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Spatial variation of *Anopheles*-transmitted *Wuchereria bancrofti* and *Plasmodium falciparum* infection densities in Papua New Guinea

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Abstract

The spatial variation of *Wuchereria bancrofti* and *Plasmodium falciparum* infection densities was measured in a rural area of Papua New Guinea where they share anopheline vectors. The spatial correlation of *W. bancrofti* was found to reduce by half over an estimated distance of 1.7 km, much smaller than the 50 km grid used by the World Health Organization rapid mapping method. For *P. falciparum*, negligible spatial correlation was found. After mass treatment with anti-filarial drugs, there was negligible correlation between the changes in the densities of the two parasites.

Findings

Geolocation and remote sensing technologies are increasingly being applied to the mapping and spatial analysis of infectious diseases, including lymphatic filariasis [1] and malaria [2]. For such maps to reflect the real pattern of infection or disease, the sampling scale must be fine enough to register its variation. Lymphatic filariasis and malaria are both currently subject to renewed control programmes, and share anopheline vectors in some parts of the world. Filariasis is being targeted for elimination, but reduction in its infection intensity could conceivably, via the removal of infection-induced vector mortality, lead to more efficient transmission of malaria [3,4]. Accurate mapping of the two infections can help monitor their control, including the detection of any unwanted interactions. Here, we present spatial analysis of both parasites in the same area of Papua New Guinea, using a recently developed technique which estimates the scale of variation, taking into account the typically highly skewed distribution of parasite counts [5].

In a rural area of the East Sepik Province, cross-sectional parasitological surveys were done of the population aged over five years, as part of a trial of diethylcarbamazine (DEC) plus ivermectin versus DEC alone against lymphatic filariasis [6]. Although, with regard to malaria, the lower age threshold is a limitation, in the nearby Wosera area, peak prevalence was not reached till after five years [7]. *Wuchereria bancrofti* microfilariae were counted microscopically on Nuclepore filters, through which 1 ml

of night-collected blood had been passed. Asexual forms of *Plasmodium falciparum* were counted per 200 white cells from thick films. *Anopheles* mosquitoes, predominantly *Anopheles punctulatus s.s.*, are the vectors of filariasis in the area [8].

Villages are divided into subunits, which we call hamlets, distinguished by names in the local languages. These were mapped with a hand-held Trimble Ensign Global Positioning System (GPS) machine. In the 1994 survey, immediately before the first round of treatment, blood samples were obtained from 2,219 people in 149 hamlets. Hamlets whose distance to their nearest neighbour was, due to GPS inaccuracy, measured as less than 10 m were combined with their nearest neighbour. There were two such instances, so reducing the total number of hamlets to 147.

As described elsewhere [5], spatial structure in the infection densities was fitted by a negative binomial model. The mean density is fitted as a log-linear function of age, sex, and the hamlet mean. In turn, the hamlet means are given a spatial structure, with closer hamlets being more highly correlated. Specifically, hamlet i adds a 'hamlet effect' u_i to the logarithm of the mean density. When exponentiated, these are similar to standardized mortality ratios (SMRs) although relate to parasite densities rather than death rates, so can be called standardized parasite density ratios. These age- and sex-adjusted hamlet effect u_{il} have a covariance matrix $(1/\phi)\exp(-d_{il}/\alpha)$, where d_{il} is the distance between hamlet i and l. The parameter α measures the scale of spatial correlation. More specifically, $\alpha\log_e 2$ is the distance over which the correlation reduces by half, which we call the 'half-distance'. The process can also be thought of a smoothing process of the raw hamlet means, adjusting for age and sex, and with a large spatial scale (α) corresponding to a greater degree of smoothing. The model was fitted by programs written in the C and FORTRAN languages, and checked in terms of ability to represent the spatial variability, and robustness to distributional assumptions.

At the individual level, the mean pre-treatment microfilaraemia density (including zeros) increased with age, till reaching 1591 mf/ml in the 40–49 year age group, then flattening out [9]. The mean *P. falciparum* density was 18 asexuals per 200 white cells in those aged 5–10 years, decreasing to below 2 for ages over 30 years. At the hamlet level, the median of the crude hamlet-specific pre-treatment mean microfilarial densities was 552 mf/ml, range 0–4625. For *P. falciparum*, the median was 2.2 asexual parasites per 200 white cells, range 0–113. The figure shows the spatial variation in the pre-treatment density of both parasites in this area, estimated from the model, taking into account age and sex effects, and spatial correlation. *W. bancrofti* had an estimated half-distance of 1.7 km (α= 2.41, ϕ= 1.79). *P. falciparum* showed virtually no spatial correlation, the half-distance being just 14 m (α= 0.0208, ϕ= 1.13), around the resolution limit of the GPS.

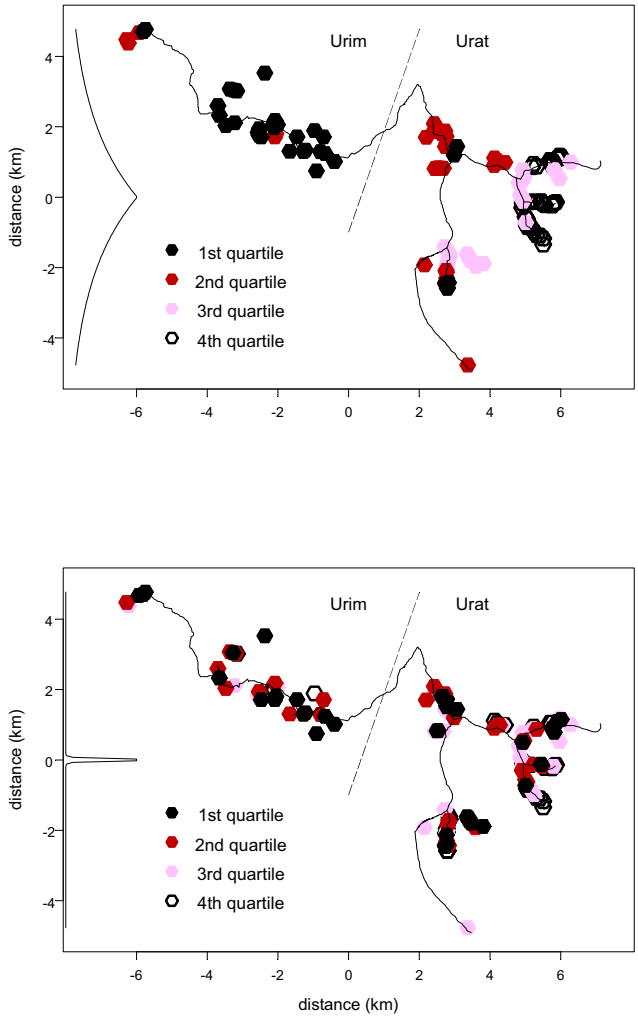

Figure 1
Spatial variation of a) *W. bancrofti* and b) *P. falciparum* in parts of Urim and Urat census districts, East Sepik Province. The scale is in kilometres with an arbitrary origin near the centre of the study area (142.7°E, 3.6°S). Each hexagon represents one hamlet, with the shading showing the quartile of the standardized parasite density ratio. For *W. bancrofti*, the 0, 25, 50, 75 and 100th percentiles are 0.27, 0.56, 1.02, 1.71 and 4.3 respectively. For *P. falciparum* they are 0.43, 0.94, 1.27, 1.80 and 11.64. The curve plotted against the vertical axis shows the rate at which correlation in mean parasite density decays with distance. The solid lines in the body of the map show unpaved roads, and the dashed line indicates the division of villages between the two census districts.

One year after the first round of mass treatment with antifilarial drugs (coverage 88%), all 14 randomized clusters showed a reduction in Williams mean *W. bancrofti* density, ranging from 47 to 96%, mean 80% [6]. All 14 clusters showed an increase in Williams mean *P. falciparum*, the increases ranging from 2 to 255%, mean 91%. However, although DEC+ivermectin was more effective against *W. bancrofti*, no tendency was seen for those clusters to have larger increases in *P. falciparum*: in 3 of the 7 pairs the DEC+ivermectin cluster had the larger increase, with 4 having the opposite tendency [3]. To further investigate the possibility that this increase was due to the treatment, the results of the spatial models were put into a hamlet-level analysis: an 'ecological' analysis in epidemiological terms. The difference in the post- and pre-treatment hamlet effects was calculated for both filariasis and malaria, and a linear relation tested using the Pearson correlation coefficient. There was negligible correlation between the changes in the densities of the two infections ($r = 0.026$, $p = 0.75$).

The World Health Organization methodology of RAGFIL (Rapid Assessment of the Geographical Distribution of Bancroftian Filariasis) is based on a 50 × 50 km grid [10]. Gyapong *et al.* have compared this to a finer 25 km grid in Ghana, with both leading to operationally similar conclusions [11]. When extended to three other countries of West Africa, the method showed filariasis to have an unexpectedly wide geographical distribution [1]. The current results suggest that, at the opposite end of the spatial scale, it may be possible for foci to persist within the interstices of a 50 × 50 km grid, or even a 25 × 25 km one; a conclusion similar to that reached by Srividya *et al.* in India [12]. However, the overall importance of any such effects will also depend on the relative magnitudes of variation at different scales, which we are unable to measure beyond the extent of our current study area. The need for accurate geographical monitoring may increase if the current elimination campaign reduces filariasis over a wide scale and proceeds from an 'attack' to a 'consolidation' phase (to borrow malaria eradication terminology).

Previous studies have found a very small scale of spatial variation of malaria [13,14]. For example, Thompson et al., found the risk of malaria varying by a factor of 6 over 500 m [15]. However, the scale of variation found in the current study was still smaller than expected, with even the closest hamlets showing little correlation. This is despite malaria and filariasis sharing the same anopheline vectors. The much smaller scale of variation of malaria is probably related to its rapid variation over time. By comparison, the risk of acquiring *W. bancrofti* infection per mosquito bite seems to be much smaller [16], but infections can last much longer. A single cross-sectional survey therefore reflects a longer-term aggregate of filariasis exposure history.

Our estimation of the hamlet effects can be seen as a smoothing method, in which the degree of smoothing is determined by the data. In this example, the west-east trend in filariasis density was not easily discernible in the raw data, while the low spatial correlation of malaria meant that the smoothed map is similar to the crude one. Any pattern presumably reflects spatial variation in factors which affect the parasite, vector or host, but which are not included in the model. In the current study, such factors are likely to include those related to vector density, such as distance to breeding sites, but this information is not available for the whole study area, and the lack of pattern in malaria infection suggests that other factors must also be involved. We view the technique as potentially useful in identifying such factors, as well as identifying 'hot spots' of infection. Our method takes account of the extreme skewness shown by most parasite distributions, which can cause problems even at the exploratory stage of analysis. For example, we found that using the common log(x+1) transformation to plot the hamlet 'geometric means' induced a spurious spatial correlation in malaria infection.

Excess mosquito mortality caused by *W. bancrofti* would make it feasible for filariasis control to enhance malaria transmission. An 'ecological' analysis did not show such an effect in this study, but monitoring should continue in those areas where *Anopheles* are vectors of both infections. For the elimination of filariasis, mapping at small as well as large scales will be necessary, including urban areas, especially as efforts proceed beyond the 'attack' phase.

List of abbreviations

DEC diethylcarbamazine

GPS Global Positioning System

RAGFIL Rapid Assessment of the Geographical Distribution of Bancroftian Filariasis

SMR standardized mortality ratio

Competing interests

none

Authors' contributions

The work originated in a drug trial of which James Kazura and Michael Alpers were the co-principal investigators, and which was led in the field by Phil Hyun and Zachary Dimber. Neal Alexander worked on the drug trial and, for this paper, made the GPS readings and wrote the first draft. Moses Bockarie also contributed to the trial,

including ensuring that the blood slides were read. The spatial model was initially developed by Neal Alexander under the supervision of Bryan Grenfell. The model was finalized by Neal Alexander, Rana Moyeed and Julian Stander, and fitted by programs written by Rana Moyeed and Julian Stander.

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