Optimal control of the spread of malaria superinfectivity

Article *in* Journal of Biological Systems · January 2014

DOI: 10.1142/S0218339013400020

CITATIONS
32

READS
552

2 authors:

Folashade B. Agusto
University of Kansas
125 PUBLICATIONS **3,100** CITATIONS
SEE PROFILE

Suzanne Lenhart
University of Tennessee at Knoxville
293 PUBLICATIONS **9,154** CITATIONS
SEE PROFILE

Journal of Biological Systems
Vol. 21, No. 4 (2013) 1340002 (26 pages)

DOI: 10.1142/S0218339013400020

World Scientific
www.worldscientific.com

OPTIMAL CONTROL OF THE SPREAD OF MALARIA SUPERINFECTIVITY

FOLASHADE AGUSTO*
Department of Mathematics and Statistics
Austin Peay State University
Clarksville, TN 37044, USA
fbagusto@gmail.com

SUZANNE LENHART
Department of Mathematics
University of Tennessee
Knoxville, 37996-1320, TN, USA
lenhart@math.utk.edu

Received 30 January 2013
Accepted 7 September 2013
Published 20 January 2014

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes. In this paper, a deterministic model for malaria transmission, that incorporates superinfection is presented. Qualitative analysis of the model reveals the presence of backward bifurcation in which a stable disease-free equilibrium co-exists with a stable endemic equilibrium when the associated reproduction threshold is less than unity. Optimal control theory is then applied to the model to study time-dependent treatment efforts to minimize the infected in individuals while keeping the implementation cost at a minimum.

Keywords: Malaria; Superinfection; Differential Equations; Optimal Control; Optimal System.

1. Introduction

Malaria is a life-threatening disease caused by parasites (species *Plasmodium*), that are transmitted to people through the bites of infected mosquitoes. *Plasmodium falciparum* and *Plasmodium vivax* are the two most common species, and *p. falciparum* is the most deadly.[1] *P. falciparum* malaria is still a major cause of mortality and morbidity in the tropical and subtropical areas of the globe. According to the 2009 Malaria World Report,[2] half of the world's population is at risk of malaria, with an estimated 243 million cases that led to about 863,000 deaths in 2008, a slight drop from the 2006 statistics. This decrease can be attributed to a number of improved policies, including increases in international funding, research, the

*Corresponding author.

use of insectide-treated bednets and artemisinin-based combination therapy, and a revival of support for indoor residential insectide spraying.[2] Despite this slight drop, there are still challenges that may lead to significant increase in the malaria burden. These include the global financial slow down and the changing climatic conditions, both of which affect the endemic malaria regions.[3,4] The number and severity of malaria cases are also being exacerbated by high levels of HIV infection that weaken the immune system rendering people with HIV more susceptible to contracting the disease[5] and also enhancing mortality in advanced HIV patients by a factor of about 25% in nonstable malaria areas.[6]

Following a successful sporozoite inoculation, *P. falciparum* is usually first detected 7–11 days later as trophozoites in the circulatory system of immunologically naive humans. Then they multiply asexually and asymptomatically for a period of 6–15 days into merozoites developing either into gametes (the form of the parasite that can infect mosquitoes) or lysing red blood cells. The lysing of red blood cells and the immune system's response to the presence of these blood stages of the parasite cause the symptoms of malaria. The merozoites are then released into the blood stream to invade other red blood cells. The gametocytes soon die and are removed by the immune system, if not ingested by a mosquito vector during a second bite. Transmission of the disease is a direct consequence of gametocyte availability.

Superinfection is a phenomenon where new infections accumulate on top of uncleared infections.[7–10] Superinfection may arise as a consequence of concurrent infections with different parasites of malaria, or from different genetic strain, or as a result of different inocula of the same strain.[8,11–14] In superinfectivity with malaria infection, an infected subject may acquire a new infection before recovering from a previous one.[8,15] This situation is different from repeated exposure in which the infected subject recovers and is again infected.[16]

Gametocytes are relatively abundant and infective during active transmission periods[17] but are scarce during inter-epidemic periods.[18] In hyperendemic places such as East Africa, an increase in the number of infective mosquitoes was followed by an increase in gametocyte prevalence, and this rising number of gametocyte carriers indirectly represent new infections.[19,20] A seasonal increase in parasite density, prevalence of gametocyte carriers and morbidity has been observed in northern Nigeria and The Gambia,[21,22] with relatively slight fluctuations in gross prevalence in both places. Similarly observed in hyperendemic Thailand is periodic fluctuation in gametocytaemia and trophozoite densities,[8] and further observation is that substantial superinfection took place, resulting in an increase in numbers of cases without a matching increase in gametocyte prevalence. Another observation from Rosenberg[8] is that superinfection of adults may contribute significantly to transmission in semi-immune population. Superinfection also explains why at least some incidence was manifested by a rise in the numbers of gametocyte carriers but not in trophozoite prevalence.[8]

A number of studies have been carried out to confirm the presence of superinfectivity; an instance is the study carried out by Coggeshall and Kumm[23] on

the serum from monkeys. Rosenberg[8] shows the presence of superinfectivity in a two-year field study on approximately 250 habitants of Ban Phluang village, in south-eastern Thailand. Rosenberg's study involves the use of blood films and confirms the presence of superinfectivity. His result further throws light unto the study carried out by Wilson,[20] which shows that a sudden increase in the number of infective mosquitoes was followed by increase in prevalence of gametocyte, even when the prevalence of *P. falciparum* trophozoite is stable, which is an indication of the presence of superinfectivity. Similarly, Dietz *et al.*[11] in their study used combined data from 16 villages amounting to about 5000 persons surveyed 5 times, at regular interval of 10 weeks in 1971 to equally show the presence of superinfectivity. In recent times, Portugal *et al.*[24] have attempted to use their study on mice to confirm lack of malaria superinfectivity. And as pointed out by van Santen *et al.*,[25] this study cannot be used to justify the lack of superinfectivity in humans. Portugal *et al.*[26] equally attempted to explain the lack of superinfectivity in children which several studies have clearly shown is high in children due to their lack of immunity as indicated by their low recovery rate from the disease.[8,13,14,27] The need to explain the low recovery rate in children by Macdonald is the basis of the debate on superinfectivity.[13]

Mathematical models have been used to assess various control strategies utilizing mathematical modeling techniques.[28–34] Some of these studies incorporate infection of the susceptible individuals by infected vector,[30,34] with emphasis on vector control and treatment of symptomatic individuals[31] but none addressed the issue of "infection of the symptomatic individuals". For instance, Chiyaka *et al.*[31] presented a delay differential model incorporating vaccination and personal protection as preventive control measures, while Blayneh *et al.*[35] presented an autonomous ordinary differential equation model with vector control and treatment and a time-dependent version of the model. Probability models of superinfectivity in malaria, have been included using Markov chains[27] and using continued fraction approximation to estimate density function of the duration of the infection.[14] Thus, it is instructive to carry out modeling studies to determine the impact of superinfectivity of the symptomatic individuals on the transmission dynamics of malaria. In this paper, we consider a model that addresses the problem of being superinfected with two broods of malaria, as against "n" number of broods as found in some other superinfection models.[8,11–14] Our model consist of basic essential features and focuses on the effect of superinfectivity, and we note that more features should be investigated after understanding this "building block" model. We use the treatment of symptomatic individuals as a control measure and then consider this time-dependent control measure using optimal control theory. Time-dependent optimal control strategies have been applied for the studies of HIV,[36–41] tuberculosis,[42] SARS,[43,44] Dengue fever[45] and malaria.[35]

The paper is organized as follows: Sec. 2 describes the dynamics of a compartmental system of ordinary differential equations for transmission of malaria reinfection. Analytical and numerical results of the autonomous model predict some

conditions which are vital to eradicate malaria in the long run. In Sec. 3, the model is extended to include controls. A suitable objective functional is introduced in this section. Using Pontraygin's Maximum Principle,[46] the derivation of the characterization of an optimal control is given. Numerical studies of the optimal controls are carried out and discussed in Sec. 4.

2. Formulation of the Malaria-Superinfectivity Model

The model is formulated with human and mosquito groups (see Fig. 1). The human population has a total of six classes. The classes represent those who are susceptible, $S_h(t)$, exposed, $E_h(t)$, infected, $I_h(t)$, superinfected, $P_h(t)$, treated, $T_h(t)$ and partially immune, $R_h(t)$. Thus, the total human population is $N_h(t) = S_h(t) + E_h(t) + I_h(t) + P_h(t) + T_h(t) + R_h(t)$. The mosquito population has three classes representing susceptible, $S_v(t)$, exposed, $E_v(t)$ and infected, $I_v(t)$. Thus, the total mosquito population is $N_v(t) = S_v(t) + E_v(t) + I_v(t)$.

Individuals move from one class to the other as their status with respect to the disease evolved. It is assumed that new recruits enter the human population at a rate θ_h via birth or immigration. There is no vertical transmission or immigration of infectious humans, thus inflow does not enter the infectious classes. All six human groups are subject to a natural death rate μ_h.

Susceptible humans are infected by the malaria parasite at a rate $f_h(t)$ and move into the exposed class. This infection rate is assumed to depend on average number of mosquito bites and on the transmission probability normalized by total

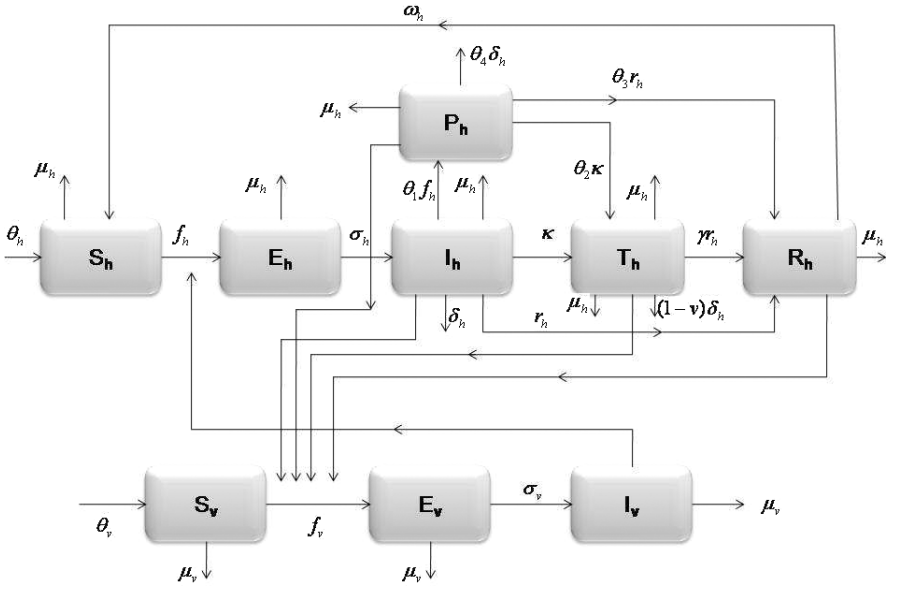


Fig. 1. Systematic flow diagram of the malaria model (2.3)–(2.11).

human population.[32] Therefore, the infection rate of susceptible humans $f_h(t)$ is given as

$$f_h(t) = \beta_h b_h I_v(t), \tag{2.1}$$

where b_h is the biting rate of female mosquitoes on a human host and β_h is the probability that a bite from an infectious mosquito leads to infection of the susceptible human.

The exposed humans enter the infectious class $I_h(t)$ at the rate σ_h. Members of the $I_h(t)$ class are either treated at a rate κ and enter the treated class $T_h(t)$, or they can recover naturally at a rate r_h to the recovered class, or they can die from the infection at a rate δ_h. Members of the class $I_h(t)$ are re-infected[7–10] (leading to superinfection) at the rate $\theta_1 f_h(t)$ and enter the $P_h(t)$ class, where $\theta_1 > 0$ is a modification parameter that accounts for increased infectivity of the infectious class $I_h(t)$. Individuals in the $P_h(t)$ class are also treated effectively at a rate $\theta_2\kappa$, where $0 < \theta_2 \leq 1$, reduces treatment efficacy rate due to increased infectivity. The $P_h(t)$ individuals also recover at a rate $\theta_3 r_h$, where the parameter $0 < \theta_3 \leq 1$, reduces recovery rate due to increased infectivity[47] and these individuals die from the disease at a rate $\theta_4\delta_h$, where $\theta_4 \geq 0$. Members of the $T_h(t)$ class are assumed to recover at a rate γr_h where $\gamma \geq 1$ is the parameter that represents the effectiveness of the drug in increasing the recovery rate, lose immunity at the rate ω_h, or die at a rate $(1 - v)\delta_h$ where $0 \leq v \leq 1$ determines the effectiveness of the drug as a reduction factor in the disease-induced death of the infectious individual.

For the mosquito population, it is assumed that susceptible mosquitoes are recruited, at the rate θ_v. All mosquitoes are subject to a natural death at a rate μ_v. Mosquitoes in the S_v class are infected by the malaria parasite at a rate $f_v(t)$, where

$$f_v = \beta_v b_v(I_h(t) + \theta_5 P_h(t) + (1 - \eta)T_h(t) + \theta_6 R_h(t)). \tag{2.2}$$

From the expression (2.2), b_v is the rate at which bites are received by a single host from the vectors and β_v is the probability that a bite from a susceptible mosquito to a human with infectious gametocytes leads to infection of the mosquito. The parameter η, where $\eta \in [0, 1]$, models the effect of the malaria drug in reducing the infectiousness of treated humans to mosquitoes. If $\eta = 0$, then the drug does not reduce infectiousness of the treated human to mosquitoes, if $\eta = 1$, then the drug is completely effective in reducing the infectiousness of the treated human. The parameter $\theta_5 \geq 0$ represents the increased infectivity of the superinfected individuals.[8,11,48] Since $R_h(t)$ are partially immune, individuals in this class can still transmit the disease, thus, parameter $\theta_6 \in [0, 1)$ gives the reduced infectivity of the partially immuned individuals.[8,12,13,49] Susceptible mosquitoes which are infected move to the exposed class and later become infectious at the rate σ_v. A schematic description of the model is depicted in Fig. 1. The assumptions result in

the following system of differential equations,

$$\dot{S}_h = \theta_h + \omega_h R_h - f_h S_h - \mu_h S_h, \tag{2.3}$$
$$\dot{E}_h = f_h S_h - \sigma_h E_h - \mu_h E_h, \tag{2.4}$$
$$\dot{I}_h = \sigma_h E_h - \kappa I_h - r_h I_h - \mu_h I_h - \delta_h I_h - \theta_1 f_h I_h, \tag{2.5}$$
$$\dot{P}_h = \theta_1 f_h I_h - \theta_2 \kappa P_h - \theta_3 r_h P_h - \mu_h P_h - \theta_4 \delta_h P_h, \tag{2.6}$$
$$\dot{T}_h = \kappa(I_h + \theta_2 P_h) - \gamma r_h T_h - \mu_h T_h - (1-v)\delta_h T_h, \tag{2.7}$$
$$\dot{R}_h = r_h(I_h + \theta_3 P_h) + \gamma r_h T_h - \omega_h R_h - \mu_h R_h, \tag{2.8}$$
$$\dot{S}_v = \theta_v - f_v S_v - \mu_v S_v, \tag{2.9}$$
$$\dot{E}_v = f_v S_v - \sigma_v E_v - \mu_v E_v, \tag{2.10}$$
$$\dot{I}_v = \sigma_v E_v - \mu_v I_v. \tag{2.11}$$

Since the model (2.3)–(2.11) represents human and mosquito populations, all parameters in the model are non-negative and one can show that the solutions of the system are non-negative, given non-negative initial values. The model (2.3)–(2.11) will be analyzed in a biologically feasible region as follows. The system (2.3)–(2.11) is split into two parts, namely the human population and the mosquitoes population. Consider the feasible region

$$\Gamma = \Gamma_h \times \Gamma_v \subset \mathbb{R}^6_+ \times \mathbb{R}^3_+$$

with,

$$\Gamma_h = \left\{ (S_h(t), E_h(t), I_h(t), P_h(t), T_h(t), R_h(t)) \in \mathbb{R}^6_+ : 0 \leq N_h(t) \leq \frac{\theta_h}{\mu_h} \right\},$$

and

$$\Gamma_v = \left\{ (S_v(t), E_v(t), I_v(t)) \in \mathbb{R}^3_+ : 0 \leq N_v(t) \leq \frac{\theta_v}{\mu_v} \right\}.$$

The following steps are followed to establish the positive invariance of Γ (i.e., solutions in Γ remain in Γ for all $t > 0$). The rate of change of the total humans and mosquitoes populations is obtained by adding the first six equations and the last three equations of the model (2.3)–(2.11) to give

$$\begin{aligned} \frac{dN_h(t)}{dt} &= \theta_h - \mu_h N_h(t) - \delta_h(I_h(t) + \theta_4 \delta_h P_h(t) + (1-v)T_h(t)), \\ \frac{dN_v(t)}{dt} &= \theta_v - \mu_v N_v(t). \end{aligned} \tag{2.12}$$

It follows that

$$\begin{aligned} \frac{dN_h(t)}{dt} &\leq \theta_h - \mu_h N_h(t), \\ \frac{dN_v(t)}{dt} &= \theta_v - \mu_v N_v(t). \end{aligned} \tag{2.13}$$

A standard comparison theorem[50] can then be used to show that $N_h(t) \leq N_h(0)\mathrm{e}^{-\mu_h t} + \frac{\theta_h}{\mu_h}(1-\mathrm{e}^{-\mu_h t})$ and $N_v(t) = N_v(0)\mathrm{e}^{-\mu_v t} + \frac{\theta_v}{\mu_v}(1-\mathrm{e}^{-\mu_v t})$. In particular, $N_h(t) \leq \frac{\theta_h}{\mu_h}$ and $N_v(t) \leq \frac{\theta_v}{\mu_v}$, if $N_h(0) \leq \frac{\theta_h}{\mu_h}$, and $N_v(0) \leq \frac{\theta_v}{\mu_v}$ respectively. Thus, the region Γ is positively invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (2.3)–(2.11) in Γ. In this region, the model is epidemiologically and mathematically well posed.[51] Thus, every solution of the basic model (2.3)–(2.11) with initial conditions in Γ remains in Γ for all $t > 0$. Therefore, the ω-limit sets of the system (2.3)–(2.11) are contained in Γ. This result is summarized below.

Lemma 2.1. *The region* $\Gamma = \Gamma_h \times \Gamma_v \subset \mathbb{R}^6_+ \times \mathbb{R}^3_+$ *is positively invariant for the basic model* (2.3)–(2.11) *with non-negative initial conditions in* $\mathbb{R}^9_+$.

2.1. *Stability of the disease-free equilibrium (DFE)*

The malaria superinfection model (2.3)–(2.11) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\mathcal{E}_0 = (S_h^*, E_h^*, I_h^*, P_h^*, T_h^*, R_h^*, S_v^*, E_v^*, I_v^*) = \left(\frac{\theta_h}{\mu_h}, 0, 0, 0, 0, 0, \frac{\theta_v}{\mu_v}, 0, 0\right).$$

The linear stability of $\mathcal{E}_0$ can be established using the next generation operator method on the system (2.3)–(2.11). We take, $E_h, I_h, P_h, T_h, R_h, E_v, I_v$, as our infected compartments, then using the notation in Ref. 52, the Jacobian matrices F and V for the new infection terms and the remaining transfer terms are respectively given by,

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta_h b_h S_h^* \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_v b_v S_v^* & \beta_v b_v \theta_5 S_v^* & \beta_v b_v (1-\eta) S_v^* & \beta_v b_v \theta_6 S_v^* & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_h & k_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_3 & 0 & 0 & 0 & 0 \\ 0 & -\kappa & -\kappa\theta_2 & k_4 & 0 & 0 & 0 \\ 0 & -r_h & -r_h\theta_3 & -r_h\gamma & k_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\sigma_v & \mu_v \end{pmatrix},$$

where $k_1 = \sigma_h + \mu_h$, $k_2 = \kappa + r_h + \mu_h + \delta_h$, $k_3 = \theta_2\kappa + \theta_3 r_h + \mu_h + \theta_4\delta_h$, $k_4 = \gamma r_h + \mu_h + (1-v)\delta_h$, $k_5 = \omega_h + \mu_h$, $k_6 = \sigma_v + \mu_v$.

It follows that the basic reproduction number of the malaria-superinfectivity system (2.3)–(2.11), denoted by $\mathcal{R}_0$, is given by

$$\begin{aligned}\mathcal{R}_0 &= \rho(FV^{-1}) \\ &= \sqrt{\frac{\beta_h b_h \sigma_h S_h^* \beta_v b_v \sigma_v S_v^* [\theta_6 r_h (k_4 + \kappa\gamma) + k_5 (k_4 + \kappa(1-\eta))]}{k_6 k_5 k_4 k_2 k_1 \mu_v}}, \end{aligned} \tag{2.14}$$

where ρ is the spectral radius.

Further, using Theorem 2 in Ref. 52, the following result is established.

Lemma 2.2. *The DFE of the malaria model* (2.3)–(2.11), *given by* $\mathcal{E}_0$, *is locally asymptotically stable* (*LAS*) *if* $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$.

The basic reproduction number ($\mathcal{R}_0$) measures the average number of new infections generated by a single infected individual in a completely susceptible population.[51–54] Thus, Lemma 2.2 implies that malaria can be eliminated from human population (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations are in the basin of attraction of the DFE, $\mathcal{E}_0$.

2.2. *Backward bifurcation analysis*

Models of disease transmission typically undergo a simple transcritical bifurcation (exchange of stability from the DFE to an endemic equilibrium) at $\mathcal{R}_0 = 1$. On the other hand, some models such as vaccination models, are known to exhibit the phenomenon of backward bifurcation, where the stable DFE co-exists with a stable endemic equilibrium when the classical epidemiological requirement of having the reproduction number less than unity is satisfied. This phenomenon has been established in a number of epidemiological settings.[34,55–63] In a backward bifurcation setting, disease control is only feasible if $\mathcal{R}_0$ is reduced further to values below another sub-threshold less than unity. The important implication of this phenomenon on public health is that the classical requirement of having the reproduction number less than unity, although necessary, is no longer sufficient for disease control. This implies that effective disease control is dependent on the initial sizes of the sub-populations of the model. It is instructive, therefore, to explore whether or not the model (2.3)–(2.11) exhibits the phenomenon of backward bifurcation. In determining this possibility in the model (2.3)–(2.11), we use the Centre Manifold theory,[64] as described in Theorem 4.1 by Castillo-Chavez and Song.[65] To apply this method, the following simplification and change of variables are made. Let, $S_h = x_1, E_h = x_2, I_h = x_3, P_h = x_4, T_h = x_5, R_h = x_6, S_v = x_7, E_v = x_8$ and $I_h = x_9$, so that $N_h = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$ and $N_v = x_7 + x_8 + x_9$. Using the vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9)^T$ together with Eqs. (2.1) and (2.2), the malaria superinfectivity model (2.3)–(2.11) can be written in the form

$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x})$, where $\mathbf{f} = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9)^T$, (with the transmission terms written out) as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \theta_h + \omega_h x_6 - \beta_h b_h x_9 x_1 - \mu_h x_1,\\
\frac{dx_2}{dt} &= f_2 = \beta_h b_h x_9 x_1 - k_1 x_2,\\
\frac{dx_3}{dt} &= f_3 = \sigma_h x_2 - k_2 x_3 - \theta_1 \beta_h b_h x_9 x_3,\\
\frac{dx_4}{dt} &= f_4 = \theta_1 \beta_h b_h x_9 x_3 - k_3 x_4,\\
\frac{dx_5}{dt} &= f_5 = \kappa(x_3 + \theta_2 x_4) - k_4 x_5,\\
\frac{dx_5}{dt} &= f_6 = r_h(x_3 + \theta_3 x_4) + \gamma r_h x_5 - k_5 x_6,\\
\frac{dx_6}{dt} &= f_7 = \theta_v - \beta_v b_v(x_3 + \theta_5 x_4 + (1-\eta)x_5 + \theta_6 x_6)x_7 - \mu_v x_7,\\
\frac{dx_7}{dt} &= f_8 = \beta_v b_v(x_3 + \theta_5 x_4 + (1-\eta)x_5 + \theta_6 x_6)x_7 - k_6 x_8,\\
\frac{dx_8}{dt} &= f_9 = \sigma_v x_8 - \mu_v x_9.
\end{aligned} \tag{2.15}$$

The Jacobian of the transformed system (2.15), at the DFE $\mathcal{E}_0$, is given by

$$J(\mathcal{E}_0) = \begin{pmatrix}
-\mu_h & 0 & 0 & 0 & 0 & \omega_h & 0 & 0 & -\beta_h b_h S_h\\
0 & -k_1 & 0 & 0 & 0 & 0 & 0 & 0 & \beta_h b_h S_h\\
0 & \sigma_h & -k_2 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & -k_3 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \kappa & \kappa\theta_2 & -k_4 & 0 & 0 & 0 & 0\\
0 & 0 & r_h & r_h\theta_3 & \gamma r_h & -k_5 & 0 & 0 & 0\\
0 & 0 & -J_1 & -\theta_5 J_1 & -J_2 & -\theta_6 J_1 & -\mu_v & 0 & 0\\
0 & 0 & J_1 & \theta_5 J_1 & J_2 & \theta_6 J_1 & 0 & -k_6 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_v & -\mu_v
\end{pmatrix}$$

with $J_1 = \beta_v b_v S_v^*$, $J_2 = (1-\eta)\beta_v b_v S_v^*$.

Consider the case when $\mathcal{R}_0 = 1$. Suppose, further, that β_v is chosen as a bifurcation parameter. Solving (2.14) for β_v from $\mathcal{R}_0 = 1$ gives

$$\beta_v^* = \frac{k_6 k_5 k_4 k_2 k_1 \mu_v}{b_h \sigma_h S_h^* \beta_h b_v \sigma_v S_v^* [\theta_6 r_h(k_4 + \kappa\gamma) + k_5(k_4 + \kappa(1-\eta))]}.$$

The transformed system (2.15) at the DFE evaluated at $\beta_v = \beta_v^*$ has a simple zero eigenvalue (and all other eigenvalues having negative real parts). Hence, the Centre Manifold theory[64] can be used to analyze the dynamics of (2.15) near $\beta_v = \beta_v^*$. We apply Theorem 4.1[65] in our Appendix A (see related Refs. 52, 59 and 64) with β_v as the bifurcation parameter and perform the following computations.

2.3. *Eigenvectors of $J(\mathcal{E}_0)|_{\beta_v=\beta_v^*}$*

The Jacobian of (2.15) at $\beta_v = \beta_v^*$, denoted by $J(\mathcal{E}_0)|_{\beta_v=\beta_v^*}$ has a right eigenvector (associated with the zero eigenvalue) given by $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9)^T$, where

$$w_1 = -\frac{(\omega_h w_6 - \beta_h b_h S_h^* w_9)}{\mu_h}, \quad w_2 = \frac{\beta_h b_h w_9 S_h^*}{k_1}, \quad w_3 = \frac{\sigma_h w_2}{k_2}, \quad w_4 = 0,$$

$$w_5 = \frac{\kappa w_3}{k_4}, \quad w_6 = \frac{r_h w_3 + \gamma r_h w_5}{k_5}, \quad w_7 = -\frac{J_1 w_3 + J_1 w_4 + J_2 w_5 + J_1 w_6}{\mu_v},$$

$$w_8 = \frac{J_1 w_3 + \theta_5 J_1 w_4 + J_2 w_5 + \theta_6 J_1 w_6}{k_6}, \quad w_9 = w_9 > 0.$$

Also, $J(\mathcal{E}_0)|_{\beta_v=\beta_v^*}$ has a left eigenvector $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)^T$ (associated with the zero eigenvalue), where

$$v_1 = 0, \quad v_2 = \frac{\sigma_h v_3}{k_1}, \quad v_3 = \frac{\kappa v_5 + r_h v_6 + J_1 v_8}{k_2},$$

$$v_4 = \frac{\kappa\theta_2 v_5 + r_h \theta_3 v_6 + \theta_5 J_1 v_8}{k_2}, \quad v_5 = \frac{\gamma r_h v_6 + J_2 v_8}{k_4},$$

$$v_6 = \frac{\theta_6 J_1 v_8}{k_5}, \quad v_7 = 0, \quad v_8 = \frac{\sigma_v v_9}{k_6}, \quad v_9 = v_9 > 0.$$

To use the result from Theorem 4.1 in Ref. 65 (given in our Appendix A), we need to calculate a and b given below.

$$\begin{aligned} a &= v_2 \sum_{i,j=1}^{9} w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_3 \sum_{i,j=1}^{9} w_i w_j \frac{\partial^2 f_3}{\partial x_i \partial x_j} \\ &\quad + v_4 \sum_{i,j=1}^{9} w_i w_j \frac{\partial^2 f_4}{\partial x_i \partial x_j} + v_8 \sum_{i,j=1}^{9} w_i w_j \frac{\partial^2 f_8}{\partial x_i \partial x_j} \\ &= 2[(v_4 - v_3) w_3 w_9 \theta_1 \beta_h b_h + v_2 w_1 w_9 \beta_h b_h \\ &\quad + v_8((1-\eta) w_5 + w_6 \theta_6 + w_3) w_7 \beta_v b_v], \end{aligned} \tag{2.16}$$

and,

$$b = v_8 \sum_{i,j=1}^{9} w_i \frac{\partial^2 f_2}{\partial x_i \partial \beta_v^*} = v_8 b_v S_v^* (w_3 + w_5(1-\eta) + \theta_6 w_6) > 0.$$

Since the coefficient b is always positive, thus the transformed model (2.15) [or, equivalently, (2.3)–(2.11)] undergoes backward bifurcation at $\mathcal{R}_0 = 1$, if the coefficient $a > 0$. This result is summarized below.

Theorem 2.1. *The malaria superinfectivity model* (2.15) *undergoes a backward bifurcation at* $\mathcal{R}_0 = 1$ *whenever the inequality* $a > 0$ *holds.*

This (backward bifurcation) phenomenon is illustrated by simulating the model (2.15), using a set of parameter values given in Table 1 (such that the inequality ($a > 0$) is satisfied). The result obtained is depicted in Fig. 2. With the set of parameter values used in these simulations, the bifurcation coefficients a and b take the values $a = 0.7321 > 0$ and $b = 0.4667 > 0$, respectively.

Table 1. Description of the parameters of the malaria models (2.3)–(2.11). The rates are given per day.

Parameter	Description	Baseline value	References
θ_h	Recruitment rate of humans	0.00011	[66]
θ_v	Recruitment rate of vectors	0.071	[53,67]
b_h	Biting rate of the vectors on a human host	0.2–0.5	[68]
b_v	Rate at which bites are received by a single host from the vectors	0.3	[69,70]
β_h	Transmission probabilities per contact for humans	0.1–0.5	[67,71]
β_v	Transmission probabilities per contact for vectors	0.2	[67,71]
b	Efficacy of personal protection	0.7	[32]
z	Compliance to personal protection	0.41	[32]
σ_h	Progression rate to infected humans	$\frac{1}{10}$	[22,53]
σ_v	Progression rate to infected vectors	$\frac{1}{11}$	[70,72,73]
θ_1	Superinfectivity factor	5.44	[27]
θ_2	Reduced treatment factor	0.06	assume
θ_3	Reduced recovery factor	0.6	[14]
θ_4	Increased disease mortality factor	0.6	assume
θ_5	Increased infectivity factor	5.44	[27]
θ_6	Recovered reduced infectivity factor	0.06	assume
μ_h	Natural mortality rate for humans	0.0000391	[66]
μ_v	Natural mortality rate for vectors	0.071	[74]
δ_h	Disease-induced mortality rate in humans	0.00000426	[75]
κ	Treatment rate	0.2	[32]
r_h	Recovery rate	$\frac{1}{100}$	[22,53,76]
γ	Modification parameter	8.04	[32]
η	Drug efficacy in reducing infectiousness	0.86	[32]
v	Drug efficacy in reducing disease-induced death	0.02	[32]
ω_h	Rate of loss of immunity rate	$\frac{1}{200}$	[53,67,76]

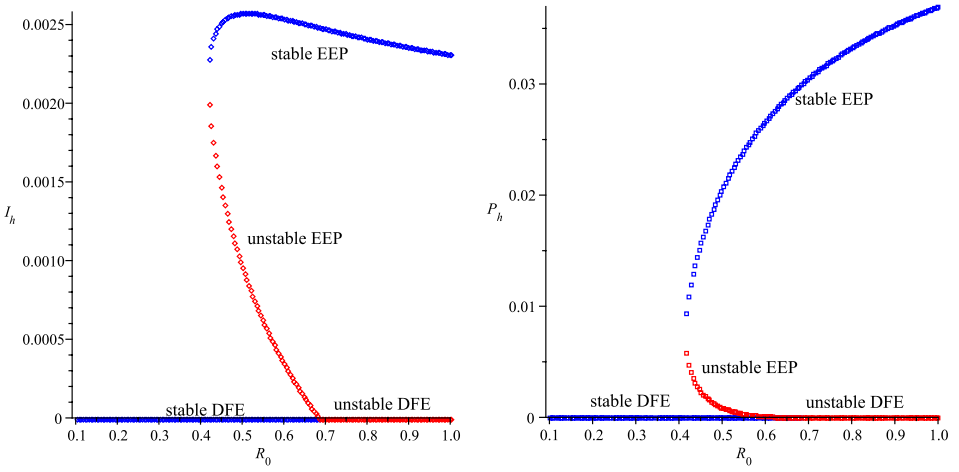


Fig. 2. Backward bifurcation plot for the models (2.3)–(2.11), using $\theta_h = 0.011, \mu_h = 0.047, \gamma = 0.6, \eta = 0.65, v = 0.67, r_h = 1/20, \kappa = 0.65, \sigma_v = 1/9, b_h = 0.5, b_v = 0.5, \beta_h = 0.75, \beta_v = 0.5258$. (a) Backward bifurcation plot for the infected human population. (b) Backward bifurcation plot for the superinfected human population.

2.4. *The role of superinfectivity on backward bifurcation*

It is worth noting that in the absence of superinfectivity ($\theta_1 = \theta_2 = \theta_3 = \theta_4 = \theta_5 = 0$), the equality (2.16) reduces to

$$a = 2[v_2 w_1 w_9 \beta_h b_h + v_8((1-\eta)w_5 + w_6\theta_6 + w_3)w_7\beta_v b_v] > 0, \tag{2.17}$$

Thus, the backward bifurcation in the model (2.3)–(2.11) might still be possible even if superinfection does not occur. It should be mentioned that this backward bifurcation phenomenon was also observed in single and repeated exposure malaria models considered in Refs. 16, 30 and 34 and in the transmission dynamics of dengue disease,[61] another vector-borne disease.

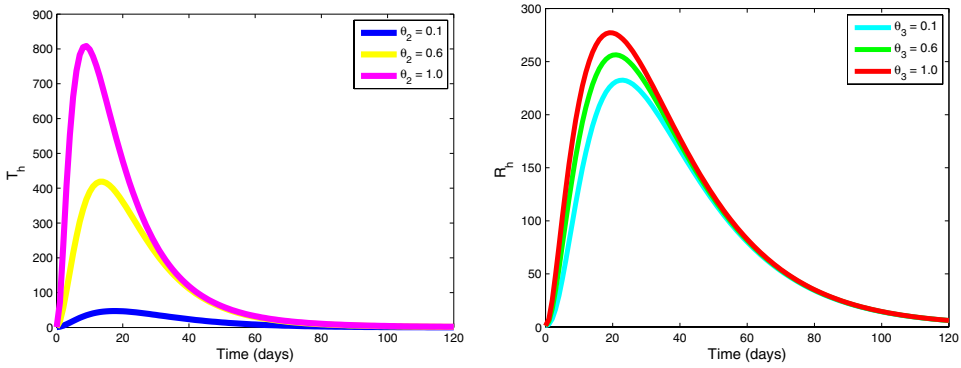
The impact of the superinfectivity-related parameters (θ_1 and θ_5) on the backward bifurcation is assessed by carrying out an analysis on the bifurcation coefficient a as follows. Differentiating a, given in (2.16), with respect to θ_1 gives

$$\frac{\partial a}{\partial \theta_1} = 2[H_1 w_3 w_9 \beta_h b_h], \tag{2.18}$$

with

$$H_1 = (v_4 - v_3) = \frac{\kappa(\theta_2 - 1)v_5 + r_h(\theta_3 - 1)v_6 + (\theta_5 - 1)J_1 v_8}{k_2}.$$

Hence, the bifurcation coefficient a is an increasing (decreasing) function of θ_1 if H_1 is positive (negative). Thus, the feasibility of superinfectivity increasing backward bifurcation increases if $H_1 > 0$. On the other hand, the coefficient a remains positive if $H_1 < 0$. Note, backward bifurcation is not eliminated if $\theta_1 = 0$.



(a) (b)

Fig. 3. Simulation results for the impact of superinfectivity on treated and recovered classes. (a) Simulation diagram for treated humans with $\theta_2 = 0.1, 0.6, 1.0$. (b) Simulation diagram for recovered humans with $\theta_3 = 0.1, 0.6, 1.0$.

Also differentiating a, given in (2.16), with respect to θ_5 gives

$$\frac{\partial a}{\partial \theta_5} = \frac{2J_1 v_8 w_3 w_9 \theta_1 \beta_h b_h}{k_2} > 0, \tag{2.19}$$

hence, the bifurcation coefficient a is an increasing function of θ_5. Thus, increased infectivity of the superinfection increases backward bifurcation.

To monitor the impact of superinfectivity on treatment and recovery in a community, the model is simulated varying superinfectivity related parameters θ_2 and θ_3, and using parameter values in Table 1, except otherwise stated, with initial conditions $S_h = 440$, $E_h = 0$, $I_h = 110$, $P_h = 0$, $T_h = 1$, $R_h = 1$, $S_v = 950$, $E_v = 0$, $I_v = 5$.

The graphs in Fig. 3(a) are obtained by varying θ_2 from 0.1 to 1.0 and this shows that as the parameter θ_2 is been increased from 0.1 to 1.0 there is a corresponding increase in the treated class T_h. Similarly, the graphs in Fig. 3(b) are obtained by varying θ_3 from 0.1 to 1.0, where Fig. 3(b) shows that as the parameter θ_3 is been increased from 0.1 to 1.0 there is a corresponding increase in the recovered class R_h.

3. Formulation and Analysis of an Optimal Control Problem

We now modify our model with time-dependent treatment effort as control for the system,

$$\dot{S}_h = \theta_h + \omega_h R_h - f_h S_h - \mu_h S_h, \tag{3.1}$$

$$\dot{E}_h = f_h S_h - \sigma_h E_h - \mu_h E_h, \tag{3.2}$$

$$\dot{I}_h = \sigma_h E_h - u(t) I_h - r_h I_h - \mu_h I_h - \delta_h I_h - \theta_1 f_h I_h, \tag{3.3}$$

$$\dot{P}_h = \theta_1 f_h I_h - \theta_2 u(t) P_h - \theta_3 r_h P_h - \mu_h P_h - \theta_4 \delta_h P_h, \tag{3.4}$$

$$\dot{T}_h = u(t) I_h + \theta_2 u(t) P_h - \gamma r_h T_h - \mu_h T_h - (1-v)\delta_h T_h, \tag{3.5}$$

$$\dot{R}_h = r_h(I_h + \theta_3 P_h) + \gamma r_h T_h - \omega_h R_h - \mu_h R_h, \tag{3.6}$$

$$\dot{S}_v = \theta_v - f_v S_v - \mu_v S_v, \tag{3.7}$$

$$\dot{E}_v = f_v S_v - \sigma_v E_v - \mu_v E_v, \tag{3.8}$$

$$\dot{I}_v = \sigma_v E_v - \mu_v I_v. \tag{3.9}$$

The function, $u(t)$ represents the rate of the system control for effective treatment of infected and superinfected individuals. Thus, $u(t)$ and $\theta_2 u(t)$, are the transfer rates ($u(t)I_h$ and $\theta_2 u(t) P_h$) out of I_h and P_h classes, which correspond to waiting times with negative exponential distributions.[44,51] We assume that the control $u(t)$ is a bounded, Lebesgue integrable function.[42,44] Equations (3.1)–(3.9) thus represent the dynamics for increasing disease treatment using time-dependent control.

The objective functional is given as:

$$J(u) = \int_0^{t_f} [A_1 I_h + A_2 P_h + Cu] dt, \tag{3.10}$$

where t_f is the final time and the coefficients, A_1, A_2, C are balancing cost factors. Then the number of individuals with malaria, as well as the costs for applying control on treatment ($u(t)$), in individuals with malaria is minimized subject to the differential equations (3.1)–(3.9). The costs can include funds needed for control implementation, hospitalization and loss of man hours due to illness. Hence, we seek to find an optimal control, $u^*(t)$, such that

$$J(u^*) = \min_{u \in \mathcal{U}} \{J(u)\}, \tag{3.11}$$

where $\mathcal{U} = \{u \colon [0, t_f] \to [a, b],\ u \text{ is Lebesgue measurable}\}$ and a, b, are fixed positive constants.

The time range in days from onset of symptoms to seeking first treatment, for instance in Ethiopia, was estimated to be less than one day and greater than 6 days.[77–79] Thus, the mean time $1/u$ is set to be between 1–8 days, which makes $u(t)$ range between 0.125–1 and hence, we set the lower bound $a = 0$ and upper bound $b = 1$, to accommodate the worst case of no treatment and treating immediately at the onset of symptoms. Due to boundedness of our states and the structure of our systems, an optimal control exists from Corollary 4.1 of Ref. 80.

3.1. *Characterization of optimal controls*

The necessary conditions that an optimal control and corresponding states must satisfy come from the Pontryagin's Maximum Principle.[46] This principle converts (3.1)–(3.9) and (3.10) into a problem of minimizing pointwise a Hamiltonian H, with respect to (u). First form the Hamiltonian from the cost functional (3.10) and

the governing dynamics (3.1)–(3.9) to obtain the optimality conditions. After some grouping of terms, the Hamiltonian becomes:

$$H = \psi u + H_0,$$

where

$$\begin{aligned}
\psi &= C - I_h\lambda_{I_h} - \theta_2 P_h\lambda_{P_h} + (I_h + \theta_2 P_h)\lambda_{T_h},\\
H_0 &= A_1 I_h + A_2 P_h + \lambda_{S_h}(\theta_h + \omega_h R_h - f_h S_h - \mu_h S_h)\\
&\quad + \lambda_{E_h}(f_h S_h - \sigma_h E_h - \mu_h E_h)\\
&\quad + \lambda_{I_h}(\sigma_h E_h - r_h I_h - \mu_h I_h - \delta_h I_h - \theta_1 f_h I_h)\\
&\quad + \lambda_{P_h}(\theta_1 f_h I_h - \theta_3 r_h P_h - \mu_h P_h - \theta_4\delta_h P_h)\\
&\quad + \lambda_{T_h}(-\gamma r_h T_h - \mu_h T_h - (1-v)\delta_h T_h)\\
&\quad + \lambda_{R_h}(r_h(I_h + \theta_3 P_h) + \gamma r_h T_h - \omega_h R_h - \mu_h R_h)\\
&\quad + \lambda_{S_v}(\theta_v N_v - f_v S_v - \mu_v S_v) + \lambda_{E_v}(f_v S_v - \sigma_v E_v - \mu_v E_v)\\
&\quad + \lambda_{I_v}(\sigma_v E_v - \mu_v I_v),
\end{aligned} \tag{3.12}$$

where the λ_{S_h}, λ_{E_h}, λ_{I_h}, λ_{P_h}, λ_{T_h}, λ_{R_h}, λ_{S_v}, λ_{E_v}, λ_{I_v} are the associated adjoints for the states $S_h, E_h, I_h, P_h, T_h, R_h, S_v, E_v, I_v$. The system of adjoint equations is found by taking the appropriate partial derivatives of the Hamiltonian (3.12) with respect to the associated state variable. Note that our problem is linear in the control, so we expect an optimal control to be bang-bang, and/or singular.

Theorem 3.1. *Given an optimal control u^* and solutions S_h^*, E_h^*, I_h^*, P_h^*, T_h^*, R_h^*, S_v^*, E_v^*, I_v^* of the corresponding state system (3.1)–(3.9) that minimizes $J(u)$ over $\mathcal{U}$, then there exists adjoint variables λ_{S_h}, λ_{E_h}, λ_{I_h}, λ_{P_h}, λ_{T_h}, λ_{R_h}, λ_{S_v}, λ_{E_v}, λ_{I_v} satisfying*

$$-\frac{d\lambda_i}{dt} = \frac{\partial H}{\partial i}, \tag{3.13}$$

and with transversality conditions

$$\lambda_i(t_f) = 0, \quad \text{where } i = S_h, E_h, I_h, P_h, T_h, R_h, S_v, E_v, I_v. \tag{3.14}$$

The representation of this optimal control is determined by the switching function $\partial H/\partial u$ (denoted by ψ),

$$u^* = \begin{cases} b, & \text{if } \psi < 0\\ a, & \text{if } \psi > 0\\ u_s, & \text{if } \psi = 0, \end{cases} \tag{3.15}$$

where the singular control u_s is optimal and is given by

$$u_s = \frac{N}{D}, \tag{3.16}$$

provided $D > 0$ and $a \le \frac{N}{D} \le b$, (see Appendix B for definition of D and N).

The proof is given in Appendix C.

For any $T > 0$, the existence of an optimal control follows from standard results.[46,80] The uniqueness of the optimal control is only guaranteed for small t_f[46] using the *a priori* boundedness of the state and adjoint functions and the resulting Lipschitz structure of the system's ODEs. This restriction on the final time t_f is due to the opposite time orientations of the optimality system; the state system has initial values, while the adjoint system has final values.

Next we solve numerically the optimality system and discuss the corresponding results of varying certain parameters, and the interpretations from various cases.

4. Numerical Illustrations

Numerical solutions to the optimality system comprising of the state equations (3.1)–(3.9), adjoint equations (3.13), control characterization (3.15) and corresponding initial/final conditions are carried out using MATLAB and using parameters in Table 1. The algorithm is the forward–backward scheme, starting with an initial guess for the optimal control u, the state variables are then solved forward in time from the dynamics (3.1)–(3.9) using a Runge–Kutta method of the fourth order. Then those state variables and initial control guess are used to solve the adjoint equations (3.13) backward in time with given final conditions (3.14), again employing a fourth order Runge–Kutta method. The control u is updated and used to solve the state and then the adjoint system. We calculate the switching function ψ and check the conditions for singular control. This iterative process terminates when current state, adjoint and control values converge sufficiently.[82] We note that the singular case did not occur in our numerical cases. Uniqueness of an optimal control may be difficult to prove for a large t_f, but there was no indication of nonuniqueness of the optimal control for the cases considered here.

We explore the malaria transmission model with superinfected individuals to study the effects of time-dependent treatment control measures, and using parameters so that reproduction number $\mathcal{R}_0 = 3.60$, indicating that malaria is endemic in the population. The following values are used for the cost on infectives and control, $A_1 = 1$, $A_2 = 1$, $C = 1$, with initial conditions $S_h(0) = 420$, $E_h(0) = 10$, $I_h(0) = 5$, $P_h(0) = 1$, $T_h(0) = 1$, $R_h(0) = 1$, $S_v(0) = 250$, $E_v(0) = 0$, $I_v(0) = 10$ and the values of following parameters different from those listed in Table 1, $\mu_h = 0.000047$, $\gamma = 6.5$, $\eta = 0.65$, $\upsilon = 0.67$, $\theta_1 = 0.004$, $\theta_2 = 0.025$, $\theta_3 = 0.025$, $\theta_4 = 0.02$, $\theta_5 = 0.46$, $\theta_6 = 0.5$, $\sigma_v = 1/9$, $\beta_h = 0.29$.

From Fig. 4(a) it is observed that the total number of infected humans in the presence of treatment is less than the total number without treatment. Now due to superinfectivity there is a reduction in the number of infected human in the I_h class and growth in the superinfected class P_h [see Fig. 4(b)], but with treatment P_h is lower. The total number in the treated class T_h is shown in Fig. 4(c) and the total number recovered is shown in Fig. 4(d). The time-dependent control u depicted in Fig. 4(e) is observed to be in the upper bound for about 60 days before switching to the lower bound.

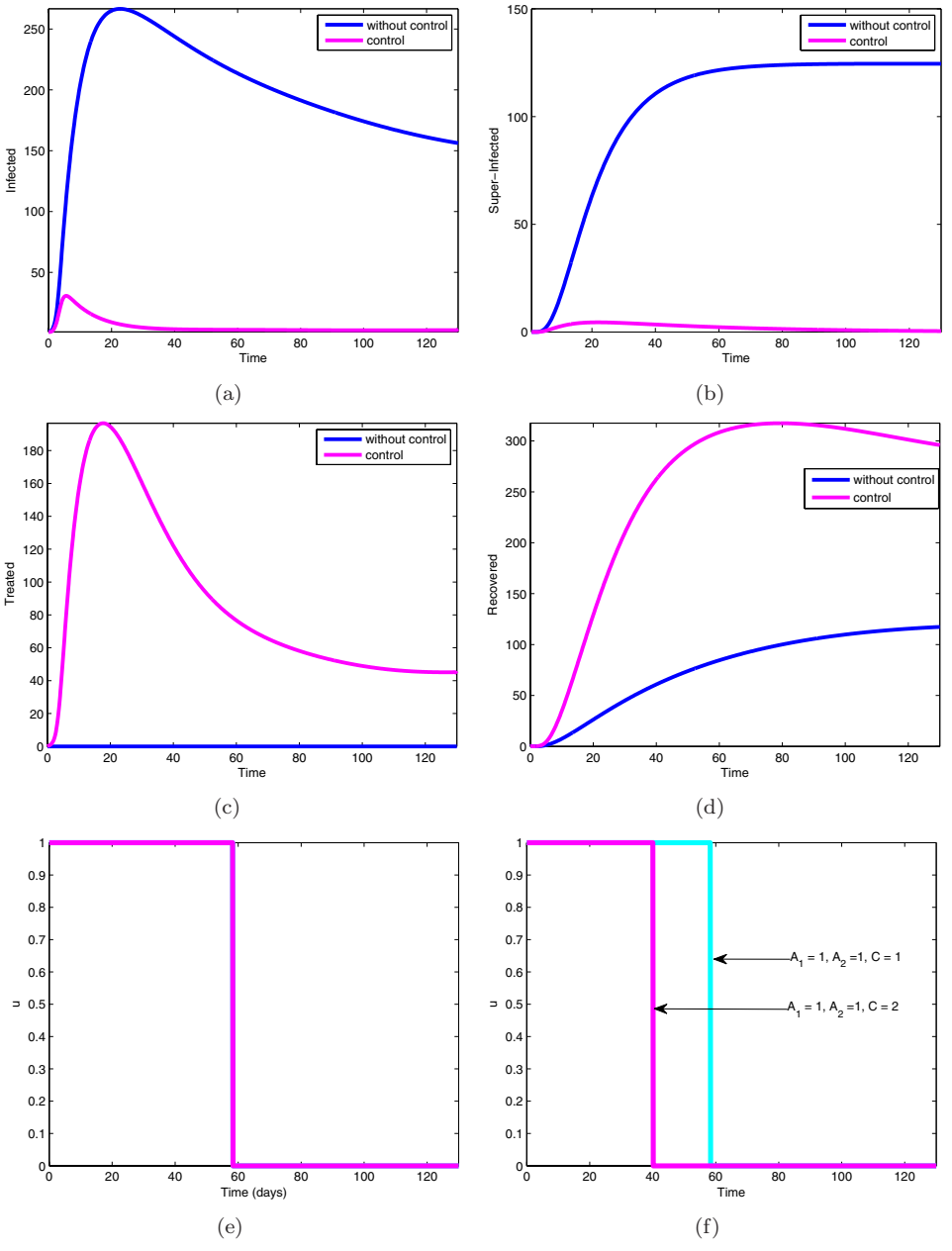
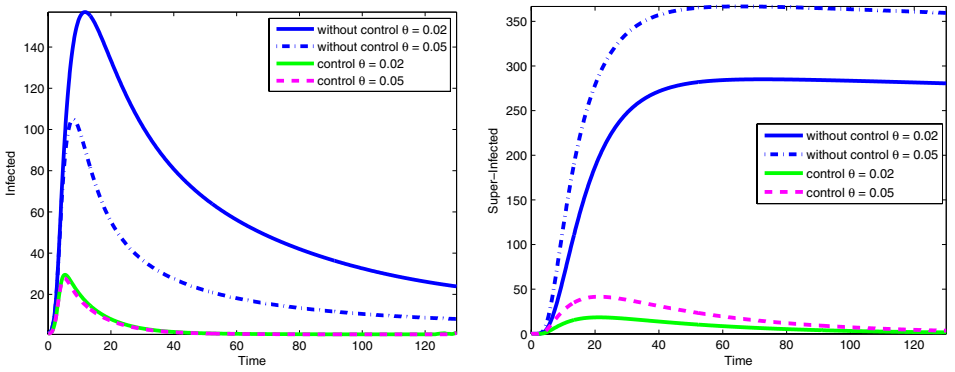


Fig. 4. Simulation results for the model (2.3)–(2.11), showing the cases with and without control. (a) Infected humans. (b) Superinfected humans with time-dependent control. (c) Treated humans. (d) Recovered humans. (e) The time-dependent optimal control. (f) Simulation diagram for control. Optimal control plot with different cost weights.



(a) (b)

Fig. 5. Simulation results for model (2.3)–(2.11) with $\theta_1 = 0.02, 0.05$. (a) Infected humans. (b) Superinfected humans.

If the weight on control cost C is doubled, it is seen that the control is at the upper bound for about 40 days before switching to the lower bound as opposed the 60 days when the weight $C = 1$, as seen in Fig. 4(f). This result is as expected, since a higher cost causes the use of less control.

Now, we consider the impact of the time-dependent treatment control while varying θ_1, the parameter that gives the increased infectivity of the infectious class $I_h(t)$. Using the values of $\theta_1 = 0.02, 0.05$, we observed that as θ_1 increases, in the absence of treatment, there is a decrease in the total number of infected individuals [see Fig. 5(a)] leading to a corresponding increase in the total number of superinfected P_h as revealed in Fig. 5(b). The application of treatment control lead to a substantial reduction in the total number of infected and superinfected humans, with $\theta_1 = 0.02$ resulting in the least total number of superinfected in Fig. 5(b). Furthermore, the increase in θ_1 leads to a corresponding decrease in the total number treated and a subsequent decrease in the total number of recovered individuals. It was also observed that when $\theta_1 = 0.05$ the control u was at the upper bound for a longer period of time before switching to the lower bound when compared to results from the $\theta_1 = 0.02$ case.

5. Conclusions

The paper considers the first system of differential equations modeling the transmission dynamics of superinfectivity in malaria, and the stability of this model is rigorously analyzed. We have also investigated optimal control of treatment efforts in such a model. Since the model is linear in the control, a careful analysis for the bang-bang and singular cases was given. Some of the main theoretical and

epidemiological findings of this study are summarized below:

(i) The model exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium, when the associated reproduction number is less than unity. The epidemiological implication of this result is that having the reproduction number less than unity, while necessary, is no longer sufficient for eliminating malaria in the population; The degree of backward bifurcation increases with increasing superinfectivity, depending on the sign of a threshold quantity (H_1);
(ii) Increasing superinfected related treatment and recovery parameters leads to an increase in number of treated and recovered individuals;
(iii) The total number infected and superinfected individuals can be reduced in the population by the application of time-dependent control. As a key, the superinfectivity parameter θ_1 increases the corresponding optimal control which is at the upper bound for a longer period of time before switching to the lower bound.

In the future, we will extend this simple model to include other features that will add further realism. The inclusion of a control constraint to represent having a limited drug supply would be interesting. Age-structure could be included to study the impact on children, who suffer the most from superinfectivity. Consideration of multi-strains in the model would also be important. The issue of drug resistance is another valid feature to investigate.

Acknowledgments

Both of the authors acknowledges the support, in part, of National Institute for Mathematical and Biological Synthesis (NIMBioS). NIMBioS is an Institute sponsored by the National Science Foundation, the U.S. Department of Homeland Security, and the U.S. Department of Agriculture through NSF Award #EF-0832858, with additional support from The University of Tennessee, Knoxville. Lenhart is partially supported by the University of Tennessee Center for Business and Economic Research. The authors are grateful to the anonymous reviewers for their constructive comments.

References

1. World Health Organization (WHO) Malaria, 2010, Available at http://www.who.int/mediacentre/factsheets/fs094/en/.
2. World Health Organization (WHO) World malaria report, 2009.
3. Lindsay SW, Martens WJM, Malaria in the African highlands: Past, present and future, *Bull WHO* **76**:33–45, 1998.
4. Zhou G, Minakawa N, Githeko AK, Yan G, Association between climate variability and malaria epidemics in the east African highlands, *Proc Natl Acad Sci USA* **101**(8):2375–2380, 2004.

5. Bush AO, Fernandez JC, Esch GW, Seedv JR, Parasitism: The Diversity and Ecology of Animal Parasites, 1st ed., Cambridge University Press, Cambridge, 2001.
6. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF, HIV infection as a cofactor for severe *falciparum* malaria in adults living in a region of unstable malaria transmission in South Africa, *Aids* **18**:547–554, 2004.
7. Cancré N, Tall A, Rogier C, Faye J, Sarr O, Trape J, Spiegel A, Bois F, Bayesian analysis of an epidemiologic model of *Plasmodium falciparum* malaria infection in ndiop, senegal, *Am J Epidemiol* **152**(8):760–770, 2000.
8. Rosenberg R, Andre RG, Ketrangse S, Seasonal fluctuation of Plasmodium falciparum gametocytaemia, *Trans R Soc Trop Med Hyg* **84**:29–33, 1990.
9. Smith DL, Dushoff J, Snow RW, Hay SI, The entomological inoculation rate and *Plasmodium falciparum* infection in African children, *Nature* **438**(7067):492–495, 2005.
10. Smith DL, Simon IH, Endemicity response timelines for Plasmodium falciparum elimination, *Malar J* **8**:87, 2009.
11. Dietz K, Molineaux L, Thomas A, A malaria model tested in the African savannah, *Bull World Health Org* **50**:347–357, 1974.
12. Nedelman J, Introductory review: Some new thoughts about some old malaria models, *Math Biosci* **73**:159–182, 1985.
13. Nedelman J, Inoculation and recovery rates in the malaria model of Dietz, Molineaux, and Thomas, *Math Biosci* **69**:209–233, 1984.
14. Parthasarathy PR, The effect of superinfection on the distribution of the infectious period — A continued fraction approximation, *IMA J Math Appl Med Biol* **14**:113–123, 1997.
15. MacDonald G, The analysis of infection rates in diseases in which superinfection occurs, *Trop Dis Bull* **47**:907–914, 1950.
16. Niger AM, Gumel AB, Mathematical analysis of the role of repeated exposure on malaria transmission dynamics, *Differ Equ Dyn Syst* **16**(3):251–287, 2008.
17. Rutledge LC, Gould DJ, Tantichareon B, Factors affecting the infection of anophelines with human malaria in Thailand, *Trans R Soc Trop Med Hyg* **63**:613–619, 1969.
18. Macdonald G, Majid A, Report on an intensive malaria survey in the karmal district, *Punjab Rec Malar Surv India* **2**:423, 1931.
19. Drakeley CJ, Secka1 I, Correa1 S, Greenwood BM, Targett GAT, Host haematological factors influencing the transmission of Plasmodium falciparum gametocytes to Anopheles gambiae s.s. mosquitoes, *Trop Med Int Health* **4**(2):131–138, 1999.
20. Wilson DB, Report of the malaria unit, Tonga, 1933–34, together with a report on a study of malaria in India, Government Printer, Dar-es-Salaam, 1936.
21. Greenwood BM, Bradley AK, Greenwood AM, Byass P, Jammeh K, Marsh K *et al.*, Mortality and morbidity from malaria among children in a rural area of the Gambia, West Africa, *Trans R Soc Trop Med Hyg* **81**:478–486, 1987.
22. Molineaux L, Gramiccia G, The Garki Project, World Health Organization, 1980.
23. Coggeshall L, Kumm HW, Effect of repeated superinfection upon the potency of immune serum of monkeys harboring chronic infections of plasmiodium knowlesi, *J Exp Med* **68**(1):17–27, 1938.
24. Portugal S, Drakesmith H, Mota MM, Superinfection in malaria: Plasmodium shows its iron will, *EMBO Rep* **12**(12):1233–1242, 2011.
25. van Santen S, de Mast Q, Swinkels DW, van der Ven AJAM, Hepcidin in malaria superinfection: Can findings be translated to humans? *Nature Med* **17**(11):1341, 2011.
26. Portugal S, Carret C, Recker M, Armitage AE, Gonalves LA, Epiphanio S, Sullivan D, Roy C, Newbold CI, Drakesmith H, Mota MM, Host-mediated regulation of superinfection in malaria, *Nat Med* **17**(6):732–738, 2011.

27. Nåsell I, On superinfection in malaria, *IMA J Math Appl Med Biol* **3**:211–227, 1986.
28. Aneke SJ, Mathematical modelling of drug resistant malaria parasites and vector populations, *Math Meth Appl Sci* **25**:335–346, 2002.
29. Bacae N, Sokna RC, A, reaction-diffusion system modeling the spread of resistance to an antimalarial drug, *Math Biosci Eng* **22**:227–238, 2005.
30. Nakul C, Cushing JM, Hyman JM, Bifurcation analysis of a mathematical model for malaria transmission, *SIAM J Appl Math* **67**:24–45, 2006.
31. Chiyaka C, Garira W, Dube S, Transmission model of endemic human malaria in a partially immune population, *Math Comput Modelling* **46**:806–822, 2007.
32. Chiyaka C, Tchuenche JM, Garira W, Dube S, A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria, *Appl Math Comput* **195**:641–662, 2008.
33. Koella JC, Antia R, Epidemiological models for the spread of antimalarial resistance, *Malar J* **2**:3, 2003.
34. Mukandavire Z, Gumel AB, Garira W, Tchuenche JM, Mathematical analysis of a model for HIV-Malaria co-infection, *Math Biosci Eng* **6**(2):333–362, 2009.
35. Blayneh K, Cao Y, Kwon H-D, Optimal control of vector-borne diseases: Treatment and prevention, *Discrete Continuous Dyn Syst-Ser B* **11**(3):587–411, 2009.
36. Felippe de Souza JAM, Caetano MAL, Yoneyama T, Optimal control theory applied to the anti-viral treatment of AIDS, *Proc 39th IEEE Conf Decision and Control* Sydney, Australia, Vol. 5, pp. 4839–4844, 2000.
37. Fister KR, Lenhart S, McNally JS, Optimizing chemotherapy in an HIV model, *Electron J Diff Equat* **32**:1–12, 1998.
38. Kwon H-D, Optimal treatment strategies derived from a HIV model with drug-resistant mutants, *Appl Math Comput* **188**:1193–1204, 2007.
39. Joshi HR, Optimal control of an HIV immunology model, *Optim Control Appl Math* **23**:199–213, 2002.
40. Karrakchou J, Rachik M, Gourari S, Optimal control and infectiology: Application to an HIV/AIDS model, *Appl Math Comput* **177**:807–818, 2006.
41. Kirschner D, Lenhart S, Serbin S, Optimal control of the chemotherapy of HIV, *J Math Biol* **35**:775–792, 1997.
42. Jung E, Lenhart S, Feng Z, Optimal control of treatments in a two-strain tuberculosis model, *Discrete Continuous Dyn Syst B* **2**(4):473–482, 2002.
43. Yan X, Zou Y, Li J, Optimal quarantine and isolation strategies in epidemics control, *World J Modell Simul* **3**(3):202–211, 2007.
44. Yan X, Zou Y, Optimal and sub-optimal quarantine and isolation control in SARS epidemics, *Math Comput Modell* **47**:235–245, 2008.
45. Caetano MAL, Yoneyama T, Optimal and sub-optimal control in Dengue epidemics, *Optim Control Appl Methods* **22**:63–73, 2001.
46. Pontryagin LS, Boltyanskii VG, Gamkrelidze RV, Mishchenko EF, *The Mathematical Theory of Optimal Processes*, Wiley, New York, 1962.
47. Aron JL, May RM, The population dynamics of malaria, in Anderson RM (ed.) *The Population Dynamics of Infectious Diseases*: *Theory and Application*, Halstead, New York, pp. 139–179, 1980.
48. Bailey NTJ, *The Biomathematics of Malaria*, Griffin, London, 1982.
49. Covell G, Relationship between malaria paresitaemia and symptoms of the disease: A review of the literature, *Bull World Health Org* **22**:605–619, 1960.
50. Lakshmikantham V, Leela S, Martynyuk AA, *Stability Analysis of Nonlinear Systems*, Marcel Dekker, Inc., New York and Basel, 1989.

51. Hethcote HW, The mathematics of infectious diseases, *SIAM Rev* **42**(4):599–653, 2000.
52. van den Driessche P, Watmough J, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math Biosci* **180**:29–48, 2002.
53. Anderson RM, May R, *Infectious Diseases of Humans*, Oxford University Press, New York, 1991.
54. Diekmann O, Heesterbeek JAP, Metz JAP, On the definition and computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, *J Math Biol* **28**:503–522, 1990.
55. Agusto FB, Gumel AB, Theoretical assessment of avian influenza vaccine, *Discrete Continuous Dyn Syst B* **13**(1):1–25, 2010, doi:10.3934/dcdsb.2009.13.1.
56. Agusto FB, Gumel AB, Quantitative analysis for a model for the transmission dynamics of low and highly pathogenic avian influenza, *Math Biosci* **243**(2):147–162, 2013.
57. Agusto FB, Del Valle SY, Blayneh KW, Ngonghala CN, Goncalves MJ, Li N, Zhao R, Gong H, The impact of bed-net use on malaria prevalence, *J Theor Biol* **320**(7):58–65, 2013.
58. Brauer F, Backward bifurcations in simple vaccination models, *J Math Anal Appl* **298**(2):418–431, 2004.
59. Dushoff J, Wenzhang H, Castillo-Chavez C, Backwards bifurcations and catastrophe in simple models of fatal diseases, *J Math Biol* **36**:227–248, 1998.
60. Elbasha EH, Gumel AB, Theoretical assessment of public health impact of imperfect prophylactic HIV-1 vaccines with therapeutic benefits, *Bull Math Biol* **68**:577–614, 2006.
61. Garba SM, Gumel AB, Abu Bakar MR, Backward bifurcations in dengue transmission dynamics, *Math Biosci* **215**(1):11–25, 2008.
62. Sharomi O, Podder CN, Gumel AB, Elbasha EH, Watmough J, Role of incidence function in vaccine-induced backward bifurcation in some HIV models, *Math Biosci* **210**:436–463, 2007.
63. Sharomi O, Podder CN, Gumel AB, Song B, Mathematical analysis of the transmission dynamics of HIV/TB co-infection in the presence of treatment, *Math Biosci Eng* **5**(1):145–174, 2008.
64. Carr J, *Applications of Centre Manifold Theory*, Springer-Verlag, New York, 1981.
65. Castillo-Chavez C, Song B, Dynamical models of tuberculosis and their applications, *Math Biosci Eng* **1**(2):361–404, 2004.
66. U.S. Census Bureau, International Database. 2007.
67. Flahault A, Le Menach A, McKenzie EF, Smith DL, The unexpected importance of mosquito oviposition behaviour for malaria: Non-productive larval habitats can be sources for malaria transmission, *Malar J* **4**:23, 2005.
68. Ariey F, Robert V, The puzzling links between malaria transmission and drug resistance, *Trends Parasitol* **19**:158–160, 2003.
69. Mbogob CM, Gu W, Killeena GF, An individual-based model of *plasmodium falciparum* malaria transmission on the coast of kenya, *Trans R Soc Trop Med Hyg* **97**:43–50, 2003.
70. Snow RW, Omumbo J, *Malaria*, *in Disease and Mortality in Sub-Saharan Africa*, 2nd edn. Jamison DT, Feachem RG, Makgoba MW *et al.*, eds. World Bank, Washington (DC), pp. 195–213, 2006.
71. Smith DL, Mckenzie EF, Statics and dynamics of malaria infection in anopheles mosquito, *Malar J* **3**:13, 2004.

72. Sherman IW, *Malaria*: *Parasite Biology*, *Pathogenesis*, *and Protection*, AMS Press, Washington DC, 1998.
73. Mitchell VS, Oaks Jr. SC, Pearson GW, *Malaria*: *Obstacles and Opportunities*, National Academy Press, Washington DC, 1991.
74. Bowman C, Gumel AB, van den Driessche P, Wu J, Zhu H, A mathematical model for assessing control strategies against West Nile virus, *Bull Math Biol* **67**:1107–1133, 2005.
75. Breman JG, Holloway CN, Malaria surveillance counts, *Am J Trop Med Hyg* **77**:36–47, 2007.
76. Ruiz D, Poveda G, Vlez ID *et al.*, Modelling entomological-climatic interactions of *plasmodium falciparum* malaria transmission in two colombian endemic-regions: Contributions to a national malaria early warning system, *Malar J* **5**:66, 2006.
77. Deressa W, Ali A, Enqusellassie F, Self-treatment of malaria in rural communities, Butajira, southern Ethiopia, *Bull World Health Org* **81**:261–268, 2003.
78. Deressa W, Chibsa S, Olana D, Treatment seeking for malaria patients in East Shewa Zone of Oromia, Ethiopia, *Ethiopian J Health Dev* **17**:9–16, 2003.
79. Deressa W, Treatment-seeking behaviour for febrile illness in an area of seasonal malaria transmission in rural Ethiopia, *Malar J* **6**:49, 2007.
80. Fleming WH, Rishel RW, *Deterministic and Stochastic Optimal Control*, Springer Verlag, New York, 1975.
81. Krener AJ, The high order maximal principle and its application to singular extremals, *SIAM J Control Optim* **15**:156–293, 1977.
82. Lenhart S, Workman JT, *Optimal Control Applied to Biological Models*, Chapman and Hall, 2007.

Appendix A. Theorem 4.1 (Castillo-Chavez and Song[65]).

Consider the following general system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), \quad f\colon \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \quad \text{and} \quad f \in \mathcal{C}^2(\mathbb{R}^n \times \mathbb{R}),$$

where 0 *is an equilibrium point of the system* (*that is*, $f(0, \phi) \equiv 0$ for all ϕ) *and assume*

A1: $A = D_x f(0; 0) = (\frac{\partial f_i}{\partial x_j}(0; 0))$ *is the linearization matrix of the system* (24) *around the equilibrium* 0 *with* ϕ *evaluated at* 0. *Zero is a simple eigenvalue of* A *and other eigenvalues of* A *have negative real parts*;

A2: *Matrix* A *has a right eigenvector* w *and a left eigenvector* v (*each corresponding to the zero eigenvalue*).

Let f_k *be the kth component of* f *and*

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0)$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0).$$

The local dynamics of the system around 0 is totally determined by the signs of a and b.

(i) $a > 0, b > 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$; 0 *is* (*LAS*) *and there exists a positive unstable equilibrium*; *when* $0 < \phi \ll 1$, 0 *is unstable and there exists a negative, LAS equilibrium*;

(ii) $a > 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, 0 *is unstable, and there exists a locally asymptotically stable negative equilibrium*; *when* $0 < \phi \ll 1$, 0 *is stable, and a positive unstable equilibrium appears.*

Particularly, if $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\phi = 0$.

Appendix B. Definition of D and N in Eq. (3.16)

$$\begin{aligned}
D = &-A_2\theta_2^2 P_h - A_1 I_h - \sigma_h E_h \lambda_{I_h} + (2\theta_2 - \theta_2^2 - 1)\theta_1\beta_h b_h I_v I_h \lambda_{Ph} \\
&+ (1 - 2\theta_2 + \theta_2^2)\theta_1\beta_h b_h I_v I_h \lambda_{T_h} + [r_h(1-\gamma) + \delta_h - (1-v)\delta_h] I_h \lambda_{T_h} \\
&+ \{\sigma_h E_h + [r_h(\theta_3 - \gamma) + \theta_4\delta_h - (1-v)\delta_h]\theta_2^2 P_h\}\lambda_{T_h} \\
&+ [r_h I_h(\gamma - 1) + r_h\theta_2^2 P_h(\gamma - \theta_3)]\lambda_{R_h} \\
&+ \{(1-\eta)I_h - I_h + \theta_2^2 P_h[(1-\eta) - \theta_5]\}\beta_v b_v S_v \lambda_{S_v} \\
&+ \{I_h - (1-\eta)I_h + \theta_2^2 P_h[\theta_5 - (1-\eta)]\}\beta_v b_v S_v \lambda_{E_v},
\end{aligned}$$

and

$$\begin{aligned}
N = &[\sigma_h E_h + (-r_h - \delta_h + (1-v)\delta_h + \gamma r_h) I_h]\frac{d\lambda_{T_h}}{dt} \\
&+ [(-\theta_4\delta_h - \theta_3 r_h + \gamma r_h + (1-v)\delta_h) P_h]\frac{d\lambda_{T_h}}{dt} \\
&\times (\lambda_{T_h} - \lambda_{I_h})\sigma_h \frac{dE_h}{dt} + [(1-\gamma)I_h + (\theta_3 - \gamma)P_h] r_h \frac{d\lambda_{R_h}}{dt} \\
&+ \{[(1-\eta) - 1]I_h + [(1-\eta) - \theta_5]P_h\}\beta_v b_v \lambda_{S_v}\frac{dS_v}{dt} \\
&+ \{[(1-\eta) - 1]I_h + [(1-\eta) - \theta_5]P_h\}\beta_v b_v S_v \frac{d\lambda_{S_v}}{dt} \\
&+ \{[1 - (1-\eta)]I_h + [\theta_5 - (1-\eta)]P_h\}\beta_v b_v \lambda_{E_v}\frac{dS_v}{dt} \\
&+ \{[1 - (1-\eta)]I_h + [\theta_5 - (1-\eta)]P_h\}\beta_v b_v S_v \frac{d\lambda_{E_v}}{dt} \\
&\times (2\sigma_h E_h - k_2 I_h - \theta_1 f_h I_h)A_1 + (\theta_1 f_h I_h - k_3 P_h)A_2 \\
&+ \sigma_h E_h \lambda_{P_h}\theta_1 f_h + (-k_2 - \theta_1 f_h)\sigma_h E_h \lambda_{I_h} \\
&+ (r_h(\gamma - 1) + \delta_h((1-v) - 1))\sigma_h E_h \lambda_{T_h}
\end{aligned}$$

$$
\begin{aligned}
&+ (r_h k_2(1-\gamma) + r_h\theta_1 f_h(1-\theta_3) + \delta_h k_2(1-(1-v)) + \delta_h\theta_1 f_h(1-\theta_4))I_h\lambda_{T_h}\\
&+ \{r_h k_3(\theta_3-\gamma) + \delta_h k_3[\theta_4-(1-v)]\}P_h\lambda_{T_h}\\
&+ \{r_h\sigma_h E_h(2-\gamma) + [r_h k_2(\gamma-1) + r_h\theta_1 f_h(\theta_3-1)]I_h + r_h k_3(\gamma-\theta_3)P_h\}\lambda_{R_h}\\
&+ \{\sigma_h E_h[(1-\eta)-1] + \theta_1 f_h I_h(1-\theta_5) + k_2 I_h[1-(1-\eta)]\\
&+ k_3 P_h[\theta_5-(1-\eta)]\}\beta_v b_v S_v\lambda_{S_v}\\
&+ \{\sigma_h E_h[1-(1-\eta)] + k_2 I_h[(1-\eta)-1] + \theta_1 f_h I_h(\theta_5-1)\\
&+ k_3 P_h[(1-\eta)-\theta_5]\}\beta_v b_v S_v\lambda_{E_v}.
\end{aligned}
$$

Appendix C. Proof of Theorem 3.1

Proof. Suppose u is an optimal control and $S_h, E_h, I_h, P_h, T_h, R_h, S_v, E_v, I_v$ are the corresponding state solutions. Using the result of Pontryagin's Maximum Principle,[46] there exist adjoint variables satisfying

$$
\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} &= \frac{\partial H}{\partial S_h}, \quad \lambda_{S_h}(t_f) = 0,\\
&\cdots\\
-\frac{d\lambda_{I_v}}{dt} &= \frac{\partial H}{\partial I_v}, \quad \lambda_{I_v}(t_f) = 0.
\end{aligned}
$$

The behavior of the control may be obtained by differentiating the Hamiltonian with respect to u at t, and we denote the switching function by ψ:

$$\frac{\partial H}{\partial u} = \psi.$$

For our problem, we use the sign of this switching function to obtain part of the characterization:

$$u = a, \quad \text{when } \psi > 0, \quad \text{and} \quad u = b, \quad \text{when } \psi < 0.$$

Next we consider the singular case. If $\psi = 0$ on some nonempty open interval of time, say (t_1, t_2), then

$$\psi = 0 \quad \text{on } (t_1, t_2) \quad \text{and} \quad \psi' = 0,$$

i.e.,

$$\psi = C + \lambda_{T_h}(I_h + \theta_2 P_h) - \lambda_{P_h}\theta_2 P_h - \lambda_{I_h} I_h = 0,$$

substituting in the respective adjoint and state equations for ψ' gives the equation

$$
\begin{aligned}
\psi' = {} & A_1 I_h + A_2\theta_2 P_h - \lambda_{I_h}\sigma_h E_h + [(1-\gamma)I_h + (-\gamma+\theta_3)\theta_2 P_h]r_h\lambda_{R_h}\\
&+ (1-\theta_2)\theta_1\beta_h b_h I_v I_h\lambda_{Ph} + (\theta_2-1)\theta_1\beta_h b_h I_v I_h\lambda_{T_h}\\
&+ \{\sigma_h E_h + [(\gamma-1)r_h + (1-v)\delta_h - \delta_h]I_h\\
&+ [(\gamma-\theta_3)r_h + (1-v)\delta_h - \theta_4\delta_h]\theta_2 P_h\}\lambda_{T_h}
\end{aligned}
$$

$$
\begin{aligned}
&+\{[(1-\eta)-1]I_h+[(1-\eta)-\theta_5]\theta_2 P_h\}\beta_v b_v S_v \lambda_{S_v}\\
&+\{[1-(1-\eta)]I_h+[\theta_5-(1-\eta)]\theta_2 P_h\}\beta_v b_v S_v \lambda_{E_v}\\
&=0.
\end{aligned}
$$

Note, ψ' does not contain any terms with control u. Taking the second derivative of ψ with respect to time (i.e., ψ'') and substituting in the respective adjoint and state equations, simplifying and collecting terms with u, we obtain

$$\psi'' = Du - N = 0,$$

where D and N are given in the theorem statement.

This singular control has order 1, since ψ' does not contain any terms with u and ψ'' contains terms with u. The generalized Legendre–Clebsch condition,[81] which in a minimization problem with a singular control of order 1 is a necessary condition for the singular control to be optimal. The malaria superinfectivity model has singular control, $u = \frac{N}{D}$, which is optimal if the generalized Legendre–Clebsch condition holds:

$$(-1)\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = -1\frac{\partial}{\partial u}\left[\frac{d^2}{dt^2}(\psi)\right] = D > 0,$$

and $0 \leq \frac{N}{D} \leq 1$. □