Schistosomiasis models with density dependence and age of infection in snail dynamics

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Abstract

New models for schistosomiasis are developed. These models incorporate several realistic features including drug treatment for human hosts, an infection age in snail hosts, density-dependent birth rate of snails, distribution of schistosomes within human hosts, and disease-induced mortality in both human and snail hosts. The qualitative and quantitative mathematical properties of the models are studied, their biological consequences and some control strategies are discussed, and the results of the new models are compared with those of simpler models. It is shown that the new model may have a bifurcation at which the unique endemic equilibrium changes the stability and stable periodic solutions exist. This is quite different from the simpler models. Explicit thresholds of treatment rate are established above which the infection will be controlled under certain levels. Evaluations of cost-effectiveness are also discussed by analyzing the sensitivity of the mean number of parasites per person to changes of other parameters. © 2002 Elsevier Science Inc. All rights reserved.

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1. Introduction

In modeling our environment one of the most difficult choices we have to make is the amount of detail we are willing to put into the model or, rather, the amount of detail we are capable of modeling due to our limited ability to gather information. This decision is especially crucial when
trying to describe biotic interactions, and it requires a delicate balance between the need for enough detail to resolve important characteristics of the dynamics of the interactions and our ability to obtain data in sufficient detail to use the model.

When modeling any ecosystem in some detail, one should begin with a simple model. If this model captures the essential features of the interactions being modeled, simulations should reflect those aspects of real-life behavior. Hopefully, a simple model can be thoroughly analyzed and then built upon to derive increasingly more complex models. At each stage these require the same type of validation concerning the new features being added and the extent to which the numbers predicted by the model compare with real data.

Several studies have addressed the dynamics of schistosomiasis and other helminth infection of humans [1–4,9,10,13–15,18,19,25,26] using systems similar to the one we are interested in. We shall consider here *Schistosoma mansoni*, a human blood fluke which causes schistosomiasis. The freshwater snail *Biomphalaria glabrata* serves as the main intermediate host. Anderson and May [1] introduced models for macroparasite–host interactions when the parasites have direct lifecycles involving only a single host population and one stage of parasites. In [19] a free-living stage of the parasite was considered in the model. Interactions between schistosome infection and molluscan intermediate hosts (snails) were studied in [2]. Multiple stages of parasites and two host populations were considered in [10] which, however, assumes a constant population size of the human host and no density dependence and age of infection in the snail population. Campaigns against *S. mansoni* frequently focus on treatment of infected humans with Praziquantal or other drugs that kill the parasites in the treated humans. Mathematical models have been used to assess community chemotherapy programs for schistosomiasis through simulations [6,7]. These models also do not include explicit snail dynamics.

We shall introduce in this paper models with more features describing the dynamics of schistosomes, snails, and humans; we shall study their qualitative and quantitative mathematical properties and deduce biological and ecological consequences. In particular, we shall model treatment of humans and establish an explicit treatment rate threshold above which parasites will die out or the infection in the population will remain below a certain level. We shall also study the sensitivity of the mean parasite load per human host to the changes in the two transmission rates: the man–snail transmission rate and the snail–man transmission rate. We shall introduce an age structure in the class of infected snails, since their cercarial production seems to be periodic in time and there is a prepatent period after initial infection (see Fig. 1, [21]). The man–schistosome interaction is modeled as a macroparasite infection and we assume a negative binomial distribution for the parasite distribution among the human hosts as in [1]. The population sizes of both human and snail hosts are variable by allowing disease-induced mortality.

We shall also compare the prediction of the new models with that of a simpler model proposed earlier by other authors [25,26], to which our model reduces if we assume no parasite-induced additional mortality in humans as well as constant cercarial production by infected snails. We shall show that this mean parasite load does not depend linearly on the transmission rate from snail to human as the simpler model predicts, but rather on the square root of this transmission rate. We shall also show (numerically) that the new model may produce a bifurcation at which the unique endemic equilibrium changes its stability and stable periodic solutions exist.
2. The model

Let $N, P, S, I, M, C$ denote the numbers of human hosts, adult parasites, uninfected snails and infected snails, free-living miracidia, and free-living cercariae, respectively. The following parameters will be used in our model:

- $A_h$: recruitment rate of human hosts
- $b_p$: per capita birth (egg-laying) rate of adult parasites
- $A_s$: recruitment rate of snails
- $\mu_h$: per capita natural death rate of human hosts
- $\mu_p$: per capita death rate of adult parasites
- $d_s$: disease-induced death rate of snails
- $\rho$: per capita (successful) rate of infection of snails by one miracidium
- $\beta$: per capita (successful) rate of infection of humans by one cercaria
- $r(\tau)$: releasing rate of cercariae by one snail of infection age $\tau$
- $\sigma$: treatment rate of human hosts

Under the assumption that individuals are born uninfected, and that the parasites are over-dispersed and have a negative binomial distribution among human hosts with the clumping parameter $k$, we have the following equations for the numbers of humans $N$ and adult parasites $P$:

\[
\frac{d}{dt} N = A_h - \mu_h N - \rho P,
\]
\[
\frac{d}{dt} P = \beta CN - (\mu_h + \mu_p + \rho + \sigma)P - \rho \left( \frac{k + 1}{k} \right) \left( \frac{P^2}{N} \right). 
\]
The system (1) is very similar to the model studied in [1] which does not include the snail dynamics and has an exponential birth rate for human hosts. Based on the observation that the parasite burden in a snail is not essential for the number of cercariae produced, we divide the snail population into two subclasses: \( I \) (infected snails) and \( S \) (uninfected snails). Let \( t \) denote time, \( \tau \) denote time since infection, i.e., infection age, \( x(t, \tau) \) denote the infection-age density of snails at time \( t \), and \( r(\tau) \) denote the rate at which infected snails of infection age \( \tau \) release cercariae. Then the total number of infected snails at \( t \) is

\[
I(t) = \int_0^\infty x(t, \tau) \, d\tau. 
\]  

(2)

Since cercariae die very quickly after being released if they cannot find a human host to infect, the total number of cercariae shed by infected snails of all ages at time \( t > 0 \) can be expressed as

\[
C(t) = \int_0^\infty r(\tau)x(t, \tau) \, d\tau. 
\]  

(3)

We assume that the average number of hatchable eggs laid by one adult parasite per unit of time is constant. Then the equations for the snail hosts with infection-age-dependent infectivity take the following form:

\[
\frac{d}{dt}S = b(S, I) - \mu_s S - \rho MS, \\
\frac{\partial}{\partial t} x(t, \tau) + \frac{\partial}{\partial \tau} x(t, \tau) = -(\mu_s + d_s)x(t, \tau), \\
x(t, 0) = \rho MS, \quad x(0, \tau) = x_0(\tau),
\]

(4)

where \( b(S, I) \) is the birth rate of snails whose form will be specified later, \( \rho MS \) is the incidence rate of snail infection, \( M = b_P P \) (since miracidia also die quickly if they cannot find a snail to infect, the total number of miracidia at time \( t \) is assumed to be proportional to the number of adult parasites). Combining (1)–(4) we have the following system that governs the disease dynamics:

\[
\frac{d}{dt} N = A_h - \mu_h N - x P, \\
\frac{d}{dt} P = \beta CN - (\mu_h + \mu_p + \alpha + \sigma)P - x \left( \frac{k + 1}{k} \right) \left( \frac{P^2}{N} \right), \\
\frac{d}{dt} S = b(S, I) - \mu_s S - \rho MS, \\
\frac{\partial}{\partial t} x(t, \tau) + \frac{\partial}{\partial \tau} x(t, \tau) = -(\mu_s + d_s)x(t, \tau), \\
x(t, 0) = \rho MS, \quad x(0, \tau) = x_0(\tau), \\
C(t) = \int_0^\infty r(\tau)x(t, \tau) \, d\tau, \quad I(t) = \int_0^\infty x(t, \tau) \, d\tau, \quad M = b_P P.
\]

(5)

The existence and uniqueness of solutions to the system (5) can be proved using standard methods (see [17,24]). Moreover, it is easy to show that all the variables remain non-negative and bounded for \( t > 0 \) for non-negative initial data.
Let
\[ B(t) = \rho M(t)S(t) = \rho b_P P(t)S(t). \]

Then, solving the \( x \) equation along the characteristics lines \( t - \tau = \text{const} \), we get
\[ x(t, \tau) = \begin{cases} e^{-(\mu_1 + d_i)\tau} B(t - \tau), & \text{if } t \geq \tau, \\ e^{-(\mu_1 + d_i)\tau} x_0(\tau - t), & \text{if } t < \tau. \end{cases} \]

Then we can rewrite \( C(t) \) and \( I(t) \) as
\[
C(t) = \int_0^t r(\tau) e^{-(\mu_1 + d_i)\tau} B(t - \tau) d\tau + F_1(t), \\
I(t) = \int_0^t e^{-(\mu_1 + d_i)\tau} B(t - \tau) d\tau + F_2(t),
\]
where
\[
F_1(t) = \int_t^\infty r(\tau) e^{-(\mu_1 + d_i)\tau} x_0(\tau - t) d\tau, \\
F_2(t) = \int_0^t e^{-(\mu_1 + d_i)\tau} x_0(\tau - t) d\tau.
\]

Introduce the notation
\[
\delta = \mu_h + \mu_p + \alpha + \sigma, \quad \xi = \rho b_P, \quad k_0 = \frac{k + 1}{k}. \tag{6}
\]

Then the equations in system (5) can be written as
\[
\frac{d}{dt} N = A_h - \mu_h N - \alpha P, \\
\frac{d}{dt} P = \beta N \int_0^t r(\tau) e^{-(\mu_1 + d_i)\tau} B(t - \tau) d\tau - \delta P - \alpha k_0 \frac{P^2}{N} + \beta NF_1(t), \\
\frac{d}{dt} S = b(S, I) - \mu_s S - B(t), \\
B(t) = \xi P(t) S(t)
\]
and
\[
I(t) = \int_0^t e^{-(\mu_1 + d_i)\tau} B(t - \tau) d\tau + F_2(t). \tag{8}
\]

In the following sections we will consider two particular forms of \( b(S, I) \): \( b_1(S, I) = A_s \) and \( b_2(S, I) = c_1 S / (c_2 + S + I) \), with \( c_1 \) and \( c_2 \) being the scaling and saturation constants of the birth rate. \( b_1(S, I) \) represents a constant recruitment and \( b_2(S, I) \) takes into account the fact that infected snails do not reproduce.

3. The basic reproductive number and disease dynamics

In this section we describe most of our analytic results for the case when the snail birth rate is \( b_1(S, I) = A_s \). The case of \( b = b_2(S, I) \) is discussed at the end of this section. Let
\[
\mathcal{R}_1 = \beta \int_0^\infty r(\tau) e^{-(\mu_1 + d_i)\tau} d\tau, \tag{9}
\]
and let
\[ R_{MS} = \left( \frac{A_s}{\mu_s} \right) \left( \frac{\xi}{\delta} \right), \quad R_{SM} = \left( \frac{A_h}{\mu_h} \right) \mathcal{K}. \]

\( R_{MS} \) represents the man–snail transmission coefficient (the number of snails infected by a schistosoma during its average lifetime, \( 1/\delta \)). \( R_{SM} \) represents the snail–man transmission coefficient (the number of schistosomes produced by an infected snail during its entire period of infection).

The basic reproductive number is
\[ R_0 = R_{MS} R_{SM}. \] (10)

It is sufficient to study the system (7) which has only three variables: \( N, P, \) and \( S \) (the large time behavior of \( I(t) \) is given by that of \( B(t) = \xi P(t) S(t) \)). The parasite-free equilibrium \( E_0 = (N_0, P_0, S_0) = (A_h/\mu_h, 0, A_s/\mu_s) \) always exists, and its stability determines whether the parasites will be able to establish themselves in the population. The following result shows that the parasites will go to extinction if \( R_0 \leq 1 \).

**Result 1.** Consider the system (7) with \( b = b_1(S, I) \). If \( R_0 \leq 1 \), then the parasite-free equilibrium \( E_0 \) is a global attractor, i.e.,
\[ \lim_{t \to \infty} (N(t), P(t), S(t)) = \left( \frac{A_h}{\mu_h}, 0, \frac{A_s}{\mu_s} \right) \]
for any positive solutions of the system (7).

Result 1 can be proved in a similar way as in [11], using methods shown in [22]. We can also show that \( E_0 \) is unstable when \( R_0 > 1 \) and that at the same time there exists an endemic equilibrium \( E_* = (N_*, P_*, S_*) \) with \( P_* > 0 \). We will look at the limiting system of (7):
\[
\begin{align*}
\frac{d}{dt} N &= A_h - \mu_h N - x P, \\
\frac{d}{dt} P &= N(K_1 * B) - \delta P - z k_0 \frac{P^2}{N}, \\
\frac{d}{dt} S &= b_1(S, I) - \mu_s S - B, \\
B &= \xi PS,
\end{align*}
\] (11)

where ‘*’ denotes convolution and
\[ K_1(\tau) = \beta r(\tau) e^{-(\mu_s + d_s)\tau}. \] (12)

The linearization of system (11) at the point \( E_0 \) has the following characteristic equation,
\[ (\lambda + \mu_h)(\lambda + \mu_s)\left(\lambda + \delta - \xi N_0 S_0 \mathcal{K}_1(\lambda)\right) = 0, \] (13)

where \( \mathcal{F}(\lambda) \) denotes the Laplace transform of \( f(\theta) \), i.e.,
\[ f'(\lambda) = \int_0^\infty e^{-\lambda \theta} f(\theta) \, d\theta. \]

It can be shown that Eq. (13) has a positive real root when \( R_0 > 1 \). Hence \( E_0 \) is unstable.

Setting the right-hand side of (11) equal to 0 we know that \( E_0 \) is a positive equilibrium if and only if \( N_0 \) is a positive solution of the equation \( h(N_0) = g(N_0) \) where

\[
\begin{align*}
  h(N_0) &= \xi K_1 A_s N_0, \\
  g(N_0) &= \left( \delta + \frac{k_0 (A_h - \mu_h N_0)}{N_0} \right) \left( \frac{\mu_s + \xi (A_h - \mu_h N_0)}{\alpha} \right). 
\end{align*}
\]

It can be shown that \( h(N_0) = g(N_0) \) has a solution on \( (0, A_h/\mu_h) \) if and only if \( h(A_h/\mu_h) > g(A_h/\mu_h) \), which is equivalent to \( R_0 > 1 \). Moreover, \( N_0 \) is unique. The following result has been established.

**Result 2.** If \( R_0 > 1, b = b_1(S,I) = A_s \), then the parasite-free equilibrium \( E_0 \) is unstable. At the same time, there exists a unique endemic equilibrium \( E_* = (N_*, P_*, S_*) \) with \( P_* > 0 \).

We remark that the uniqueness of the endemic equilibrium may not be true if different recruitment rates of human hosts are assumed. For example, if we assume an exponential growth of humans, as done in [1], then there may be several feasible endemic equilibria. This provides evidence that introduction of snail dynamics may generate qualitatively different model behaviors. We do not discuss these cases further here since our main concern in this paper is the impact of density dependence and infection age of snails.

The stability of \( E_* \) is somewhat difficult to prove due to the fact that the corresponding characteristic equation contains both the Laplace transform \( \mathcal{K}_1(\tau) \) and a polynomial of degree 3 (see Appendix A). We have managed to prove the following stability result under the assumption that the extra human mortality rate \( \alpha \) induced by one adult parasite is much smaller than other parameters, which is true for schistosomiasis.

**Result 3.** \( E_* \) is locally asymptotically stable if \( \alpha \) is small enough.

The proof of Result 3 can be found in Appendix A. Results 1, 2, and 3 are all for the case of \( b = b_1(S,I) \). For the case of \( b = b_2(S,I) \), we show that, while the result on existence and uniqueness of the endemic equilibrium is similar, the stability result is quite different.

In this case, the reproductive number is \( R'_0 = R'_MS R'_SM \), where

\[
\begin{align*}
  R'_MS &= \left( \frac{\xi}{\delta} \right) \overline{S}, \\
  R'_SM &= \left( \frac{A_h}{\mu_h} \right) \mathcal{K}_1, \\
\end{align*}
\]

and \( \overline{S} = c_1/\mu_s - c_2 > 0 \) is the carrying capacity of the snails in the absence of parasites. Similarly to Result 1, we can prove that the parasite-free equilibrium is stable when \( R'_0 < 1 \) and unstable when \( R'_0 > 1 \).
For the system (11) with \( b = b_2(S, I) \), the existence of uniqueness of the endemic equilibrium is determined by that of a positive \( N \) in the following equation,

\[
\mu_h + \frac{\xi(A_h - \mu_h N)}{\alpha} - \frac{c_1}{c_2 + \mathcal{L}(N)} = 0,
\]

where

\[
\mathcal{L}(N) = \frac{1}{\xi \mathcal{H} N} \left( \delta + k_0 \left( \frac{A_h}{N} - \mu_h \right) \right) \left( 1 + \frac{\xi(A_h - \mu_h N)}{\alpha(\mu_s + d_s)} \right).
\]

It can be shown that (15) has a unique root \( N^* \) satisfying \( 0 < N^* < A_h/\mu_h \) if and only if \( R'_0 > 1 \). Hence, for \( R'_0 > 1 \), the system (11) with \( b = b_2(S, I) \) has a unique endemic equilibrium \( E^* = (N^*, P^*, S^*) \) with \( N^* \) given by (15) and

\[
P^* = \frac{1}{\alpha} (A_h - \mu_h N^*), \quad S^* = \frac{1}{\xi \mathcal{H}} N^* \left( \delta + k_0 \left( \frac{A_h}{N^*} - \mu_h \right) \right).
\]

As for the stability of \( E^* \), we have conducted a large number of numerical calculations which show that \( E^* \) is stable only for parameters in a certain region, and that there exists a bifurcation at which \( E^* \) becomes unstable and periodic solutions appear (see Fig. 2).

In Fig. 2 we have fixed all parameters except \( c_1 \) and \( c_2 \). The parameter values are chosen to be the following: \( A_h = 6, \mu_h = 0.014, \alpha = 10^{-6}, \beta = 0.0001, \mu_p = 0.2, \sigma = 0.5, k = 0.1, \mu_s = 0.3, \)

\[
C_1=600, C_2=400
\]

\[
C_1=800, C_2=400
\]

\[
C_1=1000, C_2=400
\]

Fig. 2. Plots of the number of adult parasites \( P \) vs time for various values of \( c_1 \) and \( c_2 \). \( c_2 = 400 \) is fixed. They show that the stability of the endemic equilibrium changes from stable \( (c_1 = 600) \) to unstable \( (c_1 = 800) \) and at the same time, a stable periodic solution appears.
\[ \rho = 0.0005, \ b_p = 4, \ d_s = 0.01. \] The time units are years. The values for \( \beta \) and \( \rho \) are small because they contain many factors involved in the transmission process including the probability of successful contact of a parasite with a host. According to the data shown in Fig. 1, we choose \( r(\tau) \) to be periodic of period eight weeks, zero for \( 0 \leq \tau \leq 4 \) weeks, and having a maximum support of two years. To simplify the numerical calculations, it is also chosen to be piecewise linear. Fig. 2 presents the behavior of solutions of the system (5) with \( b = b_2(S, I) \) for three sets of values of \( c_1 \) and \( c_2 \) (only the \( P \) component is shown). In all three graphs \( c_2 = 400 \). The top graph shows that for \( c_1 = 600 \) the endemic equilibrium \( E^* \) is stable. The middle graph shows that for \( c_1 = 800 \) \( E^* \) becomes unstable and a stable periodic solution exists. This indicates that a bifurcation occurs at some critical point \( c_2^* \in (600, 800) \), such that \( E^* \) is stable for \( c_2 < c_2^* \) and unstable for \( c_2 > c_2^* \). The bottom graph shows that, when further increasing \( c_2 \), a stable periodic solution exists with a larger amplitude. This phenomenon looks very much like a Hopf bifurcation, but we do not have an analytic proof for this.

The change of stability of the endemic equilibrium as well as the periodicity exhibited in our model demonstrate to some extent the impact of snail dynamics on the disease transmission processes. Epidemiological evidence suggests that variation in schistosome prevalence and intensity occurs in time [12]. Human activity is often the source of changes in transmission patterns, but variation in rainfall can have a considerable effect on intermediate hosts. Variation between years in the pattern of rainfall has been shown to be associated with significant variation in the incidence of infection in a community in The Gambia (see [12]). Other studies have shown seasonal periodicity of prevalence of schistosome infections in snail populations [20,23]. Since our model does not incorporate seasonal variations, our study here indicates that the infertility of infected snails (incorporated in our model with \( b = b_2(S, I) \)) seems to play an important role in generating variations in time. The phenomenon that infertility of infected hosts can produce periodicity has also been observed in other models (see [9]). Note that the periodicity of the function \( r(\tau) \) does not seem to be responsible for the oscillation of solutions since no oscillations are present in the model with the same \( r(\tau) \) but \( b = b_1(S, I) \). Another observation concerns the role of parasite-induced host mortality. Some studies show that introducing the host mortality may alter the behavior of the models when combined with overdispersed distributions of parasites (see [16]). Our analysis indicates that, in the absence of density dependence and age of infection of snails, the additional (small) human mortality does not change the qualitative behavior of our model while the quantitative behaviors may be different (see Sections 4 and 5).

4. Comparison to models without snail dynamics

Various methods of schistosome control are discussed in [25,26] using mathematical models. The basic model used in these papers is an ODE system of two equations (the notations have been changed for convenience of comparison):

\[
\begin{align*}
\frac{dm}{dt} &= \beta' Vy - \mu'_p m, \\
\frac{dy}{dt} &= \xi' Nm(1 - y) - \mu'_y y,
\end{align*}
\] (16)
where $m$ denotes the mean numbers of schistosomes per human host; $y$ denotes the proportion of patent infections of snails; $V$ and $N$ denote the number of snails and humans, respectively; $\mu'_p$ and $\mu'_s$ are the per capita death rate for schistosomes and infected snails, respectively; and $\beta'$ and $\zeta'$ are the per capita rate of infection of humans and snails, respectively. From these models Woolhouse identifies two quantities: $T_{SM} = \beta'V/\mu'_p$ and $T_{MS} = \zeta'N/\mu'_s$, which have similar meanings to our quantities $R_{SM}$ and $R_{MS}$, respectively. He finds that at the endemic equilibrium the mean number $m^*$ of schistosomes per human host has the expression

$$m^* = T_{SM} \frac{1}{T_{MS}} = \frac{\beta'V}{\mu'_p} - \frac{\mu'_s}{\zeta'N}.$$  

This relation shows that $m^*$ is linearly related to $T_{SM}$ (or equivalently to $\beta'$) and is inversely related to $T_{MS}$ (or equivalently to $\zeta'$).

Several complications affecting the transmission coefficients are neglected in this model (16), among which are the duration of the prepatent period in snails, the changes in the numbers and distribution of schistosomes in human hosts, and the additional host mortality rate due to infection.

Our new model incorporates all the factors mentioned above and includes the model (16) as a special case. This can be shown as follows. Consider the special case of our model (5) in which $\alpha = 0$ and $d_t = 0$ (ignoring the infection-induced host mortality) and $r(\tau) = \bar{r}$ is constant (the cercaria-releasing rate of the snails is independent of the infection age). Note that in this case the $N$ equation becomes $dN/dt = A_h - \mu_hN$, and that $N(t) \rightarrow A_h/\mu_h$, as $t \rightarrow \infty$. Using the theory of asymptotically autonomous systems (see [5]) we can assume a constant size of human hosts: $N(t) = N = A_h/\mu_h$. By integrating the $x$ equation in (5) and using the initial condition $x(t,0) = \xi PS$ we get the equation for $I$, the number of infected snails:

$$\frac{df}{dt} = \xi PS - \mu_I.$$  

The total number $V = S + I$ of snails then satisfies the equation $dV/dt = A_s - \mu_sV$. Hence $V(t) \rightarrow A_s/\mu_s$, as $t \rightarrow \infty$, and we can assume a constant size of snail hosts: $V(t) = \bar{V} = A_s/\mu_s$. Denote $m = P/N$ and $y = I/V$. Dividing the $P$ equation in (5) by $N$ and dividing the $I$ Eq. (18) by $V$ we get

$$\frac{dm}{dt} = \beta \bar{r} V y - (\mu_h + \mu_p + \sigma)m,$$

$$\frac{dy}{dt} = \xi N m(1 - y) - \mu_s y,$$

which is exactly the same system as (16) with $N = \bar{N}$, $V = \bar{V}$, $\beta' = \beta \bar{r}$, $\mu'_p = \mu_h + \mu_p + \sigma$, $\zeta' = \xi$, $\mu'_s = \mu_s$.

A natural question is whether or not our models which incorporate more observed features of the disease generate different dynamics and predictions. The answer is yes. First, we look at the dependence of the mean parasite load $m^*$ (at the endemic equilibrium) on the transmission rates $\zeta'$ and $R_{SM}$ (or $\beta'$). Here we only present the case of $b = b_1(S, I)$. From the first equation in (11) we see that, for $\alpha > 0$, $m^* = P^*/N^* = (1/\alpha)(A_hx^* - \mu_h)$ with $x^* = 1/N^*$. Using the equations in (14) we get the unique biologically feasible solution
\[ x^* = -b + \sqrt{b^2 - 4ac} \]
\[ \frac{2a}{2a}, \]

(19)

where

\[ a = A_h k_0 (\mu_s \alpha + \zeta A_h), \]
\[ b = \alpha \mu_s (\delta - \mu_h k_0) + (\delta - 2\mu_h k_0) \zeta A_h, \]
\[ c = -\zeta \mu_h (\delta - \mu_h k_0) - \alpha \zeta A_h \mathcal{K}_1. \]

(20)

It is clear that \( x^* \) (and hence \( m^* \)) depends on the transmission coefficients \( \zeta \) and \( \mathcal{K}_1 \) in a highly non-linear way. For example, \( m^* \) depends on the square root of \( \zeta \). This is very different from the prediction by the simpler model (16) (see (17)). The formulas (19) and (20) also allow us to study how \( m^* \) is affected by the heterogeneity in parasite load within human hosts. This is because \( a, b, \) and \( c \) (hence \( x^* \) and \( m^* \)) are all dependent on \( k_0 = (k + 1/k) \), where \( k \) is the clumping parameter in the negative binomial distribution. Another important feature of our model formulation is that we can use our knowledge of \( k \) and \( m^* \) (which determine the negative binomial distribution) to compute the prevalence of morbidity, \( Q \), which is defined as the proportion of individuals whose parasite load exceeds a threshold value. The value of \( Q \) provides an important measure of the level of schistosome infection in a human population (see [8]). We will discuss this in more detail in a separate paper.

The qualitative behavior of the more complex model in this paper is also much richer than that of (16). For example, when the recruitment rate of snails is described by \( b_2(S,I) \), the numerical studies of our model show that a bifurcation occurs for some critical values of the parameters, in which case the endemic equilibrium loses its stability and periodic solutions exist (see Fig. 2). This type of dynamics is not present in the simpler model (16), for which the endemic equilibrium is always stable when it exists.

Another similar and simpler model is considered in [1] which involves only human hosts and assumes exponential growth for humans. The equations in [1] have the form of the system (1) with \( C \) replaced by \( (P/N_0 + N) \) and \( A_h \) replaced by \( b_h N \), where \( N_0 \) and \( b_h \) are constants. That model also produces no stable periodic solutions (it has a neutrally stable cycle for some parameter values).

5. Control strategies

Result 1 in Section 3 provides a condition, \( R_0 < 1 \), for the eradication of the disease. We will consider three parameters that seem to be more important in the reduction of \( R_0 \): the man–snail transmission parameter \( \zeta \), the snail–man transmission parameter \( \beta \) (or \( \mathcal{K}_1 \)), and the treatment rate \( \sigma \). Theoretically, we can rewrite the condition \( R_0 < 1 \) in terms of one or more of the three parameters. For example, we can establish an explicit treatment rate threshold \( \sigma_c \) above which \( R_0 < 1 \):

\[ \sigma_c = \mu_h + \mu_p + \alpha + \frac{\zeta \mathcal{K}_1 A_h A_s}{\mu_h \mu_s}. \]

(21)
If the transmission rates are very high such that it is difficult to achieve \( \sigma > \sigma_c \), then one may consider changing more than one parameter at the same time. Even when it is impossible to eradicate the disease, a control strategy may focus on the reduction of the level of infection. One of the measures for the level of infection is the mean parasite load \( m^* \). We will explore several interesting options on control.

Consider control strategies concerning one or more of the three parameters \( \sigma, \xi, \) and \( \beta \). The reduction in \( \xi \) may be achieved through education to change excretory behavior that reduces the successful infection rate of snails (a factor included in \( \rho \)). The reduction in \( \beta \) may be achieved by improving water supply systems which reduce contact rate of human hosts with polluted water. Fig. 3 demonstrates the sensitivity of \( m^* \) to the changes of these parameters. For the purpose of illustration, the values for \( \xi \) and \( \beta \) in Figs. 3 and 4 have been scaled by \( 10^{-4} \). Other parameter values for Figs. 3 and 4 are chosen to be \( \Lambda_h = 50, \mu_h = 0.014, x = 10^{-6}, \mu_p = 0.2, k = 0.1, A_s = 200, \mu_s = 0.3, d_s = 0.01, \) and \( \int_0^\infty r(\tau) e^{-(\mu + d_s)\tau} \, d\tau = 90 \). These figures are produced by Mathematica.

The top graph in Fig. 3 is a plot of \( m^* \) vs \( \xi \) and \( \beta \) for \( \sigma = 0 \) (no treatment). In this case \( m^* \) is related linearly to \( \beta \) but non-linearly to \( \xi \). This graph provides a prediction similar to that given in [26]: for fixed \( \xi \), \( m^* \) decreases linearly with decreasing \( \beta \); and for fixed \( \beta \), a reduction by one-half in the value of \( \xi \) may reduce \( m^* \) by less than one-half if \( m^* \) is high, but by more than one-half if \( m^* \) is low.

\[
\text{Fig. 3. The graphs demonstrate the sensitivity of the mean parasite load } m^* \text{ to the changes of the transmission parameters, } \beta \text{ and } \xi, \text{ and the treatment rate } \sigma. \text{ The top graph is a plot of } m^* \text{ vs } \beta \text{ and } \xi \text{ when there is no treatment (} \sigma = 0 \text{). In this case } m^* \text{ is related linearly to } \beta \text{ but non-linearly to } \xi. \text{ The bottom graph is a plot of } m^* \text{ vs } \sigma \text{ and } \xi \text{ for a fixed value of } \beta. \text{ It show that } m^* \text{ is related non-linearly to both } \sigma \text{ and } \xi. \]
Fig. 4. The graphs show the sensitivity of \( m^* \) to \( \beta \) and \( \sigma \) while man–snail transmission rate \( \zeta \) is unchanged. The top graph is a plot of \( m^* \) vs \( \beta \) and \( \sigma \) for a fixed value of \( \zeta \). It shows that \( m^* \) is related linearly to \( \beta \) but non-linearly to \( \sigma \). The bottom graph is a contour plot showing the regions in the \((\sigma, \beta)\) plane for which \( m^* \) falls in different intervals.

The bottom graph in Fig. 3 is a plot of \( m^* \) vs \( \beta \) and \( \zeta \) for a fixed value of \( \beta = 5 \). We see that \( m^* \) is related non-linearly to both \( \sigma \) and \( \zeta \). The graph also suggests that, for fixed \( \zeta \), say \( \zeta = 1 \), a treatment rate of \( \sigma = 0.3 \) produces a considerable reduction in \( m^* \), but an additional reduction produced by a treatment rate of \( \sigma = 0.6 \) may not justify the additional expense.

In Fig. 4 we consider the situation in which the man–snail transmission rate \( \zeta \) is unchanged, but the snail–man transmission rate \( \beta \) and the treatment rate \( \sigma \) are varied.

The top graph in Fig. 4 is a plot of the mean \( m^* \) vs \( \beta \) and \( \sigma \) for a fixed value of \( \zeta = 1 \). It shows that \( m^* \) is related linearly to \( \beta \) but non-linearly to \( \sigma \). It also provides a similar evaluation of cost-effectiveness as in Fig. 3. The bottom graph in Fig. 4 is a contour plot showing the regions in the \((\sigma, \beta)\) plane for which \( m^* \) falls in different intervals. From this graph we can determine the specific treatment rate above which the mean parasite load \( m^* \) will be controlled below a certain level. For example, for \( \beta = 6 \), we need \( \sigma > 0.185 \) in order to have \( m^* < 2 \) and we need \( \sigma > 0.425 \) to have \( m^* < 1 \).

6. Conclusions

The mathematical analysis of the new model (5) in this paper establishes some epidemiological consequences of schistosome distribution among human hosts, density-dependent snail growth
due to the infertility of infected snails, and age-dependent cercarial production of snails. The main contributions of the present study are (a) to generalize the existing simpler models to incorporate more realistic features and to provide a nearly complete qualitative analysis for the complex models and (b) to explore quantitatively several control strategies and to evaluate cost-effectiveness of drug treatment programs.

It is shown in this paper that the new model with \( b = b_2(S, I) \) (which takes into account that infected snails do not reproduce) exhibits more complex dynamics including the switch of stability of the unique endemic equilibrium and the existence of stable periodic solutions. The stability result for \( b = b_1(S, I) \) is very similar to that of the simpler model (16), i.e., the endemic equilibrium is always stable whenever it exists. This indicates that the infertility of infected snails may provide a mechanism for observed periodic occurrence of the disease in some natural populations. This finding is also consistent with earlier results from other models (see [9]).

The sensitivity analysis in Section 5 illustrates the effects of various combined changes in the values of \( \xi, \beta, \) and \( \sigma \) on the reduction of the endemic levels of infection, \( m^* \). It shows that reducing \( \xi \) may be more effective when \( m^* \) is low, but reducing \( \beta \) may be a better strategy when \( m^* \) is high. We can compute threshold values of the treatment rate \( \sigma \) above which \( m^* \) will stay below a given level. We also find that, for a range of treatment rates \( \sigma \), the infection level can be reduced significantly, and that the expense for higher treatment rates may not be justified. The clumping parameter \( k \) of the negative binomial distribution is only briefly discussed in this paper. It may play an important role in determining the levels of infection if a different measure (\( Q \)) for the disease prevalence is considered.

Many other refinements to the models can be made, among which are: reservoir hosts, host migration, seasonal heterogeneity, age-dependent human infection rate, acquired immunity, and stochastic effects. Some of these are considered and discussed in [25]. We have looked at models involving reservoir hosts and host migration, which will be published elsewhere.

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Appendix A

To prove the stability of \( E_\ast \) we look at the characteristic equation of (11) at \( E_\ast \):

\[
\det \begin{pmatrix}
\lambda + \mu_h & \alpha & 0 \\
-\mathcal{C}_\ast & \lambda + \delta + \mathcal{D}_\ast & -\xi N_0 P_0 \tilde{K}_1(\lambda) \\
0 & \xi S_\ast & \lambda + \mu_s + \xi P_\ast
\end{pmatrix} = 0, \tag{A.1}
\]

where

\[
\mathcal{C}_\ast = \mathcal{K} B_\ast + zk_0 \frac{P_\ast}{N_\ast^2},
\]

\[
\mathcal{D}_\ast = 2zk_0 \frac{P_\ast}{N_\ast} - \xi N_0 S_\ast \tilde{K}_1(\lambda). \tag{A.2}
\]
Denote the left-hand side of the characteristic equation by $G(\lambda)$. Then

$$G(\lambda) = (\lambda + \mu_h) \left[ (\lambda + \delta + \mathcal{D}_*)(\lambda + \mu_s + \xi P_s) + \xi^2 N_s P_s \tilde{K}_1(\lambda) \right] + \lambda \mathcal{E}_*(\lambda + \mu_s + \xi P_s). \quad (A.3)$$

Note that $\alpha$ is the death rate of human hosts caused by one parasite per unit time. It is much smaller than all other parameters. From (14) we realize that $N_s$ is an analytic function of $\alpha > 0$ and

$$N_s = \frac{A_h}{\mu_h} - \frac{\mu_s (\mathcal{R}_0 - 1)}{\mu_h \xi} \alpha + O(\alpha^2), \quad (A.4)$$

where $\mathcal{R}_0 = \mathcal{R}_0$ evaluated at $\alpha = 0$. Since $\alpha$ is small it is likely that $\mathcal{R}_0 > 1$ when $\mathcal{R}_0 > 1$. Using the equations on the right-hand side of (11) we can get

$$P_s = \frac{\mu_s (\mathcal{R}_0 - 1)}{\xi} + O(\alpha), \quad S_s = \left( \frac{1}{\mathcal{R}_0} \right) \left( \frac{A_h}{\mu_s} \right) + O(\alpha). \quad (A.5)$$

Rewrite the function $G$ as

$$G(\lambda) = (\lambda + \mu_h) \left[ \left( \lambda + \delta + 2\alpha k_0 \frac{P_s}{N_s} \right)(\lambda + \mu_s + \xi P_s) - \xi N_s S_s (\lambda + \mu_s) \tilde{K}_1(\lambda) \right] + \lambda \mathcal{E}_*(\lambda + \mu_s + \xi P_s). \quad (A.6)$$

Then in the limiting case, $\alpha = 0$, the characteristic equation $G(\lambda) = 0$ has a negative root $-\mu_0$ and other roots given by

$$\frac{(\lambda + \tilde{\delta})(\lambda + \mu_s + \xi \tilde{P}_s)}{\lambda + \mu_s} = \xi \tilde{N}_s \tilde{S}_s \tilde{K}_1(\lambda), \quad (A.7)$$

where $\tilde{x} = x$ evaluated at $\alpha = 0$. Note that $\tilde{N}_s = N_0$, $\tilde{S}_s = S_0 / \mathcal{R}_0$, and that when $\Re \lambda \geq 0$ we have $|\tilde{K}_1(\lambda)| \leq |\tilde{K}_1(0)| \ (= \mathcal{K}_1)$. Hence,

$$|\xi \tilde{N}_s \tilde{S}_s \tilde{K}_1(\lambda)| \leq \frac{\xi N_0 S_0 \mathcal{K}_1}{\mathcal{R}_0} = \tilde{\delta} \quad \text{if } \Re \lambda \geq 0.$$

On the other hand, since $P_s > 0$ we have

$$\left| \frac{(\lambda + \tilde{\delta})(\lambda + \mu_s + \xi \tilde{P}_s)}{\lambda + \mu_s} \right| \geq |\lambda + \tilde{\delta}| \geq \tilde{\delta} \quad \text{if } \Re \lambda \geq 0.$$

This shows that (A.7) cannot have roots with positive real part for $\alpha = 0$. It follows that $E_s$ is stable when $\alpha > 0$ is small.

References