

OPTIMAL CONTROL ANALYSIS OF MALARIA–SCHISTOSOMIASIS CO-INFECTION DYNAMICS

KAZEEM OARE OKOSUN

Department of Mathematics, Vaal University of Technology
Andries Potgieter Boulevard, Vanderbijlpark, 1911, South Africa

ROBERT SMITH?

Department of Mathematics, The University of Ottawa
585 King Edward Ave, Ottawa ON K1N6N5, Canada

(Communicated by Gerardo Chowell-Puente)

ABSTRACT. This paper presents a mathematical model for malaria–schistosomiasis co-infection in order to investigate their synergistic relationship in the presence of treatment. We first analyse the single infection steady states, then investigate the existence and stability of equilibria and then calculate the basic reproduction numbers. Both the single-infection models and the co-infection model exhibit backward bifurcations. We carrying out a sensitivity analysis of the co-infection model and show that schistosomiasis infection may not be associated with an increased risk of malaria. Conversely, malaria infection may be associated with an increased risk of schistosomiasis. Furthermore, we found that effective treatment and prevention of schistosomiasis infection would also assist in the effective control and eradication of malaria. Finally, we apply Pontryagin’s Maximum Principle to the model in order to determine optimal strategies for control of both diseases.

1. Introduction. Malaria and schistosomiasis often overlap in tropical and subtropical countries, imposing tremendous disease burdens [11, 19, 41]. The substantial epidemiological overlap of these two parasitic infections invariably results in frequent co-infections [16, 47]. The challenges facing the development of a highly effective malaria vaccine have generated interest in understanding the interactions between malaria and co-endemic helminth infections, such as those caused by *Schistosoma*, that could impair vaccine efficacy by modulating host-immune responses to *Plasmodium* infection and treatment [40, 41]. Both malaria and schistosomiasis are endemic to most African nations. However, the extent to which schistosomiasis modifies the risk of febrile malaria remains unclear.

Malaria is an infectious disease that causes morbidity and mortality in the developing world. There are an estimated 360 million cases [44], killing between one

2010 *Mathematics Subject Classification.* Primary: 92B05, 93A30; Secondary: 93C15.

Key words and phrases. Malaria, schistosomiasis, optimal control.

The authors are grateful to two anonymous reviewers whose comments greatly improved the manuscript. KOO acknowledges the Vaal University of Technology Research Office and the National Research Foundation (NRF), South Africa, through the KIC Grant ID 97192 for the financial support to attend and present this paper at the AMMCS-CAIMS 2015 meeting in Waterloo, Canada. RS? is supported by an NSERC Discovery Grant. For citation purposes, please note that the question mark in “Smith?” is part of the author’s name.

to two million people annually [6], primarily among children less than five years of age in sub-Saharan Africa [20]. Three billion people — almost half the world’s population — are at risk of malaria [29, 42, 44]. It has been estimated that one in two humans who ever lived has been killed by malaria [12]. The strategy for reducing malaria transmission is to protect individuals from mosquito bites by the distribution of inexpensive mosquito nets and insect repellents or by mosquito-control measures such as indoor spraying of insecticides and draining of stagnant water where mosquitoes breed [35]. Schistosomiasis is a water-borne disease with a complex biological cycle, involving at least two host species (human and snail), two free-living transmission stages of the parasite (cercariae and miracidia) and distinct environments. Humans are the principal definitive host for the five schistosome species. Adult worms live in the venous system of intestine (*S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum*) or the urinary bladder (*S. haematobium*) [9, 17, 28]. Flooding can lead to severe schistosomiasis outbreaks [15, 28, 48].

Mathematical modelling has been an important tool in understanding the dynamics of disease transmission and also in the decision-making processes regarding intervention mechanisms for disease control. For example, Ross [39] developed the first mathematical models of malaria transmission. His focus was on mosquito control, and he showed that, for the disease to be eliminated, the mosquito population should be brought below a certain threshold. Other studies include Koella and Anita [22], who included a latent class for mosquitoes. They considered different strategies to reduce the spread of resistance and studied the sensitivity of their results to the parameters. Another classical result is due to Anderson and May [4], who derived a malaria model with the assumption that acquired immunity in malaria is independent of exposure duration. Different control measures and the role of the transmission rate on disease prevalence were further examined. Nikolaos et al. [34] proposed a detailed analysis of a dynamical model to describe pathogenesis of HIV infection. Kribs-Zaleta and Velasco-Hernandez [23] derived a simple two-dimensional SIS (susceptible-infected-susceptible) model with vaccination and multiple endemic states. Li and Jin [27] studied the global dynamics of an SEIR (susceptible-exposed-infected-recovered) epidemic model in which latent and immune states were infective. In Chiyaka *et al.* [9], the authors constructed a deterministic mathematical model to study the transmission dynamics of schistosomiasis where the miracidia and cercariae dynamics are incorporated. A mathematical model for the human–cattle–snail transmission of schistosomiasis was proposed by Chen *et al.* [8]. Their model consisted of six ordinary differential equations that describe susceptible and infected human, cattle and snail subpopulations. Longxing *et al.* [28] examined a mathematical model of schistosomiasis transmission under flood in Anhui province, China.

There is an urgent need for co-infection models for infectious diseases, particularly those that mix neglected tropical diseases with “the big three” (HIV, TB and malaria) [19]. However, few studies have been carried out on the formulation and application of optimal control theory to schistosomiasis models. To the best of our knowledge, no work has been done to investigate the malaria–schistosomiasis co-infection dynamics or the application of optimal control methods. Recently, Mukandavire *et al.* [31] proposed a deterministic model for the co-infection of HIV and malaria in a community. Mtisi *et al.* [30] examined a deterministic model for the co-infection of tuberculosis and malaria, while Mushayabasa and Bhunu [32]

proposed a model for schistosomiasis and HIV/AIDS co-dynamics. A simple mathematical model was developed by Mushayabasa and Bhunu [33] to assess whether HIV infection is associated with an increased risk for cholera, while the co-infection dynamics of malaria and cholera were studied by Okosun and Makinde [36].

In this paper, we formulate and analyse an SIR (susceptible, infected and recovered) model for malaria–schistosomiasis co-infection, in order to understand the effect that controlling for one disease may have on the other. Our model includes five control strategies: malaria prevention (treated bednets), schistosomiasis prevention (water treatment), malaria treatment, schistosomiasis treatment and combined therapy for malaria–schistosomiasis infection. We consider these as time-dependent control strategies, in order to determine the optimal strategy for the control of the diseases.

The paper is organised as follows: Section 2 is devoted to the model description and the underlying assumptions. In Section 3, we analyse the schistosomiasis-only model, the malaria-only model and the co-infection model. In Section 4, we perform numerical simulations to illustrate our theoretical results. We conclude with a Discussion in Section 5.

2. Model formulation. Our model subdivides the total human population, denoted by N_h , into subpopulations of susceptible humans S_h , individuals infected only with malaria I_m , individuals infected with only schistosomiasis I_{sc} , individuals infected with both malaria and schistosomiasis C_{ms} , individuals who recovered from malaria R_m and individuals who recovered from schistosomiasis R_s . We make the assumption that co-infected individuals recover from either malaria or schistosomiasis first but not both simultaneously. Hence $N_h = S_h + I_m + I_s + C_{ms} + R_s + R_m$.

The total mosquito vector population, denoted by N_v , is subdivided into susceptible mosquitoes S_v and mosquitoes infected with malaria I_v . Thus $N_v = S_v + I_v$. Similarly, the total snail vector population, denoted by N_{sv} , is subdivided into susceptible snails S_{sv} and snails infected with schistosomiasis I_{sv} . Thus $N_{sv} = S_{sv} + I_{sv}$.

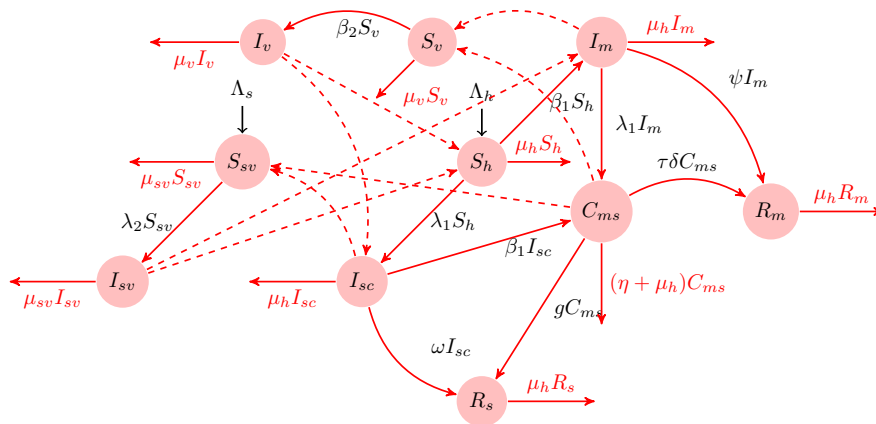


FIGURE 1. Flow diagram for the co-infection model. Dashed curves represent cross-species infection.

The model is given by the following system of ordinary differential equations:

$$\begin{aligned}
S'_h &= \Lambda_h + \epsilon R_s + \alpha R_m - \beta_1 S_h - \lambda_1 S_h - \mu_h S_h \\
I'_m &= \beta_1 S_h - \lambda_1 I_m - (\psi + \mu_h + \phi) I_m \\
I'_{sc} &= \lambda_1 S_h - \beta_1 I_{sc} - (\omega + \mu_h + \eta) I_{sc} \\
C'_{ms} &= \beta_1 I_{sc} + \lambda_1 I_m - (\delta + \mu_h + \eta + \phi) C_{ms} \\
R'_m &= \psi I_m - (\alpha + \mu_h) R_m + \tau \delta C_{ms} \\
R'_s &= \omega I_{sc} - (\epsilon + \mu_h) R_s + (1 - \tau) \delta C_{ms} \\
S'_v &= \Lambda_v - \beta_2 S_v - \mu_v S_v \\
I'_v &= \beta_2 S_v - \mu_v I_v \\
S'_{sv} &= \Lambda_s - \lambda_2 S_{sv} - \mu_{sv} S_{sv} \\
I'_{sv} &= \lambda_2 S_{sv} - \mu_{sv} I_{sv},
\end{aligned} \tag{1}$$

with the transmission rates given by

$$\beta_1 = \frac{\beta_h I_v}{N_h}, \quad \lambda_1 = \frac{\lambda I_{sv}}{N_h}, \quad \beta_2 = \frac{\beta_v (I_m + C_{ms})}{N_h}, \quad \lambda_2 = \frac{\lambda_s (I_{sc} + C_{ms})}{N_h}.$$

Here η is the schistosomiasis-related death rate and ϕ is the malaria-related death rate. We make the simplifying assumption that the death rate for co-infected individuals is the sum of the death rates for each disease. While obviously not true in general, the death rate due to schistosomiasis is much smaller than the death rate due to malaria (i.e., $\eta \ll \phi$) [9, 43]. It follows that the malaria death rate will swamp the death rate due to schistosomiasis for co-infected individuals, who will die at a rate only very slightly higher than malaria-infected individuals. Hence the sum is a reasonable approximation when η is small.

The immunity-waning rates for malaria and schistosomiasis are α and ϵ respectively, while the recovery rates from malaria, schistosomiasis and co-infection are ψ , ω and δ respectively; the term $\tau\delta$ accounts for the portion of co-infected individuals who recover from malaria, while $(1 - \tau)\delta$ accounts for co-infected individuals who recover from schistosomiasis. Mortality rates for humans, mosquitoes and snails are, respectively, μ_h , μ_v and μ_{sv} . The model is illustrated in Figure 1.

We assume that mosquitoes do not suffer disease-induced death and that individuals infected with both malaria and schistosomiasis can only infect mosquitoes with malaria parasites and snails with schistosomiasis parasites.

3. Analysis of the malaria–schistosomiasis model.

3.1. Positivity and boundedness of solutions. For the malaria transmission model (1) to be epidemiologically meaningful, it is important to prove that all solutions with nonnegative initial data will remain nonnegative for all time.

Theorem 3.1. *If $S_h(0), I_m(0), I_{sc}(0), C_{ms}(0), R_m(0), R_s(0), S_v(0), I_v(0), S_{sv}(0), I_{sv}(0)$ are nonnegative, then so are $S_h(t), I_m(t), I_{sc}(t), C_{ms}(t), R_m(t), R_s(t), S_v(t), I_v(t), S_{sv}(t)$ and $I_{sv}(t)$ for all time $t > 0$. Moreover,*

$$\limsup_{t \rightarrow \infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h} \text{ and } \limsup_{t \rightarrow \infty} N_v(t) \leq \frac{\Lambda_v}{\mu_v} \text{ and } \limsup_{t \rightarrow \infty} N_s(t) \leq \frac{\Lambda_s}{\mu_{sv}}. \tag{2}$$

Furthermore, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. If $N_v(0) \leq \frac{\Lambda_v}{\mu_v}$, then $N_v(t) \leq \frac{\Lambda_v}{\mu_v}$. If $N_s(0) \leq \frac{\Lambda_s}{\mu_{sv}}$, then $N_s(t) \leq \frac{\Lambda_s}{\mu_{sv}}$.

The feasible region for system (1) is therefore given by

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_v \times \mathcal{D}_s \subset \mathbb{R}_+^6 \times \mathbb{R}_+^2 \times \mathbb{R}_+^2 \tag{3}$$

where

$$\mathcal{D}_h = \{(S_h, I_m, I_{sc}, C_{ms}, R_m, R_s) \in \mathbb{R}_+^6 : S_h + I_m + I_{sc} + C_{ms} + R_m + R_s \leq \frac{\Lambda_h}{\mu_h}\}$$

$$\mathcal{D}_v = \{(S_v, I_v) \in \mathbb{R}_+^2 : S_v + I_v \leq \frac{\Lambda_v}{\mu_v}\}$$

$$\mathcal{D}_s = \{(S_{sv}, I_{sv}) \in \mathbb{R}_+^2 : S_{sv} + I_{sv} \leq \frac{\Lambda_s}{\mu_{sv}}\}.$$

Note that \mathcal{D} is positively invariant.

Proof. Let

$$t_1 = \sup \{t > 0 : S_h, I_m, I_{sc}, C_{ms}, R_m, R_s, S_v, I_v, S_{sv} \text{ and } I_{sv} \text{ are positive on } [0, t]\}.$$

Since $S_h(0), I_m(0), I_{sc}(0), C_{ms}(0), R_m(0), R_s(0), S_v(0), I_v(0), S_{sv}(0)$ and $I_{sv}(0)$ are nonnegative, $t_1 > 0$. If $t_1 < \infty$, then, by using the variation of constants formula on the first equation of the system (1), we have

$$S_h(t_1) = \mathcal{U}(t_1, 0)S_h(0) + \int_0^{t_1} \Lambda \mathcal{U}(t_1, \tau) d\tau,$$

where $\mathcal{U}(t, \tau) = e^{-\int_\tau^t (\lambda_1 + \beta_1 + \mu_h)(s) ds}$.

This implies that $S_h(t_1) > 0$. It can be shown in the same manner that this is the case for the other variables. This contradicts the fact that t_1 is the supremum, because at least one of the variables should be equal to zero at t_1 . Therefore $t_1 = \infty$, which implies that $S_h, I_m, I_{sc}, C_{ms}, R_m, R_s, S_v, I_v, S_{sv}$ and I_{sv} are positive for all $t > 0$.

For the second part of the proof, adding the last two equations of system (1), we obtain $\frac{dN_s}{dt} = \Lambda_s - \mu_{sv}N_s$. This implies that $N_s(t) = N_s(0)e^{-\mu_{sv}t} + \frac{\Lambda_s}{\mu_{sv}}(1 - e^{-\mu_{sv}t})$. Thus $\limsup_{t \rightarrow \infty} N_s(t) = \frac{\Lambda_s}{\mu_{sv}}$. Moreover, if $N_s(0) \leq \frac{\Lambda_s}{\mu_{sv}}$, then $N_s(t) \leq \frac{\Lambda_s}{\mu_{sv}}$.

Adding the two mosquito equations of system (1), we obtain $\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v$. This implies that $N_v(t) = N_v(0)e^{-\mu_v t} + \frac{\Lambda_v}{\mu_v}(1 - e^{-\mu_v t})$. Thus $\limsup_{t \rightarrow \infty} N_v(t) = \frac{\Lambda_v}{\mu_v}$. Moreover, if $N_v(0) \leq \frac{\Lambda_v}{\mu_v}$, then $N_v(t) \leq \frac{\Lambda_v}{\mu_v}$.

From the first seven equations of (1), we have $\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \phi I_m - m I_{sc} - (\phi + \eta)C_{ms}$. Since $0 < I_m + I_{sc} + C_{ms} \leq N_h$, then

$$\Lambda_h - (\mu_h + \phi + \eta)N_h \leq \frac{dN_h}{dt} \leq \Lambda_h - \mu_h N_h.$$

By using a standard comparison theorem [24], we obtain

$$\begin{aligned} & N_h(0)e^{-(\mu_h + \phi + \eta)t} + \frac{\Lambda_h}{\mu_h + \phi + \eta}(1 - e^{-(\mu_h + \phi + \eta)t}) \\ \leq N_h & \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t}). \end{aligned}$$

This implies that

$$\frac{\Lambda_h}{\mu_h + \phi + \eta} \leq \liminf_{t \rightarrow \infty} N_h(t) \leq \limsup_{t \rightarrow \infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}.$$

The other cases are similar.

Moreover, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. This establishes the invariance of \mathcal{D} as required. \square

From this theorem, we see that system (1) is epidemiologically feasible and mathematically well-posed in \mathcal{D} .

3.2. Schistosomiasis-only model. First we consider the schistosomiasis-only model.

$$\begin{aligned} S'_h &= \Lambda_h + \epsilon R_s - \lambda_1 S_h - \mu_h S_h \\ I'_{sc} &= \lambda_1 S_h - (\omega + \mu_h + \eta) I_{sc} \\ R'_s &= \omega I_{sc} - (\epsilon + \mu_h) R_s \\ S'_{sv} &= \Lambda_s - \lambda_2 S_{sv} - \mu_{sv} S_{sv} \\ I'_{sv} &= \lambda_2 S_{sv} - \mu_{sv} I_{sv}, \end{aligned} \quad (4)$$

where

$$\lambda_1 = \frac{\lambda I_{sv}}{N_h}, \quad \lambda_2 = \frac{\lambda_s I_{sc}}{N_h}. \quad (5)$$

3.3. Stability of the disease-free equilibrium. The schistosomiasis-only model (4) has a disease-free equilibrium (DFE), given by

$$E_{0c} = (S_h^*, I_{sc}^*, R_s^*, S_{sv}^*, I_{sv}^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_s}{\mu_{sv}}, 0 \right).$$

The linear stability of E_{0c} can be established using the next-generation operator [46] on the system (4). We thus have

$$R_{sc} = \sqrt{\frac{\lambda \lambda_s \Lambda_s \mu_h}{\Lambda_h (\eta + \omega + \mu_h) \mu_{sv}^2}}. \quad (6)$$

Note, however, that the value obtained by the next-generation method when several states are involved is the geometric mean of sub-reproduction numbers and not the true reproduction number. See [26] for more discussion.

Using Theorem 2 in van den Driessche and Watmough [46], the DFE is locally asymptotically stable if $R_{sc} < 1$ and unstable if $R_{sc} > 1$.

3.3.1. Existence of endemic equilibrium.

Lemma 3.2. *The schistosomiasis-only model has a unique endemic equilibrium if and only if $R_{sc} > 1$.*

Proof. Using the schistosomiasis force of infection λ^* from (5), the endemic equilibrium point satisfies the following polynomial:

$$P(\lambda^*) = \lambda^* [A(\lambda^*)^2 + B(\lambda^*) + C] = 0, \quad (7)$$

where

$$\begin{aligned} A &= \Lambda_h \mu_{sv} (\mu_h + \epsilon + \omega) [\lambda_s (\epsilon + \mu_h) + (\epsilon + \omega + \mu_h) \mu_{sv}] \\ B &= (\epsilon + \mu_h) \Lambda_h (m + \omega + \mu_h) \frac{\mu_{sv}^2}{\mu_h} \left(\epsilon (m + \mu_h) + \mu_h (\eta + \omega + \mu_h) \right) [R_g - R_{sc}^2] \\ C &= \mu_{sv}^2 \Lambda_h (\epsilon + \mu_h)^2 (\eta + \omega + \mu_h)^2 (1 - R_{sc}^2) \\ R_g &= \frac{\mu_h [\lambda_s (\epsilon + \mu_h) + 2(\epsilon + \omega + \mu_h) \mu_{sv}]}{\mu_{sv} (\epsilon (\eta + \mu_h) + \mu_h (\eta + \omega + \mu_h))}. \end{aligned} \quad (8)$$

\square

- Proposition 1.** 1. If $R_g \geq 1$, then system (4) exhibits a transcritical bifurcation.
 2. If $R_g < 1$, then system (4) exhibits a backward bifurcation.

Proof. 1. For $R_g \geq 1$, we obtain when $R_{sc} > 1$ that $C < 0$. This implies that system (4) has a unique endemic steady state. If $R_{sc} \leq 1$, then $C \geq 0$ and $B \geq 0$. In this case, system (4) has no endemic steady states.
 2. For $R_g < 1$, we have the following cases:
 i. If $R_{sc} > 1$, then $C < 0$, so system (4) has a unique endemic steady state.
 ii. If $R_{sc} \leq \sqrt{R_g}$, then both B and C are positive, implying that system (4) has no endemic steady states.
 iii. If $\sqrt{R_g} < R_{sc} < 1$, then $C > 0$ and $B < 0$, while the discriminant of (7), $\Delta(R_{sc}) \equiv B^2 - 4AC$, can be either positive or negative. We have $\Delta(1) = B^2 > 0$ and $\Delta(\sqrt{R_g}) = -4AC < 0$; it follows that there exists R_{0sc} such that $\Delta(R_{0sc}) = 0$, $\Delta(R_{sc}) < 0$ for $\sqrt{R_g} < R_{sc} < R_{0sc}$ and $\Delta(R_{sc}) > 0$ for $R_{0sc} < R_{sc}$. This, together with the signs of B and C , implies that system (4) has no endemic steady states when $\sqrt{R_g} < R_{sc} < R_{0sc}$, one endemic steady state when $R_{sc} = R_{0sc}$ and two endemic steady states when $R_{0sc} < R_{sc} < 1$. \square

3.4. Malaria-only model. We next consider the malaria-only model:

$$\begin{aligned} S'_h &= \Lambda_h + \alpha R_m - \beta_1 S_h - \mu_h S_h \\ I'_m &= \beta_1 S_h - (\psi + \mu_h + \phi) I_m \\ R'_m &= \psi I_m - (\alpha + \mu_h) R_m \\ S'_v &= \Lambda_v - \beta_2 S_v - \mu_v S_v \\ I'_v &= \beta_2 S_v - \mu_v I_v, \end{aligned} \tag{9}$$

where

$$\beta_1 = \frac{\beta_h I_v}{N_h}, \quad \beta_2 = \frac{\beta_v I_m}{N_h}.$$

3.5. Stability of the DFE. The DFE is given by

$$E_{0m} = (S_h^*, I_m^*, R_m^*, S_v^*, I_v^*) = \left(\frac{\Lambda_v}{\mu_h}, 0, 0, \frac{\Lambda_v}{\mu_v}, 0 \right).$$

Similar to the previous section, we calculate

$$R_{0m} = \sqrt{\frac{\Lambda_v \beta_h \beta_v \mu_h}{\Lambda_h \mu_v^2 (\psi + \phi + \mu_h)}}. \tag{10}$$

The DFE is locally asymptotically stable if $R_{0m} < 1$ and unstable if $R_{0m} > 1$.

3.5.1. Existence of endemic equilibrium.

Lemma 3.3. *The malaria-only model has a unique endemic equilibrium if and only if $R_{0m} > 1$.*

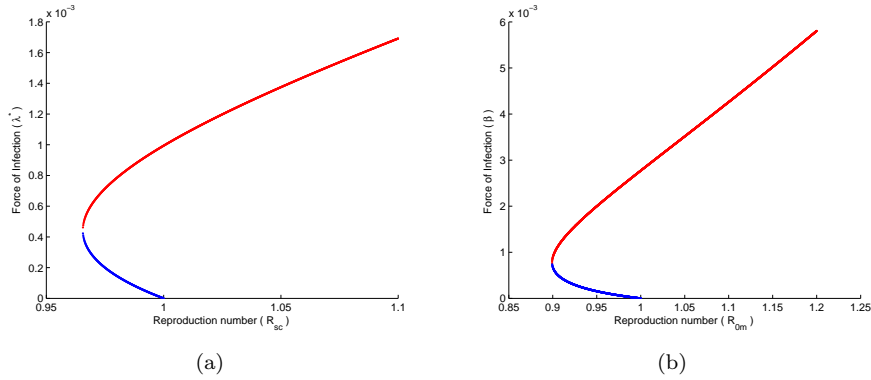


FIGURE 2. Simulations of the submodels to illustrate the occurrence of a backward bifurcation

Proof. The endemic equilibrium satisfies the following polynomial:

$$P_m(I_m^*) = \beta^* \left(A_a(\beta^*)^2 + B_b(\beta^*) + C_c \right) = 0. \tag{11}$$

where

$$\begin{aligned} A_a &= \Lambda_h \mu_v (\alpha + \psi + \mu_h) [\beta_v (\alpha + \mu_h) + (\alpha + \mu_h + \psi) \mu_v] \\ B_b &= \Lambda_h (\alpha + \mu_h) (\phi + \psi + \mu_h) \frac{\mu_v^2}{\mu_h} [\alpha \phi + \mu_h (\alpha + \phi + \psi + \mu_h)] [R_D - R_{0m}^2] \\ C_c &= \Lambda_h \mu_v^2 (\alpha + \mu_h)^2 (\phi + \psi + \mu_h)^2 (1 - R_{0m}^2) \\ R_D &= \frac{\mu_h [\beta_v (\alpha + \mu_h) + 2(\alpha + \psi + \mu_h) \mu_v]}{\mu_v [\alpha \phi + \mu_h (\alpha + \phi + \psi + \mu_h)]}. \end{aligned} \tag{12}$$

Proposition 2. 1. If $R_D \geq 1$, then system (9) exhibits a transcritical bifurcation.

2. If $R_D < 1$, then system (9) exhibits a backward bifurcation.

Proof.

1. For $R_D \geq 1$, we obtain when $R_{0m} > 1$ that $C_c < 0$. This implies that system (9) has a unique endemic steady state. If $R_{0m} \leq 1$, then $C_c \geq 0$ and $B_b \geq 0$. In this case, system (9) has no endemic steady states.
2. For $R_D < 1$, we discuss the following cases:
 - i. If $R_{0m} > 1$, then $C_c < 0$ and system (9) has a unique endemic steady state.
 - ii. If $R_{0m} \leq \sqrt{R_D}$, then both B_b and C are positive, implying that system (9) has no endemic steady states.
 - iii. If $\sqrt{R_D} < R_{0m} < 1$, then $C_c > 0$ and $B_b < 0$, while the discriminant of (11), $\Delta(R_{0m}) \equiv B_b^2 - 4A_a C_c$, can be either positive or negative. We have $\Delta(1) = B_b^2 > 0$ and $\Delta(\sqrt{R_D}) = -4A_a C_c < 0$, so there exists R_{00m} such that $\Delta(R_{00m}) = 0$, $\Delta(R_{0m}) < 0$ for $\sqrt{R_D} < R_{0m} < R_{00m}$ and $\Delta(R_{0m}) > 0$ for $R_{00m} < R_{0m}$. This, together with the signs of B_b and C_c , implies that system (9) has no endemic steady states when $\sqrt{R_D} < R_{0m} < R_{00m}$, one endemic steady state when $R_{0m} = R_{00m}$ and two endemic steady states when $R_{00m} < R_{0m} < 1$.

□

3.6. Co-infection model. The malaria–schistosomiasis model (1) has a DFE, given by

$$E_0 = (S_h^*, I_m^*, I_{sc}^*, C_{ms}^*, R_m^*, R_s^*, S_v^*, I_v^*, S_{sv}^*, I_{sv}^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, \frac{\Lambda_s}{\mu_{sv}}, 0 \right).$$

The linear stability of E_0 can be established using the next-generation method [46] on system (1).

It follows that the reproduction number of the malaria–schistosomiasis model (1), denoted by R_{msc} , is given by

$$R_{msc} = \max\{R_{sc}, R_{0m}\},$$

where

$$R_{0m} = \sqrt{\frac{\Lambda_v \beta_h \beta_v \mu_h}{\Lambda_h \mu_v^2 (\psi + \phi + \mu_h)}}$$

$$R_{sc} = \sqrt{\frac{\lambda \lambda_s \Lambda_s \mu_h}{\Lambda_h (m + \omega + \mu_h) \mu_{sv}^2}}.$$

We thus have the following theorem.

Theorem 3.4. *The DFE E_0 is locally asymptotically stable whenever $R_{msc} < 1$ and unstable otherwise.*

3.7. Impact of schistosomiasis on malaria. To analyse the effects of schistosomiasis on malaria and vice versa, we begin by expressing R_{sc} in terms of R_{0m} . We solve for μ_h to get

$$\mu_h = \frac{D_1 R_{0m}^2}{D_2 - D_3 R_{0m}^2},$$

where

$$D_1 = \Lambda_h \mu_v^2 (\psi + \phi)$$

$$D_2 = \Lambda_v \beta_h \beta_v$$

$$D_3 = \Lambda_h \mu_v^2.$$

Substituting into the expression for R_{sc} , we obtain

$$R_{sc} = \sqrt{\frac{\lambda \lambda_s \Lambda_s D_1 R_{0m}^2}{[(\eta + \omega) D_2 + (D_1 - (\eta + \omega) D_3) R_{0m}^2] \Lambda_h \mu_{sv}^2}}. \tag{13}$$

Differentiating R_{sc} partially with respect to R_{0m} leads to

$$\frac{\partial R_{sc}}{\partial R_{0m}} = \frac{(\eta + \omega) D_2 \sqrt{\frac{\lambda \lambda_s \Lambda_s D_1 R_{0m}^2}{[(\eta + \omega) D_2 + (D_1 - (\eta + \omega) D_3) R_{0m}^2] \Lambda_h \mu_{sv}^2}}}{[(\eta + \omega) D_2 R_{0m} + (D_1 - (\eta + \omega) D_3) R_{0m}^3]}.$$
 \tag{14}

Whenever (14) is strictly positive, it implies that malaria enhances schistosomiasis infection; that is, an increase in malaria cases results in an increase of schistosomiasis cases in the community. If (14) is equal to zero, malaria cases have no significant effect on the transmission dynamics of schistosomiasis. If (14) is less than zero, an increase in malaria cases results in decrease of schistosomiasis cases in the community.

Similarly, expressing μ_h in terms of R_{sc} , we get

$$\mu_h = \frac{D_4 R_{sc}^2}{D_5 - D_6 R_{sc}^2}, \quad (15)$$

where

$$\begin{aligned} D_4 &= \Lambda_h \mu_{sv}^2 (\eta + \omega) \\ D_5 &= \lambda \lambda_s \Lambda_s \\ D_6 &= \Lambda_h \mu_{sv}^2. \end{aligned}$$

Substituting into the expression for R_{0m} , we obtain

$$R_{0m} = \sqrt{\frac{D_4 \beta_h \beta_v \Lambda_v R_{sc}^2}{[(\phi + \psi) D_5 + (D_4 - (\phi + \psi) D_6) R_{sc}^2] \Lambda_h \mu_{sv}^2}}. \quad (16)$$

Differentiating R_{0m} with respect to R_{sc} , we get

$$\frac{\partial R_{0m}}{\partial R_{sc}} = \frac{(\phi + \psi) D_5 \sqrt{\frac{D_4 \beta_h \beta_v \Lambda_v R_{sc}^2}{[(\phi + \psi)(D_5 - D_6 R_{sc}^2) + D_4 R_{sc}^2] \Lambda_h \mu_{sv}^2}}}{[(\phi + \psi) R_{sc} (D_5 - D_6 R_{sc}^2) + D_4 R_{sc}^3]}. \quad (17)$$

Whenever (17) is greater than zero, an increase in schistosomiasis cases results in an increase of malaria cases in the community. If (17) is equal to zero, this implies that schistosomiasis cases have no effect on the transmission dynamics of malaria. If (17) is less than zero, an increase in schistosomiasis cases results in decrease of malaria cases in the community.

The impact of malaria treatment on schistosomiasis is evaluated by partially differentiating R_m with respect to ω . We have

$$\frac{\partial R_{0m}}{\partial \omega} = \frac{(\phi + \psi)(D_5 - D_6 R_{sc}^2) \sqrt{\frac{D_4 \beta_h \beta_v \Lambda_v R_{sc}^2}{[(\phi + \psi)(D_5 - D_6 R_{sc}^2) + D_4 R_{sc}^2] \Lambda_h \mu_{sv}^2}}}{2D_4 [(\phi + \omega)(D_5 - D_6 R_{sc}^2) + D_4 R_{sc}^2]}. \quad (18)$$

Whenever (18) is negative, R_{0m} is strictly a decreasing function of ω , so the treatment of schistosomiasis will have a positive impact on the dynamics of malaria and schistosomiasis co-infection. If (18) is positive, then the treatment of schistosomiasis will have a negative impact on the dynamics of malaria and schistosomiasis co-infection. If (18) is zero, then the treatment of schistosomiasis will have no impact on the dynamics of malaria and schistosomiasis co-infection. These results are summarised in the following lemma.

Lemma 3.5. *Treatment of schistosomiasis only in the co-infection model, will have*

1. a positive impact on the malaria and schistosomiasis co-infection if (18) < 0
2. no impact on the malaria and schistosomiasis co-infection if (18) = 0
3. a negative impact on the malaria and schistosomiasis co-infection if (18) > 0.

3.8. Sensitivity indices of R_{sc} when expressed in terms of R_{0m} . We next derive the sensitivity of R_{sc} in (13) (i.e. when expressed in terms of R_{0m}) to each of the 13 different parameters. However, the expression for the sensitivity indices for some of the parameters are complex, so we evaluate the sensitivity indices of these parameters at the baseline parameter values as given in Table (3). The sensitivity index of R_{sc} with respect to λ , for example is,

$$\Upsilon_{\lambda}^{R_{sc}} \equiv \frac{\partial R_{sc}}{\partial \lambda} \times \frac{\lambda}{R_{sc}} = 0.5. \quad (19)$$

The detailed sensitivity indices of R_{sc} resulting from the comparison to the other parameters of the model are shown in Table 1.

Parameter	Description	Sensitivity index if $R_{0m} < 1$	Sensitivity index if $R_{0m} > 1$
μ_{sv}	snail mortality	-1	-1
μ_v	mosquito mortality	0.56	0.07
λ_s	prob. of snail getting infected with schisto	0.5	0.5
Λ_s	snail birth rate	0.5	0.5
β_h	prob. of human getting infected with malaria	-0.28	-0.03
β_v	prob. of mosquito getting infected	-0.28	-0.03
Λ_v	mosquito birth rate	-0.28	-0.03
Λ_h	human birth rate	-0.22	-0.47
ϕ	malaria-induced death	0.12	-0.31
ω	recovery from schisto	-0.10	0.26
m	schisto-induced death	-0.02	0.05
ψ	recovery from malaria	0.003	-0.0084

TABLE 1. Sensitivity indices of R_{sc} expressed in terms of R_{0m}

Table 1 shows the parameters, arranged from the most sensitive to the least. For $R_{0m} < 1$, the most sensitive parameters are the snail mortality rate, the mosquito mortality rate, the probability of a snail getting infected with schisto and the snail birth rate (μ_{sv} , μ_v , λ_s and Λ_s , respectively). Since $\Upsilon_{\mu_{sv}}^{R_{sc}} = -1$, increasing (or decreasing) the snail mortality rate μ_{sv} by 10% decreases (or increases) R_{sc} by 10%; similarly, increasing (or decreasing) the mosquito mortality rate, μ_v , by 10% increases (or decreases) R_{sc} by 5.6%. In the same way, increasing (or decreasing) the prob. of snails getting infected with schistosomiasis, λ_s , increases (or decreases) R_{sc} by 5%. As the malaria parameters β_h , β_v and Λ_v increase/decrease by 10%, the reproduction number of schistosomiasis, R_{sc} , decreases by 2.8%.

For $R_{0m} > 1$, the most sensitive parameters are the snail mortality rate, the probability of a snail getting infected with schistosomiasis, the snail birth rate, the human birth rate, malaria-induced death and recovery from schistosomiasis (μ_{sv} , λ_s , Λ_s , Λ_h , ϕ , ω , respectively). Since $\Upsilon_{\lambda_s}^{R_{sc}} = 0.5$, increasing (or decreasing) by 10% increases (or decreases) R_{sc} by 5%; similarly, increasing (or decreasing) the recovery rate, ω , by 10% increases (or decreases) R_{sc} by 2.6%. Also, as the malaria parameters β_h , β_v and Λ_v increase/decrease by 10%, the reproduction number of schistosomiasis R_{sc} , decreases by only 0.3%.

It is clear that R_{sc} is sensitive to changes in R_{0m} . That is, the sensitivity of R_{sc} to parameter variations depends on R_{0m} ; whenever, $R_{0m} < 1$, R_{sc} is less sensitive to the model malaria parameters.

3.9. Sensitivity indices of R_{0m} when expressed in terms of R_{sc} . Similar to the previous section, we derive the sensitivity of R_{0m} in (16) (i.e. when expressed in terms of R_{sc}) to each of the different parameters. The sensitivity index of R_{0m} with respect to β_h , for example, is

$$\Upsilon_{\beta_h}^{R_{0m}} \equiv \frac{\partial R_{0m}}{\partial \beta_h} \times \frac{\beta_h}{R_{0m}} = 0.5. \tag{20}$$

The detail sensitivity indices of R_{0m} resulting from the evaluation to the other parameters of the model are shown in Table 2. It is clearly seen from Table 2 that the malaria reproduction number, R_m , is not sensitive to any variation in the schistosomiasis reproduction number R_{sc} .

Parameter	Description	Sensitivity index if $R_{sc} < 1$	Sensitivity index if $R_{sc} > 1$
β_v	prob. of mosquito getting infected	0.5	0.5
Λ_v	mosquito birth rate	0.5	0.5
λ	prob. of human getting infected with schisto	-0.5	-0.5
λ_s	prob. of snail getting infected with schisto	-0.5	-0.5
Λ_s	snail birth rate	-0.5	-0.5
ϕ	malaria-induced death	-0.49	-0.49
ω	recovery from schisto	0.41	0.41
m	schisto-induced death	0.09	0.09
ψ	recovery from malaria	-0.01	-0.01
μ_{sv}	snail mortality	0.0000002	0.000007
Λ_h	human birth rate	0.0000001	0.000004

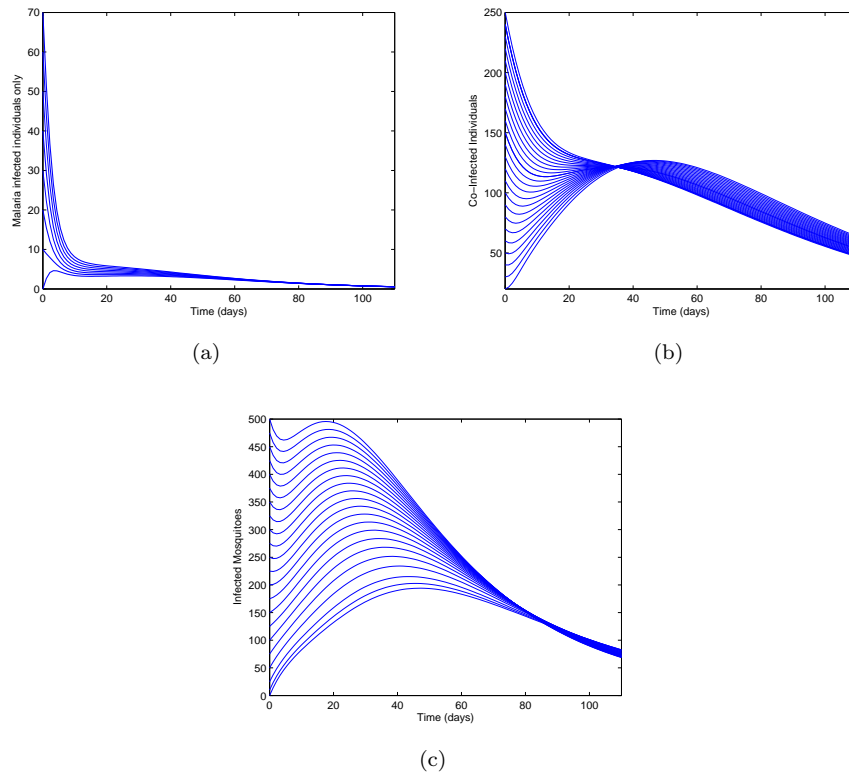
TABLE 2. Sensitivity indices of R_{0m} expressed in terms of R_{sc} 

FIGURE 3. Simulations of the malaria-schistosomiasis model with varying initial values

3.10. Existence of backward bifurcation. The existence of a backward bifurcation can be proved by applying the centre manifold theorem to a bifurcation analysis on system (1).

First, we consider the transmission rate β_h and λ as bifurcation parameters so that $R_{0m} = 1$ and $R_{sc} = 1$ if and only if

$$\beta_h = \beta_h^* = \frac{\mu_v^2 \Lambda_h (\psi + \phi + \mu_h)}{\Lambda_v \mu_h \beta_v}$$

and

$$\lambda = \lambda^* = \frac{\mu_{sv}^2 \Lambda_h (m + \omega + \mu_h)}{\mu_h \Lambda_s \lambda_s}.$$

Next we make the following change of variables: $S_h = x_1, I_m = x_2, I_{sc} = x_3, C_{ms} = x_4, R_m = x_5, R_s = x_6, R_{ms} = x_7, S_v = x_8, I_v = x_9, S_{sv} = x_{10}, I_{sv} = x_{11}$ and $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10}$.

Using vector notation $\vec{x} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10})^T$, the malaria-schistosomiasis model can be written in the form $\vec{x}' = F(\vec{x})$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10})^T$, as shown below:

$$\begin{aligned} x_1' &= \Lambda_h + \epsilon x_6 + \alpha x_5 - \beta_1 x_1 - \lambda_1 x_1 - \mu_h x_1 \\ x_2' &= \beta_1 x_1 - \lambda_1 x_2 - (\psi + \mu_h + \phi) x_2 \\ x_3' &= \lambda_1 x_1 - \beta_1 x_3 - (\omega + \mu_h + \eta) x_3 \\ x_4' &= \beta_1 x_3 + \lambda_1 x_2 - (\delta + \mu_h + \eta + \phi) x_4 \\ x_5' &= \psi x_1 - (\alpha + \mu_h) x_5 + \tau \delta x_4 \\ x_6' &= \omega x_3 - (\epsilon + \mu_h) x_6 + (1 - \tau) \delta x_4 \\ x_7' &= \Lambda_v - \beta_2 x_8 - \mu_v x_8 \\ x_8' &= \beta_2 x_8 - \mu_v x_9 \\ x_9' &= \Lambda_s - \lambda_2 x_{10} - \mu_{sv} x_{10} \\ x_{10}' &= \lambda_2 x_{10} - \mu_{sv} x_{11}, \end{aligned} \tag{21}$$

where

$$\begin{aligned} \beta_1 &= \frac{\beta_h x_9}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6} & \lambda_1 &= \frac{\lambda x_{11}}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6} \\ \beta_2 &= \frac{\beta_v (x_2 + x_4)}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6} & \lambda_2 &= \frac{\lambda_s (x_3 + x_4)}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6}. \end{aligned}$$

This method involves evaluation of the Jacobian of system (21) at the DFE \mathcal{E}_0 , denoted by $J(\mathcal{E}_0)$. This becomes

$$J(\mathcal{E}_0) = \begin{bmatrix} -\mu_h & 0 & 0 & 0 & \alpha & \epsilon & 0 & -\beta_h & 0 & -\lambda \\ 0 & -J_1 & 0 & 0 & 0 & 0 & 0 & \beta_h & 0 & 0 \\ 0 & 0 & -J_2 & J_1 & 0 & 0 & 0 & 0 & 0 & \lambda \\ 0 & 0 & 0 & -J_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \psi & 0 & J_4 & -J_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \omega & J_6 & 0 & -J_7 & 0 & 0 & 0 & 0 \\ 0 & -J_q & 0 & -J_q & 0 & 0 & -\mu_v & 0 & 0 & 0 \\ 0 & J_q & 0 & J_q & 0 & 0 & 0 & -\mu_v & 0 & 0 \\ 0 & 0 & -J_b & -J_b & 0 & 0 & 0 & 0 & -\mu_{sv} & 0 \\ 0 & 0 & J_b & J_b & 0 & 0 & 0 & 0 & 0 & -\mu_{sv} \end{bmatrix},$$

where

$$\begin{aligned} J_1 &= \psi + \phi + \mu_h & J_2 &= \omega + \mu_h + \eta & J_3 &= \delta + \eta + \mu_h + \phi \\ J_4 &= \tau\delta & J_5 &= \alpha + \mu_h & J_6 &= (1 - \tau)\delta \\ J_7 &= \epsilon + \mu_h & J_q &= \frac{\beta_v \Lambda_v \mu_h}{\Lambda_h \mu_v} & J_b &= \frac{\beta_v \Lambda_{sv} \mu_h}{\Lambda_h \mu_{sv}}. \end{aligned}$$

$J(\mathcal{E}_0)$ has a simple zero eigenvalue, with other eigenvalues having negative real parts. Hence the centre manifold theorem [7] can be applied.

We first start by calculating the right and the left eigenvectors of $J(\mathcal{E}_0)$, denoted respectively by $\vec{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}]^T$ and $\vec{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}]$. We obtain

$$\begin{aligned} w_1 &= -\frac{\Lambda_h(\alpha\phi + \mu_h(\alpha + \phi + \psi + \mu_h))\mu_v^2}{\beta_v \Lambda_v \mu_h^2(\alpha + \mu_h)} & w_2 &= \frac{\Lambda_h \mu_v^2}{\beta_v \Lambda_v \mu_h} & w_3 &= w_4 = 0 \\ w_5 &= \frac{w_2 \psi}{(\alpha + \mu_h)} & w_6 &= 0 & w_7 &= -w_8 & w_9 &= w_{10} = 0 \end{aligned}$$

and

$$\begin{aligned} v_1 &= 0 & v_2 &= \frac{\beta_v \Lambda_v \mu_h}{\Lambda_h(\phi + \psi + \mu_h)\mu_v} & v_3 &= 0 \\ v_4 &= \frac{\beta_v \Lambda_v \mu_h}{\Lambda_h(\phi + \delta + \eta + \mu_h)\mu_v} & v_5 &= v_6 = v_7 = 0 & v_9 &= v_{10} = 0, \end{aligned}$$

with w_8 and v_8 free. After rigorous computations, it can be shown that

$$\begin{aligned} a &= 2v_8 w_2 \left(w_7 \frac{\beta_v \mu_h}{\Lambda_h} - w_5 \frac{\Lambda_v \mu_h^2}{\mu_v \Lambda_h^2} - w_1 \frac{\Lambda_v \mu_h^2}{\mu_v \Lambda_h^2} \right) \\ b &= v_2 \left(w_8 - w_5 \frac{\mu_h}{\Lambda_h} \right). \end{aligned}$$

(See [7].) Whenever the coefficient b is positive, it follows from Castillo-Chavez and Song [7] that we have the following lemma.

Lemma 3.6. *Suppose $b > 0$. Then we have the following:*

1. *System (1) will undergo a backward bifurcation if the coefficient a is positive.*
2. *System (1) will undergo transcritical bifurcation if the coefficient a is negative.*

Remark. In the first case, the DFE is locally asymptotically stable but not globally stable. In the second, it may be globally stable.

3.11. Analysis of optimal control. In this section, we apply Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the malaria-schistosomiasis co-infection. We incorporate time-dependent controls into model (1) to determine the optimal strategy for controlling the disease. Hence we

have

$$\begin{aligned}
 S'_h &= \Lambda_h + \epsilon R_s + \alpha R_m - (1 - u_1)\beta_1 S_h - (1 - u_2)\lambda_1 S_h - \mu_h S_h \\
 I'_m &= (1 - u_1)\beta_1 S_h - (1 - u_2)\lambda_1 I_m - (u_3\psi + \mu_h + \phi)I_m \\
 I'_{sc} &= (1 - u_2)\lambda_1 S_h - (1 - u_1)\beta_1 I_{sc} - (u_4\omega + \mu_h + \eta)I_{sc} \\
 C'_{ms} &= (1 - u_1)\beta_1 I_{sc} + (1 - u_2)\lambda_1 I_m - (u_5\delta + \mu_h + \eta + \phi)C_{ms} \\
 R'_m &= u_3\psi I_m - (\alpha + \mu_h)R_m + u_5\tau\delta C_{ms} \\
 R'_s &= u_4\omega I_{sc} - (\epsilon + \mu_h)R_s + u_5(1 - \tau)\delta C_{ms} \\
 S'_v &= \Lambda_v - (1 - u_1)\beta_2 S_v - \mu_v S_v \\
 I'_v &= (1 - u_1)\beta_2 S_v - \mu_v I_v \\
 S'_{sv} &= \Lambda_s - (1 - u_2)\lambda_2 S_{sv} - \mu_{sv} S_{sv} \\
 I'_{sv} &= (1 - u_2)\lambda_2 S_{sv} - \mu_{sv} I_{sv},
 \end{aligned}
 \tag{22}$$

where

$$\begin{aligned}
 \beta_1 &= \frac{\beta_h I_v}{N_h} & \lambda_1 &= \frac{\lambda I_{sv}}{N_h} \\
 \beta_2 &= \frac{\beta_v(I_m + C_{ms})}{N_h} & \lambda_2 &= \frac{\lambda_s(I_{sc} + C_{ms})}{N_h}.
 \end{aligned}$$

For this, we consider the objective functional

$$\begin{aligned}
 &J(u_1, u_2, u_3, u_4, u_5) \\
 &= \int_0^{t_f} [z_1 I_m + z_2 I_{sc} + z_3 C_{ms} + z_4 I_v + z_5 I_{sv} - Au_1^2 - Bu_2^2 + Cu_3^2 + Du_4^2 + Eu_5^2] dt.
 \end{aligned}
 \tag{23}$$

The control functions $u_1(t)$, $u_2(t)$, $u_3(t)$, $u_4(t)$ and $u_5(t)$ are bounded, Lebesgue-integrable functions. Our choice of control functions agrees with other literature on control of epidemics [1, 18, 21, 25, 37]. The controls $u_1(t)$ and $u_2(t)$ represent the amount of effort required to prevent malaria and schistosomiasis infections, respectively. The control on treatment of malaria-infected individuals $u_3(t)$ satisfies $0 \leq u_3 \leq g_2$, where g_2 is the drug efficacy for treatment of malaria-infected individuals. The control on treatment of schistosomiasis-infected individuals $u_4(t)$ satisfies $0 \leq u_4 \leq g_3$, where g_3 is the drug efficacy for treatment of schistosomiasis-infected individuals. The control on treatment of co-infected individuals $u_5(t)$ satisfies $0 \leq u_5 \leq g_4$, where g_4 is the drug efficacy for treatment of co-infected individuals. Our control problem involves a situation in which the number of malaria-infected individuals, schistosomiasis-infected individuals, co-infected individuals and the cost of applying treatments controls $u_3(t)$, $u_4(t)$ and $u_5(t)$ are minimised, while prevention efforts $u_1(t)$, $u_2(t)$ are maximised subject to the system (22).

The final time t_f and the coefficients $z_1, z_2, z_3, z_4, z_5, A, B, C, D, E$ are the balancing cost factors due to scales and importance of the ten parts of the objective functional. We seek to find optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ and u_5^* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*) = \min\{J(u_1, u_2, u_3, u_4, u_5) | u_1, u_2, u_3, u_4, u_5 \in \mathcal{U}\}, \tag{24}$$

where $\mathcal{U} = \{(u_1, u_2, u_3, u_4, u_5) \text{ such that } u_1, u_2, u_3, u_4, u_5 \text{ are measurable with } 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1, 0 \leq u_3 \leq g_2, 0 \leq u_4 \leq g_3 \text{ and } 0 \leq u_5 \leq g_4, \text{ for } t \in [0, t_f]\}$ is the control set.

The necessary conditions that an optimal solution must satisfy come from the Pontryagin Maximum Principle [38]. This principle converts (22)–(23) into a problem of minimising pointwise a Hamiltonian H , with respect to u_1, u_2, u_3, u_4 and u_5 . The Hamiltonian is given by

$$\begin{aligned}
H = & z_1 I_m + z_2 I_{sc} + z_3 C_{ms} + z_4 I_v + z_5 I_{sv} - Au_1^2 - Bu_2^2 + Cu_3^2 + Du_4^2 + Eu_5^2 \\
& + M_{S_h} \{ \Lambda_h + \epsilon R_s + \alpha R_m - (1 - u_1) \beta_1 S_h - (1 - u_2) \lambda_1 S_h - \mu_h S_h \} \\
& + M_{I_m} \{ (1 - u_1) \beta_1 S_h - (1 - u_2) \lambda_1 I_m - (u_3 \psi + \mu_h + \phi) I_m \} \\
& + M_{I_{sc}} \{ (1 - u_2) \lambda_1 S_h - (1 - u_1) \beta_1 I_{sc} - (u_4 \omega + \mu_h + \eta) I_{sc} \} \\
& + M_{C_{ms}} \{ (1 - u_1) \beta_1 I_{sc} + (1 - u_2) \lambda_1 I_m - (u_5 \delta + \mu_h + \eta + \phi) C_{ms} \} \\
& + M_{R_m} \{ u_3 \psi I_m - (\alpha + \mu_h) R_m + u_5 \tau \delta C_{ms} \} \\
& + M_{R_s} \{ u_4 \omega I_{sc} - (\epsilon + \mu_h) R_s + u_5 (1 - \tau) \delta C_{ms} \} \\
& + M_{S_v} \{ \Lambda_v - (1 - u_1) \beta_2 S_v - \mu_v S_v \} \\
& + M_{I_v} \{ (1 - u_1) \beta_2 S_v - \mu_v I_v \} \\
& + M_{S_{sv}} \{ \Lambda_s - (1 - u_2) \lambda_2 S_{sv} - \mu_{sv} S_{sv} \} \\
& + M_{I_{sv}} \{ (1 - u_2) \lambda_2 S_{sv} - \mu_{sv} I_{sv} \},
\end{aligned} \tag{25}$$

where $M_{S_h}, M_{I_m}, M_{I_{sc}}, M_{C_{ms}}, M_{R_m}, M_{R_s}, M_{S_v}, M_{I_v}, M_{S_{sv}}$ and $M_{I_{sv}}$ are the adjoint variables or co-state variables. The system of equations is found by taking the appropriate partial derivatives of the Hamiltonian (25) with respect to the associated state variable.

Theorem 3.7. *Given optimal controls $u_1^*, u_2^*, u_3^*, u_4^*, u_5^*$ and solutions $S_h, I_m, I_{sc}, C_{ms}, R_m, R_s, S_v, I_v, S_{sv}$ and I_{sv} of the corresponding state system (22)–(23) that minimise $J(u_1, u_2, u_3, u_4, u_5)$ over U , there exist adjoint variables $M_{S_h}, M_{I_m}, M_{I_{sc}}, M_{C_{ms}}, M_{R_m}, M_{R_s}, M_{S_v}, M_{I_v}, M_{S_{sv}}$ and $M_{I_{sv}}$ satisfying*

$$-\frac{dM_i}{dt} = \frac{\partial H}{\partial i}, \tag{26}$$

where $i = S_h, I_m, I_{sc}, C_{ms}, R_m, R_s, S_v, I_v, S_{sv}, I_{sv}$ and with transversality conditions

$$\begin{aligned}
M_{S_h}(t_f) &= M_{I_m}(t_f) = M_{I_{sc}}(t_f) = M_{C_{ms}}(t_f) = M_{R_m}(t_f) = M_{R_s}(t_f) \\
&= M_{S_v}(t_f) = M_{I_v}(t_f) = M_{S_{sv}}(t_f) = M_{I_{sv}}(t_f) = 0
\end{aligned} \tag{27}$$

and

$$u_1^* = \max \left\{ 1, \min \left(0, \frac{\beta_h I_v S_h (M_{S_h} - M_{I_m}) + \beta_h I_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + G_y}{2AN_h} \right) \right\} \tag{28}$$

$$u_2^* = \max \left\{ 1, \min \left(0, \frac{\lambda I_{sv} (M_{S_h} - M_{I_{sc}}) S_h + \lambda I_{sv} (M_{I_m} - M_{C_{ms}}) I_m + D_x}{2BN_h} \right) \right\} \tag{29}$$

$$u_3^* = \min \left\{ 1, \max \left(0, \frac{\psi (M_{I_m} - M_{R_m}) I_m}{2C} \right) \right\} \tag{30}$$

$$u_4^* = \min \left\{ 1, \max \left(0, \frac{\omega (M_{I_{sc}} - M_{R_s}) I_{sc}}{2D} \right) \right\} \tag{31}$$

$$u_5^* = \min \left\{ 1, \max \left(0, \frac{\delta C_{ms} M_{C_{ms}} - \tau \delta C_{ms} M_{R_m} - (1 - \tau) \delta C_{ms} M_{R_s}}{2E} \right) \right\}, \tag{32}$$

where $G_y = \beta_v(I_m + C_{ms})S_v(M_{S_v} - M_{I_v})$ and $D_x = \lambda_s(I_{sc} + C_{ms})S_{sv}(M_{S_{sv}} - M_{I_{sv}})$.

Proof. Corollary 4.1 of Fleming and Rishel [14] gives the existence of an optimal control due to the convexity of the integrand of J with respect to u_1, u_2, u_3, u_4 and u_5 , *a priori* boundedness of the state solutions and the Lipschitz property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control.

Solving for $u_1^*, u_2^*, u_3^*, u_4^*$ and u_5^* subject to the constraints, the characterisation (28)–(32) can be derived. We have

$$\begin{aligned}
 0 &= \frac{\partial H}{\partial u_1} = -2Au_1 + \frac{\beta_h I_v S_h (M_{S_h} - M_{I_m}) + \beta_h I_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + \beta_v (I_m + C_{ms}) S_v (M_{S_v} - M_{I_v})}{N_h} \\
 0 &= \frac{\partial H}{\partial u_2} = -2Bu_2 + \frac{\lambda I_{sv} (M_{S_h} - M_{I_{sc}}) S_h + \lambda I_{sv} (M_{I_m} - M_{C_{ms}}) I_m + \lambda_s (I_{sc} + C_{ms}) S_{sv} (M_{S_{sv}} - M_{I_{sv}})}{N_h} \\
 0 &= \frac{\partial H}{\partial u_3} = 2Cu_3 + \psi (M_{R_m} - M_{I_m}) I_m \\
 0 &= \frac{\partial H}{\partial u_4} = 2Du_4 + \omega (M_{R_{sc}} - M_{I_{sc}}) I_{sc} \\
 0 &= \frac{\partial H}{\partial u_5} = 2Eu_5 + \delta C_{ms} M_{C_{ms}} + \tau \delta C_{ms} M_{R_m} + (1 - \tau) \delta C_{ms} M_{R_s}.
 \end{aligned} \tag{33}$$

Hence we obtain (see Lenhart and Workman [25])

$$\begin{aligned}
 u_1^* &= \frac{\beta_h I_v S_h (M_{S_h} - M_{I_m}) + \beta_h I_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + G_y}{2AN_h} \\
 u_2^* &= \frac{\lambda I_{sv} (M_{S_h} - M_{I_{sc}}) S_h + \lambda I_{sv} (M_{I_m} - M_{C_{ms}}) I_m + \lambda_s (I_{sc} + C_{ms}) S_{sv} (M_{S_{sv}} - M_{I_{sv}})}{2BN_h} \\
 u_3^* &= \frac{\psi (M_{I_m} - M_{R_m}) I_m}{2C} \\
 u_4^* &= \frac{\omega (M_{I_{sc}} - M_{R_s}) I_{sc}}{2D} \\
 u_5^* &= \frac{\delta C_{ms} M_{C_{ms}} - \tau \delta C_{ms} M_{R_m} - (1 - \tau) \delta C_{ms} M_{R_s}}{2E}.
 \end{aligned} \tag{34}$$

By standard control arguments involving the bounds on the controls, we conclude that

$$u_i^* = \begin{cases} 0 & \text{if } \xi_i^* \leq 0 \\ \xi_i^* & \text{if } 0 < \xi_i^* < 1 \\ 1 & \text{if } \xi_i^* \geq 1 \end{cases}$$

for $i \in 1, 2, 3, 4, 5$ and where

$$\begin{aligned}
 \xi_1^* &= \frac{\beta_h I_v S_h (M_{S_h} - M_{I_m}) + \beta_h I_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + G_y}{2AN_h} \\
 \xi_2^* &= \frac{\lambda I_{sv} (M_{S_h} - M_{I_{sc}}) S_h + \lambda I_{sv} (M_{I_m} - M_{C_{ms}}) I_m + \lambda_s (I_{sc} + C_{ms}) S_{sv} (M_{S_{sv}} - M_{I_{sv}})}{2BN_h} \\
 \xi_3^* &= \frac{\psi (M_{I_m} - M_{R_m}) I_m}{2C} \\
 \xi_4^* &= \frac{\omega (M_{I_{sc}} - M_{R_s}) I_{sc}}{2D} \\
 \xi_5^* &= \frac{\delta C_{ms} M_{C_{ms}} - \tau \delta C_{ms} M_{R_m} - (1 - \tau) \delta C_{ms} M_{R_s}}{2E}.
 \end{aligned}$$

□

4. Numerical simulations. We now discuss numerical solutions of the optimality system and the corresponding results of varying the optimal controls u_1, u_2, u_3, u_4 and u_5 , the parameter choices, as well as the interpretations from various cases.

The numerical solutions are illustrated using MATLAB. The optimality system, which consists of the state system and the adjoint system, was solved to obtain the optimal control solution. A fourth-order Runge–Kutta iterative scheme is used to solve the optimality system. The adjoint equations were solved by the backward fourth-order Runge–Kutta scheme using the current solutions of the state equations because of the transversality conditions (27). Then the controls were updated by using a convex combination of the previous controls and the value from the characterisations. This process was repeated, and the iterations were stopped if the values of the unknowns at the previous iterations were very close to the ones at the present iteration ([2, 3, 21, 25]).

Table 3 lists the parameter descriptions and values used in the numerical simulation of the co-infection model. The following weight constants were used: $A = 150$, $B = 230$, $C = 200$, $D = 250$, $E = 310$ and $z_1 = 210$, $z_2 = 310$, $z_3 = 400$, $z_4 = 260$, $z_5 = 300$.

Parameter	Description	value	Reference
ϕ	malaria-induced death	0.05–0.1 day ⁻¹	[43]
β_h	malaria transmissibility to humans	0.034 day ⁻¹	assumed
β_v	malaria transmissibility to mosquitoes	0.09 day ⁻¹	[5]
λ	schistosomiasis transmissibility to humans	0.406 day ⁻¹	[45]
λ_s	schistosomiasis transmissibility to snails	0.615 day ⁻¹	[9]
μ_h	Natural death rate in humans	0.00004 day ⁻¹	[5]
μ_v	Natural death rate in mosquitoes	1/15–0.143 day ⁻¹	[5]
μ_{sv}	Natural death rate in snails	0.000569 day ⁻¹	[9, 45]
α	malaria immunity waning rate	1/(60×365) day ⁻¹	[5]
ϵ	schistosomiasis immunity waning rate	0.013 day ⁻¹	assumed
Λ_h	human birth rate	800 people/day	[9]
Λ_v	mosquitoes birth rate	1000 mosquitoes/day	[5]
Λ_s	snail birth rate	100 snails/day	[13]
δ	recovery rate of co-infected individual	0.35 day ⁻¹	assumed
ω	recovery rate of schistosomiasis-infected individual	0.0181 day ⁻¹	assumed
ψ	recovery rate of malaria-infected individual	1/(2×365) day ⁻¹	[5]
τ	co-infected proportion who recover from malaria only	0.1	assumed
η	schistosomiasis-induced death	0.0039 day ⁻¹	[9]

TABLE 3. Parameters in the co-infection model

4.1. Prevention (u_1) and treatment (u_3) of malaria. The malaria prevention control u_1 (representing treated bednets) and the malaria treatment control u_3 are used to optimise the objective functional J ; the other controls (u_2, u_4 and u_5) relating to schistosomiasis are set to zero. Figure 4(a) shows that the number of malaria-infected humans I_m is significantly different compared to cases without control.

Figure 4(b) shows that this strategy for controlling the schistosomiasis-infected individuals I_{sc} yields no positive results, because there was no intervention put in place against schistosomiasis. The effect of not controlling the schistosomiasis-infected population is clearly depicted in Figure 4(e); this strategy was of no effect in controlling the infected snails I_{sv} .

The population of co-infected humans C_{ms} illustrated in Figure 4(c) shows a clear difference between the cases without control and the controlled cases. This

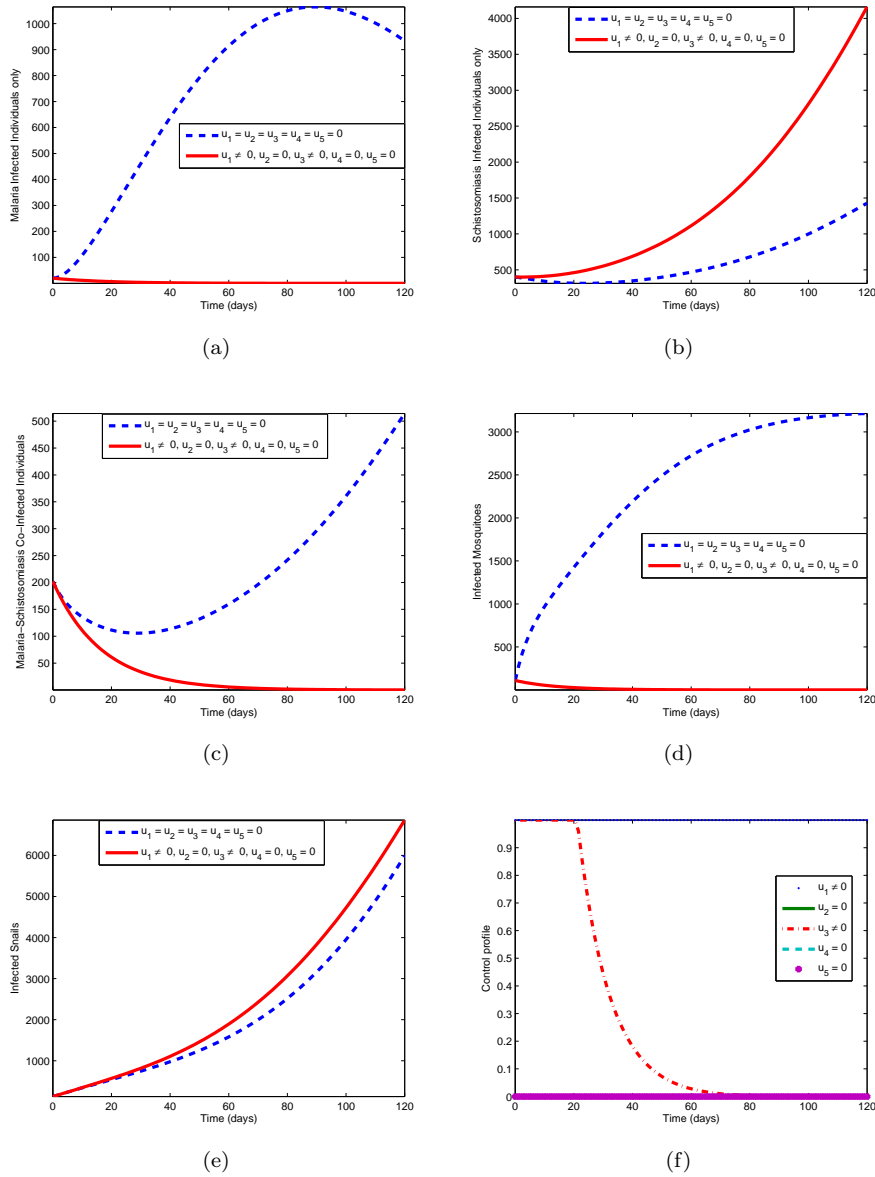


FIGURE 4. Simulations of the malaria–schistosomiasis model showing the effect of malaria prevention and treatment on transmission

same trend is also observed in Figure 4(d) in the control of the number of malaria-infected mosquitoes I_v . Figure 4(f) show the control profile. This suggest that the malaria-prevention control u_1 should be at maximum for the entire duration of the intervention, while malaria-treatment control u_3 should be at 100% for approximately 25 days before being gradually reduced to zero.

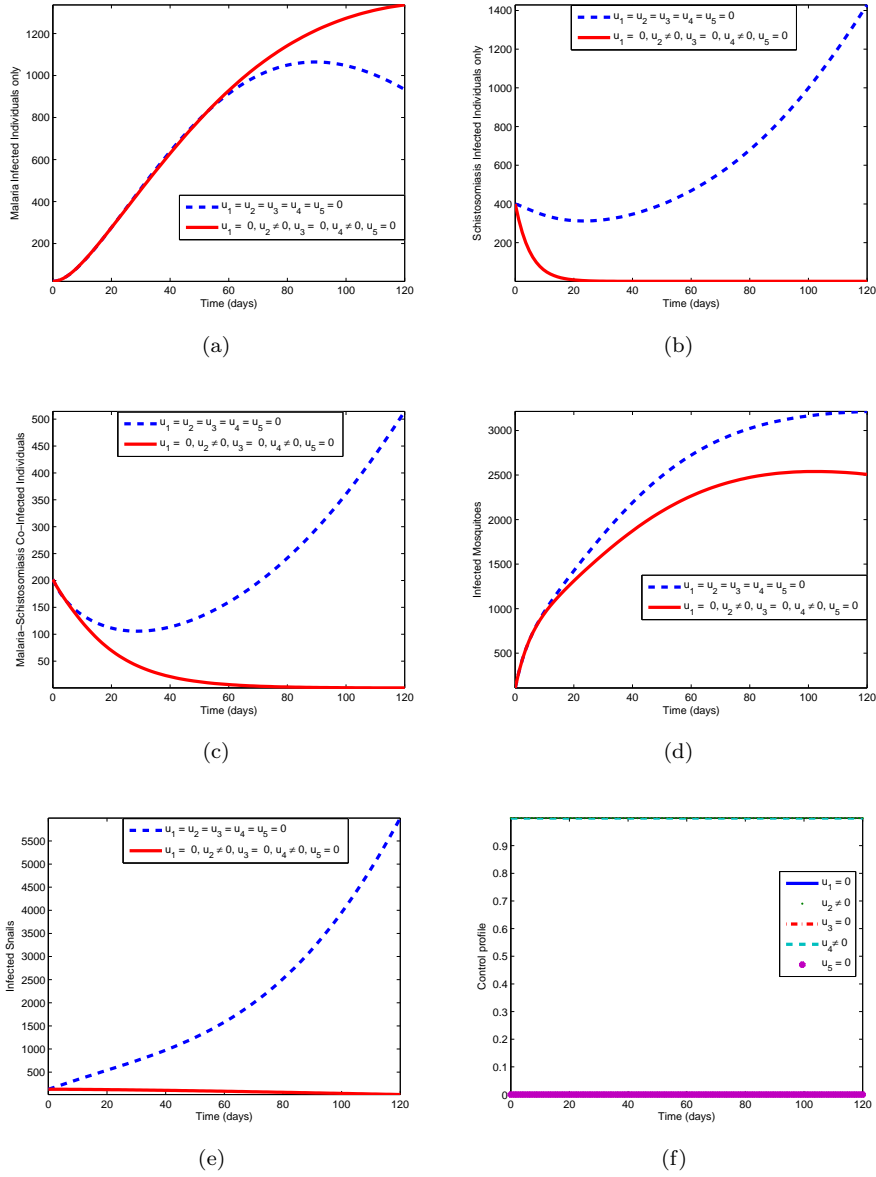


FIGURE 5. Simulations of the malaria–schistosomiasis model showing the effect of schistosomiasis prevention and treatment on transmission

4.2. Prevention (u_2) and treatment (u_4) of schistosomiasis. The schistosomiasis-prevention control u_2 and the schistosomiasis-treatment control u_4 were used to optimise the objective functional J while we set the malaria-related controls u_1 , u_3 and u_5 to zero. We observe from Figure 5(a) that this strategy shows no significant effect in reducing the number of malaria-infected humans I_m under optimal control compared to cases without control. However, Figure 5(d) shows that

the number of malaria-infected mosquitoes I_v is a bit lower under control compared to cases without control.

The results depicted in Figure 5(b) clearly suggest that this strategy is very effective in the control of the number of schistosomiasis-infected humans I_{sc} , as expected. Furthermore, there was significant control of infected snails I_{sv} as shown in Figure 5(e). The population of co-infected humans C_{ms} shown in Figure 5(c) also shows significant difference between the cases with and without control. Figure 5(d) suggests that effective treatment and prevention of schistosomiasis infection would contribute to a reduction in malaria-infected mosquitoes. The control profile in Figure 5(f) suggests that the prevention control u_2 and treatment control u_4 of schistosomiasis should both be maximised in the absence of any intervention for malaria.

4.3. Malaria and schistosomiasis combined prevention (u_1 and u_2). We next consider a prevention-only strategy, where the prevention is applied to both infections. The malaria-prevention control u_1 and the schistosomiasis-prevention control u_2 are used to optimise the objective functional J while u_3 , u_4 and u_5 are set to zero.

Figure 6(a) shows that the number of malaria-infected humans I_m was totally controlled. This effect is also observed in Figure 6(d) for the control of the number of malaria-infected mosquitoes I_v . Figure 6(b) shows that the impact of this strategy in controlling schistosomiasis-infected individuals I_{sc} also yielded significant results.

The effect of not treating the schistosomiasis-infected population is shown clearly in Figure 6(e), making this strategy of no effect in controlling the infected snail population I_{sv} . Figure 6(c) shows significant difference between the population of co-infected humans C_{ms} in the cases with control and those without. This strategy suggest that optimal preventive strategies against malaria and schistosomiasis in a community would be an effective approach to controlling either disease. The control profile in Figure 6(f) suggests that the prevention controls u_1 and u_3 should both be maximised in the absence of any treatment intervention.

4.4. Malaria and schistosomiasis treatment (u_3 , u_4 and u_5). We next examined treatment for the two infections in the absence of prevention. The malaria- and schistosomiasis-treatment controls u_3 , u_4 and u_5 were used to optimise the objective functional J while the preventive controls (u_1, u_2) were set to zero.

Figure 7(a) shows that the number of malaria-infected humans I_m is reduced but not effectively controlled. The impact of this strategy is also shown in Figure 7(d), where the number of malaria-infected mosquitoes I_v is reduced but not controlled by the end of the intervention period. Conversely, Figure 7(b) shows that this strategy is very effective in controlling the number of schistosomiasis-infected humans I_{sc} . Figure 7(e) similarly shows that the infected snail population is controlled.

The population of co-infected humans C_{ms} shown in Figure 7(c) shows significant difference between the cases with control and those without. This strategy suggests that optimal treatment for malaria and schistosomiasis in a community where both diseases co-exist would be an effective approach to control them both. The control profile in Figure 7(f), suggest that the treatment controls u_3, u_4 and u_5 of malaria and schistosomiasis should all be at maximum in the absence of any prevention interventions for the entire duration of the intervention strategy.

4.5. Malaria and schistosomiasis prevention and treatment. Finally, we examined the case where all controls, including both prevention and treatment, are

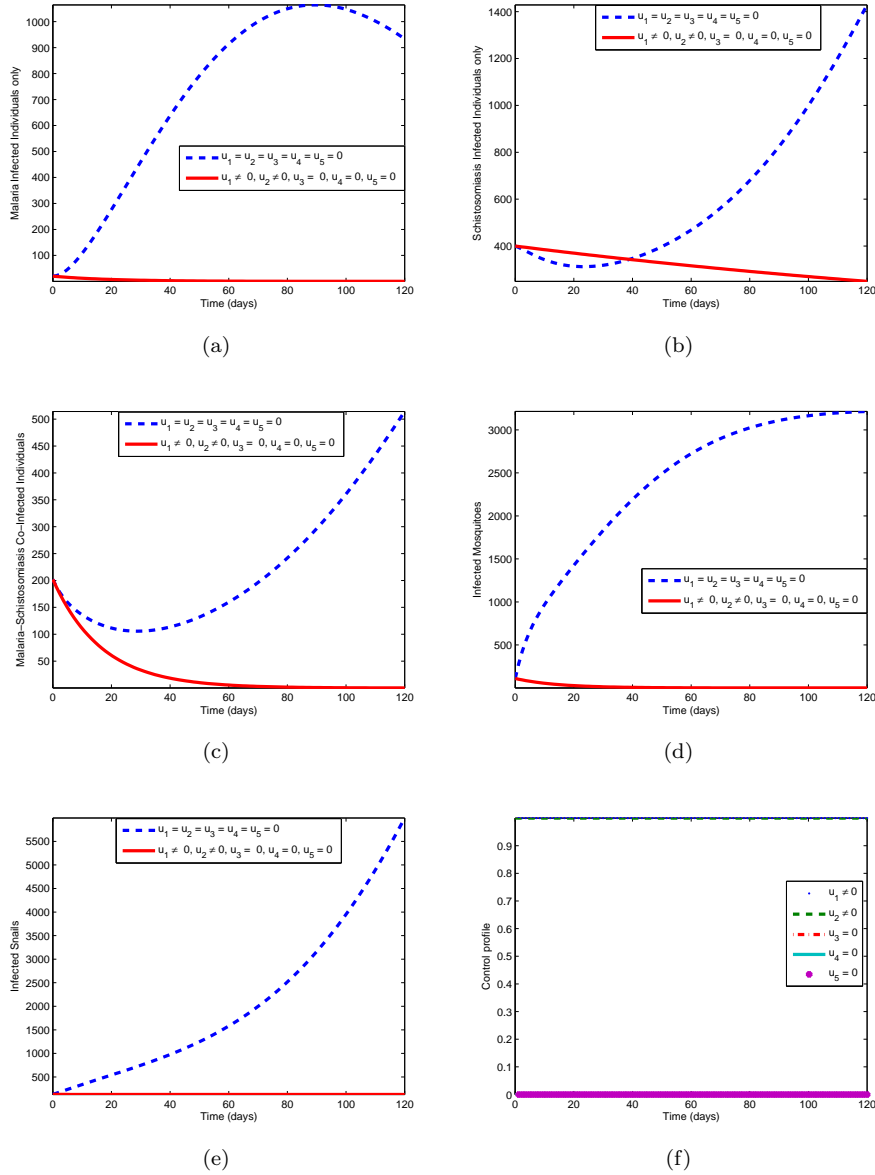


FIGURE 6. Simulations of the malaria–schistosomiasis model showing the effect of prevention of both infections on transmission

in place. In this strategy all the controls $(u_1, u_2, u_3, u_4, u_5)$ are used to optimise the objective functional J .

Figure 8(a) shows that the number of malaria-infected humans I_m is effectively controlled. The impact of this strategy is also shown in Figure 8(d), where the number of malaria-infected mosquitoes I_v is significantly reduced at the end of the intervention period.

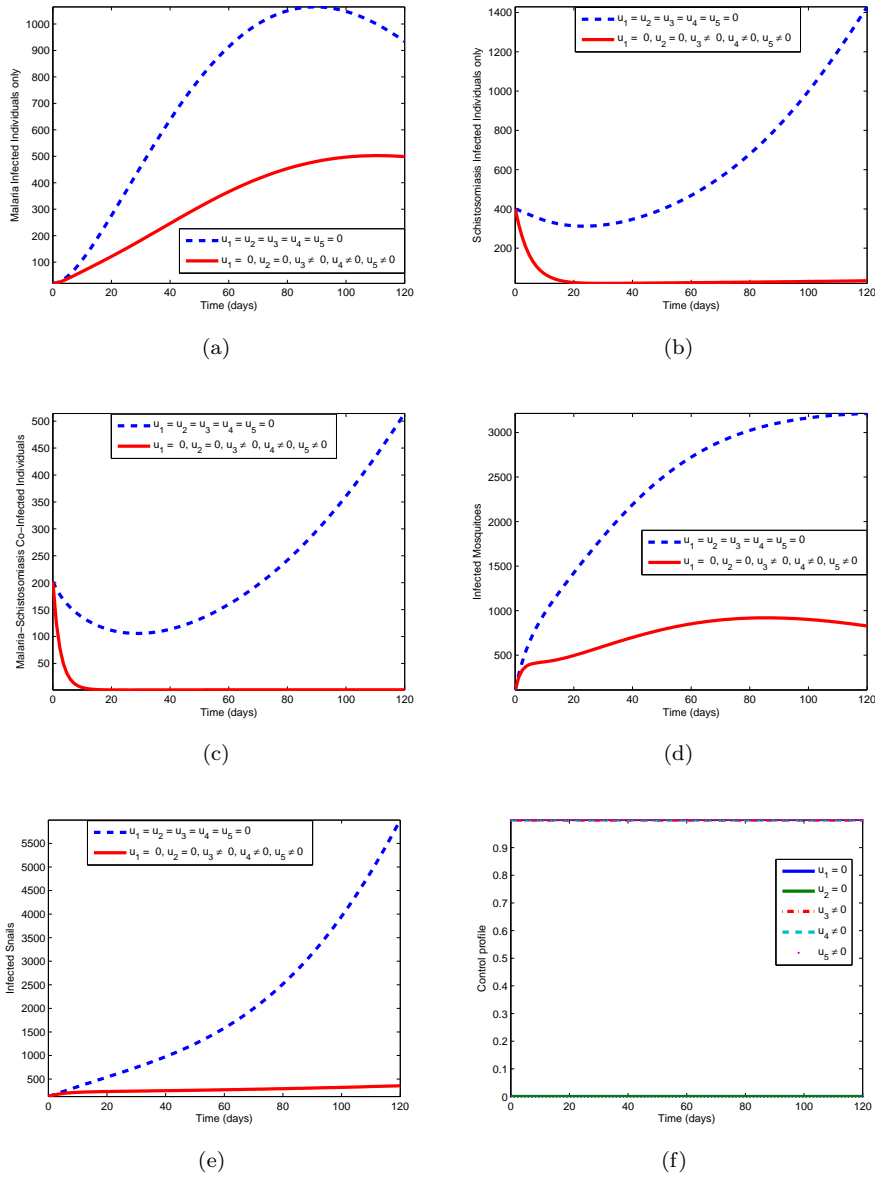


FIGURE 7. Simulations of the malaria–schistosomiasis model showing the effect of treatment of malaria and schistosomiasis transmission

Figure 8(b) suggests that this strategy is effective in controlling the number of schistosomiasis-infected humans I_{sc} , as well as the infected snail population I_{sv} , as shown in Figure 8(e). The population of co-infected humans C_{ms} shown in Figure 8(c) illustrates significant difference between the cases with control and those without. This strategy suggests that utilising all controls (if logistically possible) would be effective at controlling both diseases.

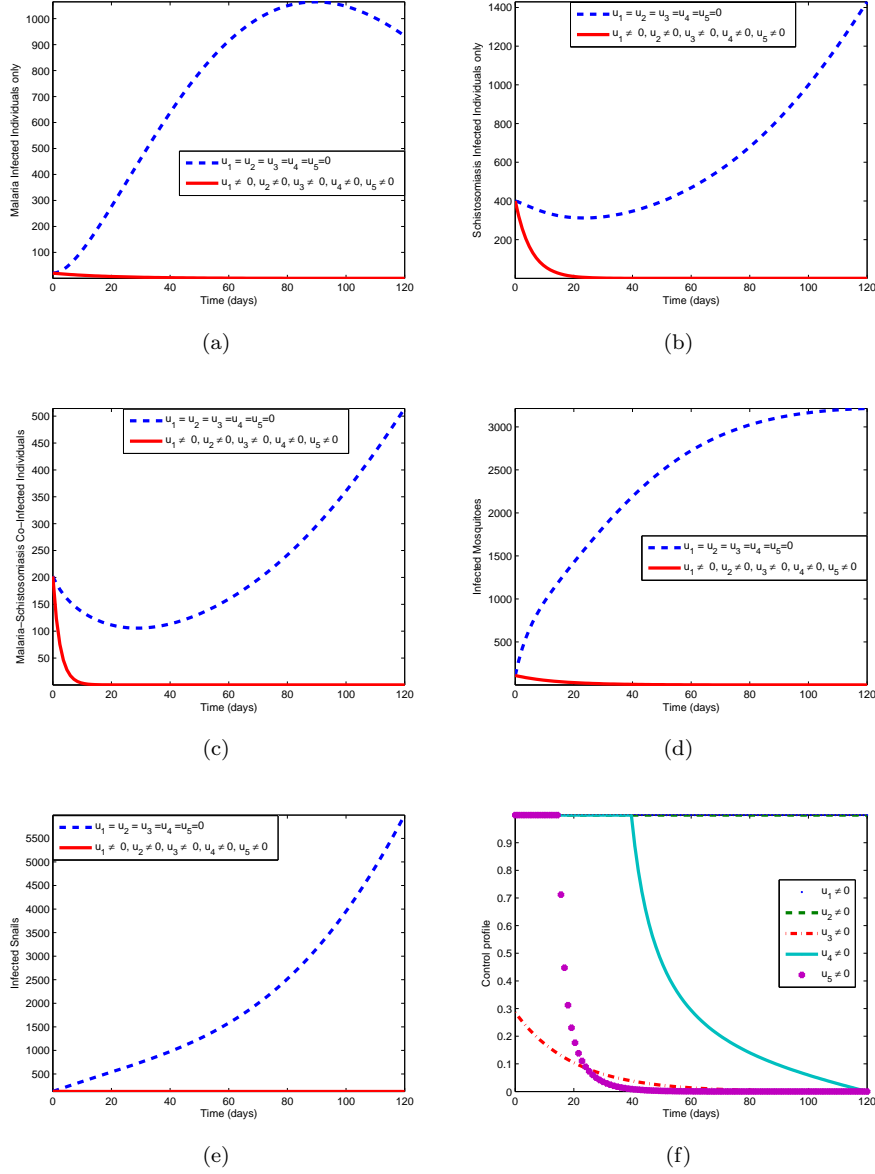


FIGURE 8. Simulations of the malaria–schistosomiasis model showing the effect of both prevention and treatment

The control profile in Figure 8(f) suggests that this strategy would require that control u_3 start at 30% before gradually decreasing to zero, while controls u_4 and u_5 should remain at maximum for 50 days and 20 days respectively before decreasing gradually to zero. Controls u_1 and u_2 should maintain maximum efforts for the entire period of intervention.

Figure 9(a)–(b) shows the effect of varying the schistosomiasis transmission parameter λ on the number of individuals infected with malaria, I_m , and the number

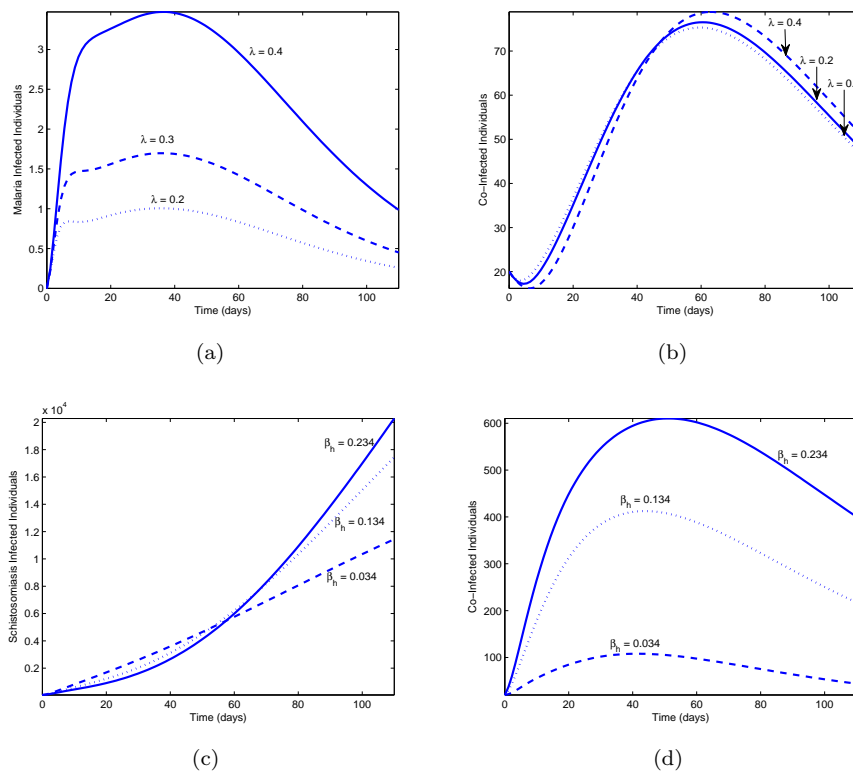


FIGURE 9. Simulations of the malaria–schistosomiasis model showing the effect of varying transmission rates

of co-infected individuals, C_{ms} . This illustrates that effective control of schistosomiasis would enhance the control of malaria. Conversely, Figure 9(c)–(d) shows the effect of varying the malaria transmission parameter β_h on the number of individuals infected with schistosomiasis, I_{sc} , and the number of co-infected individuals. This illustrates that effective control of malaria would enhance control of co-infection but have only minimal effect on schistosomiasis prevalence.

Figure 10 shows the effect of varying the death rate of mosquitoes μ_v (for example, through spraying) on the number of individuals infected with schistosomiasis and the number of co-infected individuals. As the mosquitoes are controlled, the number of individuals infected with malaria falls dramatically, as does the number of co-infected individuals, while the number of schistosomiasis-infected individuals only decreases slightly.

5. Discussion. In this paper, we formulated and analysed a deterministic model for the transmission of malaria–schistosomiasis co-infection that includes use of prevention and treatment of infectives for each disease. We determined reproduction numbers for each submodel and used sensitivity analysis to show that malaria control will affect schistosomiasis. However, schistosomiasis control has little effect on the prevalence of malaria. We also showed that a backward bifurcation is possible under some circumstances, further complicating eradication efforts.

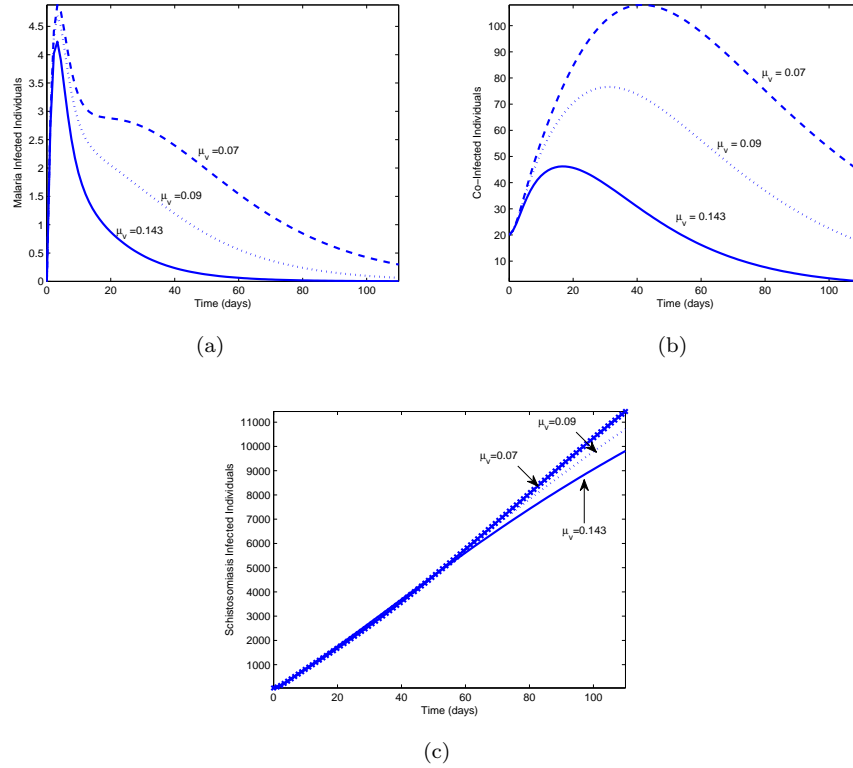


FIGURE 10. Simulations of the malaria–schistosomiasis model showing the effect of varying the mosquito death rate

Numerical simulations indicate that optimal control of schistosomiasis prevention and treatment has a moderate effect on reducing infected mosquitoes. Conversely, optimal malaria prevention and treatment plays no role in reducing infected snails. Furthermore, the control strategies in each case are quite different: schistosomiasis control should be maximised in the absence of any intervention for malaria, while malaria-treatment control should begin at 100%, but gradually reduce to zero over time.

We reconcile the differences between the results from the sensitivity analysis and those of this sub-case by noting that the sensitivity analysis takes into account variation of all factors, whereas this sub-case focuses on varying only some parameters. For example, optimal control of malaria prevention and treatment affects only the transmission rate λ_1 and the recovery rate ω , whereas R_{0m} is also affected by birth and death rates, which in practice may vary considerably.

We also showed that prevention-only strategies for both diseases are less effective than treatment-only strategies. However, utilising both prevention and treatment for both diseases is, unsurprisingly, the most effective option. Therefore, whenever there is co-infection of malaria and schistosomiasis in the community, our model suggests that control measures for both diseases should be administered concurrently for effective control.

Our model has some limitations, which should be acknowledged. We assumed that co-infected individuals recovered from one or other of the infections first; that is, there was no simultaneous recovery. We also assumed that the birth rates of all populations were constant and that infection was not affected by seasonality or migration. Spatial distributions of vector habitats may also be significant [10]. Finally, the existence of a backward bifurcation means that control efforts should not just focus on reducing the reproduction numbers below unity.

Our results illustrate the importance of developing co-infection models: results that apply to one disease may have unexpected consequences (or no consequences) for the other. While a handful of models have been developed for co-infection of diseases, we reiterate the urgency of the call for more modelling [19]. Only when a multitude of voices are included can we begin to fully understand the complexities of interacting controls against multiple infections.

REFERENCES

- [1] B. M. Adams, H. T. Banks, H. Kwon and H. T. Tran, [Dynamic multidrug therapies for HIV: Optimal and STI control approaches](#), *Mathematical Biosciences and Engineering*, **1** (2004), 223–241.
- [2] F. B. Agosto, Optimal chemoprophylaxis and treatment control strategies of a tuberculosis transmission model, *World Journal of Modelling and Simulation*, **5** (2009), 163–173.
- [3] F. B. Agosto and K. O. Okosun, [Optimal seasonal biocontrol for *Eichhornia crassipes*](#), *International Journal of Biomathematics*, **3** (2010), 383–397.
- [4] R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, 1991, Oxford.
- [5] K. W. Blayneh, Y. Cao and H. D. Kwon, [Optimal control of vector-borne diseases: Treatment and Prevention](#), *Discrete and Continuous Dynamical Systems Series B*, **11** (2009), 587–611.
- [6] J. G. Breman, M. S. Alilio and A. Mills, Conquering the intolerable burden of malaria: What's new, what's needed: A summary, *Am. J. Trop. Med. Hyg.*, **71** (2004), 1–15.
- [7] C. Castillo-Chavez and B. Song, [Dynamical model of tuberculosis and their applications](#), *Math. Biosci. Eng.*, **1** (2004), 361–404.
- [8] Z. Chen, L. Zou, D. Shen, W. Zhang and S. Ruan, Mathematical modelling and control of Schistosomiasis in Hubei Province, China, *Acta Tropica*, **115** (2010), 119–125.
- [9] E. T. Chiyaka, G. Magombedze and L. Mutimbu, [Modelling within host parasite dynamics of schistosomiasis](#), *Comp. Math. Meth. Med.*, **11** (2010), 255–280.
- [10] J. A. Clennon, C. G. King, E. M. Muchiri and U. Kitron, Hydrological modelling of snail dispersal patterns in Msambweni, Kenya and potential resurgence of *Schistosoma haematobium* transmission, *Parasitology*, **134** (2007), 683–693.
- [11] S. Doumbo, T. M. Tran, J. Sangala, S. Li and D. Doumbo et al, Co-infection of long-term carriers of *Plasmodium falciparum* with *Schistosoma haematobium* enhances protection from febrile malaria: A prospective cohort study in Mali, *PLoS Negl. Trop. Dis.*, **8** (2014), e3154.
- [12] M. Finkel, *Malaria: Stopping a Global Killer*, National Geographic, July 2007.
- [13] Z. Feng, A. Eppert, F. A. Milner and D. J. Minchella, [Estimation of parameters governing the transmission dynamics of schistosomes](#), *Appl. Math. Lett.*, **17** (2004), 1105–1112.
- [14] W. H. Fleming and R. W. Rishel, *Deterministic and Stochastic Optimal Control*, Springer Verlag, New York, 1975.
- [15] J. H. Ge, S. Q. Zhang, T. P. Wang, G. Zhang, C. Tao, D. Lu, Q. Wang and W. Wu, Effects of flood on the prevalence of schistosomiasis in Anhui province in 1998, *Journal of Tropical Diseases and Parasitology*, **2** (2004), 131–134.
- [16] P. J. Hotez, D. H. Molyneux, A. Fenwick, E. Ottesen, Ehrlich and S. Sachs et al., Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria, *PLoS Med.*, **3** (2006), e102.
- [17] M. Y. Hyun, [Comparison between schistosomiasis transmission modelings considering acquired immunity and age-structured contact pattern with infested water](#), *Mathematical Biosciences*, **184** (2003), 1–26.
- [18] H. R. Joshi, [Optimal control of an HIV immunology model](#), *Optimal Control Applications in Mathematics*, **23** (2002), 199–213.

- [19] A. Kealey and R. J. Smith?, Neglected Tropical Diseases: Infection, modelling and control, *J. Health Care for the Poor and Underserved*, **21** (2010), 53–69.
- [20] J. Keiser, J. Utzinger, M. Caldas de Castro, T. A. Smith, M. Tanner and B. Singer, Urbanization in sub-Saharan Africa and implication for malaria control, *Am. J. Trop. Med. Hyg.*, **71** (2004), 118–127.
- [21] D. Kirschner, S. Lenhart and S. Serbin, [Optimal Control of the Chemotherapy of HIV](#), *J. Math. Biol.*, **35** (1997), 775–792.
- [22] J. C. Koella and R. Anita, Epidemiological models for the spread of anti-malaria resistance, *Malaria Journal*, **2** (2003), p3.
- [23] C. M. Kribs-Zaleta and J. X. Velasco-Hernandez, A simple vaccination model with multiple endemic states, *Math. Biosci.*, **164** (2000), 183–201.
- [24] V. Lakshmikantham, S. Leela and A. A. Martynyuk, *Stability Analysis of Nonlinear Systems*, Marcel Dekker, New York and Basel, 1989.
- [25] S. Lenhart and J. T. Workman, *Control Applied to Biological Models*, Chapman and Hall, London, 2007.
- [26] J. Li, D. Blakeley and R. J. Smith?, The failure of R_0 , *Comp. Math. Meth. Med.*, **2011** (2011), Article ID 527610, 17pp.
- [27] G. Li and Z. Jin, [Global stability of a SEIR epidemic model with infectious force in latent, infected and immune period](#), *Chaos, Solutions and Fractals*, **25** (2005), 1177–1184.
- [28] Q. Longxing, J. Cui, T. Huang, F. Ye and L. Jiang, [Mathematical model of schistosomiasis under flood in Anhui province](#), *Abstract and Applied Analysis*, **2014** (2014), Article ID 972189, 7pp.
- [29] A. D. Lopez, C. D. Mathers, M. Ezzati, D. T. Jamison and C. J. Murray, Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data, *Lancet*, **367** (2006), 1747–1757.
- [30] E. Mtisi, H. Rwezaura and J. M. Tchuente, [A mathematical analysis of malaria and Tuberculosis co-dynamics](#), *Discrete and Continuous Dynamical Systems Series B*, **12** (2009), 827–864.
- [31] Z. Mukandavire, A. B. Gumel, W. Garira and J. M. Tchuente, [Mathematical analysis of a model for HIV-Malaria co-infection](#), *Mathematical Biosciences and Engineering*, **6** (2009), 333–362.
- [32] S. Mushayabasa and C. P. Bhunu, Modeling Schistosomiasis and HIV/AIDS co-dynamics, *Computational and Mathematical Methods in Medicine*, **2011** (2011), Article ID 846174, 15pp.
- [33] S. Mushayabasa and C. P. Bhunu, Is HIV infection associated with an increased risk for cholera? Insights from mathematical model, *Biosystems*, **109** (2012), 203–213.
- [34] I. S. Nikolaos, K. Dietz and D. Schenzle, [Analysis of a model for the Pathogenesis of AIDS](#), *Mathematical Biosciences*, **145** (1997), 27–46.
- [35] K. O. Okosun, R. Ouifki and N. Marcus, Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity, *BioSystems*, **106** (2011), 136–145.
- [36] K. O. Okosun and O. D. Makinde, Optimal control analysis of malaria in the presence of non-linear incidence rate, *Appl. Comput. Math.*, **12** (2013), 20–32.
- [37] K. O. Okosun and O. D. Makinde, [A co-infection model of malaria and cholera diseases with optimal control](#), *Mathematical Biosciences*, **258** (2014), 19–32.
- [38] L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelidze and E. F. Mishchenko, *The Mathematical Theory of Optimal Processes*, Wiley, New York, 1962.
- [39] R. Ross, *The Prevention of Malaria*, Murray, London, 1911.
- [40] P. Salgame, G. S. Yap and W. C. Gause, Effect of helminth-induced immunity on infections with microbial pathogens, *Nature Immunology*, **14** (2013), 1118–1126.
- [41] A. A. Semanya, J. S. Sullivan, J. W. Barnwell and W. E. Secor, Schistosoma mansoni Infection Impairs Antimalaria Treatment and Immune Responses of Rhesus Macaques Infected with Mosquito-Borne Plasmodium coatneyi, *Infection and Immunity*, **80** (2012), 3821–3827.
- [42] K. D. Silué, G. Raso, A. Yapi, P. Vounatsou, M. Tanner, E. Ngoran and J. Utzinger, Spatially-explicit risk profiling of Plasmodium falciparum infections at a small scale: A geostatistical modelling approach, *Malaria J.*, **7** (2008), p111.
- [43] R. J. Smith? and S. D. Hove-Musekwa, [Determining effective spraying periods to control malaria via indoor residual spraying in sub-saharan Africa](#), *Journal of Applied Mathematics and Decision Sciences*, **2008** (2008), Article ID 745463, 19pp.

- [44] R. W. Snow, C. A. Guerra, A. M. Noor, H. Y. Myint and S. I. Hay, The global distribution of clinical episodes of *Plasmodium falciparum* malaria, *Nature*, **434** (2005), 214–217.
- [45] R. C. Spear, A. Hubbard, S. Liang and E. Seto, Disease transmission models for public health decision making: Toward an approach for designing intervention strategies for Schistosomiasis japonica, *Environ. Health Perspect.*, **10** (2002), 907–915.
- [46] P. van den Driessche and J. Watmough, [Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission](#), *Math. Biosci.*, **180** (2002), 29–48.
- [47] R. B. Yapi, E. Hürlimann, C. A. Hounghbedji, P. B. Ndri and K. D. Silué et al., Infection and Co-infection with Helminths and *Plasmodium* among School Children in Côte d'Ivoire: Results from a National Cross-Sectional Survey, *PLoS Negl. Trop. Dis.*, **8** (2014), e2913.
- [48] X. N. Zhou, J. G. Guo and X. H. Wu et al., Epidemiology of schistosomiasis in the people's republic of China, 2004, *Emerging Infectious Diseases*, **13** (2007), 1470–1476.

Received August 06, 2015; Accepted June 03, 2016.

E-mail address: kazeemoare@gmail.com

E-mail address: rsmith43@uottawa.ca