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Mathematical Study of Malaria Transmission Dynamics with Treatment

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Abstract: *Malaria is a vector-borne infectious disease transmitted to humans by the bite of female Anopheles mosquitoes. A compartmental model is proposed to study the transmission dynamics of the disease, treating humans as hosts and mosquitoes as vectors. This work focuses on the treatment of infected humans, which plays a crucial role in controlling the transmission dynamics of malaria. It is a key factor to understand disease dynamics which helps in guiding the public health polices decisions to ensure the effective disease control strategies. The human population is divided into the five compartments, namely Susceptible, Exposed, Infectious, Treatment and Recovered and the mosquito population is divided into three compartments such as Susceptible, Exposed and Infectious.The dynamics of malaria transmission are represented through compartmental models and formulated as ordinary differential equations. We prove the positivity and boundedness properties of the model equations to ensure the well-posedness of both the population dynamics. The dimensionless quantity known as the basic reproduction number* R_0*, which determines whether the disease dies out or persists in the population, is calculated using the method of the next generation matrix. It is observed that the disease-free equilibrium point is stable, leading to the disease extinction, when* $R_0 < 1$*. Conversely, the equilibrium point is unstable for* $R_0 > 1$*, leading the disease to persist in the community. A sensitivity analysis of the model parameters on the basic reproduction number is performed to study their significance in disease transmission. Numerical simulations are presented graphically to validate the mathematical results.*

Keywords: Malaria, Treatment, Basic reproduction number, Stability, Sensitivity analysis

1 Introduction

Malaria is a vector-borne infectious disease (parasitic infection) endemic in many parts of the world [7]. It affects humans almost all ages worldwide and it is transmitted by the bites of female Anopheles mosquitoes. Globally, an estimated 3.3 billion individuals are at risk of malaria disease infection while 1.2 billion are at high risk. The burden is heaviest to Africa region. The malaria is also endemic in regions of Asia, South America, Western Europe and the some parts of the USA [19]. An estimated 90% of all malaria-related deaths occur among children under the age of five. Currently, 97 countries are affected by malaria, while in 2008, the disease was endemic in 109 countries [20]. According to WHO, approximately 214 million new malaria cases were reported and $438,000$ people died worldwide in 2015. Most cases were reported in the African region [18]. Mathematical models are assumed to be effective tools to understand the future outbreak of the disease and to design the effective control strategies. Mathematical models have been formulated to describe the transmission dynamics of various type of communicable diseases [3, 11, 12].

Ronald Ross [14] was the first to use mathematical modeling to study the transmission dynamics of malaria disease. The Rose-Macdonald model consists of the interaction between infected population of hosts and vectors. Aron and May [2] described the properties of this model, including the derivation of basic reproduction number. They continued their review by adding various factors such as incubation period of the mosquito, period of immunity of humans and super infection. Anderson and May [1] reviewed the model by incorporating various values including latent period of mosquitoes and humans, recovery rate, expected lifespan of mosquitoes and age distribution of humans. In 2000, Ngwa and Shu [8] proposed the ordinary differential equations on compartmental model for the spread of malaria with susceptible-exposed-infectious-recovered (SEIR) pattern for humans and a susceptible-exposed-infectious (SEI) pattern for mosquitoes. Chitnis, Cushing and Hyman [4] extended the similar model of the Ngwa and Shu. The extension of Ngwa and Shu includes human immigration, excludes direct recovery from the infectious to the susceptible class and generalizes the mosquito biting rate so that it can be applied to wider range of the population similar to Ngwa and Shu [8]. This model also allows humans to be temporarily immune to the disease, that still transmits the infection to susceptible mosquitoes. One of the latest studies in the malaria transmission is carried out by Okella et al. [10] to study the the spread of disease in the Nyamira town, Kenya. The disease control strategies prevention through bed nets, treatment and insecticides were incorporated by Ojo [9].

In the present work, we propose ordinary differential equations on compartmental model to study the spread of malaria with susceptible (S), exposed (E), infectious (I), treatment (T), and recovered (R) (SEITR) pattern for humans and susceptible, exposed, infectious (SEI) pattern for mosquitoes. This work is based on treatment compartment. The positivity and boundedness property of the model are also analyzed. Equilibrium points of the model, basic reproduction number and stability of the equilibrium points are discussed. Numerical simulation are carried out to study the qualitative behavior of the disease dynamics, and the conclusion of the work is presented.

2 Formulation of Model

We divide the total human (host) population N_h to five classes: S_h (Susceptible), E_h (Exposed), I_h (Infectious), T_h (Treatment) and R_h (Recovered) and the total mosquito (vector) population N_m to three classes: S_m (Susceptible), E_m (Exposed) and I_m (Infectious). The birth rate for the human population is ψ. The susceptible humans get infected (exposed state) by the bite of infectious mosquitoes at the rate of $\alpha_h = \frac{\theta_{mh}\phi I_m}{N_h}$ where, ϕ denotes the biting rate of mosquitoes, θ_{mh} is the transmission probability of infection from an infectious mosquitoes to susceptible humans. The exposed humans either die due to the natural cause or move to the infectious class at the rate β_h after showing the symptoms of the disease. Infectious humans either die due to natural death or go to the treatment class at the rate of γ_h. The humans who received the treatment either die due to disease or recover at the rate of τ_h. Let μ be natural death rate of humans and π be death rate of humans due to disease. Let σ be the rate of loss of immunity of humans and recovered humans again go to susceptible class. Similarly, susceptible mosquitoes move to the exposed class at the rate of $\alpha_m = \frac{\theta_{hm}\phi I_h}{N_h}$ and they move to the infectious class at the rate of β_m after showing the symptoms of disease. Mosquitoes are born at rate ρ and die at rate w and θ_{hm} is the transmission probability of infection from an infectious humans to susceptible mosquitoes. The malaria transmission dynamics between the hosts and the vectors population are illustrated in the Figure 1 and the corresponding compartmental models for both the populations are formulated as a system of ordinary differential equations, given in (1).

$$\begin{aligned}
\frac{dS_h}{dt} &= \psi N_h + \sigma R_h - \frac{\theta_{mh}\phi I_m}{N_h} S_h - \mu S_h \\
\frac{dE_h}{dt} &= \frac{\theta_{mh}\phi I_m}{N_h} S_h - (\mu + \beta_h) E_h \\
\frac{dI_h}{dt} &= \beta_h E_h - (\gamma_h + \mu + \pi) I_h \\
\frac{dT_h}{dt} &= \gamma_h I_h - (\tau_h + \mu + \pi) T_h \\
\frac{dR_h}{dt} &= \tau_h T_h - (\mu + \sigma) R_h \\
\frac{dS_m}{dt} &= \rho - \frac{\theta_{hm}\phi I_h}{N_h} S_m - w S_m \\
\frac{dE_m}{dt} &= \frac{\theta_{hm}\phi I_h}{N_h} S_m - (\beta_m + w) E_m \\
\frac{dI_m}{dt} &= \beta_m E_m - w I_m
\end{aligned} \tag{1}$$

Thus, the total human and mosquito population size $N_h(t)$ and $N_m(t)$ are

$$N_h = S_h + E_h + I_h + T_h + R_h, \quad N_m = S_m + E_m + I_m.$$

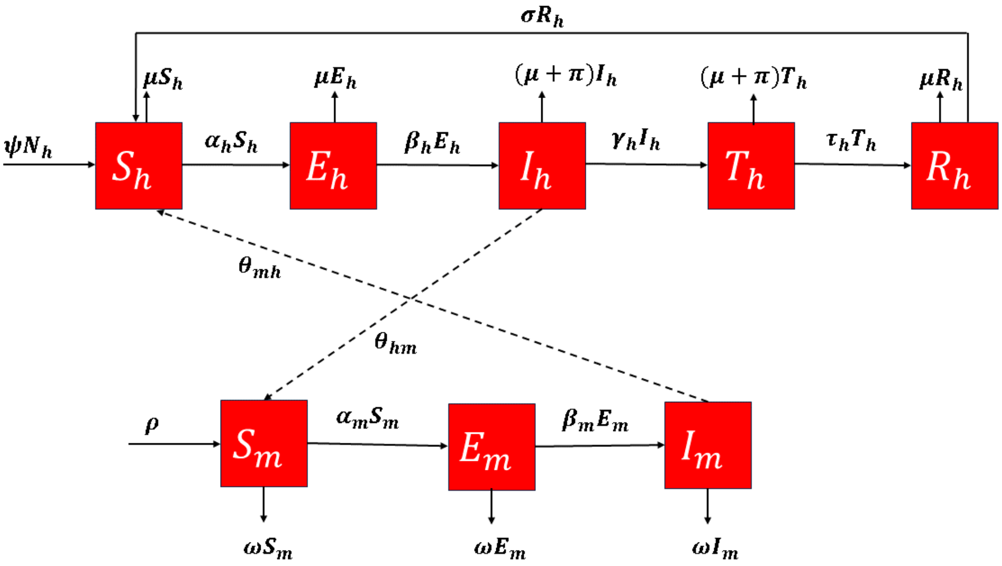

Figure 1: Disease transmission dynamics of SEITR-SEI malaria disease model.

3 Mathematical Analysis

3.1 Positivity and boundedness

In this model, there are eight state variables. In order to demonstrate that the model is well-posed and biologically valid for describing malaria transmission dynamics, we now prove that the solutions of all such state variables are non-negative and bounded. These result is shown in the following theorem.

Theorem 3.1. *If $S_h(0) > 0$, $E_h(0) \geq 0$, $I_h(0) \geq 0$, $T_h(0) \geq 0$, $R_h(0) \geq 0$, $S_m(0) > 0$, $E_m(0) \geq 0$ and $I_m(0) \geq 0$. Then the solution set $\{S_h(t), E_h(t), I_h(t), T_h(t), R_h(t), S_m(t), E_m(t), I_m(t)\}$ of the system (1) is always positive and bounded for all $t > 0$.*

Proof. Firstly, we prove that all the solutions of the system are positive.
For this, we take

$$\begin{aligned}
\frac{dS_h}{dt} &= \psi N_h + \sigma R_h - \frac{\theta_{mh}\phi I_m}{N_h} S_h - \mu S_h \\
\frac{dS_h}{dt} &> -\frac{\theta_{mh}\phi I_m}{N_h} S_h - \mu S_h \\
\text{Therefore, } S_h &> S_h(0) \quad e^{-\int(\frac{\theta_{mh}\phi I_m}{N_h}+\mu)dt} \geq 0
\end{aligned}$$

Similarly

$$\begin{aligned}
\frac{dE_h}{dt} &= \frac{\theta_{mh}\phi I_m}{N_h} S_h - (\mu+\beta_h)E_h \\
\frac{dE_h}{dt} &> -(\mu+\beta_h)E_h \\
\text{Therefore, } E_h &> E_h(0) \quad e^{-(\mu+\beta_h)t} \geq 0
\end{aligned}$$

$$
\begin{aligned}
\frac{dI_h}{dt} &= \beta_h E_h - (\gamma_h + \mu + \pi) I_h \\
\frac{dI_h}{dt} &> -(\gamma_h + \mu + \pi) I_h \\
\text{Therefore, } I_h &> I_h(0) \quad e^{-(\gamma_h + \mu + \pi)t} \geq 0 \\
\frac{dT_h}{dt} &= \gamma_h I_h - (\tau_h + \mu + \pi) T_h \\
\frac{dT_h}{dt} &> -(\tau_h + \mu + \pi) T_h \\
\text{Therefore, } T_h &> T_h(0) \quad e^{-(\tau_h + \mu + \pi)t} \geq 0 \\
\frac{dR_h}{dt} &= \tau_h T_h - (\mu + \sigma) R_h \\
\frac{dR_h}{dt} &> -(\mu + \sigma) R_h \\
\text{Therefore, } R_h &> R_h(0) \quad e^{-(\mu + \sigma)t} \geq 0 \\
\frac{dS_m}{dt} &= \rho - \frac{\theta_{hm} \phi I_h}{N_h} S_m - w S_m \\
\frac{dS_m}{dt} &> -\frac{\theta_{hm} \phi I_h}{N_h} S_m - w S_m \\
\text{Therefore, } S_m &> S_m(0) \quad e^{-\int (\frac{\theta_{hm} \phi I_h}{N_h} + w) dt} \geq 0 \\
\frac{dE_m}{dt} &= \frac{\theta_{hm} \phi I_h}{N_h} S_m - (\beta_m + w) E_m \\
\frac{dE_m}{dt} &> -(\beta_m + w) E_m \\
\text{Therefore, } E_m &> E_m(0) \quad e^{-(\beta_m + w)t} \geq 0 \\
\frac{dI_m}{dt} &= \beta_m E_m - w I_m \\
\frac{dI_m}{dt} &> -w I_m \\
\text{Therefore, } I_m &> I_m(0) \quad e^{-wt} \geq 0
\end{aligned}
$$

Hence, the solution set $\{S_h(t), E_h(t), I_h(t), T_h(t), R_h(t), S_m(t), E_m(t), I_m(t)\}$ of the system (1) is always non-negative for all $t > 0$. Next, we prove that these non-negative solutions are bounded. Adding all human compartments of differential equations of system (1) to get

$$
\begin{aligned}
\frac{dN_h}{dt} &= \frac{dS_h}{dt} + \frac{dE_h}{dt} + \frac{dI_h}{dt} + \frac{dT_h}{dt} + \frac{dR_h}{dt} \\
&= \psi N_h - \mu (S_h + E_h + I_h + T_h + R_h) - \pi I_h - \pi T_h \\
\frac{dN_h}{dt} &= \psi N_h - \mu N_h - \pi (I_h + T_h) \\
\frac{dN_h}{dt} &< (\psi - \mu) N_h \\
\text{Therefore, } N_h &< N_h(0) e^{(\psi - \mu)t}
\end{aligned}
\tag{2}
$$

Hence, the human population is bounded for all $t > 0$.

Similarly, adding all mosquito compartments of differential equations in the system (1), we get

$$
\begin{aligned}
\frac{dN_m}{dt} &= \frac{dS_m}{dt} + \frac{dE_m}{dt} + \frac{dI_m}{dt} \\
&= \rho - w (S_m + E_m + I_m) \\
\frac{dN_m}{dt} &= \rho - w N_m
\end{aligned}
$$

$$\begin{aligned}
\frac{dN_m}{dt} + wN_m &= \rho \\
\text{Therefore, } N_m &= \frac{\rho}{w} + (N_m(0) - \frac{\rho}{w})e^{-wt} \\
As \quad t \longrightarrow \infty, \quad e^{-wt} \longrightarrow 0 & \\
\text{Therefore, } N_m &= \frac{\rho}{w}
\end{aligned}$$

Hence, the mosquito population is also bounded for all $t > 0$. Thus the state variables representing the populations are non-negative and bounded. $\square$

3.2 Non-dimensionalization

For the qualitative analysis of the model equations, we perform a non-dimensionalization process by introducing the new variables as outlined below
$s_h = \frac{S_h}{N_h}$, $e_h = \frac{E_h}{N_h}$, $i_h = \frac{I_h}{N_h}$, $t_h = \frac{T_h}{N_h}$, $r_h = \frac{R_h}{N_h}$, $s_m = \frac{S_m}{\frac{\rho}{w}}$, $e_m = \frac{E_m}{\frac{\rho}{w}}$, $i_m = \frac{I_m}{\frac{\rho}{w}}$, then the system of equations (1) becomes

$$\begin{aligned}
\frac{ds_h}{dt} &= \psi + \sigma r_h - \alpha i_m s_h - \mu s_h \\
\frac{de_h}{dt} &= \alpha i_m s_h - (\mu + \beta_h)e_h \\
\frac{di_h}{dt} &= \beta_h e_h - (\gamma_h + \mu + \pi)i_h \\
\frac{dt_h}{dt} &= \gamma_h i_h - (\tau_h + \mu + \pi)t_h \\
\frac{dr_h}{dt} &= \tau_h t_h - (\mu + \sigma)r_h \\
\frac{ds_m}{dt} &= w - \theta_{hm}\phi i_h s_m - w s_m \\
\frac{de_m}{dt} &= \theta_{hm}\phi i_h s_m - (\beta_m + w)e_m \\
\frac{di_m}{dt} &= \beta_m e_m - w i_m
\end{aligned} \tag{3}$$

where,

$$\alpha = \frac{\theta_{mh}\phi\rho}{N_h w}$$

For the stability analysis of the disease model, we restrict only to infected compartments of humans (e_h, i_h, t_h) and mosquitoes (e_m, i_m), leading to following system

$$\begin{aligned}
\frac{de_h}{dt} &= \alpha i_m s_h - (\mu + \beta_h)e_h \\
\frac{di_h}{dt} &= \beta_h e_h - (\gamma_h + \mu + \pi)i_h \\
\frac{dt_h}{dt} &= \gamma_h i_h - (\tau_h + \mu + \pi)t_h \\
\frac{de_m}{dt} &= \theta_{hm}\phi i_h s_m - (\beta_m + w)e_m \\
\frac{di_m}{dt} &= \beta_m e_m - w i_m
\end{aligned} \tag{4}$$

3.3 Equilibrium points and stability analysis

In the absence of infective population, the model has a steady state solution, known as the disease free equilibrium. Exposed, infectious and treatment in human class; exposed and infectious in mosquito class are set to zero in this state. So, $e_h = i_h = t_h = r_h = e_m = i_m = 0$.

Thus the system of equations (3) has a disease free equilibrium point

$$E_0 = (s_h^*, e_h^*, i_h^*, t_h^*, r_h^*, s_m^*, e_m^*, i_m^*) = \left(\frac{\psi}{\mu}, 0, 0, 0, 0, \frac{\rho}{w}, 0, 0\right)$$

The average number of secondary infections, produced by a single infective on its infectious period is called the basic reproduction number, denoted by R_0. It serves as a metric to determine if the disease is going to persist or die out within the community. The disease can persist when the R_0 is greater than one, while the disease dies out when it is less than one. The number, R_0 is computed as $\rho(FV^{-1})$, the largest eigenvalue (spectral radius) of the matrix FV^{-1}, (F is the matrix of transmission terms and V is the matrix of transition terms) computed from the system (4).

The Jacobian matrix F at the disease free equilibrium point is

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & \alpha s_h \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \theta_{hm}\phi s_m & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Similarly, Jacobian matrix V at the disease free equilibrium point is

$$V = \begin{pmatrix} \beta_h + \mu & 0 & 0 & 0 & 0 \\ -\beta_h & \gamma_h + \mu + \pi & 0 & 0 & 0 \\ 0 & -\gamma_h & \tau_h + \mu + \pi & 0 & 0 \\ 0 & 0 & 0 & \beta_m + w & 0 \\ 0 & 0 & 0 & -\beta_m & w \end{pmatrix}$$

The expression for R_0 is derived using next generation matrix approach, by computing the spectral radius of the matrix FV^{-1} [13], that means,

$$\begin{aligned} R_0 &= \rho(FV^{-1}); \\ \implies R_0 &= \sqrt{\frac{\alpha\beta_h\beta_m s_h s_m \phi\theta_{hm}}{w(\mu+\beta_h)(\beta_m+w)(\gamma_h+\mu+\pi)}} \\ \implies R_0 &= \sqrt{\frac{\phi^2\beta_h\beta_m\mu\theta_{mh}\theta_{hm}\rho}{\psi w^2(\mu+\beta_h)(\beta_m+w)(\gamma_h+\mu+\pi)}} \qquad (5) \end{aligned}$$

where

$$S_h = N_h = \frac{\psi}{\mu}, S_m = N_m = \frac{\rho}{w}, s_m = \frac{S_m}{N_m} \text{ and } s_h = \frac{S_h}{N_h}. \text{ and } \alpha = \frac{\theta_{mh}\phi\rho}{N_h w}.$$

The disease free equilibrium point (DFE), E_0 always exists. We present the following theorem to discuss the local stability of this equilibrium point.

Theorem 3.2. *If $R_0 < 1$, the disease free equilibrium point becomes locally asymptotically stable and becomes unstable if $R_0 > 1$.*

Proof. From system (3), we have

$$\begin{aligned} \frac{de_h}{dt} &= \alpha i_m s_h - (\mu + \beta_h)e_h \\ \frac{di_h}{dt} &= \beta_h e_h - (\gamma_h + \mu + \pi)i_h \end{aligned}$$

$$\begin{aligned}
\frac{dt_h}{dt} &= \gamma_h i_h - (\tau_h + \mu + \pi)t_h \qquad (6)\\
\frac{dr_h}{dt} &= \tau_h t_h - (\mu + \sigma)r_h\\
\frac{de_m}{dt} &= \theta_{hm}\phi i_h s_m - (\beta_m + w)e_m\\
\frac{di_m}{dt} &= \beta_m e_m - w i_m
\end{aligned}$$

The eigenvalues of the Jacobian matrix J are the solution of the characteristic equation

$$|J - \lambda I| = \begin{vmatrix}
-(\beta_h + \mu + \lambda) & 0 & 0 & 0 & 0 & \alpha s_h\\
\beta_h & -(\gamma_h + \mu + \pi + \lambda) & 0 & 0 & 0 & 0\\
0 & \gamma_h & -(\tau_h + \mu + \pi + \lambda) & 0 & 0 & 0\\
0 & 0 & \tau_h & -(\mu + \sigma + \lambda) & 0 & 0\\
0 & \theta_{hm}\phi i_h s_m & 0 & 0 & -(\beta_m + w + \lambda) & 0\\
0 & 0 & 0 & 0 & \beta_m & -(w + \lambda)
\end{vmatrix} = 0$$

Which implies $\lambda = -(\sigma + \mu)$, $-(\tau_h + \pi + \mu)$.

In the disease free equilibrium point,

$$S_h = N_h = \frac{\psi}{\mu}, S_m = N_m = \frac{\rho}{w}$$

and $\alpha = \frac{\theta_{mh}\phi\rho}{N_h w}$
For the remaining eigenvalues of Jacobian matrix J,

$$(\mu + \beta_h + \lambda)(\gamma_h + \mu + \pi + \lambda)(\beta_m + w + \lambda)(w + \lambda) - \frac{\theta_{hm}\mu\rho}{\psi w}\theta_{mh}\beta_m\beta_h\phi^2 = 0 \qquad (7)$$

Let $P_1 = w$, $\quad P_2 = \beta_m + w$, $\quad P_3 = \gamma_h + \mu + \pi$, $\quad P_4 = \mu + \beta_h$, $K = \frac{\theta_{mh}\theta_{hm}\mu\beta_h\beta_m\phi^2\rho}{\psi w}$
Then, equation (7) becomes

$$(\lambda + P_1)(\lambda + P_2)(\lambda + P_3)(\lambda + P_4) - K = 0 \qquad (8)$$

Corresponding characteristic polynomial is

$$\lambda^4 + K_1\lambda^3 + K_2\lambda^2 + K_3\lambda + K_4 = 0, \qquad (9)$$

where

$$\begin{aligned}
K_1 &= P_1 + P_2 + P_3 + P_4\\
K_2 &= P_4(P_1 + P_2 + P_3) + P_3(P_1 + P_2) + P_1P_2\\
K_3 &= P_1P_2P_3 + P_2P_3P_4 + P_3P_4P_1 + P_4P_1P_2\\
K_4 &= P_1P_2P_3P_4 - K
\end{aligned}$$

The disease free equilibrium becomes stable if we could prove that all the roots of the polynomial characteristic lie in the left half of the complex plane. For this, we have to prove the Routh-Hurwitz criteria [15], $det(H_i) > 0$ for $i = 1, 2, 3, 4$.

$$det(H_1) \quad = \quad |K_1| = P_1 + P_2 + P_3 + P_4 > 0$$

$$\begin{aligned}
det(H_2) &= \begin{vmatrix} K_1 & 1 \\ 0 & K_2 \end{vmatrix} = K_1K_2 \\
&= [P_1+P_2+P_3+P_4][P_4(P_1+P_2+P_3)+P_3(P_1+P_2)+P_1P_2] > 0 \\
det(H_3) &= \begin{vmatrix} K_1 & 1 & 0 \\ K_3 & K_2 & K_1 \\ 0 & 0 & K_3 \end{vmatrix} = K_1K_2K_3 - K_3^2 = K_3[K_1K_2 - K_3] \\
&= K_3[(P_1+P_2+P_3+P_4)(P_4(P_1+P_2+P_3)+P_3(P_1+P_2)+P_1P_2) \\
&- (P_1P_2P_3+P_2P_3P_4+P_3P_4P_1+P_4P_1P_2)] \\
&= K_3[P_1^2(P_2+P_3+P_4)+P_2^2(P_3+P_4+P_1)+P_3^2(P_4+P_1+P_2) \\
&+ P_4^2(P_1+P_2+P_3)+2P_1P_2P_3+2P_2P_3P_4+2P_3P_4P_1+2P_4P_1P_2] > 0 \\
det(H_4) &= \begin{vmatrix} K_1 & 1 & 0 & 0 \\ K_3 & K_2 & K_1 & 1 \\ 0 & K_4 & K_3 & K_2 \\ 0 & 0 & 0 & K_4 \end{vmatrix} = K_4 \begin{vmatrix} K_1 & 1 & 0 \\ K_3 & K_2 & K_1 \\ 0 & K_4 & K_3 \end{vmatrix} \\
&= K_4 \left| K_1 \begin{vmatrix} K_2 & K_1 \\ K_4 & K_3 \end{vmatrix} - 1 \begin{vmatrix} K_3 & K_1 \\ 0 & K_3 \end{vmatrix} \right| \\
&= K_4[K_1(K_2K_3 - K_1K_4) - K_3^2] \\
&= K_4[K_1K_2K_3 - K_1^2K_4 - K_3^2] \\
&= K_4K_5
\end{aligned}$$

where,

$$\begin{aligned}
K_5 &= K_1K_2K_3 - K_1^2K_4 - K_3^2 \\
K_4 &= P_1P_2P_3P_4 - K
\end{aligned}$$

Here, $K_4 > 0$ if

$$\begin{aligned}
K_4 = &\quad (P_1P_2P_3P_4 - K) > 0 \\
\implies &\quad K < P_1P_2P_3P_4 \\
\implies &\quad \frac{K}{P_1P_2P_3P_4} < 1 \\
\implies &\quad \frac{\phi^2\beta_h\beta_m\mu\theta_{mh}\theta_{hm}\rho}{\psi w^2(\mu+\beta_h)(\beta_m+w)(\gamma_h+\mu+\pi)} < 1 \\
\implies &\quad R_0^2 < 1 \\
\implies &\quad R_0 < 1
\end{aligned}$$

Hence, $K_4 = P_1P_2P_3P_4 - K > 0$ if $R_0 < 1$.
Moreover,

$$\begin{aligned}
K_5 &= (K_1K_2K_3 - K_1^2K_4 - K_3^2) \\
&= (P_1+P_2+P_3+P_4)[(P_4(P_1+P_2+P_3)+P_3(P_1+P_2)+P_1P_2)] \\
&\quad \times(P_1P_2P_3+P_2P_3P_4+P_3P_4P_1+P_4P_1P_2) - (P_1+P_2+P_3+P_4)^2 \\
&\quad \times(P_1P_2P_3P_4 - K) - (P_1P_2P_3+P_2P_3P_4+P_3P_4P_1+P_4P_1P_2)^2
\end{aligned}$$

In the above expression, all the negative terms canceled out resulting $K_5 > 0$. Consequently, $det(H_4) = K_4K_5 > 0$ when $R_0 < 1$. Since all the determinants of Hurwitz matrices are positive, the polynomial (9) has the roots with negative real parts. Therefore, the disease free equilibrium point is stable if $R_0 < 1$. On the contrary, if $R_0 > 1$ then $K_4 < 0$ implying that $det(H_4) = K_4K_5 < 0$. In this case, not all the roots of polynomial (9) can have negative real parts, and the disease free equilibrium point is unstable. $\square$

3.4 Sensitivity analysis

Sensitivity analysis gives us an idea to identify which parameter values play a critical role in the spread of disease dynamics and shows how changes in these values affect the disease transmission patterns.

3.5 Normalized sensitivity index

We use normalized sensitivity index for sensitivity analysis of the disease dynamics. We have taken the baseline values displayed in Table 1. The normalized forward sensitivity index (γ_p^s) of variable s which depends on a parameter p is defined as [5]

$$\gamma_p^s = \frac{\partial s}{\partial p} \times \frac{p}{s}.$$

Here, we take $s = R_0$ and $p = \phi, \theta_{mh}, \theta_{hm}, \rho, w, \psi, \beta_m, \beta_h$.

Table 1: Sensitivity indices of R_0 evaluated at baseline parameter values

Parameters (p)	Baseline Values	Sign	Sensitivity indices $\gamma_p^{R_0}$
ϕ	0.29	+ve	1
θ_{mh}	0.062	+ve	0.5
θ_{hm}	0.24	+ve	0.5
ρ	1.8424	+ve	0.5
β_m	0.999	+ve	0.02383
β_h	0.999	+ve	0.02383
ψ	0.12	-ve	0.5
π	0.00000638	-ve	0.00002232
w	0.1042	-ve	1

Table 1 presents the sensitivity indices of the model parameters. The positive index indicates the disease transmission and basic reproduction number R_0 rise with increasing values of the parameter while the negative index shows increasing the parameter reduce them. For example, $\gamma_\phi^{R_0} = 1$ means that increasing the mosquito biting rate ϕ by 10% increases R_0 also by 10%, whereas $\gamma_w^{R_0} = -1$ implies that increasing the mosquito death rate w by 10% decreases R_0 by 10%. Since the sensitivity indices of parameters $\phi, \theta_{mh}, \theta_{hm}, \rho$ are positive, the basic reproduction number increases with them leading to rise in disease dynamics. However, sensitivity indices of parameters ψ, w are negative decreases R_0 reducing the disease dynamics. Among these, the biting rate ϕ is the most influential positive factor, and the death rate w is the most influential negative factor.

4 Numerical Results and Discussion

Since solving the system of non-linear differential equations analytically is infeasible, we employed fourth order Runge-Kutta method to approximate the solutions of the system (3). In our study, we have assumed the mosquito population size N_m is three times the human population N_h. Numerical simulations are performed to analyze the effects of the model parameters on the transmission of malaria dynamics. Certain parameter values used in the model are taken directly from the demographic statistics of Nepal. The birth rate and death rate are calculated according to National population and housing census [16]. Disease induced death rate is calculated according to the Nepal malaria strategic plan [17]. The biting rate, transmission rate, treatment rate and other parameters are chosen from journal of Chiyaka et al. [6]. The parameters value used in our simulation are presented in the Table 2.

Table 2: Parameter values and their sources

Parameters (p)	Value	Dimension	Source
ϕ	0.4	day^{-1}	Chitnis, 2008
θ_{mh}	0.56	dimensionless	Assumed
θ_{hm}	0.62	dimensionless	Assumed
ρ	0.071	no. day^{-1}	Niger, 2008
β_m	0.091	day^{-1}	Chitnis, 2008
β_h	0.071	day^{-1}	Malaria.com, 2011
ψ	0.00004373	no. day^{-1}	Nepal census, 2011
π	0.00000638	day^{-1}	Nepal malaria strategic plan 2011 − 2016
w	0.11	day^{-1}	Assumed
σ	0.2	day^{-1}	Assumed
γ_h	0.2	day^{-1}	Assumed
μ	0.00001866	day^{-1}	Nepal census, 2011
τ_h	0.14	day^{-1}	Assumed

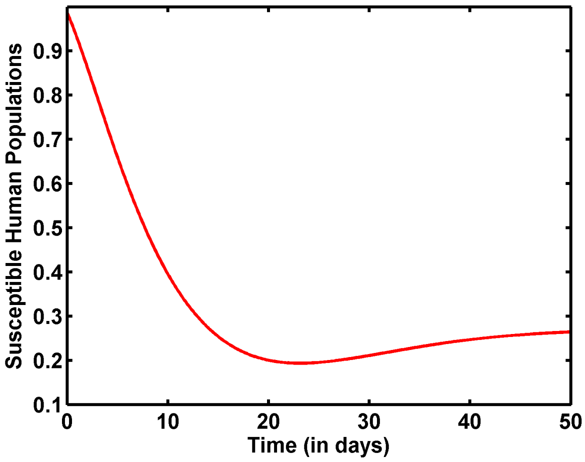

Figure 2: Dynamics of susceptible human population.

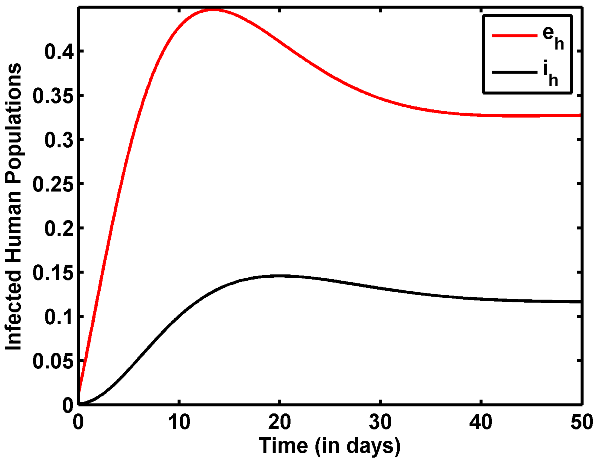

Figure 3: Dynamics of exposed and infected human population.

Figure 2 shows the dynamics of susceptible human population. When susceptible human populations are bitten by the infected mosquitoes, they are transitioned into the exposed class. As a result, susceptible human population declines in the beginning of the days. Once this population reaches to the minimum value, it begins to rise again due to the waning immunity of the recovered human and natural birth of the human population. Figure 3 shows the dynamics of exposed and infected human population. Initially, the exposed human population increases, but over the time it starts to decline as they transition into the infected class due to infection. The trend observed in the infected human population are similar to the trend of the exposed human population.

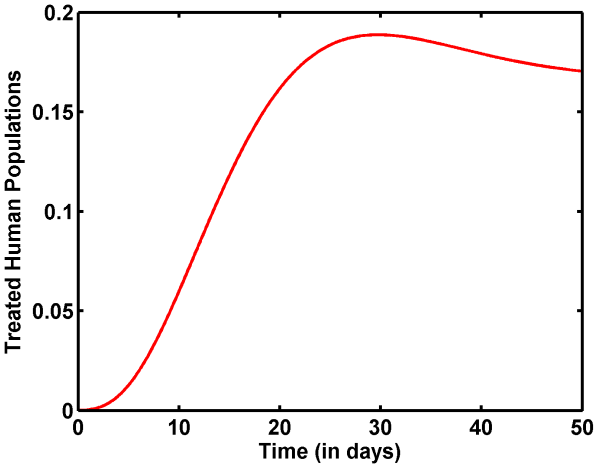

Figure 4: Dynamics of treated human population.

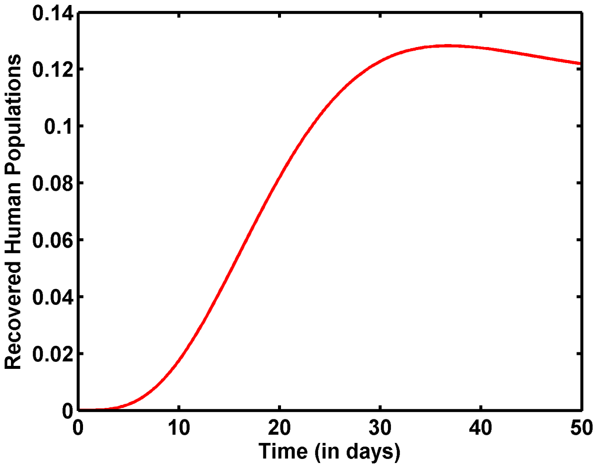

Figure 5: Dynamics of recovered human population.

Figure 4 illustrates the dynamics of treated human population. We assume that the treated individuals remain infectious for some time. The analysis of reproduction number indicates that when there is no transmission of infection from treated humans, then treatment always reduces the disease transmission. Figure 5 represents the dynamics of recovered human population. The recovered human population increases after the completion of treatment.

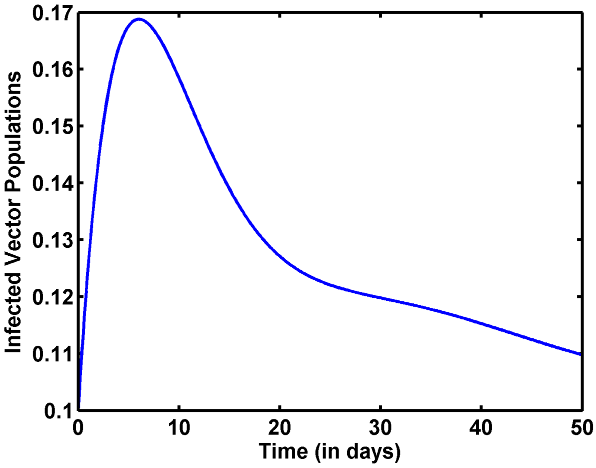

Figure 6: Dynamics of infected vector population.

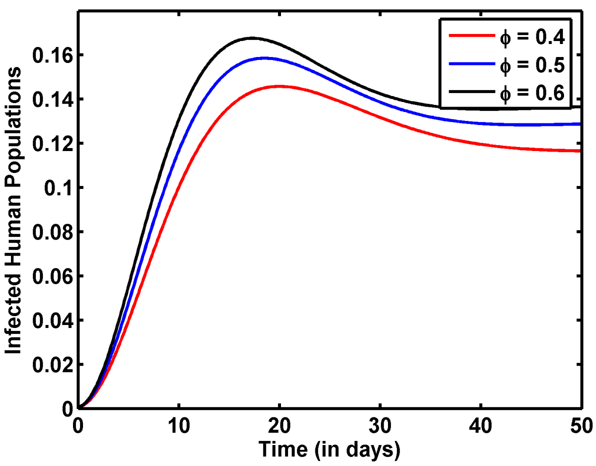

Figure 7: Effect of ϕ on I_h.

Figure 6 shows the dynamics of infected vector (mosquito) population. Initially, the infectious vector population rises because of the contact of susceptible mosquitoes with the infectious humans. Figure 7 shows the impact of biting rate on infected human population. When the biting rate of mosquito increased by 25%, the infected human population rises gradually, as shown in the simulation. When the biting rate is very high, there is a rapid transition of humans from one class to another class, leading to rise in population of infectious class. So biting rate is a critical factor in malaria transmission, where reducing the biting rate has a significant positive impact on controlling malaria disease within the model.

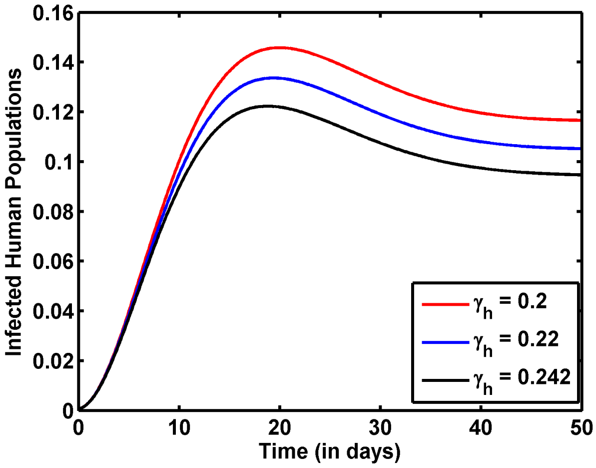

Figure 8: Effect of γ_h on I_h.

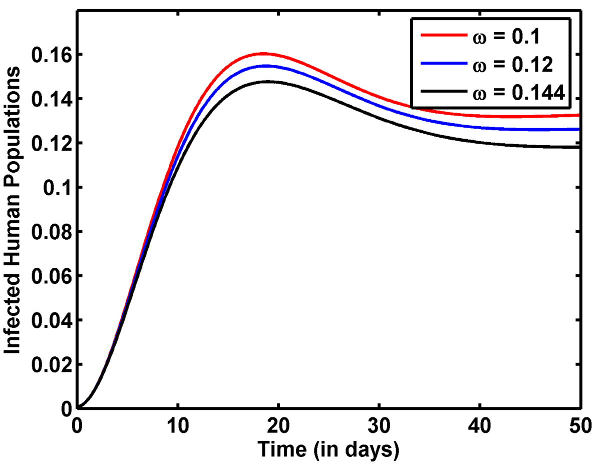

Figure 9: Effect of w on I_h.

Figure 8 illustrates the effect of treatment rate on infected human population. It can be observed that the dynamics of infected human for various values of treatment rate have a relatively similar fluctuating pattern. It can be seen that when the value of γ_h increases, population of infected human (host) decreases rapidly. If the treatment rate is increased by 10%, then infected human population decreases gradually as seen in the simulation. Figure 9 shows the effect of mosquito death rate on infected human population. The simulations show that a 10% increase in mosquito mortality leads to a reduction in the number of infected humans.

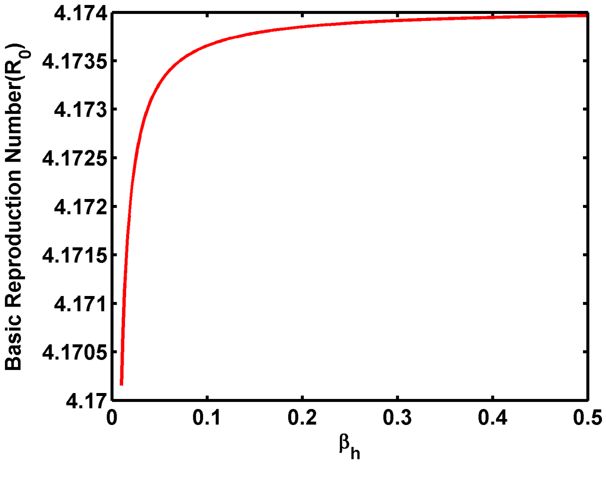

Figure 10: Effect of β_h on R_0.

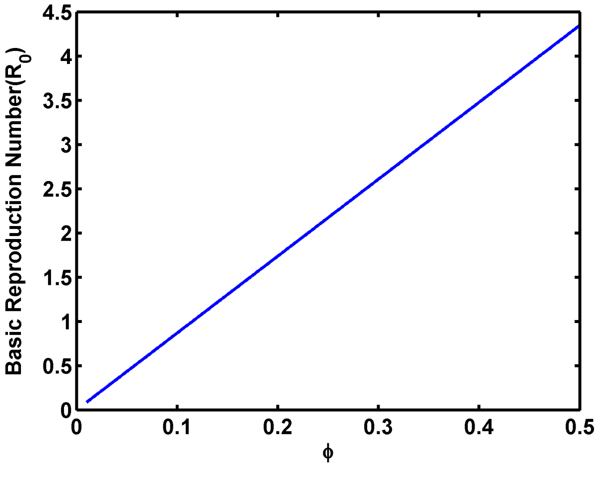

Figure 11: Effect of ϕ on R_0.

Figure 10 shows the dynamics of reproduction number with respect to rate of progression from exposed to infected human (transmission rate). It conveys that the basic reproduction number R_0 increases with the increase in the values of β_h (transmission rate). Figure 11 demonstrates the effect of mosquito biting rate on the reproduction number, revealing the linear relationship. It means that basic reproduction number R_0 is directly proportional to the biting rate ϕ, highlighting it as a most sensitive parameter in the model.

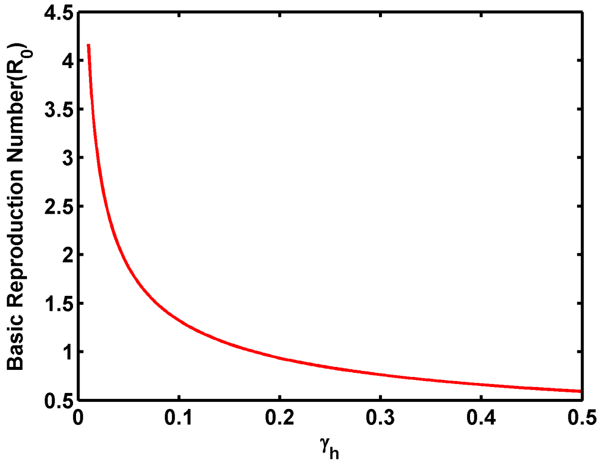

Figure 12: Effect of γ_h on R_0.

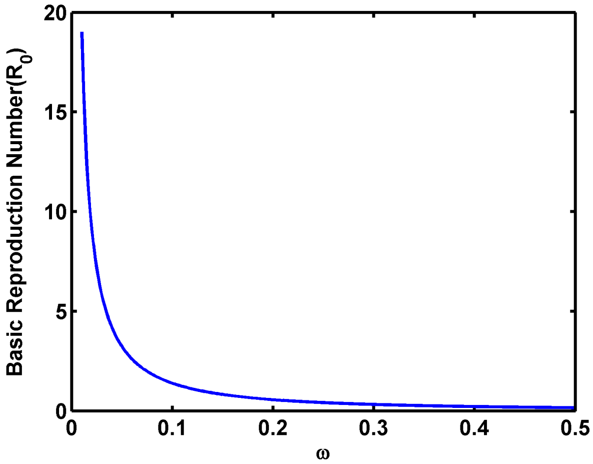

Figure 13: Effect of w on R_0.

Figure 12 shows the effect of varying treatment rates on the basic reproduction number. From simulation, we observed that increasing the treatment rate reduces the basic reproduction number R_0, resulting eventually to disease elimination. Figure 13 illustrates the influence of mosquito death rate on the reproduction number R_0. As mosquito mortality rises, R_0 decreases, a trend clearly observed in the simulation results.

5 Conclusion

We studied SEITR-SEI model of malaria transmission dynamics disease incorporating five compartments on human population and three compartments on mosquito vector population, modeled as a system of ordinary differential equations. The positivity and boundedness property of the system of non-linear differential equations have been shown, ensuring the biological validity. After the non-dimensionalization of the model equations, we analyzed the stability analysis of the model by calculating the basic reproduction number R_0 using the method of next generation matrix. The analysis reveals that disease free equilibrium point of the model is unstable when $R_0 > 1$, whereas it is locally asymptotically stable when $R_0 < 1$. We also performed the sensitivity analysis of the model parameters on basic reproduction number R_0 and found that the most sensitivity parameters are biting rate ϕ (positive) of mosquito and the death rate w (negative) of mosquito. The disease transmission increases with the increase of biting rate of mosquito and the disease transmission decreases with the increasing death rate of mosquito.

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