Original Research Paper

Optimal Control of a Malaria Transmission Model with Saturated Incidence

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Abstract: We present a vector-host deterministic model for the transmission and control of malaria, using prevention and treatment as controls. A novel addition to our model is a new prevention function that highlights the role of prevention in reducing vector populations; an essential arsenal in the fight against malaria. Another innovation is the use of a novel treatment function, which reflects the fact that, at any given time, only a proportion of the infected population has access to proper treatment; increasing this proportion is key to the effective control of malaria. Optimal control methods are used to determine a proper combination of prevention and treatment, necessary to effectively reduce malaria transmission. Simulations of the solutions of the optimality system, using varying parameter values, show that malaria infections can be drastically reduced and possibly eradicated, if contiguous communities implement appropriate prevention and treatment strategies.

Keywords: Malaria Transmission Model, Saturated Incidence, Optimal Control Formulation, Pontryagin's Maximum Principle, Forward-Backward Sweep method

Introduction

Malaria is a leading cause of mortality and morbidity in tropical and subtropical regions of the world, where an estimated two hundred million people are at constant risk of infection, with Africa being the most impacted.

The World Health Organization (WHO) reports that in Sub-Saharan Africa, malaria kills at least one million people annually and it has the potential to increase significantly due to continuous climate change. In developing countries, the disease persists and has become a severe public health and socio-economic challenge.

Human malaria is a mosquito-borne disease caused by the four species of the genus *Plasmodium*, a protozoan parasite. The following species are the causative agents for malaria in humans: *Plasmodium falciparum*, the deadliest human parasite and most prevalent in the tropics; *Plasmodium vivax*, the common cause of clinical malaria, yet it's rarely fatal; *Plasmodium malariae*, a rare cause of clinical malaria, particularly in Africa; it can last for decades as low-grade parasitaemia. *Plasmodium ovale*, causes clinically relevant but not severe disease however, it can be discovered in infections with some other species.

Transmission of the *Plasmodium* parasite is through the bite of an infected female anopheles' mosquito (Putri and Jaharuddin, 2014). The vector becomes infected when it bites an infected human.

The bites usually occur between dusk and dawn and their intensity depends on factors related to the *Plasmodium* parasite, the vector, the human, the environment and whether it chooses to bite humans or animals (WHO, 2019a). Infection of malaria in humans takes place when mosquitoes inject their saliva containing sporozoites into humans; they are carried to the liver within 30-60 min.

They then penetrate the liver hepatocytes and undergo a phase of asexual multiplication that results in the production of approximately 8-6 merozoites and these merozoites penetrate the red blood cells.

This continuous activity is responsible for the cause of malaria infection. The symptoms of malaria include fever, chills together with headache, vomiting, anemia, diarrhea, liver and neurological damage (Adamu *et al*., 2017).

Personal protection measures are the first line of defense against mosquito-borne diseases. One of the methods of personal protection is the use of mosquito repellents. These are substances applied to exposed skin or to clothing to prevent human-mosquito contact. These only repel but do not kill mosquitoes. Other techniques for personal protection are the use of Insecticide-Treated Bed Nets (ITNs) and Indoor Residual Spraying (IRS). The use of ITNs for individuals against malaria has been shown to reduce

the morbidity of childhood malaria (below five years of age) by 50% and global child mortality by 20-30% (Binka *et al.*, 1996). When used on a large scale ITNs are considered to represent efficient tools for malaria vector control. There is, however, a limiting factor of resistance in the insecticides used for impregnated nets. Resistance of the most important African malaria vector Anopheles gambiae S.l. to pyrethroid is already widespread in several West African countries most especially Ghana. In addition, government intervention comes in many forms including mass spraying of endemic areas. Many of these prevention strategies contribute to a reduction of the vector population.

The use of mathematical models to investigate the spread of infectious diseases is widely used by mathematical biologists and epidemiologists. One of the first researchers to publish a series of papers on malaria using mathematical models to study transmission processes (Ross, 1911). His research was on the formulation of a differential equation model using standard incidence and some biological factors such as the biting frequency of the mosquitoes. Therefore, it is not necessary to kill all mosquitoes in order to eradicate malaria. Several malaria models have been developed and studied. In addition, the application of optimal control methods to malaria epidemic models, to investigate prevention and treatment strategies for controlling malaria, has been investigated by several researchers. Notable among these studies include (Adamu *et al.*, 2017; Bakare and Abolarin, 2018; Bala and Gimba, 2019; Blayneh *et al.*, 2009; Nana-Kyere and Doe, 2017; Yusuf and Benyah, 2012) and others.

Formulation of the Model

We formulate an SEIRS-SI epidemic model for the spread of malaria in human and mosquito populations, respectively. The compartments in the human population consist of susceptible individuals S_h, exposed individuals E_h, infectious individuals I_h and recovered individuals R_h. The total human population $N_h(t)$, at time t, is given by

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t)$$

Similarly, the compartments in the mosquito population are susceptible vectors S_v and infectious vectors I_v. The total vector population $N_v(t)$, at time t, is given by:

$$N_v(t) = S_v(t) + I_v(t)$$

Movement from the susceptible classes to either the exposed class for humans or the infectious class for the vector population depends on the biting rate b of the mosquitoes and their transmission probabilities β_h, β_v respectively. The biting rate b is defined as the average

number of bites per mosquito per day, while the transmission probabilities β_h, β_v, is the probability that an infectious bite produces a new case in a susceptible population only.

This model is related partly, to the one in Esteva and Vargas (1998), where they assumed that apart from humans, the mosquitoes have alternative hosts available as blood sources (Esteva and Vargas, 1998). Let *m* be the number of alternative sources for a blood meal. The probability that a mosquito chooses a human as a host over the other sources is given by $\frac{N_h}{N_h+m}$. The probability that an individual receives a bite from a mosquito per unit of time is given as $\left(\frac{bN_v}{N_h}\right)\left(\frac{N_h}{N_h+m}\right)$ and the rate at which a susceptible human is being infected is $\left(\frac{\beta_h b I_v}{N_h+m}\right)$.

For the vector population, susceptible mosquitoes become infected when they bite an infected human. Once infected, they remain infected for life. The probability that a mosquito takes a human blood meal is $\left(\frac{bN_h}{N_h+m}\right)$ per unit time and the rate at which a susceptible vector is being infected is $\left(\frac{\beta_v b I_h}{N_h+m}\right)$.

In the absence of vaccination, the key intervention strategies for the effective control of malaria are prevention and treatment.

Prevention as a Means of Reducing Vector Populations

Many of the prevention methods like Indoor Residual Spraying (IRS) and Insecticide Treated bed-Nets (ITNs) kill mosquitoes and hence, contribute to a reduction in the mosquito population; the fewer the number of mosquitoes the less likelihood of a human coming into contact with a mosquito. Analysis from Ross (1911) shows that malaria can only persist if the number of mosquitoes is above a certain threshold (Ross, 1911). A major innovation in our model is the addition of a term that shows the contribution of prevention efforts in reducing mosquito populations. With a prevention rate of α per unit time, we represent by $c\alpha, (0 \leq c \leq 1)$ the proportion of the prevention effort that goes into reducing the vector populations. Given a per capita natural death rate of μ_v for the vector, we define the total per-capita death rate of the vector as:

$$\mu_v + c\alpha \qquad (1)$$

For instance, $c = 0$ corresponds to protection methods like mosquito repellents applied to exposed skin to prevent human-mosquito contact. These do not kill mosquitoes. However, the other values of $c, (0 < c \leq 1)$ corresponds to the use of prevention methods like IRS and ITNs, which kill the mosquitoes and thus, help to reduce their population.

A Novel Treatment Function

Effective treatment of malaria includes the use of appropriate medications, especially, those recommended by WHO (2019a). In all the models reviewed, the treatment (recovery) term is given as:

$$\gamma I_h \tag{2}$$

where γ is the per-capita recovery rate and I_h is the total infective population. The treatment term given above, implicitly, assumes that treatment is readily available to all infected individuals. In fact, there are many instances in which those infected do not have ready access to healthcare facilities. Besides, there are individuals who cannot afford the cost of the medication. The reality of all of this is that, at any given time, only a proportion κ, of the infected get effective treatment. Another innovation in our model, is we replace Eq. (1) with the term:

$$\gamma(\kappa I_h) \tag{3}$$

to show that, at any given time, only a proportion of the infective population receives full treatment. Bearing in mind that, all untreated cases become reservoirs for mosquitoes to further transmit malaria to healthy individuals, part of our strategies for eliminating malaria in our communities, will be to ensure that treatment is readily available to all infectious individuals.

Taking into consideration the aforementioned, the description of the SEIRS-SI model is presented in Fig. 1.

The resulting system of non-linear ordinary differential equations with saturation incidence is given as:

$$\begin{cases} \dot{S}_h = \Lambda_h - \frac{\beta_h b l_v S_h}{N_h + m} - (\mu_h + \alpha)S_h + \omega R_h \\ \dot{E}_h = \frac{\beta_h b I_h S_h}{N_h + m} - (\mu_h + \rho_h)E_h \\ \dot{I}_h = \rho_h E_h - (\mu_h + \gamma\kappa + \delta)I_h \\ \dot{R}_h = \gamma(\kappa I_h) + \alpha S_h - (\mu_h + \omega)R_h \\ \dot{S}_v = \Lambda_v - \frac{\beta_v b I_h S_v}{N_h + m} - (\mu_v + c\alpha)S_v \\ \dot{I}_v = \frac{\beta_v b I_h S_v}{N_h + m} - (\mu_v + c\alpha)I_v \end{cases} \tag{4}$$
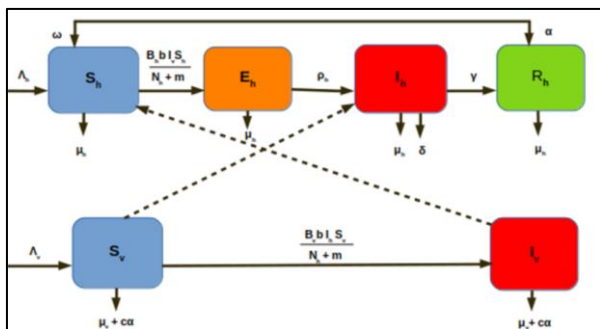
Fig. 1: Schematic diagram for the dynamics of the SEIRS-SI epidemic model

Table 1: Description of state variables

State variables	Explanation
$S_h(t)$	Susceptible humans at time t
$E_h(t)$	Exposed humans at the time t
$I_h(t)$	Infectious humans at time t
$R(t)$	Recovered humans at the time t
$S_v(t)$	Susceptible mosquitoes at time t
$I_v(t)$	Infectious mosquitoes at time t

Table 2: Description of parameters used in the model in Eq. 4

Parameters	Detailed explanation
Λ_h	Recruitment rate for humans
Λ_v	Recruitment rates for mosquitoes
β_h	Transmission rate from infectious vector to a susceptible human
β_v	Transmission rate from infectious human to a susceptible vector
μ_h	Per-capita natural death rate for humans
δ	Disease-induced death rate
γ	Per-capita recovery rate
α	Prevention rate
$c\alpha$	Prevention efforts directed at reducing the mosquito population
μ_v	Natural per-capita death rate for mosquitoes
$(\mu_v + c\alpha)$	Total per-capita death rate for mosquitoes
μ_h	Per-capita natural death rate for humans
ω	Rate of loss of immunity for recovered individuals
b	Biting rate for the mosquitoes
m	Number of alternative hosts for a blood meal
ρ_h	Progression rate from the exposed state to the infectious state
$\frac{1}{\rho_h}$	Latent period
c	A constant $0 \leq c \leq 1$
κ	A constant $0 \leq \kappa \leq 1$

The description of the state variables and parameters for the model are defined in Tables 1-2.
where:

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t)$$
$$N_v(t) = S_v(t) + I_v(t)$$

Let:

$$\begin{aligned} q_1 &= \mu_h + \alpha \\ q_2 &= \mu_h + \rho_h \\ q_3 &= \mu_h + \gamma\kappa + \delta \\ q_4 &= \mu_h + \omega \\ q_5 &= \mu_v + c\alpha \end{aligned} \tag{5}$$

Then, Eq. (4) can be written as

$$\begin{cases} \dot{S}_h = \Lambda_h - \frac{\beta_h b l_v S_h}{N_h + m} - q_1 S_h + \omega R_h \\ \dot{E}_h = \frac{\beta_h b I_h S_h}{N_h + m} - q_2 E_h \\ \dot{I}_h = \rho_h E_h - q_3 I_h \\ \dot{R}_h = \gamma\kappa I_h + \alpha S_h - q_4 R_h \\ \dot{S}_v = \Lambda_v - \frac{\beta_v b I_h S_v}{N_h + m} - q_5 S_v \\ \dot{I}_v = \frac{\beta_v b I_h S_v}{N_h + m} - q_5 I_v \end{cases} \tag{6}$$

Model Analysis

In order for the model in Eq. (6) to be mathematically and epidemiologically meaningful, all the populations and subpopulations must be non-negative for $t > 0$. This can be achieved by determining an appropriate feasible region, for the model in Eq. (4).

Positivity of Solutions

The following proposition would be used to investigate the positivity of the solutions of state variables for $t > 0$.

Proposition 1 (positivity of solutions).

Let:

$$\Omega := \Omega_h \times \Omega_v \subset \mathbb{R}^4 \times \mathbb{R}^2$$

where:

$$\Omega_h = \left\{ (S_h, E_h, I_h, R_h) \epsilon \mathbb{R}_+^4 : S_h + E_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h}, \right\}$$

and:

$$\Omega_v := \left\{ (S_v, I_v) \epsilon \mathbb{R}_+^2 : S_v + I_v \leq \frac{\Lambda_v}{\mu_v + c\alpha} \right\}$$

Suppose that the initial conditions satisfy:

$$\{ S_h(0) > 0, E_h(0) \geq 0, I_h(0) \geq 0, R_h(0) \geq 0, S_v > 0, I_v(0)) \geq 0 \} \in \Omega$$

Then the solution set:

$\{ S_h(t), E_h(t), I_h(t), R_h(t), S_v(t), I_v(t) \}$ for Eq. (6) satisfy:

$$\{ S_h(t) > 0, E_h(t) \geq 0, I_h(t) \geq 0, R_h(t) \geq 0, S_v(t) \geq 0, I_v(t) \geq 0 \} \text{ for all } t > 0$$

Proof. From Eq. (4), the time derivative of S_h satisfies:

$$\frac{dS_h}{dt} = \wedge_h - \frac{\beta_h b I_v}{N_h + m} S_h - (\mu_h + \alpha) S_h + \omega R_h$$

$$\geq - \frac{\beta_h b I_v}{N_h + m} S_h - (\mu_h + \alpha) S_h \tag{7}$$

It follows that:

$$\frac{dS_h}{dt} \geq - \left(\frac{\beta_h b}{N_h + m} I_v + (\mu_h + \alpha) \right) S_h \tag{8}$$

Separating the variables gives:

$$\frac{dS_h}{dt} \geq - \left(\frac{\beta_h b}{N_h + m} I_v + (\mu_h + \alpha) \right) dt \geq \tag{9}$$

$$- \left(\frac{\beta_h b}{N_h + m} I_v^{max} + (\mu_h + \alpha) \right) dt$$

where, I_v^{max} is the maximum of I_v in the interval $[0, T]$. Integrating both sides gives:

$$ln S_h \geq - \left(\frac{\beta_h b}{N_h + m} \int_0^t I_v^{max} d\tau + (\mu_h + \alpha) t \right) + k \geq$$

$$- \left(\frac{\beta_h b I_v^{max}}{N_h + m} t + (\mu_h + \alpha) t \right) + k \tag{10}$$

where, k is a constant of integration.
Exponentiation gives:

$$S_h(t) \geq e^{- \left(\frac{\beta_h b I_v^{max}}{N_h + m} + (\mu_h + \alpha) \right) t + k} \tag{11}$$

That is:

$$S_h(t) \geq A e^{- \left(\frac{\beta_h b I_v^{max}}{N_h + m} + (\mu_h + \alpha) \right) t} \tag{12}$$

where, $A = e^k$. From the initial condition, we have $S_h(0) \geq A$. This implies that:

$$S_h(t) \geq S_h(0) e^{- \left(\frac{\beta_h b I_v^{max}}{N_h + m} + (\mu_h + \alpha) \right) t} \geq 0 \tag{13}$$

The time derivative of E_h satisfies:

$$\frac{dE_h}{dt} = \frac{\beta_h b I_v S_h}{N_h + m} - (\mu_h + \rho_h) E_h \geq -(\mu_h + \rho_h) E_h \tag{14}$$

It follows that:

$$\frac{dE_h}{dt} \geq -(\mu_h + \rho_h) E_h \tag{15}$$

Separating the variables gives:

$$\frac{dE_h}{E_h} \geq -(\mu_h + \rho_h) dt \tag{16}$$

Integrating gives:

$$ln E_h \geq -(\mu_h + \rho_h) t + k \tag{17}$$

Exponentiation gives:

$$E_h(t) \geq e^{-(\mu_h + \rho_h) t + k} \tag{18}$$

where, k is a constant. The expression can now be written as:

$$E_h(t) \geq B e^{-(\mu_h + \rho_h) t} \tag{19}$$

where, $B = e^k$. With the given initial condition and at $t = 0$, we have $E_h(0) \geq B$.

Therefore:

$$E_h(t) \geq E_h(0) e^{-(\mu_h + \rho_h) t} \geq 0 \tag{20}$$

Similarly, it can be shown that:

$$I_h(t) \geq I_h(0) e^{-(\mu_h + \gamma \kappa) t} \geq 0 \tag{21}$$

and:

$$R_h(t) \geq R_h(0) e^{-(\mu_h + \omega) t} \geq 0 \tag{22}$$

$$S_v(t) \geq S_v(0) e^{- \left(\frac{\beta_v b I_h^{max}}{N_h + m} + (\mu_v + \alpha c) \right) t} \geq 0 \tag{23}$$

and:

$$I_v(t) \geq I_v(0)e^{-(\mu_h + \alpha c)t} \geq 0 \qquad (24)$$

Proposition 2 (invariant region). The region $\Omega = \Omega_h \times \Omega_v$ defined by:

$$\Omega_h = \left\{ (S_h, E_h, I_h, R_h) \epsilon \mathbb{R}_+^4 : S_h + E_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h}, S_h > 0, E_h > 0, I_h > 0, R_h > 0 \right\}$$

and:

$$\Omega_v = \left\{ (S_v, I_v) \epsilon \mathbb{R}_+^2 : S_v + I_v \leq \frac{\Lambda_v}{\mu_v + c\alpha}, S_v > 0, I_v > 0 \right\}$$

Is positively invariant under the flow given by the system in (6).

Proof. Using the expression for total human population:

$$N_h = S_h + E_h + I_h + R_h \text{ we have:}$$

$$\dot{N}_h = \dot{S}_h + \dot{E}_h + \dot{I}_h + \dot{R}_h = \Lambda_h - \mu_h N_h - \delta I_h \qquad (25)$$

From the last equation in Eq. (25), we obtain we obtain:

$$\dot{N}_h + \mu_h N_h = \Lambda_h - \delta I_h$$
$$\dot{N}_h + \mu_h N_h \leq \Lambda_h \qquad (26)$$

Using integrating factor $e^{\mu_h t}$, the solution of the linear system in Eq. (26) gives:

$$N_h(t) \leq \frac{\Lambda_h}{\mu_h} + k_1 e^{-\mu_h t} \qquad (27)$$

where, the constant $k_1 = N_h(0) - \frac{\Lambda_h}{\mu_v}$. Substituting into (27) and re-arranging gives

$$N_h(t) + \left(\frac{\Lambda_h}{\mu_h} - N_h(0) \right) e^{-\mu_h t} \leq \frac{\Lambda_h}{\mu_h} \qquad (28)$$

The inequality in (28), shows that:

$$N_h(0) \leq \frac{\Lambda_h}{\mu_h} \Rightarrow N(t) \leq \frac{\Lambda_h}{\mu_h}, \forall t \geq 0$$

That is, if the initial population $N_h(0)$, lies within the feasible region Ω_h, then $N_h(t)$ lies in the feasible region for the all-time $t > 0$:

$$\limsup_{t \to \infty} N_h(t) = \frac{\Lambda_h}{\mu_h}$$

The host population is bounded above by its carrying capacity $K_h = \frac{\Lambda_h}{\mu_h}$.

Similarly, for the vector population, it can be shown that:

$$N_v(0) \leq \frac{\Lambda_v}{\mu_v + c\alpha} \Rightarrow N_v(t) \leq \frac{\Lambda_v}{\mu_v + c\alpha}, \forall t \geq 0$$

That is, if the initial vector $N_v(0)$, lies within the feasible region Ω_v, then $N_v(t)$ lies in the feasible region for the all-time $t > 0$:

$$\limsup_{t \to \infty} N_h(t) = \frac{\Lambda_h}{\mu_h + c\alpha}$$

The vector population is bounded above by its carrying $K_v = \frac{\Lambda_v}{\mu_v + c\alpha}$.

The region $\Omega = \Omega_h \times \Omega_v$ is, therefore, positively invariant. Hence, the model in Eq. (6) is mathematically and epidemiologically well-posed.

Equilibrium Points

Without loss of generality, we determine the equilibrium points of the system in Eq. (6), with $\kappa = 1$. The equilibrium points are the solutions of:

$$\dot{S}_h = \dot{E}_h = \dot{I}_h = \dot{R}_h = \dot{S}_v = \dot{I}_v = 0 \qquad (29)$$

The system has unique disease-free and endemic equilibrium points denoted respectively, by:

$$\Theta^0 = \left(S_h^0, E_h^0, I_h^0, R_h^0, S_v^0, I_v^0 \right)$$

and:

$$\Theta^* = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$$

The *DFE* is given by:

$$\Theta_0 = \left(\frac{\Lambda_h(\mu_h + \omega)}{\mu_h(\alpha + \mu_h + \omega)}, 0, 0, \frac{\Lambda_h \alpha}{\mu_h(\alpha + \mu_h + \omega)}, \frac{\Lambda_v}{\alpha c + \mu_v}, 0 \right) \qquad (30)$$

The endemic equilibrium point is given by:

$$\Theta = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$$

where:

$$S_h^* = \frac{\begin{array}{c}(K_h + m)^2 q_2 q_3 q_5^2 (q_2 q_3 q_4 - \gamma \kappa \omega \rho_h) \\ + q_2 q_3 q_4 q_5 \Lambda_h b \beta_v (K_h + m)\end{array}}{\begin{array}{c}\Lambda_v b^2 \beta_h \beta_v \rho_h (q_2 q_3 q_4 - \gamma \kappa \omega \rho_h) \\ + b \beta_v q_2 q_3 q_5 \rho_h (K_h + m)[q_1 q_4 - \alpha \omega]\end{array}}$$

$$E_h^* = \frac{\begin{array}{c}\left(q_2 q_3^2 q_5^2 (K_h + m)^2 (q_1 q_4 - \alpha \omega) \right) \\ -\Lambda_h \Lambda_v b^2 \beta_h \beta_v \rho_h q_h q_3^2 q_4\end{array}}{\begin{array}{c}\Lambda_v b^2 \beta_h \beta_v \rho_h (q_2 q_3 q_4 - \gamma \kappa \omega \rho_h) \\ + b \beta_v q_2 q_3 q_5 \rho_h (K_h + m)[q_1 q_4 - \alpha \omega]\end{array}}$$

$$I_h^* = \frac{\begin{array}{c}\left(q_2 q_3 q_5^2 (K_h + m) 2^2 (q_1 q_4 - \alpha \omega) \right) - \\ \Lambda_h \Lambda_v b^2 \beta_h \beta_v \rho_h q_4\end{array}}{\Lambda_v b^2 \beta_h \beta_v \rho_h (q_2 q_3 q_4 - \gamma \kappa \omega \rho_h) + b \beta_v q_2 q_3 q_5 \rho_h (Kh + m)[q_1 q_4 - \alpha \omega]}$$

$$R_h^* = \frac{\left(K_h + m\right)^2 q_2 q_3 q_5^2 \left(\alpha q_3 - \gamma \kappa q_1\right) + \Lambda_h \Lambda_v b^2 \beta_h \beta_v \gamma \kappa \rho_h^2 + \Lambda_h \alpha b \beta_v \rho_h q_2 q_3 q_5 \left(K_h + m\right)}{\Lambda_v b^2 \beta_h \beta_v \rho_h \left(q_2 q_3 q_4 - \gamma \kappa \omega \rho_h\right) + b \beta_v q_2 q_3 q_5 \rho_h \left(Kh + m\right)\left[q_1 q_4 - \alpha \omega\right]}$$

$$S_v^* = \frac{\Lambda_v b \beta_h \left(N_h + m\right)\left[q_2 q_3 q_4 - \gamma \kappa \omega \rho_h\right] + q_2 q_3 q_5 \left(Kh + m\right)^2 \left[q_1 q_4 - \alpha \omega\right]}{b \beta_h q_5 \left(Kh + m\right)\left[q_2 q_3 q_4 - \gamma \kappa \omega \rho_h\right] + \Lambda_h b^2 \beta_h \beta_v q_4 \rho_h}$$

$$I_v^* = \frac{q_2 q_3 q_5^2 \left(K_h + m\right)^2 \left[q_1 q_4 - \alpha \omega\right] - \Lambda_h \Lambda_v b^2 \beta_h \beta_v q_4 \rho_h}{b \beta_h q_5 \left(Kh + m\right)\left[q_2 q_3 q_4 - \gamma \kappa \omega \rho_h\right] + \Lambda_h b^2 \beta_h \beta_v q_4 \rho_h}$$

The Basic Reproduction Number

In epidemiology, the next-generation matrix is a method used to derive the basic reproduction number, for a compartmental model of the spread of infectious diseases and the method is given by Van den Driessche and Watmough (2002); Diekmann *et al.* (1990). Many of today's most important emerging infectious diseases are multi-host infections by their very nature. As a result, they require a slightly more complex formalism for investigating epidemic thresholds, etc. The basic tool for examining epidemic thresholds in complex, structured models is the so-called next-generation matrix. Consider a population of individuals (or species) subdivided into n compartments, of which m are infected. Let x_i represent the proportion of the population in the ith compartment and let the vector of the proportions in all the compartments be x.

In order to compute $\Re_0$, it is important to distinguish new infections from all other changes in the population.

Let:

- $F_i(x)$ the rate of appearance of new infections in compartment i
- $V_i^{+(x)}$ is the rate of transfer of individuals into compartment I by all other means and
- $V_i^{-(x)}$ is the rate of transfer of individuals out of compartment i

It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of non-negative initial conditions together with the following system of equations:

$$\dot{x}_i = f_i(x) = F_i(x) - V_i(x), i = 1, \dots, n \tag{31}$$

where, $V_i = V_i^- - V_i^+$ We define the matrices:

$$F = \left[\frac{\partial F_i}{\partial x_j}(E^0)\right], V = \left[\frac{\partial V_i}{\partial x_j}(E^0)\right]$$

where, E^0 denotes the disease-free equilibrium and the indices $i, j = 1, \cdots, m$. The matrix G, given by:

$$G = FV^{-1}$$

is called the next-generation matrix, (Diekmann *et al.*, 1990). The entries of the matrix give the rate at which infected individuals of state j generate new infections of type i.

The basic reproduction number $\Re_0$, is the dominant eigenvalue of G denoted by $\rho(G)$. That is:

$$\Re_0 = \rho(G) = \rho(FV^{-1}) \tag{32}$$

One important aspect of the basic reproduction number is that; it determines whether a disease will persist or die out if there is an outbreak or there is a small perturbation of the system. Therefore, using the next-generation matrix approach (Diekmann *et al.*, 1990) the appearance of new cases of infections F_i and the rate of transfer of infectious from one compartment to a different one in the systems V_i for Eq. (6) is given as:

$$F_i = \begin{bmatrix} \dfrac{\beta_h b I_v s_h}{K_h + m} \\ 0 \\ \dfrac{\beta_v b I_h S_v}{K_h + m} \end{bmatrix} \text{ and } V_i = \begin{bmatrix} (\rho_h - \mu_h) E_h \\ (\delta + \kappa \gamma + u_h) I_h \\ (u_v + c\alpha) I_v \end{bmatrix}$$

The corresponding Jacobian matrix F and V evaluated at the DFE respectively is given as:

$$F = \begin{bmatrix} 0 & 0 & \dfrac{S_h b \beta_h}{K_h + m} \\ 0 & 0 & 0 \\ 0 & \dfrac{S_v b \beta_v}{K_h + m} & 0 \end{bmatrix}$$

and:

$$V = \begin{bmatrix} \mu_h + \rho_h & 0 & 0 \\ -\rho_h & \delta + \kappa \gamma + \mu_h & 0 \\ 0 & 0 & \alpha c + \mu_v \end{bmatrix}$$

The next generation matrix $G = FV^{-1}$ is given as:

$$G = \begin{bmatrix} 0 & 0 & \dfrac{(\Lambda_h \mu_h + \Lambda_h \omega) b \beta_h}{\Psi_1} \\ 0 & 0 & 0 \\ \dfrac{\Lambda_v b \beta_v \rho_h}{\Psi_2} & \dfrac{\Lambda_v b \beta_v}{\Psi_2} & 0 \end{bmatrix}$$

where:

$$\Psi_1 = (\alpha c + \mu_v)(\alpha \mu_h + \mu_h^2 + \mu_h \omega)(K_h + m)$$
$$\Psi_2 = (\alpha c + \mu_v)(\delta + \kappa \gamma + \mu_h)(K_h + m)$$

The eigenvalues obtained from G are:

$$\Re_1(\alpha) = + \sqrt{\frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v (\mu_h + \omega) \rho_h}{(\alpha + \mu_h + \omega)(\delta + \kappa \gamma + \mu_h)(\mu_h + \rho_h)}}$$
$$\mu_h(\alpha c + \mu_v)^2 (K_h + m)^2$$

$$\Re_2(\alpha) = - \sqrt{\frac{\frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v (\mu_h + \omega) \rho_h}{(\alpha + \mu_h + \omega)(\delta + \kappa \gamma + \mu_h)(\mu_h + \rho_h)}}{\mu_h(\alpha c + \mu_v)^2 (K_h + m)^2}} \tag{33}$$

The spectral radius is the dominant eigenvalue obtained in Eq. (33). The basic reproduction number, with prevention at the rate α, denoted by $R_o(\alpha)$, is given by:

$$\mathfrak{R}_0(\alpha) = \sqrt{\frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v (\mu_h + \omega)\rho_h}{\begin{matrix}\mu_h(\alpha c + \mu_v)(K_h + m)(\alpha + \mu_h + \omega)\\(\delta + k\gamma + \mu_h)(\mu_h + \rho_h)\end{matrix}}} \quad (34)$$

The corresponding basic reproduction number without prevention ($\alpha = 0$) is:

$$\mathfrak{R}_o(0) = \sqrt{\frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v \rho_h}{\mu_h(\mu_v)^2(K_h + m)^2(\delta + k\gamma + \mu_h)(\mu_h + \rho_h)}} \quad (35)$$

From Eqs. 34-35 it is easy to see that:

$$\mathfrak{R}_0(\alpha) \leq \mathfrak{R}_0(0) \quad (36)$$

The inequality in indicates that it is easier to control the spread of an infectious disease when there is prevention than without prevention.

The Endemic Equilibrium Point Expressed in Terms of $\mathfrak{R}_0$

Using $\kappa = 1$, the endemic equilibrium is expressed in terms of the basic reproduction number as fellow:

$$S_h^* = \frac{\begin{matrix}A(q_2 q_3 q_4 - \gamma\omega\rho_h)\\+Bq_4\,\mathfrak{R}_o^2(\alpha)(q_1 q_4 - \gamma\omega)\end{matrix}}{C\,\mathfrak{R}_o^2(\alpha)(q_1 q_4 - \gamma\omega)}$$

$$E_h^* = \frac{D(\mathfrak{R}_o^2(\alpha) - 1)}{C}$$

$$I_h^* = -\frac{Dq_3(\mathfrak{R}_o^2(\alpha) - 1)}{C}$$

$$R_h^* = \frac{\begin{matrix}A\rho_h(\alpha q_3 - \gamma\kappa q_1)\\+(A\rho_h + B)\,\mathfrak{R}_o^2(\alpha)(q_1 q_4 - \alpha\omega)\end{matrix}}{C\,\mathfrak{R}_o^2(\alpha)(q_1 q_4 - \alpha\omega)}$$

$$S_v^* = \frac{G q_5\,\mathfrak{R}_o^2(\alpha) + A q_4}{H q_5\,\mathfrak{R}_o^2(\alpha)}$$

$$I_v^* = -\frac{D(\mathfrak{R}_o^2(\alpha) - 1)}{H}$$

where:

$$A = \Lambda_h \Lambda_v b^2 \beta_h \beta_h \rho_h$$
$$B = \Lambda_h b \beta_v \rho_h q_2 q_3 q_5 (K_h + m)$$
$$C = \Lambda_v b^2 \beta_h \beta_v \rho_h (q_2 q_3 q_4 - \gamma\omega\rho_h)$$
$$+b^2 \beta_v \rho_h q_2 q_3 q_5 (K_h + m)(q_1 q_4 - \gamma\omega)$$
$$D = q_2 q_3 q_5^2 (K_h + m)^2 (q_1 q_4 - \alpha\omega)$$
$$G = \Lambda_v b \beta_h (K_h + m)(q_2 q_3 q_4 - \gamma\omega\rho_h)$$
$$H = \Lambda_h b^2 \beta_h \beta_v \rho_h q_4 + b\beta_h q_5 (K_h + m)(q_2 q_3 q_4 - \gamma\omega\rho_h) \quad (37)$$

Stability Analysis

Local Stability Analysis of the Disease-Free Equilibrium Point

The following theorem establishes the local stability of the disease-free equilibrium point.

Theorem 1. The disease-free equilibrium point for the model in 4 is locally asymptotically stable in Ω if $\mathfrak{R}_o(0) < 1$ and unstable if $\mathfrak{R}_o(0) > 1$.

Proof. The Jacobian matrix J, for linearizing the system of differential equation in Eq. 4 at the DFE, with $\alpha = 0$, is given by:

$$j = \begin{bmatrix} \frac{-1_v b\beta_h}{K_h + m} - \mu_h & 0 & 0 & \omega & 0 & -\frac{S_h b\beta_h}{K_h + m} \\ \frac{1_v b\beta_h}{K_h + m} & -q_2 & 0 & 0 & 0 & \frac{S_h b\beta_h}{K_h + m} \\ 0 & \rho_h & -q_3 & 0 & 0 & 0 \\ 0 & 0 & k\gamma & -q_4 & 0 & 0 \\ 0 & 0 & -\frac{S_v b\beta_v}{K_h + m} & 0 & -\frac{1_h b\beta_v}{K_h + m} & 0 \\ 0 & 0 & \frac{S_v b\beta_v}{K_h + m} & 0 & \frac{1_h b\beta_v}{K_h + m} & -\mu_v \end{bmatrix}$$

Evaluating J at DFE gives:

$$J(\alpha_0) = \begin{bmatrix} -\mu_h & 0 & 0 & \omega & 0 & \frac{-\Lambda_h b\beta_h}{(K_h + m)\mu_h} \\ 0 & -q_2 & 0 & 0 & 0 & \frac{\Lambda_h b\beta_h}{(K_h + m)\mu_h} \\ 0 & \rho_h & -q_3 & 0 & 0 & 0 \\ 0 & 0 & \kappa\gamma & -q_4 & 0 & 0 \\ 0 & 0 & -\frac{\Lambda_v b\beta_v}{(K_h + m)\mu_v} & 0 & -\mu_v & 0 \\ 0 & 0 & \frac{\Lambda_v b\beta_v}{(K_h + m)\mu_v} & 0 & 0 & -\mu_v \end{bmatrix} \quad (38)$$

Three of the eigenvalues of $J(\theta_0)$ is given as:

$$\lambda_{1,2,3} = -\mu_v, -\mu_h, -(\mu_h + \omega) < 0 \quad (39)$$

Respectively we now use the corollary of gershgorin's circle theorem given in Appendix A, to establish the stability of the 3×3 sub-matrix $J_3(\alpha_0)$, given by:

$$J_3(\alpha_0) = \begin{bmatrix} -\rho_h - \mu_h & 0 & \frac{\Lambda_h b\beta_h}{\mu_h(K_h + m)} \\ \rho_h & -\delta - \kappa\gamma - \mu_h & 0 \\ 0 & \frac{\Lambda_v b\beta_v}{(K_h + m)\mu_v} & -\mu_v \end{bmatrix} \quad (40)$$

Applying the corollary of Gershgorin's circle theorem to the Jacobian matrix $J_3(\alpha_0)$ gives the inequalities.

$$-(\rho_h + \mu_h) < -\left(\frac{\Lambda_h b\beta_h}{(K_h + m)\mu_h}\right) \quad (41)$$

$$-(\delta + k\gamma + \mu_h) < -\rho_h \quad (42)$$

$$-\mu_v < -\left(\frac{\Lambda_v b\beta_v}{(K_h + m)\mu_v}\right) \quad (43)$$

The above inequalities can be rewritten respectively, as:

$$1 > \left(\frac{\Lambda_h b\beta_h}{(K_h + m)(\rho_h + \mu_h)\mu_h}\right) \quad (44)$$

$$1 > \left(\frac{\rho_h}{(\delta + \kappa\gamma + \mu_h)}\right) \quad (45)$$

$$1 > \left(\frac{\Lambda_v b \beta_v}{(K_h+m)\mu_v^2} \right) \tag{46}$$

Multiplying the inequalities 44-46 gives:

$$1 > \frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v \rho_h}{\mu_h \mu_v^2 (K_h+m)^2} = \mathcal{R}_o^2(0) \tag{47}$$

This implies that:

$$\mathcal{R}_o^2(0) < 1 \tag{48}$$

This shows that all the eigenvalues of the 3×3 sub-matrix in (40) are negative, or have negative real parts.

Therefore, DFE is locally asymptomatically stable.

Local Stability of Endemic Equilibrium Point

The following theorem establishes the local stability of the EE, with $\kappa = 1$.

Theorem 2. The endemic equilibrium is locally asymptotically stable in Ω if $\mathcal{R}_o(\alpha) > 1$ and unstable if $\mathcal{R}(\alpha) < 1$.

Proof. The Jacobian matrix evaluated at the EE θ_* is:

$$J\left(\theta_*\right) =$$

$$\begin{bmatrix} -Z_1-q_1 & 0 & 0 & \omega & 0 & -\frac{\tau_1}{C(K_h+m)} \\ Z_1 & -q_2 & 0 & 0 & 0 & \frac{\tau_1}{C(K_h+m)} \\ 0 & \rho_h & -q_3 & 0 & 0 & 0 \\ \alpha & 0 & \kappa\gamma & -q_4 & 0 & 0 \\ 0 & 0 & -Z_2 & 0 & -Z_3-q_5 & 0 \\ 0 & 0 & Z_2 & 0 & Z_3 & -q_5 \end{bmatrix} \tag{49}$$

where:

$$\tau_1 = \left((q_1 q_4 - \alpha\omega)BR_0^2(\alpha)q_4 + (q_2 q_3 q_4 - k\gamma\omega\rho_h)A \right)(q_1 q_4 - \alpha\omega)R_0^2(\alpha)b\beta_h$$

$$z_1 = \frac{\left(R_0^2(\alpha)-1\right)Db\beta_h}{H(K_h+m)}$$

$$z_2 = \frac{\left(GR_0^2(\alpha)q_5 + Aq_4\right)R_0^2(\alpha)b\beta v q_5}{H(K_h+m)}$$

$$z_3 = \frac{\left(R_0^2(\alpha)-1\right)Db\beta v q_3}{C(K_h+m)}$$

Using the corollary of Gershgorin's circle theorem in Appendix A, we have:

$$-(q_1+Z_1) < -\left(\omega + \frac{\tau_1}{C(K_h+m)}\right) \tag{50}$$

$$-q_2 < -\left(Z_1 + \frac{\tau_1}{C(K_h+m)}\right) \tag{51}$$

$$-q_3 < -\rho_h \tag{52}$$

$$-q_4 < -(\alpha + \kappa\gamma) \tag{53}$$

$$-(q_5+Z_3) < -\frac{(GR_0^2(\alpha)q_5 + Aq_4)R_0^2(\alpha)b\beta_v q_5}{H(K_h+m)} \tag{54}$$

$$-q_5 < -\frac{(GR_0^2(\alpha)q_5 + Aq_4)}{H(K_h+m)} \frac{R_0^2(\alpha)b\beta_v q_5}{H(K_3+m)} - Z_3 \tag{55}$$

The inequalities in Eqs. 51-55 can be rewritten respectively, as:

$$(q_1+Z_1) - \left(\omega + \frac{\tau_1}{C(K_h+m)}\right) > 0 \tag{56}$$

$$q_2 - \left(Z_1 + \frac{\tau_1}{C(K_h+m)}\right) > 0 \tag{57}$$

$$q_3 - \rho_h > 0 \tag{58}$$

$$q_4 - (\alpha + \kappa\gamma) > 0 \tag{59}$$

$$(q_5+Z_3) - \left(\frac{(GR_0^2(\alpha)q_5 + Aq_4)R_0^2(\alpha)b\beta_v q_5}{H(K_h+m)}\right) > 0 \tag{60}$$

$$q_5 - \left(\frac{(GR_0^2(\alpha)q_5 + Aq_4)R_0^2(\alpha)b\beta_v q_5}{H(K_h+m)} + Z_3\right) > 0 \tag{61}$$

Adding the inequalities in Eqs. 56-61 gives:

$$2\frac{(R_0^2(\alpha)-1)Db\beta_v q_3}{C(K_h+m)} + 2\frac{(R_0^2(\alpha)-1)Db\beta_h}{H(K_h+m)} + Z_4 > 0 \tag{62}$$

where:

$$Z_4 = q_1 + q_2 + q_3 + q_4 + 2q_5 + \omega + \rho_h + (\alpha + \omega) \tag{63}$$
$$+ 2\left(\omega + \frac{\tau_1}{C(K_h+m)}\right) + 2\left(\frac{(GR_0^2(\alpha)q_5 + Aq_4)R_0^2(\alpha)b\beta_v q_5}{H(K_h+m)}\right)$$

The inequality in (64) can be rewritten as:

$$\left(\mathcal{R}_o^2(\alpha) - 1\right)\left(2\frac{Db\beta_v q_3}{C(K_h+m)} + 2\frac{Db\beta_h}{H(K_h+m)}\right) + Z_4 > 0 \tag{64}$$

Since $Z_4 > 0$, then the inequality in (64) is satisfied provided:

$$\left(\mathcal{R}_o^2(\alpha) - 1\right)\left(2\frac{Db\beta_v q_3}{C(K_h+m)} + 2\frac{Db\beta_h}{H(K_h+m)}\right) > 0 \tag{65}$$

Again, the inequality in (66) is positive if:

$$(\mathcal{R}_o^2(\alpha) - 1) > 0 \tag{66}$$

That is:

$$\mathcal{R}_o^2(\alpha) > 1 \tag{67}$$

Or equivalently:

$$\mathcal{R}_o(\alpha) > 1 \tag{68}$$

Hence, the endemic equilibrium is locally asymptotically stable provided $\mathcal{R}_o(\alpha) > 1$ and unstable otherwise.

Global Stability of Disease-Free Equilibrium Point

In order to ensure that DFE is independent of the initial size of the sub-population of the model, it is

necessary to show that the DFE is globally asymptotically stable. One of the approaches to studying the global asymptotic stability of DFE is to construct an appropriate Lyapunov function (Lazarus, 2018). The following theorem describes the global stability.

Theorem 3. The DFE is globally asymptotically stable in Ω if $\Re_o \leq 1$.

Proof. Consider a Lyapunov function:

$$V = c_0 E_h + c_1 I_h + c_2 I_v$$

where:

$$c_0 > 0, c_1 > 0, c_2 > 0$$

The time derivative of the Lyapunov function V gives the following expression:

$$\dot{V} = c_0 \dot{E}_h + c_1 \dot{I}_h + c_2 \dot{I}_v$$

Substituting $\dot{E}_h, \dot{I}_h$ and $\dot{I}_v$ into the equation above gives us:

$$\dot{V} = c_0 \left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \rho_h) E_h \right] \tag{69}$$
$$+ c_1 [\rho_h E_h - (\mu_h + \gamma\kappa + \delta) I_h]$$
$$+ c_2 \left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + c\alpha) I_v \right]$$

Note that:

$$S_h = \frac{\Lambda_h(\mu_h + \omega)}{\mu_h(\mu_h + \alpha + \omega)} \text{ and } S_v = \frac{\Lambda_v}{\mu_v + \alpha c} \tag{70}$$

Substituting Eq. (70) into Eq. (69) gives:

$$\dot{V} = c_0 \left[\frac{\beta_h b I_v \Lambda_h(\mu_h + \omega)}{\mu_h(\mu_h + \alpha + \omega)(K_h + m)} - (\mu_h + \rho_h) E_h \right] \tag{71}$$
$$+ c_1 [\rho_h E_h - (\mu_h + \gamma\kappa + \delta)] I_h$$
$$+ c2 \left[\frac{\beta_v b I_h \Lambda_v}{(\mu_v + \alpha c)(K_h + m)} - (\mu_v + \alpha c) I_v \right]$$

Grouping Eq. (71) into E_h, I_h and I_v gives:

$$\dot{V} = [c_1 \rho_h - c_0(\mu_h + \rho_h)] E_h \tag{72}$$
$$+ \left[c2 \frac{\beta_v b \Lambda_v}{(\mu_v + \alpha c)(K_h + m)} - c1(\mu_h + \gamma k + \delta) \right] I_h$$
$$+ \left[c_0 \frac{\beta_h b \Lambda_h(\mu_h + \omega)}{\mu_h(\mu_h + \alpha + \omega)(K_h + m)} - c_2(\mu_v + c\alpha) \right] I_V$$

Further simplification gives:

$$\dot{V} = c_0(\mu_h + \rho_h) \left[\frac{c_1 \rho_h}{c_0(\mu_h + \rho_h)} - 1 \right] E_h \tag{73}$$
$$+ c_1(\mu_h + \delta + \gamma)\kappa \begin{bmatrix} c_2 \beta_v b \Lambda_v \\ c_1(\mu_h + \delta + \gamma\kappa) \\ (\mu_v + c\alpha)(K_h + m) \end{bmatrix} I_h$$
$$+ c_2(\mu_v + \alpha c) \left[\frac{c_0 \beta_h b \Lambda_h(\mu_h + \omega)}{c_2(\mu_v + \alpha c)\mu_h(\mu_h + \alpha + \omega)(K_h + m)} - 1 \right] I_v$$

Considering the coefficient of I_v in Eq. (72), we choose the constant c_0, c_1, c_2 respectively as:

$$c_0 = \frac{c_2 \mu_h(\mu_h + \alpha\omega)(\mu_v + c\alpha)(K_h + m)}{\beta_h b \Lambda_h(\mu_h + \omega)}$$
$$c_1 = \frac{c_0(\mu_h + \rho_h)}{\rho_h}$$
$$c_2 = \frac{c_1(\mu_h + \delta + \gamma\kappa)(\mu_v + c\alpha)(K_h + m)}{\beta_v b \Lambda_v}$$

Substituting c_0, c_1 and c_2 into Eq. (73) gives:

$$\dot{V} = c_0(\mu_h + \rho_h) \left[\frac{c_0(\mu_h + \rho_h)\rho_h}{c_0 \rho_h(\mu_h + \rho_h)} - 1 \right] E_h$$
$$+ c_1(\mu_h + \delta + \gamma\kappa) \begin{bmatrix} c_1(\mu_h + \delta + \gamma\kappa)(\mu_v + c\alpha) \\ \frac{(K_h + m)\beta_v b \Lambda_v}{c_1(\mu_h + \delta + \gamma\kappa)(\mu_v + c\alpha)} - 1 \\ (K_h + m)\beta_v b \Lambda_v \end{bmatrix} I_h \tag{74}$$
$$+ c_2(\mu_v + \alpha c) \begin{bmatrix} c_0 \beta_v \beta_h b^2 \Lambda_v \Lambda_h(\mu_h + \omega)\rho_h \\ c_1(\mu_h + \delta + \gamma\kappa)(\mu_v + c\alpha)^2 \\ \mu_h(\mu_h + \alpha + \omega)(K_h + m)^2 \end{bmatrix} I_v.$$

Simplifying Eq. (74) gives:

$$\dot{V} = c_2(\mu_v + \alpha c) \begin{bmatrix} c_0 \beta_v \beta_h b^2 \Lambda_v \Lambda_h(\mu_h + \omega)\rho_h \\ c_1(\mu_h + \delta + \gamma\kappa)(\mu_v + c\alpha)^2 \\ \mu_h(\mu_h + \alpha + \omega)(K_h + m)^2 \end{bmatrix} I_v \tag{75}$$

Again, substituting c_1 and q_5 from Eq. (77) and Eq. gives:

$$\dot{V} = c_2(q_5) \begin{bmatrix} \frac{c_0 \beta_v \beta_h b^2 \rho_h \Lambda_v \Lambda_h(\mu_h + \omega)\rho_h}{c_0(\mu_h + \rho_h)(\mu_h + \delta + \gamma\kappa)} - 1 \\ (q_5)^2 \mu_h(\mu_h + \alpha + \omega)(K_h + m)^2 \end{bmatrix} I_v, \tag{76}$$

Which can be expressed in terms of R_o^2 as:

$$\dot{V} = c_2(\mu_v + \alpha c)[\Re_o^2(\alpha) - 1] I_v \tag{77}$$

Therefore:

$$\begin{cases} \dot{V} = 0 & \text{if} \quad \Re_o^2 = 1 \\ \dot{V} < 0 & \text{if} \quad \Re_o^2 < 1 \end{cases} \tag{78}$$

Hence, the DFE is globally asymptotically stable in Ω if $\Re_o^2 \leq 1$.

Global Stability of the Endemic Equilibrium

The following theorem will be used to prove for global stability of the EE.

Theorem 4. The EE is globally asymptotically stable in Ω if $\Re_o(\alpha) > 1$.

Proof. We define the following candidate logarithmic Lyapunov function as:

$$\dot{V} = c_1 \left(S_h - S_h^* - S_h^* \log \frac{S_h}{S_h^*} \right) +$$

$$c_2\left(E_h - E_h^* - E_h^* \log\frac{E_h}{E_h^*}\right) +$$

$$c_3\left(I_h - I_h^* - I_h^* \log\frac{I_h}{I_h^*}\right) +$$

$$c_4\left(S_v - S_v^* - S_v^* \log\frac{S_v}{S_v^*}\right) +$$

$$c_5\left(I_v - I_v^* - I_v^* \log\frac{I_v}{I_v^*}\right)$$

where, $(c_1, c_2, c_3, c_4, c_5) > 0$, are to be determined. Note that $V = 0$ when $(S_h, Eh, Ih, Sv, I_v) = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$ and $V > 0$, otherwise. Hence, V is radially unbounded. We need to show that the derivative $V > 0$. The time derivative of V is given by:

$$\dot{V} = c_1\left(1 - \frac{S_h^*}{S_h}\right)\dot{S}_h + c_2\left(1 - \frac{E_h^*}{E_h}\right)\dot{E}_h + c_3 \quad (79)$$

$$\left(1 - \frac{I_h^*}{I_h}\right)\dot{I}_h + c_4\left(1 - \frac{S_v^*}{S_v}\right)\dot{S}_v + c_5\left(1 - \frac{I_v^*}{I_v}\right)\dot{I}_v$$

Substitute $\dot{S}_h, \dot{E}_h, \dot{I}_h, \dot{S}_v, \dot{I}_v$ into Eq. (79) gives:

$$\dot{V} = c_1\left(\frac{S_h - S_h^*}{S_h}\right)\left[\Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \alpha)S_h + \omega R_h\right] + c_2$$

$$\left(\frac{E_h - E_h^*}{E_h}\right)\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \rho_h)E_h\right] + c_3\left(\frac{I_h - I_h^*}{I_h}\right)[\rho_h E_h -$$

$$(\mu_h + \gamma\kappa + \delta)I_h] + c_4\left(\frac{S_v - S_v^*}{S_v}\right)\left[\Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v +$$

$$\alpha c)S_v\right] + c_5\left(\frac{I_v - I_v^*}{I_v}\right)\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)I_v\right] \quad (80)$$

Replacing Λ_h and Λ_v with the corresponding values at the endemic equilibrium points gives:

$$\dot{V} = c_1\left(\frac{S_h - S_h^*}{S_h}\right)\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \alpha)S_h^* - \omega R_h^*\right] \quad (81)$$

$$-c_1\left(\frac{S_h - S_h^*}{S_h}\right)\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \alpha)S_h^* - \omega R_h^*\right]$$

$$+c_2\left(\frac{E_h - E_h^*}{E_h}\right)\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \rho_h)E_h\right]$$

$$+c_3\left(\frac{I_h - I_h^*}{I_h}\right)[\rho_h E_h - (\mu_h + \gamma\kappa + \delta)I_h]$$

$$+c_4\left(\frac{S_v - S_v^*}{S_v}\right)\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v = \alpha c)S_v^*\right]$$

$$-c_4\left(\frac{S_v - S_v^*}{S_v}\right)\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)S_v\right]$$

$$+c_5\left(\frac{I_v - I_v^*}{I_v}\right)\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)I_v\right]$$

Factorizing like terms gives:

$$\dot{V} = c_1\left(\frac{S_h - S_h^*}{S_h}\right)\left[\left(\frac{\beta_h b I_v^* S_h}{K_h + m} - \frac{\beta_h b I_v S_h}{K_h + m}\right)\right] \quad (82)$$

$$-c_1\left(\frac{S_h - S_h^*}{S_h}\right)\left[(\mu_h + \alpha)\left(S_h - S_h^*\right) - \omega\left(R_h - R_h^*\right)\right]$$

$$+c_2\left(\frac{E_h - E_h^*}{E_h}\right)\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu + \rho h)E_h\right]$$

$$+c_3\left(\frac{I_h - I_h^*}{I_h}\right)[\rho_h E_h - (\mu_h + \gamma\kappa + \delta)I_h]$$

$$+c_4\left(\frac{S_v - S_v^*}{S_v}\right)\left[\frac{\beta_v b I_h^* S_v^*}{K_h + m} - \frac{\beta_v b I_h S_v}{K_h + m}\right]$$

$$-c_4\frac{S_v - S_v^*}{S_v}\left((\mu_v + \alpha c)\left(S_v - S_v^*\right)\right)$$

$$+c_5\left(\frac{I_v - I_v^*}{I_v}\right)\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)I_v\right]$$

Multiplying out all of Eq. (82) is given as:

$$\dot{V}$$
$$= \frac{c_1 \beta_h b I_v^* S_h^*}{K_h + m} - \frac{c_1 \beta_h b I_v^* S_h^{*2}}{(K_h + m)S_h} - \frac{c_1 \beta_h b I_v S_h}{K_h + m} + \frac{c_1 \beta_h b I_v^* S_h^{*2}}{K_h + m}$$

$$- \frac{c_1(\mu_h + \alpha)\left(S_h - S_h^*\right)^2}{S_h} \frac{+c_1\omega\left(R_h - R_h^*\right)\left(S_h - S_h^*\right)}{S_h}$$

$$+ \frac{c_2\beta_h b S_h I_v}{(K_h + m)} \frac{-c_2\beta_h b S_h I_v E_h^*}{(K_h + m)E_h} - c_2(\mu_h + \rho_h)E_h$$

$$+ c_2(\mu_h + \rho_h)E_h^* + c_3\rho_h E_h - \frac{c_3\rho_h E_h I_h^*}{I_h}$$

$$- c_3(\mu_h + \gamma k + \delta)I_h + c_3(\mu_h + \gamma k + \delta)I_h^* + \frac{c_4\beta_v b I_h^* S_v^*}{K_h + m}$$

$$- \frac{c_4\beta_v b I_h^* S_v^2}{(K_h + m)S_v} \frac{-c_4\beta_v b I_h S_v}{K_h + m} + \frac{c_4\beta_v b I_h S_v^*}{K_h + m}$$

$$- \frac{c_4(\mu_v + c\alpha)\left(S_v - S_v^*\right)^2}{S_v} \frac{+c_5\beta_v b I_h S_v}{K_h + m} - \frac{c_5\beta_v b I_h S_v I_v^*}{(K_h + m)I_v}$$

$$-c_5(\mu_v + \alpha c)\left(I_v - I_v^*\right) \quad (83)$$

It is clearly seen that when $c_1 = c_2$, $-\frac{c_1\beta_h b I_v S_h}{K_h + m}$ cancels $\frac{c_2\beta_h b I_v S_h}{K_h + m}$; when $c_4 = c_5$, $-\frac{c_4\beta_v b I_h S_v}{K_h + m}$ cancels $\frac{c_5\beta_v b I_h S_v}{K_h + m}$ and when $c_3 = \frac{c_2(\mu_h + \rho_h)}{\rho_h}$, $c_3\rho_h E_h$ cancels $-c_2\rho_h)E_h$.

Equation (83) now simplifies to:

$$\dot{V} = -\frac{c_2(\mu_h + \alpha)(S_h - S_h^*)^2}{S_h} + \frac{c_2\beta_h bI_v^* S_h^*}{K_h + m} - \frac{c_2\beta_h bI_v^* S_h^{*2}}{(K_h + m)S_h} +$$

$$\frac{c_2\beta_h bI_v S_h^* I_v^*}{K_h + m I_v^*} + \frac{c_2\omega(R_h - R_h^*)(S_h - S_h^*)}{S_h} - \frac{c_2\beta_h bS_h^* I_v^*}{(K_h + m)}.$$

$$\frac{E_h^* S_h I_v}{E_h S_h^* I_v^*} + c_2(\mu_h + \rho_h)E_h^* - c_3(\mu_h + \gamma k + \delta)I_h -$$

$$c_3(\mu_h + \gamma k + \delta)I_h - c_3\rho_h E_h^* \frac{I_h^*}{I_h E_h^*} + c_3(\mu_h + \gamma k + \gamma)I_h^* - \tag{84}$$

$$\frac{c_4(\mu_v + c\alpha)(S_v - S_v^*)^2}{S_v} + \frac{c_4\beta_v bI_h^* S_v^{*2}}{(K_h + m)S_v} +$$

$$\frac{c_4\beta_v bI_h S_v^*}{K_h + m} - \frac{c_4\beta_v bI_h^* S_v^*}{(K_h + m)} \frac{I_v^* I_h^* S_v}{I_v I_h^* S_v^*}$$

From the Equilibrium points in Eq. (80), we obtain the following:

$$(\mu + \rho)E_h^* = \frac{\beta_h bS_h^* I_v^*}{K_h + m}$$

$$c_3(\mu + \gamma k + \delta)I_h^* = c_2(\mu_h + \rho_h)E_h^*$$

$$= \frac{c_2\beta_h bS_h^* I_v^*}{K_h + m} \quad c_3\rho_h E_h^* \frac{I_h^* E_h}{I_h E_h^*} = c_2(\mu_h + \rho_h) \tag{85}$$

$$E_h^* \frac{I_h^*}{I_h E_h^*} = \frac{c_2\beta_h bS_h^* I_v^*}{K_h + m} \frac{I_h^* E_h}{I_h E_h^*}$$

Now, we have:

$$\dot{V} = \frac{-c_2(\mu_h + \alpha)\left(S_h - S_h^*\right)^2}{S_h} + \frac{c_2\beta_h b I_v^* S_h^*}{K_h + m} \frac{-c_2\beta_h b I_v^* S_h^2}{(K_h + m)S_h} +$$

$$\frac{c_2\beta_h b I_v^* S_h^* I_v^*}{(K_h + m)I_v^*} + c_2\omega\left(R_h - R_h^*\right)\left(S_h - S_h^*\right)}{S_h} - \frac{c_2\beta_h b S_h^* I_v^*}{(K_h + m)}.$$

$$\frac{E_h^* S_h I_v}{E_h S_h^* I_v^*} + c_2\beta_h b S_h^* I_v^*}{K_h + m} - \frac{c_2\beta_h b S_h^* I_v^*}{K_h + m} \frac{I_h^* E_h}{I_h E_h^*} + \frac{c_2\beta_h b S_h^* I_v^*}{K_h + m} -$$

$$c_3(\mu_h + \gamma k + \delta)I_h - \frac{c_4(\mu_v + c\alpha)\left(S_v - S_v^*\right)^2}{S_v} + c_4\beta_v b I_h^* S_v^*}{K_h + m} -$$

$$\frac{c_4\beta_v b I_h^* S_v^2}{(K_h + m)S_v} + \frac{c_4\beta_v bI_h S_v^*}{K_h + m} \cdot \frac{I_h^*}{I_h} \frac{-c_4\beta_v b I_h^* S_v^*}{(K_h + m)} \cdot \frac{I_v^* I_h S_v}{I_v I_h^* S_v^*} - c_4(\mu_v +$$

$$\alpha c)\left(I_v - I_v^*\right) \tag{86}$$

This implies that:

$$\dot{V} = \frac{-c_2(\mu_h + \alpha)\left(S_h - S_h^*\right)^2}{S_h} + \frac{c_2\beta_h b I_v^* S_h^*}{K_h + m}$$

$$\left[3 - \frac{S_h^*}{S_h} - \frac{E_h^* I_v S_h}{E_h I_v^* S_h^*} - \frac{I_h^* E_h}{I_h E_h^*}\right]$$

$$+ \frac{c_2\beta_h b I_v S_h^*}{K_h + m} + \frac{c_1\omega\left(R_h - R_h^*\right)\left(S_h - S_h^*\right)}{S_h}$$

$$-c_3(\mu_h + \gamma k + \delta)I_h$$

$$-\frac{c_4(\mu_v + c\alpha)\left(S_v - S_v^*\right)^2}{S_v} + \frac{c_2\beta_h b I_h^* S_v^*}{K_h + m}$$

$$\left[2 - \frac{S_v^*}{S_v} - \frac{I_v^* I_h S_v}{I_v I_h^* S_v^*}\right] + \frac{c_2\beta_h b I_h S_v^*}{K_h + m}$$

$$-c_4(\mu_v + \alpha c)\left(I_v - I_v^*\right) \tag{87}$$

Again, suppose we have the relation $c_2 = \frac{c_4(\mu_v + c\alpha)(K_h + m)}{\beta_h b S_h^*}$ and $c_3 = \frac{c_4\beta_v b S_v^*}{(\mu_h + \gamma\kappa + \delta)(K_h + m)}$, then Eq. (87) becomes:

$$\dot{V} = \frac{-c_2(\mu_h + \alpha)\left(S_h - S_h^*\right)^2}{S_h} \frac{+ c_2\beta_h b I_v^* S_h^*}{K_h + m}$$

$$\left[3 - \frac{S_h^*}{S_h} - \frac{E_h^* I_v S_h}{E_h I_v^* S_h^*} - \frac{I_h^* E_h}{I_h E_h^*}\right] \frac{+ c_4(\mu_v + c\alpha)(K_h + m)}{\beta_h b S_h^*} \tag{88}$$

$$\cdot \frac{\beta_h b I_v S_h^*}{K_h + m} + \frac{c_1\omega\left(R_h - R_h^*\right)\left(S_h - S_h^*\right)}{S_h}$$

$$\frac{- c_4\beta_v b \ S_v^* \left(\mu_h + \gamma\kappa + \delta\right)I_h}{\mu_h + \gamma\kappa + \delta \left(K_h + m\right)}$$

$$- \frac{c_4\left(\mu_v + c\alpha\right)\left(S_v - S_v^*\right)^2}{S_v} + \frac{c_4\beta_v bI_h^* S_v^*}{K_h + m}$$

$$\left[2 - \frac{S_v^*}{S_v} - \frac{I_v^* I_h S_v}{I_v I_h^* S_v^*}\right] - \frac{c_4\beta_v bI_h^* S_v^*}{K_h + m}$$

$$-c_4(\mu_v + \alpha c) I_v^*$$

This simplifies to:

$$\dot{V} = \frac{-c_2(\mu_h + \alpha)\left(S_h - S_h^*\right)^2}{S_h} + \frac{c_2\beta_h bI_v^* S_h^*}{K_h + m}$$

$$\left[3 - \frac{S_h^*}{S_h} - \frac{E_h^* I_v \ S_h}{E_h \ I_v^* \ S_h^*} - \frac{I_h^* E_h}{I_h E_h^*}\right] + \frac{c_2\omega\left(R_h - R_h^*\right)\left(S_h - S_h^*\right)}{S_h} -$$

$$\frac{c_4(\mu_v + c\alpha)\left(S_v, S_v^*\right)^2}{S_v} + \frac{c_4\beta_v b \ I_h^* \ S_v^*}{K_h + m}\left[2 - \frac{S_v^*}{S_v} - \frac{I_v^* \ I_h \ S_v}{I_v \ I_h^* \ S_v^*}\right] -$$

$$c_4(\mu_v + \alpha c)\left(I_v^*\right) \tag{89}$$

Substituting I_v^* into Eq. (89) gives:

$$\dot{V} = \frac{-c_2(\mu_h + \alpha)\left(S_h - S_h^*\right)^2}{S_h} + \frac{c_2\beta_h b \ I_v^* \ S_h^*}{K_h + m}\left[3 - \frac{S_h^*}{S_h} - \right.$$

$$\frac{E_h^* I_v \ S_h}{E_h \ I_v^* \ S_h^*} - \frac{I_h^* E_h}{I_h E_h^*}\left.\right] + \frac{c_2\omega\left(R_h - R_h^*\right)\left(S_h - S_h^*\right)}{S_h} -$$

$$\frac{c_4(\mu_v + c\alpha)\left(S_v - S_v^*\right)^2}{S_v} + \frac{c_4\beta_v b \ I_h^* \ S_v^*}{K_h + m}$$

$$\left[2 - \frac{S_v^*}{S_v} - \frac{I_v^* \ I_h \ S_v}{I_v \ I_h^* \ S_v^*}\right] -$$

$$\left(\begin{array}{c} \frac{c_4(\mu_h + \rho_h)(\mu_h + \gamma\kappa + \delta)K^2}{(\mu_h(\mu_h + \alpha + \omega))[R_o^2(\alpha) - 1]} \\ \overline{b\beta_h K[\mu_h(\mu_h + \gamma\kappa + \delta)(\mu_h + \omega) + \omega\rho_h(\mu_h + \delta)]} \\ + \Lambda_h b^2 \beta_h \beta_v(\mu_h + \omega)\rho_h \end{array}\right) \tag{90}$$

where, $K = (\mu_v + c\alpha)(K_h + m)$.

The term $\dfrac{c_1\omega(R_h - R_h^*) \ (S_h - S_h^*)}{S_h}$ is non-positive

because S_h decreases monotonically S_h^* and R_h increases monotonically to R_h^*. The expression in Eq is, therefore, negative if $\Re_o^2(\alpha) > 1$.

Hence, the endemic equilibrium is globally asymptotically stable in Ω, if $\Re_o^2(\alpha) > 1$.

Parameter Estimation

The main tool for estimating the parameters of the model given in Eq. (91), is the use of demographic estimates and implementation of the least-square method approach in Python, using the daily confirmed cases in Ghana, obtained from WHO from 2004-2017.

Demographic Estimates

Here, pre-estimating some demographic parameters such as Λ_h and μ_h using information obtained from (FactBook, 2019; WHO, 2019b).

The total population of Ghana as of 2016 was given as 28,207,000 and the life expectancy at birth was given as 64 years (WHO, 2019b).

Hence, the estimated daily natural death μ_h rate is given as:

$$\mu_h = \frac{1}{64 \times 365} = 0.000042808219$$

We assume that the $birthrate = deathrate = \mu_h$. The carrying capacity for humans K_h is given as

$$K_h = \frac{\Lambda_h}{\mu_h}$$

So the recruitment rate is given by:

$$\Lambda_h = K_h \times \mu_h$$

Therefore, the estimated daily recruitment rate for humans is computed as:

$$\Lambda_h = K_h \times \mu_h = 28000000 \times 0.000042808219. \approx 1200$$

The life expectancy for mosquitoes to live is 30 days (WHO, 2018). Hence, the estimated death rate for mosquitoes was given as:

$$\mu_v = \frac{1}{30} = 0.03$$

The remaining parameters $\Lambda_v, b, \beta_h, \beta_v, \gamma, \alpha, \omega, \delta$ and m were obtained by fitting the model solution to the observed infection data.

Ghana Malaria Infection Data Sets and the Curve Fitting Process

The data for confirmed cases of malaria from Ghana obtained from WHO ranges from the year 2004 to the year 2017 and is shown in Table 3.

The data points in Table 3 is graphically represented in Fig. 2.

Table 3: Yearly Confirmed cases of malaria in Ghana from 2004-17

Years	Confirmed cases
2004	475441
2005	655093
2006	472255
2007	476484
2008	1094483
2009	1104370
2010	1071637
2011	1041260
2012	3755166
2013	1639451
2014	3415912
2015	4319919
2016	4535167
2017	4348694
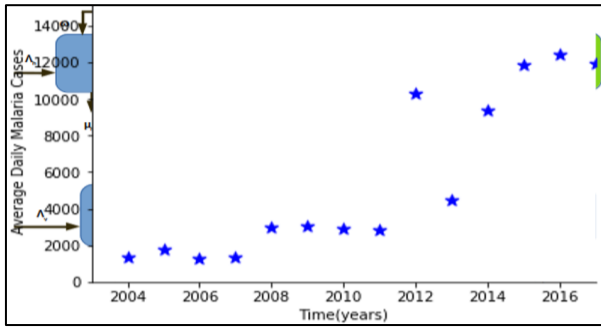
Fig. 2: Plot of average daily cases of malaria from the world health organization
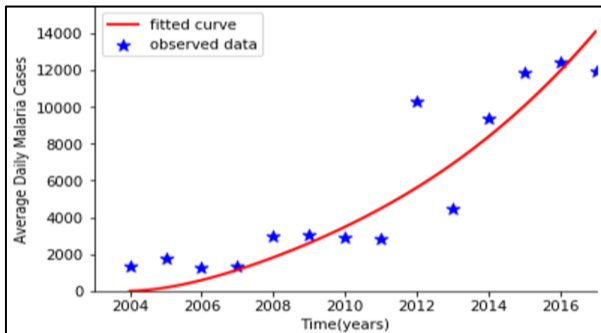
Fig. 3: Model in Eq. (4) fitted to the data in Table 1

Table 4: Parameters obtained from the best fit and demographics

Parameters	Units (day^{-1})	Values	Sources
Λ_h	day^{-1}	2367	(WHO)
Λ_v	day^{-1}	11007.6970	Estimated from data
β_h	day^{-1}	0.61844195	Estimated from data
β_v	day^{-1}	0.62695935	Estimated from data
μ_h	day^{-1}	$\frac{1}{(64 \times 365)}$	(fact book) and (WHO)
δ	day^{-1}	0.00900000	Estimated from data
γ	day^{-1}	[0.1, 0.2]	Per-capita treatment rate
α	day^{-1}	[0.05, 0.8]	Per-capita prevention rate
μ_v	day^{-1}	0.03	Estimated from data
ω	day^{-1}	0.00100000	Estimated from data
b	day^{-1}	0.79276092	Estimated from data
c	day^{-1}	[0,1]	Constant of proportionality
m	day^{-1}	3	Assumed
ρ_h	day^{-1}	0.07142857	Estimated from data

Figure 2 the blue stars represent the data points. The least square best fit is shown in Fig. 3.

A plot of the daily infection is shown with a representation of the data in Fig. 2 fit for the model is done using an implementation of the least square's curve fit approach in Python to estimate a new set of values of parameters at a given bound. The estimated values of parameters obtained from the demographic point of view were maintained. The best-fit diagram is given in Fig. 3.

Figure 3 The blue star represents the data while the red solid colored curve represents the curve of best fit to the data.

The parameters obtained from the best fit and the demographics are given in Table 4.

Optimal Control Formulation

In this section, we formulate the strategy for effective control of malaria transmission as an optimal control problem. We then use pontryagin's maximum principle to determine an optimal combination of the prevention and treatment efforts needed to reduce the transmission. Numerical simulations will then be performed to determine the evolution of the disease, over a finite time horizon.

Let $u_1(t)$ represent the rate of preventio*n* and $u_2(t)$ the rate at which infected individuals get treatment.

Replacing α and γ in the model Eq. (4) with the *controls* $u_1(t)$ and $u_2(t)$ respectively, gives:

$$
\begin{cases}
\dot{S}_h = \Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h S_h - u_1(t) S_h + \omega R_h \\
\dot{E}_h = \frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \rho_h) E_h \\
\dot{I}_h = \rho_h E_h - \mu_h I_h - \kappa u_2(t) I_h - \delta I_h \\
\dot{R}_h = \kappa u_2(t) I_h - \mu_h R_h - \omega R_h + u_1(t) S_h \\
\dot{S}_v = \Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t) c) S_v \\
\dot{I}_v = \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t) c) I_v
\end{cases}
\tag{91}
$$

We define our objective functional as

$$
J(u_1, u_2) = I_h(T) + I_v(T) + \frac{1}{2} \int_0^T (B_1 u_1^2 + B_2 u_2^2) \, dt
\tag{92}
$$

With $u_1, u_2 \in U$, the set of admissible controls of the Lebesgue measure is defined as:

$$
U = \{u_1(t), u_2(t) \in L'(0, T) \vee 0 \le u_i \le 1\}
$$

The terms $\frac{1}{2} B_1 u_1^2$ and $\frac{1}{2} B_2 u_2^2, (B_1, B_2 > 0)$ gives the cost associated with implementing prevention and treatment. The choice of the quadratic cost for the controls indicates that the cost of applying the controls is nonlinear. The interval $[0, T]$ is the time horizon and T is the terminal time.

Also, $I_h(T)$ and $I_v(T)$ represent the number of infected humans and vectors respectively, at the end of the terminal time.

The maximum values for u_1 and u_2 are denoted by $u_{1\,\text{max}}$ and $u_{2\,\text{max}}$ respectively.

The optimal control pair $\mu_1^* \, \mu_2^*$ is given by:

$$
J\left(\mu_1^* \, \mu_2^* \right) = \min_{u_1, u_2} \{J(u_1, u_2) : (u_1, u_2) \in U\}
\tag{93}
$$

*Existence of the Optimal Control Pai*r

The necessary condition for the existence of the optimal control pair proposed by Fleming and Rishel (2012); Panetta and Fister (2000); Yusuf and Benyah (2012) is established in this section. According to Fleming and Rishel (2012), the

existence of an optimal control pair $\left(\mu_1^* \ \mu_2^*\right)$ is guaranteed by the compactness of the states and the convexity of the problem. Therefore, the essential requirement cited in Yusuf and Benyah (2012) is given by:

1. The set of all solutions to system (91) with corresponding admissible control functions in U is non-empty
2. The state system can be written as a linear function of the control variables $u_i''s$, with coefficients depending on time and the state variables
3. The integrand of $J(u_1, u_2)$ is convex on U and is bounded above by:

$$B_1\|(u_1, u_2)\|^2 - B_2$$

where:

$$B_1, B_2 > 0$$

First Order Necessary Condition

In this section, we establish conditions that would help us solve our objective function. Using Pontryagin's Maximum Principles, the necessary conditions are derived using the following theorem by Panetta and Fister (2000).

Theorem 5. Suppose $\left(\mu_1^*, \mu_2^*\right)$ is an optimal control pair, with corresponding optimal states, $S_h^* E_h^* I_h^* R_h^* S_v^* I_v^*$ that minimizes the objective functional in Eq. 92, then there exists a co-state variables $\lambda_1^*, \ldots, \lambda_6^*$ such that the following necessary conditions are satisfied.

State equations:

$$\frac{dS_h}{dt} = \frac{\partial H}{\partial \lambda_1}, \cdots, \frac{dI_v}{dt} = \frac{\partial H}{\partial \lambda_6}$$

where:

$$\frac{dS_h}{dt} = \Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h S_h - u_1(t)S_h + \omega R_h \frac{E_h}{dt} = \frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \rho_h)E_h \frac{dI_h}{dt} = \rho_h E_h - \mu_h I_h - \kappa u_2(t)I_h - \delta I_h \frac{dR_h}{dt} = \kappa u_2(t)I_h - \mu_h R_h - \omega R_h + u_1(t)S_h \frac{dS_v}{dt} = \Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t)c)S_v \frac{dI_v}{dt} = \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t)c)I_v \tag{94}$$

With initial conditions:

$$S_h(0) > 0, E_h(0) > 0, I_h(0) > 0, R_h(0) \\ 0, S_v(0) > 0, I_v(0) > 0$$

Co-state equations:

$$\frac{d\lambda_1}{dt} = \frac{-\partial H}{\partial S_h}, \cdots, \frac{d\lambda_6}{dt} = \frac{-\partial H}{\partial I_v}$$

Given by:

$$\frac{d\lambda_1}{dt} = -\left[\left(\frac{-\beta_h b I_v}{K_h + m} - \mu_h - u_1(t)\right)\lambda_1 + \frac{\beta_h b I_v \lambda_2}{K_h + m} + u_1(t)\lambda_4\right],$$

$$\frac{d\lambda_2}{dt} = -[-(\mu_h \rho_h)\lambda_2 + \rho_h \lambda_3]$$

$$\frac{d\lambda_3}{dt} = -\frac{d\lambda_4}{dt} = -[\omega\lambda_1 - (\omega + \mu_h)\lambda_4]$$

$$\frac{d\lambda_5}{dt} = -\left[\left(\frac{-\beta_v b I_h}{K_h + m} - (\mu_v + u_1(t)c)\right)\lambda_5 + \frac{\beta_v b I_h \lambda_6}{K_h + m}\right]$$

$$\frac{d\lambda_6}{dt} = -\left[\frac{-\beta_h b S_h \lambda_1}{K_h + m} + \frac{\beta_h b S_h \lambda_2}{K_h + m} - (\mu_v + u_1(t)c)\lambda_6\right] \tag{95}$$

With the transversality condition:

$$\begin{array}{ll} \lambda_1(T) = \lambda_2(T) = \lambda_4(T) & \lambda_5(T) = 0, \quad \text{and} \\ \lambda_3(T) & \lambda_6(T) = 1, \end{array} \tag{96}$$

Optimality conditions:

$$\frac{\partial H}{\partial u_1} = B_1 u_1 + (\lambda_4 - \lambda_1)S_h - (\lambda_5 S_v + \lambda_6 I_v)c = 0 \\ \frac{\partial H}{\partial u_2} = B_2 u_2 + (\lambda_4 - \lambda_3)I_h = 0 \tag{97}$$

where, H is the Hamiltonian of the system given by:

$$H = \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2) + \lambda_1\left[\Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h S_h - u_1(t)S_h + \omega R_h\right] + \lambda_2\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \rho_h)E_h\right] + \lambda_3[\rho_h E_h - \mu_h I_h - u_2(t)I_h - \delta I_h] + \lambda_4[u_2(t)I_h - \mu_h R_h - \omega R_h + u_1(t)S_h] + \lambda_5\left[\Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t)c)S_v\right] + \lambda_6\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t)c)I_v\right]$$

Solving Eqs. 95-97 and for u_1 and u_2 gives respectively, the optimal controls:

$$\mu_1^* = \frac{(\lambda_1 - \lambda_4)S_h^* + \left(\lambda_5 S_v^* + \lambda_6 I_v^*\right)c}{B_1} \quad \mu_2^* = \frac{(\lambda_3 - \lambda_4)I_h^*}{B_2} \tag{98}$$

Since the controls are bounded, that is, $0 \le \mu_1 \le \mu_{1max}, 0 \le \mu_2 \le \mu_{2max}$ the optimal controls in (98) are replaced by:

$$\mu_1^* = \min\left\{\max\left\{0, \frac{(\lambda_1 - \lambda_4)S_h^* + \left(\lambda_5^* S_v^* + \lambda_6 I_v^*\right)c}{B_1}\right\}\right\}$$

$$\mu_2^* = \min\left\{\max\left\{0, \frac{(\lambda_3 - \lambda_4)I_h^*}{B_2}\right\}\right\} \tag{99}$$

Numerical Solution of the Optimality System

The two-point boundary-value problem given in Eqs. (94-97), was solved using the forward-backward sweep method, developed by (Lenhart and Workman, 2007).

The values of the constants B_1, $B_2 > 0$ in the integrand are chosen first, to balance the units in the objective functional. Secondly, varying the constants during numerical simulations, show the effects of emphasizing one control over the other.

The procedure outlined below was implemented in Octave, a MATLAB-like public domain software. Choose an initial guess for μ_1^* μ_2^* and.

Solve the state Eq. (94), with the given initial conditions forward in time and solve the costate Eq. (94). With the given transversality conditions backward in time, Update the expression for μ_1^* μ_2^* and in Eq. (99). with the new values of the state and the costate variables. Repeat steps (2-4) until convergence criteria are met.

Simulations on the Effect of Weight B_1, B_2 on Infected Human Populations

We investigate how different weight combinations affect the infected human populations.

We consider three cases: (a) $B_1 < B_2$, (b) $B_1 = B_2$ and (c) $B_1 > B_2$.

The numerical values of B_1 and B_2 used in our simulations were selected from the set $\{400000, 800000\}$. These values were chosen first, to balance the units in the objective function and secondly, to investigate the effects on the infected human populations, by putting different weights on each control.

The plots in Figs. 4a-c, show the infected human populations, when (Figs. 4a-c) respectively.

Figure 4, different combination of the weights reduces the human population respectively.

The plots in Fig. (5a-c) shows prevention functions, when; (Figs. 5a-c) respectively.
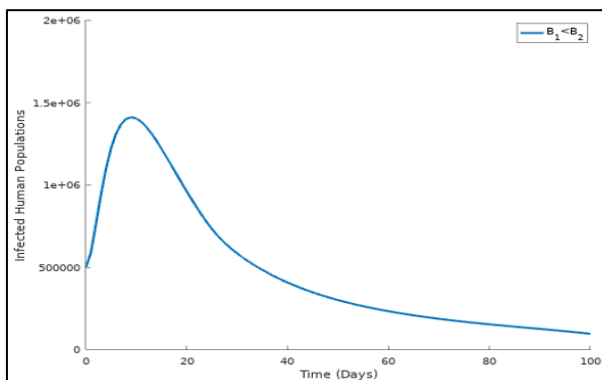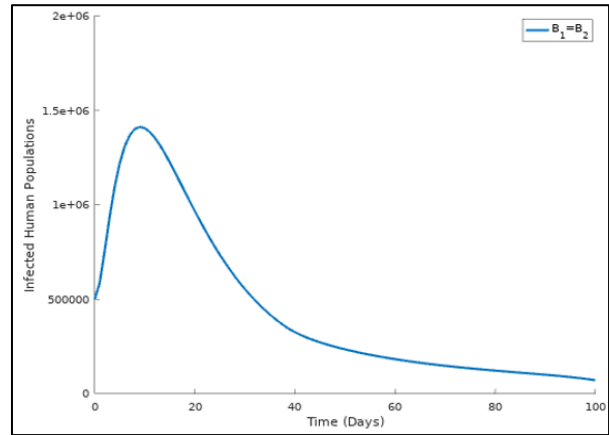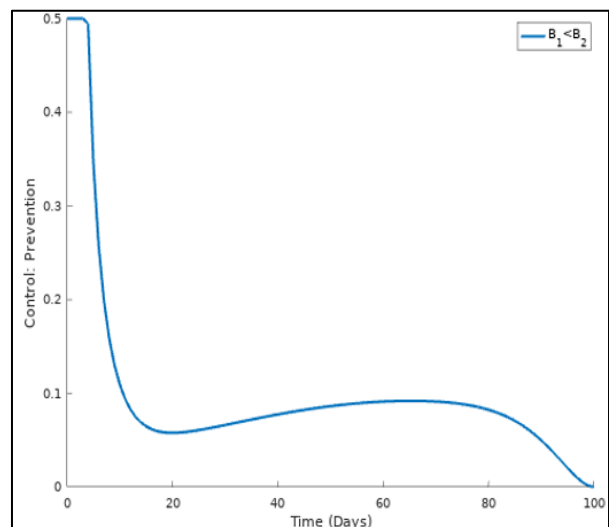

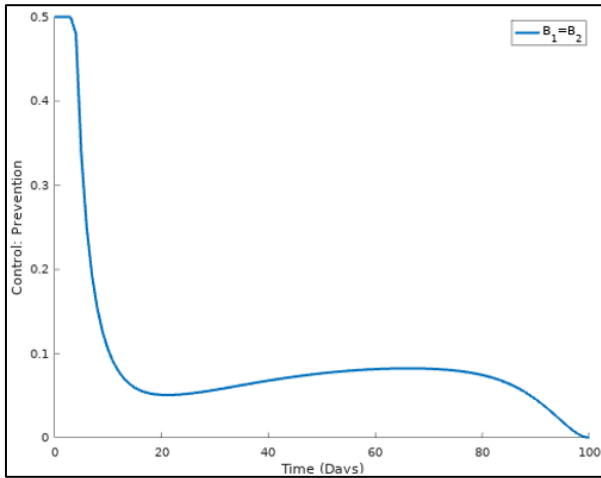
(b)
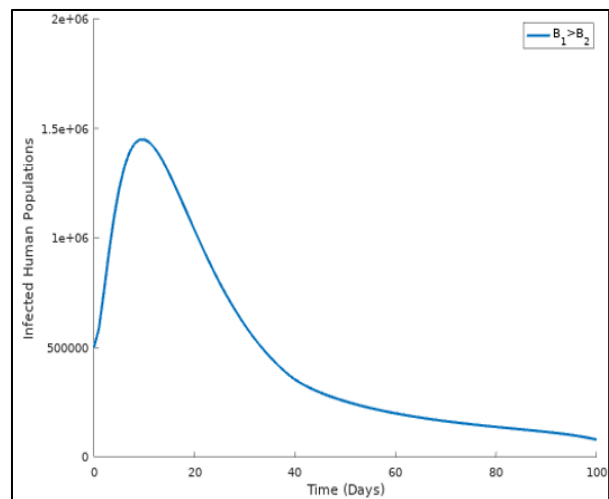
(c)
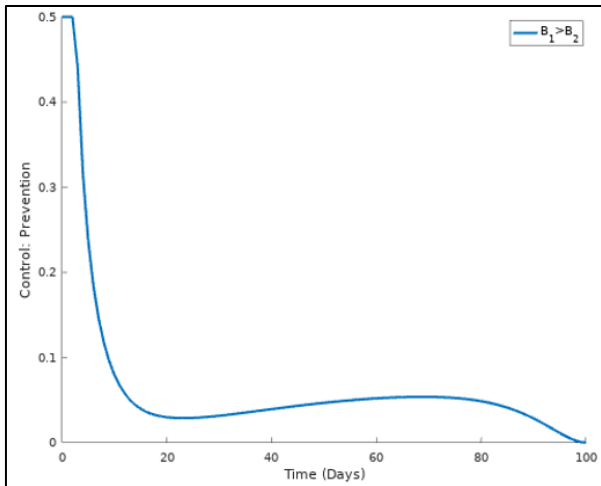
Fig. 4: Infected human populations when; (a) $B_1 < B_2$; (b) $B_1 = B_2$; (c) $B_1 > B_2$
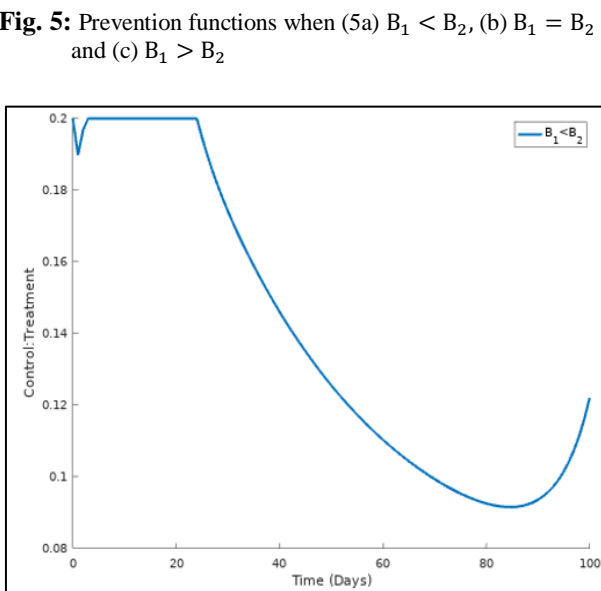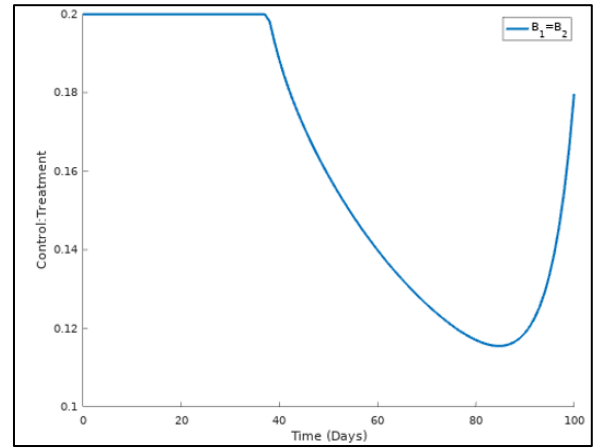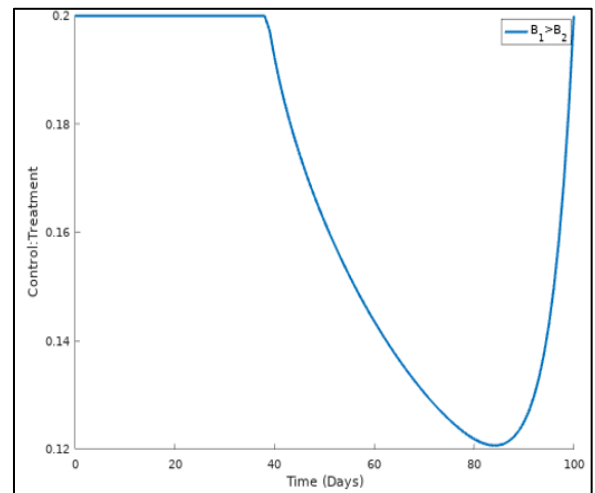

(a)

(a)

32

(b)

(b)

(c)

(c)

Fig. 5: Prevention functions when (5a) $B_1 < B_2$, (b) $B_1 = B_2$ and (c) $B_1 > B_2$
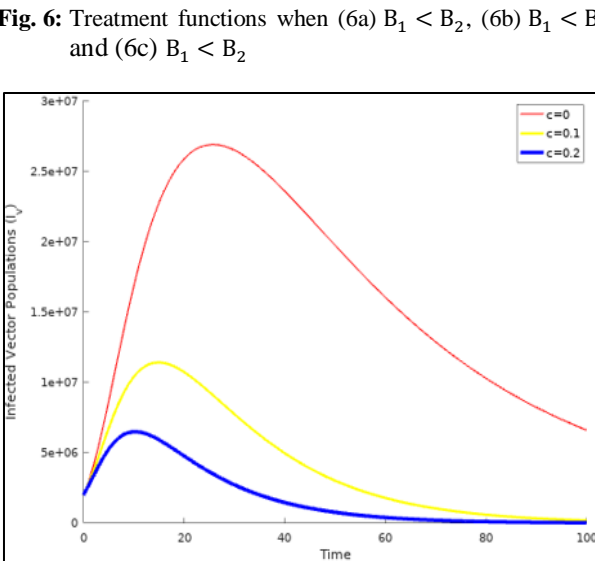
Fig. 6: Treatment functions when (6a) $B_1 < B_2$, (6b) $B_1 < B_2$ and (6c) $B_1 < B_2$

(a)
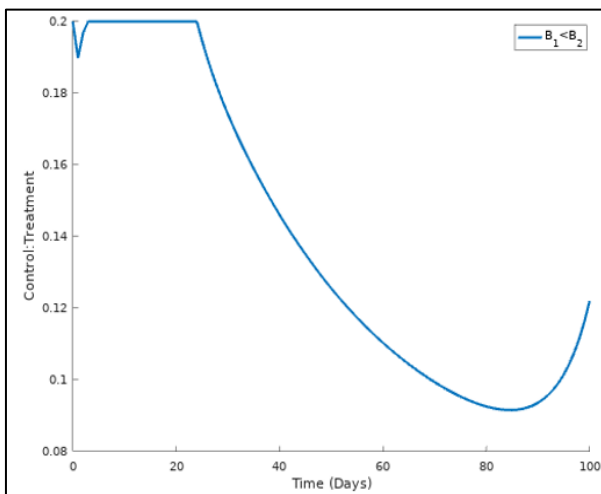
Fig. 7: Infected vector populations with $u_{1max} = 0.5, u_{2max} = 0.2$

Figure 5 giving equal weights, $B_1 = -B_2$ reduces the vector population than giving different combination of the weights.

The plots in Figs. 6a-c shows treatment functions, when respectively.

Figure 6, giving more weights to B_1 reduces the treatment function than giving equal or more weight to B_2.

Materials and Methods

The yearly malaria transmission data for Ghana, from 2004-17, obtained from WHO, was used to obtain a least-squares estimate of the parameters for the model. To determine an optimal combination of prevention and treatment, we formulated an optimal control problem. Pontryagin's maximum principle was used to obtain the first-order necessary conditions. A forward-backward sweep method was then used to solve the optimality system.

Numerical Simulations

The following simulations were performed using optimal control functions $\mu_1^*(t)$ and $\mu_2^*(t)$, with parameter values:
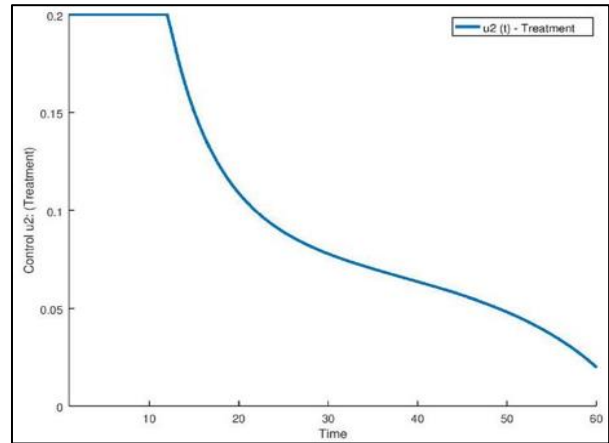
$u_{1max} = 0.5$, so that $u_{1max}S_h$ represents a maximum of 50% of the susceptible population using adequate prevention methods. $u_2max = 0.2$, corresponds to a treatment period of about $1/0.2 = 5$ days and weights $B_1 = B_2 = 400000$.

Simulations on the Effect of c on Infected Vector Population

We investigate the effect of the parameter c on the vector population using increasing values of $c = 0.0, 0.1, 0.2$, with the following fixed values of u_{1max}, u_{2max} and κ.
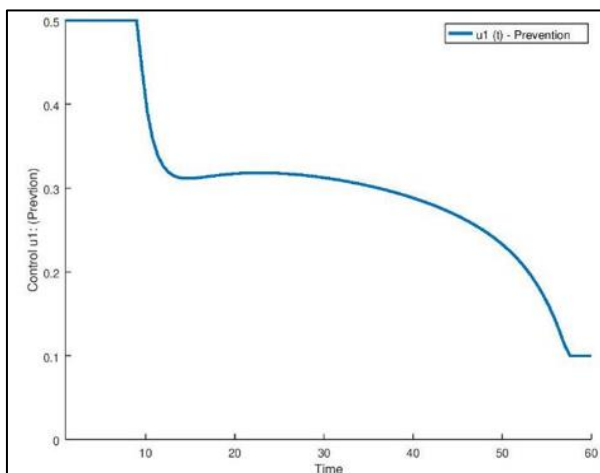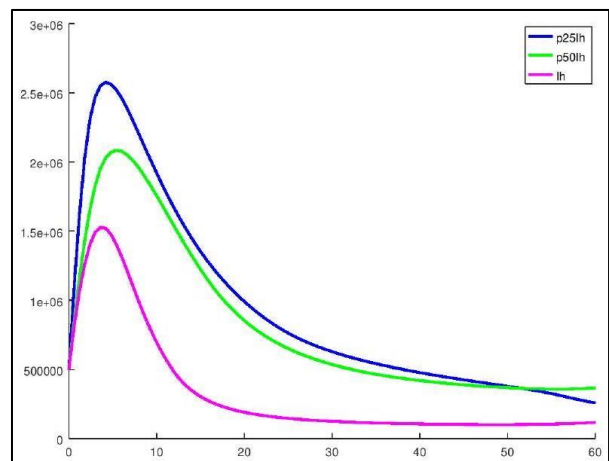

(a)

(b)

Fig. 8: Optimal Function with $u_{1max} = 0.5, u_{2max} = 0.2$; (a) Optimal control function $u_1(t)$; (b) Optimal control function $u_2(t)$

Fig. 9: Infected human populations with differential treatment regimes

$u_{1max} = 0.5$, so that $u_{1max}S_h$ represents a maximum of 50% the susceptible population using adequate prevention methods.

Let $\kappa = 1$, so that $\gamma \times (\kappa I_h) = \gamma I_h$, gives the best scenario for treatment availability.

Figure 7 shows a plot of the infected vector populations, with $c = 0.0, 0.10, 0.20$ respectively. Figure 7, we notice a dramatic reduction in the infected vector population, with increasing values of c.

The corresponding optimal control functions are displayed in Fig. 8a-b.

The control functions prevention μ_1 and treatment μ_2 in Fig. 8 starts from maximum 0.5 and 0.2 respectively and decreases gradually as infected population also decreases in Fig. 7.

Simulations with Differential Treatment $\gamma(\kappa I_h)$ Regimes

We investigate the effects on the total infected human populations when effective treatment is only available to a proportion $0 \leq \kappa \leq 1$ of the infected population in Fig. 9. This scenario happens for a variety of reasons including, lack of medical facilities in some communities, as well as affordability for the cost of treatment. The labels "$p25I_h$", "$p50I_h$" and "pI_h" in Fig. 9 represents respectively, the effect on the total infected human populations, when 25, 20 and 100% of the infected population receive treatment.

Figure 9 shows that the total infected human populations decrease faster, when treatment is accessible to a greater proportion of those infected.

Results and Discussion

A unique and novel feature of our model is the effect of prevention on reducing the vector population by increasing their death rate Eq. (1); a key strategy in controlling malaria. A proportion $c\alpha$; ($0 \leq c \leq 1$) of the prevention effort α, is directed at increasing the vector death rate. Our simulations clearly shows that increasing the parameter c reduces the vector population. Furthermore, increasing the prevention rate α ($= \mu_1$), has the dual effect of reducing the susceptible human population as well as increasing the vector death rate even further.

Another unique feature of our model is our treatment function Eq. (2) which models the fact that only a proportion κ, of the infected population have access to effective treatment. Our simulations show that increasing the parameter κ ensures more access treatment for diagnosed cases, which reduces the overall infected human population. The fewer the infected population, the less the transmission rate. In fact, every untreated case becomes a reservoir for mosquitoes to further transmit malaria.

Conclusion

The key to successfully containing the spread of malaria lies in prevention as well as effective and rapid treatment for those infected with the disease. The fewer the infected population, the less the transmission rate. Proper prevention efforts in contiguous communities, can play the role of a vaccine and therefore are essential for the eventual eradication of malaria. The simulations show that if at least, 50% of the susceptible population follows proper prevention protocols, the reduction in transmission will be remarkable. A rapid reduction in the infected population through effective treatment, may be achieved by making treatment accessible to everyone infected.

The following recommendations are based on the results of our simulation, together with the maxim that the key to effectively controlling any infectious disease lies in a rapid reduction in the susceptible population, through appropriate prevention efforts, plus a rapid reduction in the infected population through effective treatment.

Prevention methods that reduce vector populations include:

1. Indoor spraying with residual insecticides. This is when the inside of house structures is prayed once or twice a year with insecticide spray. This activity should be regularly done since it reduces the proportion of the resident mosquitoes whether susceptible or infectious
2. The use of insecticide-treated mosquito Nets (ITN). This reduces the contact rates
3. Larval control. This activity may be implemented through environmental modification such as draining and killing or the use of larvacides

Treatment strategies must include:
1. Early diagnosis and effective treatment. Each untreated case becomes a reservoir for mosquitoes to further transmit to other susceptible
2. The use of WHO-approved Anti-malarial medications including Coartem 80/480, Hydroxyl-Chloroquine and Fansidar (Sulfadoxine and Pyrimethamine)

In order to eradicate malaria, especially in developing countries, where most people cannot afford the cost of treatment:

- Malaria medication must be free, or at least, highly subsidized in order to ensure a rapid reduction in the infected population
- The prevention methods listed above must be enforced in all contiguous neighborhoods

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Author's Contributions

Perpetual Appiah: Formal analysis and proofs, data collection, algorithm and software programming, written-original drafted, written reviewed and analysis.

Henry Amankwah: Methodology, formal analysis and validations.

Francis Benyah: Supervision, conceptualization, methodology and written of the final version.

Ethics

On behalf of the authors, the corresponding author declares no conflict of interest and no external funding was received for this manuscript. Moreover, the work described is original research that has not been published previously and is not under consideration for publication elsewhere.

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Appendix A

Corollary to Gershgorin's Circle Theorem

Let M be an $n \times n$ matrix with real entries m_{ij}. If the diagonal entries m_{ii}, of M satisfy:

$$m_{ii} \leq r_i, \text{ where } r_i = \sum_{j=1, j \neq i} |m_{ij}| \, i, j = 1 \ldots n \qquad (100)$$

then, all the eigenvalues of M are negative or have negative real parts.