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Past exposure and the dynamics of lymphatic filariasis infection in young children

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SUMMARY

This study utilizes parallel, longitudinal entomological and parasitological data collected during a 5-year vector control programme in Pondicherry, South India, to quantify *Wuchereria bancrofti* transmission from the vector to the human population. A simple mathematical model, derived from the standard catalytic model, is used to examine the hypothesis that current infection prevalence in young children is a dynamical function of their cumulative past exposure to infective bites. Maximum likelihood fits of the model to the observed data indicate a constant child infection rate with age, above a threshold representing the pre-patent period, or equivalently, the cumulative biting intensity required to produce patent infections. Extrapolation of the model allows the crude estimation of the equilibrium microfilaria age-prevalence curve due to control. The results suggest that vector control alone may have little impact on the overall age-prevalence of infection even when sustained for long periods. These observations are discussed in terms of the likely impact of density dependent mechanisms, such as acquired immunity, on model predictions.

INTRODUCTION

A central task in the modelling of lymphatic filariasis transmission is to quantify the dynamics of parasite transmission from human to vector population (and *vice versa*) and the clinical consequences of various levels of infection. A number of studies have considered various aspects of these problems [1–9], though there are very few which examine the overall transmission cycle [10, 11]. The great value of the latter approach is in generating estimates of the critical density of biting mosquitoes below which transmission will cease [10–12].

These previous studies have concentrated on estimating overall transmission rates in communities. In fact, a large body of recent work has emphasized the importance of heterogeneities in infection rate, in particular, with age [epidemiological, 13–20; immunological, 21–26]. Specifically, in the present context, much the best measure of changes in transmission is the rate of acquisition of infection in younger children. This is because the infection rate in that group is less likely to be confounded by immunity than in other groups.

A second conclusion to emerge from the recent literature is that infection and disease in lymphatic filariasis are dynamic processes [13–18, 20]. Ideally, we should therefore estimate the overall transmission rate between vectors and humans based on longitudinal studies recording the impact on human infection rates of perturbation of vector density, such as vector control programmes. In fact, though vector control

programmes have contributed significantly to our knowledge of filariasis epidemiology [5, 7, 9, 27–29] they have rarely been used specifically to quantify the relationship between entomological and parasitological variables.

In this paper, we address the problem of how changes through time in the density of biting mosquitoes affect the dynamics of filariasis infection in young children, measured by the microfilarial (mf) age-prevalence. The analysis is based on a detailed longitudinal data set on bancroftian filariasis collected by the Vector Control Research Centre of the Indian Council of Medical Research in Pondicherry, South India, in the period 1981–9. The availability of parallel entomological and parasitological data for this period allows us to quantify the effects of an integrated Vector Management (IVM) programme, which reduced the density of the main vector (*Culex quinquefasciatus*) by as much as 90% during the period 1981–6 (7, 9).

The main aim of the paper is to use the monitored reduction in transmission caused by vector control to model the relationship between infection rate and the dynamics of infection in children. In the rest of the paper, we introduce the data set and basic epidemiological and entomological patterns and describe simple models for age incidence of infection in young children as a function of vector biting rate. Finally, we extrapolate these results to calculate equilibrium age incidence of infection due to control.

DATA SET AND ESTIMATION OF VECTOR BITING RATE

Entomology

We require an index of infection intensity by mosquitoes before and during the period of vector control in Pondicherry. A measure of intensity of transmission by the vector population (RI), which successfully describes the relationship between the infectivity status of the vector population to that of the infection prevalence in the human population has recently been suggested by Vanamail and colleagues [29]. RI is similar to the risk of infection index by de Meillon and colleagues [2], except that it takes into account the parous rate of biting mosquitoes (i.e. the proportion that have taken a blood meal and are therefore potentially infective). Specifically, RI is calculated as follows [30]:

$$\mathrm{RI} = A \times B \times C$$

where, A = parous mosquitoes collected per man-hour, B = average L3 larvae/parous mosquito, C = proportion of L3 larvae penetrating the host from one bite.

Full details of the estimate are given by Vanamail and colleagues (29). The advantage of RI over standard measures of risk of infection (2) is that it excludes nulliparous mosquitoes, which are not involved in filariasis transmission to humans.

Mosquito resting collections from 17 sites were used to calculate the intensity of transmission RI during the years 1981–5. It should be noted that for the years 1986–9, only six stations were monitored and from 1989 onwards only two stations were monitored. The entomological data from these stations were taken as representative for the entire vector population of the control area.

Parasitology

Human parasitological data for this study were collected from the control area by mass blood surveys in 1981 (pre-control), and 1 and 4 years post-control; in 1986 and 1989, respectively (for full details see [7, 9]). In brief, approximately 10% of the population in each year had their blood examined for microfilariae using the standard 20 mm^3 smear technique. An age-stratified random sampling protocol designed to give a minimum coverage of at least 5% of the population in any one age class was followed. Approximately 25000 individuals were examined per survey in each of the 3 years studied.

OBSERVED ENTOMOLOGICAL AND EPIDEMIOLOGICAL PATTERNS

These are described in detail by Das and colleagues [9]. Figure 1 summarizes the entomological situation during and after the control programme in Pondicherry, using a plot of annual intensity of transmission measured using RI in the period 1981–9. Vector control effectively reduced the infective biting density of *Culex quinquefasciatus* to 20% of the (1981) pre-control level by 1984, although there is a variable recovery of vector density following the cessation of the programme.

The equivalent parasitological picture in the human population is shown in Figure 2 in terms of age-prevalence profiles for 1981, 1986 and 1989. As described elsewhere [7, 9], although vector control significantly reduced the prevalence of infection in

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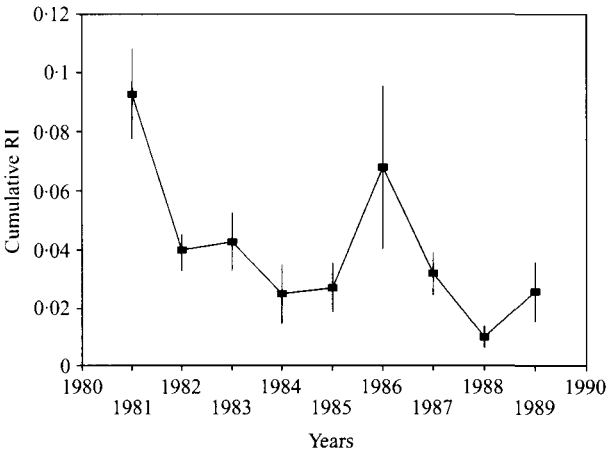

Fig. 1. Intensity of transmission in the IVM area in terms of the vector population (RI) during the years 1981–9. Vertical bars denote the estimated standard errors of the means.

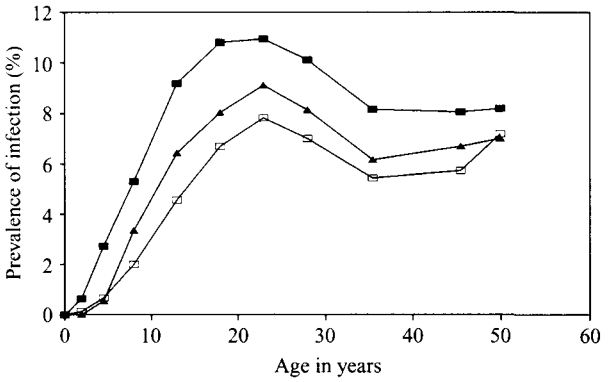

Fig. 2. Age specific prevalence of microfilaraemia during 1981 (■), 1986 (▲) and 1989 (□) in the IVM area of Pondicherry.

children aged ⩽ 10 years ($P < 0{\cdot}001$), the longevity of adult parasites lessened the difference between pre-control (1981) and post-control (1986, 1989) infection rates in adults. Although mean age-intensity also showed a reduction after control, these differences were not significant in all age classes, since the underlying distributions are highly variable [14, 15]. The following analysis therefore concentrates on mf age-prevalence.

The age-prevalence curves for children ⩽ 10 years of age are shown in more detail in Figure 3. The impact of reduction in infection due to control after 1981 not only reduces the infection rate in young children but also increases the observed pre-patent period (i.e. the age when prevalence rises from zero), from 3 years in 1981 to 4–5 years in 1986 and 1989. This effect could arise from the lower infection rate, probably reflecting reduced parasite mating probabilities at low transmission intensities. In order to

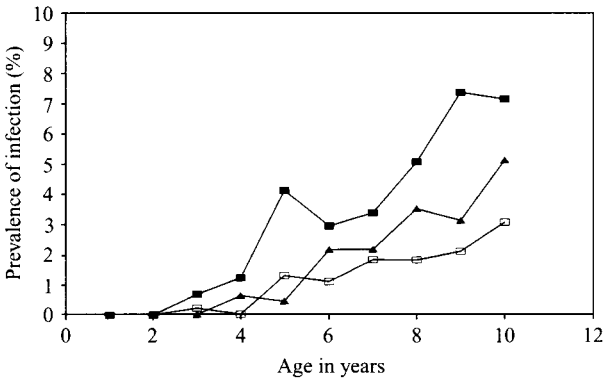

Fig. 3. Comparison of age specific mf-prevalence in young children (up to 10 years) during 1981 (■), 1986 (▲) and 1989 (□).

quantify the dynamics of control, we need to relate entomological and parasitological data via a simple model, which is described in the following section.

THEORETICAL ANALYSES

The model

We begin by considering the age prevalence curves (Fig. 2), concentrating on young children (of age ⩽ 10 years) to minimize the complicating effects of previous infections and potential acquisition of immunity. Since the average duration of carriage of mf is around 5 years [13], we can assume that few individuals in this age range lose infection after gaining it. We can therefore adapt standard catalytic age prevalence models [1, 13]. Using the simple rate equation,

$$\mathrm{d}I(a)/\mathrm{d}a = \begin{pmatrix} 0 & a \leqslant a_0 \\ \lambda(a)(1-I(a)) & a > a_0 \end{pmatrix} \tag{1}$$

for the rate of increase of the proportion infected (I), as a function of age, a. The parameter $\lambda(a)$ is the *per capita* infection rate, or force of infection and a_0 is the prepatent period. Given that $I(0) = 0$, equation (1) leads to a standard solution:

$$I(a) = \begin{pmatrix} 0 & a \leqslant a_0 \\ 1-\exp\left(-\int_{a_0}^{a} \lambda(s)\,\mathrm{d}s\right) & a > a_0 \end{pmatrix}. \tag{2}$$

Assuming that the probability of acquiring new infection in a short interval is proportional to the number of infective larvae penetrating, we can replace the time scale in equation (1) by cumulative bites. In order to convert the age prevalence into prevalence as a function of previous exposure to infection, we use RI, the index of vector biting density defined above.

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Previous exposure (X) to infection of an individual age 'a' in year 't' is then:

$$X(a,t) = \sum_{i=1}^{a-1} \mathrm{RI}(t-i) \qquad (3)$$

(for example, 3 year olds in 1985 have experienced infection in 1983 and 1984) leading to the following modification of equation (2):

$$I(X) = \begin{cases} 0 & X \leqslant X_0 \\ 1-\exp\left(-\int_{x_0}^{x} \lambda'(s)\,\mathrm{d}s\right) & X > X_0 \end{cases} \qquad (4)$$

(approximating the discrete variable X as a continuous variable) $\lambda'(X)$ (units X^{-1}) is now the force of infection as a function of cumulative past exposure rather than age, and X_0 measures the prepatent period in terms of previous infective biting exposure. Fitting this model to the age-prevalence data, from groups with different exposure histories (particularly 1981 *vs.* 1986 and 1989) allows us to examine whether the dynamics of current infection in young children can be modelled in terms of past exposure. These models make a number of assumptions (particularly with respect to the distribution of biting rate and acquired immunity by age), which we return to in the discussion.

Estimation

Given the observed age prevalence data, ($r(a)$ positives out of $n(a)$ at age $a = 1 \ldots n$) and cumulative exposure X, we can estimate the force of infection (as a function of exposure X) by binomial maximum likelihood. Maximum likelihood parameter estimates for each force of infection model are calculated by minimizing the scaled deviance [31]; differences in deviance between models are used to assess the significance of adding the linear and quadratic terms to the model. The residual deviance is asymptotically χ^2, providing an approximate goodness of fit test. The threshold cumulative exposure, X_0, is estimated as the value of X corresponding to the first non-zero observed prevalence in young children. This is a relatively crude estimate of the threshold, but the following results are not sensitive to it.

RESULTS

Figure 4*a* shows the observed mf age-prevalence curves for 1–10 year olds in the years 1981, 1986 and 1989, plotted against cumulative intensity of transmission (X). The change of scale from age to intensity brings the prevalences from the 3 years into similar curves – an analysis of covariance with binomial errors illustrates that the prevalence profiles of the three surveys were not significantly different ($P = 0{\cdot}22$) over their common range of X. Figure 4*b* shows a maximum likelihood fit to these data of the catalytic model defined by equation (4). Three models, respectively assuming a constant force of infection, a linearly increasing force of infection ($\lambda'(X) = \alpha_0 + \alpha_1 X$), and a quadratic ($\lambda'(X) = \alpha_0 + \alpha_1 X + \alpha_2 X^2$) were used to fit the data. The fits are summarized in Table 1, and indicate that a model assuming a constant force of infection provides the best fit to the data.

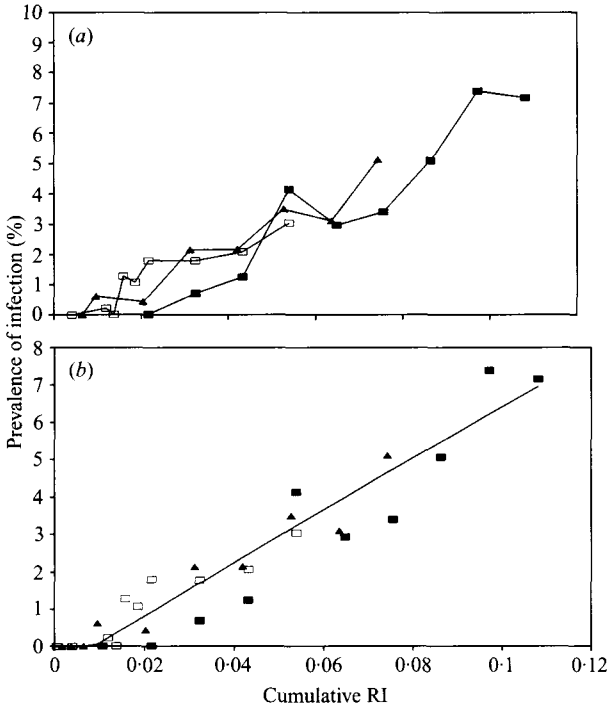

Fig. 4. (*a*) Comparison of age specific mf-prevalence of children during 1981 (■), 1986 (▲) and 1989 (□) scaled in relation to cumulative RI. (*b*) Fit of the constant force of infection model linking age specific mf-prevalence to cumulative RI in children. Symbols denote the observed age specific mf prevalences in children up to 10 years in 1981 (■), 1986 (▲) and 1989 (□), while the solid curve represents the fit of the catalytic model defined by equation (4) in the text.

These results support the hypothesis outlined above, that the differences in mf age-prevalence in young children observed before and after a control programme can be explained simply in terms of differences in their past exposure to infection. The three observed age-prevalence curves all now have similar intercepts on the X axis; the estimated value of

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Table 1. *Parameter estimates and deviances arising from fits of the constant, linear and quadratic force of infection models described in the text*

Model	α_0	α_1	α_2	Deviance	D.F.	P
Constant	0·7145			19·44	28	0·88
Linear	0·7566	−1·4060		19·31	27	0·86
Quadratic	1·4326	−33·1298	−12·2708	16·05	26	0·94

The changes in deviances resulting from fits of both the linear and quadratic models when compared with the constant model are not significant ($P = 0·72$ and $P = 0·18$, respectively).

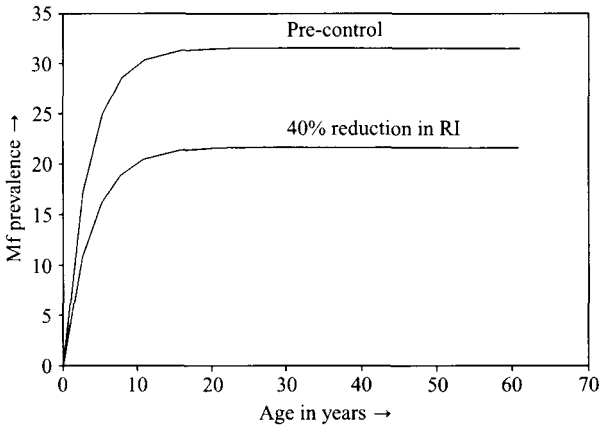

Fig. 5. Predicted change in the age-prevalence of microfilaraemia as a result of reducing the biting vector density to 40% of the pre-control level. The standard (reversible) catalytic age prevalence model (Hairston and Jachowski, 1968; Vanamail et al. 1989) was used to model the equilibrium age-prevalence mf curve following vector control assuming that a reduction in RI simply decreases the force of infection λ by the same factor. Both λ and μ, the instantaneous rate of loss of infection, are taken to be constants and independent of age respectively.

the lower threshold, $X_0 = 0·009$ (= no. of penetrating L3 larvae per hour).

This suggests that observed parasitological patterns in young human hosts can be simply explained using independently observed entomological patterns. This has several implications for the performance of vector control strategies. In particular, the fact that the rise in mf prevalence in children depends only on the average level of transmission scaled by age, allows us to model the eventual equilibrium effects of constant levels of vector control as follows. If, for example, the average annual biting rate (measured by RI) is lowered by 40% (as occurred in the IVM area over the 8-year period, 1982–9 (Fig. 1)), then this simply scales down the value of accumulated previous exposure (X in equations (3) and (4)) by the same factor. Figure 5 illustrates the application of this simple model, and portrays the change expected at equilibrium to the pre-control age-prevalence curve as a result of a 40% reduction in RI.

The results show that, although sustained vector control may reduce the mf prevalence, unless this achieves the exposure threshold (X_0 in equation (4)), infection will continue to persist at relatively high levels. The model predicts a reduction of only 28% in peak prevalence with the steady 40% reduction in biting rates achieved by the IVM programme. This corresponds closely to the 29% reduction in the peak prevalences of mf actually observed in the IVM area between the pre-control (1981) and 1989 surveys (Fig. 2).

DISCUSSION

The above results provide an explicit link between the dynamics of the vector population and the age-prevalence of infection in bancroftian filariasis in young children. Expressing changes in age prevalence during a vector control programme in terms of cumulative exposure provides a framework for relating infection status in the human population to the intensity of transmission in the vector population. In terms of overall transmission models, a more useful relationship could be provided by a model linking mf *intensity* in the human population with intensity of transmission from the vector population, RI. However, intensity data are very variable [8, 14–15], and preliminary work indicates that it may be necessary to take into account the spatial distribution of vector and human infection intensities in order to model their relationship properly.

In terms of prevalence, the shift from age to cumulative exposure produces a significant improvement in agreement between age-prevalence curves

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before and after the control programme. The resulting catalytic model indicates a constant force of infection with age in young children, above a threshold representing the pre-patent period. These results do not therefore indicate any significant increase in the force of infection with age (over the range 0–10 years), which might have been predicted from physical factors, such as increase in surface area. There is also no strong evidence in these young hosts for acquired immunity or other forms of age-dependent resistance in limiting prevalence. By contrast, in older individuals in Pondicherry, (after *c.* age 20 years), infection rates decline, possibly due to acquired immunity [13].

The cumulative exposure threshold X_0 is linked to the overall transmission threshold for persistence of infection [10]. However, the transmission threshold is also a function of the impact of parasitism in humans on vector infection rates (including phenomena such as facilitation and limitation [12], and the longevity of the adult worms [11]. Analyses of these processes are also necessary before the results presented here can be incorporated into a dynamic model of the impact of control. However, even at this stage, the model for mf prevalence as a function of previous exposure allows us to produce a crude estimate of the projected equilibrium age-prevalence curve following long periods of vector control at a constant level, as shown and described in Figure 5.

By analogy with many other infectious diseases [32], we might also expect control to increase the mean age at first infection, as indeed occurred in the area where vector control was implemented (Fig. 3). Given the immunological complexities of chronic disease [25–26, 33], this might have unpredictable effects on disease prevalence [18, 20]. In fact, Figure 5 implies only a slight decrease in the initial rate of increase of mf prevalence as a result of reduced infection pressure. Note that this analysis is very crude and, in particular, does not allow for density dependent effects. For example, if as seems likely, there is a significant level of acquired immunity in human hosts [13, 15, 21, 23–24], reduced infection rates might well be expected to increase the prevalence in older individuals.

We are currently examining the role of such density dependent mechanisms on disease control, through an analysis of comparative and detailed field data on entomological, parasitological and clinical variables. The present work provides an initial framework for assessing the dynamical effects of these processes, and their incorporation into overall transmission models for filariasis infection and control.

In Pondicherry, appreciable reduction in vector density and transmission intensity achieved through the 5 year IVM strategy was able to reduce the mf prevalence by 29% and mf intensity only partially [7]. It may be possible to reduce the mf prevalence and intensity to ultra low levels in a short time by chemotherapeutic means using diethylcarbamazine (DEC). But, it is well known that culicines are capable of picking up mf and developing infective stage larvae after feeding even on ultra low level mf carriers [34]. Thus, neither vector control nor chemotherapy alone may achieve the goal of eradication of filariasis. However, 98% reduction in vector density achieved through vector control combined with mass chemotherapy with DEC have reduced mf prevalence in the target community by as high as 68% within 1 year [35]. Thus combined measures of vector control and chemotherapy may be ideal for the control of bancroftian filariasis transmitted by *Culex quinquefasciatus*.

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