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DEVELOPMENTS IN FILARIASIS RESEARCH

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Lymphatic filariasis in Papua New Guinea: prospects for elimination

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Abstract Lymphatic filariasis is a significant public health problem in several Pacific island countries. Papua New Guinea is one of the most populous countries in this region, and 39% of its residents are estimated to be infected with *Wuchereria bancrofti*. The Ministries of Health of the 22 islands and territories in the Pacific region are committed to taking action against lymphatic filariasis. Accordingly, a regional collaborative effort aimed at the control of filariasis has been organized under the auspices of a program referred to as PacELF. The main objective of PacELF is to eliminate filariasis as public health problem in the Pacific region by the year 2010, 10 years before global elimination of this infectious disease has been targeted. This contribution describes the epidemiology and ecological features of filariasis and prospects for its elimination in Papua New Guinea. The frequencies of microfilaremia, chronic lymphatic disease, and acute filarial morbidity in Papua New Guinea are higher than in many other endemic countries of the Pacific, Africa, and South America. All possible combinations of these three manifestations of filariasis exist. They occur independently of each other, and there is no association between chronic lymphatic disease and microfilarial status. *Anopheles punctulatus* mosquitoes are the main vectors throughout the country. Transmission intensity is heterogeneous and a major determinant of local patent infection and morbidity rates. Annual transmission potential and annual infective biting rates are positively associated with the village-specific microfilarial rate, mean intensity of microfilaremia, and prevalence of leg edema. Children and adults have similar worm burdens, assessed by circulating filarial antigen levels, in areas of high transmission, whereas worm burdens increase with age in areas of lower transmission. Intensity of exposure to infective third-stage larvae (L3) is significantly correlated with filarial antigen-specific lymphocyte proliferation and cytokine production, possibly by a mechanism that alters APC function. Historical evidence suggests that residual insecticide spraying conducted for malaria control in some parts of the country interrupted transmission of *W. bancrofti* as it did in the Solomon Islands. Prospects for eliminating lymphatic filariasis in Papua New Guinea are good and may be achieved by the end of the second decade of the twenty-first century if an integrated control approach using mass drug administration with vector control is adopted.

Keywords Epidemiology · Lymphatic filariasis · Microfilaremia · Papua New Guinea · *Wuchereria bancrofti*

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Introduction

Lymphatic filariasis is a major cause of acute and chronic lymphatic disease and economic underproduction in tropical and subtropical areas of Asia, Africa, the Western Pacific and some parts of the Americas. Over 20% of the world's population is at risk of infection with *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori* [23]. Lymphatic filariasis is highly prevalent in the Pacific island countries, with high rates of microfilaremia in Papua New Guinea. Some 39% of the population of the country is microfilarial-positive [23], suggesting that at least twice as many persons are infected but microfilarial-negative. *W. bancrofti*, the only known causative agent of lymphatic filariasis in Papua New Guinea, has a complex life cycle involving humans and an obligatory mosquito vector. Infection is initiated during blood feeding by mosquitoes when L3 are deposited on the skin. The larvae penetrate the skin and migrate to the lymphatic system where they eventually

mature into male and female worms in afferent lymphatic vessels. Lymphatic-dwelling filariae are diecious and undergo ovoviviparous reproduction resulting in the release of microfilariae from females, first-stage larvae that circulate in the bloodstream. The life cycle is completed when microfilariae are ingested by mosquito vector. Microfilariae penetrate the mosquito's gut wall, migrate to the flight muscles, and develop into L3 over one to 2 weeks. The main vectors of *W. bancrofti* in Papua New Guinea are members of the *Anopheles punctulatus* group of mosquitoes [3, 8].

The availability of safe, single-dose drug regimens capable of reducing microfilaremia to nearly nil for 1 year or more along with improvement in techniques for diagnosing the infection has resulted in a sense of optimism for a global strategy to eliminate lymphatic filariasis. The absence of a nonhuman reservoir of *W. bancrofti* suggests that transmission can be interrupted by elimination of the reservoir of microfilariae through community-wide treatment, by reduction in human-vector contact, or an integrated strategy combining the two approaches.

The World Health Assembly in 1997 adopted a resolution calling for the elimination of lymphatic filariasis as a public health problem. The World Health Organization in collaboration with other international agencies in the public and private sectors launched a global campaign to eliminate lymphatic filariasis by the year 2020 [35]. The main goal of the Global Programme to Eliminate Lymphatic Filariasis is to break the cycle of transmission of the disease between mosquitoes and humans [24]. The Ministries of Health of the 22 islands and territories in the Pacific region have embarking on a regional collaborative effort (PacELF) for the elimination of the disease. PacELF's main objective is to eliminate filariasis by the year 2010, 10 years before global elimination is anticipated [14].

This paper reviews the epidemiology and ecology of filariasis in Papua New Guinea and examines the prospects for its eliminating in the country.

History and distribution

Elephantiasis was widespread in the Pacific region when Europeans first made contact with island communities during the seventeenth and eighteenth centuries [19]. In his review of the global dispersal of bancroftian filariasis Laurence [19] speculated that humans were infected by *W. bancrofti* in present day Southeast Asia about 3000 years ago. Sea-faring Malay-speaking people moved eastwards into the Pacific carrying the parasite with them. The island of New Guinea was the first in the Pacific region to come into contact with the parasite. *W. bancrofti*, which was originally transmitted by *Anopheles* and *Aedes* mosquitoes in southeast Asia, easily adapted to the common anthropophilic *Anopheles punctulatus* group of mosquitoes. Lymphatic filariasis is now known to be endemic in at least ten provinces in coastal areas, highlands, and offshore islands of Papua New Guinea [5, 6, 8, 22]. Village-specific microfilarial rates range from 10% to 92%. Antigenemia rates, which detect nonpatent as well as patent infection, up to 98% have been reported [33].

Infection and disease

A recent review of *W. bancrofti* infection and disease in Papua New Guinea [1] suggests that work conducted in the East Sepik Province [2, 4, 16, 18, 33] has yielded community-based prospective data on filarial infection and disease that are comprehensive in terms of their contribution to our understanding of the ecology of this infectious disease. Only a handful of other studies are comparable in their scope [10, 11, 27, 28]. The frequencies of microfilaremia, chronic lymphatic disease and acute filarial disease are higher than in other filariasis endemic countries. All possible combinations of the three manifestations exist in Papua New Guinea, and there is not a consistent relationship between chronic disease manifestations such as elephantiasis and microfilarial status. A high incidence of acute disease was observed in the Dreikikir area of East Sepik Province, where 0.31 episodes of symptoms that included acute adenolymphangitis per person-year were experienced in the leg alone [2]. The incidence of acute disease of the leg and arm increased with age whereas acute disease episodes affecting the female breast were concentrated in women of reproductive age. Men had a slightly higher incidence of acute lymphangitis than women. Chronic lymphedema of the legs was strongly associated with acute disease incidence. Microfilaremia was associated with acute disease of the leg, arm, and breast but not the male genitalia.

Transmission intensity is a major determinant of patent infection and chronic disease rates in Papua New Guinea [16]. The prevalences of microfilaremia and clinical morbidity were lowest in persons under 20 years old and thereafter increased progressively with age. Annual transmission potentials (ATP) and annual infective biting rates (AIBR) were monitored in five villages where *An. punctulatus and Anopheles koliensis* are the only vectors of *W. bancrofti*. Both entomological measures of exposure were positively associated with the village-specific microfilarial rate, geometric mean intensity of microfilaremia, and prevalence of leg edema.

The relationship between filarial Og4C3 antigenemia and lymphatic pathology was recently described. Tisch et al. [33] showed that prevalence of antigenemia varied from 61.7% to 98.2% in several East Sepik Province villages, and did not vary according to gender. Antigen levels increased with ATP and AIBR in the four villages where these entomological indices were determined. Antigenemia was associated positively with age in villages with ATP less than 404 L3/person per year but was distributed evenly across all age groups in villages with higher levels of transmission (ATP $>$ 1485 L3 larvae per

person per year). These data suggest that children and adults have similar worm burdens in areas of high transmission whereas worm burdens tend increase with age in areas with lower levels of transmission.

Infection and immunity

Recent research conducted in Papua New Guinea indicates that the intensity of exposure to L3 has a major impact on T-cell immunity to filariae [18]. T-cell proliferation and cytokine responses were measured and compared in 97 residents of two villages in East Sepik Province. Transmission intensity in the two villages differed by 63-fold (37 vs. 2355 L3 per person per year). Adult worm antigen-driven lymphocyte proliferation and type 1 cytokine production (interferon-γ, IFN-γ) were markedly poorer in residents of the high-transmission than the low-transmission village, even when the subjects were matched for microfilaremia levels and antigenemia. In contrast, filarial antigen-driven interleukin-5 production was 5.5-fold greater and plasma interleukin-4 and transforming growth factor β levels were 4-fold and 34% higher in residents of the high-transmission than the low-transmission village. The data suggest that the intensity of exposure to L3 affects lymphocyte responsiveness and cytokine bias, possibly by a mechanism that alters function of antigen presenting cells.

Vectors

The *An. punctulatus* group of mosquitoes, including *An. punctulatus*, *An. koliensis* and *An. farauti* s.l., are the principal vectors of periodic *W. bancrofti* in Papua New Guinea [3, 8]. *Anopheles faurati* is present mainly in coastal areas, and breeds in fresh or brackish water and permanent swamps or temporary pools. *Anopheles koliensis* favors near coastal areas and generally breeds in temporary pools, grasslands, and pools at the edge of jungles. *Anopheles punctulatus* prefers breeding in sun lit water, road ruts and drains. *Culex* and *Mansonia* species may be involved in transmission in some areas of Papua New Guinea but are much less widely distributed than *Anopheles* mosquitoes. Vector infections rates tend to be higher in Papua New Guinea compared to those found in *Anopheles* mosquitoes in other regions of the world. Village-specific infection rates reported for biting catches of *An. punctulatus* s.l. in the Dreikikir area of the East Sepik Province ranged from 2% to 11.7% and infective rates from 0.4% to 3.5% [3]. The highest rates of samples collected from more than 100 *An. gambiae* in endemic villages in Tanga, Tanzania, were 6.8% infected and 1.6% infective [20]. The high infection rates reported for *Anopheles* mosquitoes from other Pacific countries were determined from resting catches, which tend to have a greater proportion of older mosquitoes relative to landing collections. Burkot et al. [9] working in the Madang Province showed that the infection rates of indoor resting *An. punctulatus* could be up to four times higher than that of biting mosquitoes caught in the same village.

Vector-parasite relationships

Rational planning of filariasis control measures requires an understanding of the quantitative aspects of filariasis transmission. An important determinant of transmission efficiency is the relationship between parasite yield, the success rate of ingested microfilariae becoming L3 in the mosquito vector, and the density of microfilaremia in the human host. For filariasis transmission to be interrupted, vector density or microfilarial intensity needs to be driven below a threshold such that a sufficient number of microfilariae no longer develop to L3 so that new infections of the human host cannot be established. Three epidemiologically and ecologically significant categories of the relationship between filarial parasites and their mosquito vectors are now recognized: proportionality, limitation, and facilitation. Limitation, a concept that is primarily relevant to culicine transmitted filariasis, occurs when the proportion of ingested microfilariae that survive to become L3 decreases as more microfilariae are ingested. In the case of facilitation, a relationship that is associated with anopheline transmitted filariasis, the yield of L3 increases as the number of microfilariae increases from very low up to an intermediate number. The yield is reduced at higher microfilarial densities. Of less epidemiological significance is a third relationship called proportionality, which is when the parasite yield remains at a constant proportion, neither increasing nor decreasing as the uptake of microfilariae increases.

Prospects for eliminating filariasis in Papua New Guinea

Bockarie et al. [4], working in an area of intense perennial transmission of *W. bancrofti* by *An. punctulatus* in East Sepik Province, reported that no infective mosquitoes were captured for several months following a single dose of mass treatment with diethylcarbamzine (DEC) plus ivermectin (Fig. 1). Analyses are underway to determine the impact of four annual single-dose treatments with DEC alone and DEC plus ivermectin in this endemic area. The highly focal distribution of lymphatic filariasis observed in this area and other areas of Papua New Guinea have been attributed to the facilitation [32] which implies that sustained interruption of transmission can be achieved by reducing density of parasites through mass treatment. It will thus be of great interest whether these short-term results are maintained in the long term.

House spraying with dichlorodiphenyl-trichloroethane (DDT) has led to reduction or interruption of the transmission of *W. bancrofti* by *An. punctulatus* in the Solomon Islands [34] and West Papua, Indonesia [15].

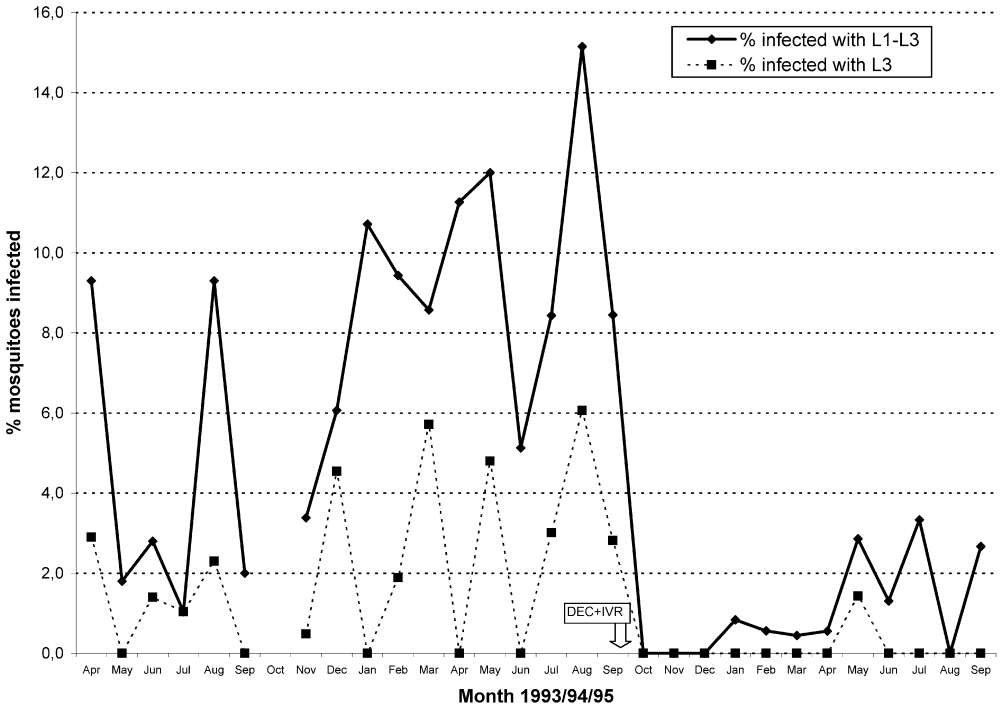

Fig. 1 The impact of single-dose mass treatment with diethylcarbamzine (*DEC*) in combination with ivermectin (*IVR*) on the *Wuchereria bancrofti* infection (*solid lines*) and infective (*broken lines*) rates of *Anopheles punctulatus* in a village in Papua New Guinea. Collections were not performed in October 1993 for logistical reasons

Recent studies comparing the effect of permethrin-impregnated bed nets and DDT house spraying against malaria transmission in the Solomon Islands showed the former to be more effective [12, 17], suggesting that insecticide-treated bed nets may be as effective as house spraying in controlling lymphatic filariasis. Introduction of permethrin-impregnated bednets in a filariasis endemic area of Kenya led to reductions in the indoor resting densities of *An. gambiae* s.l. by 94.6% and *An. funestus* by 96.7%. There is evidence that DDT house spraying carried out in the Maprik area of the East Sepik Province to control malaria in the 1960s interrupted the transmission of filariasis, which was highly endemic in the area before spraying started. Microfilarial densities and mosquito infection rates recorded for Maprik before spraying started could only be associated with intense filariasis transmission. In 1959 an adult male resident of Maprik who donated blood had a microfilarial density of 5250 parasites per milliliter blood [21]. Peters and Christian [25] recorded a *W. bancrofti* infection rate of 3.8% in 546 dissected *An. punctulatus*. Filariasis is no longer transmitted in Maprik but malaria remains highly endemic. It has been predicted that facilitation would make introduction of *W. bancrofti* into uninfected areas difficult while limitation would favor geographical spread of infection. It therefore appears that residual insecticide spraying in the Maprik area interrupted transmission of filariasis just as it did in the Solomon Islands [34] and West Papua [15].

The impact of untreated bednets on the prevalence of *W. bancrofti* infection and disease was investigated on the island of Bagabag in Madang Province, where both malaria and filariasis are transmitted by the *An. punctulatus* mosquitoes [7]. Overall usage of bednets among residents was 60.6%, with the mean age of users (25.6 years) similar to that of nonusers (22.5 years). The overall *W. bancrofti* microfilaremia and antigenemia rates were 28.5% and 53.1%, respectively. There was a lower prevalence of microfilaremia, antigenemia, and hydroceles among bednet users than among nonusers. In comparison, there no differences between two the two groups in the prevalence and intensity of *Plasmodium falciparum* and *P. vivax* infections. The impact of bednet usage on rates of microfilaremia and antigenemia remained significant even when confounding factors such as age, location and sex were taken into account. Taken together, the data suggest that untreated bednets afford a modest degree of protection against *W. bancrofti* infection.

Mass drug treatment is also very effective in reducing community microfilarial load and vector infection rates in Papua New Guinea. In a study comparing the impact of an annual community-wide single-dose treatment with DEC alone or with DEC plus ivermectin on microfilaremia and transmission in 14 communities in the East Sepik Province, greater decreases were seen in community-specific microfilarial intensity with combined therapy (91.1%) than with DEC alone (69.8%). Annual transmission potential monitored in selected communities decreased by between 75.7% and 98.8% in combined-therapy communities and between 75.6% and 79.4% in communities given diethylcarbamazine alone. Transmission was almost interrupted in two communities treated with combined therapy [4].

An integrated community-based intervention involving mass drug administration and use of treated bednets in the Mount Bosavi region of the Southern Highlands Province of Papua New Guinea reduced rates of

microfilaremia from 92% to 6% [26]. Integrated control efforts involving mass treatment and vector control have also reduced microfilarial carrier rates in the Ok Tedi area of Western Province [30], Lihir island in New Ireland Province [13], and the island of Misima in Milne Bay Province [31]. Mass treatment with DEC-fortified salt has been implemented with positive results in the Milne Bay Province [29]. Mass treatment programs have also been carried out successfully in hunter-gatherer groups in Madang Province [5, 6]. The impact of mass treatment on community microfilarial load and transmission intensity in Papua New Guinea and the potential for insecticide treated bednets to dramatically reduce patent infection and disease suggest that the prospects for eliminating lymphatic filariasis in Papua New Guinea are good. This goal may be achieved by 2010 if an integrated control approach using mass drug administration and vector control is adopted.

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