OPTIMAL CONTROL ANALYSIS OF MALARIA–SCHISTOSOMIASIS CO-INFECTION DYNAMICS

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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 [41], killing between one
to two million people annually \cite{6}, primarily among children less than five years of age in sub-Saharan Africa \cite{20}. Three billion people — almost half the world’s population — are at risk of malaria \cite{20,12,44}. It has been estimated that one in two humans who ever lived has been killed by malaria \cite{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 \cite{25}. 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 (\textit{S. mansoni}, \textit{S. japonicum}, \textit{S. mekongi} and \textit{S. intercalatum}) or the urinary bladder (\textit{S. haematobium}) \cite{9,17,28}. Flooding can lead to severe schistosomiasis outbreaks \cite{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 \cite{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 \cite{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 \cite{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. \cite{34} proposed a detailed analysis of a dynamical model to describe pathogenesis of HIV infection. Kribs-Zaleta and Velasco-Hernandez \cite{23} derived a simple two-dimensional SIS (susceptible-infected-susceptible) model with vaccination and multiple endemic states. Li and Jin \cite{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. \cite{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 \textit{et al.} \cite{8}. Their model consisted of six ordinary differential equations that describe susceptible and infected human, cattle and snail subpopulations. Longxing \textit{et al.} \cite{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) \cite{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 \textit{et al.} \cite{31} proposed a deterministic model for the co-infection of HIV and malaria in a community. Mtisi \textit{et al.} \cite{30} examined a deterministic model for the co-infection of tuberculosis and malaria, while Mushayabasa and Bhunu \cite{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 a 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 \( N_h = S_h + I_m + I_{sc} + C_{ms} + R_m + R_s \).

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 \( N_{sv} = S_{sv} + I_{sv} \).

\[
\begin{align*}
S_h &\quad \Lambda_h \\
I_m &\quad \mu_h I_m \\
I_{sc} &\quad \mu_v I_v \\
C_{ms} &\quad \lambda_{is} S_{sv} \\
R_m &\quad \mu_h R_m \\
R_s &\quad \mu_v R_v \\
S_{sv} &\quad \lambda_{sv} S_{sv} \\
I_{sv} &\quad \mu_{sv} I_{sv} \\
(\eta + \mu_h)C_{ms} &\quad gC_m \\
\end{align*}
\]

**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:

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

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 \(\eta\) is the schistosomiasis-related death rate and \(\phi\) 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., \(\eta \ll \phi\)) \cite{33}. 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 \(\eta\) is small.

The immunity-waning rates for malaria and schistosomiasis are \(\alpha\) and \(\epsilon\) respectively, while the recovery rates from malaria, schistosomiasis and co-infection are \(\psi\), \(\omega\) and \(\delta\) 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, \(\mu_h\), \(\mu_v\) and \(\mu_{sv}\). 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,

\[
\begin{align*}
\limsup_{t \to \infty} N_h(t) &\leq \frac{\Lambda_h}{\mu_h} \quad \text{and} \quad \limsup_{t \to \infty} N_v(t) \leq \frac{\Lambda_v}{\mu_v} \quad \text{and} \quad \limsup_{t \to \infty} N_s(t) \leq \frac{\Lambda_s}{\mu_{sv}}.
\end{align*}
\]  

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
\[ D = D_h \times D_v \times D_s \subset \mathbb{R}_+^6 \times \mathbb{R}_+^2 \times \mathbb{R}_+^2 \] 
where
\[ D_h = \{(S_h, I_m, I_{sc}, C_{ms}, R_m, R_s) \in \mathbb{R}_+^6 : S_h + I_m + I_{sc} + C_{ms} + R_m + R_s \leq \frac{\Lambda_h}{\mu_h} \} \]
\[ D_v = \{(S_v, I_v) \in \mathbb{R}_+^2 : S_v + I_v \leq \frac{\Lambda_v}{\mu_v} \} \]
\[ D_s = \{(S_{sv}, I_{sv}) \in \mathbb{R}_+^2 : S_{sv} + I_{sv} \leq \frac{\Lambda_s}{\mu_{sv}} \}. \]
Note that \( D \) 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 \( S_h(0), I_m(0), I_{sc}(0), C_{ms}(0), R_m(0), R_s(0), S_v(0), I_v(0), S_{sv}(0) \text{ and } I_{sv}(0) \) 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
\[ S_h(t_1) = U(t_1, 0)S_h(0) + \int_0^{t_1} \mathcal{U}(t_1, \tau)d\tau, \]
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 \( S_h, I_m, I_{sc}, C_{ms}, R_m, R_s, S_v, I_v, S_{sv} \text{ and } I_{sv} \) are positive for all \( t > 0. \)

For the second part of the proof, adding the last two equations of system (1), we obtain \( \frac{dN_v}{dt} = \Lambda_v - \mu_v N_v. \) This implies that \( N_v(t) = N_v(0)e^{-\mu_v t} + \frac{\Lambda_v}{\mu_v}(1 - e^{-\mu_v t}). \)
Thus \( \limsup_{t \to \infty} N_v(t) = \frac{\Lambda_v}{\mu_v}. \) Moreover, if \( N_v(0) \leq \frac{\Lambda_v}{\mu_v}, \) then \( N_v(t) \leq \frac{\Lambda_v}{\mu_v}. \)

Adding the two mosquito equations of system (1), we obtain \( \frac{dN_s}{dt} = \Lambda_s - \mu_s N_s. \) This implies that \( N_s(t) = N_s(0)e^{-\mu_s t} + \frac{\Lambda_s}{\mu_s}(1 - e^{-\mu_s t}). \) Thus \( \limsup_{t \to \infty} N_s(t) = \frac{\Lambda_s}{\mu_s}. \) Moreover, if \( N_s(0) \leq \frac{\Lambda_s}{\mu_s}, \) then \( N_s(t) \leq \frac{\Lambda_s}{\mu_s}. \)

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
\[ N_h(0)e^{-\mu_h t + (\phi + \eta)} + \frac{\Lambda_h}{\mu_h + (\phi + \eta)}(1 - e^{-\mu_h t}) \]
\[ \leq N_h \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t}). \]
This implies that
\[ \frac{\Lambda_h}{\mu_h + (\phi + \eta)} \leq \liminf_{t \to \infty} N_h(t) \leq \limsup_{t \to \infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}. \]
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.

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. \( S_h' = \Lambda_h + \epsilon R_s - \lambda_1 S_h - \mu_h S_h \)
\( I_{sc}' = \lambda_1 S_h - (\omega + \mu_h + \eta) I_{sc} \)
\( R_s' = \omega I_{sc} - (\epsilon + \mu_h) R_s \)
\( S_{sv}' = \Lambda_s - \lambda_2 S_{sv} - \mu_{sv} S_{sv} \)
\( I_{sv}' = \lambda_2 S_{sv} - \mu_{sv} I_{sv} \),

where \( \lambda_1 = \frac{\lambda_{sv}}{N_h}, \quad \lambda_2 = \frac{\lambda_{sc}}{N_h} \). \( (5) \)

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
\( R_{sc} = \sqrt{\frac{\lambda_1 \lambda_2 \Lambda_{sv} \mu_h}{\Lambda_h (\eta + \omega + \mu_h) \mu_{sv}^2}} \).

(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 \( \lambda^* \) from \( (6) \), the endemic equilibrium point satisfies the following polynomial:
\( P(\lambda^*) = \lambda^* \left[ A(\lambda^*)^2 + B(\lambda^*) + C \right] = 0 \),

(7)

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

(8)
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), \( \Delta(R_{sc}) = B^2 - 4AC \), 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 \( R_{0sc} < R_{sc} < 1 \).

3.4. Malaria-only model. We next consider the malaria-only model:
\[
\begin{align*}
S_h' &= \Lambda - \beta_1 S_h - \mu_h S_h \\
I_m' &= \beta_1 S_h - (\psi + \mu_h + \phi) I_m \\
R_m' &= \psi I_m - (\alpha + \mu_h) R_m \\
S_v' &= \Lambda - \beta_2 S_v - \mu_v S_v \\
I_v' &= \beta_2 S_v - \mu_v I_v,
\end{align*}
\]
(9)
where
\[
\beta_1 = \frac{\beta_v I_v}{N_h}, \quad \beta_2 = \frac{\beta_v I_v}{N_h}.
\]

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
\[
R_{0m} = \sqrt{\frac{\Lambda_v \beta_h \beta_v \mu_h}{\Lambda_h \mu_h \psi (\psi + \phi + \mu_h)}},
\]
(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 \( R_{0m} > 1 \).
Proposition 2.  1. If $R_D > 1$, then system [4] exhibits a transcritical bifurcation.
2. If $R_D < 1$, then system [4] exhibits a backward bifurcation.

Proof.

1. For $R_D > 1$, we obtain when $R_{0m} > 1$ that $C_c < 0$. This implies that system [4] has a unique endemic steady state. If $R_{0m} \leq 1$, then $C_c \geq 0$ and $B_b > 0$. In this case, system [4] 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 [4] has a unique endemic steady state.
   ii. If $R_{0m} > \sqrt{R_D}$, then both $B_b$ and $C$ are positive, implying that system [4] 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 [12], $\Delta(R_{0m}) = B_b^2 - 4A_a C_c$, 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 [4] 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

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

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

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

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

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 \(\mu_h\) 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

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

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 $\mu_h$ in terms of $R_{sc}$, we get

$$\mu_h = \frac{D_4 R_{sc}^2}{D_5 - D_6 R_{sc}^2},$$  \hspace{1cm} (15)$$

where

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

Substituting into the expression for $R_{om}$, we obtain

$$R_{om} = \sqrt{\frac{D_4 \beta_h \beta_s \Lambda_s R_{sc}^2}{[(\phi + \psi)D_5 + (D_4 - (\phi + \psi)D_6)R_{sc}]\Lambda_h \mu_{sv}^2}}.$$ \hspace{1cm} (16)

Differentiating $R_{om}$ with respect to $R_{sc}$, we get

$$\frac{\partial R_{om}}{\partial R_{sc}} = \frac{(\phi + \psi)D_5 \sqrt{D_4 \beta_h \beta_s \Lambda_s R_{sc}^2}}{[(\phi + \psi)R_{sc}(D_5 - D_6 R_{sc}^2) + D_4 R_{sc}^3 \Lambda_h \mu_{sv}^2]},$$  \hspace{1cm} (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 $R_{om}$ with respect to $\omega$. We have

$$\frac{\partial R_{om}}{\partial \omega} = \frac{(\phi + \psi)(D_5 - D_6 R_{sc}^2) \sqrt{D_4 \beta_h \beta_s \Lambda_s R_{sc}^2}}{2D_4 [(\phi + \omega)(D_5 - D_6 R_{sc}^2) + D_4 R_{sc}^3 \Lambda_h \mu_{sv}^2]}.$$ \hspace{1cm} (18)$$

Whenever (18) is negative, $R_{om}$ is strictly a decreasing function of $\omega$, 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 $R_{om}$

We next derive the sensitivity of $R_{sc}$ in (13) (i.e. when expressed in terms of $R_{om}$) 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 $\lambda$, for example is,

$$\gamma_{\lambda}^{R_{sc}} = \frac{\partial R_{sc}}{\partial \lambda} \times \frac{\lambda}{R_{sc}} = 0.5.$$ \hspace{1cm} (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 $R_{0m} > 1$ |
|-----------|-------------|---------------------------------|---------------------------------|
| $\mu_s$   | snail mortality | -1                              | -1                              |
| $\mu_v$   | mosquito mortality | 0.56                           | 0.07                            |
| $\lambda_s$ | prob. of snail getting infected with schisto | 0.5                            | 0.5                            |
| $\lambda$  | snail birth rate | 0.5                             | 0.5                            |
| $\beta_h$ | prob. of human getting infected with malaria | -0.28                          | -0.03                          |
| $\beta_v$ | prob. of mosquito getting infected | -0.28                          | -0.03                          |
| $\Lambda_s$ | mosquito birth rate | -0.28                          | -0.03                          |
| $\Lambda_h$ | human birth rate | -0.22                          | -0.47                          |
| $\phi$     | malaria-induced death | 0.12                           | -0.31                          |
| $\omega$   | recovery from schisto | -0.10                          | 0.26                           |
| $m$        | schisto-induced death | -0.02                          | 0.05                           |
| $\psi$     | 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 ($\mu_s$, $\mu_v$, $\lambda$, and $\Lambda_s$, respectively). Since $\frac{R_{sc}}{\mu_s} = -1$, increasing (or decreasing) the snail mortality rate $\mu_s$ by 10% decreases (or increases) $R_{sc}$ by 10%; similarly, increasing (or decreasing) the mosquito mortality rate, $\mu_v$, 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, $\lambda_s$, increases (or decreases) $R_{sc}$ by 5%. As the malaria parameters $\beta_h$, $\beta_v$ and $\Lambda_v$ 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 ($\mu_s$, $\lambda_s$, $\Lambda_s$, $\beta_h$, $\phi$, $\omega$, respectively). Since $\frac{R_{sc}}{\lambda_s} = 0.5$, increasing (or decreasing) by 10% increases (or decreases) $R_{sc}$ by 5%; similarly, increasing (or decreasing) the recovery rate, $\omega$, by 10% increases (or decreases) $R_{sc}$ by 2.6%. Also, as the malaria parameters $\beta_h$, $\beta_v$ and $\Lambda_v$ 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 $\beta_h$, for example, is

$$\gamma_{R_{0m}}^{\beta_h} = \frac{\partial R_{0m}}{\partial \beta_h} \times \frac{\beta_h}{R_{0m}} = 0.5.$$  \hspace{1cm} (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, $R_{0m}$, is not sensitive to any variation in the schistosomiasis reproduction number $R_{sc}$.  

### Table 2. Sensitivity indices of $R_{om}$ expressed in terms of $R_{sc}$

| Parameter | Description                                | Sensitivity index if $R_{sc} < 1$ | Sensitivity index if $R_{sc} > 1$ |
|-----------|--------------------------------------------|----------------------------------|----------------------------------|
| $\beta_v$ | prob. of mosquito getting infected          | 0.5                              | 0.5                              |
| $\Lambda_v$ | mosquito birth rate                         | 0.5                              | 0.5                              |
| $\lambda$ | prob. of human getting infected with schisto | $-0.5$                          | $-0.5$                          |
| $\lambda_s$ | prob. of snail getting infected with schisto | $-0.5$                          | $-0.5$                          |
| $\phi$ | malaria-induced death                       | $-0.49$                          | $-0.49$                          |
| $\omega$ | recovery from schisto                       | 0.41                             | 0.41                             |
| $m$ | schisto-induced death                       | 0.09                             | 0.09                             |
| $\psi$ | recovery from malaria                       | $-0.01$                          | $-0.01$                          |
| $\mu_{sv}$ | snail mortality                             | 0.00000002                       | 0.0000007                       |
| $\Lambda_{hi}$ | human birth rate                              | 0.0000001                         | 0.0000004                       |

**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 $\beta_h$ and $\lambda$ as bifurcation parameters so that $R_{0m} = 1$ and $R_{sc} = 1$ if and only if

$$\beta_h = \beta^*_h = \frac{\mu^2_s \Lambda_h (\psi + \phi + \mu_h)}{\Lambda_v \mu_h \beta_v}$$

and

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

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

$$\begin{align*}
x_1' &= \Lambda_h + cx_6 + \alpha x_5 - \beta_1 x_1 - \lambda_1 x_1 - \mu_h x_1 \\
x_2' &= \beta_1 x_1 - \lambda_1 x_2 - (\psi + \mu_h + \phi)x_2 \\
x_3' &= \lambda_1 x_1 - \beta_1 x_3 - (\omega + \mu_h + \eta)x_3 \\
x_4' &= \beta_1 x_3 + \lambda_1 x_2 - (\delta + \mu_h + \eta + \phi)x_3 \\
x_5' &= \psi x_4 - (\alpha + \mu_h)x_5 - \tau \delta x_4 \\
x_6' &= \omega x_3 - (\epsilon + \mu_h)x_6 + (1 - \tau) \delta x_4 \\
x_7' &= \Lambda_v - \beta_2 x_7 - \mu_v x_7 \\
x_8' &= \beta_2 x_7 - \mu_v x_9 \\
x_9' &= \Lambda_s - \lambda_2 x_9 - \mu_{sv} x_{10} \\
x_{10}' &= \lambda_2 x_{10} - \mu_{sv} x_{11}.
\end{align*} \tag{21}$$

where

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

This method involves evaluation of the Jacobian of system \[21\] at the DFE $E_0$, denoted by $J(E_0)$. This becomes

$$J(E_0) = \begin{bmatrix}
-\mu_h & 0 & 0 & 0 & \alpha & \epsilon & 0 & -\beta_h & 0 & -\lambda \\
0 & -J_1 & 0 & 0 & 0 & 0 & 0 & \beta_h & 0 & 0 \\
0 & 0 & -J_2 & J_1 & 0 & 0 & 0 & 0 & 0 & \lambda \\
0 & 0 & 0 & -J_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \psi & 0 & J_4 & -J_5 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \omega & J_6 & 0 & -J_7 & 0 & 0 & 0 & 0 \\
0 & -J_q & 0 & -J_q & 0 & 0 & -\mu_v & 0 & 0 & 0 \\
0 & J_q & 0 & J_q & 0 & 0 & 0 & -\mu_v & 0 & 0 \\
0 & 0 & -J_b & -J_h & 0 & 0 & 0 & 0 & -\mu_{sv} & 0 \\
0 & 0 & J_b & J_h & 0 & 0 & 0 & 0 & 0 & -\mu_{sv}
\end{bmatrix}.$$
where

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

\( J(\mathcal{E}_0) \) 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

\[ w_1 = -\frac{\Lambda_h (\alpha \phi + \mu_h (\alpha + \phi + \psi + \mu_h)) \mu_v^2}{\beta_v \Lambda_v \mu_h (\alpha + \mu_h)} \quad w_2 = \frac{\Lambda_h \mu_v^2}{\beta_v \Lambda_v \mu_h} \quad w_3 = w_4 = 0 \]
\[ w_5 = \frac{w_2 w_7}{\mu_v^2 (\alpha + \mu_h)} \quad w_6 = 0 \quad w_7 = -w_8 \quad w_9 = w_{10} = 0 \]

and

\[ v_1 = 0 \quad v_2 = \frac{\beta_v \Lambda_v \mu_h}{\Lambda_h (\phi + \psi + \mu_h) \mu_v} \quad v_3 = 0 \]
\[ v_4 = \frac{\beta_v \Lambda_v \mu_h}{\Lambda_h (\phi + \delta + \eta + \mu_h) \mu_v} \quad v_5 = v_6 = v_7 = 0 \quad v_9 = v_{10} = 0, \]

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

\[ a = 2w_8 w_2 \left( \frac{\mu_h}{\Lambda_h} - \frac{\Lambda_v \mu_h^2}{\mu_v \Lambda_v} - w_5 \frac{\Lambda_v \mu_h^2}{\mu_v \Lambda_v^2} \right) \]
\[ b = v_2 \left( w_8 - w_5 \frac{\mu_h}{\Lambda_h} \right). \]

(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 \([7]\) will undergo a backward bifurcation if the coefficient \( a \) is positive.
2. System \([8]\) 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 \([10]\) to determine the optimal strategy for controlling the disease. Hence we
have

\[ S'_h = \Lambda_h + \epsilon R_s + \alpha R_m - (1 - u_1)\beta_1 S_h - (1 - u_2)\lambda_1 S_h - \mu_h S_h \]
\[ I'_m = (1 - u_1)\beta_1 S_h - (1 - u_2)\lambda_1 I_m - (u_3\psi + \mu_h + \phi)I_m \]
\[ I'_{sc} = (1 - u_2)\lambda_1 S_h - (1 - u_1)\beta_1 I_{sc} - (u_4\omega + \mu_h + \eta)I_{sc} \]
\[ C'_{ms} = (1 - u_1)\beta_1 I_{sc} + (1 - u_2)\lambda_1 I_m - (u_5\delta + \mu_h + \eta + \phi)C_{ms} \]
\[ R'_m = u_3\psi I_m - (\alpha + \mu_h)R_m + u_5\tau\delta C_{ms} \]
\[ R'_v = u_4\omega I_{sc} - (\epsilon + \mu_h)R_v + u_5(1 - \tau)\delta C_{ms} \]
\[ S'_v = \Lambda_v - (1 - u_1)\beta_2 S_v - \mu_v S_v \]
\[ I'_v = (1 - u_1)\beta_2 S_v - \mu_v I_v \]
\[ S'_{sv} = \Lambda_v - (1 - u_2)\lambda_2 S_{sv} - \mu_{sv}S_{sv} \]
\[ I'_sv = (1 - u_2)\lambda_2 S_{sv} - \mu_{sv}I_{sv} \]

where

\[ \beta_1 = \frac{\beta_h I_v}{N_h} \quad \lambda_1 = \frac{M_{sv}}{N_h} \]
\[ \beta_2 = \frac{\beta_v(I_m + C_{ms})}{N_h} \quad \lambda_2 = \frac{\lambda_s(I_{sc} + C_{ms})}{N_h} \]

For this, we consider the objective functional

\[
J(u_1, u_2, u_3, u_4, u_5) = \int_0^{t_f} \left[ z_1 I_m + z_2 I_{sc} + z_3 C_{ms} + z_4 I_v + z_5 I_{sv} - A u_1^2 - B u_2^2 + C u_3^2 + D u_4^2 + E u_5^2 \right] dt.
\]

(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 [11 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 \( u_1^*, u_2^*, u_3^*, u_4^*, u_5^* \) such that

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

(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.
Theorem 3.7. Given optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ 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)-(25) 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

\[
- \frac{dM_i}{dt} = \frac{\partial H}{\partial i},
\]

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

\[
M_{S_h}(t_f) = M_{I_m}(t_f) = M_{I_{sc}}(t_f) = M_{C_{ms}}(t_f) = M_{R_m}(t_f) = M_{R_s}(t_f) = 0
\]

and

\[
u_1^* = \max \left\{ 1, \min \left( 0, \frac{\beta h I_v S_h (M_{S_h} - M_{I_m}) + \beta h I_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + G_y}{2 AN_h} \right) \right\}
\]

\[
u_2^* = \max \left\{ 1, \min \left( 0, \frac{\lambda_{sv} (M_{S_h} - M_{I_{sc}}) S_h + \lambda_{sv} (M_{I_m} - M_{C_{ms}}) I_m + D_z}{2 BN_h} \right) \right\}
\]

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

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

\[
u_5^* = \min \left\{ 1, \max \left( 0, \frac{\delta_{C_{ms}} M_{C_{ms}} - \tau \delta_{C_{ms}} M_{R_m} - (1 - \tau) \delta_{C_{ms}} M_{R_s}}{2 E} \right) \right\},
\]

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

**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, 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

\[
0 = \frac{\partial H}{\partial u_1} = -2A u_1 + \frac{\beta_h I_v S_h (M_{Sh} - M_{I_{Im}}) + \beta_v I_{sc} (M_{I_{sc}} - M_{C_{ms}})}{N_h} \quad (33)
\]

\[
0 = \frac{\partial H}{\partial u_2} = -2B u_2 + \frac{\lambda_s (M_{Sh} - M_{I_{Iv}}) S_h + \lambda_s (M_{I_{Im}} - M_{C_{ms}}) I_m + \lambda_s (I_{sc} + C_{ms}) S_{sv} (M_{sv} - M_{I_{sv}})}{N_h} \quad (33)
\]

\[
0 = \frac{\partial H}{\partial u_3} = 2C u_3 + \psi (M_{Rm} - M_{I_{Im}}) I_m \quad (33)
\]

\[
0 = \frac{\partial H}{\partial u_4} = 2D u_4 + \omega (M_{R_{sc}} - M_{I_{sc}}) I_{sc} \quad (33)
\]

\[
0 = \frac{\partial H}{\partial u_5} = 2E u_5 + \delta C_{ms} M_{C_{ms}} + \tau \delta C_{ms} M_{Rm} + (1 - \tau) \delta C_{ms} M_{R_{sc}} \quad (33)
\]

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

\[
u_1^* = \frac{\beta_h I_v S_h (M_{Sh} - M_{I_{Im}}) + \beta_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + G_y}{2A N_h}
\]

\[
u_2^* = \frac{\lambda_s (M_{Sh} - M_{I_{Iv}}) S_h + \lambda_s (M_{I_{Im}} - M_{C_{ms}}) I_m + \lambda_s (I_{sc} + C_{ms}) S_{sv} (M_{sv} - M_{I_{sv}})}{2B N_h}
\]

\[
u_3^* = \frac{\psi (M_{I_{Im}} - M_{Rm}) I_m}{2C}
\]

\[
u_4^* = \frac{\omega (M_{I_{sc}} - M_{R_{sc}}) I_{sc}}{2D}
\]

\[
u_5^* = \frac{\delta C_{ms} M_{C_{ms}} - \tau \delta C_{ms} M_{Rm} - (1 - \tau) \delta C_{ms} M_{R_{sc}}}{2E}
\]

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

\[
\xi_1^* = \frac{\beta_h I_v S_h (M_{Sh} - M_{I_{Im}}) + \beta_v I_{sc} (M_{I_{sc}} - M_{C_{ms}}) + G_y}{2A N_h}
\]

\[
\xi_2^* = \frac{\lambda_s (M_{Sh} - M_{I_{Iv}}) S_h + \lambda_s (M_{I_{Im}} - M_{C_{ms}}) I_m + \lambda_s (I_{sc} + C_{ms}) S_{sv} (M_{sv} - M_{I_{sv}})}{2B N_h}
\]

\[
\xi_3^* = \frac{\psi (M_{I_{Im}} - M_{Rm}) I_m}{2C}
\]

\[
\xi_4^* = \frac{\omega (M_{I_{sc}} - M_{R_{sc}}) I_{sc}}{2D}
\]

\[
\xi_5^* = \frac{\delta C_{ms} M_{C_{ms}} - \tau \delta C_{ms} M_{Rm} - (1 - \tau) \delta C_{ms} M_{R_{sc}}}{2E}
\]
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 |
|-----------|-------------|-------|-----------|
| $\phi$    | malaria-induced death | 0.05–0.1 day$^{-1}$ | \[43\] |
| $\beta_h$ | malaria transmissibility to humans | 0.034 day$^{-1}$ | assumed |
| $\beta_v$ | malaria transmissibility to mosquitoes | 0.09 day$^{-1}$ | \[5\] |
| $\lambda$ | schistosomiasis transmissibility to humans | 0.406 day$^{-1}$ | \[35\] |
| $\lambda_s$ | schistosomiasis transmissibility to snails | 0.615 day$^{-1}$ | \[3\] |
| $\mu_h$ | Natural death rate in humans | 0.00004 day$^{-1}$ | \[5\] |
| $\mu_v$ | Natural death rate in mosquitoes | 1/15–0.143 day$^{-1}$ | \[5\] |
| $\mu_{sv}$ | Natural death rate in snails | 0.000569 day$^{-1}$ | \[9, 45\] |
| $\alpha$ | malaria immunity waning rate | 1/(60×365) day$^{-1}$ | \[5\] |
| $\epsilon$ | schistosomiasis immunity waning rate | 0.013 day$^{-1}$ | assumed |
| $\Lambda_h$ | human birth rate | 800 people/day | \[7\] |
| $\Lambda_v$ | mosquitoes birth rate | 1000 mosquitoes/day | \[5\] |
| $\Lambda_s$ | snail birth rate | 100 snails/day | \[13\] |
| $\delta$ | recovery rate of co-infected individual | 0.35 day$^{-1}$ | assumed |
| $\omega$ | recovery rate of schistosomiasis-infected individual | 0.0181 day$^{-1}$ | assumed |
| $\psi$ | recovery rate of malaria-infected individual | 1/(2×365) day$^{-1}$ | \[2\] |
| $\tau$ | co-infected proportion who recover from malaria only | 0.1 | assumed |
| $\eta$ | 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(c); 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
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.
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 observed 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(c) 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
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.
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 $\lambda$ 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 $\beta_h$ 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 $\mu_v$ (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.
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 $\lambda_1$ and the recovery rate $\omega$, 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.

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