Microfilarial distribution of *Loa loa* in the human host: population dynamics and epidemiological implications

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SUMMARY

Severe adverse events (SAEs) following ivermectin treatment may occur in people harbouring high *Loa loa* microfilarial (mf) densities. In the context of mass ivermectin distribution for onchocerciasis control in Africa, it is crucial to define precisely the geographical distribution of *L. loa* in relation to that of *Onchocerca volvulus* and predict the prevalence of heavy infections. To this end, we analysed the distribution of mf loads in 4183 individuals living in 36 villages of central Cameroon. Mf loads were assessed quantitatively by calibrated blood smears, collected prior to ivermectin distribution. We explored the pattern of *L. loa* mf aggregation by fitting the (zero-truncated) negative binomial distribution and estimating its overdispersion parameter k by maximum likelihood. The value of k varied around 0·3 independently of mf intensity, host age, village and endemicity level. Based on these results, we developed a semi-empirical model to predict the prevalence of heavy *L. loa* mf loads in a community given its overall mf prevalence. If validated at the continental scale and linked to predictive spatial models of loiasis distribution, this approach would be particularly useful for optimizing the identification of areas at risk of SAEs and providing estimates of populations at risk in localities where *L. loa* and *O. volvulus* are co-endemic.

Key words: *Loa loa*, microfilarial aggregation, ivermectin, Cameroon.

INTRODUCTION

The African filarial worm *Loa loa* is well known for spectacularly migrating under the eye conjunctiva, and its association with transient oedemas called 'Calabar swelling'. Even if these signs make it one of the primary causes of consultation in the endemic areas (Boulesteix and Carme, 1986), loiasis is not regarded as a very serious disease. However, individuals harbouring high microfilaraemias may, exceptionally, develop serious spontaneous neurological or renal complications (Cauchie *et al*. 1965; Zuidema, 1971). More significantly, it is well known that high microfilarial (mf) loads are associated with a risk of developing neurological serious adverse events (SAEs) after treatment with the filaricidal drugs diethylcarbamazine (DEC) and ivermectin (Fain, 1978; Carme *et al*. 1991; Gardon *et al*. 1997*a*; Boussinesq *et al*. 1998). Thus, following ivermectin treatment, it has been demonstrated that individuals presenting with high mf loads (>8000 mf/ml), and those with very high mf loads (>30 000 mf/ml) had, respectively, an increased risk of developing severe adverse reactions without neurological involvement, and SAEs (Gardon *et al*. 1997*a*). In the context of the Community Directed Treatment with Ivermectin (CDTI) carried out in Africa, these SAEs are of crucial concern as they can lead to fatal outcomes and jeopardize the success of the African Programme for Onchocerciasis Control (APOC) (Twum-Danso, 2003).

In loiasis, many individuals do not present with microfilariae (mfs) in their peripheral blood, a phenomenon usually described as 'occult loiasis', yet they may prove to be infected because of previous history of subconjunctival worm passage. While genetic epidemiology (Garcia *et al*. 1999) and immunological studies (Winkler *et al*. 1999; Akué *et al*. 2002; Walker-Deemin *et al*. 2004) have brought useful insights into understanding the processes leading to some individuals developing *L. loa* microfilaraemia, the population dynamics of *L. loa* remains poorly documented. In a previous paper, we presented a detailed analysis of the structure of the microfilarial reservoir of *L. loa* in an endemic

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population through the study of host age- and sex-specific parasitological profiles in terms of prevalence and intensity of microfilaraemia (Pion *et al.* 2004). Our results indicate that the prevalence of microfilaraemia increases with age, is higher for males than females and, more unexpectedly, that, for a given level of endemicity, the mean intensity among microfilaraemic individuals remains nearly unchanged with host age.

The prevalence and intensity of an infection are but two characteristics of the distribution of parasites among hosts. In addition, parasite distributions are typically overdispersed. The degree of parasite overdispersion is a key parameter of the stability and dynamics of a host-parasite system (May and Anderson, 1978; Dobson and Hudson, 1992) and, according to some authors, it is constant and characteristic for a given host-parasite system (Bliss and Fisher, 1953; Pichon *et al.* 1975, 1980; Quinnell *et al.* 1995). However, it would be expected that the distribution of parasites per host is a dynamic property within a given host-parasite system depending, for instance, on the intensity of transmission, the age-structure of the host population, and the operation of age-dependent and/or density-dependent processes (Adler and Kretzschmar, 1992; Pugliese *et al.* 1998). Since, to our knowledge, mf aggregation has never been characterized for *L. loa*, we focus, in the present paper, on the distribution of the *L. loa* mf loads in the human population.

Besides the population dynamics aspects, characterizing the distribution of *L. loa* mfs among humans may be particularly useful for assessing the proportion of the host population at risk of post-treatment SAEs. In particular, the negative binomial distribution (NBD) provides a simple relationship between the prevalence and the mean intensity of infection which depends on the magnitude and functional form of the overdispersion parameter (Anderson, 1982). This relationship has been used to investigate the distribution of helminths parasites in humans (Anderson and May, 1985; Guyatt *et al.* 1990; Basáñez and Boussinesq, 1999), wildlife hosts (Shaw and Dobson, 1995; Shaw *et al.* 1998), and vectors (Cheke *et al.* 1982; Renz, 1987; Basáñez *et al.* 1995). If the overdispersion parameter can be determined for *L. loa*, it would be possible, in principle, to estimate the mean mf load in a community given its prevalence. This approach has been used successfully for *Onchocerca volvulus* in humans (Basáñez *et al.* 2002) and vectors (Basáñez *et al.* 1998).

Since a predictive spatial model for prevalence of *L. loa* microfilaraemia from environmental data obtained by remote sensing has been developed and validated (Thomson *et al.* 2004), prevalence estimates can easily be obtained for the whole distribution area of the parasite. If the NBD model were also validated, merging the results obtained by the Thomson *et al.* model with a well-defined relationship between community prevalence of microfilaraemia and prevalence of heavy infections, would provide a useful tool to aid SAEs surveillance in CDTI campaigns.

In the present study, we explore the patterns of *L. loa* mf aggregation in endemic populations, and develop and test a model to predict the prevalence of heavy *L. loa* mf loads in a community given its mf prevalence.

PATIENTS AND METHODS

Study area and parasitological surveys

The study areas and the methods used for selecting and examining subjects have been previously described (Gardon *et al.* 1997*a*; Boussinesq *et al.* 2001; Pion *et al.* 2004). Briefly, the data analysed in the present paper were collected as part of a trial conducted in 1995–1996 in the Lékié Division (Central Province, Cameroon) to evaluate the incidence of *L. loa* related post-ivermectin SAEs and to identify risk factors associated with the latter. During this trial, 4183 subjects aged $\geqslant$15 years were examined in 36 communities. This age group was chosen because, at the time of this trial, all the SAEs reported so far had occurred in individuals $\geqslant$15 years.

From each consenting individual, a blood sample was collected by finger-prick, between 10.00 and 16.00 h, in a non-heparinized capillary tube, and calibrated thick blood films were immediately prepared, using 50 μl of blood. Each Giemsa-stained smear was then examined under a low-power microscope and all the *L. loa* mfs present on the slide were identified and counted. All the persons examined had been questioned as to whether they had received any antifilarial treatment previously, and the data from those few who had been treated during the last 5 years were discarded from analysis.

Statistical analysis

Method to assess overdispersion. Various methods to assess the degree of parasite contagion or aggregation have been advocated in the literature, among which the variance to mean ratio (VMR) investigates discrepancy from the Poisson or random distribution (VMR = 1), and the index of discrepancy measures departures from the uniform distribution (all hosts harbour the same number of parasites) (Poulin, 1993; Poulin and Morand, 2000). We chose to assess aggregation through the parameter k of the NBD fitted to observed mf distributions in population strata as defined in the following section. However, during preliminary analyses, the NBD model, when fitted to the complete observed distributions of mf densities (including zero densities), did not provide satisfactory fits, whereas the zero-truncated NBD model provided adequate fits. Thus, assuming that the zero count class may not be reliable because only

$\sim$60% of the infected population would be genetically predisposed to present with microfilaraemia (Garcia *et al*. 1999), and that some individuals may be false-negatives (due to the lack of sensitivity of the blood film method when microfilaraemia is low), we chose the zero-truncated NBD (tNBD) model (Pichon *et al*. 1980; Grenfell *et al*. 1990).

Estimates of k (and corresponding variance) were obtained using the maximum likelihood method (MLM) proposed by Sampford (1955) and confidence intervals were obtained by bootstrapping (1000 simulations for each stratum). The fits to tNBD and calculations of confidence intervals were performed using Stata 9.0. Goodness of fit was tested using χ^2 tests with the number of degrees of freedom equal to the number of frequency classes – 3 (Elliott, 1977).

Patterns of microfilarial aggregation with host age and sex by level of endemicity. Investigation of parasite overdispersion with age and transmission intensity has been used to obtain insights into the possible operation of age- or parasite density-related processes regulating population dynamics (Anderson and Gordon, 1982; Pacala and Dobson, 1988; Fulford *et al*. 1992; Woolhouse *et al*. 1994; Das *et al*. 1995; Filipe *et al*. 2005). We classified the villages according to 3 endemicity levels based on the prevalence of microfilaraemia in the population aged $\geqslant$15 years, as a proxy for transmission intensity. These levels were: low endemicity (<25% mf prevalence), moderate endemicity (25–34·9%) and high endemicity ($\geqslant$35%). In each of these categories, the populations were subsequently sorted by sex and age according to the following age classes: 15–19, 20–29, 30–39, 40–49, 50–59 and $\geqslant$60 years. The total population was thus divided in 36 different strata (3 prevalence classes × 2 sexes × 6 age classes). We estimated k for each separate stratum. We then tested whether k varied by group using a linear regression of k on age-sex-endemicity group; such a method has been used to investigate aggregation patterns of *Schistosoma haematobium* in human populations (Woolhouse *et al*. 1994).

Predicting prevalence of heavy infection given mf prevalence. We aimed at developing a model to predict the prevalence of heavy *L. loa* mf loads in a community given the prevalence of microfilaraemia in those aged $\geqslant$15 years in such a community. To this end, we considered the village as the epidemiological unit, so this part of the analysis was conducted at community level.

Let X_i denote the random variable equal to the mf count in an individual aged $\geqslant$15 years old and living in community i; x_i the actual value of X_i; π_i the overall prevalence of microfilaraemia in those aged $\geqslant$15 years in community i (i.e. $\pi_i = \text{Prob}(X_j > 0)$), and T the microfilaraemia threshold above which an individual is considered to have heavy infection. Then, following the results obtained in the first part of the analysis, we assume that, in a given village (i), the frequency distribution of mf counts in those microfilaraemic follows a truncated NBD with parameter M_i, the mean mf intensity, and k_i, the overdispersion index, i.e.

$X_i \sim \text{tNBD}(M_i, k_i)$. Thus, the proportion of people in community i presenting with more than T mf/ml is:

$$P_i(X_i > T) = [1 - \sum_{x_i=1}^{T} p_i(x_i)]\ \pi_i \qquad \text{Equation (1)}$$

Explicitly, the tNBD of mf counts is given by:

$$p_i(x) = \frac{\Gamma(x+k_i)}{\Gamma(k_i)x!} \frac{q_i^x(1-q_i)^{k_i}}{[1-(1-q_i)^{k_i}]}$$

where $q_i = \frac{M_i}{M_i + k_i}$ and Γ is the gamma function.

Our aim was to render expression (1) exclusively in terms of π_i. For this purpose, we modelled, on the one hand, M_j as a function of π_i, and, on the other hand, k_i as a function of π_i.

(*i*) *Relationship between M_i and π_i*
As the simplest possible approximation and motivated by inspection of the data, we assumed a linear relationship, across communities, between the mean microfilarial load and the microfilarial prevalence in those aged $\geqslant$15 years,

$$M_i = A_i \pi_i \qquad \text{Equation (2)}$$

(*ii*) *Relationship between k_i and M_i*
Parameter k_i was estimated for each separate village i using the maximum likelihood method described in the first part of the analysis. Then, parameter k_i was included in equation (1) using 2 alternative functional forms: a constant value $k_c = 0{\cdot}3$ (the mean k value obtained either in the 'per age and sex stratum' analysis or in the 'per village' analysis of the current data, see Results section), and a log-linear relationship with mean mf intensity, $k_i = \alpha + \beta \log(M_i)$. This model has been chosen because $M_i > 0$. In this latter model, we also used the relationship between M_i and π_i derived from equation (2). The empirical relationships between M_i and π_i, and between k_i and M_i were fitted to the current study data using the least squares method, analogous to the linear regression approach used above.

We applied expression (1) to 2 different threshold values: $T = 8000$ mf/ml and 30 000 mf/ ml. The first value corresponds to the threshold above which there is a significant increase in the relative risk of occurrence of functional impairment following ivermectin treatment, and the second threshold, to the value above which the risk of occurrence of serious neurological reactions is increased (Gardon *et al*. 1997*a*). Deviation of these predictions from the observed data was assessed using χ^2 tests.

Table 1. Number of individuals presenting with *Loa loa* microfilaraemia among the total number of subjects examined and arithmetic mean of the positive microfilarial loads (in parentheses) for each sex-, age- and endemicity (measured as the mf prevalence) category in the 36 villages of the Lékié division surveyed in 1995–1996

(A total of 8, 15 and 13 villages were respectively grouped in the <25%, 25–35% and ⩽35% endemicity categories.)

Endemicity (mf prevalence)	Males			Females		
	<25%	25–35%	⩽35%	<25%	25–35%	⩽35%
15–19 years	27/210 (228·33)	29/166 (538·31)	21/102 (518·81)	22/137 (328·18)	28/160 (467·29)	28/115 (492·96)
20–29 years	28/118 (309·32)	38/128 (634·95)	31/109 (681·74)	15/92 (450·80)	36/174 (518·67)	42/133 (628·50)
30–39 years	22/62 (730·64)	41/98 (413·20)	36/88 (957·11)	12/80 (440·67)	29/134 (394·79)	34/97 (431·85)
40–49 years	16/47 (585·88)	39/72 (376·18)	30/56 (913·93)	13/81 (363·92)	44/183 (480·43)	45/142 (366·42)
50–59 years	17/61 (197·71)	48/87 (469·33)	58/116 (559·07)	15/70 (367·53)	46/179 (454·70)	64/149 (583·44)
⩾60 years	14/40 (104·29)	74/144 (563·03)	61/103 (441·11)	17/78 (485·29)	80/201 (345·66)	76/171 (551·21)
Total	124/538 (363·67)	269/695 (503·88)	237/574 (646·57)	94/538 (401·74)	263/1031 (429·33)	289/807 (521·18)

RESULTS

Patterns of microfilarial aggregation amongst the different strata of the host population

Table 1 shows the number of microfilaraemic individuals out of the total number of subjects examined and the arithmetic mean of the positive mf loads in the 36 different strata of the population. The 36 values of k estimated by MLM ranged between 0·07 and 0·66 (Fig. 1). The average, common k, k_c, calculated as the mean of the age-, sex- and endemicity-specific k values, weighted by the reciprocal of each value's estimated variance, was 0·30. According to χ^2 tests, the tNBD provided satisfactory fits to the observed data in all but 1 stratum (males aged 15–19 years in high endemicity villages, $k=0{\cdot}29$). The use of k_c to represent k_i for each village is supported by the linear regression model, in which parameter k was independent of sex and age of the host, or level of endemicity in the village, either as main effect or included in 2-way interactions (Table 2). It should be noted that the test is approximate, and that a non-significant regression coefficient for any of the factors considered only indicates such a factor is likely to be unrelated to k.

Predicting the prevalence of high microfilarial loads from the prevalence of microfilaraemia

Relationships between mean intensity. M_i and microfilarial prevalence π_i at community level. As a first approximation, a linear relationship between the prevalence and mean intensity of *L. loa* microfilaraemia for every village did not provide a very satisfactory fit (coefficient of determination, $R^2=0{\cdot}27$). To obtain a more robust relationship to be used in the subsequent modelling, we aggregated the villages according to their π_i values, in the 6 following groups [12–22], [22–27], [27–32], [32–35], [35–38] and ⩾38%, with 6 villages in each group. The linear

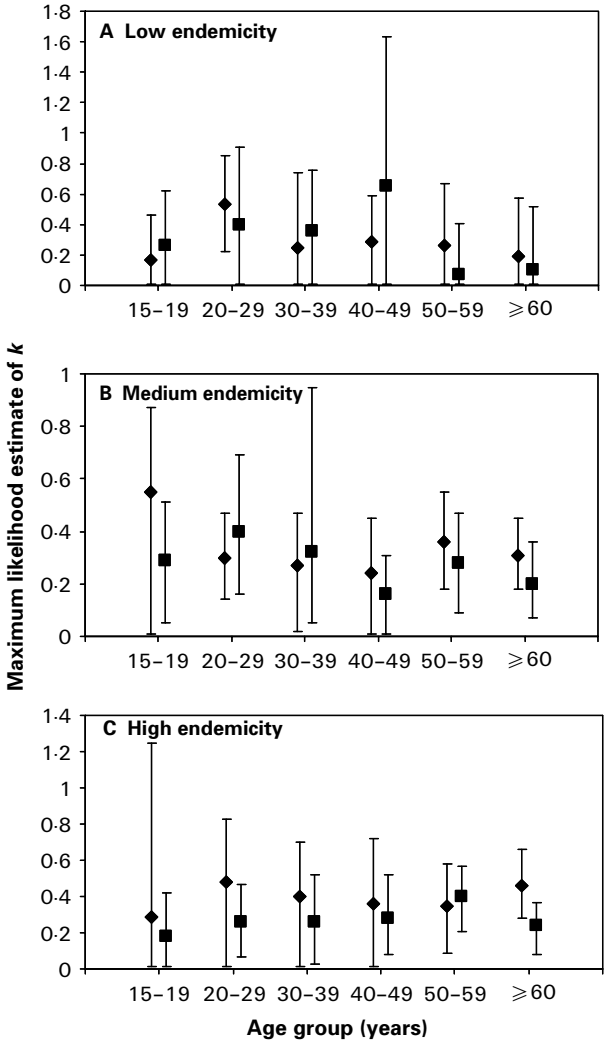

Fig. 1. The degree of microfilarial overdispersion in *Loa loa*, assessed by the k parameter of zero-truncated negative binomial distribution, according to host age and sex (◆: males; ■: females) for different endemicity levels: (A) prevalence of microfilaraemia in the population aged ⩾15 years, $\pi_i<25\%$, (B) $25\leqslant(\pi_i)<35\%$ and (C) $(\pi_i)\geqslant35\%$.

Table 2. Estimates of the linear regression coefficients of the NBD overdispersion parameter k on individual-level variables (host age and sex) and village-level variable (endemicity level) for the distribution of *Loa loa* microfilarial loads in the Lékié Division, Central Province, Cameroon

(Model is: $k=\beta_0+\beta_1$ (Sex) $+\beta_2$ (Age group) $+\beta_3$ (Endemicity) $+\beta_4$ (Sex) $\times$ (Age group) $+\beta_5$ (Sex) $\times$ (Endemicity) $+\beta_6$ (Age group) $\times$ (Endemicity).)

Variable	Coefficient	95% CI	*P-value*
Sex	−0·111	−0·411–0·190	0·457
Age group	−0·064	−0·131–0·003	0·059
Endemicity	−0·125	−0·273–0·022	0·092
Sex × Age group	0·004	−0·043–0·051	0·860
Sex × Endemicity	0·073	−0·026–0·171	0·143
Age group × Endemicity	0·024	−0·005–0·053	0·102
Intercept	0·609	0·273–0·944	0·001

relationship obtained using this grouping ($M_i=316{\cdot}4\pi_i$) was very similar to that obtained when considering separate communities ($M_i=314\pi_i$) but considerably improved the fit ($R^2=0{\cdot}78$); while the improvement was largely due to a reduction in the number of data points and therefore in the variability of the data, the similarity of the fits suggests that the regression estimate is essentially independent of data grouping (Fig. 2).

Relationship between aggregation parameter k_i and mean intensity M_i. Values of k_i assessed for each separate village ranged between 0·09 and 0·81 (Fig. 3). There was no trend in the variation of k with the mean mf load; the slope coefficient of the log-linear regression ($k_i=\alpha_i+\beta_i \log(M_i)$, with $\alpha=-0{\cdot}31$ and $\beta=0{\cdot}07$) was not significantly different from zero ($t=0{\cdot}16$; $P<0{\cdot}317$), supporting the hypothesis that the degree of mf aggregation is not affected by the level of microfilarial intensity in the community.

Predicting the proportion of heavy microfilarial loads. The predicted prevalence of heavy infections (eqn 1), for $T=8000$ and $T=30\,000$ mf/ml, respectively, were in good agreement with the observed distribution of heavy mf loads (Fig. 4A and B). The model assuming a constant value for the degree of mf aggregation ($k_c=0{\cdot}3$) gave satisfactory fits, with non-significant departures between data and models for both the 8000 ($\chi^2=39{\cdot}36$, D.F. $=36$, $P<0{\cdot}66$) and 30 000 ($\chi^2=46{\cdot}98$, D.F. $=36$, $P<0{\cdot}10$) mf/ml thresholds. The model assuming a log-linear function, $k_i=0{\cdot}07 \log(M_i)-0{\cdot}31$ provided similar goodness-of-fit values ($\chi^2=39{\cdot}01$, $P<0{\cdot}34$, D.F. $=36$ for $T=8000$; and $\chi^2=48{\cdot}11$, $P<0{\cdot}09$, D.F. $=36$ for $T=30\,000$).

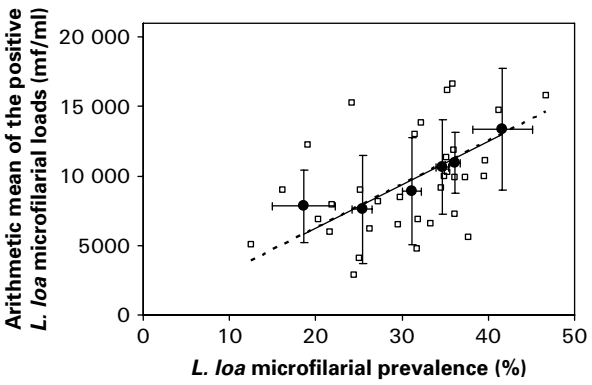

Fig. 2. Relationship between the intensity of microfilarial (mf) loads in the population aged ⩾15 years in the community and the *Loa loa* microfilarial prevalence in the same age-group. The squares represent the different villages and the bins (black dots) represent the same villages grouped according to their microfilarial prevalence (6 classes, see text). Vertical error bars indicate standard errors of the mean within prevalence bins; horizontal error bars are the standard errors for the mf prevalence using the normal approximation to the binomial distribution. The dotted line is the regression line with individual village ($M_i=314\pi_i$; $R^2=0{\cdot}27$); the solid line is the regression line for the grouped villages ($M_i=316{\cdot}4\pi_i$; $R^2=0{\cdot}78$).

DISCUSSION

Population dynamics insights

At the time of the surveys, mass ivermectin distribution had not been initiated, and to our knowledge, no significant environmental or ecological changes had taken place in the area. Therefore, our assumption is that the *L. loa* population was at endemic equilibrium with its human and vector hosts. Our work thus contributes to the characterization of the distribution of *L. loa* among humans and to highlight its epidemiological implications in natural, non-intervened settings.

One of the main motivations for using the NBD model is that once the degree of overdispersion has been characterized, the theoretical frequency distribution is entirely defined by the arithmetic mean. As the latter is related to the prevalence, it is possible to estimate, from prevalence values, the proportion of hosts harbouring mf densities above an arbitrary threshold (Guyatt and Bundy, 1991). However, the standard NBD model did not fit well the distribution of the *L. loa* mf loads probably because in southern Cameroon only ∼60% of the population is genetically predisposed to present with microfilaraemia (Garcia *et al.* 1999). Instead, the zero-truncated negative binomial distribution, used to describe *Wuchereria bancrofti* (Pichon *et al.* 1980; Das *et al.* 1990; Grenfell *et al.* 1990) and *Brugia malayi* (Srividya *et al.* 1991) mf densities in some foci of lymphatic filariasis, was found to fit particularly

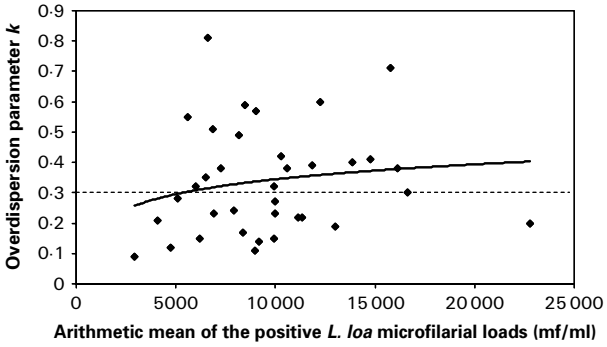

Fig. 3. Relationship between the degree of microfilarial aggregation among the positive individuals aged ⩾15 years, assessed by the parameter k of zero-truncated negative binomial distributions, and the intensity of microfilarial loads in the community, expressed as the arithmetic mean of the positive microfilarial counts. Solid line: logarithmic function $k_j = 0{\cdot}07 \log(M_j) - 0{\cdot}31$; dashed line: constant function $k_j = 0{\cdot}3$.

well the distributions of *L. loa* mf loads among the positives.

Some of the models proposed to understand the mechanisms generating overdispersion in host-parasite systems, predict a decrease in the level of aggregation (increase of k) with host age in the presence of down regulatory density dependence. Such a trend has been taken to indicate operation of parasite-induced mortality of individuals harbouring high parasite densities (Anderson and Gordon, 1982; Pacala *et al*. 1988) or the development of acquired immunity with age and exposure to infection (Woolhouse *et al*. 1991; Fulford *et al*. 1992). We observed a very stable degree of aggregation in the different strata of the population. The fact that we did not observe any trend in the overdispersion pattern with host age does not, however, necessarily imply the absence of processes regulating abundance of *L. loa* mfs within an individual. Different complex processes, acting simultaneously, may lead to this apparently simple pattern (Duerr *et al*. 2003). In the case of loiasis, since spontaneous lethal complications are quite uncommon, it seems reasonable to discard a process of parasite-induced mortality of heavily infected hosts in the absence of antifilarial treatment.

Comparison with previous studies on aggregation in filarial infections

Comparing values of k between different species for which the mean infection intensities are different has some limitations (Taylor *et al*. 1979; Gregory and Woolhouse, 1993). Nonetheless, the range of over-dispersion values observed for *L. loa* was very similar to those observed for other filarial species such as *W. bancrofti*. For this species the value of k has been estimated, using the tNBD model and from independent population samples, as ∼0·3 (Pichon *et al*. 1980; Grenfell *et al*. 1990). For *O. volvulus*, an age-structured model using a zero-inflated NBD yielded k around 0·5 for hosts aged ⩾15 years (Filipe *et al*. 2005).

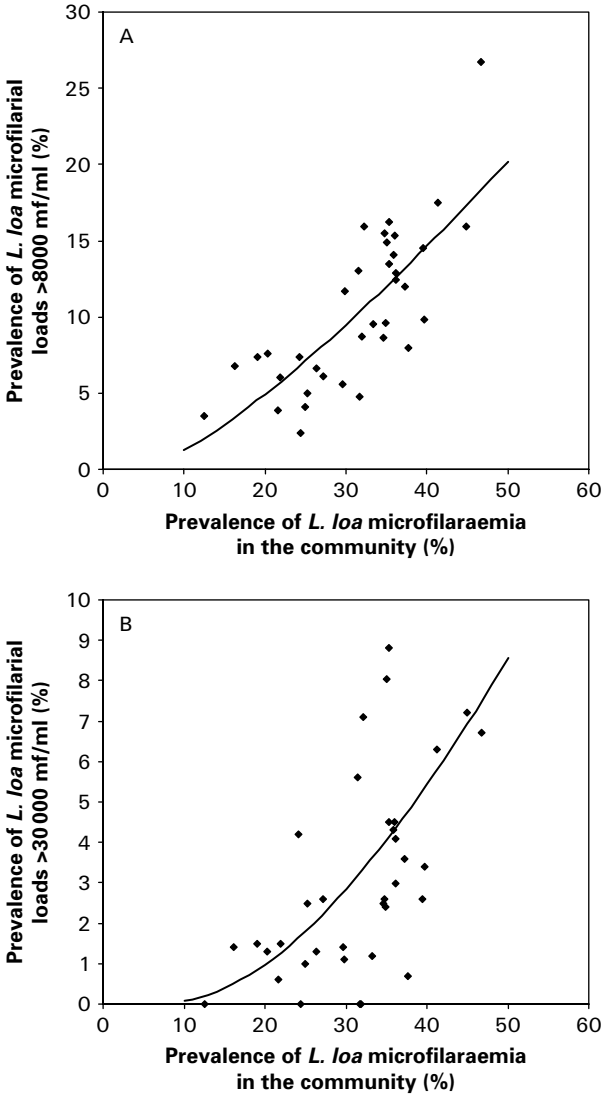

Fig. 4. Relationship between the proportion (in %) of individuals with microfilarial loads above (A) 8000 mf/ml and (B) 30 000 mf/ml and the prevalence of *Loa loa* microfilaraemia among those aged ⩾15 years in the community. Diamonds: observed values; solid line, predicted relationship with $M_i = 314\pi_i$ and $k_c = 0{\cdot}3$.

Predictions of the proportion of the population at risk of SAEs

We developed a semi-empirical model, aiming at predicting the proportion of the population at risk of post-filaricidal treatment SAEs given the prevalence of microfilaraemia among those aged ⩾15 years in the community. We developed 2 alternative models, incorporating different assumptions about the relationship $k_i(M_i)$ between overdispersion and mean mf load among the positives in a community: one

with k_i varying with M_i and another with a common k_i, k_c. The predictions were not very sensitive to the assumption about k_i, so adopting a constant value for k ($k=0{\cdot}3$) would be the most parsimonious and practical approach.

However, if $k_c \sim 0{\cdot}3$ corresponds to endemic equilibrium, the patterns of aggregation are likely to change in communities where large-scale filaricidal treatment is organized. This might constitute a limitation of our present modelling approach, which stands on the analysis of undisturbed populations. Yet, the SAEs are most likely to occur among individuals receiving their first treatment with ivermectin, the post-treatment mf loads usually remaining below the risk threshold until the next treatment round (Gardon *et al*. 1997*b*). A model including a $k_i(M_i)$ function would, in principle, be better suited for tracking changes with mean mf densities following treatments.

The maps provided by the model developed by Thomson *et al*. (2004) are now used to support APOC's activities, when setting up the CDTI in ivermectin-naïve areas. Such maps give a particularly useful indication of locations where the SAEs surveillance procedures have to be strengthened. As a useful addition to the information generated by the spatial maps, our model would provide information on the proportion of the population at risk of SAEs. The Thomson *et al*. model gives an indication of location and overall prevalence but not of likely numbers to be affected. If we were able to validate our predictive models at the continental scale across regions where *L. loa* is endemic, either using constant or dynamical overdispersion parameters, we should be able to link the maps of predicted prevalences with maps of population at risk of post-treatment SAEs generated by distributional assumptions. This would constitute a breakthrough regarding the '*Loa* challenge' APOC is now facing.

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