Lymphatic filariasis in Papua New Guinea: interdisciplinary research on a national health problem

James W. Kazura and Moses J. Bockarie

Center for Global Health and Diseases, Case Western Reserve University, Cleveland, OH 44106, USA

Bancroftian filariasis is a major public health problem in Papua New Guinea, where the level of transmission by the mosquito vector, human infection rates and clinical morbidity are among the highest in the world. Coordinated research efforts within the country, involving the disciplines of epidemiology, vector biology, immunology and genetics, have led to new insights into the ecology and pathogenesis of human lymphatic filariasis. Recent work using this knowledge base should be helpful in assessing local and global strategies aimed at eliminating *Wuchereria bancrofti* and in guiding research that will facilitate achievement of this goal.

Lymphatic filariasis is a major infectious disease and public health problem in Papua New Guinea (PNG) and other island nations of the Pacific region. Evidence of the disease in this area of the world was first recorded in the 17th and 18th centuries when Europeans made contact with island communities [1]. Iyengar's review of the distribution and epidemiology of filariasis cites a report by Deising in 1899 that describes a resident of the north coast of the island of New Guinea with *Filaria bancrofti* infection [2]. Microfilaria (Mf)-positive infections of residents of modern day Western, New Ireland and New Britain Provinces of PNG (the nation comprising the eastern half of the island of New Guinea) were described between 1901 and 1911. In 1946, Avery [3] and Hopla [4] reported Mf-positive prevalences of 35% to 55% in Milne Bay Province. In 1950, Bearup and Lawrence [5] observed that the prevalence of *Wuchereria bancrofti* microfilaremia was high in Morobe Province. Infection with *Brugia malayi* or *Brugia timori* has not been reported in PNG or the western half of the island of New Guinea governed by Indonesia.

Lymphatic filariasis as a public health problem

A recent assessment of the distribution of lymphatic filariasis in PNG showed that the infection is endemic in 16 out of the 20 provinces of the country, including the National Capital District* [6–9]. The infection is endemic in coastal areas, the highlands and several offshore islands (Fig. 1). Local prevalences of Mf-positive infections vary from 10% to 92%. Prevalences of infection as high as 98.2% have been reported in East Sepik Province, when more-sensitive diagnostic tests that detect infection in the absence of circulating microfilariae are used (i.e. filarial antigenemia) [10]. Reports of the rate of circulating antigen-positive persons in several areas of the country indicate that microfilaremia alone underestimates the overall prevalence of infection.

At a national level, the proportion of persons with lymphatic filariasis in PNG is among the highest in the Pacific region. Over one million residents are infected with *W. bancrofti*. An additional three million people are estimated to be at risk out of a total population of approximately five million people [10,11]. The current ten-year (2001–2010) National Health Plan of the Ministry of Health recognizes lymphatic filariasis as a major health problem that has not received the attention it deserves. The priorities of this plan include revitalization and sustenance of integrated vector control programmes against filariasis, diagnostic and treatment services, and expansion of community-wide treatment efforts. A National Task Force for the Elimination of Filariasis was established in 2002.

Vectors and ecology of lymphatic filariasis

The focal distribution of lymphatic filariasis in lowland regions of PNG where malaria is widespread first gave the impression that *Anopheles* mosquitoes were not involved in the transmission of *W. bancrofti*. However, studies carried out between 1940 and 1970 unexpectedly showed that *Culex* spp. were not important vectors of *W. bancrofti* [4,12,13]. More recent entomological studies have shown that *Anopheles* spp. mosquitoes transmit filariasis. The vector–parasite relationship is one of facilitation: the yield of infective larvae in the mosquito increases as the number of microfilariae increases from very low (e.g. ~10 Mf per ml of blood) up to an intermediate number (e.g. ~100 Mf per ml of blood), with a reduction in development at higher microfilarial densities (e.g. ~1000 Mf per ml of blood) [14]. The principal vectors are members of the *Anopheles punctulatus* group [8,15].

Previous studies of the ecology of the *An. punctulatus* group were based on species identification using morphological criteria. Only three species were thought to transmit filariasis in PNG. These included *Anopheles farauti* s.l., *Anopheles koliensis* and *An. punctulatus* [8,15–17].

Corresponding author: James W. Kazura (jxk14@po.cwru.edu).

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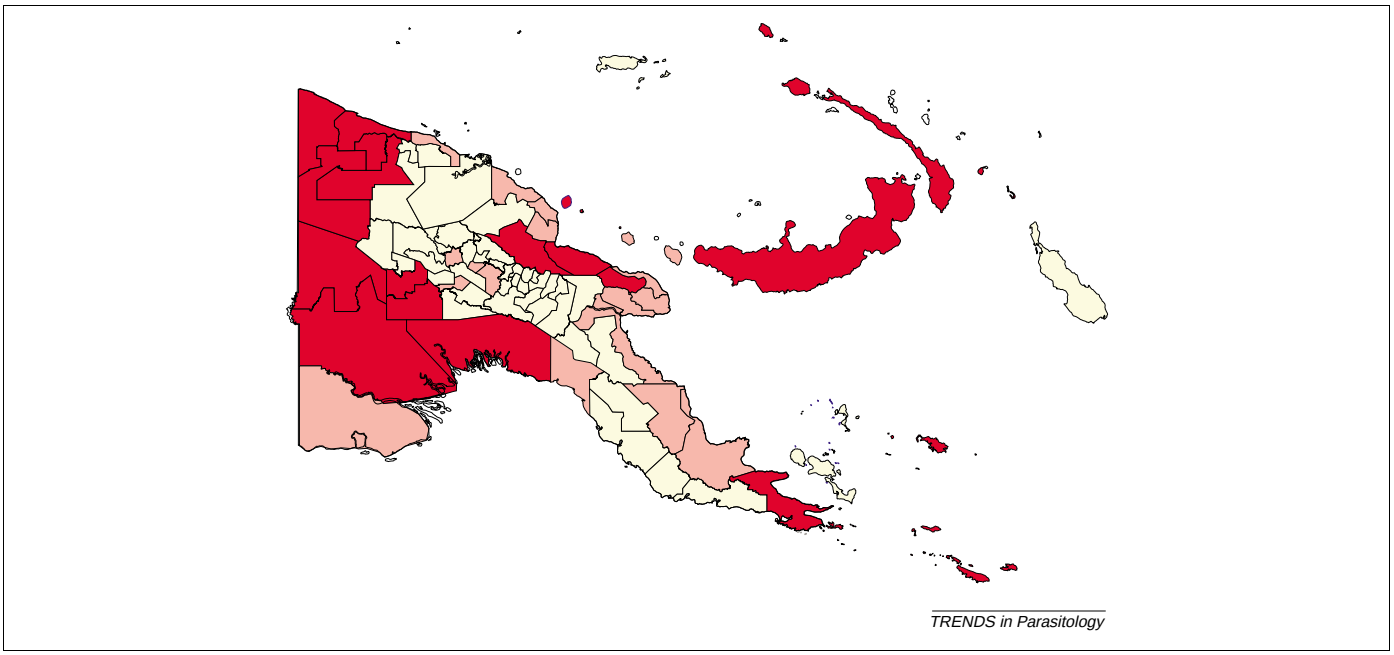

Fig. 1. Level of endemicity of *Wuchereria bancrofti* infection in Papua New Guinea. Key: red, highly endemic (>30%; pink, moderately endemic (>1–30%); cream, uncertain.

All three species are widespread. *Anopheles farauti* is most common in coastal villages, *An. koliensis* at lower elevations of inland areas and *An. punctulatus* in hills [18]. *Anopheles farauti* s.l mosquitoes lay eggs in habitats that include streams, brackish water and permanent swamps. *Anopheles punctulatus* preferentially breeds in sun-lit water, road ruts and on the edges of streams and rivers. *Anopheles koliensis* is present mainly in inland areas and breeds in temporary pools and around the edges of forests. All three species are anthropophilic and anthropophagic, but feeding on humans is reduced dramatically by the local availability of other mammalian hosts.

The use of allozyme and PCR techniques for species identification has recently revealed that there are at least 11 sibling species within the *An. punctulatus* group [19]. Mosquitoes previously identified as *An. farauti* by morphological criteria belong to a species complex consisting of at least seven sibling species [20,21]. Six of these exist in PNG: *An. farauti* s.s. (previously named *An. farauti* No. 1); *Anopheles hinesorum* (previously *An. farauti* No. 2); *Anopheles torresiensis* (previously *An. farauti* No. 3); and *An. farauti* Nos. 4 to 6 [20,22]. The importance of these newly classified sibling species as vectors of filariasis has not yet been resolved.

Risk factors for infection and lymphatic disease

Given the heterogeneity in the spatial distribution of infection rate and frequency of overt lymphatic disease in various areas of the world where bancroftian filariasis is endemic, a series of studies have been conducted in PNG to determine how the interaction among ecological, demographical and immunological variables contributes to local infection and disease burdens. Research of this type is especially well suited to rural areas of the country because large-scale human migrations are less profound than in many developing countries and because infection rates have not been significantly affected by self-administration of diethylcarbamazine (DEC), which has not been widely available until recently. A study of residents of 14 villages located near Dreikikir in East Sepik Province showed that the village-specific prevalence of microfilaremia and lymphoedema of the leg increased continuously with transmission intensity [23]. By contrast, the prevalence of hydrocele was similar in villages where the annual transmission potential varied from ~130 to 2300 infective larvae per person per year. These findings suggest that the frequency of hydroceles in a population reaches a plateau at lower transmission intensities than lymphoedema of the extremities. The level of cumulative exposure to *W. bancrofti* infective larvae, however, continuously increases the risk of chronic lymphoedema of the extremities. The level of microfilaremia and filarial antigen levels also showed a positive correlation with lymphatic pathology of the legs and the frequency of attacks of acute adenolymphangitis [24].

Immunity

The variables that contribute to susceptibility to infection and to the pathogenesis of lymphatic disease in bancroftian filariasis are poorly understood and might be related to variability in host immunity to filarial parasites. Research conducted in the mid-1980s showed that sera from individuals classified according to the level of microfilaremia and filarial antigenemia could be used to identify putatively protective filarial antigens [25–27]. Sera obtained from persons classified in this manner could then be used to screen complementary DNA (cDNA) expression libraries for antigen-encoding genes relevant to protection against infection [28–30]. With respect to pathology, several investigations have shown an association between type 1 interferon-γ (IFN-γ) pro-inflammatory responses to filarial worm antigens and chronic lymphatic disease manifestations such as elephantiasis,

whereas type 2 allergic responses were associated with lack of lymphatic pathology [31–33]. Moreover, it has been proposed that maternal filarial infection induces immunological tolerance in the developing newborn, thereby increasing susceptibility to microfilaraemia, but decreasing the propensity to develop lymphatic pathology later in life [34]. These issues have been addressed in several studies in PNG. Immune responses to filarial antigens by residents of two endemic areas where transmission intensity differed by 63-fold (annual transmission potential of 2533 versus 37 infective larvae per person per year) were compared [35]. Residents of the high-transmission area had strong filarial antigen-driven type 2 cytokine responses [increased interleukin (IL)-4, IL-5 and IL-10] and poor lymphocyte proliferation responses compared with that in residents of the low-transmission area who had increased IFN-γ production and strong lymphocyte proliferation responses. These differences in immunity were evident even when subjects of the two endemic areas were matched for age and infection intensity quantified by microfilaremia and filarial Og4C3 antigenaemia. These data are consistent with the notion that transmission intensity might be a major determinant of antigen-specific T-cell immunity. Future studies of the pathogenesis of lymphatic disease will thus require additional studies on the impact of transmission versus antigen load on immunity.

The relationship between microfilaremia in mothers and their children was investigated in a highly endemic area of East Sepik Province to assess whether maternal infection during the pre-natal period predisposes the child to infection in years to come. Although there was a correlation between maternal and child microfilaremia, it was not significantly different than that of paternal–child pairs [36], suggesting that local transmission conditions, rather than maternally induced tolerance, determine intensity of infection.

Research on control of lymphatic filariasis

Studies of the efficacy of antifilarial drugs have been conducted in PNG since the early 1980s [37]. The main findings from this work, performed in collaboration with the WHO which designed similar studies in other filariasis-endemic areas, established that single dose of DEC (6 mg per kg body weight) or ivermectin (400 mg per kg body weight), or a combination of the two drugs reduced the intensity of microfilaremia by 50-90% for one year (e.g. from approximate mean levels of 100–10000 Mf per ml of blood to 10–1000 Mf per ml blood), and that the efficacy of these regimens was similar to that of previously recommended 10–14-days courses of antifilarial drugs. These studies have been important in the development of the formal declaration by the World Health Assembly that bancroftian filariasis should be considered a target of elimination as a public health problem and ultimately eradication (i.e. sustained interruption of transmission) by the year 2020. In this regard, a prospective study of 2500 persons living in a rural area of East Sepik Province showed that a single dose of DEC or DEC plus ivermectin reduced microfilarial carrier rate by 57.5% and 30.6%, respectively, and the annual transmission potential by 75.7–79.4% and 75.6–98.9%, respectively, after one year. The combination of the two drugs was more effective than DEC alone [14]. More recently, annual mass administration of DEC alone or DEC plus ivermectin continued for four years was reported to: (1) nearly eliminate establishment of new Mf-positive infections in children; (2) decrease the overall prevalence of limb disfigurement in the population by 25%; and (3) reverse pre-existing elephantiasis and hydroceles by 69 and 87%, respectively [7]. These findings support the notion that annual single-dose mass treatment will be valuable in the control of lymphatic filariasis even in high endemicity areas such as PNG. With respect to the ultimate goal of eradication, however, it is still not known how long mass drug administration will be required, whether the duration of this treatment will vary according to local transmission intensity, if the efficacy of albendazole plus DEC is equivalent or superior to DEC, and if community acceptance of treatment programs can be sustained. Given that the estimated median life span of *W. bancrofti* adult worms is five years, the results underscore the need for additional basic and clinical research to develop newer antifilarial drugs with greater efficacy against adult worms, and additional control strategies, such as bednets and vaccines.

Several studies have addressed these issues in PNG. The impact of bednets not treated with insecticides on the prevalence of *W. bancrofti* infection and disease is currently being investigated on Bagabag island in Madang Province, where both malaria and filariasis are endemic [38]. Bednet usage among residents was 60.6%, and the mean age of users (25.6 years) was similar to non-users (22.5 years). The overall *W. bancrofti* microfilaraemia and antigenemia rates on the island are 28.5% and 53.1%, respectively. Bednet users had lower prevalence of *W. bancrofti* microfilaraemia, antigenaemia and hydroceles than that of non-users. An integrated community-based intervention involving mass drug administration and insecticide-treated bednets in the Mount Bosavi region of the southern highlands reduced prevalences of microfilaraemia in one village from 92% to 6% [39]. Integrated control efforts involving mass treatment and vector control have also reduced Mf-positive rates in the Ok Tedi area [40], and Lihir and Misima islands [41].

Future perspective

Great strides in our understanding of the pathogenesis of lymphatic filariasis and methods to control this infectious disease have recently been made. Discovery that *W. bancrofti* contain endosymbiotic *Wolbachia* raises the possibility that endotoxin-like or other putative molecules produced by these organisms induce inflammatory reactions that contribute to lymphatic inflammation, bias filarial-specific immunity and regulate the reproductive potential of the parasite. Studies from PNG and elsewhere suggest that simple mass treatment with inexpensive and safe drugs, such as DEC and albendazole, hold promise for reducing transmission and disease burden in endemic areas. Continuing research activities on these and related topics such as the contribution of host genetics to infection and disease susceptibility should be a high priority to translate promising results of research done in the past to

prevention and potentially the eradication of lymphatic filariasis in the future.

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