A schistosomiasis model with an age-structure in human hosts and its application to treatment strategies

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Abstract

We study a system of partial differential equations which models the disease transmission dynamics of schistosomiasis. The model incorporates both the definitive human hosts and the intermediate snail hosts. The human hosts have an age-dependent infection rate and the snail hosts have an infection-age-dependent cercaria releasing rate. The parasite reproduction number $R$ is computed and is shown to determine the disease dynamics. Stability results are obtained via both analytic and numerical studies. Results of the model are used to discuss age-targeted drug treatment strategies for humans. Sensitivity and uncertainty analysis is conducted to determine the role of various parameters on the variation of $R$. The effects of various drug treatment programs on disease control are compared in terms of both $R$ and the mean parasite load within the human hosts.

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1. Introduction

The spread and persistence of schistosomiasis have always been among 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 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. These features preclude modeling the system through traditional (microparasite) SIR models. Macroparasite models are considered more appropriate as they take into consideration the distribution of parasites within human hosts [22]. A number of mathematical models have been developed for schistosomiasis using a variety of approaches. The earliest models of schistosomiasis consider the population sizes of both humans and snails to be constant [21,23]. Several recent studies have addressed the dynamics of schistosomiasis and other helminth (e.g., onchocercasis) infection of humans [1–5, 9,10,15,16,19,20,22,25,33]. These models have made contributions to the understanding of the transmission dynamics of schistosomes. However, most existing models for schistosomiasis do not include explicitly the dynamics of the intermediate snail host.

Another important feature associated with schistosomiasis infection is the age-dependent prevalence in humans [7]. Epidemiological studies have shown that children of school age usually exhibit the highest prevalence of schistosome infections ([27,30] whereas adults exhibit some of the more serious consequences of infection [17,32]. Various age-targeted treatments have been adopted in different populations and mathematical models have been used to assess the cost-effectiveness of the disease control programs [6,7]). However, the models also do not consider explicit snail population dynamics.

We have previously studied mathematical models that include mass chemotherapy in human hosts with explicit snail dynamics [11,12] and schistosome mating biology [34]. However, none of these models include an age-structure in humans. Results in these studies suggest that while the incorporation of schistosome mating biology does not alter the model behaviors dramatically, the inclusion of an explicit interaction with the snail population will have important impact on the disease dynamics. For example, the mean parasite load of human hosts does not depend linearly on the transmission rate from snail to human as simpler models (simpler snail dynamics) predict, but rather on the square root of this transmission rate. The density dependence considered in snail dynamics may produce a bifurcation at which the unique endemic equilibrium changes its stability and stable periodic solutions exist.

In this paper, we develop a new mathematical model which includes both an age-structure of the human population and explicit snail population dynamics. The model is studied both analytically and numerically in terms of steady states and their stability as well as possible bifurcations. We also use techniques based on Latin hypercube sampling to identify quantitatively the most influential parameters in affecting the magnitude of threshold conditions through the uncertainty and sensitivity analysis. Results from this model are applied to the study of disease control via age-targeted treatment of humans. Two criteria are used to assess the effect of various age-dependent control programs. The first one is to use the overall mean parasite load (defined by the ratio of the total number of parasites to the total number of humans) and the mean parasite load within each age group, and the second one is to look at the reduction in the reproductive number $R_0$. 

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Our paper is organized as follows. Section 2 introduces the age-dependent model; Section 3 carries out the local and global stability analysis of the steady states and shows that periodic solutions can arise via a Hopf bifurcation; applications of the model results to the assessment of age-dependent treatment strategies are given in Section 4; and in Section 5 we summarize our findings.

2. The model formulation

In the literature, there are two different approaches to modeling macroparasite infections. The first approach combines the classical Lotka/Sharpe–McKendrick model for a population structured by the age of hosts. In this approach, one counts the hosts of age $a$ carrying $i$ parasites which leads to an infinite sequence of renewal equations numbered by $i$, and this infinite system is then reduced to a single equation by the use of the generating function \[16,19\]. The other approach uses special interaction coefficients to account a posteriori for the observed clumping of parasites in human hosts. This approach leads to an infinite ODE system which is then reduced to a two-dimensional system for the total number of hosts and the total number of parasites \[2\]. The first approach provides more information including how many hosts of age $a$ carry $i$ parasites while the second approach gives only the numbers of hosts and parasites.

In this paper, we take a mixed approach. We structure the human host population according to age and adult parasite population according to the age of the host which carries the particular parasite. Hence, with this state space, we know how many humans there are of a given age, and for humans of a given age how many parasites are carried on average, while the parasite distribution among the hosts of a given age is not tracked.

Let $N(t)$, $P(t)$, and $C(t)$ denote the numbers of human hosts, adult parasites, and free-living cercariae, respectively. Assume that individuals are born uninfected. Based on the models in Anderson and May \[2\] and Dobson \[10\] we have considered an age-independent model (see \[11\]) in which the equation for the total number of adult parasites $P$ and the human hosts $N$ have the form:

$\frac{dN}{dt} = \Lambda_h - \mu_h N - zP,$

$\frac{dP}{dt} = \beta CN - (\mu_h + \mu_p + z + \sigma/\theta)P - z\left(\frac{1 + k}{k}\right)\frac{P^2}{N},$ (1)

where $\beta$ is the instantaneous rate of infection of human hosts by one cercaria, $\mu_h$ is the per capita natural death rate of human hosts, $\mu_p$ is the per capita death rate of adult parasites, $z$ is the disease-induced death rate of humans per parasite; $\sigma$ is the treatment rate of human hosts, $k$ is the clumping parameter of the negative binomial distribution of parasites. $C(t)$ is determined by the number of infected snails whose equation is given later in the system for snails. All parameters and variables with their definitions are listed in Table 1.

To incorporate an age structure of humans into the equations in (1), we let $n(t,a)$, $p(t,a)$ denote the density functions of human hosts of age $a$ at time $t$ and parasites within human hosts of age $a$, respectively. We remark that $a$ denotes the age of humans (not of parasites). Hence,
\[ N(t) = \int_0^\infty n(t,a) \, da \quad \text{and} \quad P(t) = \int_0^\infty p(t,a) \, da \]

are the total number of humans and the total number of adult parasites, respectively. \( P/N \) represents the mean parasite load within humans. Using a similar argument as before we can derive the equations for \( n(t,a) \) and \( p(t,a) \) and get:

\[
\frac{\partial}{\partial t} n(t,a) + \frac{\partial}{\partial a} n(t,a) = -\mu_h(a)n(t,a) - \alpha p(t,a),
\]

\[
\frac{\partial}{\partial t} p(t,a) + \frac{\partial}{\partial a} p(t,a) = \beta(a) Cn(t,a) - \delta_p(a)p(t,a) - \frac{1 + k}{k} \frac{P(t)}{N(t)} p(t,a),
\]

where

\[
\delta_p(a) = \mu_h(a) + \mu_p + \alpha + \sigma(a). \tag{3}
\]

The boundary conditions are \( n(t,0) = A_h \) (birth rate of human hosts), \( p(t,0) = 0 \) (humans are born uninfected), and initial conditions are \( n(0,a) = n_0(a) \), \( p(0,a) = p_0(a) \) for some given functions \( n_0 \) and \( p_0 \). Notice that, in the special case when the parameter functions \( \beta(a), \mu_h(a) \) and \( \sigma(a) \) are constants, the equations in (2) reduce to those in (1) by integration.

For the snail dynamics, we can use similar equations introduced in Feng et al. [12], which takes into consideration realistic features including an infection-age-dependent cercariae release rate of infected snails and a density-dependent snail birth rate due to the infertility of infected snails:
\[
\frac{d}{dt}S = b(S,I) - \mu_s S - \rho MS,
\]
\[
\frac{\partial}{\partial t}x(t,\tau) + \frac{\partial}{\partial \tau}x(t,\tau) = -(\mu_s + \delta_s)x(t,\tau),
\]
\[
x(t,0) = \rho MS, \quad x(0,\tau) = x_0(\tau),
\]
\[
C(t) = \int_0^\infty r(\tau)x(t,\tau) d\tau.
\]

\(S\) denotes the number of uninfected snails, \(I\) denotes the total number of infected snails given by \(I(t) = \int_0^\infty x(t,\tau) d\tau\). Here, \(\tau\) denotes the time since infection, i.e., infection-age, and \(x(t,\tau)\) denotes the infection-age density of snails at time \(t\). \(M = \gamma P\) is the number of free-living miracidia (since miracidia 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) and \(\gamma\) is the per capita (effective egg-production rate of adult parasites). Other parameters are: \(b(S,I)\) is the birth function of uninfected snails, \(\mu_s\) is the per capita natural death rate of snails, \(\delta_s\) is the disease-induced death rate of snails, \(\rho\) is the per capita rate of infection of snails, and \(r(\tau)\) denotes the rate at which infected snails of infection-age \(\tau\) release cercariae.

Two forms of the birth function \(b(S,I)\) will be considered as we did in Feng et al. [12]. One example will be a Michaelis–Menten type: \(b(S,I) = c_1 S/(c_2 + S + I)\), which assumes that infected snails do not reproduce and that the snail population is bounded; \(c_1\) and \(c_2\) are, respectively, the scaling and saturation constants.

We remark that the infertility of infected snails and the periodicity in the cercaria production are two of the special features of schistosomiasis, and that it has been shown that the inclusion of snail dynamics may produce different dynamics (see [12]). Hence, we include both population dynamics explicitly in the model even though the time scales of the human dynamics (50–70 years) and the snail dynamics (2–4 years) may be different.

The combination of (2) and (4) leads to the following integro-differential initial-boundary value problem that governs the disease dynamics:

\[
\begin{aligned}
\frac{d}{dt}n(t,a) + \frac{d}{da}n(t,a) &= -\mu_h(a)n(t,a) - zp(t,a), \\
\frac{d}{dt}p(t,a) + \frac{d}{da}p(t,a) &= \beta(a)Cn(t,a) - \delta_p(a)p(t,a) - x(t,a) + \frac{\rho(a)}{N(t)}p(t,a), \\
\frac{d}{dt}S(t) &= b(S,I) - \mu_s S - \rho S(t) \int_0^\infty p(t,a) da, \\
\frac{d}{dt}x(t,\tau) + \frac{\partial}{\partial \tau}x(t,\tau) &= -(\mu_s + \delta_s)x(t,\tau), \\
P(t) &= \int_0^\infty p(t,a) da, \quad C(t) = \int_0^\infty r(\tau)x(t,\tau) d\tau, \quad I(t) = \int_0^\infty x(t,\tau) d\tau, \\
n(t,0) = A_h, \quad p(t,0) = 0, \quad x(t,0) = \rho S(t) \int_0^\infty p(t,a) da, \\
n(0,a) = n_0(a), \quad p(0,a) = p_0(a), \quad S(0) = S_0, \quad I(0) = I_0, \quad x(0,\tau) = x_0(\tau).
\end{aligned}
\]

The large number of parameters involved in system (5) can be significantly reduced as many of the parameters can be lumped together. However, we choose to keep these parameters since they are more readily related to field data. We shall use techniques based on Latin hypercube sampling (see [26]) to identify quantitatively the most influential parameter(s) in affecting the magnitude of threshold conditions through the uncertainty and sensitivity analysis.
3. Analysis

In this section, we compute the reproductive number $R$ and show that it determines the existence and stability of possible equilibrium points. For mathematical convenience, we consider a different formulation of the system (5) as shown below.

3.1. Reformulation of the system (5)

For ease of notation, we introduce a new variable $B$:

$$B(t) = \rho \gamma S(t) \int_0^{\infty} p(t,a) \, da = \rho \gamma S(t) P(t).$$

Solving the $x$ equation along characteristic lines we get

$$x(t, \tau) = \begin{cases} e^{-(\mu + \delta)x} B(t - \tau), & t \geq \tau, \\ e^{-(\mu + \delta)x} x_0(\tau - t), & t < \tau. \end{cases}$$

Then $I(t)$ and $C(t)$ can be expressed in terms of $B(t)$:

$$C(t) = \int_0^t r(\tau) e^{-(\mu + \delta)x} B(t - \tau) \, d\tau + F_1(t),$$

$$I(t) = \int_0^t e^{-(\mu + \delta)x} B(t - \tau) \, d\tau + F_2(t),$$

where

$$F_1(t) = \int_t^\infty r(\tau) e^{-(\mu + \delta)x} x_0(\tau - t) \, d\tau,$$

$$F_2(t) = \int_t^\infty e^{-(\mu + \delta)x} x_0(\tau - t) \, d\tau.$$

Using the new notation we can rewrite the system (5) as

$$\frac{d}{dt} n(t,a) + \frac{\partial}{\partial a} n(t,a) = -\mu_n(a)n(t,a) - \alpha p(t,a),$$

$$\frac{d}{dt} p(t,a) + \frac{\partial}{\partial a} p(t,a) = \beta(a)n(t,a) \int_0^t r(\tau) e^{-(\mu + \delta)x} B(t - \tau) \, d\tau$$

$$\quad - \delta_p(a)p(t,a) - \alpha k_0 \frac{P(t)}{N(t)} p(t,a) + \beta(a)n(t,a)F_1(t),$$

$$\frac{d}{dt} S(t) = b(S,I) - \mu S(t) - B(t),$$

$$B(t) = \zeta P(t) S(t),$$

where
The existence and uniqueness of the system (6) can be shown using the standard method. Notice that $F_1(t) \to 0$ as $t \to \infty$. The limiting system of (6) is:

$$\begin{align*}
\frac{\partial}{\partial t} n(t, a) + \frac{\partial}{\partial a} n(t, a) &= -\mu_h(a)n(t, a) - \alpha p(t, a), \\
\frac{\partial}{\partial t} p(t, a) + \frac{\partial}{\partial a} p(t, a) &= \beta(a)n(t, a)(K * B)(t) - \delta_p(a)p(t, a) - \alpha k_0 \frac{P(t)}{N(t)} p(t, a), \\
\frac{d}{dt} S(t) &= b(S, I) - \mu_s S(t) - B(t), \\
B(t) &= \xi P(t) S(t),
\end{align*}$$

(7)

where

$$K(\tau) = r(\tau)e^{-(\mu_h + \delta_p)\tau}.$$  

In the rest of this section, we will consider the limiting system (7).

### 3.2. The reproductive number of the parasite

As is done in Feng et al. [12], we consider two forms of the snail birth function $b(S, I)$.

**Case 1:** $b_1(S, I) = \Lambda_s$ (constant birth rate).

The system (7) always has the parasite-free equilibrium

$$E_0 = (n_s(a), p_s(a), S_s, B_s) = (\Lambda_h \pi(a), 0, A_s/\mu_s, 0).$$

As in most epidemiology models, the stability of $E_0$ is dependent of the basic reproductive number (ratio) of the parasites, or the reproductive ratio of the parasites if the host population is under some influence of a control/prevention program, which is the case our models consider. We define the reproductive ratio of the parasites as

$$R = \int_0^\infty \beta(w) \mathcal{H} \Lambda_h \pi(w) \int_0^\infty \xi \frac{A_s}{\mu_s} e^{-\int_0^w \delta_p(\theta) d\theta} dw,$$

(8)

where

$$\pi(w) = e^{-\int_0^w \mu_s(\theta) d\theta}$$

represents the survival probability of a person up to age $a$, $\delta_p(\theta) = \mu_h(\theta) + \mu_p + \alpha + \sigma(\theta)$ is the sum of death rates of the parasites within a human host of age $\theta$, and

$$\mathcal{H} = \int_0^\infty r(\tau)e^{-(\mu_s + \delta_p)\tau} d\tau$$
represents the total number of cercariae released by an infected snail during its life of infection. For convenience of interpretation, we consider the secondary number of infected snails (instead of parasites) produced by a typical infected snail during its entire period of infection. The quantity 

\[ \beta(w)KA_h\pi(w) \]

represents the average number of human hosts of age \( w \) becoming infected by one infected snail during its entire period of infection. \( e^{-\int_w^{w+u} \delta_p(t)dt} \) is the survival probability of a parasite in a human host of age \( w + u \) who was infected at age \( w \), and the average number of snails the parasite \( (u \) time units after the host was infected, or parasite of age \( u \)) is capable of infecting is \( \xi A_s/\mu_s e^{-\int_w^{w+u} \delta_p(t)dt} \).

Thus, the total number of snails infected by a typical parasite during its entire lifetime is

\[ \int_0^\infty \frac{\xi A_s}{\mu_s} e^{-\int_w^{w+u} \delta_p(t)dt} du. \]

It follows that the number of secondary infected snails due to a human host of age \( w \) is

\[ \beta(w)KA_h\pi(w) \int_0^\infty \frac{\xi A_s}{\mu_s} e^{-\int_w^{w+u} \delta_p(t)dt} du. \]

(9)

Integrating over all ages \( w \in [0, \infty) \) we obtain the overall average number of secondary infected snails, which is the number \( \mathcal{R} \) given in (8).

Case 2: \( b_2(S, I) = c_1S/(c_2 + S + I) \) (density-dependent birth rate).

Here, \( c_1 \) and \( c_2 \) are the scaling and saturation constants. In this case the reproductive number is

\[ \mathcal{R}' = \int_0^\infty \beta(w)KA_h\pi(w) \int_0^\infty \frac{\xi A_s}{\mu_s} e^{-\int_w^{w+u} \delta_p(t)dt} du dw, \]

(10)

where

\[ \bar{S} = \frac{c_1}{\mu_s} - c_2 > 0 \]

(11)

is the carrying capacity of the snails in the absence of parasites, and \( \pi(w) \) is the same survival function as given before.

3.3. Steady states and their stability in the case of \( b_1(S, I) \)

In this section, we consider the case of constant snail recruitment rate, i.e., \( b_1(S, I) = A_s \). As is in most epidemiology models, the reproductive ratio \( \mathcal{R} \) calculated above provides threshold conditions that determines whether the parasites will go extinct or will persist in the host population. The next result shows that parasite population will go extinct if \( \mathcal{R} \) is below 1.

**Result 1.** The disease-free steady state \( E_0 \) of the system (7) is locally asymptotically stable (l.a.s.) if \( \mathcal{R} < 1 \) and unstable if \( \mathcal{R} > 1 \).

**Proof.** Linearize the system (7) about the \( E_0 \) and consider exponential solutions of the form

\[ p(t, a) = p_1(a)e^{i\lambda t} + o(e^{2\lambda t}), \quad B(t) = B_1e^{i\lambda t} + o(e^{2\lambda t}). \]
Then the linear parts of the $p$ and $B$ equations are of the form

$$\frac{dp_1(a)}{da} = \beta(a)A_h \pi(a)B_1 \hat{K}(\lambda) - (\delta_p(a) + \lambda) p_1(a),$$

$$B_1 = \xi \frac{A_k}{\mu_s} \int_0^\infty p_1(a) da,$$

where $\hat{f}(\lambda)$ denotes the Laplace transform of $f(\tau)$, i.e.,

$$\hat{f}(\lambda) = \int_0^\infty e^{-\lambda \tau} f(\tau) d\tau.$$

Solving the $p_1$ equation in (12) and noticing that $p_1(0) = 0$ we get

$$p_1(a) = \int_0^a \beta(u) \hat{K}(\lambda) B_1 A_h \pi(u) e^{-\int_u^a (\delta_p(s) + \lambda) ds} du.$$

Substituting the above expression for $p_1(a)$ in the $B_1$ equation in (12) we have

$$B_1 = \xi \frac{A_k}{\mu_s} \int_0^\infty \int_0^a \beta(u) \hat{K}(\lambda) B_1 A_h \pi(u) e^{-\int_u^a (\delta_p(s) + \lambda) ds} du da.$$ \hspace{1cm} (13)

By changing the order of integration, introducing $\tau = a - u$, and dividing both sides by $B_1$ (since $B_1 \neq 0$) in (13) we get the characteristic equation

$$1 = \int_0^\infty \int_0^\infty \beta(u) \hat{K}(\lambda) A_h \pi(u) \xi \frac{A_k}{\mu_s} \int_u^\infty e^{-\int_u^{a} (\delta_p(s) + \lambda) ds} du.$$

Let $G(\lambda)$ denote the right hand side of (14). Then, at $\lambda = 0$,

$$G(0) = \int_0^\infty \beta(u) \hat{K}(\lambda) A_h \pi(u) \xi \frac{A_k}{\mu_s} \int_0^\infty e^{-\int_0^{a} (\delta_p(s) + \lambda) ds} du.$$ \hspace{1cm} (15)

Clearly, $G(0) = \mathcal{R}$. It is easy to see $G'(\lambda) < 0$, $\lim_{\lambda \to -\infty} G(\lambda) = 0$, $\lim_{\lambda \to -\infty} G(\lambda) = \infty$. It follows that the equation $G(\lambda) = 1$ has a unique real root $\lambda^* < 0$ if $G(0) < 1$ (or $\mathcal{R} < 1$), and $\lambda^* > 0$ if $G(0) > 1$ (or $\mathcal{R} > 1$). Let $\lambda = x + iy$ be an arbitrary complex solution to $G(\lambda) = 1$. Then

$$1 = G(\lambda) = |G(x + iy)| \leq G(x),$$

which implies that $\lambda^* > x$. It follows that the parasite-free steady state is l.a.s. if $\mathcal{R} < 1$, and unstable if $\mathcal{R} > 1$. When $\mathcal{R} > 1$ our next result shows that an endemic steady state exists. \hfill $\square$

**Result 2.** When $\mathcal{R} > 1$ the system (7) has an unique endemic steady state and it is locally asymptotically stable.

**Proof.** Recall that $\alpha$ represents the disease-induced human death rate by a single parasite. Thus, $\alpha$ is very small. For the analytic proof of this result we let $\alpha = 0$. For the case of $\alpha > 0$ the result is confirmed through numerical simulations. Let $E^* = (n^*(a), p^*(a), S^*, B^*)$ denote the endemic steady state with positive components, and let $N^* = \int_0^\infty n^*(a) da$ and $P^* = \int_0^\infty p^*(a) da$. Let $\alpha = 0$. Then $n^*(a) = A_h \pi(a)$, and $E^*$ satisfies
\[ \frac{d}{da} p^*(a) = \beta(a) A_h \pi(a) \mathcal{H} B^* - \delta_p(a) p^*(a), \]
\[ 0 = A_k - \mu_s S^* - B^*, \]
\[ B^* = \xi P^* S^*. \]  
(16)

Solving for \( p^*(a) \) we get
\[ p^*(a) = \int_0^a \beta(u) A_h \pi(u) B^* \mathcal{H} e^{-\int_u^a \delta_p(s) ds} \, du. \]  
(17)

Substituting this into the \( B^* \) equation in (16) we get
\[ B^* = \xi S^* \int_0^\infty \int_0^a \beta(u) A_h \pi(u) B^* \mathcal{H} e^{-\int_u^a \delta_p(s) ds} \, du \, da. \]  
(18)

By changing the order of integration, introducing \( \tau = a - u \), and dividing both sides by \( B^* \) we get the following equation for \( S^* \):
\[ 1 = \int_0^\infty \beta(u) \mathcal{H} A_h \pi(u) \int_0^\infty \xi S^* e^{-\int_u^a \delta_p(s) ds} \, d\tau \, du =: H(S^*). \]  
(19)

For \( E^* \) to be biologically feasible, we need to require \( S^* \in (0, A_s/\mu_s) \). Since \( H(0) = 0 \) and \( H(A_s/\mu_s) = \mathcal{R} > 1 \), the monotonicity of \( H(S^*) \) implies that \( H(S^*) = 1 \) has a unique root \( S^* \) in \((0, A_s/\mu_s)\). In fact, \( S^* = (A_s/\mu_s)(1/\mathcal{R}) \). We can then get \( B^* \) and \( p^*(a) \) using the second equation in (16) and the equation (17), respectively. Thus, we have an unique endemic steady state \( E^* \) when \( \mathcal{R} > 1 \). We proceed to show the stability of \( E^* \). Since \( a = 0 \), the system (7) becomes
\[
\begin{align*}
\frac{\partial}{\partial t} n(t, a) + \frac{\partial}{\partial a} n(t, a) &= -\mu_h(a)n(t, a), \\
\frac{\partial}{\partial t} p(t, a) + \frac{\partial}{\partial a} p(t, a) &= \beta(a)n(t, a)(K * B)(t) - \delta_p(a)p(t, a), \\
\frac{d}{dt} S(t) &= b(S, I) - \mu_s S(t) - B(t), \\
B(t) &= \xi P(t)S(t).
\end{align*}
\]  
(20)

Note that at \( E^* \)
\[ n^*(a) = A_h \pi(a), \quad P^* = \frac{\mu_s}{\xi} \left( \tilde{\mathcal{R}} - 1 \right), \quad S^* = \frac{1}{\mathcal{R}} A_s \frac{A_s}{\mu_s}. \]  
(21)

where \( \tilde{\mathcal{R}} = \mathcal{R} \) evaluated at \( a = 0 \). Solving the \( n \) equation in (20) along the characteristic lines
\[ n(t, a) = \begin{cases} 
A_h \pi(a), & t > a \\
n_0(a), & t \leq a
\end{cases} \]  
(22)

and substituting this into the \( p \) equation in (20) we get
\[
p(t, a) = \begin{cases} 
A_k (K * B)(t) \int_0^a \beta(w) \pi(w)e^{-\int_u^a \delta_p(s) ds} \, dw, & t > a \\
q(t, a), & t \leq a
\end{cases}
\]  
(23)
where
\[ q(t, a) = n_0(a)(K * B)(t) \frac{\pi(a)}{\pi(a - t)} \int_0^a \beta(w)\pi_1(w)e^{-\mu_s w} dw + \pi(a)\pi_1(a)e^{-\mu_s a} p_0(t) - \frac{\mu_s}{\xi}(K * B)(t) + Q(t) \]

Then
\[ P(t) = \tilde{\mathcal{R}} \frac{1}{\xi} \frac{\mu_s}{A_s} (K * B)(t) + Q(t) \]

where \( Q(t) = \int_0^t q(t, a) da \). Noticing that \( Q(t) \to 0 \) as \( t \to \infty \), we have the following limiting system for \( P(t) \) and \( S(t) \) (see (20))
\[
\begin{align*}
P(t) &= \tilde{\mathcal{R}} \frac{1}{\xi} \frac{1}{\mathcal{K}} \frac{\mu_s}{A_s} (K * (PS))(t), \\
\frac{d}{dt} S(t) &= A_s - \mu_s S(t) - \xi P(t) S(t).
\end{align*}
\]

The linearization of (24) at \((P^*, S^*)\) \((P^* \text{ and } S^* \text{ are given in (21)})\) yields the following characteristic equation
\[
\hat{\lambda} + \mu_s \tilde{\mathcal{R}} + \mu_s \frac{\hat{K}(\lambda)}{\mathcal{K}} \frac{1}{1 - K(\lambda)} (\tilde{\mathcal{R}} - 1) = 0,
\]

where \( \hat{\lambda} \) is an eigenvalue and \( \hat{K}(\lambda) \) denotes the Laplace transform of \( f \). We need to show that (25) has no roots with a non-negative real part when \( \tilde{\mathcal{R}} > 1 \). Suppose not. Then (25) has a root \( \hat{\lambda} = x + iy \) for which \( x \geq 0 \) and
\[
\begin{align*}
x + iy + \mu_s \tilde{\mathcal{R}} + \mu_s \frac{\hat{K}(x + iy)}{\mathcal{K} - K(x + iy)} (\tilde{\mathcal{R}} - 1) &= 0. \\
\end{align*}
\]

Introducing the notation
\[
\begin{align*}
\mathcal{K}_c &= \int_0^\infty K(t)e^{-xt} \cos yt \ dt, \\
\mathcal{K}_s &= \int_0^\infty K(t)e^{-xt} \sin yt \ dt.
\end{align*}
\]

Noticing that
\[
\begin{align*}
\frac{\hat{K}(x + iy)}{\mathcal{K} - \mathcal{K}_c} &= \frac{\int_0^\infty K(t)e^{-xt} \ cos yt \ dt}{\int_0^\infty K(t)e^{-xt} \ dt} - 1 \\
\frac{\hat{K}(x + iy)}{\mathcal{K} - \mathcal{K}_s} &= \frac{\int_0^\infty K(t)e^{-xt} \ sin yt \ dt}{\int_0^\infty K(t)e^{-xt} \ dt} - 1 \\
\frac{\mathcal{K}_c}{\mathcal{K}_c^2 + (\mathcal{K}_s)^2} &= 1 + \left( -\frac{\mathcal{K}_s}{\mathcal{K}_c^2 + (\mathcal{K}_s)^2} \right) i
\end{align*}
\]
and separating the real and imaginary parts of the left hand side of (26) we get
\[
\begin{aligned}
x + \mu_s \Re + \mu_s \left( \frac{x(x-x_c)}{(x-x_c)^2 + (x_s)^2} - 1 \right) (\Re - 1) &= 0, \\
y - \mu_s \left( \frac{x(x-x_c)}{(x-x_c)^2 + (x_s)^2} - 1 \right) (\Re - 1) &= 0.
\end{aligned}
\] (27)

From the second equation in (27), we have
\[
\frac{\mathcal{N}}{[\mathcal{N} - \mathcal{N}_c]^2 + (\mathcal{N}_s)^2} = \frac{y}{\mu_s} \frac{1}{\Re - 1} \frac{1}{\mathcal{N}_s},
\]
and substituting this into the first equation in (27), we have
\[
x + \mu_s \Re + \mu_s \left( \frac{\mathcal{N}}{\mathcal{N}_c} \frac{1}{\mu_s} \frac{1}{\Re - 1} \frac{1}{\mathcal{N}_s} - 1 \right) (\Re - 1) = 0,
\]
which simplifies to
\[
x + y \frac{\mathcal{N} - \mathcal{N}_c}{\mathcal{N}_s} + \mu_s = 0.
\] (28)

However, from
\[
\frac{\mathcal{N}}{[\mathcal{N} - \mathcal{N}_c]^2 + (\mathcal{N}_s)^2} = \frac{y}{\mu_s} \frac{1}{\Re - 1} \frac{1}{\mathcal{N}_s} = \frac{y}{\mu_s} \frac{1}{\Re - 1} \frac{1}{\mu_s},
\]
we have \(\frac{x}{\mathcal{N}_s} > 0\), which yields
\[
x + y \frac{\mathcal{N} - \mathcal{N}_c}{\mathcal{N}_s} + \mu_s > 0
\]
as \(\mathcal{N}_c < \mathcal{N}\) and \(x \geq 0\). This contradicts with (28). Hence all eigenvalues will have negative real parts. It follows that for solutions near \(E^0 P(t) \to P^*\) and \(S(t) \to S^*\) as \(t \to \infty\). Consequently, \(p(t,a) \to p^*(a)\) as \(t \to \infty\) [see (17)]. From (22), it is clear that \(n(t,a) \to n^*(a)\) as \(t \to \infty\). Therefore, \(E^*\) is l.a.s. if \(x = 0\). This result is confirmed for the case of \(x > 0\) by numerical simulations (see Fig. 1). Fig. 1 illustrates that the number of parasites \(P(t)\) will go to zero if \(\Re < 1\) [see Fig. 1(a)] and it will stabilize at a positive level if \(\Re > 1\) [see Figs. 1(b) and (c)]. The parameter values used in Fig. 1 are chosen based on [12,13] and they are: \(k = 0.243, \mu_s = 0.3, \mu_p = 0.2, \rho = 0.0005, \gamma = 4, d_s = 0.01, \alpha = 10^{-5}\) (the time unit is year). \(r(t)\) is a periodic function of period eight weeks which is chosen to be piecewise linear in our simulation. \(\beta(a) = 2 \times 10^{-4}\) and \(\sigma(a) = 0.2\) are both constant, and \(\mu_{hl}(a)\) is obtained from the census of United States in the year of 2000. The proof of Result 2 is complete. \(\Box\)

The following result shows that when \(\Re < 1\) the parasite-free steady state is actually globally asymptotically stable.

**Result 3.** If \(\Re < 1\) then \(E_0\) is a global attractor, i.e.
\[
\lim_{t \to \infty} (n(t,a), p(t,a), S(t)) = \left( A_{n} \pi(a), 0, \frac{A_s}{\mu_s} \right)
\]
for all positive solutions of the system (7).
Proof. Let
\[ p_1(a) = \limsup_{t \to \infty} p(t, a), \quad S_1 = \limsup_{t \to \infty} S(t), \quad P_1 = \limsup_{t \to \infty} P(t), \quad P_1 = \liminf_{t \to \infty} P(t). \]
Using the Corollary 2.4 in Thieme [29], we can choose a sequence \( t_n \to \infty \) such that \( \frac{dS(t_n)}{dt} \to 0 \) and \( S(t_n) \to S^\infty \) as \( n \to \infty \). Using this sequence and the \( S \) equation in (24) we get
\[ 0 \leq A_s - \mu_s S^\infty - \xi P_1 S^\infty. \]
Since \( P_\infty \geq 0 \), from the above inequality
\[ S^\infty \leq \frac{A_s}{\mu_s + \xi P_\infty} \leq \frac{A_s}{\mu_s}. \]
Then from the \( P \) equation in (24) we have
\[ P^\infty \leq P^\infty S^\infty \frac{\mu_s}{A_s} \leq P^\infty \frac{\tilde{R}}{A_s}. \]
Since \( \tilde{R} < 1 \), the above inequality implies that \( P^\infty = 0 \), i.e., \( \lim_{t \to \infty} P(t) = 0 \). Using this and the \( S \) equation in (24) we get \( \lim_{t \to \infty} S(t) = A_d/\mu_s \). Noticing that \( \lim_{t \to \infty} B(t) = \lim_{t \to \infty} \xi P(t) S(t) = 0 \) we have from (23) that \( \lim_{t \to \infty} p(t, a) = 0 \) for all \( a \). It is obvious from (22) that \( \lim_{t \to \infty} n(t, a) = A_h \pi(a) \) for all \( a \). This completes the proof of Result 3.

3.4. Steady states and stability for the case of \( b_2(S, I) \)

In this case, the reproductive number \( \mathcal{R}' \) is given by (10). The parasite-free steady state is
\[ E'_0 = (A_h \pi(a), 0, \bar{S}), \]
where \( \bar{S} \) is given by (11). Similarly to the case of \( b_1(S, I) \), we have the following global stability of \( E'_0 \).

Result 4. \( E'_0 \) is a global attractor if \( \mathcal{R}' < 1 \) and it is unstable if \( \mathcal{R}' > 1 \).
Proof. The proof is the same as that for the case of $b_1(S,I)$ (see Results 1 and 3).

The existence and the stability of the endemic steady state are more difficult to prove than that for the case constant birth rate of snails. In fact, the following result shows that the endemic steady state is not always stable in the case of density dependent birth rate of snails, $b_2(S,I)$.

Result 5. (a) The system (7) has a unique endemic equilibrium $E^\diamond$ if $R_0 > 1$; (b) When the model parameters (except $c_1$) are chosen in a realistic region, a Hopf bifurcation may occur at a critical point $c_1 = \tilde{c}_1$ such that $E^\diamond$ is l.a.s. if $c_1 < \tilde{c}_1$ and unstable if $c_1 > \tilde{c}_1$ in which case stable periodic solutions exist.

Proof. (a) Again our analytical proof is for the case of $a = 0$. Our numerical simulations support the result for the case of $a > 0$. Let $n^\diamond(a), p^\diamond(a), S^\diamond$ and $I^\diamond$ denote the steady state values of the corresponding variables at $E^\diamond$, and let $P^\diamond = \int_0^\infty p^\diamond(a)\,da$. Then $P^\diamond > 0$, $n^\diamond(a) = A_h\pi(a)$, and $p^\diamond(a), S^\diamond, I^\diamond$ satisfy the equations

\[ \frac{d}{da}p^\diamond(a) = \beta(a)\lambda_0\pi(a)\varphi\xi S^\diamond - \delta(p^\diamond(a)) p^\diamond(a), \]

\[ 0 = \frac{c_1 S^\diamond}{c_2 + S^\diamond + I^\diamond} - \mu_s S^\diamond - \xi p^\diamond S^\diamond, \]

\[ I^\diamond = \frac{\xi p^\diamond S^\diamond}{\mu_s + \delta_s}. \]

Solving the first equation for $p^\diamond(a)$ we have

\[ p^\diamond(a) = P^\diamond S^\diamond \int_0^\alpha e^{-\int_0^\alpha \delta_p(w)\,dw} \beta(w)\lambda_0\pi(w)\varphi\xi \,dw. \]

Integrating both sides from 0 to $\infty$, dividing both sides of the resulting equation by $P^\diamond$, and using (10) we get $1 = S^\diamond \tilde{R}' / \tilde{S}$ or

\[ S^\diamond = \frac{1}{\tilde{R}'}, \]

where $\tilde{R}' = R'$ evaluated at $a = 0$ and $\tilde{S} > 0$ is given in (11). Using (31) and the last two equations in (30) we get

\[ \frac{c_1}{c_2 + \frac{1}{\tilde{R}'} \frac{1}{\mu_s + \delta_s} S^\diamond + \frac{1}{\tilde{R}'}} = \mu_s + \xi P^\diamond \]

which can be written as

\[ a_2(P^\diamond)^2 + a_1 P^\diamond + a_0 = 0 \]

with
\[ a_0 = \mu_s \left( c_2 + \frac{1}{R_0} S \right) - c_1 = \mu_s \bar{S} \left( \frac{1}{R_0} - 1 \right), \]
\[ a_1 = \xi \left( c_2 + \frac{S}{R_0} + \frac{c_s}{\mu_s + \delta_s} \bar{S} \right), \]
\[ a_2 = \frac{\xi^2 \bar{S}}{R_0} \frac{1}{\mu_s + \delta_s}. \]

Obviously, \( a_1 > 0 \) and \( a_2 > 0 \). It is also clear that \( a_0 < 0 \) if \( R_0 > 1 \) and \( a_0 > 0 \) if \( R_0 < 1 \). Therefore, the equation (32) has a unique positive solution if \( R' > 1 \) and no positive solutions if \( R' \leq 1 \). This finishes the proof of the part (a).

Fig. 2. Plots of the number of adult parasites \( P(t) \) vs. time. In (a) and (b) \( R' < 1 \) and the parasite-free steady state is stable. In (c) and (d) \( R' > 1 \) and \( R' \) is not too big. The endemic steady state is stable. In (e) and (f) \( R' > 6 \) and stable periodic solutions exist.
We do not have an analytic proof for part (b), but our numerical simulations show that a Hopf bifurcation may occur for parameters in a certain range (see Fig. 2). In Fig. 2, we choose $c_1$ as a bifurcation parameter. Other parameters are fixed at the same values as in Fig. 1 and $c_2 = 600$. For this set of parameters a Hopf bifurcation occurs at some critical value of $R_0 \in (5, 6)$ or $c_1 \in (650, 700)$. We have chosen $c_1$ (or equivalently the ratio $c_1/c_2$) to be the bifurcation parameter to make apparent the effect of the density-dependent snail recruitment (due to the infertility of infected snails) on the dynamics.

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 [14]. 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 [14]. Other studies have shown seasonal periodicity of prevalence of schistosome infections in snail populations [24,31]. Since our model does not incorporate seasonal variations, our study indicates that the infertility of infected snails (notice that in $b_2(S,I)$ it has been assumed, based on epidemiological evidence, that only susceptible snails can reproduce) 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 (e.g., [9]).

4. An application to disease control

The model analysis presented in the previous sections suggests that the reproductive number $R$ is directly related to the disease prevalence, and that effective intervention towards disease control can be achieved by reducing $R$. A visible advantage of the age-structure in our model is that it can help design age-targeted treatment strategies. In Section 4.1, we first study how the variability of $R$ depends on the uncertainty in the estimation of model parameters that may influence $R$. Then we look at the effect of certain parameter changes on the reduction of $R$, and explore how various age-dependent treatments may affect the disease prevalence. In Section 4.2, we consider age-targeted treatment strategies. Although other methods for the control of schistosomiasis may be considered (e.g., controlling the snail population or reducing the contact of humans with contaminated water sources), in this section we discuss only control programs by treating infected humans. The effectiveness of various treatment programs is assessed using the mean parasite load within human hosts.

4.1. Sensitivity and uncertainty analysis

Among all parameters involved in the model, there are several parameters or (age-dependent) parameter functions whose values are difficult to obtain. Two of such examples are the human-to-snail transmission rate $\rho$ [or equivalently the parameter $\xi = \rho \gamma$ in the system (7)] and the age dependent snail-to-man transmission rate $\beta(a)$. To study the influence of the uncertainty of these
parameters on the variability of $R$ we use the Latin hypercube sampling (LHS) method which allows each of the input parameters to have a distribution instead of a single value.

According to Sturrock [28] and Cristiano [8], schistosomiasis infection is highest among the age group 11–20. For ease of demonstration, we assume that the population of all ages can be divided into the following age groups:

$$a_{i-1} < a \leq a_i \text{ (group } i \text{)}$$

where $a_i = 10i$ (e.g., $a_0 = 0, a_1 = 10$, etc.), and that $\beta(a)$ is a step function with $\beta(a) = \beta_i$ (where $\beta_i$ is a constant) for $a_{i-1} < a \leq a_i$. Similarly, $\sigma(a)$ is also assumed to be a step function with $\sigma(a) = \sigma_i$ (where $\sigma_i$ is a constant) for $a_{i-1} < a \leq a_i$. That is,

$$\beta(a) = \begin{cases} \beta_i & \text{if } a_{i-1} < a \leq a_i, \quad i = 1, 2, \ldots, 7, \\ 0 & \text{if } a > 70, \end{cases}$$

$$\sigma(a) = \begin{cases} \sigma_i & \text{if } a_{i-1} < a \leq a_i, \quad i = 1, 2, \ldots, 7, \\ 0 & \text{if } a > 70, \end{cases}$$

where $\beta_i$ and $\sigma_i$ are constants.

For simplicity we demonstrate our approach by considering only the first three age groups (i.e., $i = 1, 2, 3$). For the calculation of $R$, some of the parameters are assumed to have a certain distribution. For example, in Table 2 we list some of these distributions for $\beta_1$, $\beta_2$, $\sigma_1$, $\rho$, $\gamma$, and for these parameters the histograms of the values obtained from the LHS (from a sample size of 1000) are shown in Fig. 3. $\beta_3$ is similar to $\beta_1$, and $\sigma_2$ and $\sigma_3$ are similar to $\sigma_1$ which are not shown. For other parameters we use fixed values adopted from other sources. For example, $K_h = 6$, $\mu_p = 0.2$, $\alpha = 10^{-6}$, $\mu_s = 0.3$ and $\delta_s = 0.01$ have been used in Feng et al. [12]. The age-specific human natural death rate $\mu_h(a)$ is adopted from Hoyert [18].

Using the input parameter distributions chosen above and the method of Latin hypercube sampling, we obtain the simulation results for the distribution of $R$ which are shown in Fig. 4. The histograms show the distributions of $R$ with treatment (light) and without treatment (dark). The results show that, in the absence of treatment, the mean and variance of the distribution of $R$ are 1.4 and 0.12, respectively, and the probability of $R$ being greater than 1 is 1 (see Table 3). Under the treatment described in Table 2, the mean and variance of the distribution of $R$ are 0.94 and 0.09, respectively, and the probability of $R$ being less than 1 is 0.76 (see Table 3).

The independent influence of a single parameter on the variation of $R$ can be determined by looking at some of the statistics obtained from the sensitivity analysis such as the partial rank correlation coefficients (PRCCs) which are given in Table 4. The ordering of these PRCCs directly corresponds to the level of statistical influence on the variability of $R$ that the associated input parameter has due to its own estimation uncertainty. For example, the PRCC value for $\sigma_2$ is

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_2$</td>
<td>Between (0.00008, 0.00012), with peak at 0.00001</td>
</tr>
<tr>
<td>$\beta_1$, $\beta_3$</td>
<td>Between (0.000064, 0.000096), with peak at 0.00008</td>
</tr>
<tr>
<td>$\sigma_i$ ($i = 1, 2, 3$)</td>
<td>Between (0.32, 0.48), with peak at 0.4</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Between (0.0004, 0.0006), with peak at 0.0005</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Between (3.2, 4.8), with peak at 4</td>
</tr>
</tbody>
</table>
negative and has the largest absolute value among the three $r_i$ values, which suggests that increasing the treatment rate for the age group 11–20 is more effective in reducing $R$ (if only one age group were to be chosen to increase the treatment rate). From Table 4, we also observe that the PRCC value of $\xi$ is much higher than those of $\beta_i$, $i = 1, 2, 3$. This indicates that, for the set of parameter values used for this calculation, the human-to-snail transmission rate is statistically more influential to the variation of $R$ than the snail-to-human transmission rate.
We can also explore the effectiveness of various treatment programs in reducing $R$ by directly examining the formula for $R$ (i.e., without assuming distributions for input parameters and using the LHS). Consider the case of $b_1(S, I)$ for the birth rate of snails. A formula for $R$ is given in (8) which can be rewritten as (by exchanging the order of integration and letting $a = w + u$)

$$R = \xi A_0 \frac{\mu_0}{\mu_s} \int_0^\infty \int_0^a \beta(w) A_h \pi(w) \mathcal{K} e^{-\int_w^{\mu_h(S) + \mu_p + \sigma(a) + \mu_0} \text{d}r} \text{d}w \text{d}a = C \sum_{i=1}^7 I_i,$$

(34)

where $C = \xi \frac{A_0}{\mu_s} A_h \mathcal{K}$ is a constant (independent of $\beta$ and $\sigma$) and

$$I_i = \int_{a_i-1}^{a_i} \int_0^a \beta(w) e^{-\int_w^{\mu_h(S) + \mu_p + \sigma(a) + \mu_0} \text{d}r} \text{d}w \text{d}a.$$

For simplicity, we assume that the natural human death rate $\mu_0(a)$ is constant and that only $\sigma$ values for the first three groups are changing. Using (33) for $\beta(a)$ and $\sigma(a)$ we can evaluate $R$ by evaluating each $I_i$. Notice that $I_i$ depends on $\sigma_j$ and $\sigma_i$ for all $j \leq i$. For example, denoting $\mu_h + \mu_p + \sigma$ by $d$ we have

Table 3
Estimates of $R$ from 10 Latin hypercube sampling replications

<table>
<thead>
<tr>
<th>Replication No.</th>
<th>Without treatment</th>
<th>With treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Var.</td>
</tr>
<tr>
<td>1</td>
<td>1.4082377</td>
<td>0.1177867</td>
</tr>
<tr>
<td>2</td>
<td>1.4082623</td>
<td>0.1177707</td>
</tr>
<tr>
<td>3</td>
<td>1.4082566</td>
<td>0.1177971</td>
</tr>
<tr>
<td>4</td>
<td>1.4082367</td>
<td>0.1177797</td>
</tr>
<tr>
<td>5</td>
<td>1.4082570</td>
<td>0.1177962</td>
</tr>
<tr>
<td>6</td>
<td>1.4082557</td>
<td>0.1177934</td>
</tr>
<tr>
<td>7</td>
<td>1.4082435</td>
<td>0.1177990</td>
</tr>
<tr>
<td>8</td>
<td>1.4082607</td>
<td>0.1177828</td>
</tr>
<tr>
<td>9</td>
<td>1.4082576</td>
<td>0.1177621</td>
</tr>
<tr>
<td>10</td>
<td>1.4082492</td>
<td>0.1177785</td>
</tr>
<tr>
<td>Mean</td>
<td>1.4082544</td>
<td>0.11778462</td>
</tr>
<tr>
<td>SE</td>
<td>$8.41 \times 10^{-6}$</td>
<td>$1.22 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

Table 4
PRCC values of the input parameters

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>PRCC</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$</td>
<td>0.49549</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.59268</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>0.49277</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\sigma_1$</td>
<td>-0.13021</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>-0.21368</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\sigma_3$</td>
<td>-0.13313</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\xi$</td>
<td>0.97769</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>
\[ I_2 = \int_0^{a} \int_0^{10} \beta(w) e^{-\int_0^{10} \frac{(d + r(s))}{C_0} \, ds} \, dw \, da \]
\[ = \int_0^{10} \int_0^{a} \beta_1 e^{-\int_0^{10} \frac{(d + r_1)}{C_0} \, ds} \, dw \, da \]
\[ + \int_0^{10} \left[ \int_0^{a} \beta_2 e^{-\int_0^{10} \frac{(d + r_2)}{C_0} \, ds} \, dw \right] \frac{d \sigma_1}{C_0} \, da \]
\[ = \frac{10\beta_1}{d + \sigma_1} + \frac{\beta_1 \left[ e^{-10(d + r_1)}(d + r_1) - 1 \right]}{(d + \sigma_1)^2} + \frac{\beta_1 \left[ e^{-10(d + r_1)}(d + r_1) - 1 \right]}{(d + \sigma_1)(d + \sigma_2)} \]
\[ + \frac{10\beta_2}{d + \sigma_2} + \frac{\beta_2 \left[ e^{-10(d + r_2)} - 1 \right]}{(d + \sigma_2)^2} . \]

To see the effect of each \( \sigma_i \) \( (i = 1, 2, 3) \) on the reduction of \( R \) we look at the partial derivative of \( R \) (or equivalently the partial derivative of \( I \)) with respect to \( \sigma_i \) \( (i = 1, 2, 3) \). If an index \( i \) corresponds to the largest value of \( \left| \frac{dR}{d\sigma_i} \right| \) then an increased treatment in the \( i \)th age-group will be more effective in reducing \( R \). We examine various distributions of \( \beta_i \) and results are shown in Fig. 5. In Fig. 5(a) a higher \( \beta_1 \) value is chosen and it shows that \( R \) is more sensitive to \( \sigma_1 \). Similarly, a higher value for \( \beta_2 \) and \( \beta_3 \) is used in Figs. 5(b) and 5(c), respectively. These figures suggest that treatment strategies should target at the age group that has a higher infection rate.

### 4.2. Age-targeted treatment strategies

The above sensitivity analysis for the reproductive number \( R \) suggests that a control program would be more effective if more treatment effort is given to the age group that has a higher infection rate. We now compare this result with results obtained by looking at the mean parasite load (defined below) within humans under various treatment programs. We remark that the parameter \( \sigma_i \) is actually a product of several parameters including the fraction of treated humans in the age group \( i \) and how soon an infected person gets treated. In this section we assume that an increase in \( \sigma_i \) is due to an increased fraction of treated humans in the age-group \( i \).

The measure we use here to assess the effectiveness of age-dependent treatment strategies is the mean parasite load within humans. The overall mean parasite load is defined as the ratio of the total number of parasites to the total number of humans, which we denote by \( M_k \) for a strategy.

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Fig. 5. Plots of \( \left| \frac{dR}{d\sigma_i} \right| \) vs \( \sigma_i \) \( (i = 1, 2, 3) \) showing the sensitivity of \( R \) to \( \sigma_i \) for various distribution of \( \beta_i \) \( (i = 1, 2, 3) \). In (a) \( \beta_1 = 0.0012, \beta_2 = \beta_3 = 0.0008 \). In (b) \( \beta_1 = \beta_3 = 0.0008, \beta_2 = 0.0012 \). In (c) \( \beta_1 = \beta_2 = 0.0008, \beta_3 = 0.0012 \).
indexed by $k$. We also look at the mean parasite load within each age group which is denoted by $m_{ki}$, with the index $i$ denoting the $i$th age group.

Of course, an ideal scenario would be to treat all infected humans. However, in many cases this is impossible to do due to limited access and/or resources. The problem we study, here, concerns a different scenario. Suppose that there is a current treatment program, and that health officials want to choose one or more age groups to increase their treatment rate. Which age group(s) should be targeted? To answer this question, we compare the outcomes (in terms of the mean parasite load—both the overall and the age-specific) under different age-targeted treatment strategies. Here, the overall effort for a treatment program is simply defined as the sum of the treatment rates $\sum_{i=1}^{3}\sigma_i$ (which is independent of the age-distribution of humans), and we compare the mean parasite loads under different age-targeted treatment programs that have the same level of overall effort.

Some questions associated with cost-effectiveness will also be considered by comparing treatment programs that have different levels of overall effort. This can be done by looking at the percentage of reduction in the mean parasite load in relation to the percentage of increase in the treatment effort of certain age groups. We remark that our goal here is not to identify the optimal treatment strategy given a constraint on the effort (though this would be a useful optimization problem) in which case the effort for an age-dependent control program should involve the age-distribution of humans.

Assume that a baseline treatment program is described by $\sigma_i = 0.2$ for $i = 1, 2, 3$. First, we consider the case in which only one age group will be devoted a higher treatment effort. For example, for one group $\sigma$ is increased to 0.4 while for other age groups $\sigma$ remains at 0.2. Table 5 lists three such treatment strategies that have the same overall effort. The function $\beta(a)$ is chosen such that the age group 11–20 has a higher value than other age groups.

The overall mean parasite load is obtained by numerically integrating the system (5) for a given set of parameter values. After the system has stabilized we calculate the total number of parasites and the total number of humans under a given age-targeted treatment program, which will give us the values of $M_k$ and $m_{ki}$. Fig. 6 shows the outcomes of these three strategies listed in Table 5. Fig. 6(a) shows that the strategy that targets at the age group 11–20 is the most effective one (in the sense that it results in a lowest overall mean parasite load), while the strategy that targets at the age group 0–10 is the least effective one. More detailed age-dependent distributions of the parasite load corresponding to these treatment programs are given in Fig. 6(b), which shows that the strategy II results in a more uniform parasite distribution among all age groups.

Next, we consider treatment programs that target at several age groups (i.e., these targeted age groups will have a higher treatment rate while other groups have the same baseline treatment rate.

<table>
<thead>
<tr>
<th>Control strategies targeted at only one age group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment value $\sigma(\cdot)$</strong></td>
</tr>
<tr>
<td>Age 0–10</td>
</tr>
<tr>
<td>Strategy 1</td>
</tr>
<tr>
<td>Strategy 2</td>
</tr>
<tr>
<td>Strategy 3</td>
</tr>
</tbody>
</table>
In this case, as the overall treatment efforts are different among these programs, instead of looking at which program will produce a lower mean parasite load, we consider questions associated with cost-effectiveness such as what percentage reduction of the mean parasite load will result from a given percentage increase in the treatment effort of certain age groups.

Table 6 lists five treatment programs with the first one being the baseline treatment. We assess the effect of each of the four programs \((k = II, III, IV, V)\) by looking at the reduction in the parasite load relative to the baseline treatment program (Strategy I). That is, we look at the ratio of the overall mean parasite loads \(M_k/M_1\) and the ratio of age-specific mean parasite loads \(m_{ki}/m_{1i}\) \((i = 1, 2, 3)\). These ratios are plotted in Fig. 7. Fig. 7(a) shows that Strategy II, which targets at the

**Table 6**

<table>
<thead>
<tr>
<th>Treatment value</th>
<th>Age 0–10</th>
<th>Age 11–20</th>
<th>Age 21–30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy I</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Strategy II</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Strategy III</td>
<td>0.2</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Strategy IV</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Strategy V</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Fig. 6. Outcomes of different strategies when infection rate is higher between age 11 and 20. In (a) it shows the mean parasite load among all individuals between age 0 and 30. In (b) it shows the mean parasite load in each age group under different strategies.

Fig. 7. Outcomes of the treatment strategies I through V listed in Table 6.
single age group 11–20, can further reduce the mean parasite load by about 11% \( (M_2/M_1 \approx 0.89) \). When the treatment coverage is doubled (i.e., two of the age groups will receive an additional treatment effort – Strategies III and IV), the resulted additional reduction in the mean parasite load is around 20% \( (M_k/M_1 \approx 0.80 \text{ for } k = 3, 4) \). When the treatment coverage is tripled (i.e., three age groups will receive an additional treatment effort – Strategies V), the additional reduction in the mean load is around 28% \( (M_5/M_1 \approx 0.72) \). Fig. 7(b) presents a more detailed distribution of the mean parasite load within each age group under the five treatment programs. It seems that the reduction in the parasite load within these age groups will follow the same pattern as the distribution of treatment efforts.

5. Discussion

In this paper, we studied an integro-differential equation model that describes the disease transmission of schistosomiasis. Partial differential equations are used because of the age structures of both human hosts and snail hosts. The age structure of human hosts is needed to incorporate the factor that the infection rate of human hosts is highly dependent on the age of the host, and the age structure of snail hosts is needed because of the fact that the cercaria releasing rate of infected snails is dependent of the infection age of the snail. Mathematical properties of the model are analyzed in terms of the stability of possible steady states. The reproductive number \( R \) is calculated and shown to determine the stability of the steady states. We considered two cases for the snail birth rate: (1) constant birth rate \( b_1(S, I) \) and (2) density-dependent birth rate \( b_2(S, I) = c_1S/(c_2 + S + I) \). For both cases we proved that the disease-free steady state \( E_0 \) is globally asymptotically stable if \( R < 1 \) (Case 1) or \( R < 1 \) (Case 2) and it is unstable if \( R > 1 \) or \( R > 1 \). For Case 1, we proved that when \( R > 1 \) an unique endemic steady state \( E^* \) exists and is locally asymptotically stable. The stability of \( E^* \) is proved analytically only for the case when \( \alpha = 0 \) and is extended to the case of \( \alpha > 0 \) numerically. For Case 2 we have an analytic proof only for the existence of an unique endemic steady state \( E^* \) and its stability is studied numerically. The numerical simulations show that \( E^* \) may lose its stability and stable periodic solutions exist via a Hopf bifurcation at some critical point.

We then studied the effect of various age-dependent treatment strategies on the disease control for the case of \( b_1(S, I) = \Lambda \) using two approaches. The first approach is to study the sensitivity of \( R \) to changes in the age-specific treatment rate, and the second approach is to consider the reduction in the mean parasite load within human hosts. Both approaches seem to suggest that control strategies that target the age group with a higher infection rate is the most effective strategy. We have not considered the cost factor that may be associated with a given age-dependent control program or the possible development of parasite resistance to chemotherapy. The consideration of drug resistance will lead to a model with multiple parasite strains (see [11], for a model without an age-structure).

Although the introduction of an age-structure of human hosts makes the model much more difficult to analyze, it provides an important advantage for the study of age-dependent treatment strategies, especially when the human infection rate is highly age-dependent. In this paper, we have only considered a simple age-structure, i.e., the age-dependent infection rate \( \beta(a) \) and treatment rate \( \sigma(a) \) have been assumed to be step functions over several age groups. More insights may
be obtained if these assumptions can be relaxed. Nevertheless, the results in this paper may provide a theoretical guidance for designing age-targeted treatment strategies.

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References