Optimal control of a two-group malaria transmission model with vaccination

S.Y. Tchoumi[1,2]*, C.W. Chukwu [3], M.L. Diagne [4], H. Rwezaura [5], M.L. Juga [6], J.M. Tchuenche [7]
[1] Department of Mathematics and Computer Sciences ENSAI,
University of NGaoundere, P. O. Box 455 Ngaoundere, Cameroon
[2] Department of Mathematics and Applied Mathematics,
University of Pretoria, South Africa
[3] Division of Infectious Diseases and Global Public Health,
University of California, San Diego, CA, USA
[4] Departement de Mathematiques, UFR des Sciences et Technologies,
Universite de Thies, Thies, Senegal
[5] Mathematics Department, University of Dar es Salaam, P.O. Box 35062,
Dar es Salaam, Tanzania
[6] Department of Mathematics and Applied Mathematics,
University of Johannesburg, Auckland Park, 2006, South Africa
[7]School of Computer Science and Applied Mathematics,
University of the Witwatersrand, Private Bag 3, Wits 2050, Johannesburg, South Africa
[8]School of Computational and Communication Sciences and Engineering, Nelson
Mandela African Institution of Science and Technology,
P.O. Box 447, Arusha, Tanzania

Abstract

Malaria is a vector-borne disease that poses major health challenges globally, with the highest burden in children less than 5 years old. Prevention and treatment have been the main interventions measures until the recent groundbreaking highly recommended malaria vaccine by WHO for children below five. A two-group malaria model structured by age with vaccination of individuals aged below 5 years old is formulated and theoretically analyzed. The disease-free equilibrium is globally asymptotically stable when the disease-induced death rate in both human groups is zero. Descarte's rule of signs is used to discuss the possible existence of multiple endemic equilibria. By construction, mathematical models inherit the loss of information that could make prediction of model outcomes imprecise. Thus, a global sensitivity analysis of the basic reproduction number and the vaccination class as response functions using Latin-Hypercube Sampling in combination with partial rank correlation coefficient are graphically depicted. As expected, the most sensitive parameters are related to children under 5 years old. Through the application of optimal control theory, the best combination of interventions measures to mitigate the spread of malaria is investigated. Simulations results show that concurrently applying the three intervention measures, namely: personal protection, treatment, and vaccination of childreen under-five is the best strategy for fighting against malaria epidemic in a community, relative to using either single or any dual combination of intervention(s) at a time.

Keywords: Malaria, Vaccination, Optimal control, Sensitivity analysis

1 Introduction

Malaria is a vector-borne disease transmitted during blood meal by infectious Anopheles mosquitoes via insertion of sporozoites in the blood of susceptible humans [24]. The worldwide casualties of malaria are huge, particularly in sub-Sahara Africa, and especially in the children population [4]. The World Health Organization (WHO) estimated about 241 million malaria cases globally in 2020 that resulted in 627,000 deaths. The tropical

*Corresponding author S.Y. Tchoumi email: sytchoumi83@gmail.com

and sub-tropical regions (mainly Africa) carry a disproportionately high share of the global malaria burden with as much as 95% of malaria cases, 96% of malaria deaths with about 80% of these deaths are the children less than 5 years of age [3].

Malaria is a severe life-threatening vector-borne disease, and with the ongoing COVID-19 pandemic, malaria morbidity and mortality could increase [29]. While several prevention and therapeutic measures have been implemented to fight against this deadly disease, the recent groundbreaking malaria vaccine for children now recommended by the WHO [4] after successful pilots in Ghana, Kenya, and Malawi, is expected to help strengthen the fight against malaria infection [1]. Also, the development of Transmission Blocking Drugs (TBDs) conferring protection against malaria will play a significant role in mitigating morbidity and mortality in malaria-prone regions [33]. It is expected that the widespread use of the RTS malaria vaccine (trade name Mosquirix), a recombinant protein-based malaria vaccine in children in sub-Saharan Africa and other areas with moderate or high transmission of *Plasmodium falciparum* malaria along with other preventive measures could help mitigate the spread and eventually the eradication of the disease [1].

Since the eighteen century, the development of mathematical models has been critical in to provide framework and understanding of the dynamics of infectious diseases [9, 21, 13]. Several mathematical models of malaria dynamics investigating various aspects of the disease have flourished in the literature [18]. While mosquito's population fluctuates between climatic seasons, seasonal factor tends to impact on the dynamics of infected mosquitoes and human populations in regions with hot climate [18, 28]. Because of mathematical tractability and convenience, though important, we will not account for seasonality in the birth rate of mosquitoes. For several decades, concerted global stringent efforts have been underway to develop effective and safe vaccine for use against malaria in humans [14, 20], with several candidate vaccines targeting different stages of the malaria parasite's lifecycle [32]. An overview of integrated mathematical models for predicting the epidemiologic and economic effects of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria both at the individual and population level has been reported in [26, 6]. It is noted that these models provide a unique platform for predicting both the short- and long-term effects of malaria vaccines on the burden of disease, allowing for the temporal dynamics of effects on immunity and transmission. With mathematical models being increasingly used to inform decisions throughout product development pathways from pre-clinical studies to country implementation of novel health interventions, Galactionova et al., [16] illustrate the utility of simulation approaches by reviewing malaria vaccine modelling studies. A mathematical model of vaccine combination adapted to murine malaria studies based on simple probabilistic assumptions was developed in [6].

Transmission-blocking vaccines of malaria have been investigated in [34, 27] where as expected, vaccination has a positive impact on reducing the disease burden, while malaria could be controlled if the duration of efficacy is in the order of a human life-span [22] . Public health impact of dynamics model of a transmission-blocking alongside existing interventions suggests that school-aged children are an attractive population to target for vaccination [11]. That is, benefit of vaccination distributed across the population averts the greatest number of cases in younger children. Even an imperfect anti-malaria vaccine (with a modest efficacy and coverage rate) can lead to effective disease control [30]. Handari et al., [17] analyze an optimal control model of malaria incorporating pre-erythrocytic vaccine and transmission-blocking treatment.

Previous studies have been theoretical because there was no approved/licensed malaria vaccine, and also vaccination was applied to the entire population. As predicted in [11, 19], the first approved malaria vaccine is for children age five and below, and consequently, we propose a mathematical model of malaria transmission dynamic by extending our previous work [29], incorporating vaccination in the class of children less than 5 years old, but with no seasonal birth rate [18]. The population of children 5 months (minimum age to take the vaccine) to 5 years are vaccinated at a certain rate. The vaccinated class comprises fully vaccinated children (i.e., those who have taken all the 4 doses of the S/AS01 (RTS,S) vaccine). It is important to note that in [29], the authors studied a two-group malaria model structured by age with no vaccination, while herein, while herein, to realistically capture what is currently know about the state of the vaccine development, we incorporate vaccination for children less than five years old only to capture the recently approved children vaccine. To the best of our knowledge, this is the first mathematical model investigating the impact of the newly approved children malaria vaccine on the dynamics of the disease.

Here is the outline of the rest of the paper. The mathematical model of our proposed malaria model with vaccination of children under five years old with no seasonality is formulated in Section 2.1. Theoretical analyses of the model using the fundamental theory of dynamical systems is carried out in Section 3. In Section 4, we formulate an optimal control problem to investigate the impact of the optimal control strategy on mitigating the

spread of the disease. Conditions for the existence of optimal control and the optimality system are established using the Pontryagin's Maximum Principle. Numerical simulations along with global sensitivity analysis using the vaccinated class as our response variable are carried out in Section 5. while Section 6 is the conclusion.

2 Malaria model without control

2.1 Model formulation

A deterministic compartmental modeling approach is used to describe the disease transmission dynamics. The model flow is a susceptible-vaccinated-exposed-infected-recovered-susceptible $SVEI(R)S$ malaria model in the human population, and SEI in the mosquitoes population. Susceptibles (S_e) under 5 years old are recruited at the constant rate Λ_e and can die naturally at the rate μ_h, or grow to become susceptible over 5 years old at the rate ξ, becoming vaccinate (V_e) at the rate ϑ_e, or infected (E_e) after a bite from an infectious mosquito with a strength of infection λ_e. After a latency period $\frac{1}{\sigma_e}$, infected individuals become infectious (I_e), they can recover and become susceptible again at the rate ω_e, or die naturally at the rate μ_h or as a result of an illness at rate d_1. Entry into susceptible humans over 5 years old (S_a) comes from the growth of susceptible humans under 5 years old, who can die naturally at the rate μ_h, become infected (E_a) with the infection strength equal to λ_a. Infected individuals become infectious (I_a) at the rate σ_a or die naturally at the rate μ_h. An infectious over 5 years recovers at the rate ω_a and becomes susceptible (S_a), or recovered (R_a) with probability $1-p$ and p respectively, or dies naturally at the rate μ_h or due to illness at rate d_2. A treated human over 5 years old can die at rate μ_h, or lose immunity at rate δ_a to become susceptible. Similarly, following an infectious bite, susceptible mosquitoes (S_v) can become infected (E_v) with the strength of the infection λ_v before becoming infectious themselves (I_v) at rate σ_v. Mosquitoes do not recover from malaria, they all die naturally at the rate μ_v. The schematic flow diagrams of human and mosquito components of the model are depicted in Figures 1 and 2.1.

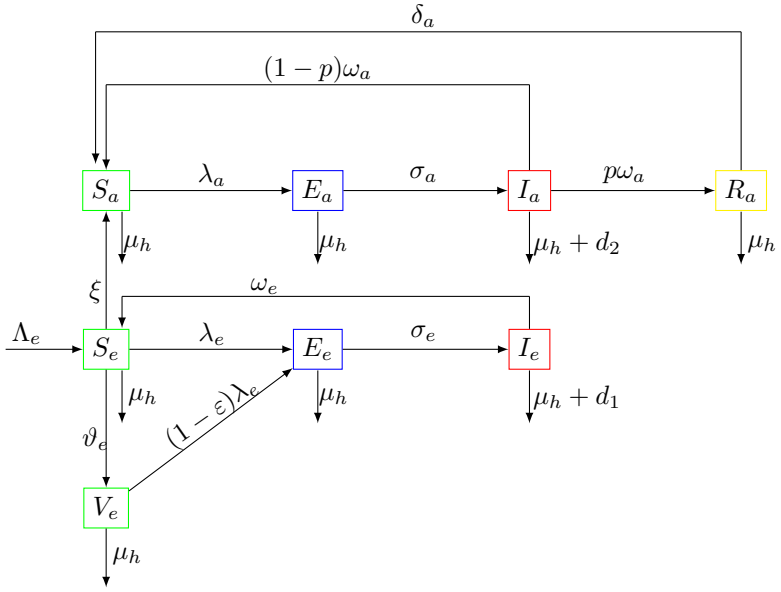


Figure 1: Model flow diagram of the human component of the model

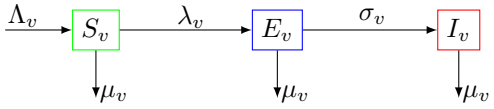


Figure 2: Model flow diagram of the mosquito component of the model

2.2 The Model

The variables and parameters values of the model are presented in the following Tables 1 and 2, respectively.

Table 1: Variable of model

Variable	Description
Humans	
S_e	Population of susceptible humans under 5 years old
V_e	Population of vaccinated humans under 5 years old
E_e	Population of infected humans under 5 years old
I_e	Population of infectious humans under 5 years old
S_a	Population of humans over 5 years old
E_a	Population of infected humans over 5 years old
I_a	Population of infectious humans over 5 years old
R_a	Population of recovered humans over 5 years old
Mosquitoes	
S_v	Population of susceptible mosquitoes
E_v	Population of infected mosquitoes
I_v	Population of infectious mosquitoes

Table 2: Model parameter

Parameter	Description
b_1	Average biting rate of mosquitoes on susceptible humans over 5 years old
b_2	Average biting rate of mosquitoes on susceptible humans under 5 years old
Λ_e	Recruitment rate of humans under 5 years old
σ_e	Progression rate from exposed to infectious for humans under 5 years old
ω_e	Recovery rate of infectious humans under 5 years old
ϑ_e	Vaccination rate of susceptible humans under 5 years old
ε	Vaccination efficacy
β_e	Probability of infection of susceptible humans under 5 years old per mosquito bite
d_1	Disease-induced mortality rate for humans under 5 years old
ξ	Maturation rate for human under 5 years old
σ_a	Progression rate from exposed to infectious for humans over 5 years old
ω_a	Recovery rate of infectious humans over 5 years old
u	Proportion of infectious humans over 5 years old that becomes immune
β_a	Probability of infection of susceptible humans over 5 years old per mosquito bite
δ_a	Rate of loss of natural immunity for humans over 5 years old
μ_h	Natural death rate of humans
d_2	Disease-induced mortality rate for humans over 5 years old
Λ_v	Birth rate of adult mosquitoes
σ_v	Progression rate from exposed to infectious mosquitoes
β_v	Probability of infection of susceptible vectors per mosquito bite of the infected human
μ_v	Natural death rate of mosquitoes

Based on our model description and assumptions, we establish the following system of non-linear system of ordinary differential equations.

$$
\begin{cases}
S_e' &= \Lambda_e + \omega_e I_e - (\lambda_e + \vartheta_e + \xi + \mu_h) S_e, \\
V_e' &= \vartheta_e S_e - ((1-\varepsilon)\lambda_e + \mu_h) V_e, \\
S_a' &= \xi S_e + u\omega_a I_a + \delta_a R_a - (\lambda_a + \mu_h) S_a, \\
E_e' &= \lambda_e (S_e + (1-\varepsilon) V_e) - (\sigma_e + \mu_h) E_e, \\
E_a' &= \lambda_a S_a - (\sigma_a + \mu_h) E_a, \\
I_e' &= \sigma_e E_e - (\omega_e + \mu_h + d_1) I_e, \\
I_a' &= \sigma_a E_a - (\omega_a + \mu_h + d_2) I_a, \\
R_a' &= (1-u)\omega_a I_a - (\delta_a + \mu_h) R_a, \\
S_v' &= \Lambda_v - (\lambda_v + \mu_v) S_v, \\
E_v' &= \lambda_v S_v - (\sigma_v + \mu_v) E_v, \\
I_v' &= \sigma_v E_v - \mu_v I_v,
\end{cases} \tag{1}
$$

with initial conditions

$$
(S_e(0), V_e(0), S_a(0), S_v(0), E_e(0), E_a(0), E_v(0), I_e(0), I_a(0), I_v(0), R_a(0)) \in \mathbb{R}_+^{11}
$$

.

The forces of infections are given by

$$
\lambda_e = \frac{b_2 \beta_e}{N_h} I_v, \ \lambda_a = \frac{b_1 \beta_a}{N_h} I_v, \ \lambda_v = \frac{\beta_v [b_2 I_e + b_1 I_a]}{N_h}.
$$

3 Model Analysis

3.1 Existence, uniqueness and positivity of solutions

The functions on the right-hand side of the system (1) are Lipschitz continuous, therefore by Picard's existence Theorem, the system (1) has a solution.

Theorem 3.1 *The solutions of the model system (1) with non-negative initial conditions are all non-negative.*

Proof. Assume that there exists a time $\tilde{t}$ such that $S_e(\tilde{t}) = 0$, $S_e'(\tilde{t}) < 0$, $S_e(t) > 0$, $S_a(t) > 0$, $I_e(t) > 0$, $I_a(t) > 0$, $V_e(t) > 0$, $E_e(t) > 0$, $E_a(t) > 0$, $E_v(t) > 0$, $R_a(t) > 0$, $S_v(t) > 0$, $I_v(t) > 0$, for $0 < t < \tilde{t}$. From the first equation of (1), we have

$$
\frac{dS_e(\tilde{t})}{dt} = \Lambda_e + w_e I > 0.
$$

This contradicts the assumption that $S_e'(\tilde{t}) < 0$. Therefore $S(t)$ is positive.
Similarly, $S_a(t)$, $I_e(t)$, $I_a(t)$, $V_e(t)$, $E_e(t)$, $E_a(t)$, $E_v(t)$, $R_a(t)$, $S_v(t)$, $I_v(t)$ are all positive. ∎

Theorem 3.2 *Solutions the model system (1) are bounded in the invariant region*

$$
\Omega = \left\{ (S_e, S_a, I_e, I_a, V_e, E_e, E_a, E_v, R_a, S_v, I_v,) \in \mathbb{R}_+^{11} : N_h(t) \leq \frac{\Lambda_e}{\mu_h}, \ N_v(t) \leq \frac{\Lambda_v}{\mu_v} \right\}.
$$

Proof. Given $N_h(t) = S_a(t) + S_e(t) + I_e(t) + I_a(t) + V_e(t) + E_e(t) + E_a(t) + R_a(t)$ and $N_v(t) = +E_v(t) + S_v(t) + I_v(t)$.

$$
\begin{aligned}
\frac{dN_h}{dt} &= (\Lambda_e - \mu_h N_h) - (d_1 I_e + d_2 I_a), \\
&\leq \Lambda_e - \mu_h N_h.
\end{aligned}
$$

Solving the differential inequality, we obtain

$$
N_h(t) \leq \frac{\Lambda_e}{\mu_h} + \left(\frac{\Lambda_e}{\mu_h} - N_h(0) \right) \exp(-\mu_h t).
$$

Therefore,

$$
\limsup_{t \longrightarrow \infty} N_h(t) = \frac{\Lambda_e}{\mu_h}.
$$

Since $N_h(t) = S_a(t)+S_e(t)+I_e(t)+I_a(t)+V_e(t)+E_e(t)+E_a(t)+R_a(t)$, it follows that $S_e(t) \leq \frac{\Lambda_e}{\mu_h}$, $S_a(t) \leq \frac{\Lambda_e}{\mu_h}$, $E_e(t) \leq \frac{\Lambda_e}{\mu_h}$, $E_a(t) \leq \frac{\Lambda_e}{\mu_h}$, $I_e(t) \leq \frac{\Lambda_e}{\mu_h}$, $I_a(t) \leq \frac{\Lambda_e}{\mu_h}$, $V_e(t) \leq \frac{\Lambda_e}{\mu_h}$, $R_a(t) \leq \frac{\Lambda_e}{\mu_h}$.

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v.$$

Thus, the solution of this differential equation is

$$N_v(t) = \frac{\Lambda_v}{\mu_v} - \left(\frac{\Lambda_v}{\mu_v} - N_v(0)\right) \exp\left(-\mu_v t\right).$$

Therefore,

$$\limsup_{t \longrightarrow \infty} N_v(t) = \frac{\Lambda}{\mu_v},$$

and it follows that $S_v(t) \leq \frac{\Lambda_v}{\mu_v}$, $E_v(t) \leq \frac{\Lambda_v}{\mu_v}$ and $I_v(t) \leq \frac{\Lambda_v}{\mu_v}$. ■

In what follows, for simplicity, let $k = (\vartheta_e + \xi + \mu_h)$, $k_0 = (\sigma_e + \mu_h)$, $k_1 = (\sigma_a + \mu_h)$, $k_2 = (\omega_e + \mu_h + d_1)$, $k_3 = (\omega_a + \mu_h + d_2)$, $k_4 = (\mu_h + \delta_a)$, and $k_5 = (\sigma_v + \mu_v)$.

3.2 Disease-free equilibrium and basic reproduction number

We first show the existence of a trivial disease-free equilibrium (DFE) for our malaria model without control (MMWC) which is used in computing the basic reproduction number. The MMWC DFE is

$$\mathcal{M}^0 = \left(S_e^0, V_e^0, S_a^0, S_v^0, E_e^0, E_a^0, E_v^0, I_e^0, I_a^*, I_v^*, R_a^*\right) = \left(\frac{\Lambda_e}{k}, \frac{\vartheta_e \Lambda_e}{\mu_h k}, \frac{\xi \Lambda_e}{\mu_h k}, \frac{\Lambda_v}{\mu_v}, 0, 0, 0, 0, 0, 0, 0\right).$$

To calculate the basic reproduction number, we apply the next generation method in [31]. We now have that

$$\mathcal{F} = \begin{pmatrix} \lambda_e(S_e + (1-\varepsilon)V_e) \\ \lambda_a S_a \\ \lambda_v S_v \\ 0 \\ 0 \\ 0 \end{pmatrix}, \text{ and } \mathcal{V} = \begin{pmatrix} k_0 E_e \\ k_1 E_a \\ k_5 E_v \\ k_2 I_e - \sigma_e E_e \\ k_3 I_a - \sigma_a E_a \\ \mu_v I_v - \sigma_v E_v \end{pmatrix}$$

$$\mathcal{F} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\beta_e b_2 \left(k + (1-\varepsilon)\vartheta_e\right)}{k} \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_a b_1 \xi}{k} \\ 0 & 0 & 0 & \frac{\beta_v b_2 \Lambda_v \mu_h}{\mu_v \Lambda_e} & \frac{\beta_v b_1 \Lambda_v \mu_h}{\mu_v \Lambda_e} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \text{ and } \mathcal{V} = \begin{pmatrix} k_0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_5 & 0 & 0 & 0 \\ -\sigma_e & 0 & 0 & k_2 & 0 & 0 \\ 0 & -\sigma_a & 0 & 0 & k_3 & 0 \\ 0 & 0 & -\sigma_v & 0 & 0 & \mu_v \end{pmatrix}.$$

Hence,

$$\mathcal{R}_C^m = \sqrt{\frac{\Lambda_v \beta_v \mu_h \sigma_v \left[b_2^2 \beta_e k_1 k_3 \sigma_e (\mu_h + (1-\varepsilon)\vartheta_e) + b_1^2 \beta_a k_0 k_2 \sigma_a \xi\right]}{\Lambda_e \mu_v^2 k k_0 k_1 k_2 k_5}}.$$

3.3 Global stability of the DFE

To prove the global asymptotically stability (GAS) of the DFE, we use the approach as described in [10]. We then re-write the malaria model (1) as follows

$$\begin{cases} \frac{dX}{dt} = F(X, I), \\ \frac{dI}{dt} = \mathcal{G}(X, I), \quad \mathcal{G}(X, 0) = 0, \end{cases} \tag{2}$$

in which $X = \left(S_e, V_e, S_a, R_a, S_v\right) \in \mathbb{R}^5$ and $I = \left(E_e, E_a, E_v, I_e, I_a, I_v\right) \in \mathbb{R}^6$. We note here that X and I represents the classes of the un-infectious and infectious individuals, respectively. Let the DFE from Section 3.2 to be

$$\mathcal{M}^0 = (X_0, 0) = \left(S_e^0, V_e^0, S_a^0, R_a, {}^0\, S_v^0, E_e^0, E_a^0, E_v^0, I_e^0, I_a^0, I_v^0\right) = \left(\frac{\Lambda_e}{k}, \frac{\vartheta_e \Lambda_e}{\mu_h k}, \frac{\xi \Lambda_e}{\mu_h k}, 0, \frac{\Lambda_v}{\mu_v}, 0, 0, 0, 0, 0, 0\right).$$

For the model to be GAS at $\mathcal{M}^0$, it needs to satisfy the following conditions as adopted from [10], which are

$\mathcal{C}_1$) Local stability is guaranteed at $\mathcal{M}^*$ whenever $\mathcal{R}_C^m < 1$.

$\mathcal{C}_1$) At $\dfrac{dX}{dt} = F(X_0, 0)$ the DFE is globally asymptotically stable.

$\mathcal{C}_3$) $\mathcal{G}(X, I) = \mathcal{A}I - \hat{\mathcal{G}}(X, I)$, $\hat{\mathcal{G}}(X, I) \geq 0$ for $(X, I) \in \Omega$, where $\mathcal{A} = \mathcal{D}_I \mathcal{G}(\mathcal{M}^0)$ is an Metzler matrix, and Ω is the model biologically feasible region defined earlier.

Theorem 3.3 *If the disease-induced rate is zero ($d_1 = d_2 = 0$), then the disease-free equilibrium $\mathcal{M}^0$ is globally asymptotically (GAS) stable when $\mathcal{R}_C^m < 1$.*

Proof. To prove that the DFE is GAS when $\mathcal{R}_C^m < 1$, we have to verify the conditions $\mathcal{C}_1$ to $\mathcal{C}_3$.

Using the approach in [31], we obtain that the DFE $\mathcal{M}^0$ is LAS when $\mathcal{R}_C^m < 1$, so the condition $\mathcal{C}_1$ is verified.

Next, we re-write the model system (1) in the form given in (2) as

$$\frac{dX}{dt} = F(X, I) = \begin{pmatrix} \Lambda_e + \omega_e I_e - (\lambda_e + k) S_e \\ \vartheta_e S_e - ((1-\varepsilon)\lambda_e + \mu_h) V_e \\ \xi S_e + u \omega_a I_a + \delta_a R_a - (\lambda_a + \mu_h) S_a \\ \Lambda_v - (\lambda_v + \mu_v) S_v, \\ (1-u)\omega_a I_a - k_4 R_a \end{pmatrix}, \text{ and } \frac{dI}{dt} = G(X, I) = \begin{pmatrix} \lambda_e (S_e + (1-\varepsilon) V_e) - k_0 E_e \\ \lambda_a S_a - k_1 E_a \\ \lambda_v S_v - k_5 E_v \\ \sigma_e E_e - k_2 I_e \\ \sigma_a E_a - k_3 I_a \\ \sigma_v E_v - \mu_v I_v \end{pmatrix}. \tag{3}$$

We have

$$\frac{dX}{dt} = F(X_0, 0) \Leftrightarrow \begin{cases} \dot{S}_e = \Lambda_e - k S_e, \\ \dot{V}_e = \vartheta_e S_e - \mu_h V_e, \\ \dot{S}_a = \xi S_e + \delta_a R_a - \mu_h S_a, \\ \dot{R}_a = -k_4 R_a, \\ \dot{S}_v = -\mu_v S_v. \end{cases} \tag{4}$$

This equation has a unique equilibrium point $\left(\dfrac{\Lambda_e}{k}, \dfrac{\vartheta_e \Lambda_e}{\mu_h k}, \dfrac{\xi \Lambda_e}{\mu_h k}, 0, \dfrac{\Lambda_v}{\mu_v}\right)$ which is globally asymptotically stable.

Therefore, the condition $\mathcal{C}_2$ is satisfied.

Linearizing the second matrix in equation (3) gives the Metzler Matrix

$$\mathcal{A} = \mathcal{D}_Z \mathcal{G}(\mathcal{M}^*) = \begin{pmatrix} -k_0 & 0 & 0 & 0 & 0 & \dfrac{\beta_e b_2}{N_h^*}(S_e^* + (1-\varepsilon) V_e^*) \\ 0 & -k_1 & 0 & 0 & 0 & \dfrac{\beta_a b_1}{N_h^*} S_a^* \\ 0 & 0 & -k_5 & \dfrac{\beta_v b_1}{N_h^*} S_v^* & \dfrac{\beta_v b_2}{N_h^*} S_v^* & 0 \\ \sigma_e & 0 & 0 & -k_2 & 0 & 0 \\ 0 & \sigma_a & 0 & 0 & -k_3 & 0 \\ 0 & 0 & \sigma_v & 0 & 0 & -\mu_v \end{pmatrix}.$$

Computing $\hat{\mathcal{G}}(X, Z)$ and after some algebraic simplifications, we have

$$\hat{\mathcal{G}}(X, I) = \mathcal{A}I - \mathcal{G}(X, I) = \begin{pmatrix} \beta_e b_2 I_v \left[\dfrac{S_e^*}{N_h^*} - \dfrac{S_e}{N_h} + (1-\varepsilon)\left(\dfrac{V_e^*}{N_h^*} - \dfrac{V_e}{N_h}\right)\right] \\ \beta_a b_1 I_v \left[\dfrac{S_a^*}{N_h^*} - \dfrac{S_a}{N_h}\right] \\ \beta_v \left(b_2 I_e + b_1 I_a\right) \left[\dfrac{S_v^*}{N_h^*} - \dfrac{S_v}{N_h}\right] \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Thus,

$$\hat{\mathcal{G}}(X,I) \geq \begin{pmatrix} \beta_e b_2 I_v \left[S_e^* + (1-\varepsilon)V_e^*\right]\left(\dfrac{1}{N_h^*} - \dfrac{1}{N_h}\right) \\ \beta_a b_1 I_v S_a^* \left(\dfrac{1}{N_h^*} - \dfrac{1}{N_h}\right) \\ \beta_v \left(b_2 I_e + b_1 I_a\right) S_v^* \left(\dfrac{1}{N_h^*} - \dfrac{1}{N_h}\right) \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Since for $\left(\dfrac{1}{N_h^*} - \dfrac{1}{N_h}\right) = \dfrac{N_h - N_h^*}{N_h N_h^*}$, when $d_1 = d_2 = 0$, $N_h(t) - N_h^* = \left(\dfrac{\Lambda_e}{\mu_h} - N_h(0)\right)\exp\left(-\mu_h t\right)$ is positive, and we obtain $\hat{\mathcal{G}}(X,I) \geq 0$. The condition $\mathcal{C}_3$ is satisfied. We can conclude that if $d_1 = d_2 = 0$, then, the DFE is GAS when $\mathcal{R}_C^m < 1$.

■

Remark 3.1 *When the disease-induced death rate is not zero, the condition $\mathcal{R}_C^m < 1$ is not sufficient for the global stability of disease-free equilibrium and the phenomenon of backward bifurcation may occur. In this case, to mitigate the spread of the disease, it is necessary to reduce $\mathcal{R}_C^m$ to less than another threshold, say $\mathcal{R}_C^{\#} < \mathcal{R}_C^m < 1$.*

3.4 Existence of the endemic equilibrium

By setting the left-hand side of the model system 1 to zero and solving it, we obtain the endemic equilibrium point as follows:

$$S_e^* = \frac{\left(\Lambda_v^* b_2 \beta_e (1-\varepsilon)\lambda_v^* \sigma_v + N_h^* k_5 \lambda_v^* \mu_h \mu_v + N_h^* k_5 \mu_h \mu_v^2\right)\Lambda_e N_h^* k_0 k_2 k_5 (\lambda_v^* + \mu_v)\mu_v}{\Lambda_e N_h^* b_2 \beta_e \sigma_v \lambda_v^* \left[k_5 \mu_v (\lambda_v^* + \mu_v)((1-\varepsilon)(k k_0 k_2 - \omega_e \sigma_e \vartheta_e) + \mu_h (k_0 k_2 - \omega_e \sigma_e))\right] + k_6}, \tag{5}$$

where $k_6 = (\Lambda_v b_2 \beta_e \sigma_v \lambda_v)^2 (1-\varepsilon)(k_0 k_2 - \omega_e \sigma_e) + N_h^* k k_0 k_2 k_5 \mu_h \mu_v^2 (\lambda_v + \mu_v)^2$, and $N_h^* = \dfrac{\Lambda_e}{\mu_h}$.

We also have

$$\begin{gathered} S_v^* = \frac{\Lambda_v}{\lambda_v + \mu_v}, \qquad E_v^* = \frac{\lambda_v S_v^*}{k_5}, \qquad I_v^* = \frac{\sigma_v E_v^*}{\mu_v}, \\ \lambda_e^* = \frac{b_2 \beta_e I_v^*}{N_h^*}, \quad V_e^* = \frac{\vartheta S_e^*}{(1-\varepsilon)\lambda_e^* + m u_h}, \quad E_e^* = \frac{\lambda_e^*(S_e^* + (1-\varepsilon)V_e^*)}{k_0}, \quad I_e = \frac{\sigma_e E_e^*}{k_2} \end{gathered}, \tag{6}$$

$$S_a^* = \frac{\Lambda_e S_e^* k_1 k_3 k_4 k_5 \xi (\lambda_v^* + \mu_v)}{\mu_v \left[\Lambda_e k_1 k_3 k_4 k_5 \mu_v (\lambda_v^* + \mu_v) + \Lambda_v b_1 \beta_a \sigma_v \lambda_v^* (k_1 k_3 k_4 - \delta_a \omega_a \sigma_a - u \omega_a \sigma_a \mu_h)\right]}, \tag{7}$$

$$\lambda_a^* = \frac{b_1 \beta_a I_v^*}{N_h^*}, \quad E_a^* = \frac{\lambda_a^* S_a^*}{k_1}, \quad I_a^* = \frac{\sigma_a E_a^*}{k_3}, \quad R_a^* = \frac{(1-u)\omega_a I_a^*}{k_4}. \tag{8}$$

Substituting the expressions for I_a^* and I_e^* into the expression for λ_v, we obtain the polynomial

$$a_3 \lambda_v^{*3} + a_2 \lambda_v^{*2} + a_1 \lambda_v^* + a_0, \tag{9}$$

where the expressions of a_0, a_1, a_2 and a_3 are given in the Appendix.

Because the model monitors human populations, all associated state variables should be non-negative for all time $t \geq 0$. We therefore use Descarte's rule of signs to discuss the existence of possible positive roots of equation (9). The results are summarized in Table 3

Case	a_3	a_2	a_1	a_0	Possible positive roots	R_0 Condition
(1)	+	+	+	−	1	$R_0 < 1$
(2)	+	+	+	+	0	$R_0 > 1$
(3)	+	+	−	−	1	$R_0 < 1$
(4)	+	+	−	+	0 or 2	$R_0 > 1$
(5)	+	−	+	−	1 or 3	$R_0 < 1$
(6)	+	−	+	+	0 or 2	$R_0 > 1$
(7)	+	−	−	−	1	$R_0 < 1$
(8)	+	−	−	+	0 or 2	$R_0 > 1$
(9)	−	+	+	−	0 or 2	$R_0 < 1$
(10)	−	+	+	+	1	$R_0 > 1$
(11)	−	+	−	−	0 or 2	$R_0 < 1$
(12)	−	+	−	+	1 or 3	$R_0 > 1$
(13)	−	−	+	−	0 or 2	$R_0 < 1$
(14)	−	−	+	+	1	$R_0 > 1$
(15)	−	−	−	−	0	$R_0 < 1$
(16)	−	−	−	+	1	$R_0 > 1$

Table 3: Number of possible positive roots of equation (9) using Descarte's rule of signs.

The following remark summarizes the results in Table 3

Remark 3.2
- *If all the coefficients of the polynomial* (9) *have the same signs, then the model system* (1) *has no endemic equilibrium point,*
- *If* $R_0 \neq 1$, *then the system has zero, one, two or three endemic equilibrium points,*
- *If* $R_0 = 1$, *then the system has either zero, one or two endemic equilibrium points.*

The last two conditions above imply that the model system (1) could exhibit the phenomenon of backward/subcritical bifurcation, when a stable DFE co-exists with a stable endemic equilibrium. This is an epidemiological situation in which the classical requirement of having the basic reproduction number less than unity although necessary is not sufficient to eliminate the disease.

4 Optimal control model

The application of optimal control enables us to forecast or choose the best scenario that if well implemented could help mitigate the spread of the disease. Thus, to investigate the potential impact of the implemented intervention measures, the following control variables are incorporated into the model system 1:

$c_1(t)$ representing the use of personal protection measures to prevent mosquitoes bites during the day and the night such as the use of insecticide-treated nets, application of repellents to skin or spraying of insecticides,

$c_2(t)$ representing the treatment, and

$c_3(t)$ representing the use of vaccination to prevent malaria,

as follows

$$\begin{cases} S_e' &= \Lambda_e + c_2\omega_e I_e - ((1-c_1)\lambda_e + c_3\vartheta_e + \xi + \mu_h)S_e, \\ V_e' &= c_3\vartheta_e S_e - ((1-c_1)(1-\varepsilon)\lambda_e + \mu_h)V_e, \\ S_a' &= \xi S_e + (1-p)c_2\omega_a I_a + \delta_a R_a - ((1-c_1)\lambda_a + \mu_h)S_a, \\ E_e' &= (1-c_1)\lambda_e(S_e + (1-\varepsilon)V_e) - (\sigma_e + \mu_h)E_e, \\ E_a' &= (1-c_1)\lambda_a S_a - (\sigma_a + \mu_h)E_a, \\ I_e' &= \sigma_e E_e - (c_2\omega_e + \mu_h + d_1)I_e, \\ I_a' &= \sigma_a E_a - (c_2\omega_a + \mu_h + d_2)I_a, \\ R_a' &= pc_2\omega_a I_a - (\mu_h + \delta_a)R_a, \\ S_v' &= \Lambda_v - ((1-c_1)\lambda_v + \mu_v)S_v, \\ E_v' &= (1-c_1)\lambda_v S_v - (\sigma_v + \mu_v)E_v, \\ I_v' &= \sigma_v E_v - \mu_v I_v. \end{cases} \tag{10}$$

Consider the following quadratic objective functional which measures the cost of the control. This cost includes the above interventions. The the nonlinear objective function is

$$J(c_1, c_2, c_3) = \int_0^T \left[A_1E_e(t) + A_2E_a(t) + A_3I_e(t) + A_4I_(t) + A_5N_v(t) + \frac{w_1}{2}c_1^2 + \frac{w_2}{2}c_2^2 + \frac{w_3}{2}c_3^2\right]dt, \tag{11}$$

where T is the final time, $A_i,\ i = 1, \cdots, 5$ are positive weight constants, $N_v = S_v + +E_v + I_v$ and $w_i,\ i = 1, \cdots, 3$ are weight constants for the strategies and treatments against proliferation of the Malaria. The fact that the controls are linearly in (10) and quadratic in the objective functional allows the Hamiltonian, associated to the optimal control problem to be maximized. Therefore, we seek to find, using the maximum principle of Pontryagin [25], an optimal control $(c_1^*, c_2^*, c_3^*) \in U$ satisfying (10), such that

$$J(c_1^*, c_2^*, c_3^*) = \min\left\{J(c_1, c_2, c_3) \mid (c_1, c_2, c_3) \in U\right\}. \tag{12}$$

The associated pseudo-Hamiltonian is

$$
\begin{aligned}
H &= A_1E_e(t) + A_2E_a(t) + A_3I_e(t) + A_4I_a(t) + A_5N_v(t) + \frac{w_1}{2}c_1^2 + \frac{w_2}{2}c_2^2 + \frac{w_3}{2}c_3^2 \\
&+ \xi_1\Big[\Lambda_e + c_2\omega_eI_e - ((1-c_1)\lambda_e + c_3\vartheta_e + \xi + \mu_h)S_e\Big] \\
&+ \xi_2\Big[c_3\vartheta_eS_e - ((1-c_1)(1-\varepsilon)\lambda_e + \mu_h)V_e\Big) \\
&+ \xi_3\Big[\xi S_e + (1-u)c_2\omega_aI_a + \delta_aR_a - ((1-c_1)\lambda_a + \mu_h)S_a,\Big] \\
&+ \xi_4\Big[(1-c_1)\lambda_e(S_e + (1-\varepsilon)V_e) - (\sigma_e + \mu_h)E_e\Big] \\
&+ \xi_5\Big[(1-c_1)\lambda_aS_a - (\sigma_a + \mu_h)E_a\Big] \\
&+ \xi_6\Big[\sigma_eE_e - (c_2\omega_e + \mu_h + d_1)I_e\Big] \\
&+ \xi_7\Big[\sigma_aE_a - (c_2\omega_a + \mu_h + d_2)I_a\Big] \\
&+ \xi_8\Big[uc_2\omega_aI_a - (\mu_h + \delta_a)R_a\Big] \\
&+ \xi_9\Big[\Lambda_v - ((1-c_1)\lambda_v + \mu_v)S_v\Big] \\
&+ \xi_{10}\Big[(1-c_1)\lambda_vS_v - (\sigma_v + \mu_v)E_v\Big] \\
&+ \xi_{11}\Big[\sigma_vE_v - \mu_vI_v\Big],
\end{aligned} \tag{13}
$$

where the ξ_1, ξ_2, ξ_3, ξ_4, ξ_5, ξ_6, ξ_7, ξ_8, ξ_9, ξ_{10}, ξ_{11} are the associated adjoints for the states $S_e, V_e, S_a, E_e, E_a, I_e, I_a, R_a, S_v, E_v, I_v$. The system of equations is found by taking the appropriate partial derivatives of the Hamiltonian (13) with respect to the associated state variable.

where $\xi_i,\ i = 1, \cdots, 11$ are the adjoint variables satisfying

$$
\begin{aligned}
\xi_1^{'} &= -\frac{\partial \mathbb{H}}{\partial S_e} & \xi_2^{'} &= -\frac{\partial \mathbb{H}}{\partial V_e}, \\
\xi_3^{'} &= -\frac{\partial \mathbb{H}}{\partial S_a} & \xi_4^{'} &= -\frac{\partial \mathbb{H}}{\partial E_e}, \\
\xi_5^{'} &= -\frac{\partial \mathbb{H}}{\partial E_a} & \xi_6^{'} &= -\frac{\partial \mathbb{H}}{\partial I_e}, \\
\xi_7^{'} &= -\frac{\partial \mathbb{H}}{\partial I_a} & \xi_8^{'} &= -\frac{\partial \mathbb{H}}{\partial R_a}, \\
\xi_9^{'} &= -\frac{\partial \mathbb{H}}{\partial Sv} & \xi_{10}^{'} &= -\frac{\partial \mathbb{H}}{\partial E_v}. \\
\xi_7^{'} &= -\frac{\partial \mathbb{H}}{\partial I_v} & &.
\end{aligned} \tag{14}
$$

That is,

$$
\begin{aligned}
\xi_1^{'} &= \lambda_e(1-c_1)(\xi_1-\xi_4)+c_3\vartheta_e(\xi_1-\xi_2)+\xi(\xi_1-\xi_3)+\frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)\\
&+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\frac{(1-\varepsilon)\lambda_e V_e}{N_h}(1-c_1)(\xi_4-\xi_2)+\mu_h\xi_1,\\
\xi_2^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\lambda_e(1-c_1)(1-\varepsilon)(\xi_2-\xi_4)\\
&+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+\mu_h\xi_2,\\
\xi_3^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+(1-c_1)\lambda_a(\xi_3-\xi_5)\\
&+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\mu_h\xi_3,\\
\xi_4^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+\sigma_e(\xi_4-\xi_6)\\
&+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\mu_h\xi_4-A_1,\\
\xi_5^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+\sigma_a(\xi_5-\xi_7)\\
&+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\mu_h\xi_5-A_2,\\
\xi_6^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+c_2\omega_e(\xi_6-\xi_1)\\
&\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\frac{b_2\beta_v S_v}{N_h}(1-c_1)(\xi_9-\xi_{10})+(\mu_h+d_1)\xi_6-A_3,\\
\xi_7^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+\frac{b_1\beta_v S_v}{N_h}(1-c_1)(\xi_9-\xi_{10})\\
&-c_2\omega_a(u\xi_8+(1-u)\xi_3)+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+(c_2\omega_a+\mu_h+d_2)\xi_7-A_4,\\
\xi_8^{'} &= \frac{\lambda_e S_e}{N_h}(1-c_1)(\xi_4-\xi_1)+\frac{\lambda_e V_e}{N_h}(1-c_1)(1-\varepsilon)(\xi_4-\xi_2)+\frac{\lambda_a S_a}{N_h}(1-c_1)(\xi_5-\xi_3)+\delta_a(\xi_8-\xi_3)\\
&+\frac{\lambda_v S_v}{N_h}(1-c_1)(\xi_{10}-\xi_9)+\mu_h\xi_8,\\
\xi_9^{'} &= \lambda_v(1-c_1)(\xi_9-\xi_{10})+\mu_v\xi_9-A_5,\\
\xi_{10}^{'} &= \sigma_v(\xi_{10}-\xi_{11})+\mu_v\xi_{10}-A_5,\\
\xi_{11}^{'} &= \lambda_e S_e(1-c_1)(\xi_1-\xi_4)+\lambda_e V_e(1-\varepsilon)(1-c_1)(\xi_2-\xi_4)+\lambda_a S_a(1-c_1)(\xi_3-\xi_5)+\mu_v\xi_{11}-A_5,
\end{aligned}
$$

Considering the optimality conditions, the Hamiltonian function is differentiated with respect to the control variables resulting in

$$
\begin{aligned}
0 = \frac{\partial H}{\partial c_1} &= w_1 c_1 + (\xi_1 - \xi_4)\lambda_2 S_e + (\xi_2 - \xi_4)\varepsilon\lambda_3 V_e + \xi_4\lambda_e V_e + (\xi_3 - \xi_5)\lambda_a V_a + (\xi_9 - \xi_{10})\lambda_v S_v \\
0 = \frac{\partial H}{\partial c_2} &= w_2 c_2 + (\xi_1 - \xi_6)\omega_e I_e + (\xi_8 - \xi_3)p\omega_a I_a + (\xi_3 - \xi_7)\omega_a I_a. \\
0 = \frac{\partial H}{\partial c_3} &= w_3 c_3 + (\xi_2 - \xi_1)\vartheta_e S_e,
\end{aligned} \tag{15}
$$

on the interior of the control set $\mathcal{U}$. Then, solving for c_1^* (on the interior of the control set) gives

$$
\begin{aligned}
c_1^* &= \frac{\lambda_2 S_e(\xi_4 - \xi_1) + (1-\varepsilon)\lambda_e V_e(\xi_4 - \xi_2) + \lambda_a S_a(\xi_5 - \xi_3) + \lambda_v S_v(\xi_{10} - \xi_9)}{w_1}, \\
c_2^* &= \frac{\omega_e I_e(\xi_6 - \xi_1) + \omega_a I_a(\xi_7 - \xi_3) + u\omega_a I_a(\xi_3 - \xi_8)}{w_2}, \\
c_3^* &= \frac{\vartheta_e S_e(\xi_1 - \xi_2)}{w_3}
\end{aligned} \tag{16}
$$

Using the bounds on the controls, we obtain the characterization, and hence

$$
\begin{aligned}
c_1^* &= min\left\{b, max\left[a, -\frac{(\xi_1 - \xi_4)\lambda_2 S_e + (\xi_2 - \xi_4)\varepsilon\lambda_3 V_e + (\xi_3 - \xi_5)\lambda_a V_a + (\xi_9 - \xi_{10})\lambda_v S_v}{w_1}\right\}\right., \\
c_2^* &= min\left\{d, max\left[c, -\frac{(\xi_1 - \xi_6)\omega_e I_e + (\xi_8 - \xi_3)p\omega_a I_a + (\xi_3 - \xi_7)\omega_a I_a}{w_2}\right\}\right. \\
c_3^* &= min\left\{d, max\left[c, -\frac{(\xi_2 - \xi_1)\vartheta_e S_e}{w_3}\right\}\right..
\end{aligned}
$$

5 Numerical simulations

Graphical representations using the model parameter values in Table 4 are illustrated below. Because when $c_1(t) = 0$ there is no vaccination at all, we set the lower bound of the controls to 0 and the upper bound to 1, that is, $a = c = 0$, $b = d = 1$. Thus, $0 \leq c_1(t), c_2(t) \leq 1$. The model parameter values in Table Table 4 are taken from the literature, or assumed for illustrative purpose.

Table 4: Model parameter values

Parameter	Value/units	Ref.
b_1	[0.1,0.75]	[7]
b_2	[0.1,0.5342]	[7]
Λ_e	1520	[15]
σ_e	0.10333	[5]
ω_e	0.0027	[15]
ϑ_e	0.0085	Assumed
ε	[0,1]	Varried
β_e	0.471	[29]
d_1	$\frac{274,000}{409,000 * 635} = 0.00183542$	[2]
ξ	0.00000986	[5]
σ_a	0.08333	[5]
ω_a	0.0027	[15]
u	0.01	Assumed
β_a	0.471	[29]
δ_a	0.0000174	[15]
μ_h	0.00004	[5]
d_2	$\frac{627000}{24100000 * 365}$=0.0000071278	[2]
Λ_v	5000	[15]
σ_v	0.091	[5]
β_v	0.833	[5]
μ_v	0.05	[5]

5.1 Global sensitivity analysis of R_C and V_e

This subsection is devoted to the global sensitivity analyses of the model reprodcution number R_C and the vaccination compartment V_e. The threshold R_C is chosen because of its crucial role in forecasting the spread/persistence of an epidemic, while the vaccination class is chosen considering *'prevention is better than cure'*. In general, mathematical models possess some uncertainties due to variations such as demography and geographical location incorporated during the model formulation. Due to these uncertainties, we have an inherent epistemic uncertainty in our model parameterization for those estimated or calculated [23]. For this reason, we will investigate these uncertainties in the model parameters by applying the method of Latin-Hyper-Cube Sampling (LHS) with a combination of partial rank correlation coefficient (PRCC) to bypass unbiased estimates of the parameters [23, 8]. This method takes an input variable and generates an output containing the tornado and/or scatter plots [8]. More details on this can be found in [18, 12] and the references therein. Following [8], parameters with PRCC value output less than -0.5 or greater than 0.5 are assumed to be most sensitive while below these ranges are less significant. the global sensitivity analysis is carried out using Matlab and R softwares.

Figure 3 is the tornado plot for the PRCC of the model parameters from the reproduction number R_C, while Figure 4 depicts the scatter plots obtained against the vaccination compartment.

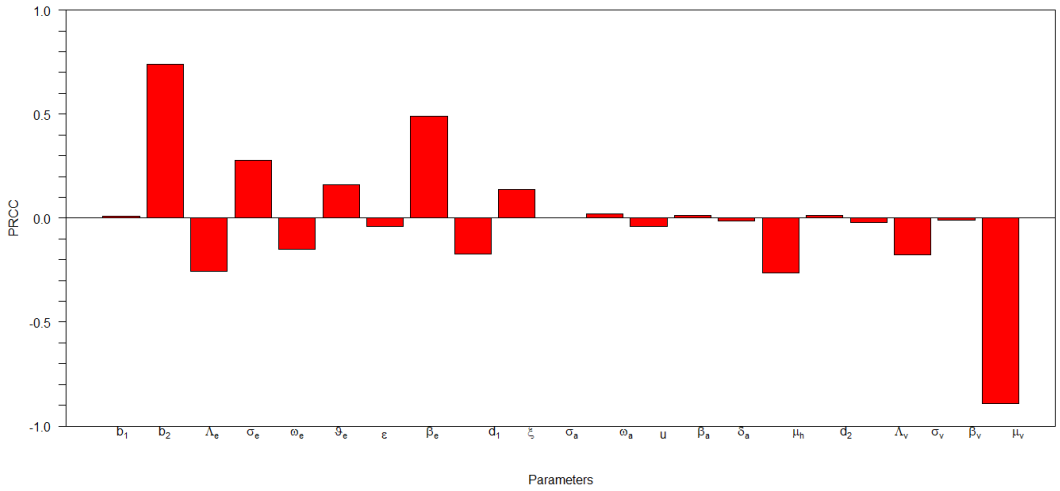


Figure 3: Tonardo plot showing all the model parameters against R_C. The longer the bar, the more sensitive if the corresponding parameter.

Table 5: PRCC values and p-values with their significant impact.

Symbol	PRCC	p-value	Keep?
β_s	0.513775674	0.0000	TRUE
β_h	0.481893775	0.0000	TRUE
β_a	0.024026121	0.4503	FALSE
γ_a	0.001059474	0.9734	FALSE
γ_h	0.532874887	0.0000	TRUE
γ_s	0.513588913	0.0000	TRUE
μ_c	-0.526427244	0.0000	TRUE
μ_m	-0.516304961	0.0000	TRUE
μ_s	-0.776046728	0.0000	TRUE
τ_1	0.433204750	0.0000	TRUE
τ_2	0.444561365	0.0000	TRUE

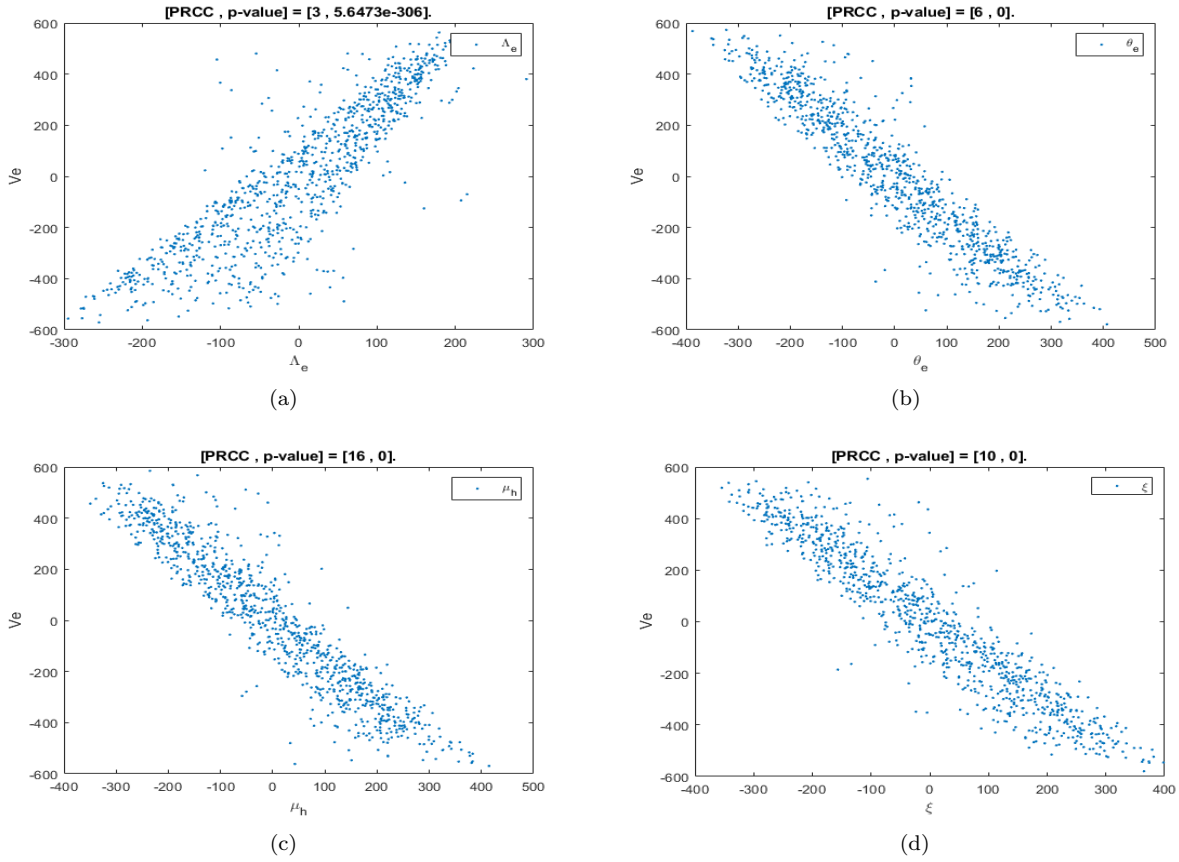


Figure 4: Scatter plots simulation showing the PRCC values of parameters λ_a ϑ_e, ξ and μ_h against the vaccination class V_e.

From Figure 3, the parameter b_2, β_e and β_v are strongly positively correlated with positive PRCC, while the parameter μ_v has a strong negative PRCC value. The biological implication of the positive PRCC values implies their increase will certainly increase the numerical value of the R_C, and the contrast is true for the negative PRCC values. Last, with a 1000 sample size and a unit 1, we performed a global sensitivity using the V_e class as our response variable. The results are presented using a scatter plot for visualization of the sensitivity of the model parameters. It can be seen that λ_a has a strong positive correlation, while ϑ_e, ξ and μ_h have a strong negative PRCC values. These suggest a need to decrease the transmission parameters and increase vaccination of children less than 5 years old, a strategy that could help contain the spread of malaria in the human population. Importantly, Table 5 gives the PRCC values of each model parameter in the R_C with the associated p-values showing the level statistically significance. Those parameters with p-values less than 0.05 are said to be significant and have more effect on the reproduction number when compared to other parameters.

5.2 Effect of implementing control measures

5.2.1 Personal protection $c_1 \neq 0$, treatment $c_2 \neq 0$, and vaccination $c_3 \neq 0$

Figure 5 below depicts the time series of the scenario when the three control measures, namely personal protection $c_1 \neq 0$, Treatment $c_2 \neq 0$,and vaccination of children under 5 years old $c_3 \neq 0$ are implement.

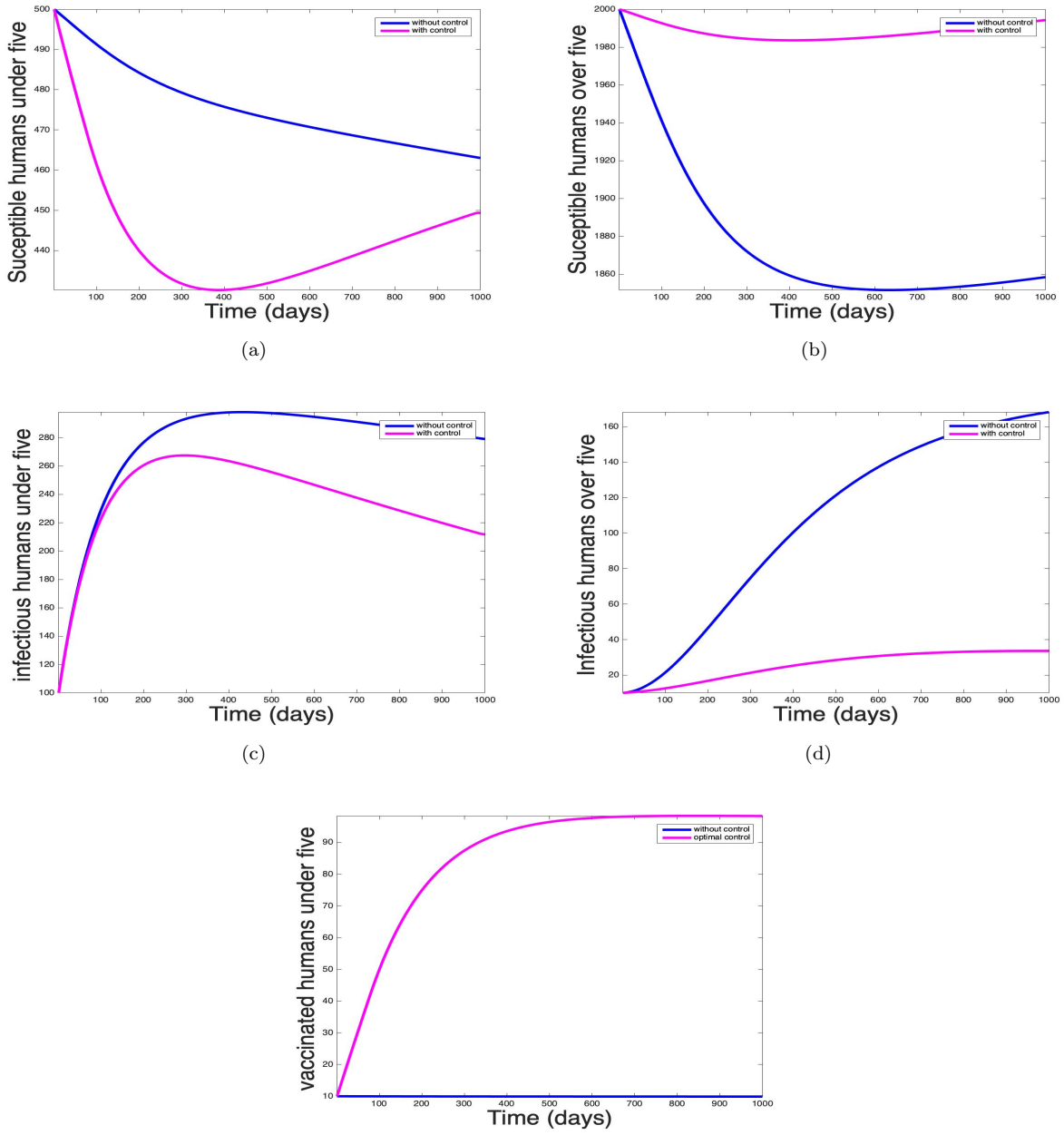
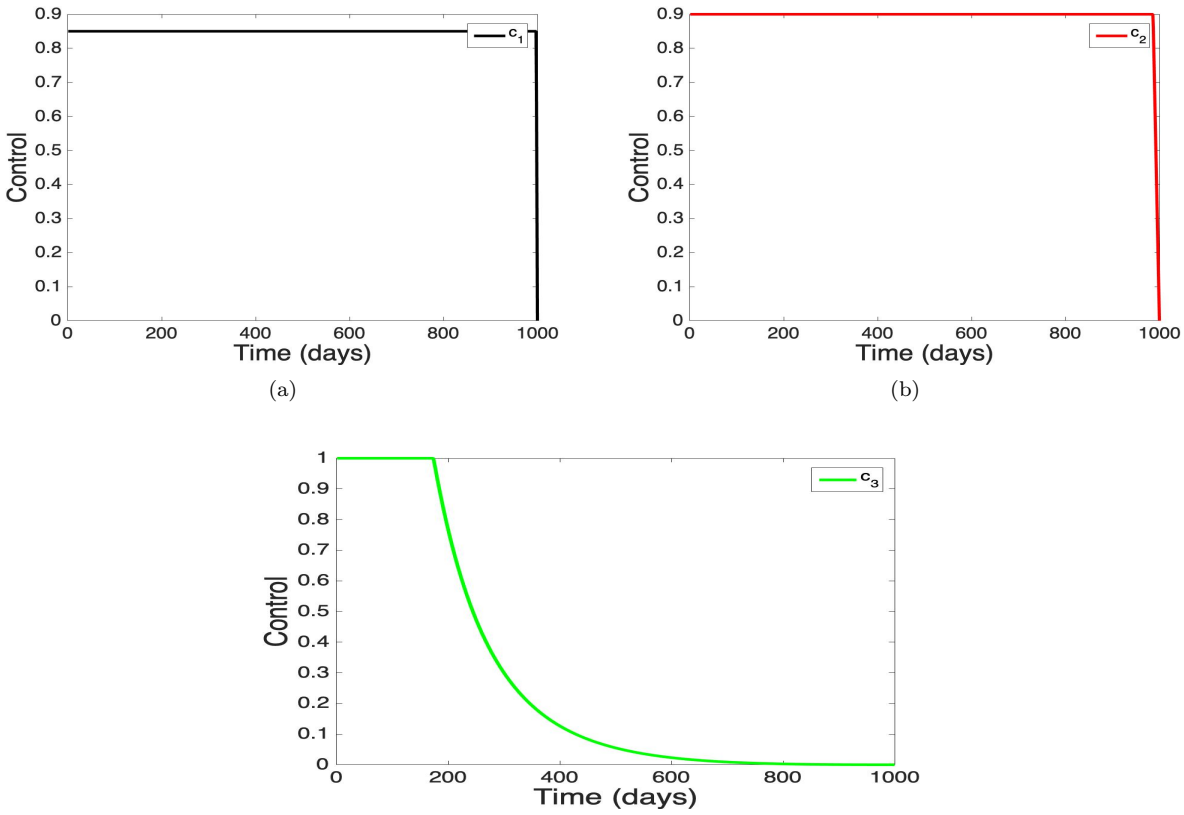


Figure 5: Effect of implementing controls of the model state variables for (a) Susceptible humans under 5-years. (b) Susceptible humans over 5-years. (c) Infectious humans under 5-years. (d) Infectious humans over 5-years. (e) Vaccinated humans under 5-years.

Results of the strategy that combines the three intervention measures indicate that the number of susceptible humans under over 5-years of age decreases, whereas the number of susceptible individuals over 5-years increase in time, as seen in Figures 5(b) and 5(a) respectively. On the other hand, in the presence of control measures, we have a reduced number of infectious individuals in both of these sub-groups of less and greater than five as shown in Figures 5(d) and 5(c). This very interesting result suggests a need for simultaneous implementation of treatment, vaccination of less than 5-years old, and personal protective measures to help mitigate the spread of malaria outbreak(s). In addition, Figure 5(e) shows that the use of vaccination does have a significant positive impact on individuals under the age of five, this is significant as this group bears the highest burden of malaria morbidity and mortality in the community. This results further asserts the WHO recommendation to vaccinate children under five [4], and thanks to the availability of the vaccine currently for this age group.



(a) (b) (c)

Figure 6: Control profiles for the use of optimal control variables (a) c_1-personal protective measures. (b) c_2-Treatment effort (c) c_3-vaccination effort.

Figure 6 shows the control profiles for three types of controls we considered in this paper. It can be seen in Figures 6(a) and 6(b) that it is important to keep the use of personal protective measures and the treatment effort at its maximum level throughout the modeling time to achieve the control of malaria. In contrast, vaccination is effective at the start of the simulation for about 200 days, but start to reduce, Figure 6(c). This may not be surprising as mass vaccination is expected because the vaccine has just been available for the first time recently, but it is expected that after a while, vaccination rate will decrease. This results can be ascertain as well based on the Covid19 vaccination campaign in the early 2021 which has now drastically fade down.

5.2.2 Personal protection $c_1 \neq 0$, treatment $c_2 = 0$, and vaccination $c_3 = 0$

The implementation of personal protection alone has a positive impact on reducing the malaria spread in the community as depicted in Figure 7. The control profile of c_1 is at its maximum value through the intervention period, Figure 7(f).

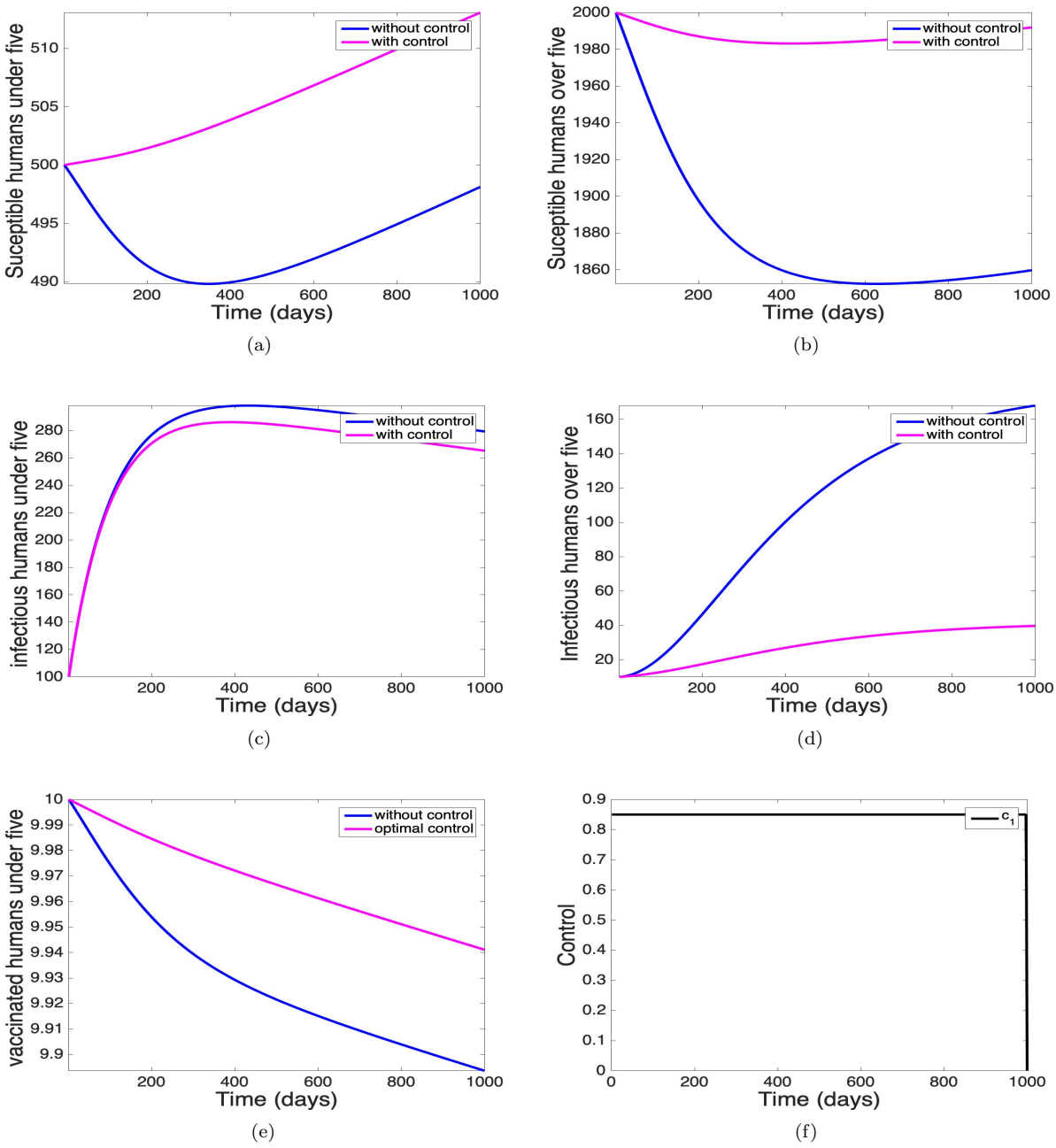


Figure 7: Effect of implementing only control c_1 of the model state variables for (a) Susceptible humans under 5-years. (b) Susceptible humans over 5-years. (c) Infectious humans under 5-years. (d) Infectious humans over 5-years. (e) Vaccinated humans under 5-years.

5.2.3 Personal protection $c_1 = 0$, treatment $c_2 \neq 0$, and vaccination $c_3 = 0$

The implementation of treatment as a sole control measure is depicted in Figure 8. As in the case of singly implementing personal protection only, though treatment alone has a positive population level impact, it is not sufficient to eradicate the disease. The control profile of c_2 is at its maximum value through the intervention period, Figure 8(f).

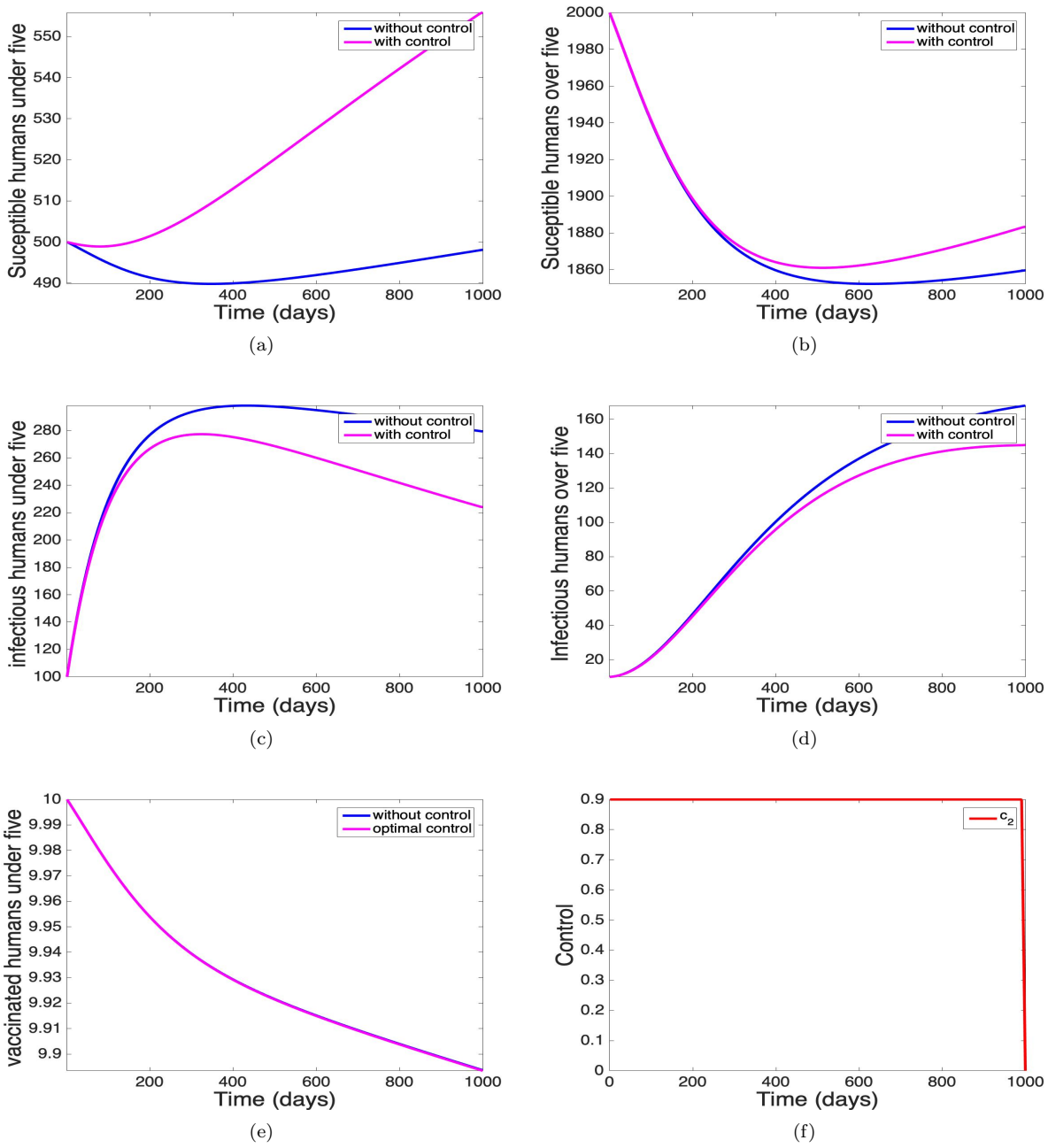


Figure 8: Effect of implementing only control c_2 of the model state variables for (a) Susceptible humans under 5-years. (b) Susceptible humans over 5-years. (c) Infectious humans under 5-years. (d) Infectious humans over 5-years. (e) Vaccinated humans under 5-years.

5.2.4 Personal protection $c_1 = 0$, treatment $c_2 = 0$, and vaccination $c_3 \neq 0$

Vaccination of children under five also has a positive population level impact, see Figure 9. But, in this case, the vaccination should be kept at its maximum for about 600 days, which is about 3 times more than when the three intervention strategies are concurrently implemented, Figure 9(f).

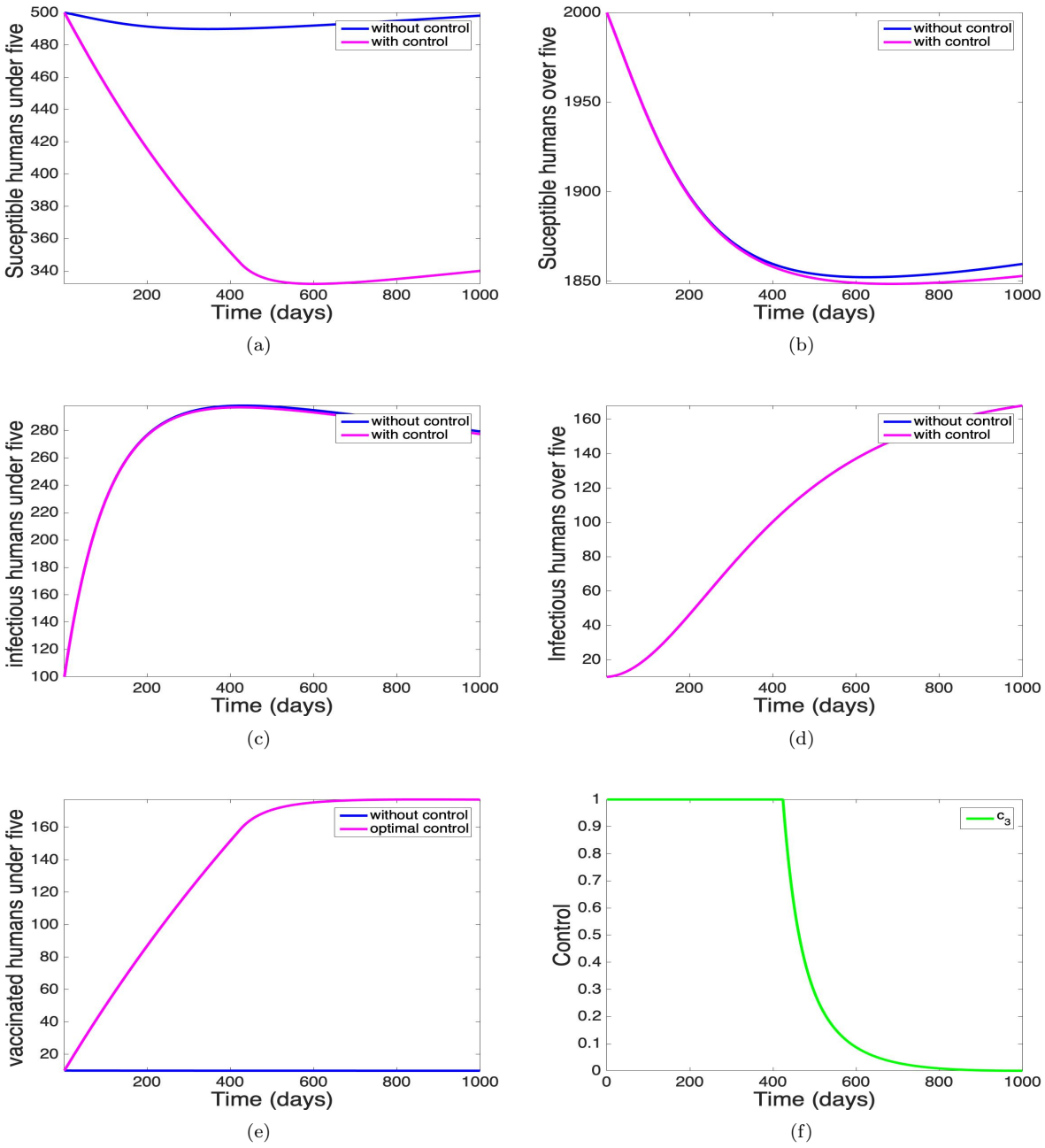


Figure 9: Effect of implementing only control c_3 of the model state variables for (a) Susceptible humans under 5-years. (b) Susceptible humans over 5-years. (c) Infectious humans under 5-years. (d) Infectious humans over 5-years. (e) Vaccinated humans under 5-years.

When treatment is the only implemented control measure, it takes more than 3 years of treatment of infected individuals at the maximum control level as depicted in Figure 8(f) to have a meaningful population-level impact. On the other hand, in Figure 9(f), when vaccination alone is implemented for children less than 5 years old, it takes about a year of optimally administering vaccination for a meaningful population-level impact.

6 Conclusion

Malaria is an infectious vector-borne disease of global public health concern, with children less than 5 years old bearing the highest burden. While several prevention and therapeutic measures have been implemented to fight against malaria, the recent groundbreaking RTS malaria vaccine (trade name Mosquirix), a recombinant protein-based malaria vaccine for children age five and below, recommended by the WHO could be a game changer.

A two-group malaria model structured by age with individuals above and below five years of age is formulated and

analyzed. The basic reproduction number defined as the expected number of secondary infections generated by one infected individual during its entire period of infectiousness in a naive population is computed using the next generation method. The disease-free equilibrium is shown to be globally asymptotically stable when the disease-induced death rate in both human groups is zero. Descarte's rule of signs is used to discuss the possible existence of multiple endemic equilibria, in which case the model undergoes a backward or subcritical bifurcation. This epidemiological implication of this situation when a stable DFE co-exists with a stable endemic equilibrium is that having the basic reproduction number less than unity although necessary is not sufficient to eliminate the disease.

By construction, mathematical models inherit the loss of information that could make model outcomes imprecise. Therefore, global sensitivity analysis of the basic reproduction number and the vaccination class using Latin-Hyper Cube Sampling (LHS) in combination with partial rank correlation coefficient (PRCC) are investigated and results depicted graphically. The most sensitive parameters are related to children under five years old such as the average biting rate of mosquitoes on susceptible individuals under 5 years old b_2, the progression rate from exposed to infectious for humans under 5 years old σ_e, and the probability of infection of susceptible humans under 5 years old per mosquito bite β_e.

To mitigate the spread of infectious diseases, intervention measures (both therapeutic and non-therapeutic) are paramount. Consequently, we extended the proposed model by incorporating three time-dependent controls, namely personal protection, treatment, and vaccination of children under-five. Using Pontryagin's maximum principle, we prove the existence of an optimal control problem and find the optimal control combination. Numerical simulations reveal that concurrently applying the three intervention measures is the best scenario for fighting against malaria epidemic in a community, compared to using either single or any dual combination of intervention(s) at a time. While singly or dual intervention measure implemented at a time still has a positive population effect, they are all less effective than concurrently implementing the triple intervention strategy at a time.

The proposed model has some limitations. We considered that individuals in the population mix homogeneously. The model could be extended by developing an agent-based two-group malarial model. Also, since the new malaria vaccine for children less than five years old is not yet widely available, a stochastic version of the model is another avenue that warrant further investigation. As countries data become available, fitting the model to real data could enable better estimation of some model parameters, which herein are mainly extracted from existing literature. In general, the density of mosquitoes fluctuates between climatic seasons. For this reason, accounting for seasonal factor (in the birth rate of mosquitoes) as well as the influence of climate (temperature-dependent model), two important drivers of the malaria dynamics are important.

Acknowledgments

SYT acknowledges with thanks the financial support from the DST/NRF SARChI Chair in Mathematical Models and Methods in Biosciences and Bioengineering at the University of Pretoria, Grant No. N00317.

Conflict of Interest

None.

References

[1] https://www.who.int/fr/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk accessed august 18, 2022.

[2] https://data.unicef.org/topic/child-health/malaria/, accessed august 20, 2022.

[3] https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021, accessed September 10, 2022.

[4] https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk, accessed september 11, 2022.

[5] FB Agusto, AB Gumel, and PE Parham. Qualitative assessment of the role of temperature variations on malaria transmission dynamics. *Journal of Biological Systems*, 23(04):1550030, 2015.

[6] E Atcheson, K Bauza, and A Reyes-Sandoval. A probabilistic model of pre-erythrocytic malaria vaccine combination in mice. *Plos one*, 14(1):e0209028, 2019.

[7] S Bala and B Gimba. Global sensitivity analysis to study the impacts of bed-nets, drug treatment, and their efficacies on a two-strain malaria model. *Mathematical and Computational Applications*, 24(1):32, 2019.

[8] AL Bauer, IB Hogue, S Marino, and DE Kirschner. The effects of hiv-1 infection on latent tuberculosis. *Mathematical Modelling of Natural Phenomena*, 3(7):229–266, 2008.

[9] D Bernoulli. Essai d'une nouvelle analyse de la mortalité causée par la petite vérole, et des avantages de l'inoculation pour la prévenir. *Histoire de l'Acad., Roy. Sci.(Paris) avec Mem*, pages 1–45, 1760.

[10] C Castillo-Chavez, Z Feng, W Huang, et al. On the computation of ro and its role on. *Mathematical approaches for emerging and reemerging infectious diseases: an introduction*, 1:229, 2002.

[11] JD Challenger, D Olivera Mesa, DF Da, RS Yerbanga, T Lefèvre, A Cohuet, and TS Churcher. Predicting the public health impact of a malaria transmission-blocking vaccine. *Nature communications*, 12(1):1–12, 2021.

[12] CW Chukwu and F Nyabadza. A theoretical model of listeriosis driven by cross contamination of ready-to-eat food products. *International Journal of Mathematics and Mathematical Sciences*, 2020, 2020.

[13] K Dietz and JAP Heesterbeek. Daniel bernoulli s epidemiological model revisited. *Mathematical biosciences*, 180(1-2):1–21, 2002.

[14] F Forouzannia and AB Gumel. Mathematical analysis of an age-structured model for malaria transmission dynamics. *Mathematical biosciences*, 247:80–94, 2014.

[15] F Forouzannia and AB Gumel. Dynamics of an age-structured two-strain model for malaria transmission. *Applied Mathematics and Computation*, 250:860–886, 2015.

[16] K Galactionova, TA Smith, and MA Penny. Insights from modelling malaria vaccines for policy decisions: the focus on rts, s. *Malaria journal*, 20(1):1–8, 2021.

[17] BD Handari, RA Ramadhani, CW Chukwu, SHA Khoshnaw, and D Aldila. An optimal control model to understand the potential impact of the new vaccine and transmission-blocking drugs for malaria: A case study in papua and west papua, indonesia. *Vaccines*, 10(8):1174, 2022.

[18] FF Herdicho, Williams Chukwu, H Tasman, et al. An optimal control of malaria transmission model with mosquito seasonal factor. *Results in Physics*, 25:104238, 2021.

[19] AVS Hill. Vaccines against malaria. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 366(1579):2806–2814, 2011.

[20] K Karunamoorthi. Malaria vaccine: a future hope to curtail the global malaria burden. *International journal of preventive medicine*, 5(5):529, 2014.

[21] WO Kermack and AG McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character*, 115(772):700–721, 1927.

[22] JC Koella. On the use of mathematical models of malaria transmission. *Acta tropica*, 49(1):1–25, 1991.

[23] S Marino, IB Hogue, CJ Ray, and DE Kirschner. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *Journal of theoretical biology*, 254(1):178–196, 2008.

[24] S Niare, JM Berenger, C Dieme, O Doumbo, D Raoult, P Parola, and L Almeras. Identification of blood meal sources in the main african malaria mosquito vector by maldi-tof ms. *Malaria journal*, 15(1):1–15, 2016.

[25] LS Pontryagin, VG Boltyanskii, RV Gamkrelidze, and EF Mishchenko. The mathematical theory of optimal control process, vol. 4, 1986.

[26] T Smith, GF Killeen, N Maire, A Ross, L Molineaux, F Tediosi, G Hutton, J Utzinger, K Dietz, and M Tanner. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of plasmodium falciparum malaria: Overview. *The American journal of tropical medicine and hygiene*, 75(2_suppl):1–10, 2006.

[27] E Takashima, M Tachibana, M Morita, H Nagaoka, BN Kanoi, and T Tsuboi. Identification of novel malaria transmission-blocking vaccine candidates. *Frontiers in Cellular and Infection Microbiology*, page 1224, 2021.

[28] H Tasman, UD Purwati, FF chocho, CW Chukwu, et al. An optimal control problem of malaria model with seasonality effect using real data. *Commun. Math. Biol. Neurosci.*, 2021:Article–ID, 2021.

[29] SY Tchoumi, EZ Dongmo, JC Kamgang, and JM Tchuenche. Dynamics of a two-group structured malaria transmission model. *Informatics in Medicine Unlocked*, 29:100897, 2022.

[30] MI Teboh-Ewungkem, CN Podder, and AB Gumel. Mathematical study of the role of gametocytes and an imperfect vaccine on malaria transmission dynamics. *Bulletin of mathematical biology*, 72(1):63–93, 2010.

[31] P Van den Driessche and J Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1-2):29–48, 2002.

[32] MT White, R Verity, TS Churcher, and AC Ghani. Vaccine approaches to malaria control and elimination: Insights from mathematical models. *Vaccine*, 33(52):7544–7550, 2015.

[33] WA Woldegerima, R Ouifki, and J Banasiak. Mathematical analysis of the impact of transmission-blocking drugs on the population dynamics of malaria. *Applied Mathematics and Computation*, 400:126005, 2021.

[34] X Zhao, Y Hu, Y Zhao, L Wang, Z Wu, MT Soe, MP Kyaw, L Cui, X Zhu, and Y Cao. Genetic diversity in the transmission-blocking vaccine candidate plasmodium vivax gametocyte protein pvs230 from the china–myanmar border area and central myanmar. *Parasites & Vectors*, 15(1):1–15, 2022.

Appendix

The coefficients a_0, a_1, a_2 and a_3 of the polynomial 9 are given below.

$$
\begin{aligned}
a_3 &= (1-\varepsilon)(\Lambda_v b_2\beta_e\sigma_v)^2(k_0k_2-\omega_e\sigma_e)+\Lambda_e\Lambda_v b_2\beta_e k_5\mu_v\sigma_v(1-\varepsilon)(kk_0k_2-\omega_e\sigma_e\vartheta_e)\\
&\quad+\Lambda_e\Lambda_v b_2\beta_e k_0k_2k_5\mu_h\mu_v\sigma_v\left[\Lambda_v b_1\beta_a\sigma_v(k_4\omega_a\sigma_a u+\delta_a\omega_a(1-u)-k_1k_3k_4)-\Lambda_e k_1k_3k_4k_5\mu_v\right]\\
&\quad-\Lambda_e\Lambda_v b_2\beta_e k_5\mu_h\mu_v\omega_e\sigma_e\sigma_v+\Lambda_e^2 kk_0k_2k_5^2\mu_v^2\\
a_2 &= -\Lambda_v^3 b_1b_2^3\beta_a\beta_e^2\beta_v(1-\varepsilon)k_4\mu_h^2\omega_a\sigma_a\sigma_e\sigma_v^3u-\Lambda_v^3 b_1b_2^3\beta_a\beta_e^2\beta_v\delta_a(1-\varepsilon)\mu_h^2\omega_a\sigma_a\sigma_e\sigma_v^3(1-u)\\
&\quad+\Lambda_v^3 b_1b_2^3\beta_a\beta_e^2\beta_v(1-\varepsilon)k_1k_3k_4\mu_h^2\sigma_e\sigma_v^3\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v(1-\varepsilon)k_4k_5\mu_h\mu_v\omega_a\sigma_a\sigma_e\sigma_v^2u\vartheta_e-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v\delta_a(1-\varepsilon)k_5\mu_h\mu_v\omega_a\sigma_a\sigma_e\sigma_v^2(1-u)\vartheta_e\\
&\quad+\Lambda_e\Lambda_v^2 b_2^3\beta_e^2\beta_v(1-\varepsilon)k_1k_3k_4k_5\mu_h^2\mu_v\sigma_e\sigma_v^2+\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e(1-\varepsilon)kk_0k_2k_4k_5\mu_v^2\omega_a\sigma_a\sigma_v^2u\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v k_4k_5\mu_h^2\mu_v\omega_a\sigma_a\sigma_e\sigma_v^2u+\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e\delta_a(1-\varepsilon)kk_0k_2k_5\mu_v^2\omega_a\sigma_a\sigma_v^2(1-u)\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v\delta_a k_5\mu_h^2\mu_v\omega_a\sigma_a\sigma_e\sigma_v^2(1-u)+\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v(1-\varepsilon)k_1k_3k_4k_5\mu_h\mu_v\sigma_e\sigma_v^2v\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e(1-\varepsilon)k_4k_5\mu_v^2\omega_a\omega_e\sigma_a\sigma_e\sigma_v^2u\vartheta_e-\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e\delta_a(1-\varepsilon)k_5\mu_v^2\omega_a\omega_e\sigma_a\sigma_e\sigma_v^2(1-u)\vartheta_e\\
&\quad+\Lambda_e\Lambda_v^2 b_1^2b_2\beta_a\beta_e\beta_v(1-\varepsilon)k_0k_2k_4k_5\mu_h\mu_v\sigma_a\sigma_v^2\xi-\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e(1-\varepsilon)kk_0k_1k_2k_3k_4k_5\mu_v^2\sigma_v^2\\
&\quad-\Lambda_e\Lambda_v^2 b_2^2\beta_e^2(1-\varepsilon)k_0k_1k_2k_3k_4k_5\mu_h\mu_v^2\sigma_v^2+\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v k_1k_3k_4k_5\mu_h^2\mu_v\sigma_e\sigma_v^2\\
&\quad+\Lambda_e\Lambda_v^2 b_2^2\beta_e^2(1-\varepsilon)k_1k_3k_4k_5\mu_h\mu_v^2\omega_e\sigma_e\sigma_v^2+\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e k_0k_2k_4k_5\mu_h\mu_v^2\omega_a\sigma_a\sigma_v^2u\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e k_4k_5\mu_h\mu_v^2\omega_a\omega_e\sigma_a\sigma_e\sigma_v^2u+\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e\delta_a k_0k_2k_5\mu_h\mu_v^2\omega_a\sigma_a\sigma_v^2(1-u)\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e\delta_a k_5\mu_h\mu_v^2\omega_a\omega_e\sigma_a\sigma_e\sigma_v^2(1-u)+\Lambda_e^2\Lambda_v b_2^2\beta_e\beta_v(1-\varepsilon)k_1k_3k_4k_5^2\mu_h\mu_v^2\sigma_e\sigma_v\vartheta_e\\
&\quad+\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e(1-\varepsilon)k_1k_3k_4k_5\mu_v^2\omega_e\sigma_e\sigma_v^2v-2\,\Lambda_e^2\Lambda_v b_2\beta_e(1-\varepsilon)kk_0k_1k_2k_3k_4k_5^2\mu_v^3\sigma_v\\
&\quad+\Lambda_e^2\Lambda_v b_2^2\beta_e\beta_v k_1k_3k_4k_5^2\mu_h^2\mu_v^2\sigma_e\sigma_v-\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e k_0k_1k_2k_3k_4k_5\mu_h\mu_v^2\sigma_v^2\\
&\quad+\Lambda_e\Lambda_v^2 b_1b_2\beta_a\beta_e k_1k_3k_4k_5\mu_h\mu_v^2\omega_e\sigma_e\sigma_v^2+2\,\Lambda_e^2\Lambda_v b_1\beta_a kk_0k_2k_4k_5^2\mu_v^3\omega_a\sigma_a\sigma_v u+2\,\Lambda_e^2\Lambda_v b_1\beta_a\delta_a kk_0k_2k_5^2\mu_v^3\omega_a\sigma_a\sigma_v(1-u)\\
&\quad+2\,\Lambda_e^2\Lambda_v b_2\beta_e(1-\varepsilon)k_1k_3k_4k_5^2\mu_v^3\omega_e\sigma_e\sigma_v v+\Lambda_e^2\Lambda_v b_1^2\beta_a\beta_v k_0k_2k_4k_5^2\mu_h\mu_v^2\sigma_a\sigma_v\xi-2\,\Lambda_e^2\Lambda_v b_1\beta_a kk_0k_1k_2k_3k_4k_5^2\mu_v^3\sigma_v\\
&\quad-2\,\Lambda_e^2\Lambda_v b_2\beta_e k_0k_1k_2k_3k_4k_5^2\mu_h\mu_v^3\sigma_v+2\,\Lambda_e^2\Lambda_v b_2\beta_e k_1k_3k_4k_5^2\mu_h\mu_v^3\omega_e\sigma_e\sigma_v-3\,\Lambda_e^3 kk_0k_1k_2k_3k_4k_5^3\mu_v^4\\
a_1 &= -\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v(1-\varepsilon)k_4k_5\mu_h\mu_v^2\omega_a\sigma_a\sigma_e\sigma_v^2u\vartheta_e-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v\delta_a(1-\varepsilon)k_5\mu_h\mu_v^2\omega_a\sigma_a\sigma_e\sigma_v^2(1-u)\vartheta_e\\
&\quad+\Lambda_e\Lambda_v^2 b_2^3\beta_e^2\beta_v(1-\varepsilon)k_1k_3k_4k_5\mu_h^2\mu_v^2\sigma_e\sigma_v^2-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v k_4k_5\mu_h^2\mu_v^2\omega_a\sigma_a\sigma_e\sigma_v^2u\\
&\quad-\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v\delta_a k_5\mu_h^2\mu_v^2\omega_a\sigma_a\sigma_e\sigma_v^2(1-u)+\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v(1-\varepsilon)k_1k_3k_4k_5\mu_h\mu_v^2\sigma_e\sigma_v^2\vartheta_e\\
&\quad+\Lambda_e\Lambda_v^2 b_1^2b_2\beta_a\beta_e\beta_v(1-\varepsilon)k_0k_2k_4k_5\mu_h\mu_v^2\sigma_a\sigma_v^2\xi+\Lambda_e\Lambda_v^2 b_1b_2^2\beta_a\beta_e\beta_v k_1k_3k_4k_5\mu_h^2\mu_v^2\sigma_e\sigma_v^2\\
&\quad+2\,\Lambda_e^2\Lambda_v b_2^2\beta_e\beta_v(1-\varepsilon)k_1k_3k_4k_5^2\mu_h\mu_v^3\sigma_e\sigma_v v-\Lambda_e^2\Lambda_v b_2\beta_e(1-\varepsilon)kk_0k_1k_2k_3k_4k_5^2\mu_v^4\sigma_v\\
&\quad+2\,\Lambda_e^2\Lambda_v b_2^2\beta_e\beta_v k_1k_3k_4k_5^2\mu_h\mu_v^3\sigma_e\sigma_v+\Lambda_e^2\Lambda_v b_1\beta_a kk_0k_2k_4k_5^2\mu_v^4\omega_a\sigma_a\sigma_v u+\Lambda_e^2\Lambda_v b_1\beta_a\delta_a kk_0k_2k_5^2\mu_v^4\omega_a\sigma_a\sigma_v(1-u)\\
&\quad+\Lambda_e^2\Lambda_v b_2\beta_e(1-\varepsilon)k_1k_3k_4k_5^2\mu_v^4\omega_e\sigma_e\sigma_v\vartheta_e+2\,\Lambda_e^2\Lambda_v b_1^2\beta_a\beta_v k_0k_2k_4k_5^2\mu_h\mu_v^3\sigma_a\sigma_v\xi-\Lambda_e^2\Lambda_v b_1\beta_a kk_0k_1k_2k_3k_4k_5^2\mu_v^4\sigma_v\\
&\quad-\Lambda_e^2\Lambda_v b_2\beta_e k_0k_1k_2k_3k_4k_5^2\mu_h\mu_v^4\sigma_v+\Lambda_e^2\Lambda_v b_2\beta_e k_1k_3k_4k_5^2\mu_h\mu_v^4\omega_e\sigma_e\sigma_v-3\,\Lambda_e^3 kk_0k_1k_2k_3k_4k_5^3\mu_v^5\\
a_0 &= N_h^{*2}kk_0k_1k_2k_3k_4k_5^3\mu_h^2\mu_v^6\left(\mathcal{R}_C^m-1\right).
\end{aligned}
\tag{17}
$$