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Acquired Immunity on a Schistosomiasis Transmission Model—Fitting The Data

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A semi-stochastic model is proposed to analyse the effects of acquired immunity on the transmission of schistosomiasis in the human host. The basic model's assumptions are as follows. The human host is assumed to build up an immune response after elapsing a fixed period of time L from the first infection. This acquired immunity is assumed to be partially effective and it is never lost. The parasite infection event is a Poisson process with multiple occurrences, i.e., in each event one or more cercaria are assumed to invade the host. The model treats deterministically the age distribution of human host. The model shows a good retrieving capacity of real data from two endemic areas of schistosomiasis: Touros, Brazil (*Schistosoma mansoni*) and Misungwi, Tanzania (*Schistosoma haematobium*).

1. Introduction

Schistosomiasis has probably the most complex biological cycle of all human infections, involving at least two host species (human and snail), two free-living transmission stages of the parasite (cercariae and miracidiae) and distinct environments.

Humans are the principal, definitive host for the five schistosome species. Adult worms live in the venous system of intestine (*Schistosoma mansoni*, *Schistosoma japonicum*, *Schistomosa mekongi* and *Schistomosa intercalatum*) or the urinary bladder (*Schistosoma haematobium*) (Mahmoud, 1990). As a result of the sexual reproduction of the parasite in different human organs, the characteristically shaped eggs pass through the vesical or intestinal wall in order to find their way to outside via the host excreta. In fresh water the eggs hatch and release ciliated, motile miracidia that soon penetrate into the snail (the intermediate host). Inside the snail the miracidia multiply asexually, and in 4–6 weeks hundreds of thousands of motile, forked-tail cercaria emerge. These are the forms infective to the human host. For each species of schistosome and for each geographic region there is a specific snail as the intermediate host. Therefore, it is believed that the geographic distribution of schistosomiasis depends on the distribution of the specific snails. On encountering human skin, the cercaria actively penetrate it, causing a local reaction. In the process of invasion, the cercaria lose their tails and change into schistosomula, which then migrate to the lungs and liver; in about 6 weeks they mature to adult worms, mate and descend, via the venous system, to their final habitat. The lifespan of adult worms is still a controversy, ranging from 5–10 years to more than 30 years (Harris *et al.*, 1984; Vermund *et al.*, 1983).

For mathematical models to be of any use they must be sufficiently realistic and grounded in

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what is understood of the schistosome biology (Woolhouse *et al*., 1991). But, as the life cycle of schistosomes is extremely complex, it is very difficult to understand the quantitative contribution of different components of transmission to the level of infection in a human population. Therefore, we restrict our scope to the inclusion of biological detail, such as the role of acquired immunity on the disease transmission.

Acquired immunity among humans has important consequences for the epidemiology of schistosome infection (Anderson & May, 1985; Crombie & Anderson, 1985; Woolhouse, 1991; Woolhouse *et al*., 1991). The question of whether humans mount an immune response to schistosomiasis is of basic biological interest, and is important in the context of disease control (Fulford *et al*., 1993). There is accumulating evidence that the human host develops a protective immune response to schistosome infection (Clegg *et al*., 1970; Hagan, 1987). However, the immune response to this and other large parasites differs from that of viruses and bacteria, and appears to be acquired gradually, concomitant, and may afford only partial protection against further infections. In addition, acquired host responses can act to reduce rates of parasite establishment, fecundity and survival (Anderson & May, 1991).

The incorporation of acquired immunity in models dealing with schistosome transmission has been shown to have some important consequences (Fulford *et al*., 1993, 1995; Woolhouse *et al*., 1991). There is a lowering of the overall susceptibility of humans to infection which results in a decreasing of the age-related prevalence of schistomiasis. An interesting result, mentioned by Anderson & May (1991), is that acquired immunity does not affect the basic reproduction ratio, R_0. Models that incorporate neither the acquired resistance nor the age-dependent exposure to infection cannot reproduce typical age intensity or age prevalence patterns. For a recent review of schistosome infection modelling see (Woolhouse, 1991, 1992).

We present a simple model incorporating acquired immunity against schistosomiasis (Yang, 1990). This acquired immunity is partially protective: we consider that after the first infection there is a fixed length of time L after which the rate of infection is dramatically reduced (Butterworth, 1994; Gryseels, 1994; Terry, 1994). An infection can be initiated by one or more cercaria with a given probability.

We analyse the steady state model, its ability to fit real data, and the stability of the endemic disease level. The following, briefly described, main epidemiological data are the linkage between the biological cycle of schistosomiasis and the quantifying of the schistosomiasis transmission.

The most used epidemiological data to describe the schistosomiasis is the so-called age prevalence curve $P(a)$, that is, the proportion of individuals shedding viable eggs in feces (or urine) plotted against age. The essential shape of age prevalence data is a build up in the early years, peaking around 10–20 years of age, dropping thereafter, and stabilizing at some endemic level (Bradley & McCullough, 1973; Hairston, 1965). The second most used data is the age-dependent egg output curve, with aspects similar to the prevalence curve, but the peaking is slightly earlier (Costa *et al*. 1985). From these data, assuming that each worm produces a certain number of eggs, it can be derived the age-dependent, mean number of worms harbored by the human population, $m(a)$. The third kind of data is the age-dependent variance in the egg output among the human population. This kind of data is difficult to obtain but is very important to what follows. This variance divided by mean egg output is the well-known age-dependent dispersion curve $d(a)$, and typically assumes high values at lower ages, dropping quickly to a minimum value around 10–15 years, raising thereafter to stabilize at a certain level (Bradley & McCullough, 1973).

It is necessary to explain the latter two types of data. There are various ways in which mean egg output are reported in the literature (Banáñez *et al*., 1994): the simple arithmetic, the Williams' (logarithm transformed) mean (Williams, 1937) and the square root transformed mean. In the data by Bradley & McCullough (1973), to be used later, only the arithmetic mean and the Williams' mean are used. We shall call the Williams' mean as the log-transformed data. Since the egg output (and its dispersion) is acquired to measure worm burden (and its dispersion), the question arises as to which mean is better to evaluate the worm burden. Since the egg output varies greatly with random factors that cannot be included in a simple model we believe that the log-transformed data, by smoothing the data and normalizing it, is the more appropriate. A justification for this can be found in the classical paper by Williams (1973). Therefore, in this paper we will use only the log-transformed data.

This paper is organized as follows. Section 2 describes the model which is fitted to the data in Section 3 and discussed upon in Section 4. Here we conclude one of the main points of this paper, asking if acquired immunity plus multiple entrances of cercariae per infecting event can reproduce the over-dispersion of the worms as observed in the field.

2. The Model

In this paper we construct a semi-stochastic model which is fitted to the prevalence curve. Since the role of immunity in controlling reinfection is not entirely known (Fulford *et al*., 1993), we have to construct a model assuming its existence. The model proposed is based on the following assumptions:

(1) the human host builds up an immune response after elapsing a fixed period of time L from the first infection at age A. This immunity is partially effective, that is, protection against further infections is not fully avoided but controlled to some extent, and everlasting, that is, in the absence of the adult worm the immunity processes do not fade away;

(2) the infection event is assumed to be Poisson process of rate λ with multiple occurrences (Cox & Miller, 1992), i.e., in each infection one or more cercaria are assumed to invade the host per infective event. Considering that the probability of the inocula $b(i)$ is binomially distributed, and there is a maximum number of invading viable cercaria r, then we have $\Sigma_{i=1}^{r} b(i) = 1$ where $b(i)$ is the shorthand notation for the $Bi(i, 0.5)$. It also reflects the fact that not all invading cercaria per event maturate to adult form but only viable cercaria. Hence, the acquisition of worms by humans is treated stochastically regarded to the immune status:

(2i) the probability of a person with age between a and $a + da$ being infected by i worms, given that the individual is non-immune but has k worms is

$$Prob.[w(a + da, A) = k + i | w(a, A) = k] = \lambda_s b(i) da + o(da), \quad (1)$$

where λ_s stands for the Poisson process rate for non-immune individuals, $o(da)$ denotes a function tending to zero more rapidly than da, and $w(a, A)$ (Appendix A) is a random variable that describes the distribution of the number of adult worms with $A \leqslant a < A + L$;

(2ii) the probability of a person with age between a and $a + da$ being infected by i worms, while the individual has k worms is

$$Prob.[w(a + da, A) = k + i | w(a, A) = k] = \lambda_c b(i) da + o(da), \quad (2)$$

where λ_c stands for the Poisson process rate for immune individuals with age $a \geqslant A + L$, i.e., the individuals that had their first worm L time periods before.

The Poisson process rates that appear in eqns (1) and (2), hereafter called as the forces of infection, are assumed to be related by

$$\lambda_c = f(\zeta)\lambda_s \quad (3)$$

where ζ is the time interval counted from the first infection and $f(\zeta)$ represents the effect of immunity and for the purposes of this paper we consider

$$f(\zeta) = \begin{cases} 1; & \text{for } 0 \leqslant \zeta < L \\ f < 1; & \text{for } \zeta \geqslant L; \end{cases} \quad (4)$$

(3) adult worms inside the host die with a constant rate μ_w; and

(4) the human population is treated deterministically with a constant death rate μ_h.

The acquired immunity, a special kind of immunity assumed in the model, as can be noted from assumptions (2), (2i) and (2ii), is less stringent than the concomitant immunity consideration model (Nåsell, 1977; Yang, 1985). For this reason, we are modelling schistosomiasis transmission applicable to hyper-endemic areas. In schistosomiasis highly endemic areas, the acquired immunity assumption, which describes the immune response against infection by virus and bacteria very well, leads to a reasonable modelling. It is due to the two biological details: the high frequency of contact with the parasite (during the elapsing period, L, individuals are in a regular contact with parasite to build up the immunity) and the slow (some years) decaying of the antibodies (immune individuals who have discharged their harbored parasites attain their previous immunity condition quickly when in persistent contact with the parasites). Nevertheless, the picture is quite different when the above two features are not verified, i.e. in schistosomiasis lower endemic areas, where the acquired immunity leads to an unrealistic modelling.

The above assumptions can be set as a system of forward difference differential equations that describes the dynamics of the schistosomiasis transmission [see Yang *et al*. (1995) for mathematical details]. We call this a semi-stochastic model, because the distribution of worms among the human population is treated stochastically and the deterministic treatment is used for the demographic structure (age distribution) of human population.

From the model in the steady state, we can yield the following semi-stochastic functions. The first function relates the probability generating function (*pgf*) for the number of worms distributed among non-immune individuals with age between a and $a + da$ (Appendix A), which is given by

$$F_s(a,x)=\begin{cases} S_0\,e^{-\mu_h a}\left\{e^{\lambda_s\left[\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(x-1)^j\frac{1-e^{-j\mu_w a}}{j\mu_w}\right]}-e^{-\lambda_s a}\right\}; & \text{for } a<L \\ S_0\,e^{-\mu_h a}\left\{e^{-\lambda_s\left[(a-L)-\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(x-1)^j\frac{1-e^{-j\mu_w L}}{j\mu_w}\right]}-e^{-\lambda_s a}\right\}; & \text{for } a\geqslant L. \end{cases} \tag{5}$$

The other function relates the *pgf* for the number of worms distributed among the immune individuals with age between a and $a+da$, and is given by

$$F_c(a,x)=S_0\,e^{-\mu_h a}\int_0^{a-L}\left[1+\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(x-1)^j\,e^{-j\mu_w(a-A)}\right]\lambda_s$$

$$\times e^{-\lambda_s}\left\{A-\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(x-1)^j\frac{\frac{\lambda_c}{\lambda_s}+\left[\left(1-\frac{\lambda_c}{\lambda_s}\right)e^{j\mu_w L}-1\right]e^{-j\mu_w(a-A)}}{j\mu_w}\right\}dA; \quad \text{for } a\geqslant L. \tag{6}$$

In both eqns (5) and (6), S_0 is the newborn rate. These functions tell us that all the individuals that have had the first infection at age A will become immune after a period of time L.

Using eqns (5) and (6) for the distributions of worms among individuals with age between a and $a+da$, and eqn (27) from Appendix A, we derive the age prevalence curve $P(a)$, the age-dependent, mean worm burden per individual $m(a)$, and the age-dependent dispersion of worms per individual $d(a)$. These three expressions take into account only the random distribution of the worms among the human population with age between a and $a+da$.

The age prevalence curve is given by

$$P(a)=\begin{cases} 1-e^{\lambda_s\left[\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(-1)^j\frac{1-e^{-j\mu_w a}}{j\mu_w}\right]}; & \text{for } a<L \\ 1-e^{-\lambda_s\left[(a-L)-\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(-1)^j\frac{1-e^{-j\mu_w L}}{j\mu_w}\right]}-\int_0^{a-L}\left[1+\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(-1)^j\,e^{-j\mu_w(a-A)}\right] & \\ \times\,\lambda_s\,e^{-\lambda_s}\left\{A-\sum_{i=1}^{r} b(i)\sum_{j=1}^{i}\binom{i}{j}(-1)^j\frac{\frac{\lambda_c}{\lambda_s}+\left[\left(1-\frac{\lambda_c}{\lambda_s}\right)e^{j\mu_w L}-1\right]e^{-j\mu_w(a-A)}}{j\mu_w}\right\}dA; & \text{for } a\geqslant L. \end{cases} \tag{7}$$

The age-dependent, mean worm burden per individual is given by

$$m(a)=\begin{cases} \bar{\omega}\,\frac{\lambda_s}{\mu_w}\,(1-e^{-\mu_w a}); & \text{for } a<L \\ \bar{\omega}\,\frac{\lambda_s}{\mu_w}f_1(a,a-L); & \text{for } a\geqslant L, \end{cases} \tag{8}$$

where

$$\bar{\omega}=\sum_{i=1}^{r} ib(i) \tag{9}$$

is the mean number of parasite entering per contact with infested water, and the function $f_1(a,a-L)$ is

$$f_1(a,a-L)=\frac{\lambda_c}{\lambda_s}+\left(1-\frac{\lambda_c}{\lambda_s}\right)$$

$$\times\left[\frac{\lambda_s}{\lambda_s-\mu_w}\,e^{-\mu_w(a-L)}-\frac{\mu_w}{\lambda_s-\mu_w}\,e^{-\lambda_s(a-L)}\right]-e^{-\mu_w a}. \tag{10}$$

From eqn (8) we can calculate the average number of adult worms per person in a community (Appendix A), $\bar{m}$, as

$$\bar{m}=\bar{\omega}\left[\frac{\lambda_s}{\mu_w+\mu_h}-\left(1-\frac{\lambda_c}{\lambda_s}\right)\frac{\lambda_s^2\,e^{-\mu_h L}}{(\lambda_s+\mu_h)(\mu_w+\mu_h)}\right]. \tag{11}$$

The age-dependent dispersion of worms per individual is given by

$$d(a) = \begin{cases} 1 + \dfrac{\sigma_b}{2\bar{\omega}} \dfrac{1 - e^{2\mu_w a}}{1 - e^{-\mu_w a}}; \\ \\ 1 + \dfrac{f_2(L, a-L) + \left(1 - \dfrac{\lambda_c}{\lambda_s}\right) f_3(L, a-L)}{\bar{\omega} \dfrac{\lambda_s}{\mu_w} f_1(a, a-L)} - \bar{\omega} \dfrac{\lambda_s}{\mu_w} f_1(a, a-L); \quad \text{for } a < L, \end{cases} \tag{12}$$

where

$$\sigma_b = \sum_{i=1}^{r} i(i-1)b(i) \tag{13}$$

is the second moment of the parasite entering per contact with infested water and the functions $f_2(L, a-L)$ and $f_3(L, a-L)$ are

$$f_2(L, a-L) = \left[\left(\bar{\omega} \frac{\lambda_c}{\mu_w}\right)^2 + \frac{\sigma_b \lambda_c}{2\mu_w}\right]$$

$$- \left[2\left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \frac{\lambda_c}{\lambda_s} e^{-\mu_w L}\right] e^{-\mu_w (a-L)}$$

$$- \left\{\left[\left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \left(1 - \frac{\lambda_c}{\lambda_s} - e^{-\mu_w L}\right) + \frac{\sigma_b \lambda_s}{2\mu_w} e^{-\mu_w L}\right] e^{-\mu_w L}\right\}$$

$$\times\ e^{-2\mu_w (a-L)} \tag{14}$$

and

$$f_3(L, a-L) = \left[\left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \left(1 + \frac{\lambda_c}{\lambda_s} - e^{-\mu_w L}\right) + \frac{\sigma_b \lambda_s}{2\mu_w}\right] e^{-\lambda_s (a-L)} + 2\left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \frac{\lambda_c}{\lambda_s - \mu_w}$$

$$\times \left[\, e^{-\mu_w (a-L)} - e^{-\lambda_s (a-L)}\right] + \left[\left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \times \left(1 - \frac{\lambda_c}{\lambda_s} - e^{-\mu_w L}\right) + \frac{\sigma_b \lambda_s}{2\mu_w}\right] \frac{\lambda_c}{\lambda_s - 2\mu_w}$$

$$\times \left[e^{-2\mu_w (a-L)} - e^{-\lambda_s (a-L)}\right]. \tag{15}$$

The dispersion of worms per person in a community, from eqn (12), takes the form

$$\bar{d} = 1 - \bar{\omega}\left[\frac{\lambda_s}{\mu_w + \mu_h} - \left(1 - \frac{\lambda_c}{\lambda_s}\right) \times \frac{\lambda_s^2\, e^{-\mu_h L}}{(\lambda_s + \mu_h)(\mu_w + \mu_h)}\right] + \frac{f_4 + \left(1 - \dfrac{\lambda_c}{\lambda_s}\right) f_5(L) - \left[1 - \left(\dfrac{\lambda_c}{\lambda_s}\right)^2\right] \bar{\omega} \dfrac{\lambda_s}{\mu_w} e^{-\mu_h L}}{\bar{\omega}\left[\dfrac{\lambda_s}{\mu_w + \mu_h} - \left(1 - \dfrac{\lambda_c}{\lambda_s}\right) \dfrac{\lambda_s^2\, e^{-\mu_h L}}{(\lambda_s + \mu_h)\,(\mu_w + \mu_h)}\right]}, \tag{16}$$

where f_4 and $f_5(L)$ are

$$f_4 = \left[\left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \frac{\mu_w}{\mu_w + \mu_h} + \frac{\sigma_b \lambda_s}{2\mu_w}\right] \frac{2\mu_w}{2\mu_w + \mu_h} \tag{17}$$

and

$$f_5(L) = \left(\bar{\omega} \frac{\lambda_s}{\mu_w}\right)^2 \times \left[\frac{2\lambda_c}{\lambda_s + \mu_h} + \frac{3\mu_w + \mu_h}{2\mu_w + \mu_h} e^{-\mu_w L}}{\mu_w + \mu_h} + \frac{\left(1 + \dfrac{\lambda_c}{\lambda_s} - e^{-\mu_w L}\right) + \left(1 - \dfrac{\lambda_c}{\lambda_s} - e^{-\mu_w L}\right) \dfrac{\lambda_s}{2\mu_w + \mu_h}}{\lambda_s + \mu_h}\right] \times \mu_h\, e^{-\mu_h L} - \sigma_b \frac{\lambda_s^2}{(\lambda_s + \mu_h)(2\mu_w + \mu_h)} e^{-\mu_h L}. \tag{18}$$

Up to this point we developed the acquired immune model in the definitive host. In next section we deal with fitting the data.

3. Fitting the Data

In this section we are concerned with the fitting the age prevalence curve of schistosomiasis, with the aim of estimating the force of infection in the human population. We will use the maximum likelihood estimation method (Appendix B) to fit the age prevalence curve, eqn (7), to two distinct highly

TABLE 1(a)
The four parameters fitted from the prevalence data (Schistosoma mansoni) *of Touros, Brazil*

r	λ_s(years^{-1})	μ_w(years^{-1})	λ_c(years^{-1})	L(years)	l(10 df)
1	0.122 ± 0.010	0.092 ± 0.025	0.049 ± 0.013	8.00 ± 0.10	−1493.63
11	0.097 ± 0.012	0.205 ± 0.029	0.047 ± 0.009	3.905 ± 0.174	−1490.93
21	0.092 ± 0.011	0.241 ± 0.029	0.045 ± 0.008	3.513 ± 0.190	−1490.19
35	0.094 ± 0.000	0.286 ± 0.000	0.046 ± 0.000	3.307 ± 0.000	−1490.03

TABLE 1(b)
The four parameters fitted from the prevalence data (Schistosoma haematobium) *of region of Misungwi, Tanzania*

r	λ_s(years^{-1})	μ_w(years^{-1})	λ_c(years^{-1})	L(years)	l(34 df)
1	0.224 ± 0.010	0.087 ± 0.010	0.048 ± 0.007	10.645 ± 0.033	−2531.25
11	0.175 ± 0.007	0.178 ± 0.012	0.045 ± 0.004	9.247 ± 0.030	−2520.01
21	0.168 ± 0.007	0.212 ± 0.013	0.043 ± 0.004	8.770 ± 0.030	−2517.58
35	0.170 ± 0.000	0.250 ± 0.000	0.045 ± 0.000	8.516 ± 0.000	−2516.65

endemic areas, namely Touros district, Brazil (Matta *et al*., 1977) and the region of Misungwi, Tanzania (Bradley & McCullough, 1973). In the first region, schistosomiasis is due only to *S. mansoni*, while in the second, it is due only to *S. haematobium*. The logarithm of likelihood, disregarding a constant term,

$$\text{is } l = \sum_{i=1}^{n} \{np_i \ln[P(a_i)] + nn_i \ln[1 - P(a_i)]\}, \quad (19)$$

where n is the number of age intervals; np_i and nn_i are the number of individuals with and without parasite eggs, respectively, in each age interval a_i.

Tables 1(a) and (b) show the estimated model's parameters for each maximum number of invading cercaria per event r: the rates λ_s, μ_w and λ_c, the elapsing time L and the logarithm of likelihood of the fitting l for the prevalence data from Touros and Misungwi, respectively. The human mortality rate μ_h was obtained from actuarial data, and its value was found to be 0.015 years^{-1}. From Tables 1(a) and (b) we can observe that the values of the force of infection λ_c, when considering their standard deviation, are the same for the two areas considered, and for all values of r. Assuming that the parameters are normally distributed, the confidence intervals can be easily derived from the standard deviation given in the Tables 1(a) and (b).

Figs 1(a) and (b) show the age prevalence curves fitted to epidemiological data from Touros and Misungwi areas, respectively. It can be noted from the figures that the fittings to the prevalence curves do not vary greatly with the maximum number of invading cercaria, r. In other words, asymptotic curve is rapidly reached. This is expected because the prevalence curve is only a measure of the proportion of infected population, not a measure of worm burden. It is remarkable that this behavior of the prevalence curve is observed even when the prevalence is very low, reaching a peak of only 5% (Dias *et al*., 1989).

The sets of parameters of our model fitted from the prevalence data can now be used to calculate the average number of adult worms per person, eqn (11), and the dispersion of worms per person, eqn (16), for the two areas. These values are shown in Table 2. Even though the maximum number of invading cercaria per event, r, does not improve the maximum likelihood estimation of the prevalence curve, we can observe from Table 2 that high values of r produce high values of $\bar{d}$. Therefore, higher values of r produces a more negative binomially distributed form (Bundy *et al*., 1992). It can also be observed that both worm burden and dispersion show a strong sensitivity to this parameter. The results for the Misungwi present more dispersion than the results for Touros.

The above sets of the fitted parameters can also be used to generate indirectly the age-dependent mean worm burden per individual from eqn (8), and the age-dependent dispersion of worms per individual from eqn (12). For this we assume that the observed number of eggs released by infected person with age between a and $a + da$, $e(a)$, is proportional to $m(a)$, that is,

$$e(a) = \kappa_m m(a) \quad (20)$$

and the observed egg dispersion is proportional to $d(a)$, i.e.,

$$d_e(a) = \frac{10^{\sigma^2(a)} - 1}{10^{e(a)} - 1} = \kappa_d d(a), \quad (21)$$

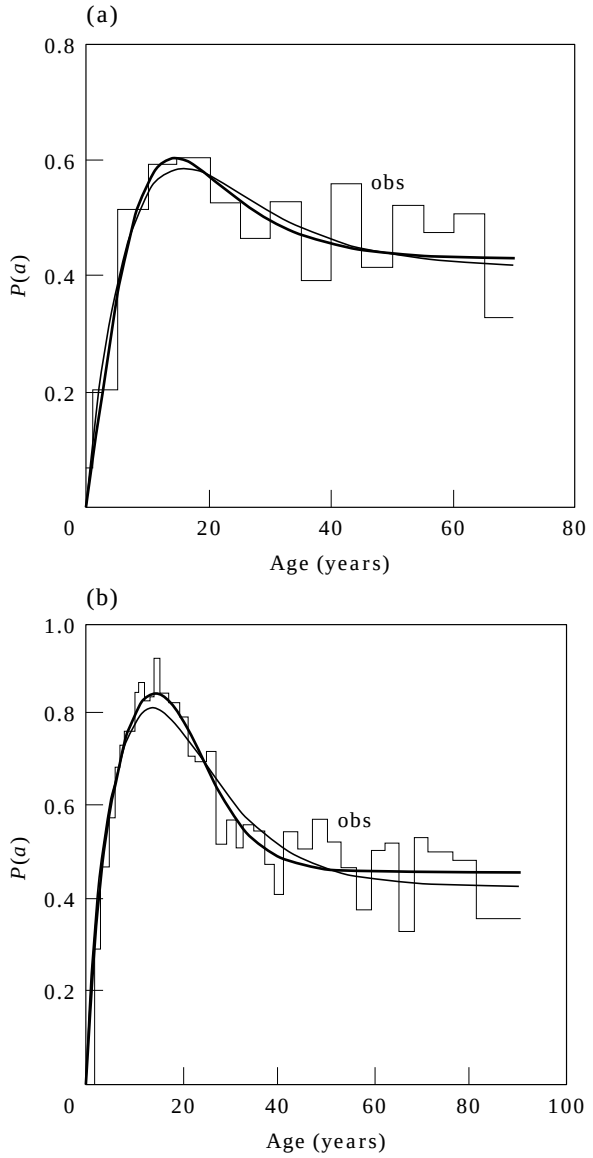

FIG. 1. (a) Age-prevalence curves fitted to data (*S. mansoni*) from Touros, Brazil. The curves show the fit for $r = 1$ (thin curve) and 21 (thick curve). (b) Age-prevalence curves fitted to data (*S. haematobium*) from region of Misungwi, Tanzania. The curves show the fit for $r = 1$ (thin curve) and 21 (thick curve).

with $\sigma^2(a)$ being the variance of egg output. For the log-transformed data we used the geometric mean (Stuart & Ord, 1987) as the anti-logarithm of Williams' mean minus one. We can estimate κ_m and κ_d as follows.

The eqns (20) and (21) are used to fit data from Bradley & McCullough (1973) and McCullough & Bradley (1973), who counted the egg output per 10 ml of urine and the corresponding standard deviation in the region of Misungwi, Tanzania. From these data, the constants κ_m, eggs per 10 ml of urine per worm, and k_d were estimated using the least square method

TABLE 2

The average number of adult worms per person and the dispersion per person of Touros, Brazil, and region of Misungwi, Tanzania

	Touros, Brazil		Misungwi, Tanzania	
r	$\bar{m}$	$\bar{d}$	$\bar{m}$	$\bar{d}$
1	0.602	1.580	0.819	5.412
4	0.937	3.645	1.283	8.916
8	1.287	5.081	1.816	12.627
11	1.538	6.202	2.168	15.058
16	1.924	8.198	2.744	19.550
21	2.300	10.508	3.274	24.174
35	3.274	16.240	4.679	35.443

(Press *et al*., 1989). By doing this we ignore possible density dependence and inflammatory reactions on the host that could compromise the egg releasing with the age of the person. It should be mentioned that, for the Touros region, there is no data to be compared with the fitting. Again we emphasize that the mean value commonly used in parasitological literature is the arithmetic mean. However, when data are originally over-dispersed ($d \gg 1$, Table 2) as in our case, it is more appropriate, as mentioned before and also according to Basáñez *et al*. (1994), to apply the log-transformation that normalizes the distribution of the counts. In Table 3 we show the estimated constants for the region of Misungwi, Tanzania.

Fig. 2 shows the age-dependent mean egg output, $e(a) = \kappa_m m(a)$, for the region of Misungwi.

It can be noted that the peak of egg output (or the mean worm burden) shifts leftward in comparison with the prevalence curve. This shift is enhanced with increasing number of invading cercaria per event. The shift to the left is commonly reported in the literature (Costa *et al*., 1985). The best fitting was obtained with a maximum of seven $[\chi^2_m(10^4) = 0.399]$ invading cercaria per event. The fitted value κ_m reflects the mean egg laid per female in 10 ml of urine per day.

Finally, Fig. 3 shows the age-dependent dispersion, $d_e(a) = \kappa_d d(a)$, for the region of Misungwi. In spite of its simplified assumptions, it is interesting that the model reproduces the patterns (the fitting is poor)

TABLE 3

The estimated constant of proportionalities: data from Misungwi, Tanzania

r	κ_m	$\chi^2_m(10^4)$	κ_d	χ^2_d
1	16.93	0.477	0.810	7.922
4	10.69	0.403	0.414	7.161
8	7.531	0.401	0.267	6.742
11	6.240	0.407	0.212	6.601
16	4.900	0.416	0.159	6.471
21	4.050	0.424	0.127	6.394

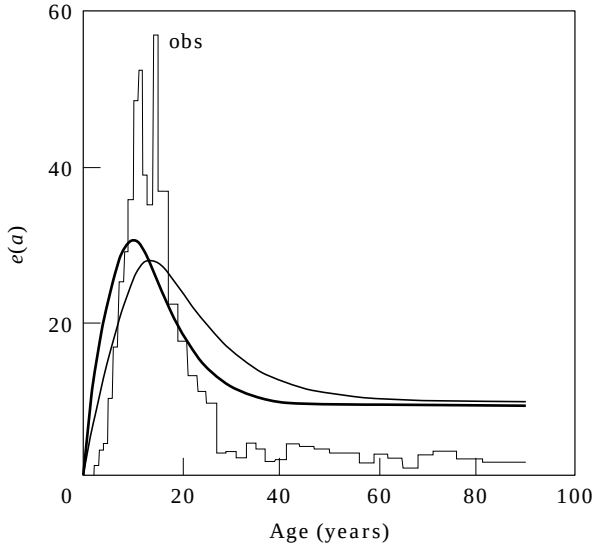

FIG. 2. Age-dependent mean egg output curves fitted to log-transformed data from region of Misungwi, Tanzania. The curves show the fit for $r = 1$ (thin curve) and 21 (thick curve).

observed in real data. This shows the necessity either of more parameters to fit both prevalence and mean worm burden curves or of fitting the two curves at the same time. The reason is that, in macroparasite infection, the prevalence alone is not a good epidemiological measure, but it requires the intensity of infection (Bundy *et al*., 1992). The maximum number of invading cercaria per event can be used as an extra parameter between the prevalence and the intensity of infection.

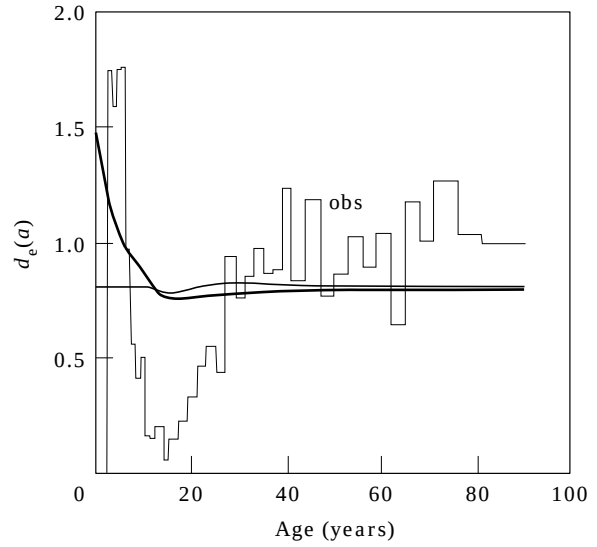

FIG. 3. Age-dependent dispersion of egg output curves fitted to log-transformed data from region of Misungwi, Tanzania. The curves show the fit for $r = 1$ (thin curve) and 21 (thick curve).

TABLE 4

Fitting data from Touros, Brazil, considering different L's *for* r = 1 *fixed*

λ_s(years^{-1})	μ_w(years^{-1})	λ_c(years^{-1})	L(years)	l(10 df)
0.119	0.054	0.028	0.875	−1494.0
0.114	0.054	0.027	1.811	−1493.8
0.112	0.057	0.027	3.118	−1493.8
0.122	0.082	0.044	5.402	−1493.6*
0.121	0.091	0.048	7.202	−1493.7
0.122	0.097	0.052	9.280	−1493.9
0.125	0.104	0.056	10.632	−1494.2

Although the model is structured with only five parameters, it fits real data with some accuracy. Of the five parameters, one may at first sight think that μ_w and L are constants and independent on the endemic level, whilst λ_s, λ_c, and r vary from region to region. However, all the five are likely to covariate. The importance of this will be discussed below.

Finally, it should be mentioned that a recent paper by Barbour & Kafetzaki (1993) has attempted to explain the dispersion of worms by invoking concomitant immunity and multiple entrance of parasites.

4. Discussion

A few comments about the above results are now required.

First, the field data available to us were fitted. The result is a wide range of the four parameters of the model and the maximum number of cercaria entering per event, with almost no variation in the likelihood of the fitting. Therefore, the sets of parameters shown above should be taken as relatives, since they covariate. This indetermination can be reduced if we consider the prevalence curve for early ages (i.e., before the development of the immune response). As can be seen in eqns (7) and (8), this phase of the curves depends only on r, λ_s, and μ_w. In the case of Misungwi region the best fit for $m(a)$ is obtained with $r = 7$. If this is to be taken as baseline value, it implies that the worms have an average life-span of 6.6 years, which is compatible with current epidemiological beliefs [5]. The range of the average worm lifespan for *S. mansoni* is $3.5(r = 35) - 10.9(r = 1)$ years [Table 1(a)] and for *S. haematobium* is $4.0(r = 35) - 11.5(r = 1)$ years [Table 1(b)] (Fulford *et al*., 1995).

Second, the values of λ_c are remarkably similar for both areas. This, on the one hand, should be expected if acquired immunity would operate by reducing the value of the force of infection to a maximum value, which happened in both regions. On the other hand,

one should expect that λ_c would be determined by a competition with μ_w which clearly varies. However, note that the value of r, the maximum number of worms allowed in each infective event, also varies, thus "washing out" this competition.

Third, the comparison of the values of L for both regions points out to an unexpectedly different time taken to build the immune response up for each of those regions. This is biologically unreasonable. However, we should stress that the estimation of the fitting gives a likelihood that is rather insensitive to great variations in L. Indeed, variations in L by a factor of 10 gives variations in the likelihood in the fourth decimal figure. This is illustrated in Table 4, which shows that, when the data for the region of Touros, with $r = 1$, are fitted by maximum likelihood estimation, give us several local extrema with L that varies between 0.875 and 10.632 years. The range of variations of L shows that the rate of development of the protective response is slow, which depends on prolonged and cumulative exposure to the antigen(s) (Butterworth, 1994), and that the development of the appropriate immune response would take years, possibly because high levels of blocking antibodies would temporarily inhibit cellular responses against incoming larvae in children (Gryseels, 1994). Based on the experiments on the development of concomitant immunity to schistosome in rhesus monkeys, Terry (1994) summarized that authentic parasite antigens, perhaps by synthesis and release, may continue to stimulate an immune response that is effective against fresh invading schistosomula but not so against the established, disguised parasites. But Gryseels (1994) points out that this may not be relevant to humans. This means that the seemly different values of L are actually compatible with a rough average of 5 years for both areas. The value of λ_s is not sensitive to the variation of L because it describes the ascendent phase of the prevalence curve, but the other two rates, μ_w and λ_c, are. Both rates covariate positively with L. The fourth row (marked by *) provides the best fitting.

To summarize, we conclude that the model considering both acquired immunity via the elapsing time L and the multiple entrance of parasites per infective event reproduces the age prevalence curve rather well. Also, using the same fitted parameters to the prevalence curve, the shape of the age-dependent mean worm burden per individual and the age-dependent dispersion of worms per individual are roughly reproduced. Whereas, the model without immunity (May, 1977) is unable to fit the prevalence curve: it increases and reaches an asymptote.

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APPENDIX A

Some Mathematical Results

The basic mathematical details were presented elsewhere (Yang *et al*., 1995), but some equations are transported from there to a better understanding.

Let $w(a, A)$ be a random variable that describes the distribution of the number of adult worms k among the fraction of the human host population with age between a and $a + da$ that got the first infection at age A. From the consideration that the human host has deterministic treatment with respect to age, the total number of worms over all age interval irrespective of the age of first infection, $W(a)$, is given by

$$\begin{cases} W_s(a) = \displaystyle\int_{a-L}^{a} w(a, A)dA \\ W_c(a) = \displaystyle\int_{0}^{a-L} w(a, A)dA, \end{cases} \tag{A.1}$$

where the subscripts s and c stand for human hosts who are not immune and those who have already built up the immune reaction, respectively. These integrals represent count of worms harbored by individuals with age between a and $a + da$.

From assumptions (1–4) in the main text, the resulting system of semi-stochastic difference differential equations in terms of the random variable $w(a, A)$ in the steady state is

$$\begin{aligned} &\frac{d}{da}S(a) = (-\lambda_s + \mu_h)S(a) \\ &\qquad \mu_w(x-1)\frac{\partial}{\partial x}f_s(a, A, x) + \frac{\partial}{\partial a}f_s(a, A, x) \\ &= \left\{\lambda_s\left[\sum_{i=1}^{r} b(i)x^i - 1\right] - \mu_h\right\}f_s(a, A, x); \\ &\qquad\qquad \text{for } a < A + L \\ &\mu_w(x-1)\frac{\partial}{\partial x}f_c(a, A, x) + \frac{\partial}{\partial a}f_c(a, A, x) \\ &= \left\{\lambda_c\left[\sum_{i=1}^{r} b(i)x^i - 1\right] - \mu_h\right\}f_c(a, A, x); \\ &\qquad\qquad \text{for } a \geqslant A + L, \end{aligned} \tag{A.2}$$

where $f_s(a, A, x)$ and $f_c(a, A, x)$ are the *pgf* of, respectively, non-immune and immune individuals, and $S(a)$ is the age distribution of individuals who have never got the infection.

The solutions of (A.2) can be integrated over all age A to yield $F_s(a, x)$ and $F_c(a, x)$, i.e.,

$$\begin{aligned} F_s(a, x) &= \int_{a-L}^{a} f_s(a, A, x)dA \\ F_c(a, x) &= \int_{0}^{a-L} f_c(a, A, x)dA, \end{aligned} \tag{A.3}$$

where the limits of integration are regarded to (A.1). These functions, given explicitly by eqns (5) and (6) in the main text, relate the *pgf* for the number of worms and the age distribution of individuals in the community. For instance, the *pgf* for the distribution of worms among non-immune individuals with age between a and $a + da$ [eqn (5), the first one], is expressed as

$$pgf_1 = e^{\lambda_s}\left[\sum_{i=1}^{r} b(i) \sum_{j=1}^{i} \binom{i}{j}(x-1)^j \frac{1-e^{-j\mu_w a}}{j\mu_w}\right]. \quad \text{(A.4)}$$

The semi-stochastic feature of the functions (A.3) are better understood when we set $x = 1$. In this case we are not concerned with the probabilistic distribution of the worms in the human host, and the human host is distributed according to

$$F_s(a) = \begin{cases} S_0 e^{-\mu_h a}(1 - e^{-\lambda_s a}); & a < L \\ S_0 e^{-\mu_h a}[e^{-\lambda_s (a-L)} - e^{-\lambda_s a}]; & a \geqslant L \end{cases}$$

$$F_c(a) = S_0 e^{-\mu_h a}[1 - e^{-\lambda_s (a-L)}]; \quad a \geqslant L. \quad \text{(A.5)}$$

The functions $F_s(a)$ and $F_c(a)$ describe the age distribution of non immune and immune individuals, respectively. The age distribution of individuals that never have had contact with worms is, from the first equation of (A.2), given by

$$F_0(a) = S_0 e^{-\mu_h a} e^{-\lambda_s a}. \quad \text{(A.6)}$$

Therefore, summing $F_s(a)$, $F_c(a)$ and $F_0(a)$, we have the age distribution of the human population disregarding worm contacts experience given by

$$F(a) = S_0 e^{-\mu_h a}. \quad \text{(A.7)}$$

Finally, the average number of adult worms per person in a community $\bar{m}$ can be calculated by

$$\bar{m} = \frac{\int_0^\infty m(a)F(a)da}{\int_0^\infty F(a)da}, \quad \text{(A.8)}$$

and $\bar{d}$ by above formulae replacing $m(a)$ by $d(a)$.

APPENDIX B

Likelihood Estimation Method

The logarithm of likelihood function (19), disregarding a constant term, is estimated by likelihood method. To perform this estimation, the initial guess must be provided by the least square method. Let p_i be the observed value. Then the sum of squares, which approximates to the χ^2 value, is

$$\chi^2(\Omega) = \sum_{i=1}^{n} [P(a_i, \Omega) - p_i]^2 \quad \text{(B.1)}$$

where $P(a_i, \Omega)$ is eqn (7) with $\Omega = [\lambda_s\ \mu_w\ \lambda_c\ L]^T$ being the space of model's parameters to be fitted, and n is the number of age intervals considered. The chi-square function (B.1) minimizes at

$$y(\Omega) = \frac{1}{2}\frac{\partial}{\partial \Omega}\chi^2(\Omega) = \sum_{i=1}^{n} [P(a_i, \Omega) - p_i] \times \frac{\partial}{\partial \Omega} P(a_i, \Omega) = 0 \quad \text{(B.2)}$$

because the inverse of the covariance matrix, neglecting the second derivatives of the chi-square in relation to the parameters ($\Sigma_{i=1}^{n}[\partial/\partial\Omega\ P(a_i, \Omega)]^2 \gg \Sigma_{i=1}^{n}[P(a_i, \Omega) - p_i]\partial^2/\partial\Omega^2\ P(a_i, \Omega)$) given by

$$\Sigma^{-2}(\Omega) = \frac{1}{2}\frac{\partial^2}{\partial \Omega^2}\chi^2(\Omega) \sim \sum_{i=1}^{n}\left[\frac{\partial}{\partial \Omega} P(a_i, \Omega)\right]^2, \quad \text{(B.3)}$$

has positive value. The estimator $\hat{\Omega}$ that obeys eqn (B.2) is the value searched.

The estimator $\hat{\Omega}$ is used as the initial guess in the maximum likelihood estimation method with the logarithm of the likelihood function (19). This expression maximizes at

$$y(\Omega) = \frac{\partial}{\partial \Omega} l(\Omega) = \sum_{i=1}^{n}\left[\frac{np_i}{P(a_i, \Omega)} - \frac{nn_i}{1 - P(a_i, \Omega)}\right] \times \frac{\partial}{\mathrm{q}\Omega} P(a_i, \Omega) = 0 \quad \text{(B.4)}$$

because the inverse of the covariance matrix, neglecting the second derivatives of the likelihood function in relation to the parameters given by

$$\Sigma^{-2}(\Omega) = -\frac{\partial^2}{\partial \Omega^2} l(\Omega) \sim \sum_{i=1}^{n}\left\{\frac{np_i}{[P(a_i, \Omega)]^2} + \frac{nn_i}{[1 - P(a_i, \Omega)]^2}\right\} \times \left[\frac{\partial}{\partial \Omega} P(a_i, \Omega)\right]^2, \quad \text{(B.5)}$$

has negative value. The estimator that obeys (B.4), $\hat{\Omega}$, is the value searched.

Due to the approximation in the second derivative, both the least square and likelihood estimations are

obtained by the Levenberg–Marquardt nonlinear fitting method. This method is the modified Newton–Raphson method, where the increments in the new set of parameters are given by

$$\Sigma_{LM}^{-2}(c) = \begin{cases} \sigma^{-2}(\Omega)(1+\epsilon), & \text{on the diagonal} \\ \eta^{-2}(\Omega), & \text{off the diagonal,} \end{cases} \tag{B.6}$$

where σ^2 and η^2 are, respectively, the variance and covariance of matrices (B.3) and (B.4), and ϵ is an auxiliary parameter (Press *et al*., 1989).

The parameter L is dependent on the step (or Heaviside) function $\theta(x)$, which has the derivative

$$\frac{\partial}{\partial L}\theta(L-t) = \delta(L-t), \tag{B.7}$$

where $\delta(x)$ is the Dirac delta function.