Estimation of some parameters governing the transmission dynamics of schistosomes from field and laboratory data

*Mathematics Department, Purdue University
**Biology Department, Purdue University

December 24, 2002

Abstract

The clumping parameter related to schistosomiasis is obtained by fitting a negative binomial distribution to data collected from a village in Brazil; the natural uninfected and parasite-induced snail host mortality rates are obtained from laboratory data. These values are used in a schistosomiasis model proposed earlier by the authors, and a disease transmission parameter from snails to humans is estimated. Then, the effect of chemotherapy of humans is assessed using prevalence of morbidity as a measure of the level of schistosome infection in a human population.

1 Introduction

Schistosomes are dioecious helminth parasites with indirect life cycles. Several species exist within the genus Schistosoma, and our study will focus on Schistosoma mansoni, which infects humans and Biomphalaria freshwater snails in South and Central America, the Caribbean, and Africa. It is estimated that about 200 million people are infected with schistosomes. Adults of this species occur as mated male and female worms within the hepatic portal vasculature of the human host. The female worms produce an average of about 300 eggs/day that are either excreted in the host’s feces or swept by the flow of blood to the host’s liver, where they can induce severe pathology. In the most extreme cases, this pathology includes debilitating enlargement of the liver and spleen, and eventually leads to liver failure. Those eggs that make it into a water body and survive develop into a stage called miracidium, that can then infect the intermediate host, Biomphalaria freshwater snail. Infected snails shed the next stage, called cercaria, that may infect humans who
bathe in infected waters by penetrating through the skin and going via the blood to establish themselves and mature into worms within the hepatic portal vasculature of the host.

In the absence of a vaccine, current control programs for schistosome infections have focused on chemotherapy, which reduces morbidity by killing adult worms and diminishing egg deposition. Praziquantel (PZQ) remains the drug of choice for the treatment of schistosomiasis, but recent epidemiological evidence suggests the emergence of PZQ-resistant schistosomes.

The spread and persistence of schistosomiasis has always been one of the more complex host-parasite processes to model mathematically, because of the several different forms that the parasites take while infecting two separate hosts (definitive human hosts and intermediate snail hosts) during their life cycle. For schistosome (and other helminth) parasites, the number of parasites infecting an individual vertebrate host (i.e., the intensity of the infection) plays an important role in determining the outcome of an infection. Thus, transmission rates, pathogenicity, and development of host immunity are all typically assumed to depend upon intensity.

2 Model and parameter estimation

In (Feng et al. 2002) the following mathematical model of schistosomiasis was described and analyzed:

\[
\frac{d}{dt}N = \Lambda_h - \mu_h N - \alpha P,
\]

\[
\frac{d}{dt}P = \beta C N - (\mu_h + \mu_p + \alpha + \sigma)P - \alpha \left( \frac{k + 1}{k} \right) \left( \frac{P^2}{N} \right),
\]

\[
\frac{d}{dt}S = \Lambda_s - \mu_s S - \xi PS,
\]

\[
\frac{\partial}{\partial t}x(t, \tau) + \frac{\partial}{\partial \tau}x(t, \tau) = - (\mu_s + d_s)x(t, \tau),
\]

\[
x(t, 0) = \xi PS, \quad x(0, \tau) = x_0(\tau), \quad C(t) = \int_0^\infty r(\tau)x(t, \tau)d\tau.
\]

where \( N, P, S, I, C \) denote the numbers of human hosts, adult parasite pairs, uninfected snails and infected snails, and free-living cercariae, respectively. The notation \( t \) denotes time, \( \tau \) denotes time since infection, i.e., infection-age, and \( x(t, \tau) \) denotes the infection-age density of snails at time \( t \). \( \Lambda_h \) is the recruitment rate of human hosts; \( \Lambda_s \) is the recruitment rate of snails; \( \mu_h \) is the per capita natural death rate of human hosts; \( \mu_p \) is
the per capita death rate of adult parasites; \( \mu_s \) is the per capita natural death rate of snails; \( \alpha \) is the disease-induced death rate of humans per parasite; \( d_s \) is the disease-induced death rate of snails; \( \xi \) is the per capita (successful) rate of infection of snails by miracidia produced by one adult parasite; \( \beta \) is the per capita (successful) rate of infection of humans by one cercaria; \( r(\tau) \) is the releasing rate of cercariae by one snail of infection-age \( \tau \); \( \sigma \) is the treatment rate of human hosts.

Parameters associated with infection of human hosts are quite difficult to estimate, mostly because of ethical constraints on the manipulation of human subjects. Some parameter values are described in Anderson and May (1979, 1985) and Woolhouse (1991, 1992). Nevertheless, 3-5 years is a widely accepted value for the life expectancy of adult worms (1/\( \mu_p \)), while parasite-induced mortality (pathogenicity) in the human host (\( \alpha \)) is considered to be very small. Based on the data shown in Theron (1981), we can choose \( r(\tau) \) to be periodic, the latent period, and having a maximum support. In addition, it is known that a mated pair of schistosomes is responsible for 200-300 eggs/day being excreted in the feces of an infected patient. Notice that the parameter \( \xi \) is a product of several factors including the number of eggs produced by one adult parasite, the probability that the eggs get into water and the probability of successfully infecting a susceptible snail. We assume that \( \xi=0.0004/\text{year} \) (per capita snail infection rate by one adult parasite), \( \mu_h=1/(70 \text{ years}) \), and \( \mu_p=1/(5 \text{ years}) \). Other parameters including \( \Lambda_h \) and \( \Lambda_s \) will be chosen for given populations. In this paper we will estimate four of the remaining parameters, \( k \), \( \beta \), \( d_s \), and \( \mu_s \) using the data and our model results.

Fig. 1(a) is the patient infection data from a Brazilian village (see figure 1 in Bethony et al. 2001). The original data is in the form of the numbers of schistosome eggs (in increments of 12) per gram of feces (EPG) for each patient. Based on the results in Gryseels and de Vlas (1996) that the ratio of eggs to parasite pairs is 1:1, Since the total number of individuals in the data set is \( N_d = 597 \) and the total number of units of parasites is 5659 (or the total number of parasites is \( P_d = 67908 \)), the mean parasite load \( m_d \) is 9.5 units (or 114 in number). Assuming a negative binomial distribution (NBD) for which the probability of human hosts carrying \( i \) units of parasites is equal to

\[
\frac{(k + i - 1)!}{i!(k - 1)!} \left( \frac{k}{m_d + k} \right)^k \left( \frac{m_d}{m_d + k} \right)^i,
\]

and using the least squares fit we obtain an estimated value of \( k = 0.243 \). Fig. 1(b) is a plot of the NBD with mean equal to \( m_d = 9.5 \) and \( k = 0.243 \), and Fig. 2 compares the least squares fit with the data.
The parasite-induced snail mortality $d_s$ is estimated from our laboratory data (shown in Figure 3, dotted plots). The experiment was conducted as follows: *Biomphalaria glabrata* snails were exposed to different numbers of *Schistosoma mansoni* miracidia to determine whether the number of miracidia infecting a snail influences host survival. Four different groups were evaluated: exposure to 1 miracidium, exposure to 5 miracidia, exposure to 10 miracidia, and a control group of unexposed snails. A total of 528 snails were exposed to 1 miracidium, while the 3 other groups initially had 96 snails each. This difference was to account for the low rate of infectivity for monomiracidial infections. Snails were shed beginning approximately at the thirtieth day to determine whether they were infected. As infected snails were found, they were separated from uninfected ones. Six weeks post-exposure all infected snails had been identified and separated, and the four groups kept under observation for the following 153 days consisted of 78, 50, 59, and 91 snails, respectively in the four groups mentioned above. At that point, only the mortality of infected snails was evaluated (except, of course, for the control group in which all snails were uninfected and unexposed). The number of live snails in each group was recorded every day until the last of the infected snails had died (on day 195). We show in Figure 3 the data for the first three groups (time $t$ shown in days after day 42 of the experiment) together with the least squares fit by an exponential curve $N_0 e^{-\left(\mu_s + d_s\right)t}$. We see an excellent fit for snails exposed to 10 miracidia, resulting in $\mu_s + d_s = 0.018$/day, that is a median life expectancy for that group of 55.5 days, or 0.1522 years. A slightly worse fit results from snails exposed to 5 miracidia, giving $\mu_s + d_s = 0.019$, that is a median life expectancy for that group of 52.6 days, or 0.1442 years. Finally, the negative exponential fit of the data from snails exposed to a single miracidium is even worse, and it results in $\mu_s + d_s = 0.022$, that is a median life expectancy for that group of 45.5 days, or 0.1245 years.

From the control group we are able to estimate $\mu_s$ by finding the least squares fit of the data by a negative exponential $N_0 e^{-\mu_s t}$. This results in $\mu_s = 0.00058$, that is a median life expectancy for unexposed snails of 1724 days, or 4.7 years. We show in Figure 4 the data and the least squares fit by a negative exponential for the unexposed snails, as well as for all 3 groups of exposed snails combined. The fitted value, 4.7 years, is not realistic as snails tend to live much longer under optimal laboratory. Adult life-expectancy for Biomphalaria in the field has been estimated to be on the order of 1-6 months, while laboratory estimater are on the order of several years (Appleton, 1974; Woolhouse, 1992). If we use the value $\mu_s=1/(2\text{ years})$ then we obtain a good estimate for $d_s$, $d_s=0.0180602$/day-$0.0013699$/day=$0.01669$/day.

To estimate the parameter $\beta$ (the per capita rate of infection of humans by one cercaria), we will use the analytical results obtained from the system (2). The parasite reproductive number can be calculated from this model as

$$R_0 = \left(\frac{\Lambda_s}{\mu_s (\mu_h + \mu_p + \alpha + \sigma)} \right) \left(\beta K \frac{A_h}{\mu_h}\right),$$

4
where
\[ K = \int_0^\infty r(\tau)e^{-(\mu_s + d_s)d\tau}. \]

The first factor represents the man-snail transmission coefficient (the number of snails infected by a schistosome during its average life-time, \(1/(\mu_h + \mu_p + \alpha + \sigma)\)) and the second factor represents the snail-man transmission coefficient (the number of schistosomes produced by an infected snail during its entire period of infection). It is shown in et al. (2002) that the system (2) has a stable parasite-free equilibrium when \(R_0 \leq 1\). When \(R_0 > 1\), and \(\alpha\) is sufficiently small (a biologically realistic assumption) the system has a stable endemic equilibrium at which the mean parasite load is given by
\[ m_s = \frac{P_s}{N_s} = \frac{\mu_s \mu_h}{\xi \Lambda_h} (R_0 - 1) + O(\alpha), \tag{1} \]
where \(O(\alpha)\) denotes terms that are very small if \(\alpha\) is very small. We can then use the formula (1) to estimate the parameter \(\beta\) by setting the mean \(m_s\) equal to \(m_d = 114\). Let \(\sigma = 0\) (i.e., there is no treatment). Choose the parameter values as specified above, and choose the function \(r(\tau)\) to be periodic of period 30 days, zero for 0 \(\leq \tau \leq 30\) days, and having a maximum support of 90 days. Then the equation, \(m_s = m_d\), produces an approximate value of \(\beta = 0.000027\).

### 3 Assessment of control programs

We now provide a simple assessment of the effect of control programs through drug treatment on the prevalence of morbidity, \(Q\), which is defined to be the proportion of individuals whose rate of egg output (or, equivalently, the number of parasites) exceeds a prescribed threshold value (see Cheever, 1977). Notice from (1) that \(m_s\) is a function of the treatment rate \(\sigma\). Let \(\sigma > 0\), \(k = 0.243\), \(\beta = 0.000027\), and all other parameters have values given before. The \(NBD(m_s, k)\) and hence the \(Q\) value will depend on \(\sigma\). Let the threshold number of parasites be \(i_0\). Then
\[ Q = \sum_{i > i_0} \frac{(k + i - 1)!}{i!(k - 1)!} \left( \frac{k}{m_s + k} \right)^k \left( \frac{m_s}{m_s + k} \right)^i. \]

Figure 5 is a plot of \(Q\) as a function of \(\sigma\) for \(i_0 = 12\).

From figure 5 we see that \(Q = 0.24\) when there is no treatment \((\sigma = 0)\), and that, in order for \(Q\) to be below 0.1, the treatment rate needs to satisfy \(\sigma \geq 0.23\).

We remark that, for demonstration purposes, the above discussion concerns only drug treatment of humans as a control strategy. We have also considered other control strategies involving other parameters such as the man-snail transmission rate \((\xi)\) and the snail-man
transmission coefficients ($\beta$ and $K$) (see Feng et al., 2002). Other control measures have also been discussed using simpler models without parasite distributions among human hosts and/or an age-structure in snail populations (see, for example, Anderson and May, 1985; Woolhouse, 1992).

4 Conclusions

We have shown how to obtain reliable estimates of four relevant parameters for the modeling of schistosomiasis dynamics from field and laboratory data.

First, we obtained an excellent fit by a negative binomial with mean $m_d = 114$ and clumping parameter $k = 0.0243$ for field data of parasite intensity for a population of $N_d = 597$ individuals and a total number of parasites $P_d = 67908$.

Next, we estimated from laboratory data the natural uninfected mortality and the parasite-induced mortality rates of snails, obtaining excellent fits for the total mortality when the snails were exposed to 10 miracidia. Snail mortality did not differ substantially as parasite levels increased.

Using these values, we were able to estimate the per capita rate of infection of humans by one cercaria from a theoretical relation between that parameter and the mean parasite load.

Finally, we incorporate these parameter values into our model to show explicitly the necessary treatment rates to keep the prevalence of morbidity below a certain threshold. Model results can provide valuable information for health care providers.
References


Figure 1: Data and theoretical distribution of parasites among human hosts.
Figure 2: Comparision of data and the least square fit of a negative binomial distribution to the data.

Figure 3: Data (dotted plots) of the number of snails surviving post exposure to (a) 1 miracidium, (b) 5 miracidia, and (c) 10 miracidia, and the least squares fits by negative exponentials \( N(t) = N_0e^{-(\mu_s + d_s)t} \) (solid curves). The estimated total snail mortality rates are (a) \( \mu_s + d_s = 0.022/\text{day} \), (b) \( \mu_s + d_s = 0.019/\text{day} \), (c) \( \mu_s + d_s = 0.018/\text{day} \), respectively.
Figure 4: Data of the number of snails surviving (a) unexposed to miracidia, and (b) post exposure to miracidia, and the least squares fits by negative exponentials (solid curves). The estimated snail mortality rates are (a) $\mu_s = 0.00042$, (b) $\mu_s + d_s = 0.02016$, respectively.

Figure 5: A plot of the prevalence of morbidity $Q$ vs. treatment rate $\sigma$ for $i_0 = 12$. 