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Applied Mathematics Letters 17 (2004) 1105–1112
Applied Mathematics Letters
www.elsevier.com/locate/aml

Estimation of Parameters Governing the Transmission Dynamics of Schistosomes

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(Received January 2003; revised and accepted February 2004)

Abstract—The clumping parameter related to the distribution of schistosome parasites is obtained by fitting a negative binomial distribution to data collected from patients in 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. Finally, 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.

Keywords—Parameter estimation, Mathematical model, Schistosomiasis, Control strategy.

1. INTRODUCTION

Schistosomes are dioecious, helminth parasites with indirect life cycles. Several species exist within the genus *Schistosoma*, but 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 worldwide are infected with schistosomes, and that infection results in a range of symptoms from chronic disease to death. 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 [1]. Praziquantel (PZQ) remains the drug of choice for the treatment of schistosomiasis, but recent epidemiological evidence suggests the emergence of PZQ-resistant schistosomes [2]. We have modeled the genetic

This research is partially supported by the NSF Grants DMS-9974389 and DMS-0314575.

0893-9659/04/$ - see front matter Typeset by $\mathcal{A}\mathcal{M}\mathcal{S}$-TEX
doi:10.1016//j.aml.2004.02.002

consequences of drug-resistant parasite strains in [3] and schistosomiasis control strategies via chemotherapy in [4].

The spread and persistence of schistosomiasis has always been one of the more complex host-parasite processes to model mathematically because of the different larval forms assumed by the parasite and the requirement of two 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. To incorporate this feature into models of schistosomiasis, a negative binomial distribution is usually assumed for the number of adult parasites within the human population [5]. The model we use to estimate the disease parameters in this paper takes into consideration many realistic features of the disease, including life history traits of both humans and snails serving as hosts in the life cycle.

2. MODEL AND PARAMETER ESTIMATION

The following mathematical model of schistosomiasis was described and analyzed in [4]:

$$\begin{aligned}
&\frac{d}{dt}N = \Lambda_h - \mu_h N - \alpha P,\\
&\frac{d}{dt}P = \beta C N - (\mu_h + \mu_p + \alpha + \sigma)P - \alpha\left(\frac{k+1}{k}\right)\left(\frac{P^2}{N}\right),\\
&\frac{d}{dt}S = \Lambda_s - \mu_s S - \xi P S,\\
&\qquad \frac{\partial}{\partial t}x(t,\tau) + \frac{\partial}{\partial \tau}x(t,\tau) = -(\mu_s + d_s)x(t,\tau),\\
&x(t,0) = \xi P S, \qquad x(0,\tau) = x_0(\tau), \qquad C(t) = \int_0^\infty r(\tau)x(t,\tau)\,d\tau.
\end{aligned} \tag{1}$$

Here, N, P, S, C denote the numbers of human hosts, adult parasite pairs, uninfected snails, and free-living cercariae, respectively. The notation t denotes time, τ denotes time since infection, i.e., infection-age, and $x(t,\tau)$ denotes the infection-age density of snails at time t. k is the clumping parameter which determines the degree of over-dispersion in the negative binomial distribution. Λ_h is the recruitment rate of human hosts; Λ_s is the recruitment rate of snails; μ_h is the per capita natural death rate of human hosts; μ_p is the per capita death rate of adult parasites; α is the disease-induced death rate of humans *per parasite*; σ is the effective treatment rate of human hosts; μ_s is the per capita natural death rate of snails; d_s is the disease-induced death rate of snails; ξ is the per capita (successful) rate of infection of snails by miracidia produced by one pair of adult parasites (which is defined in [4] as ρb_p, the product of number of miracidia produced by one pair of parasites and the per capita successful rate of infection of snails by one miracidium); β 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 τ, which is assumed to be periodic in time with a prepatent period after initial infection (see [6]). All the variables and parameters are listed in Table 1. Model (1) and the threshold conditions derived from this model provide means for estimating some of the disease parameters.

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 [5,7,8]. Nevertheless, 3–5 years is a widely accepted value for the life expectancy of adult worms ($1/\mu_p$), while parasite-induced mortality in the human host (α) is considered to be very small. Based on the data shown by Theron [6], we can choose $r(\tau)$ to be piecewise linear and periodic, zero for the prepatent period and for the time after the maximum age of releasing

Table 1. Definition of variables and parameters. The time unit is year.

Name	Description	Value
N	Numbers of human hosts	
P	Numbers of adult parasites	
S	Number of uninfected snails	
C	Number of free-living cercariae	
$x(t,\tau)$	Infection-age density of snails	
k_i	Clumping parameter	Estimated
Λ_h	Recruitment rate of humans	8
Λ_s	Recruitment rate of snails	25
μ_h	Per capita natural death rate of humans	0.014
μ_p	Per capita natural death rate of parasites	0.2
μ_s	Per capita natural death rate of snails	Estimated
α	Disease-induced death rate of humans *per parasite*	10^{-5}
d_s	Disease-induced death rate of snails	Estimated
σ	Effective treatment rate of humans	Discussed
ξ	Per capita (successful) rate of infection of snails	0.0004
β	Per capita (successful) rate of infection of humans	Estimated
$r(\tau)$	Cercariae releasing rate by one snail of infection-age τ	See Figure 3

cercariae. 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. Note that the parameter ξ is a product of several factors including the number of eggs produced by one pair of adult parasites, the probability that the eggs get into water and the probability of successfully infecting a susceptible snail. The first one is of the order of 10^5/year, but the second and third are certainly quite small, and values in the order of 10^{-5} to 10^{-4} might be realistic. We then assume that $\xi = 0.0004$/year (per capita snail infection rate by one pair of adult parasites), $\mu_h = 0.014$/year (the life expectancy of humans is assumed to be about 70 years), and $\mu_p = 0.2$/year (the life expectancy of parasites is assumed to be about five years). Other parameters will be chosen for given populations. For example, $\Lambda_h = 8$/year and $\Lambda_s = 25$/year. In this paper, we will estimate four of the remaining parameters, k, d_s, μ_s, and β using the data and our model results.

Figure 1 presents the patient infection data from a Brazilian village (see [9, Figure 1]). 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 [10], we assume 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 $9.5 \times 12 = 114$ in number). Let $\mathrm{NB}(m_d, k)$ denote the negative binomial distribution with mean $= m_d$ and the clumping parameter k of adult parasites within the human hosts. Then the probability of human hosts carrying i units of parasites is equal to

$$\frac{(k+i-1)!}{i!(k-1)!}\left(\frac{k}{m_d+k}\right)^k\left(\frac{m_d}{m_d+k}\right)^i.$$

Using the least squares fit, we obtain an estimated value of $k = 0.243$. The distribution $\mathrm{NB}(9.5, 0.243)$ is plotted in Figure 1 (dotted curve), which seems to provide a very good approximation to the data (the histogram bars).

The parasite-induced snail mortality d_s is estimated from our laboratory data (shown in Figure 2, dotted plots). The experiment was conducted for four different groups of snails according to the number of *Schistosoma mansoni* miracidia they were exposed to: exposure to 1 miracidium, exposure to 5 miracidia, exposure to 10 miracidia, and a control group of unexposed snails. Six

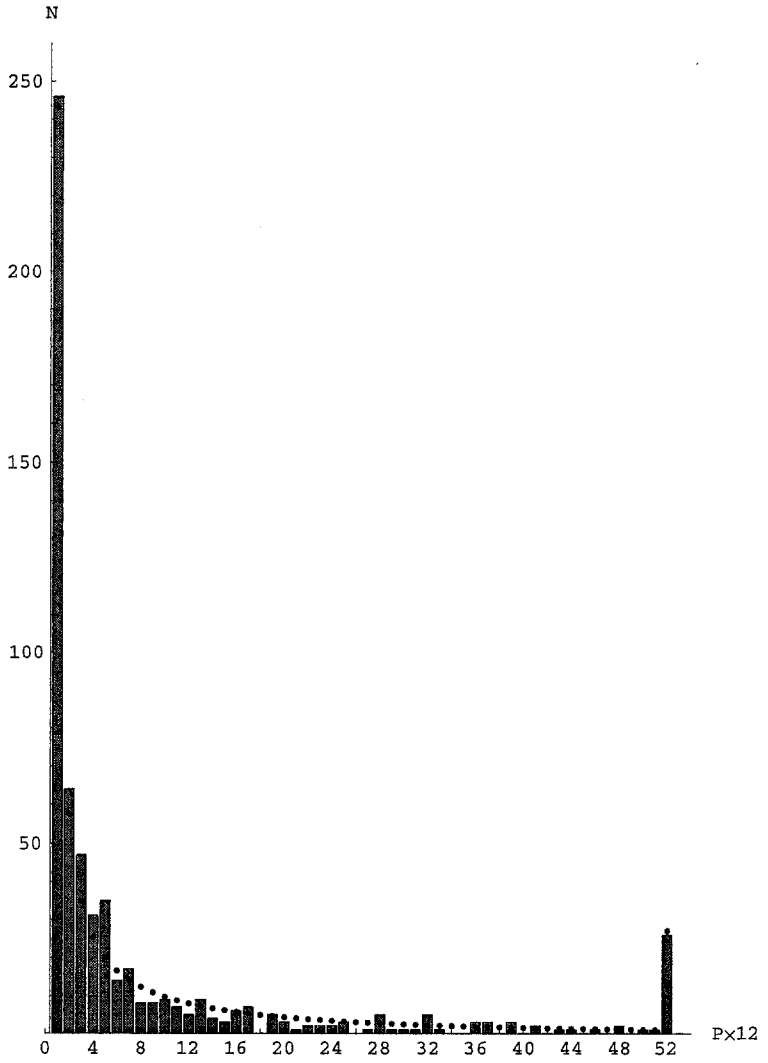
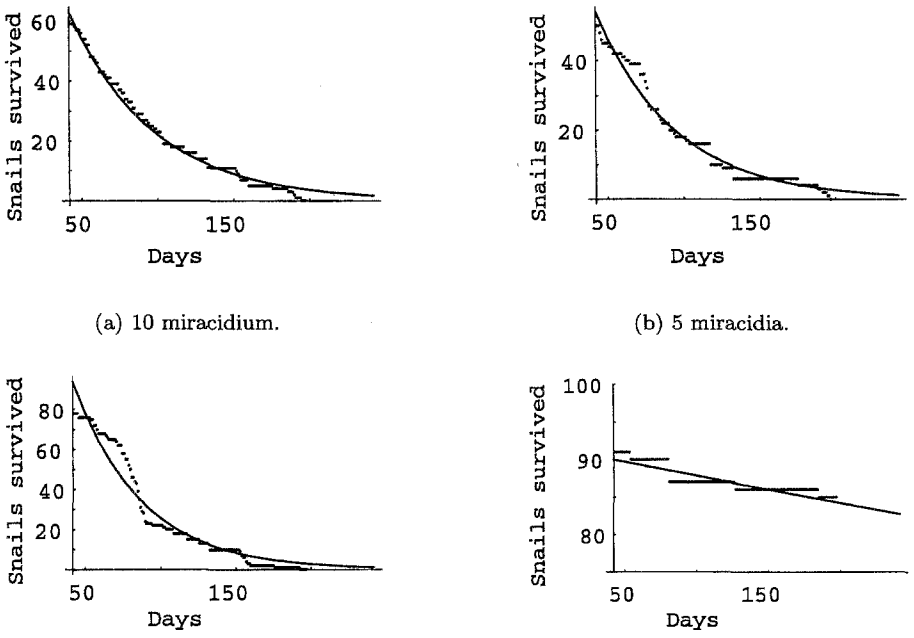


Figure 1. Data and theoretical distribution of parasites among human hosts. The histogram bars are observed values and the dotted curve denotes the least squares fit. The last value on the right represents the sum of the tail of the distribution. The estimated value of the clumping parameter obtained using the least squares fit is $k = 0.243$.

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. The number of live snails in each group was recorded every day until the last of the infected snails had died (on day 195). Snail survival data were analyzed using Kaplan-Meier survival curves (Systat). The Kaplan-Meier estimate involves computing the number of organisms (snails) that die at a certain time point, divided by the number of organisms (snails) that remain alive in the study at that time. These probabilities are multiplied by any earlier computed probabilities. Survival curves can then be compared between (or among) groups using a log-rank test that allows you to either reject the null hypothesis (that the curves are different—$P < 0.05$) or fail to reject the null hypothesis (the curves are the same—$P > 0.05$). Based on this survival analysis, no detectable differences were observed among the three infected groups ($P = 0.972$). We show in Figures 2a–2c the data for the three infected groups (time t shown in days after day 42 of the experiment) together with the least squares fit by an exponential curve $N_0 e^{-(\mu_s + d_s)t}$. We see an excellent fit for snails exposed to 10 miracidia (Figure 2a), resulting in $\mu_s + d_s = 0.018$/day, that is, a mean life expectancy for that group of 55.5 days, or 0.1522 years. A reasonably good fit results from snails exposed to 5 miracidia (Figure 2b), giving $\mu_s + d_s = 0.019$/day, that is, a mean



(a) 10 miracidium.

(b) 5 miracidia.

(c) 1 miracidia.

(d) 0 miracidia.

Figure 2. Data (dotted plots) of the number of snails surviving post exposure to (a) 10 miracidium, (b) 5 miracidia, (c) 1 miracidia, and (d) 0 miracidia, and the least squares fits by negative exponentials (solid curves).

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 slightly worse (Figure 2c), and it results in $\mu_s + d_s = 0.022$/day, that is, a mean life expectancy for that group of 45.5 days, or 0.1245 years. This seems consistent with the analysis using Kaplan-Meier estimate, given that all three survival functions follow relatively similar trajectories. It also provides justification for using the overall mortality rate that was calculated using rates from all three groups (next paragraph).

From the control group, we are able to estimate μ_s by finding the least squares fit of the data by a negative exponential $N_0 e^{-\mu_s t}$. This results in $\mu_s = 0.00058$/day, that is, a mean life expectancy for unexposed snails of 1724 days, or 4.7 years. We show in Figure 2d the data and the least squares fit by a negative exponential for the unexposed snails. The fitted value, 4.7 years, is not realistic, as snails tend to live much longer under optimal laboratory conditions. Adult life-expectancy for *Biomphalaria* in the field has been estimated to be on the order of 1–12 months, while laboratory estimates are on the order of several years [11,12]. If we use the values $\mu_s = 0.5$/year and $\mu_s + d_s = 0.0180602$/day which is an estimated value for all three groups of exposed snails combined, and assume the disease-induced death rate of snails is the same for the laboratory and for the the field, then we obtain a good estimate for d_s, $d_s = 0.0180602$/day–0.0013699/day $= 0.01669$/day.

To estimate the parameter β (the per capita rate of infection of humans by one cercaria), we will use the analytical results obtained from system (1). The parasite reproductive number can be calculated from this model as $\mathcal{R}_0 = T_{\mathrm{MS}} T_{\mathrm{SM}}$, where

$$T_{\mathrm{MS}} = \frac{\Lambda_s}{\mu_s} \frac{\xi}{\mu_h + \mu_p + \alpha + \sigma}$$

represents the man-snail transmission coefficient (the number of snails infected by a pair of adult parasites during its average life-time, $1/(\mu_h + \mu_p + \alpha + \sigma)$, and

$$T_{\mathrm{SM}} = \frac{\Lambda_h}{\mu_h} \int_0^\infty \beta r(\tau) e^{-(\mu_s + d_s)\tau} \, d\tau$$

represents the snail-man transmission coefficient (the number of adult parasite pairs produced by an infected snail during its entire period of infection). It is shown in [4] that system (1) has a stable parasite-free equilibrium when $\mathcal{R}_0 \leq 1$. When $\mathcal{R}_0 > 1$, and α is sufficiently small (a biologically realistic assumption), the system has a stable endemic equilibrium at which the mean parasite load is given by

$$m_* = \frac{P_*}{N_*} = \frac{\mu_s}{\xi}\frac{\mu_h}{\Lambda_h}\left(\widetilde{\mathcal{R}}_0 - 1\right) + O(\alpha), \tag{2}$$

where $O(\alpha)$ denotes terms that are very small if α is very small. For (2), we have used formulas (A.4) and (A.5) in [4], i.e., N_* and P_* are analytic functions of $\alpha > 0$ and

$$N_* = \frac{\Lambda_h}{\mu_h} - \frac{\mu_s\left(\widetilde{\mathcal{R}}_0 - 1\right)}{\mu_h \xi}\alpha + O\left(\alpha^2\right), \qquad P_* = \frac{\mu_s\left(\widetilde{\mathcal{R}}_0 - 1\right)}{\xi} + O(\alpha), \tag{3}$$

where $\widetilde{\mathcal{R}}_0 = \mathcal{R}_0$ evaluated at $\alpha = 0$, i.e.,

$$\widetilde{\mathcal{R}}_0 = \left(\frac{\Lambda_s}{\mu_s}\right)\left(\frac{\Lambda_h}{\mu_h}\right)\left(\frac{\xi}{\mu_h + \mu_p + \sigma}\right)\int_0^\infty \beta r(\tau) e^{-(\mu_s + d_s)\tau}\, d\tau.$$

We can then use formula (2) to estimate the parameter β by setting the mean m_* 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 piecewise linear and periodic of period 35 days, zero for $0 \leq \tau < 35$ days (prepatent period) and for $\tau > 140$ days (maximum time of releasing cercariae). Figure 3 shows an example of such function multiplied by the probability of survival. Then the equation $m_* = m_d$ produces an approximate value of $\beta = 0.000027$.

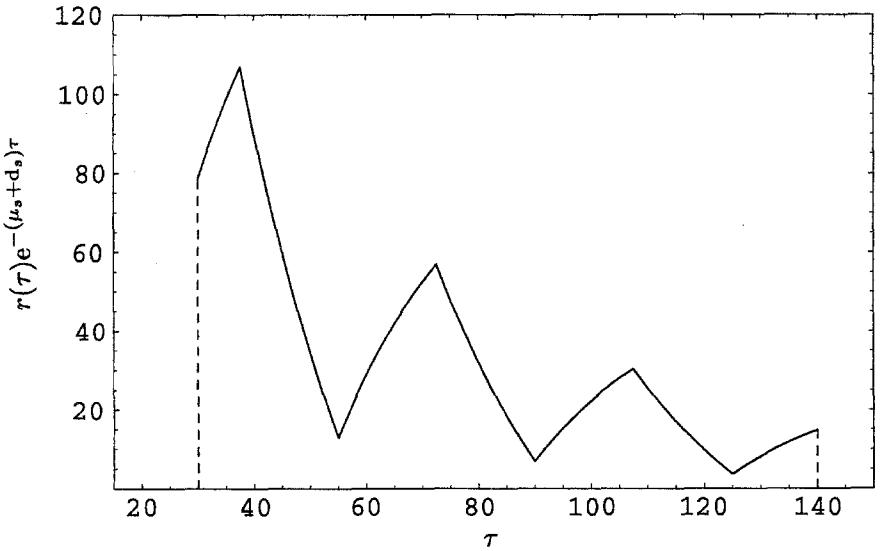


Figure 3. A plot of the number of cercaria released by a snail as a function of infection-age. The death rate of snails is chosen to be $\mu_s + d_s = 0.018$, the latent period is 30 days, and the maximum day that a snail releases cercariae is 140.

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 [13]). Let $\sigma > 0$, $k = 0.243$, $\beta = 0.000027$, and all other parameters have values given before. Notice from formula (2) that m_* is a function of the treatment rate σ. Hence, the

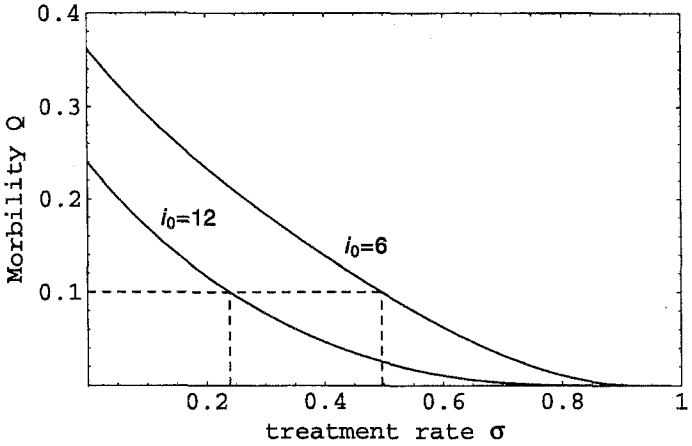


Figure 4. A relationship between the prevalence of morbidity Q and the treatment rate σ for $i_0 = 6$ and $i_0 = 12$.

negative binomial distribution $\mathrm{NB}(m_*(\sigma), k)$ and, hence, the Q value will depend on σ. Let the threshold number of parasites be i_0. Then $Q(\sigma)$ is the summation of the terms in $\mathrm{NB}(m_*(\sigma), k)$ with $i > i_0$. Figure 4 is a plot of Q as a function of σ for $i_0 = 6$ and $i_0 = 12$. From Figure 3, we see, for example, that $Q = 0.36$ or $Q = 0.24$, respectively, for these two i_0 values when there is no treatment ($\sigma = 0$), and that, in order for Q to be below 0.1, the treatment rate needs to satisfy, respectively, $\sigma \geq 0.49$ or $\sigma \geq 0.23$. We assume here that treatment with Praziquantel is 100% effective. Therefore, $\sigma \geq 0.23$ means that 23% of the population needs to be screened every year, and all individuals thus identified as infected need to be treated. For example, in a population of $1,500$ individuals, $0.23 \times 1,500 = 345$ must be screened per year at a constant rate of approximately one individual per day. Most chemotherapeutic control efforts easily exceed this treatment rate often targeting all available infected individuals in the population.

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 (ξ) and the snail-man transmission coefficients (β, see [4]). 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, [7,8]).

4. CONCLUSIONS

A combination of mathematical models and empirical studies will help us understand disease epidemiology and the consequences of control strategies. In this paper, we report estimates of four relevant parameters obtained from field and laboratory data for the modelling of schistosomiasis dynamics. First, we obtained an excellent fit by a negative binomial with mean $m_d = 114$ and clumping parameter $k = 0.243$ for field data of parasite intensity for a population of $N_d = 597$ individuals and a total number of parasites $P_d = 67908$. The value of k has been estimated for other helminth infections and for different populations (see [7,14,15]). For example, it has been estimated using a negative binomial distribution that $k = 0.32$ for a sample size of 853 people (*Ascaris lumbricoides* in a rural community in Korea) and $k = 0.67$ for a sample size of 292 people (*Wuchereria bancrofti* in Samoa). Next, we estimated from laboratory data the natural uninfected mortality and the parasite-induced mortality rates (d_s) 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 (β) 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. It is demonstrated that model results can provide new insights into disease dynamics and potentially valuable information for health care providers.

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