of the 94 persons examined in a coastal Kenyan village to carry both malaria and filariasis parasites. Three of the above studies found *P. falciparum* to co-occur more often with *W. bancrofti* than other *Plasmodium* species (Ghosh and Yadav 1995; Chadee et al. 2003; Muturi et al. 2006b), and one study found *P. vivax* and *W. bancrofti* to be the most common combination (Prasad et al. 1990). From these studies, it was evident that the most prevalent malaria parasite in an area was the one that co-occurred more often with *W. bancrofti*. Moreover, it was shown that coinfections of malaria and filariasis were least likely to occur when the prevalence of either of the two parasites was low (Muturi

et al. 2006b). The lowest threshold prevalence in which coinfections of the two diseases are unlikely to occur has not been established and remains a matter of guess. An epidemiological study along the Kenyan coast did not detect any coinfections of malaria and LF in a study site with 17.4% malaria prevalence and 2.8% LF prevalence (Muturi et al. 2006b). However, the sample size in this study was not large enough and, therefore, might have underestimated the true prevalence of LF and coinfections with the two diseases in the area. This is particularly so because microfilariae are not evenly distributed in the blood and, therefore, blood samples from microfilaremic humans might still yield negative results (Ngwira et al. 2002). Moreover, some studies have shown that mosquitoes are still able to pick filarial infections from ultralow microfilariae carriers (World Health Organization 1983; Lowrie et al. 1989). Because high worm load reduces mosquito survivorship (Klein 1986), mosquitoes that ingest low microfilariae densities are likely to survive longer, a factor that is likely to increase their chances of picking malaria parasites as well. Confirmatory work using animal models is warranted to establish to minimum parasite and prevalence threshold required to sustain the occurrence of coinfections of malaria and filariasis.

Interaction of malaria and filariasis parasites within a single host has been least studied in humans than it is in other vertebrate hosts. Both malaria and filarial infections are known to induce inflammatory cytokines (Richard et al. 1991, Das et al. 1996), and the two diseases have been reported to have antagonistic effect on immunoregulatory T lymphocytes. In *Aotus trivirgatus* monkeys, individuals concurrently infected with microfilariae and *P. falciparum* followed a more benign malaria course than amicrofilaremic individuals (Schmidt and Esslinger 1981). Inoculation of experimental mice with third stage larvae of filarial nematode *B. pahangi* activated Th2 response that conferred protective immunity to *Plasmodium bergei* cerebral malaria (Yan et al. 1997). A more recent study has shown that mice coinfected with filarial nematode *Litomosoides sigmodontis* and non-cerebral malaria clone of *Plasmodium chabaudi chabaudi* were more anemic and lost more body mass than mice infected with malaria only even after controlling for parasitemia (Graham et al. 2005). Their study demonstrated that in amicrofilaremic mice, filariasis interferes with delicate immunological balance in malaria infection and aggravates malaria-induced immunopathology. Previous studies had shown that helminth coinfection can impair mechanisms necessary to control malaria parasitemia and/or prevent immunopathological malaria (Mosmann and Sad 1996; Jankovic and Sher 2001; Maizels and Yazdanbakhsh 2003). However, there are also reports that *W. bancrofti* infection has no significant effect on *P. falciparum* parasitemia in humans (Muturi et al. 2006b). Collectively, these findings emphasize the need to understand the interactions of malaria and filaria parasites in co-endemic areas before implementation of control or elimination programs (Kelly-Hope et al. 2006).

Strategies for reducing the prevalence of coinfections of malaria and filariasis

Control of coinfections of malaria and LF is easier than control of either of the two diseases. This is because transmission of such infections by a single vector is rare, their prevalence in humans is low, and they are more likely to occur when the prevalence of both diseases is high. Because of possible negative effects that might result from differential control of one disease (Kelly-Hope et al. 2006; Muturi et al. 2006a; Muturi et al. 2006b), integrated control of the two diseases is the most efficient way of managing coinfections of malaria and filariasis.

Vector control can help reduce vector densities and the risk of disease transmission. Vector control by indoor spraying of dichlorodiphenyltrichloroethane (DDT) in doses insufficient to interrupt malaria transmission led to successful elimination of filariasis in the Pacific island (Burkot et al. 2002), Solomon Islands (Wada 1974; Webber 1977; Webber 1979), and some parts of Papua New Guinea (Bockarie 1994). The disappearance of *Brugian* filariasis in 18 of the 21 foci previously recognized in Sri Lanka was attributed to the destruction of the aquatic plant *Pistia stratiotes* that is associated with the breeding of *Mansonia* vectors after a malaria vector control program (Abdulcader 1967). Source reduction was one of the methods used to achieve effective eradication of malaria in the United States, Italy, Israel (Kitron and Spielman 1989) and Zambian copper belt (Utzinger et al. 2002). The same method was used to eradicate *A. gambiae* in northeast Brazil, where it was well established and an important vector of malaria (Soper and Wilson 1943).

Currently, vector control in Africa targets adult populations mainly through use of insecticide-treated bed nets (ITNs). ITNs may reduce vector populations by killing them directly through contact with insecticides or by preventing them from feeding, through reduced house entry or early exiting (Mbogo et al. 1996; Bogh et al. 1998; Lengeler 2004; Lindblade et al. 2006). Untreated bed nets have been reported to substantially reduce malaria transmission and significantly reduce LF transmission (Burkot et al. 1990; Bockarie et al. 2002; Mwangi et al. 2003), but the impact is great when they are treated with insecticides (Bogh et al. 1998; Pedersen and Mukoko 2002). The greater impact of bed nets on LF than malaria control is because transmission of LF is very inefficient. There is no parasite multiplication in the vector, and only continuous exposure to infective mosquitoes can produce a patent infection of *W. bancrofti* (Southgate 1992). Nonetheless, it

is now becoming a reality that ITNs alone are insufficient to achieve large scale reduction in vector densities and transmission interruption, and thus, source reduction is being reappraised as an essential component of vector control after five decades of neglect (Fillinger et al. 2003; Fillinger et al. 2004; Killeen et al. 2004).

Chemotherapy is also used widely in the treatment of malaria and LF. In addition to reducing the mortality and morbidity associated with the two diseases, chemotherapy also reduces the number of infected people that can serve as infective agents to the mosquitoes. Interestingly, Ivermectin and DEC; two of the three drugs used in the Global Program for Elimination of Lymphatic Filariasis (World Health Organization 2001) have been reported to possess mosquitocidal activity. Under laboratory conditions, Pampiglione et al (1985) reported mortality of adult mosquitoes of *A. aegypti*, *Culex pipiens*, and *Anopheles stephensi* after ingestion of ivermectin in sugar solutions or after feeding on mice previously inoculated with the chemical. Tesh and Guzman (1990) reported death and reduced fecundity in *A. aegypti*, *Aedes albopictus*, and *Culex quinquefasciatus* mosquitoes fed blood–ivermectin mixture through a chick skin membrane. Cartel et al. (1991) demonstrated for the first time a significant reduction in mosquito survival rates after feeding on people treated with ivermectin and DEC up to 3 months previously. However, the lethal effect of ivermectin was too short-lived to impact significantly on wild-caught mosquitoes fed naturally on ivermectin-treated people following their normal life styles (Bockarie et al. 1999). Collectively, these findings suggest that timely DEC and ivermectin treatment of people at risk and their livestock on whom the vector populations depends on for blood meal may block epidemics of mosquito-borne diseases and may represent an additional tool in control of malaria, filariasis and coinfections of the two diseases. Surprisingly, despite the proven mosquitocidal effects of DEC and ivermectin, little is known about their specific effects on the major vectors of malaria and filariasis in the world.

Conclusion

The evidence provided here demonstrates the epidemiological significance of coinfections of malaria and LF. The literature shows that the two parasites might interact within the vector and human populations in a way that may alter the dynamics of transmission and the course of disease development in humans. To achieve successful results in the ongoing global campaigns for malaria and LF control, it is important to understand the interactions between malaria and LF parasites in areas where they co-occur. More importantly, it is evident that timely provision of treatment to infected humans along with vector control in endemic communities can drastically reduce the prevalence of malaria, LF, and their coinfections.

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