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Acquired Immunity of a Schistosomiasis Transmission Model—Analysis of the Stabilizing Effects

HYUN MO YANG*† AND FRANCISCO ANTONIO BEZERRA COUTINHO‡

*IMECC—Depart. Mat. Aplicada, Universidade Estadual de Campinas, Caixa Postal 6065, CEP 13081-970 Campinas, SP, Brasil and
‡USP-M, DIM, Av. Dr. Arnaldo, 455, SP, Brasil

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A semi-stochastic model for schistosomiasis was developed based on the immune response built up by human host after elapsing a fixed period of time L from the first infection, and on the parasite infection with multiple occurrences.

Both acquired immunity and multiple parasite infections reproduced a great endemic stability for the disease and a high value for the *basic reproduction ratio*.

1. Introduction

In a previous paper (Yang *et al.*, 1997), we developed a semi-stochastic model taking into account the acquired immunity and the multiple entrance of cercaria per infective event. When the model is fitted to the data, it matches the age prevalence data well but can only capture the general trends for the egg output and dispersion of this output.

However, we would like to stress that the goodness of fit by itself should not be considered sufficient for accessing to model adequacy. For instance, the model by Holford & Hardy (1976), which encompasses the age-dependent frequency contact with infested water, fits the prevalence extremely well with four parameters, but it fails in two aspects: to explain the observed strong stability, as in May's model (see below), and underestimates more than May's model the *basic reproduction ratio* (Yang, 1985). Holford & Hardy explained the descendent phase of the prevalence curve due to the reduction in the water contact rate with age (Chandiwana & Woolhouse, 1991; Dalton & Pole, 1978). This is not entirely supported by experimental evidence (Barbour, 1985; Wilkins, 1977). The latter work compared the egg outputs by males and females and found essentially no difference, although the two groups have different water contact rates. Therefore, the model should explain the observed stability of the steady state.

First, we transport the following steady-state findings from Yang *et al.* (1997). The forces of infection λ_s and λ_c for the non-immune and immune individuals, respectively, were assumed to be related by

$$\lambda_c = f(\zeta)\lambda_s, \tag{1}$$

where ζ is the time interval counted from the first infection and $f(\zeta)$ represents the effect of

†Author to whom correspondence should be addressed. E-mail: hyunyang@ime.unicamp.br

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immunity and for the purposes of this paper we consider

$$f(\zeta) = \begin{cases} 1; & \text{for } 0 \leqslant \zeta < L \\ f < 1 & \text{for } \zeta \geqslant L. \end{cases} \tag{2}$$

The other result is the average number of adult worms per person in a community m, given by

$$\overline{m} = \overline{\omega}\left[\frac{\lambda_s}{\mu_w + \mu_h} - \left(1 - \frac{\lambda_c}{\lambda_s}\right) \times \frac{\lambda_s^2 \mathrm{e}^{-\mu_h L}}{(\lambda_s + \mu_h)(\mu_w + \mu_h)}\right), \tag{3}$$

where μ_w and μ_h are, respectively, the harbored worm by host and the human host mortality rates, L is the time period elapsed to build up the immunity, and $\overline{\omega}$ is the average parasite entrance per infective event.

Equation (3) for the average number of worms per person in a community itself is not a complete schistosomiasis model. In fact, λ_s and λ_c are unrelated up to this moment to the snail population. Hence, we need the proportion of snails that are infected and shedding cercaria to close the vital cycle, and then, to perform the analysis of the stability of the steady state. In order to do this we shall use May's model (May, 1977) for the snail population. Briefly, May's model treats deterministically a constant size snail population and considers that the snails begin to release cercaria (shedding snails) after a period of time τ from the first infection (called latent snails, those already infected but not releasing cercaria yet) (Sturrock & Webbe, 1971).

In this paper we address the problem: is acquired immunity capable of explaining the stability of the steady state? We conclude that we can improve on this with our model.

2. Epidemiological Implications of Acquired Immunity

In this section we analyse the main epidemiological implications of the acquired immunity on a schistosomiasis transmission model. As we shall see, a model without immunity is almost incapable of explaining the stability of the disease, a point already stressed by Barbour (1978, 1982). To perform the stability analysis, we use the result of May's model (May, 1977) for snails. From this model, the proportion of shedding snails, $\bar{z}$, in equilibrium, is given by

$$\bar{z} = \left(\frac{\mu_s''}{a_s \mathrm{e}^{-\mu_s' \tau}} + \frac{1}{z^*}\right)^{-1}, \tag{4}$$

where a_s is the snail transmission rate, μ_s' is the mortality rate of latent snails, μ_s'' is the mortality rate of the shedding snails, i.e. the infected snails (latents) that had survived the incubation period τ and are eliminating cercaria, and z^* is the maximum attainable value for the proportion of shedding snails which is

$$z^* = \frac{\mathrm{e}^{-\mu_s' \tau}}{\dfrac{\mu_s''}{\mu_s'} - \left(\dfrac{\mu_s''}{\mu_s'} - 1\right)\mathrm{e}^{-\mu_s' \tau}}. \tag{5}$$

May's model is a modification of Macdonald's (1965) model encompassing the above differential mortality rates and the incubation period τ.

The average number of adult worms per person in a community, eqn (3), and the average proportion of shedding snails, eqn (4), give the stationary scenario of the epidemic. It is usual to express these average values in terms of two dimensionless transmission parameters T_1 and T_2 (Bradley & May, 1978) and the *basic reproduction ratio* R_0. The latter can also be expressed in terms of T_1 and T_2. For completeness we define the two dimensionless transmission parameters T_1 and T_2, which were used by Nåsell & Hirsch (1973) and May (1977).

The parameter T_1 is the overall transmission from human to snail which encompasses all the probabilistic events occurring in the environment. It is given by

$$T_1 = \frac{\frac{1}{2}\eta_E P_1 N_h}{\mu_s''} \tag{6}$$

where η_E is the number of eggs shed by each couple of schistosomes per unit of time; P_1 is the probability of a released egg to develop to

miracidia and to infect a snail and N_h is the total population of human host. As we are not concerned about the mating between male and female worms, given by mating function $\phi(\overline{m})$ (May, 1977), for this reason we set a half for the probability of mating when there is $\overline{m}$ average adult worms per person. This constant mating function also describes hermaphroditic helminthiasis modelling (Nåsell, 1985).

The second parameter T_2 is the overall transmission from snail to human which encompasses all the probabilistic events occurring in the environment. It is given by

$$T_2 = \frac{\eta_C P_2 N_s}{\mu_w} \tag{7}$$

where η_C is the number of cercaria released by an infected snail per unit of time; P_2 is the probability of a cercariae to infect a human host and N_s is the total population of snails.

Therefore, the stationary picture can be seen in terms of the transmission parameters T_1 and T_2. Hence, the parasite transmission rate among non-immune individuals (λ_s), the parasite transmission rate among immune individuals (λ_c) and the snail transmission rate (a_s) must be defined in terms of these parameters. The snail transmission rate can be defined as

$$a_s = \mu_s'' \overline{m} T_1 \tag{8}$$

and the parasite transmission rate among non-immune individuals as

$$\lambda_s = (\mu_w + \mu_h)\, \bar{z} T_2 \tag{9}$$

Both rates are dependent on the environment through T_1 and T_2. The two transmission rates come from the migration rates in the stochastic model by Nåsell & Hirsch (1973) set to be proportional to the expected values of shedding snails and mated worms. Finally, the parasite transmission rate among immune individuals will be defined separately according to our assumptions regarding to it (obviously λ_s is always dependent on the environment):

(1) λ_c is dependent on the environment, that is, it is proportional to both the proportion of shedding snails and the dimensionless transmission parameters (Subsection 2.1);

(2) λ_c is independent on the environment, but is determined only by immunity, that is, it is not proportional to both the proportion of shedding snails and the dimensionless transmission parameters (Subsection 2.2).

Next, we analyse the stability of the epidemiological parameters to the variations of T_1 and T_2, which are expected to vary widely from region to region. We show that a much greater variation in T_1 and T_2 is allowed in a model with acquired immunity than in Macdonald's and May's models.

Let us first consider a model without immunity (May, 1977), that is, we present the May's model findings. From the average number of adult worms per person given by May's model ($\overline{m} = \lambda_s/\mu_w$) and from eqn (4), using the definitions (8) and (9), we can rewrite the proportion of shedding snails as

$$\bar{z}(R_0) = z^* \left(1 - \frac{1}{R_0}\right), \tag{10}$$

where R_0 is the *basic reproduction ratio*,

$$R_0 = \mathrm{e}^{-\mu_s' \tau} T_1 T_2, \tag{11}$$

and T_1 and T_2 are the two dimensionless transmission parameters, which were defined above.

In our model, the average number of adult worms per person is given by (3) and the proportion of shedding snails is given by (4) as May's model. Using definitions (8) for the snail transmission rate and (9) for the parasite transmission rate among non-immune individuals, we can rewrite the average number of adult worms per person and the proportion of shedding snails at equilibrium in terms of one of the transmission parameters, say T_2, and of the *reproduction ratio* R. Since the parasite transmission rate among immune individuals λ_c will be defined in following subsections according to cases (1) and (2) above, meanwhile we can express $\overline{m}$ and $\bar{z}$ as functions of generic parameters M_1 and M_2 related to the expressions

concerned to λ_c. Hence, after some algebraic manipulations, we obtained

$$\overline{m}(R,T_2) = \frac{\overline{\omega} M_2 T_2 z^*}{2(\delta + T_2 z^*)} \left\{ T_2 z^* \left(\frac{M_1}{M_2} - \frac{1}{\delta R} \right) - \left(\frac{2}{R} - 1 \right) + \sqrt{\left[T_2 z^* \left(\frac{M_1}{M_2} - \frac{1}{\delta R} \right) - \left(\frac{2}{R} - 1 \right) \right]^2 + 4 \frac{\delta + T_2 z^*}{\delta R} \left(1 - \frac{1}{R} \right)} \right\} \tag{12}$$

and

$$\bar{z}\,(R,T_2) = \left(2 \frac{M_1}{M_2} T_2 \right)^{-1} \left\{ T_2 z^* \left(\frac{M_1}{M_2} - \frac{1}{\delta R} \right) - 1 + \sqrt{\left[T_2 z^* \left(\frac{M_1}{M_2} - 1 \delta R \right) - 1 \right]^2 + 4 \frac{M_1 T_2 z^*}{M_2} \left(1 - \frac{1}{R} \right)} \right\} \tag{13}$$

where the *reproduction ratio* R is

$$R = \overline{\omega} \mathrm{e}^{-\mu_s' \tau} \frac{M_2}{\delta} T_1 T_2 \tag{14}$$

and the relative life expectancy between worms and humans is

$$\delta = \frac{L_w}{L_h} \tag{15}$$

with the life expectancy of humans and worms being $L_h = (\mu_h)^{-1}$ and $L_w = (\mu_w + \mu_h)^{-1}$, respectively.

2.1. MODEL 1: λ_c DEPENDS ON THE ENVIRONMENT

In this case, we set the parasite transmission rate among immune individuals, substituting $f(\zeta)$ in eqn (1) by β, as

$$\lambda_c = \beta \lambda_s \tag{16}$$

with, of course, $0 \leqslant \beta < 1$. As λ_s depends on the environment, then the relation (16) reflects the fact that the environment also affects the transmission of parasite among individuals who had built up the immune response.

When λ_c depends on the environment, the expressions M_1 and M_2 take the forms

$$M_1 = 1 - (1 - \beta)\, \mathrm{e}^{-\mu_h L} \tag{17}$$

and

$$M_2 = \delta \tag{18}$$

whereas R is here defined as the *basic reproduction ratio* R_0 as (from $M_2 = \delta$)

$$R_0 = \overline{\omega} \mathrm{e}^{-\mu_s' \tau} T_1 T_2 \tag{19}$$

This value of R_0 is identical to that obtained in May's model, eqn (11), when multiple entries of cercaria are allowed. This result is in agreement with Anderson & May's (1991) statement that immunity does not affect R_0.

Let us observe now how this model fits to the field data. From data described by Sturrock, for *Biomphalaria glabrata* (1972) and for *Bulinus* (*Physopsis*) *nasutus productus* (1967) snails, using $\mu_s' = 10.8$ years^{-1}, $\mu_s'' = 21.6$ years^{-1} and $\tau = 0.083$ years, we first estimate the snail transmission rate. The result was $a_s = 0.921$ years^{-1} (Yang, 1990). Those values of μ_s', μ_s'' and τ will be applied to fit the model to epidemiological data from Touros region (*Biomphalaria glabrata*) and from Misungwi region (*Bulinus truncatus*). The resulted estimation of z^* is about 0.25 for both regions. The steady-state value for z was arbitrarily set at 0.1.

By doing this, the results of the model with λ_c depending on the environment show clear advantages over the model by May (1977): this can be seen observing the stability region, dependent on the two dimensionless transmission parameters, obtained from eqns (12) and (13) with relations (17), (18) and (19). In Fig. 1, we illustrate some of our findings.

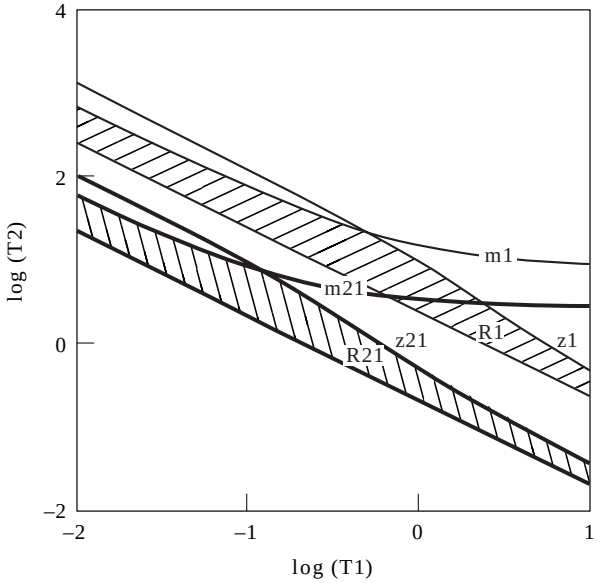

FIG. 1. Stability region for the model 1: λ_c depends on the environment, for $r = 1$ (thin curves, with region demarcated by ///) and 21 (thick curves, with region demarcated by \).

The figure shows two sets of curves for $\overline{m}$ [from Table II of Yang *et al.* (1997)], $\bar{z} = 0.1$, and the thresholds ($R_0 = 1$, which we took, for practical purposes, as the threshold; see, however, Nåsell, 1993 for stochastic threshold values). The $\overline{m}$-curves correspond to the best fit for the average number of adult worms per person $\overline{m} = 0.819$ and 3.327, for Misungwi region, for $r = 1$ and 21, respectively. The point at which the curve m_r crosses the curve z_r represents the values of T_1 and T_2 at which the model shows best fit to the data. The region bounded by the intersection among m_r, z_r and R_r curves represents how much T_1 and T_2 can vary before reaching the threshold lines R_r. In Fig. 2 we illustrated the same set of curves for the model by May.

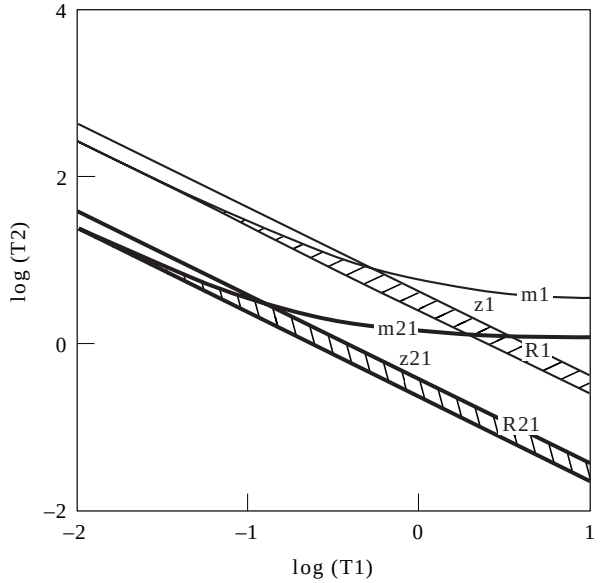

FIG. 2. Stability region for the model proposed by May, for $r = 1$ (thin curves, with region demarcated by ///) and 21 (thick curves, with region demarcated by \).

Although R_0 is not affected by acquired immunity, the range of T_1 and T_2, for which the existence of disease is possible, is greatly enlarged.

From Figs 1 and 2, we can observe that the influence of multiple entrance is to increase the region of the parameters T_1 and T_2 where the disease can exist, since the threshold lines move to the origin of the axis with increasing r. As noted before, the *basic reproduction ratio* is not influenced by immunity in this model. On the other hand, for values of T_1 lower than 1, we observe that acquired immunity influences strongly the stability of the disease and the range of variation in T_2 is greatly enlarged in this model, as compared with May's. This is a highly desirable feature in models dealing with schistosomiasis because, in fact, T_1 and T_2 are expected to vary greatly from region to region in an uncorrelated fashion for the same epidemiological pattern.

2.2. MODEL 2: λ_c DOES NOT DEPEND ON THE ENVIRONMENT

In this case the relation (1) is not obeyed, and β' is a bounded constant that does not dependent on $\bar{z}$ and T_2. Here we set the parasite transmission rate among immune individuals as

$$\lambda_c = (\mu_w + \mu_h)\,\beta' \tag{20}$$

where the new parameter β',

$$0 \leqslant \beta' \leqslant \beta'_{max},$$

could be chosen as a function of the time period elapsed to build up the immunity and the number of parasite entrance per infective event, or as a constant to be fitted to data, and the supremum of transmission rate among immune individuals obeys

$$\lim_{\beta' \longrightarrow \beta'_{\max}} \lambda_c = \lambda_s. \tag{21}$$

Note that if $\lambda_s = 0$, both $\overline{m}$ and $\overline{z}$ are zero even when $\lambda_c \neq 0$. The significance of this will be discussed later.

When λ_c does not depend on the environment, the expressions M_1 and M_2 take the forms

$$M_1 = 1 - e^{-\mu_h L} \tag{22}$$

and

$$M_2 = \delta + \beta' e^{-\mu_h L}, \tag{23}$$

whereas R is here defined as the *net reproduction ratio* R^* as

$$R^* = \overline{\omega} e^{-\mu_s' \tau}(1 + \varphi) T_1 T_2, \tag{24}$$

where φ is the immunity contribution to the *net reproduction ratio* given by

$$\varphi = \frac{\beta' e^{-\mu_h L}}{\delta}. \tag{25}$$

This value of R^* is different from that obtained in the May's model even if considering multiple entries of cercaria. Equation (24) demonstrates how acquired immunity affects the *reproduction ratio* for schistosomiasis. The expression for R^* is a composition of the environment (R_0) and the acquired immunity (R_{im}) contributions. It is better seen from the particular form that the expression M_2 takes for the two models, (18) for model 1 and (23) for model 2: both expressions depend on the relative life expectancy of the parasites and the humans, while the latter also depends on the immunity parameters.

The definition for the *basic reproduction ratio* is the average number of female offspring produced throughout the lifetime of a mature female parasite, which themselves achieve reproductive maturity in the absence of density-dependent constraints (Anderson & May, 1991). Based on this definition, model 1 produces the very well understood *basic reproduction ratio*. But in model 2 we have dependencies on the immunity parameters and, therefore, we called it *as net reproduction ratio* ($R^* = R_0 + R_{im}$). In the absence of immunity, the average number of female offspring during L_w appears in the *basic reproduction ratio* R_0. But, when the immunity is built up, it implies decreasing in the average number of adult worms and, hence, the egg production is increased by the density-dependent

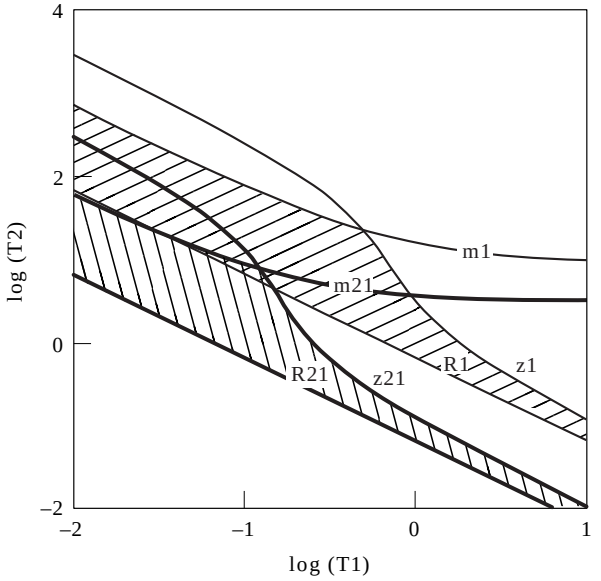

FIG. 3. Stability region for the model 2: λ_c does not depend on the environment, for $r = 1$ (thin curves, with region demarcated by ///) and 21 (thick curves, with region demarcated by \).

constraints, which appears in the *immunity constrained reproduction ratio* R_{im}.

In model 1 the two parasite transmission rates (λ_s and λ_c) are affected by the environment due to T_2. So the overall disease transmission is affected only by the environment. But in model 2 only one of the transmission rates (λ_s) is dependent on T_2 and the other (λ_c) is independent of this transmission parameter but dependent only on the immunity parameters. Then the overall disease transmission is controlled by both the environment and the human acquired immunity.

The fitting to the data was performed as before. The values of β' obtained from both studied areas are very similar (Yang *et al*., 1997). This is probably due to the fact that both areas are highly endemic, so β' is close to β'_{max}.

By doing this the results of the model with λ_c independent of the environment show clear advantages over our first model (model 1) in which immunity is considered to depend also on the environment: now, R^* resulted in values (see *Discussion*) much higher than those resulting from May's model for any set of T_1 and T_2. This is in sharp contrast with the previous model of immunity, and in disagreement with Anderson & May (1991). Furthermore, the range of T_1 and

T_2, for which the existence of disease is possible, is even more enlarged. This can be seen from eqns (12) and (13) with relations (22), (23) and (24). Figure 3 illustrates some of our findings.

Figure 3 shows two sets of curves for $\overline{m}$ [from Table II of Yang *et al*. (1997)], $\bar{z} = 0.1$ and the threshold, calculated by setting $R^* = 1$. The $\overline{m}$-curves correspond to the best fit for the average number of adult worms per person, for Misungwi region, for $r = 1$ and 21. The point at which the curve m_r crosses the curve z_r represents the values of T_1 and T_2 which the model fits best to the data. The region represents how much T_1 and T_2 can vary before reaching the threshold lines R_r. We have set arbitrarily $\bar{z} = 0.1$. Nevertheless, if we set the proportion of shedding snails at lower (higher) than the fixed value, then the upper frontier of stability region moves inward (outward) to the origin of the axis, diminishing (increasing) the region.

From Fig. 3 we can note that the multiple entrance influences are the same as the findings of model 1, except that the *net reproduction ratio* is influenced by immunity. However, one should note that, from relations (9) and (20), it is

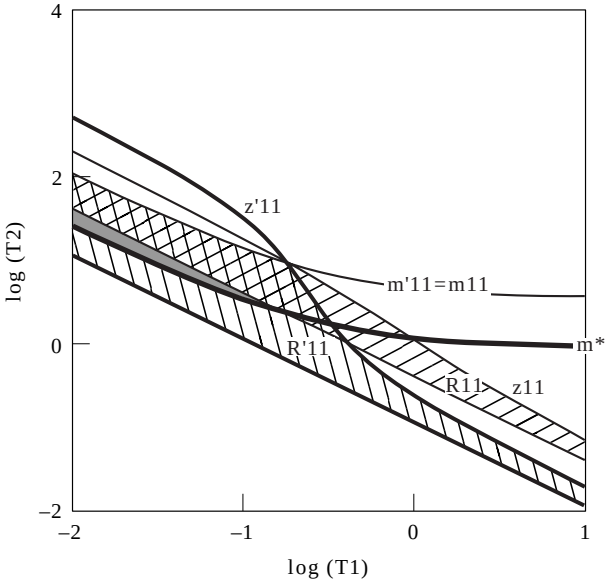

FIG. 4. Stability region for the two models: λ_c depends on the environment (thin curves, with region demarcated by ///) and λ_c (′) does not depend on the environment (thick curves, with region demarcated by \), for $r = 11$. When $m = m^*(\lambda_s = \lambda_c)$, the two models have the same curve. The area (filled region) between m^* and R_{11} curves is a small enlargement of disease possible region of model 2 in relation to model 1 for low values of T_1.

generated a curve, m^* (shown in Fig. 4), on which $\lambda_s = \lambda_c$ (21), and below which $\lambda_s < \lambda_c$. The point at which the curve $m_{11}(= m'_{11})$ crosses the curve z_{11} (or z'_{11}) represents the values of T_1 and T_2 which the model fits best to the data. The region represents how much T_1 and T_2 can vary before reaching the threshold lines R_{11} (or R'_{11}). The assumption of the independence (dependence) of λ_c on the environments is represented by primed (unprimed) legend.

From this figure we note that the region of stability for the case where λ_c is independent on the environment is larger than the case where λ_c is dependent on the environment. However, most of these points are below the curve m^* (when $\lambda_s = \lambda_c$) and, therefore $\lambda_s < \lambda_c$. This is clearly not a physical phenomenon. In spite of this, it can be noted from the figure that there is a small increase in the physical region of stability for the situation which λ_c does not depend on the environment (filled area). Moreover, if we set β' as a constant, then μ_w, L and r could be fitted again in order to avoid this problem. It shows that the stability region is not well defined, but movable, depending on the level of immunity. Alternatively, we could set β' as a function of r and L. By doing so the curve, on which $\lambda_s = \lambda_c$, is shown in Fig. 4, and it can be pushed down and made almost parallel to the line $R'_{11} = 1$.

On the other hand, for values of T_1 lower than 1, model 2 shows an even more remarkable difference when compared with May's and our model 1. The overall disease transmission is much more influenced by immunity and the range of the variation of T_2 is even more enlarged even if we take into account that values below the curve on which $\lambda_s = \lambda_c$ result in a non-physical situation (as shown in Fig. 4). Otherwise, for values of T_1 higher than 1, the three models apparently display the same behavior, that is, the disease is regulated in the snail population and immunity does not influence the stability. It should be noted that the threshold lines are lowered in relation to May's and our model 1.

3. Discussion

We developed a semi-stochastic model to understand the transmission of schistosomiasis

in highly endemic areas. One of the main points of our model is the role of human acquired immunity in explaining the remarkable stability of the disease. When T_1 is higher than 1 (T_2 is lower than 10) May's model, and our models 1 and 2 have the same stability, but when T_1 is lower than 1 (T_2 is higher than 10) May's model and our models 1 and 2 display quite different behavior.

In fact regions where the environment is not favorable for the surviving and mobility of miracidia to find and infect intermediate host, we have low values for the overall transmission from human to snail (T_1). The disease can be maintained if this hostile inhabitat is overcome by an increase in egg output. This is possible by an increase in the overall transmission from snail to human (T_2). As a consequence, the mean worm burden of the community increases. In the absence of immunity in the human host, we must have hyper-infection to maintain the disease. But, if the human host mounts an acquired immunity, which regulates the transmission of schistosomiasis, we do not need to have this hyper-infection (models 1 and 2). The hyper-infection is avoided because the acquired immunity both protects the human host from further cercaria invasions avoiding the high worm burden in the community, and over-disperses the worm harbored by this community [see Table II in Yang *et al*. (1997)] explaining why there is a core of individuals who have a heavy worm charge whilst the population as a whole has a low worm burden. The latter consideration makes reasonable our approximation of half value to the mating function introduced by May (1977). Conversely, when T_1 has high values (favorable environment), the acquired immunity does not matter because in this region the human host is exposed to low values of T_2 and the population has low worm burden.

Both acquired immunity models 1 and 2 present the same values for the mean worm burden and dispersion as a function of the fitted model's parameters. However, the picture is different when the stability of the disease is analysed. When the relation (1) is obeyed (model 1), the acquired immunity would enlarge the stability region but the environment dependence in the transmission of schistosomiasis prevents this enlargement of the stability region. On the other hand, when (1) is not obeyed (model 2), then in the immune individuals only the acquired immunity influences the transmission of schistosomiasis, and the stability region is enlarged. Consequently a model with acquired immunity has the transmission of schistosomiasis better regulated than a model where only environment regulates the transmission. When T_2 has low values (the overall transmission from snail to human is not favorable) the model 1 is better than the model 2. The reason is due to the low force of infection (contact with parasite) and there is not full build up of the immunity, hence this community, with only partially effective acquired immunity, suffers the influence of the environment to regulate the disease. Conversely, when the cercariae has high efficiency to search and penetrate the human host (high values of T_2), the acquired immunity is well established and further invasion of cercaria in humans is controlled exclusively by this immunity mechanism.

The other main factor that affects the stability region is the multiple entrance of parasites in each contact with infested water. The stability region, with width practically unchanged, is shifted downwardly increasing the region where the disease can exit, when the multiple entrance parameter is increased. The multiple entrance of parasites allows much lower values for the transmission parameters T_1 and T_2, thus increasing the stability region as described above. The

TABLE 1

The basic (*May's model and model* 1) *and* net (*model* 2) reproduction ratios *for Touros, Brazil and region of Misungwi, Tanzania*

	May's Model & Model 1	Model 2	
r	Touros & Misungwi	Touros	Misungwi
1	1.199	4.672	4.469
4	2.997	11.014	10.593
8	5.394	20.976	19.157
11	7.193	28.466	25.780
16	10.189	40.431	36.296
21	13.186	50.721	46.329
31	19.180	78.760	70.883
35	21.578	84.820	78.231

multiple entrance also over-disperses the harboring of parasites in the community.

Finally, we analysed the effect of acquired immunity and the multiple entrance of parasites on the *basic* (*net*) *reproduction ratio*. The two overall transmission parameters were arbitrarily set from Figs 1, 2 and 3 as $T_1 \sim 0.6$ and $T_2 \sim 12$, and assumed equal for both regions, Touros (Brazil) and Misungwi (Tanzania). These overall transmission parameters provide the *basic reproduction ratio* for May's model (single cercariae penetration per contact with infested water), $R_0 = 1.199$, which is lower than that predicted by Macdonald's (1965) model, $R_0 = 7.2$. In Table 1 we show the *basic reproduction ratio* for the modified May's model and our model 1, given by eqn (19), and *net reproduction ratio* for our model 2, given by eqn (24).

We observe that May's model and our model 1 have the same value for the *basic reproduction ratio*, which increases with increasing of the maximum number of parasite entrance per infective contact. This is a consequence of the fact that in both models the transmission is regulated by environmental factors. The *basic reproduction ratio* is higher than that predicted by Macdonald's model only for $r > 11$. Our model 2 with acquired immunity also controlling the transmission presents much higher values than model 1 for the *net reproduction ratio* and differs for both regions. In the region of Touros the *net reproduction ratio* is slightly higher than in Misungwi region. In the former we have *S. mansoni* and for the latter, *S. haematobium*. The *net reproduction ratio* is higher than that predicted by Macdonald's model for $r > 2$. Table 1 shows that the *immunity constrained reproduction ratio* (R_{im}) increases faster than the *basic reproduction ratio* (R_0) when the maximum number of invading viable cercaria (r) increases. Hence, both acquired immunity and the multiple entrance of parasites in each infective event have to be considered in efforts towards controlling the disease (Jordan, 1969; Warren, 1973).

We summarize our findings in three points.

(1) For values of T_1 higher than 1, the stability regions for all the three models are similar, but for values of T_1 lower than 1 the model 2 showed the stability region greatly enlarged. The model by May and our model 1 have well defined and fixed stability region. However, our model 2 presents a flexible stability region which implies an extra source of difficulty to control the disease.

(2) The effect of allowing multiple parasite entering although does not influence the estimation of the prevalence curve parameters, it acts strongly on the *basic* (*net*) *reproduction ratio* and on the stability region. In our model we did not explore totally this heterogeneity when we fixed the form of the distribution of the number of worms allowed to enter the host in each contagious event. The number of invading cercaria can be assumed to be a constant value or any form of distribution probability (we used a binomial distribution). In fact, Barbour & Kafetzaki (1993) assumed that when a host is exposed to infection then he (or she) acquires a number of parasites which has a Poisson distribution. This assumption is sufficient to obtain the over-dispersion of the worms in the host.

(3) The incorporation of the acquired immunity to schistosomiasis transmission modelling improved in the problems of fitting model's parameters (Yang *et al*., 1997), of explaining the stability of the disease and of controlling the disease. But, models without immunity fail to give a satisfactory answer to the above questions. For instance, the model developed by Holford & Hardy (1976) comprising the age structured frequency of contact with infested water (age-dependent exposure model) fits very well the prevalence curve, but their model predicts quite the same small stability region as the model by May and underestimates *basic reproduction ratio* (Yang, 1985).

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REFERENCES

Anderson, R. M. & May, R. M. (1991). *Infectious Diseases of Human. Dynamics and Control*. Oxford: Oxford University Press.

Barbour, A. D. (1978). A stochastic model for the transmission of bilharzia. *Math. Biosci*. **38,** 303–312.

BARBOUR, A. D. (1982). Schistosomiasis. In: *Population Dynamics of Infectious Diseases* (Anderson, R. M., ed.). London: Chapman & Hall.

BARBOUR, A. D. (1985). The importance of age and water contact patterns in relation to *Schistosoma haematobium* infection. *Trans. R. Soc. Trop. Med. Hyg.* **79,** 152–153.

BARBOUR, A. D. & KAFETZAKI, M. (1993). A host–parasite model yielding heterogeneous parasite load. *J. Math. Biol.* **31,** 157–176.

BRADLEY, D. J. & MAY, R. M. (1978). Consequences of helminth Aggregation for The Dynamics of Schistosomiasis. *Trans. R. Soc. Trop. Med. Hyg.* **72**(3), 262–273.

CHANDIWANA, S. K. & WOOLHOUSE, M. E. (1991). Heterogeneities in water contact pattern and the epidemiology of *Schistosoma haematobium*. *Parasitology* **103,** 363–370.

DALTON, P. R. & POLE, D. (1978). Water contact patterns in relation to *Schistosoma haematobium* infection. *Bull. WHO* **56,** 417–426.

HOLFORD, T. R. & HARDY, R. J. (1976). A stochastic model for the analysis of age-specific prevalence curves in schistosomiasis. *J. Chron. Dis.* **29,** 445–458.

JORDAN, P. (1969). Schistosomiasis: research to control. *Am. J. Trop. Med. Hyg.* **26,** 877–886.

MAY, R. M. (1977). Togetherness amongst schistosome: its effects on the dynamics of the infection. *Math. Biosci.* **35,** 301–343.

MACDONALD, G. (1965). The dynamics of helminth infections, with special reference to schistosomes. *Trans. R. Soc. Trop. Med. Hyg.* **5,** 489–506.

NÅSELL, I. & HIRSCH, W. M. (1973). The transmission dynamics of schistosomiasis. *Comm. Pr. Appl. Math.* **26,** 395–453.

NÅSELL, I. (1985). Hybrid models of tropical infections. In: *Springer Verlag Lecture Notes in Biomathematics* **59**. Berlin: Springer.

NÅSELL, I. (1993). The threshold concept in deterministic and stochastic models (pre-print).

STURROCK, B. M. (1967). The effects of infection with *Schistosoma haematobium* on the growth and reproduction rates of *Bullinus* (*physopsis*) *nasutus productus*. *Ann. Trop. Med. Para.* **61,** 321–325.

STURROCK, R. F. & WEBBE, G. (1971). The application of catalytic models to schistosomiasis in snails. *J. Helmintol.* **45,** 189–200.

STURROCK, R. F. (1972). Field studies on the transmission of *Schistosoma mansoni* and on the bionomics of its intermediate host *Biomphalaria glabrata* on Santa Lucia, West Indies. *Int. J. Para.* **3,** 175–194.

WARREN, K. S. (1973). Regulation of prevalence and intensity of schistosomiasis in man: immunology or ecology? *J. Infect. Dis.* **127,** 595–609.

WILKINS, H. A. (1977). *Schistosoma haematobium* in a Gambiam community—I: The intensity and prevalence of infection. *Ann. Trop. Med. Parasitol.* **71,** 53–58.

YANG, H. M. (1985). Esquistossomíase: modelo matemático incorporando a imunidade concomitante (port.). Dissertation. Instituto de Física da USP.

YANG, H. M. (1990). Estudo Matemático do Mecanismo de Regulação da Esquistossomíase (port.). Doctoral Thesis. Instituto de Física da USP.

YANG, H. M., COUTINHO, F. A. B. & MASSAD, E. (1997). Acquired immunity on a schistosomiasis transmission model—fitting the data. *J. theor. Biol.* **188,** 495–506.