The Stabilizing Effects of the Acquired Immunity on the Schistosomiasis Transmission Modeling - The Sensitivity Analysis

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*A mathematical model is proposed to analyze the effects of acquired immunity on the transmission of schistosomiasis in the human host. From this model the prevalence curve dependent on four parameters can be obtained. These parameters were estimated fitting the data by the maximum likelihood method. The model showed a good retrieving capacity of real data from two endemic areas of schistosomiasis: Touros, Brazil (*Schistosoma mansoni*) and Misungwi, Tanzania (*S. haematobium*). Also, the average worm burden per person and the dispersion of parasite per person in the community can be obtained from the model. In this paper, the stabilizing effects of the acquired immunity assumption in the model are assessed in terms of the epidemiological variables as follows. Regarded to the prevalence curve, we calculate the confidence interval, and related to the average worm burden and the worm dispersion in the community, the sensitivity analysis (the range of the variation) of both variables with respect to their parameters is performed.*

Key words: schistosomiasis - acquired immunity - mathematical model - epidemiological values - sensitivity analysis

Schistosomiasis is probably the human infection with the most complex biological cycle, involving at least two host species (human and snail), two free-living transmission stages of the parasite (cercariae and miracidia) 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, S. japonicum, S. mekongi* and *S. intercalatum*) or the urinary bladder (*S. haematobium*) (Mahmoud 1990). As a result of the parasite sexual reproduction 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 four to six weeks hundreds of thousands of motile forked-tail cercaria emerge. These are the infective forms 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 that migrate to the lungs and liver; in about six 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 (Vermund et al. 1983, Harris 1984).

The question of whether humans mount an immune response to schistosomiasis is of basic biological interest and 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).

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Acquired immunity among the humans has important consequences for the epidemiology of schistosome infection (Anderson & May 1985, Crombie & Anderson 1985, Woolhouse et al. 1991, Woolhouse 1991, 1992). Mathematical models have great potential for advancing the understanding of schistosome transmission and as a tool for the design of control programmes (Woolhouse 1991). As the life-cycle of schistosome 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. For the same reason, it is difficult to predict the quantitative effects of intervention on human infection and disease. As prediction is central to the question of decision about competing intervention options, models with predictive capacity can be a powerful tool to help the disease control problems. To be of any use, however, models must be sufficiently realistic and grounded in what is understood of the schistosome biology (Woolhouse 1991). This implies the inclusion of some biological details such as the role of acquired immunity on the disease dynamics.

The main epidemiological data used to quantify schistosomiasis transmission are as follows. The most used epidemiological data to describe the schistosomiasis is the so-called *prevalence curve*, denoted *p(a)*, that is, the proportion of individuals shedding viable eggs in faeces (or urine) plotted against age. The essential relationship between prevalence and age, which is repeatedly observed in the studies of age-specific prevalence data of schistosomiasis, is a build up in the early years, peaking around 10-20 years of age, dropping thereafter, and stabilizing at some endemic level (Holford & Hardy 1976). It is remarkable that this behaviour of the prevalence curve is observed even when the prevalence is very low, reaching a peak of only 5 % (Dias et al. 1989).

The second most used data is the age-dependent *egg output curve*, *m(a)*. This curve is also characterized by an early build up, peaking slightly earlier than the prevalence curve (Costa et al. 1985). Following this peak, there is a decline in the egg output but the decline does not reach zero, rather it approaches some other asymptote (Hairston 1965, Bradley & McCullough 1973). There are various ways in which mean egg output are reported in the literature (Banáñez et al. 1994): the simple arithmetic, the Williams' mean (logarithmic transformation) and the square root transformed mean. Since the egg output varies greatly with random factors that cannot be included in a simple model we believe that the Williams' mean, by smoothing the data and normalizing it, is the more appropriate. A justification for this can be found in the classical paper by Williams (1937).

The third kind of data is the age-dependent *variance in the egg output d(a)* 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 dispersion curve 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). For instance, if the dispersion assumes the unity value, then the parasite is distributed randomly among the individuals in the community, which corresponds to the Poisson distribution. However, if the dispersion assumes a value higher than unity, then we have a great number of parasites harboured by few individuals while all other individuals harbour small amount of parasites and, in this case, the parasite distribution in the population can be described by the negative binomial distribution.

From the second and third kind of data we can obtain, by calculating the average values regarding age, the average worm burden per person *m*, and the worm dispersion per person *d*. These epidemiological variables show the distribution trend of the worms in the community (over- or under-dispersion).

The fourth type of data described in the literature is the proportion of shedding snails (those releasing cercaria), or the combined proportion of latent (those already infected but not releasing cercaria yet) and shedding snails (Sturrock & Webbe 1971).

Another less used data is the observed frequency of contact among humans with presumably contaminated water (Dalton & Pole 1978, Barbour 1985, Chandiwana & Woolhouse 1991). The introduction of this kind of information is the basis of Holford and Hardy model (1976).

The incorporation of acquired immunity in models dealing with schistosome transmission has shown to have some important consequences (Woolhouse et al. 1991, Fulford et al. 1993). There is a lowering of the overall susceptibility of humans to infection which results in a decreasing of the age-related prevalence of schistosomiasis. An interesting result, mentioned by Anderson and May (1991), is that acquired immunity does not affect the *basic reproduction ratio*, R_0. This ratio is related to the average number of female offspring produced throughout the lifetime of a mature female parasite, and is one of the fundamental pa-

rameters in the quantitative epidemiology. For this reason, this value must be taken into account when schistosomiasis controlling mechanisms are applied in a community.

Models which incorporate neither the acquired resistance to infection nor the age-dependent parameters cannot reproduce typical age intensity or age prevalence patterns. For a recent review of schistosome infection modeling see Woolhouse (1991, 1992). The consequences of a simple model for acquired immunity against schistosomiasis were analyzed elsewhere (Yang et al. 1995, 1997, Yang & Coutinho 1998). Yang et al. (1995, 1997) proposed a semi-stochastic model to analyze the effects of acquired immunity on the transmission of schistosomiasis in the human host. We call this as semi-stochastic model, because the distribution of worms among the human population is treated probabilistically and the deterministic treatment is used for the demographic structure (age distribution) of human population. The basic model's assumptions were as follows. The human host was assumed to build up an immune response after elapsing a fixed period of time *L* from the first infection. This acquired immunity was assumed to be partially effective (Terry 1994, Butterworth 1994, Gryseels 1994). Any infection can be done by one or more cercaria with a given probability. The model treated deterministically the age-distribution of human host.

In this paper, we analyze the effects of the acquired immunity on the stability of the schistosomiasis transmission. For this purpose, following a different way that done by Yang and Coutinho (1998), we present the confidence interval for fitted prevalence curve *p(a)*, and perform the sensitivity analysis of the average worm burden per person (*m*) and the worm dispersion per person (*d*) with respect to their parameters. The sensitivity analysis provides us with the range of the variations of *m* and *d* when the parameters are varied.

MATERIALS AND METHODS

In this section we briefly describe the semi-stochastic approach proposed by Yang et al. (1995, 1997) to assess the effects of acquired immunity on the transmission of schistosomiasis in the human host. The model's assumptions were as follows.

1. The human host build an immune response up 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 (random) process of rate $\mathtt{l}$ 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 must have $\sum_{i=1}^{r} b(i) = 1$. It also reflects the fact that not all invading cercaria per event maturate to adult form but only viable cercaria. Therefore, from the consideration of the acquired immunity, we have for the Poisson process rates $\mathtt{l}_s$ and $\mathtt{l}_c$ the special names, respectively, the forces of infection of non-immune and immune individuals.

3. Adult worms inside the host die with a constant rate $\mathtt{mw}$.

4. The human population is treated deterministically with a constant death rate $\mathtt{m}_h$.

Based on the first assumption, the human population can be divided into non-immune (completely susceptible) and partially immune individuals. The second and third assumptions are related to the worm distribution in the human host, which is given by the probabilistic events of parasite entrance and its mortality. Finally, the last assumption is related to the age-distribution of the human population. All the above considerations are used to obtain, by means of the stochastic process modeling, a system of difference-differential equations that describes the dynamics of the schistosomiasis. Note that the term difference is related to the discrete (integer number) counting of parasites, while the term differential is related to the age which is considered as a continuous variable.

Here we transport the equilibrium solutions from the model proposed by Yang et al. (1997). The steady state probability generating function (pgf) for the number of worms distributed among non-immune individuals with age between *a* and *a+da* is given by

$$F_s(a,x) = \begin{cases} S_0 e^{-\mu_h a}\left[e^{\lambda_s \Psi\left(\frac{1-e^{-j\mu_\omega a}}{j\mu_\omega}\right)} - e^{-\lambda_s a}\right]; & \text{for } a < L \\ S_0 e^{-\mu_h a}\left\{ e^{-\lambda_s\left[(a-L)-\Psi\left(\frac{1-e^{-j\mu_\omega L}}{j\mu_\omega}\right)\right]} - e^{-\lambda_s a}\right\}; & \text{for } a \geq L \end{cases}$$

and, for the partially immune individuals, we have

$$F_c(a,x) = S_0 e^{-\mu_h a} \int_0^{a-L} \left[1 + \Psi\left(e^{-j\mu_\omega (a-A)}\right)\right] \lambda_s e^{-\lambda_s \left\{ A - \Psi\left(\frac{\frac{\lambda_c}{\lambda_s} + \left[\left(1 - \frac{\lambda_c}{\lambda_s}\right) e^{-j\mu_\omega L} - 1\right] e^{-j\mu_\omega (a-A)}}{j\mu_\omega} \right) \right\}} dA \ ; \ for\, a \geq L,$$

where S_0 is the new-born rate and the auxiliary notation

$$\Psi(\xi) = \sum_{i=1}^{r} b(i) \sum_{j=1}^{i} \binom{i}{j} (x-1)^j \xi \ ,$$

with the combinatory being given by

$$\binom{i}{j} = \frac{i!}{j!(i-j)!} \ .$$

Observe that *i! = i´ (i-1) ´ (i-2) ´...´2´1*.

From $F_s(a,x)$ and $F_c(a,x)$ we can obtain the following three epidemiological variables. These variables, which were discussed in the Introduction, are the age-prevalence curve *p(a)*, the average worm burden *m* and the average worm dispersion in the community *d*. The procedures to obtain these variables, which were described in Yang et al. (1995, 1997), are not given here.

The age-prevalence curve *p(a)* is given by

$$p(a) = \begin{cases} 1 - e^{\lambda_s \Psi_0\left(\frac{1 - e^{-j\mu_\omega a}}{j\mu_\omega}\right)} \ ; \ for\, a < L \\ \left\{ 1 - e^{-\lambda_s \left[(a-L) - \Psi_0\left(\frac{1 - e^{-j\mu_\omega L}}{j\mu_\omega}\right)\right]} - \int_0^{a-L} \left[1 + \Psi_0\left(e^{-j\mu_\omega (a-A)}\right)\right] \lambda_s \right\} \\ \times e^{-\lambda_s \left\{ A - \Psi_0\left(\frac{\frac{\lambda_c}{\lambda_s} + \left[\left(1 - \frac{\lambda_c}{\lambda_s}\right) e^{-j\mu_\omega L} - 1\right] e^{-j\mu_\omega (a-A)}}{j\mu_\omega} \right) \right\}} dA \ ; \ for\, a \geq L, \end{cases}$$

where

$$\Psi_0(\xi) = \sum_{i=1}^{r} b(i) \sum_{j=1}^{i} \binom{i}{j} (-1)^j \xi .$$

The average worm burden per person *m* is given by

$$m = \frac{\varpi \lambda_s}{\mu_\omega + \mu_h} \left[1 - (\lambda_s - \lambda_c) \frac{e^{-\mu_h L}}{\lambda_s + \mu_h} \right],$$

where ν is the mean parasite entrance per infective event, given by

$$\varpi = \sum_{i=1}^{r} i b(i).$$

Finally, the worm dispersion per person in the community *d* is given by

$$d = 1 - m + \frac{f_1 + f_2 - f_3}{m} \ ,$$

where f_1, f_2 and f_3 are the auxiliary functions

$$\begin{cases} f_1 = \left(\frac{\varpi^2 \lambda_s^2}{\mu_\omega + \mu_h} + \frac{\sigma_b \lambda_s}{2} \right) \frac{2}{2\mu_\omega + \mu_h} \\ f_2 = \frac{\varpi^2 \lambda_s (\lambda_s - \lambda_c) \mu_h e^{-\mu_h L}}{\mu_\omega^2} \left[\frac{2\lambda_c}{\lambda_s + \mu_h} + \frac{3\mu_\omega + \mu_h}{2\mu_\omega + \mu_h} \frac{e^{-\mu_\omega L}}{\mu_\omega + \mu_h} \right. \\ \left. + \frac{\frac{\lambda_c + \lambda_s \left(1 - e^{-\mu_\omega L}\right)}{\lambda_s} + \frac{-\lambda_c + \lambda_s \left(1 - e^{-\mu_\omega L}\right)}{2\mu_\omega + \mu_h}}{\lambda_s + \mu_h} \right] - \frac{\sigma_b \lambda_s (\lambda_s - \lambda_c) e^{-\mu_h L}}{(\lambda_s + \mu_h)(2\mu_\omega + \mu_h)} \\ f_3 = \left(\lambda_s^2 - \lambda_c^2\right) \frac{\varpi e^{-\mu_h L}}{\lambda_s \mu_\omega} \end{cases}$$

and

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

is the second moment of the parasite entrance per infective event.

The epidemiological variables *p(a)*, *m* and *d* are given as a function of the parameters l_s, l_c, m_w and *L*. These values can be estimated by an appropriate method, but due to the unreliability of the observed data, they will be approximated values of the true values. The sensitivity analysis deal with this question of the parameters that are given as an approximated values, and from which other variables are derived.

Now, we present the sensitivity analysis (Bailey & Duppenthaler 1980) in the modeling of schistosomiasis transmission. Let $y(\mathrm{q})$ be one of the previously defined and calculated epidemiological variables, that is, *p(a)*, *m* or *d*, with q being the model's parameter-set, given by the column vector

$$\theta = \left[\lambda_s \ \ \mu_w \ \ \lambda_c \ \ L\right]^T \ ,$$

where the superscript *T* stands for the transposition of the matrix.

The parameter-set q can be fitted by the maximum likelihood estimation method using the observed prevalence data. In practice, these data are unreliable. Therefore, the estimated parameter-set q can be set as

$$\hat{\theta} = \theta_0 + \delta\hat{\theta} ,$$

where q_0 is the true value, $\hat{\theta}$ is an unbiased estimator provided by the likelihood method and $\delta\hat{\theta}$ is the deviation from the true value. By the fact that $\hat{\theta}$ is an unbiased estimator, we must have for its expectation,

$$E(\hat{\theta}) = E(\theta_0 + \delta\hat{\theta}) = \theta_0 ,$$

that is, the average value of the deviation from the true value is zero, or

$$E(\delta\hat{\theta}) = 0 .$$

On the other hand, the average value of the square of the deviation from the true value, designed by S, is not zero and is given by

$$\Sigma \equiv E\left(\left[\delta\hat{\theta}\right]^2\right) = E\left(\left[\hat{\theta} - \theta_0\right]^2\right) .$$

This is the covariance (symmetric) matrix, whose elements are denoted by $\rho_{ij}\ (= \rho_{ji})$, if $i \neq j$, and σ_i^2, otherwise. Note that σ_i^2 is the variance.

By the fact that the parameters are not accurately estimated, when we calculate the epidemiological variables, we must bear in mind that these variables are also imprecise. For this reason, it is interesting to calculate the range of variations of the epidemiological variables. Therefore, the variation in the epidemiological variables can be calculated, in the first approximation, as

$$\Delta y = y(\theta_0 + \delta\hat{\theta}) - y(\theta_0) \cong H^T \delta\hat{\theta} ,$$

where *H* (see the appendix), defined as

$$H = \left.\frac{\partial y}{\partial \theta}\right|_{\theta_0} ,$$

is the sensitivity matrix, whose elements are designed by h_i, where *i=1,2,3* and *4* related to the parameters. Using the fact that $\hat{\theta} = \theta_0 + \delta\hat{\theta}$, we have the expectations of the epidemiological variables given by

$$E(\Delta y) = 0$$

and

$$E\left(\left[\Delta y\right]^2\right) = E\left(\left[H^T\delta\hat{\theta}\right]^2\right) = H^T E\left(\left[\delta\hat{\theta}\right]^2\right) H = H^T \Sigma H ,$$

from $\Sigma = E\left(\left[\delta\ \hat{\theta}\right]^2\right)$. Hence, we have

$$\sigma_y^2 = H^T \Sigma H$$

for the variance of the epidemiological variable.

In the next section we present the sensitivity analysis of the epidemiological variables with respect to their parameters. Firstly, by using the parametrized prevalence curve, the model's parameters are fitted to prevalence data from Touros, Brazil (Motta et al. 1977), and region of Misungwi, Tanzania (Bradley & McCullough 1973). Thereafter, we apply this estimated set of parameters to assess the variations in the epidemiological variables: we calculate the confidence interval for *p(a)*, and for the average worm burden per individual *m* and the dispersion per individual *d*, we present the rank of the sensitivity of the model's parameters.

RESULTS

In this section, we present the stabilizing effects of the acquired immunity consideration in the model. First, we present the parameters fitted to prevalence data found from region of Misungwi, Tanzania and Touros, Brazil.

In Table I a and b we show the fitted parameters by the maximum likelihood estimation method, for 3 arbitrarily chosen values for the maximum parasite entrance per infective event.

TABLE I

The parameters fitted to prevalence data from region of Misungwi (*Schistosoma haematobium*), Tanzania (I.a) and Touros (*S. mansoni*), Brazil (I.b), for *r* =1, 13 and 25. The symbols *y* and *l* stand, respectively, for year and likelihood value

I.a

r	1	13	25
$\lambda_s(y^{-1})$	0.227	0.175	0.168
$\mu_w(y^{-1})$	0.089	0.194	0.211
$\lambda_c(y^{-1})$	0.049	0.047	0.042
$L(y)$	11.0	9.80	7.39
$-l$	2531.0	2519.1	2516.8

I.b

r	1	13	25
$\lambda_s(y^{-1})$	0.117	0.096	0.084
$\mu_w(y^{-1})$	0.076	0.199	0.241
$\lambda_c(y^{-1})$	0.039	0.044	0.065
$L(y)$	5.81	1.47	0.25
$-l$	1493.4	1490.6	1490.0

We observe that the fitting becomes better in proportion to the increasing in the maximum number of parasite entrance per infective event (there is an increasing in the value of the maximum likelihood). The corresponding elements of the covariance matrix related to the estimated parameters are given in Table II a and b.

TABLE II

The elements of the covariance matrix related to the fitted parameters given in Table I, for region of Misungwi (*Schistosoma haematobium*), Tanzania (II.a) and Touros (*S. mansoni*), Brazil (II.b), for r =1, 13 and 25

II.a

r	1	13	25
s_1^2	0.0002	0.00006	0.00004
r_{12}	0.0002	0.0003	0.0003
r_{13}	0.0002	0.00008	0.00007
r_{14}	0.02	0.03	0.03
s_2^2	0.0004	0.003	0.01
r_{23}	0.0003	0.0008	0.002
r_{24}	0.04	0.3	1.1
s_3^2	0.0002	0.0002	0.0005
r_{34}	0.03	0.07	0.2
s_4^2	5.1	27.2	113.4

II.b

r	1	13	25
s_1^2	0.0002	0.0004	0.00004
r_{12}	0.0007	0.0009	-0.0001
r_{13}	0.0004	0.0002	-0.00002
r_{14}	0.1	0.2	-0.09
s_2^2	0.004	0.2	0.3
r_{23}	0.002	0.04	0.05
r_{24}	0.8	44.6	111.9
s_3^2	0.001	0.009	0.009
r_{34}	0.5	10.0	20.5
s_4^2	149.7	11,223.6	45,334.2

We observe that the covariance (especially the covariance with the parasite mortality rate μ_ω) and variance values related to the periods of time elapsed to build up an immune response (L) are high. Also the estimation related to Touros, Brazil showed more imprecise than that found for region of Misungwi, Tanzania.

Based on the values of the parameters and their covariance matrices given in Tables I and II, we perform the sensitivity analysis. Note that the confidence interval for the prevalence curve, when the fitted parameters are considered with regard to their estimated covariance elements, must be narrowed in proportion to the model's adequacy to describe the strong stability of the disease stability (in the sense of a broad range of variation of the model's parameters). Nevertheless, besides of the insensitivity of the prevalence curve with respect to the variation of the model's parameters, we must observe a large variation in the average worm burden and the worm dispersion in order to explain the difficulty encountered in the eradication programmes. It is worth to stress the fact that both the confidence interval and sensitivity analysis are strongly dependent on the values attributed to the parameters, that is, it is a local analysis in the sense that the variations in the parameters are regarded around the chosen values.

With respect to the prevalence curve, we determine the confidence interval. Let us assume that $\hat{\theta}$ is an unbiased estimator with distribution approximately normal, which is reasonable since it is estimated by maximum likelihood and the size of observed prevalence data is not small. Hence, to the prevalence curve, which is a proportion, we have the 100´(1-α) % confidence interval given by

$$p\left(\hat{\theta}\right) + z_{\frac{1}{2}\alpha}\sigma_y^2 < p(\theta_0) < p\left(\hat{\theta}\right) + z_{1-\frac{1}{2}\alpha}\sigma_y^2,$$

where z_α is the 100α percentile obtained from the normal distribution (Dixon & Massey 1983). In this paper, we will consider α=0.05, which yields in $z_{0.025}$ =-1.96 and $z_{0.975}$ =1.96. Therefore, the above interval will no longer ensure a 95 percent chance that the confidence limit will include θ_0.

In Figs 1.a, 1.b and 1.c we show the age-prevalence fitting $p\left(\hat{\theta}\right)$, based on Tables I and II, for three maximum parasite entrance per infective event, r =1, 13 and 25.

The 95 percent confidence interval for both curves are very close, practically coinciding with the curves shown (Figs 1a, b). For instance, the maximum relative range of variation of the confidence interval $\Delta p / p$ are 0.0065 (r =1), 0.003 (r =13) and 0.003 (r =25) at age 90 years, for region of Misungwi, Tanzania (Fig. 1a), and 0.01 (r =1 at age 5.81), 0.0064 (r =13 at age 70) and 0.69 (r =25 at age 24.5), for Touros, Brazil (Fig. 1b). However, the confidence interval is large (see below) for data from Touros when we use r =25 (Fig. 1c).

The large confidence interval obtained to Touros, Brazil for r =25 can be understood based on the parameter L. From Fig. 1.b, we observe that the asymptotic prevalence is slightly lower than its peak. For this reason, the increase number of maximum parasite entrance per infective event becomes an important feature to the estimation process. The value L=0.25 years was fixed arbitrarily, and the remaining parameters fitted, because the best fitting assigns to L a negative value, which has no biological interpretation. In this situation, the multiple parasite entrance per infective event can be evoked to explain the prevalence curve, but at the expense of enlarging the confidence interval. Note that, in this estimation, we have $\lambda_s \gg \lambda_c$, which is the situation where the acquired immunity does not matter.

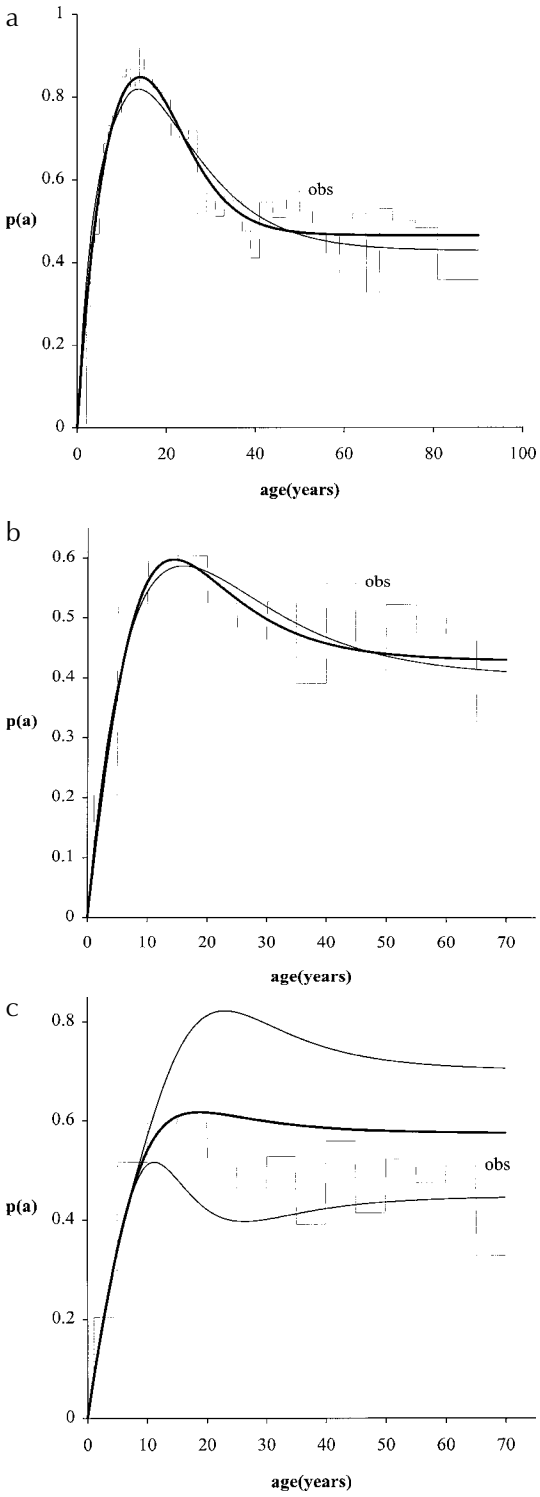

Fig. 1: age-prevalence curves fitted to data from region of Misungwi (*Schistosoma haematobium*), Tanzania (a) and from Touros (*S. mansoni*), Brazil (b). The thin curves correspond to r =1 and thick curves, to r =25 (Misungwi) and 13 (Touros). For Touros, when we fitted the data considering r =25, the confidence interval enlarges for the prevalence curve calculated at higher ages (c).

We observe that, in spite of the broad range of the estimated parameters, especially of the parameter L, which has very high variance, the prevalence curve is practically unchanged by the variation of the parameters with respect to their covariance values. This shows that the acquired immunity consideration taken into account by the model stabilizes the disease transmission.

Nevertheless, we would like to stress that the goodness of fit by itself should not be considered sufficient for accessing to model adequacy. For instance, a model without immunity, which encompasses the age-dependent frequency contact with infested water (Holford & Hardy 1976), fits the prevalence extremely well with four parameters, but it fails in two aspects: to explain the observed strong stability and underestimates the *basic reproduction ratio*. Moreover, both acquired immunity and multiple parasite infections reproduced a great endemic stability for the disease and a high value for the *basic reproduction ratio* (Yang & Coutinho 1998), which are important features observed with respect to the schistosomiasis transmission. Of course, in this kind of schistosomiasis modeling we must obtain a large confidence limit for the prevalence curve (Fig. 1c).

With respect to the average worm burden per person and the worm dispersion per person, the sensitivity analysis (Frank 1978) regarded to their parameters can be done by calculating

$$\sigma_y^2 = \sum_{i=1}^{4} \sigma_y^2(\theta_i),$$

where $\sigma_y^2(\theta_i)$ is the overall contribution of the i-th parameter of the model to the variation of m or d given by

$$\sigma_y^2(\theta_i) = \sum_{j=1}^{4} h_i \, \rho_{ij} \, h_j \ ,$$

remembering that h_i and r_{ij} are, respectively, the elements of the sensitivity vector H and covariance matrix S. Observe that the central contribution of the ith parameter, that is, the isolated contribution of the variance of the ith parameter, is given by $h_i^2 \sigma_i^2$.

In Table III a and b we show the sensitivity analysis of the average worm burden per person with respect to its parameters. The average worm burden per person for region of Misungwi, Tanzania (Touros, Brazil) are: for r =1, m =0.83 (0.59), for r =13, m =2.44 (1.69) and for r =25, m =3.70 (3.45).

TABLE III

The sensitivity analysis of the average worm burden per individual to region of Misungwi (*Schistosoma haematobium*), Tanzania (III.a) and Touros (*S. mansoni*), Brazil (III.b), for r =1, 13 and 25. The isolated contributions of each parameter with the total variation are shown. The indexes 1, 2, 3 and 4 refer, respectively, to λ_s , μ_ω , λ_c and L

III.a

r	1	13	25
$h_1^2\sigma_1^2$	0.0005	0.002	0.002
$h_2^2\sigma_2^2$	0.022	0.40	2.8
$h_3^2\sigma_3^2$	0.011	0.15	1.0
$h_4^2\sigma_4^2$	0.002	0.07	0.92
σ_m^2	0.0007	0.0049	0.114

III.b

r	1	13	25
$h_1^2\sigma_1^2$	0.0003	0.0004	0.001
$h_2^2\sigma_2^2$	0.18	11.0	50.4
$h_3^2\sigma_3^2$	0.12	6.9	17.2
$h_4^2\sigma_4^2$	0.016	5.2	6.5
σ_m^2	0.0046	2.53	0.18

TABLE IV

The sensitivity analysis of the worm dispersion per individual to region of Misungwi (*Schistosoma haematobium*), Tanzania (IV.a) and Touros (*S. mansoni*), Brazil (IV.b), for r =1, 13 and 25. The isolated contributions of each parameter with the total variation are shown. The indexes 1, 2, 3 and 4 refer, respectively, to parameters λ_s , μ_ω , λ_c and L

IV.a

r	1	13	25
$h_1^2\sigma_1^2$	0.3	1.1	2.9
$h_2^2\sigma_2^2$	2.1	15.6	160.6
$h_3^2\sigma_3^2$	0.5	6.5	68.8
$h_4^2\sigma_4^2$	0.09	3.1	62.3
σ_d^2	3.9	56.3	781.5

IV.b

r	1	13	25
$h_1^2\sigma_1^2$	0.2	0.5	0.4
$h_2^2\sigma_2^2$	8.5	131.7	33.9
$h_3^2\sigma_3^2$	1.0	93.2	91.4
$h_4^2\sigma_4^2$	0.1	21.7	0.03
σ_d^2	14.7	653.9	242.7

We note that the most sensitive parameter is μ_ω , followed by λ_c and L, and the least sensitive is λ_s . This ranking of the parameters which contribute to vary the average worm burden is maintained to all values of the estimated parameters. Therefore, due to the fact that the variation in the force of infection related to the non-immune individuals affects so little to the variation of the average worm burden, we can conclude that the acquired immunity consideration permits us to explain the strong stability of the schistosomiasis transmission. Observe that the variation in the average worm burden does not surpass its average value, except for Touros when we consider r =13.

In Table IV a and b, we show the sensitivity analysis of the worm dispersion per person with respect to its parameters. The worm dispersion per person for region of Misungwi, Tanzania (Touros, Brazil) are: for r =1, d=5.08 (2.16), for r =13, d=15.96 (7.89) and for r =25, d=30.67 (9.19).

Differently to the average worm burden, the ranking of the sensitivity does not maintain to all values of parameters considered. We note that the most sensitive parameter is μ_ω , followed by λ_c and λ_s and the least sensitive is L, if we consider low values of r. However, for great values of r, we have the same ranking observed in relation to the average worm burden, which is μ_ω , followed by λ_c and L, and the least sensitive is λ_s . Observe that the variation in the worm dispersion per person corresponding to higher values of r increases many times its value.

The above findings show the stabilizing effects when the acquired immunity is considered in the schistosomiasis transmission model. Besides the low worm burden per person and high worm dispersion, we obtained the following important aspect. When controlling or eradicating mechanism is introduced in a community (by varying the model's parameters), we observe that the pattern of the disease transmission (prevalence curve) is practically unchanged, the average worm burden per person is lowered reasonably, but the worm dispersion is changed broadly. This suggests that the worm distributes more and more in negative binomially shape if the host-parasite system is perturbed.

Finally, note that we have considered an acquired immunity which is never lost. Yang and Silveira (1998) showed, for the directly transmitted infections, that the loss of immunity decreases the estimation of the basic reproduction ratio R_0 , and it attains the maximum value when the immunity is life-long. Therefore, if we deal with the return of the immune individuals to the susceptible status, we must bear in the mind that all the above results are the upper bound of possible outcomes.

DISCUSSION

In this paper we analyzed the stabilizing effects of the acquired immunity consideration in the schistosomiasis transmission modeling. To do this, we determined the confidence interval for the prevalence curve, and performed the sensitivity analysis of the average worm burden per person and the worm dispersion per person in the community.

All the results presented in this paper confirm the fact that the acquired immunity consideration stabilizes the transmission of the schistosomiasis. When there is a variation in the model's parameters, the prevalence curve is practically unchanged, while the parasite dispersion is strongly affected.

Therefore, the acquired immunity is one of explanation to the strong stability of the schistosomiasis transmission, i.e., the disease is maintained in an endemic level even in the presence of controlling or eradication mechanisms. The model taking into account the acquired immunity results in a very low estimation for the average worm burden per person, and a very high value for the worm dispersion. This suggests that the worms are negative binomially distributed in the community, which is enhanced when perturbation is introduced in form of controlling or eradicating effort.

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APPENDIX

The sensitivity matrix H (here is a vector, since we are dealing with one variable) can be obtained by partial differentiation of the variable with respect to the parameters. We show some expressions corresponding to the elements of the sensitivity matrix.

In relation to the prevalence curve we have four partial derivatives: $\partial p(a)/\partial \lambda_s$, $\partial p(a)/\partial \mu_\omega$, $\partial p(a)/\partial \lambda_c$ and $\partial p(a)/\partial L$. For instance, we have

$$h_3 \equiv \frac{\partial p(a)}{\partial \lambda_c} = \begin{cases} 0 \; ; \; for\, a < L \\ -\int_0^{a-L} \left[1+\Psi_0\left(e^{-j\mu_\omega(a-A)}\right)\right]\Psi_0\left(\frac{1-e^{-j\mu_\omega(a-L-A)}}{j\mu_\omega}\right)\lambda_s \\ \times\, e^{-\lambda_s\left\{A-\Psi_0\left(\frac{\frac{\lambda_c}{\lambda_s}+\left[\left(1-\frac{\lambda_c}{\lambda_s}\right)e^{-j\mu_\omega L}-1\right]e^{-j\mu_\omega(a-A)}}{j\mu_\omega}\right)\right\}} dA \; ; \; for\, a \geq L \end{cases}$$

and

$$h_4 \equiv \frac{\partial p(a)}{\partial L} = \begin{cases} 0 \; ; \; for\, a < L \\ -\int_0^{a-L} \left[1+\Psi_0\left(e^{-j\mu_\omega(a-A)}\right)\right]\Psi_0\left(\left(\lambda_s-\lambda_c\right)e^{-j\mu_\omega(a-L-A)}\right)\lambda_s \\ \times\, e^{-\lambda_s\left\{A-\Psi_0\left(\frac{\frac{\lambda_c}{\lambda_s}+\left[\left(1-\frac{\lambda_c}{\lambda_s}\right)e^{-j\mu_\omega L}-1\right]e^{-j\mu_\omega(a-A)}}{j\mu_\omega}\right)\right\}} dA \; ; \; for\, a \geq L \, . \end{cases}$$

In relation to the average worm burden per person *m*, we have the following elements for the sensitivity matrix,

$$\begin{cases} h_1 \equiv \dfrac{\partial m}{\partial \lambda_s} = \dfrac{\varpi}{\mu_\omega + \mu_h}\left[1 - \dfrac{(\lambda_s - \lambda_c)e^{-\mu_h L}}{\lambda_s + \mu_h} - \dfrac{\lambda_s(\lambda_c + \mu_h)e^{-\mu_h L}}{(\lambda_s + \mu_h)^2}\right] \\ h_2 \equiv \dfrac{\partial m}{\partial \mu_\omega} = -\dfrac{\varpi \lambda_s}{(\mu_\omega + \mu_h)^2}\left[1 - \dfrac{(\lambda_s - \lambda_c)e^{-\mu_h L}}{\lambda_s + \mu_h}\right] \\ h_3 \equiv \dfrac{\partial m}{\partial \lambda_c} = \dfrac{\varpi \lambda_s e^{-\mu_h L}}{(\mu_\omega + \mu_h)(\lambda_s + \mu_h)} \\ h_4 \equiv \dfrac{\partial m}{\partial L} = \dfrac{\varpi \lambda_s(\lambda_s - \lambda_c)\mu_h e^{-\mu_h L}}{(\mu_\omega + \mu_h)(\lambda_s + \mu_h)}. \end{cases}$$

In relation to the average worm dispersion per person in the community *d*, we have the following partial derivatives as elements of the sensitivity matrix,

$$\begin{cases} h_1 \equiv \dfrac{\partial d}{\partial \lambda_s} = -\dfrac{\partial m}{\partial \lambda_s} + \dfrac{\left[\dfrac{\partial f_1}{\partial \lambda_s} + \dfrac{\partial f_2}{\partial \lambda_s} - \dfrac{\partial f_3}{\partial \lambda_s}\right]m - (f_1 + f_2 - f_3)\dfrac{\partial m}{\partial \lambda_s}}{m^2} \\ h_2 \equiv \dfrac{\partial d}{\partial \mu_\omega} = -\dfrac{\partial m}{\partial \mu_\omega} + \dfrac{\left[\dfrac{\partial f_1}{\partial \mu_\omega} + \dfrac{\partial f_2}{\partial \mu_\omega} - \dfrac{\partial f_3}{\partial \mu_\omega}\right]m - (f_1 + f_2 - f_3)\dfrac{\partial m}{\partial \mu_\omega}}{m^2} \\ h_3 \equiv \dfrac{\partial d}{\partial \lambda_c} = -\dfrac{\partial m}{\partial \lambda_c} + \dfrac{\left[\dfrac{\partial f_1}{\partial \lambda_c} + \dfrac{\partial f_2}{\partial \lambda_c} - \dfrac{\partial f_3}{\partial \lambda_c}\right]m - (f_1 + f_2 - f_3)\dfrac{\partial m}{\partial \lambda_c}}{m^2} \\ h_4 \equiv \dfrac{\partial d}{\partial L} = -\dfrac{\partial m}{\partial L} + \dfrac{\left[\dfrac{\partial f_1}{\partial L} + \dfrac{\partial f_2}{\partial L} - \dfrac{\partial f_3}{\partial L}\right]m - (f_1 + f_2 - f_3)\dfrac{\partial m}{\partial L}}{m^2}, \end{cases}$$

where, for instance, we have

$$\begin{cases} \dfrac{\partial f_1}{\partial \lambda_s} = \dfrac{2}{2\mu_\omega + \mu_h}\left(\dfrac{2\varpi^2 \lambda_s}{\mu_\omega + \mu_h} + \dfrac{\sigma_b}{2}\right) \\ \dfrac{\partial f_1}{\partial \mu_\omega} = -\dfrac{2\varpi^2 \lambda_s^2}{(\mu_\omega + \mu_h)^2(2\mu_\omega + \mu_h)} - \left(\dfrac{\varpi^2 \lambda_s}{\mu_\omega + \mu_h} + \dfrac{\sigma_b}{2}\right)\dfrac{4\lambda_s}{(2\mu_\omega + \mu_h)^2} \\ \dfrac{\partial f_1}{\partial \lambda_c} = 0 \\ \dfrac{\partial f_1}{\partial L} = 0 \end{cases}$$

and

$$\begin{cases} \dfrac{\partial f_3}{\partial \lambda_s} = \dfrac{(\lambda_s^2 + \lambda_c^2)\varpi e^{-\mu_h L}}{\lambda_s^2 \mu_\omega} \\ \dfrac{\partial f_3}{\partial \mu_\omega} = -\dfrac{(\lambda_s^2 - \lambda_c^2)\varpi e^{-\mu_h L}}{\lambda_s \mu_\omega^2} \\ \dfrac{\partial f_3}{\partial \lambda_c} = -\dfrac{2\lambda_c \varpi e^{-\mu_h L}}{\lambda_s \mu_\omega} \\ \dfrac{\partial f_3}{\partial L} = -\dfrac{(\lambda_s^2 - \lambda_c^2)\varpi \mu_h e^{-\mu_h L}}{\lambda_s \mu_\omega}. \end{cases}$$

All other partial derivatives, being so extensive, were omitted.