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Herd immunity to filarial infection is a function of vector biting rate

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Despite the existence of an impressive body of work on human immune responses against filarial infections, the occurrence of a protective response to infection remains unclear. Here, we use a combined modelling and comparative data analysis framework to address this issue for human infections with the filarial parasite, *Wuchereria bancrofti*. By analogy with previous work, the analysis involves the comparison of observed field patterns of infection with epidemiological patterns predicted by a mathematical model of parasite immunity. Unlike most other human helminths, which are transmitted by ingestion or dermal penetration, exposure to infection with lymphatic filariasis can be measured explicitly in terms of vector mosquito biting rates, thereby also allowing, probably for the first time, examination of the suggested role of exposure in generating herd immunity to macroparasites. Observed field patterns in this study were derived from 19 different published studies, which gave parallel estimates of community exposure rates and the corresponding age–prevalence patterns of infection, while predictions of the epidemiological impact of herd immunity were obtained using a catalytic model framework. The results provide the first conclusive evidence to date that variations in the observed age–prevalence patterns of infection in filariasis can be effectively explained by the occurrence of an exposure-driven acquisition of herd immunity. We discuss this result in terms of implications for the new World Health Organization-led initiative for the global control of this parasitic disease.

Keywords: lymphatic filariasis; *Wuchereria bancrofti*; catalytic models; epidemiology; herd immunity; mosquitoes

1. INTRODUCTION

The problem of whether humans mount a protective immune response to lymphatic filariasis is important not only for basic understanding of the processes governing infection, but also because it is significant in the context of the new World Health Organization-led global initiative for controlling this parasitic infection of more than 120 million people, based on mass chemotherapy (Michael *et al.* 1996; Turner & Michael 1997). However, despite the existence of a large body of work, which demonstrates unequivocally that filariasis infection can elicit a wide variety of immune responses in humans, the evidence for the occurrence of a protective response to infection has so far remained equivocal (Ottesen 1992; Maizels *et al.* 1995).

By contrast, the epidemiological impact of acquired immunity to helminth infection has been successfully investigated using mathematical models of host–parasite infection dynamics in conjunction with analyses of comparative age–infection data from field studies (Anderson & May 1985; Woolhouse *et al.* 1991; Fulford *et al.* 1992; Woolhouse 1994). This work has shown that both simple and age-structured immigration–death models of macroparasite infection can provide testable predictions of the epidemiological effects of acquired immunity on infection intensity. Analysis of human hookworm (Anderson & May 1985) and *Schistosoma haematobium* infections (Woolhouse *et al.* 1991) has predicted that acquired immunity, engendered by accumulated past experience of infection and acting to moderate the rate of parasite establishment, will cause age–infection profiles to become more convex in areas of higher transmission, resulting in larger and earlier peaks of intensity: the so-called 'peak-shift' phenomenon (Woolhouse *et al.* 1991; Fulford *et al.* 1992). Reductions in transmission, due to mass chemotherapy for example, will therefore act to diminish the peak intensity. However, they may also delay the onset of immunity and move the peak of intensity into an older age class (Anderson & May 1985).

These studies assume that the observed age–infection profile is a reflection of the dynamic interaction between exposure and acquired herd immunity (Anderson & May 1985; Woolhouse *et al.* 1991). Yet the parasitic infections upon which these studies are based allow no direct estimates of exposure, which is estimated retrospectively from the levels of infection achieved, although attempts to examine the impact of water contact patterns on age patterns of infection have been made for schistosomiasis (Hagan 1992; Woolhouse 1994). Parallel estimates of community exposure rates and age–infection profiles are, however, readily available for the mosquito-borne lymphatic filariasis (Southgate 1992), and thus allow not only the examination of the role of herd immunity in

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observed age–infection patterns, but also the direct examination of the proposed relationship between exposure and the generation of this immunity for this parasite.

Here we report on an analysis of human infection with *W. bancrofti*, which we believe provides the first explicit demonstration of exposure-driven occurrence of herd immunity in filariasis. As with previous work (Woolhouse *et al.* 1991; Fulford *et al.* 1992), the basic framework of analysis entailed the comparison of observed field patterns with predictions of a mathematical model describing the expected epidemiological effects of acquired immunity. Unlike the previous studies, however, observed field patterns in the present study were elucidated from comparative analyses of data derived from independent surveys of bancroftian filariasis published in recent parasitological literature.

2. METHODS

(a) *The model*

In *W. bancrofti* infection, the primary measure of infection at the community level continues to be the age–prevalence relationship of microfilaraemia (Mf), which constitutes an indirect measure of the prevalence of adult worm infection (WHO 1992). Thus, the major approach to modelling the dynamics has been based on compartmental age–prevalence models (Hairston & Jachowski 1968; Vanamail *et al.* 1989; Bundy *et al.* 1991; Grenfell & Michael 1992), which describe the change in proportions of microfilaraemics (infecteds) and amicrofilaraemics (uninfecteds) through time in a cohort of individuals. With the basic model, an initially uninfected but susceptible proportion (X) gains infection at a per capita rate h' to become infected (proportion P) before losing the infection at a per capita rate τ ($1/\tau$ = lifespan of infection) to again become amicrofilaraemic. The effect of acquired immunity can be incorporated into this framework by simply allowing the proportion recovering from infection to be resistant to further infection (proportion R). This is embodied in the two-stage catalytic model (Muench 1959), which by letting X, P, and R stand for susceptibles, infecteds and immunes, respectively, and assuming a constant population size, predicts changes in infection prevalence, P, of a cohort of individuals through age, a (equivalent to time), through the following set of linear differential equations:

$$dX/dt = \gamma R - h'X \tag{1}$$

$$dP/dt = h'X - \tau Y \tag{2}$$

$$dR/dt = \tau Y - \gamma R. \tag{3}$$

Here, h' is the per capita rate at which individuals gain infection, or is the force of infection, and it can be linked to infective vector biting rates for the community by writing

$$h' = May^{*}b, \tag{4}$$

where May^{*} represents the annual infective biting rate (AIBR), and b, the coefficient of transmission (Dye 1986; Southgate 1992). Given a constant b, the model assumes a proportional relationship between vector biting intensity and h', and thus explicitly allows the direct examination of the effect of variations in exposure intensity in generating immunity to infection. The parameter τ in the model is the per capita rate at which infected individuals lose infection and become resistant, whereas γ represents the corresponding per capita rate at which these resistant individuals become susceptible to reinfection. For the special case of $\gamma = 0$ (corresponding to permanent resistance), equations (1–3) can be solved to give P as a function of a:

$$P(a) = \frac{h'}{h' - \tau}(\exp(-\tau a) - \exp(-h'a)), \tag{5}$$

provided $h' \not\equiv \tau$.

(b) *Data sources*

The present analysis required parallel field observations on filariasis infection prevalence within age groups, $P(a)$, and the corresponding community vector biting intensities. An extensive survey of the recent parasitological literature located a total of 19 studies on bancroftian filariasis, with large enough sample sizes, meeting these data requirements. These surveys encompass the major endemic regions and vector mosquito species, as well as a broad range of local community and vector infection rates (see details in table 1).

(c) *Data and statistical analyses*

Blood sampling volumes used for estimating infection prevalence were found to differ between those studies with culicine transmission (20 µl), and those in which infection was transmitted by other mosquito species, notably anophelines (100 µl). To enable comparability of the observed infection prevalences, the data from studies using the smaller 20 µl blood sampling volume (see table 1) were transformed to reflect sampling by the larger 100 µl blood volumes used by the rest of the studies, using the methods given by Hairston & de Meillon (1968) and Grenfell *et al.* (1990). Briefly, this uses the observed relationship between mean infection intensity and prevalence in conjunction with the parameter k of the negative binomial distribution, to estimate changes brought about in the prevalence as a result of blood sampling volume variations using the following equation:

$$p(0) = [1 + (\mu V)/(Vk)]^{-Vk}, \tag{6}$$

where $p(0)$ is the zero probability of the negative binomial distribution, μ is the mean Mf count, V is the blood sampling volume (as a multiple of the difference between comparison volumes (Grenfell *et al.* 1990)) and k is the shape parameter of the distribution. Here, we use the simplest assumption and available evidence for mean intensity (Dreyer *et al.* 1992); that increasing the blood sampling volume from 20 µl to 100 µl increases both the mean intensity and the parameter k fivefold. The result is to increase the peak prevalences estimated from those studies sampled originally using 20 µl finger-prick blood volumes. Note that a disproportionate effect on k did not lead to a significant change in the depicted relationship; for example, a much lower twofold increase in k demonstrated a decrease of only 3–4% and 2%, respectively, for the higher and lower peak prevalences shown in the figure for the culicine transmission sites.

Peak prevalences, $P(a^{*})$, from each study were estimated where possible by fitting quadratic logistic regression curves to the age–prevalence data (Fulford *et al.* 1992). Where the curvilinear regression appeared to be insignificant, which corresponded only to those cases where observed peaks tended to occur in the oldest age classes (>50 years), $P(a^{*})$ values were estimated using the respective observed prevalence maxima (sample size in each case >50 individuals) (Woolhouse *et al.* 1991).

The one-tailed, non-parametric, Spearman's rank correlation test was used to assess the observed relationships derived from the

Table 1. *Details of published studies used in the comparative data analyses*

country/study site	sample size	blood volume (μl)	overall Mf positive (%)	mosquito vector species	annual infective biting rate (AIBR)[a]	reference
India						
Haldipada	4664	20	10.8	*Culex quinquefasciatus*	241.3	Rath *et al.* (1984)
Gopalpur	4659	20	9.4	*Cx quinquefasciatus*	177.4	Rath *et al.* (1984)
Calcutta	582	20	15.0	*Cx quinquefasciatus*	1739.1	Gubler & Bhattacharya (1974)
East Godavari	11 210	20	15.1	*Cx quinquefasciatus*	709.0	Rao *et al.* (1980) Rao *et al.* (1981)
Vetavalam	7976	20	11.7	*Cx quinquefasciatus*	1003.8	Ramaiah *et al.* (1989)
Pondicherry	1549	20	17.8	*Cx quinquefasciatus*	1106.3	Rajagopalan *et al.* (1977)
Indonesia						
Jakarta	922	20	6.3	*Cx quinquefasciatus*	646.7	Self *et al.* (1978)
Philippines						
Paraiso	328	1 ml	22.6	*Aedes poicillius*	80.3	Grove *et al.* (1978) Valeza & Grove (1979)
Liberia						
Bolilo	103	20	21.3	*Anopheles gambiae*, *An. funestus*	236.1	Zielke & Chlebowski (1979) Kuhlow & Zielke (1978)
Gbandu	90	20	20.0	*An. gambiae*	546.7	Zielke & Chlebowski (1979) Kuhlow & Zielke (1978)
Tanzania						
Tawalani	367	100	31.1	*An. gambiae* *An. funestus*	189.0	McMahon *et al.* (1981)
Moa	546	100	24.2	*Cx quinquefasciatus* *An. gambiae*	187.0	McMahon *et al.* (1981)
Machui	642	100	18.5	*Cx quinquefasciatus* *An. gambiae*	41.0	McMahon *et al.* (1981)
Kwale	449	100	15.6	*An. gambiae*	24.0	McMahon *et al.* (1981)
Zanzibar	655	100	49.5	*Cx quinquefasciatus*	612.0	Maxwell *et al.* (1990)
Kenya						
Mambrui	787	100	21.7	*Cx quinquefasciatus*	46.0	Wijers & Kinyanjui (1977) Wijers & Kiilu (1977)
Jaribuni	1007	100	22.0	*An. gambiae* *An. funestus*	155.0	Wijers & Kinyanjui (1977) Wijers & Kiilu (1977)
Comoros						
Sada	1426	20	35.3	*Cx quinquefasciatus* *An. gambiae*	466.5	Brunhes (1975)
Trinidad						
Northern Coast	565	25, 100, 1 ml	15.4	*Cx quinquefasciatus*	179.5	Nathan (1981) Nathan *et al.* (1982)

[a] Calculated according to the following formula (Walsh *et al.* 1978): AIBR = ABR × (% of caught mosquitoes with L3 larvae), where ABR, the annual biting rate, is given by the following expression: ABR = (no. of mosquitoes caught per day × days per year)/(days mosquitoes caught).

data between peak prevalence of infection and age of peak prevalence, and between the community infective vector biting rates and the above infection parameters.

3. RESULTS

The equilibrium age–prevalence curves generated by the model for varying rates of infection, h', are shown in figure 1. They illustrate that the effect of incorporating a resistant class has three main consequences as the infection rate increases. First, an increase in the convexity of the age–prevalence curve; second, an increase in the peak prevalence of infection, $P(a^*)$; and third, a decrease in the age of peak prevalence, a^*. Assuming a proportional relationship between overall community infective vector biting intensity (AIBR) and h', these patterns will clearly

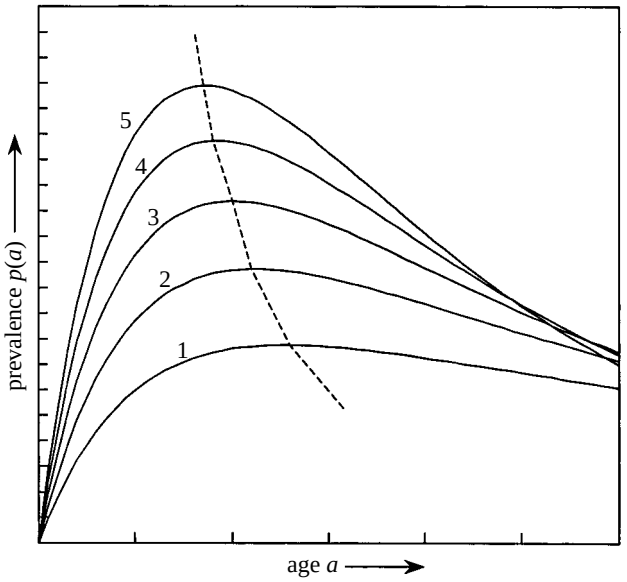

Figure 1. Predicted age-related changes in infection prevalence generated by the compartmental age–prevalence model incorporating the development of a resistant class following infection. The solid lines in the figure represent equilibrium age–prevalence curves predicted by equation (5) with parameter values $\tau = 0.1$ (equivalent to a duration of ten years for infection (Hairston & Jachowski 1968; Vanamail *et al.* 1989)) throughout and $h' = 0.01$, 0.015, 0.02, 0.025 and 0.03 for curves labelled 1–5, respectively. The broken curve shows the shift in the predicted peak prevalence of infection, $P(a^*)$, with the predicted age of peak prevalence, a^*. This relationship is produced entirely by variation in h'.

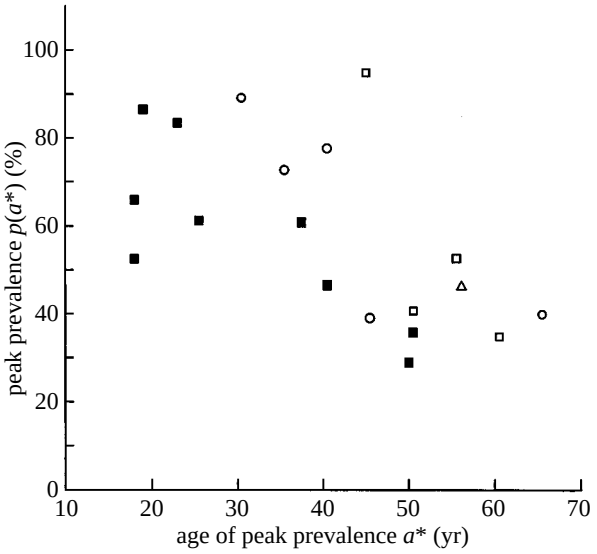

Figure 2. Observed relationship between peak prevalence of infection, $P(a^*)$, and age of peak prevalence, a^*, for human *W. bancrofti* infections. Symbols differentiate the data by the type of mosquito species implicated in transmission at each study site as follows: filled squares, culicine transmission; open circles, anopheline transmission; open squares, mixed culicine and anopheline transmission; open triangles, *Aedes* transmission. The depicted relationship between $P(a^*)$ and a^* is in the direction predicted by the model incorporating acquired immunity (figure 1). The relationships are statistically significant for both areas with culicine transmission and transmission by other vector species: Spearman's rank correlation, respectively (one-tailed test for a significant negative association in each case): $r_s = -0.648$, $n = 19$, $p < 0.005$ (overall); $r_s = -0.704$, $n = 9$, $p < 0.025$ (transmission by *Culex* species); and $r_s = -0.733$, $n = 10$, $p < 0.025$ (transmission by other vector species).

also reflect the impact of increasing infective mosquito biting rates if acquired immunity plays a role in regulating infection. Predictions two and three imply a negative association between $P(a^*)$ and a^* for communities with varying h' or mosquito biting intensity.

The model predictions are compared with the observed field data in figure 2. The results show that there is a statistically significant negative correlation between $P(a^*)$ and a^* across the 19 studies for all mosquito species. Note that a qualitatively similar pattern was obtained for the untransformed data from the culicine transmission sites (not shown): the data transformation performed here using equation (6) merely allowed the comparison of these data with the largely untransformed data obtained from the other vector transmission sites. The plots in figure 3 demonstrate that this pattern correlates with variations in mosquito biting intensity, although there appear to be between-vector species differences in the observed patterns. Culicines appear less efficient than anophelines in transmitting filariasis infection, as has been suggested on biological grounds (Southgate 1992).

4. DISCUSSION

The present analysis has shown conclusively, probably for the first time, that observed field infection patterns for bancroftian filariasis are consistent with the occurrence and operation of an effective herd immunity in endemic human communities. We further show that the effect of this immunity is greater and occurs earlier in areas with a higher rate of mosquito biting. To our knowledge, these findings provide the first explicit demonstration to date that human acquired immunity to macroparasites is correlated with infection exposure (Anderson & May 1985; Crombie & Anderson 1985).

Recently, it has been observed that epidemiological patterns predicted by models of parasite immunity could arise from the action of non-density-dependent factors (Fulford *et al.* 1992). However, as pointed out by Woolhouse *et al.* (1991), these factors are likely to influence patterns only if they vary systematically between studies, which appears most unlikely in the present analysis of independently collected data sets.

The predictions of the effect of acquired immunity in the present study are based on the simplest assumption, that individuals who lose infection become refractory to further infection. Recent work (Bundy *et al.* 1991; Michael *et al.* 1994) suggests that immunity may not necessarily be long-term. Current understanding precludes the reliable modelling of this effect, but note that the qualitative predictions of such a model would be similar to those of the present model especially if the rate of loss of immunity is not too large (Aron & May 1982; Woolhouse 1994). Similarly, further biological information is also required to model reliably the effects of other factors that may play a role in filariasis infection, such as the impact of superinfections (Hairston & Jachowski 1968), potential differential effects of immunity on Mf output (Grenfell *et al.* 1990), and the possible impact of immunity on parasite survival.

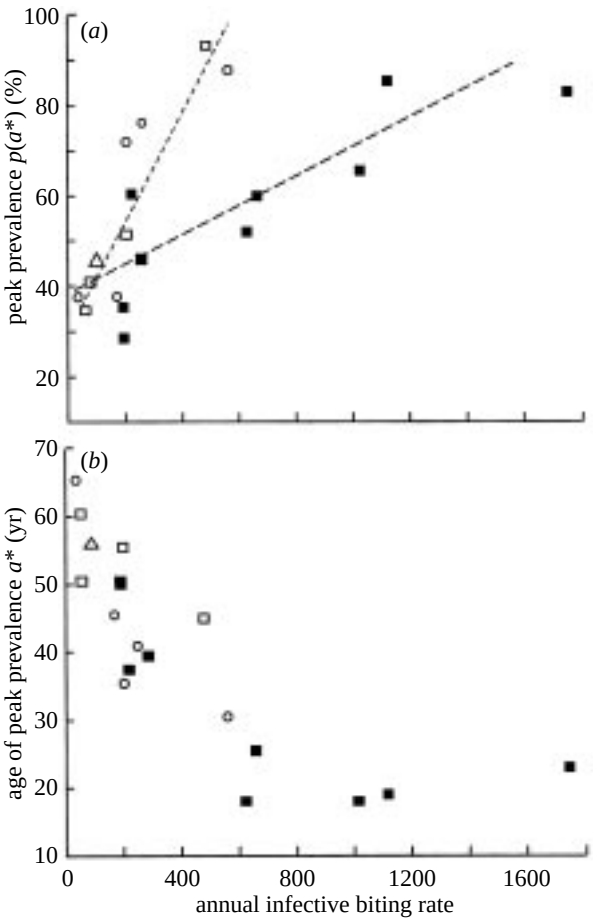

Figure 3. Relationships between community infective vector biting rates (AIBR) and (*a*) peak infection prevalence, $P(a^*)$, and (*b*) age of peak prevalence, a^*. Symbols are as detailed in the legend to figure 2. The graphs show that both relationships lie in the directions expected for a positive effect of mosquito biting rate in generating acquired immunity to filarial infection, namely, in (*a*) a positive correlation between biting intensity and peak prevalence (statistically significant for both culicine transmission and transmission by other vector species: Spearman's rank correlation, $r_s = 0.917$, $n = 9$, $p < 0.01$ and $r_s = 0.892$, $n = 10$, $p < 0.005$, respectively (both one-tailed tests for a significant positive association)) and in (*b*) a corresponding negative association between the age of peak prevalence and biting intensity (Spearman's rank correlation, $r_s = -0.763$, $n = 9$, $p < 0.025$ and $r_s = -0.891$, $n = 10$, $p < 0.005$, respectively, for culicine transmission and transmission by other vectors (one-tailed test for a significant negative correlation in each case)). The depicted patterns support the occurrence of a proportional (= constant coefficient of transmission, b; see equation (4)) relationship between vector biting rate and the force of infection, h', and indicate that the generation of acquired resistance to filarial infection is correlated to variations in exposure intensity. The parameter b (equation (4)) or the coefficient of transmission is a function encompassing all the factors, from climatological to specific host–vector–parasite responses, relevant to the transfer of infective larvae during a blood meal (Dye 1986; Southgate 1992). The relationships depicted in (*a*) indicate that this function may be significantly lower for culicines, supporting suggestions (Southgate 1992) that they are less efficient than other species, notably anophelines, in transmitting filariasis infection. The broken curves in (*a*) represent simple scatterplot smoothers fitted by local regression in order to portray more clearly the observed between-vector species variation.

These results have major implications for the growing global momentum to control filariasis based on mass chemotherapy (Ottesen & Ramachandran 1995; Turner & Michael 1997). The results following population dynamic analysis of the use of mass chemotherapy for other helminthiases of humans suggest that, if control is implemented at a level less than that required to eradicate the parasite, it has the potential to significantly reduce the level of herd immunity in a population and raise the infection burden in the older age classes above the levels pertaining before control, especially in areas of previously high transmission (Anderson & May 1985). This is not an argument against control, but is a strong indication that it may be prudent to carefully define control components (e.g. target age groups and coverage), perhaps with the aid of model predictions, if filariasis control is to be successfully implemented on a large scale.

This study indicates that gaining a more detailed understanding of the interrelationships between exposure, immune responses and the epidemiological effects of control is likely to be crucial in this context.

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