

Full Length Research Paper

A study of the effect of drug resistance in malaria transmission and the most effective control measure

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We derive and analyze a deterministic model for the transmission of malaria disease with drug resistance in the infectives. Firstly, we calculate the basic reproduction number, R , and investigate the existence and stability of equilibria. The system is found to exhibit backward bifurcation, with this occurrence, the classical epidemiological requirement for effective eradication of malaria, $R < 1$, is no longer sufficient, even though necessary. Secondly, by using optimal control theory, we derive the conditions for optimal control of the disease using Pontryagin's Maximum Principle. Finally, numerical simulations are performed to illustrate the analytical results.

Key words: Malaria, bifurcation, stability, optimal control.

INTRODUCTION

Malaria is a public health problem in more than 90 countries, caused by parasites that are transmitted to people through the bites of infected mosquitoes, which resulted in the death of a child from malaria every 30 s. There are 247 million cases of malaria in 2006, causing nearly 1 million deaths, mostly among African children. This is estimated to be well over 2,000 young lives lost daily across the globe. These estimates render malaria the pre-eminent tropical parasitic disease and one of the top three killers among communicable disease (Sachs, 2002).

There are strong social and economic ways to the burden of the disease, which in so many ways affects fertility, population growth, saving and investment, worker productivity, absenteeism, premature mortality and medical costs (Sachs, 2002). In areas where malaria is highly endemic, young children bears a larger burden in terms of the disease morbidity and mortality and affects fetal development during early stage of pregnancy in women due to loss of immunity. Currently, strategies of

controlling the disease includes, the use of chemotherapy, intermittent preventive treatment for children and pregnant women (preventive doses of *sulfadoxine-pyrimethamine* (IPT/ST)), and use of insecticides treated bed nets and insecticides against the vector. The challenge posed by the resistance of parasites against drugs and resistance of mosquitoes against insecticides calls for urgent need for a better understanding of important parameters in the disease transmission and develops effective and optimal strategies for prevention and control of the spread of malaria disease.

Mathematical modeling of the spread of infectious diseases continues to provide important insights into diseases behaviour and control. Over the years, it has also become an important tool in understanding the dynamics of diseases and in decision making processes regarding intervention programs for controlling these diseases in many countries. Greenhalgh (1992) studied an infectious disease model with population-dependent death rate using computer simulation. Ghosh et al. (2004), studied the environmental effect on a susceptible/infected/susceptible (SIS) model for bacteria and the spread of carrier-dependent infectious diseases, like cholera, diarrhoea. Elsayd (2008) studied the Mathematical effect of improving the function of the thymus on the viral growth and T cell population of an HIV-immune dynamic system.

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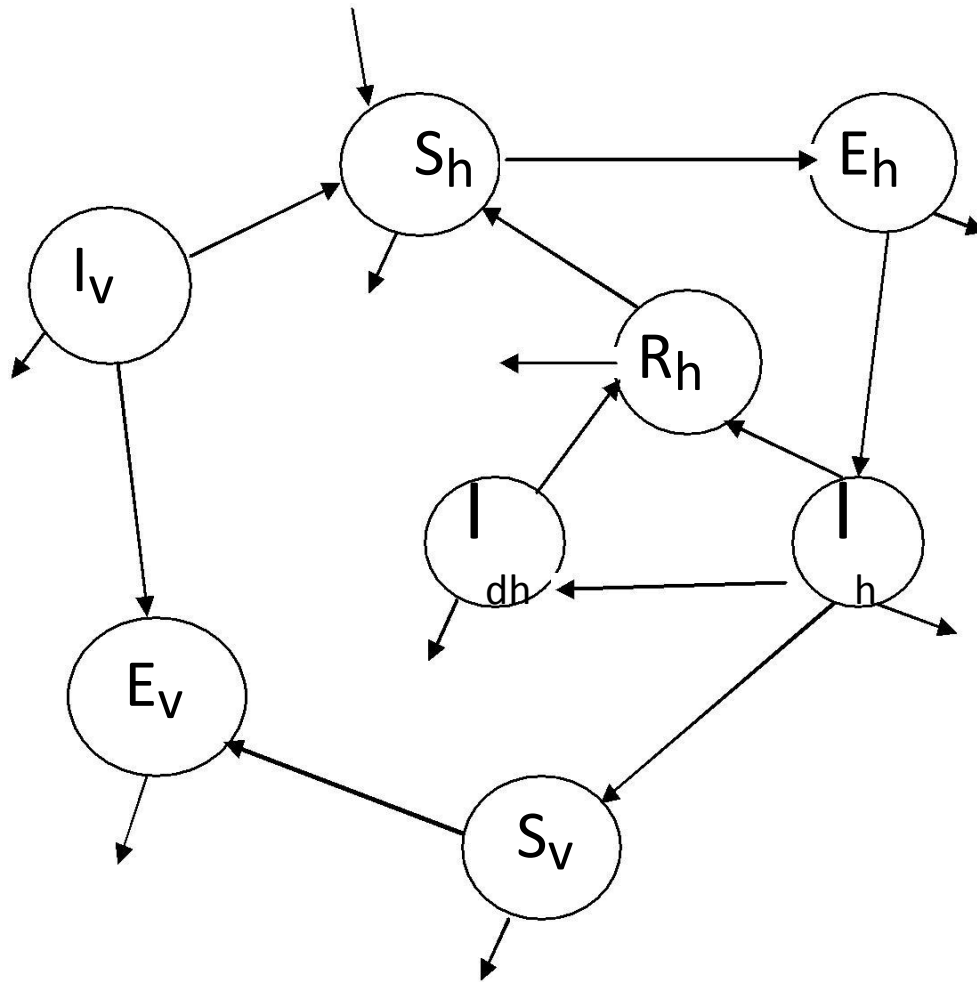


Figure 1. The flow diagram for malaria disease transmission.

Anderson and May (1991) derived a malaria model with the assumption that acquired immunity in malaria is independent of exposure duration, different control measures and role of transmission rate on the disease prevalence were further examined. Puntani and I-ming (2010) studied the transmission of *Plasmodium falciparum* and *Plasmodium vivax* malaria in a mixed population of Thais and migrant Burmese living along the Thai-Myanmar border using a mathematical model. Hyun (2000), using mass action incidence studied malaria transmission model for different levels of acquired immunity and temperature dependent parameters, relating also to global warming and local socioeconomic conditions. Isao et al. (2004) examined the combined use of insecticide spray and zooprophyllaxis as malaria control strategy. Dietz et al. (1974) proposed a model that account for acquired immunity in a mass action model. Jia (2008) formulated and examined a compartmental mathematical model for malaria transmission that includes incubation periods for both infected human hosts and mosquitoes (Figure 1).

In particular, there have been studies of epidemiological

models where optimal control methods were applied. Okuonghae and Aihie (2010) applied optimal control theory to a system of ordinary differential equations modeling the population dynamics of tuberculosis with isolation and immigration of infective. Castilho (2006) specifically applied optimal control methods in a simplified susceptible-infective-removed (SIR) model, to study the best strategy for educational campaigns during the outbreak of an epidemic. Zaman et al. (2008) studied a general SIR epidemic model and applied stability analysis theory to investigate the equilibrium solutions and then used optimal control to determine the optimal vaccination strategies to reduce the susceptible and infective individuals. Suresh (1978) formulated and analyzed an optimal control problem with a simple epidemic model to examine effect of a quarantine program. He also considered an optimal control problem to study the effect of the level of medical program effort in minimizing the social and medical costs.

Gupta and Rink (1973) considered the application of optimal control to investigate the most economical use of active and passive immunization in controlling infectious

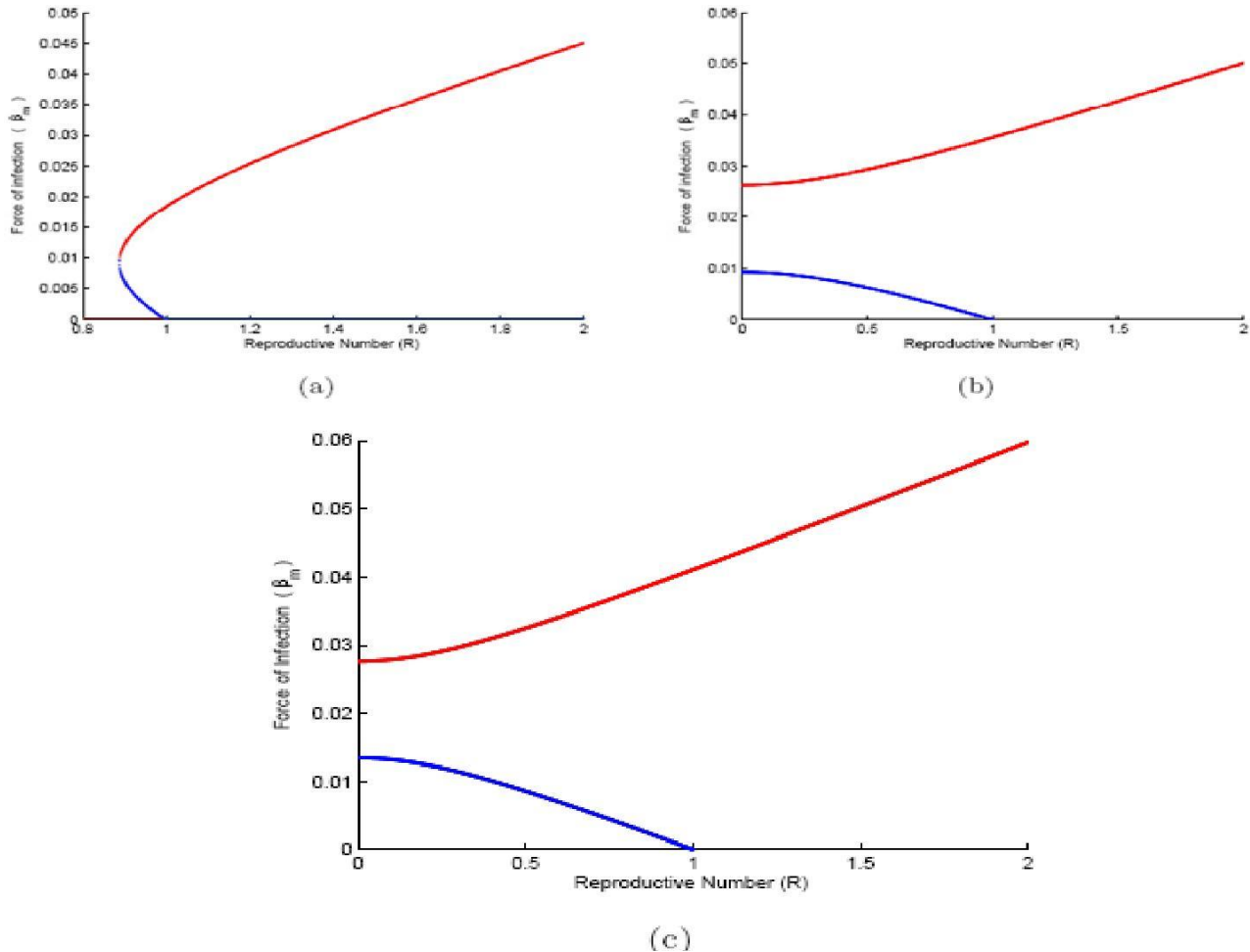


Figure 2. Simulations of the malaria model showing the effect of drug resistance on malaria spread. The red lines indicates the stable regions of the equilibrium while the blue lines shows the unstable equilibrium points. (a) for $p < 0.3$ and $u_2 = 0.6$. (b) for $u_2 = 0$ and $p = 0.0065$ an endemic equilibrium exists for all positive values of the reproductive number R , whenever there is no effective treatment in the presence of drug resistance number and in(c), $p \geq 0.5$ and $u_2 = 0.6$.

disease. Xiefei et al. (2007) applied optimal control methods to study the outbreak of severe acute respiratory syndrome (SARS) using Pontryagin's Maximum Principle and genetic algorithm. Marco and Takashi (2001) used optimal control to study dengue disease transmission.

Rafikov et al. (2009) formulated a continuous model for malaria vector control with the aim of studying how genetically modified mosquitoes should be introduced in the environment using optimal control problem strategies. Kbenesh et al. (2009) presented an autonomous ordinary differential equation model with vector-control and treatment model and a time dependent counter part of the model involving an optimal control of vector-borne diseases with treatment and prevention as control measures. Okosun (2010) and Okosun et al. (2011) applied optimal control theory to a continuous malaria model that includes treatment and vaccination with waning immunity to study the impact of a possible vaccination with treatment strategies in controlling the spread of malaria.

Makinde and Okosun (2011) presented impact of optimal control strategies on malaria spread with infective immigrants. All these work did not consider the drug resistance problem.

The model we consider in this paper differs from that of previous work because it incorporates a time dependent control measures and the class of drug resistance individuals into the population. The main question to be addressed is know to what level is drug resistance influencing disease spreading and also informs control and eradication process. In this study, we derive and analyse a malaria disease transmission mathematical model with drug resistant individuals (Figure 2). We study and determine the possible impact of optimal treatment and control of drug resistance on the spread of malaria. Theoretically, we analyze its stability properties and determine conditions on the parameters for the existence of equilibrium solutions. We also carried out detailed qualitative optimal control analysis of the resulting model

and we find the necessary conditions for optimal control of the disease using Pontryagin's Maximum Principle in order to determine optimal strategies for controlling the spread of the disease.

Our main goal is to develop mathematical model with individuals with drug resistance in order to investigate the role of drug resistance individuals in malaria transmission.

MODEL FORMULATION

The model sub-divides the total human population, denoted by N_H , into sub-populations of susceptible individuals (S_H), those exposed to malaria parasite (E_H), individuals with malaria symptoms (I_H), individuals with drug resistance symptoms (I_{DH}) and recovered human (R_H). So that $N_H = S_H + E_H + I_H + I_{DH} + R_H$.

The total vector (mosquito) population, denoted by N_V , is sub-divided into susceptible mosquitoes (S_V), mosquitoes exposed to the malaria parasite (E_V) and infectious mosquitoes (I_V). Thus, $N_V = S_V + E_V + I_V$.

Susceptible individuals are recruited at a rate Λ_H , susceptible individuals acquires malaria through contact with infectious mosquitoes at a rate β_M . Exposed individuals move to the infectious class at a rate α_1 . Individuals with malaria are treated

$$\tau U_2(T)$$

are individuals who recovered spontaneously. A proportion of infectious individuals, $\rho\tau$, without drug resistance moves to the recovered class, while progresses to individuals with drug resistance class. Individuals with drug resistance recover at a rate σ . Non treated infected individuals die at a rate ψ . Recovered individual loose immunity at a rate K and become susceptible again. α_H is the natural death rate.

Susceptible mosquitoes (S_V) are generated at a rate Λ_V and acquire malaria through contacts with infected humans at a rate λ_V . Mosquitoes are assumed to suffer death due to natural causes and various control measures (insecticides, destruction of mosquitoes breeding sites, etc.) at a rate α_V . Newly-infected mosquitoes move to the exposed class (E_V), and progress to the class of symptomatic

mosquitoes (I_V) at a rate α_2 . Where

$$\beta_M = \frac{\beta \epsilon \varphi I_V}{S_H + E_H + I_H + I_{DH} + R_H},$$

$\lambda_V = \frac{\lambda \epsilon \varphi (I_H + \eta I_{DH})}{S_H + E_H + I_H + I_{DH} + R_H}$ where β s the transmission probability per bite, ϵ is the per capita biting rate of

mosquitoes and φ is the contact rate of vector per human per unit time and λ is the probability for a vector to get infected by an infectious human. The resulting system of equation is shown as follows:

$$\frac{dS_h}{dt} = \Lambda_h + \kappa R_h - \beta_m S_h - \mu_h S_h$$

$$\frac{dE_h}{dt} = \beta_m S_h - (\alpha_1 + \mu_h) E_h$$

$$\frac{dI_h}{dt} = \alpha_1 E_h - (b + \tau u_2(t) + \psi + \mu_h) I_h$$

$$\frac{dI_{dh}}{dt} = u_2(t)(1 - \rho)\tau I_h - (\mu + \psi + \sigma) I_{dh}$$

$$\frac{dR_h}{dt} = u_2(t)\rho\tau I_h + \sigma I_{dh} - (\kappa + \mu_h) R_h$$

$$\frac{dS_v}{dt} = \Lambda_v - \lambda_v S_v - \mu_v S_v$$

$$\frac{dE_v}{dt} = \lambda_v S_v - (\alpha_2 + \mu_v) E_v$$

$$\frac{dI_v}{dt} = \alpha_2 E_v - \mu_v I_v.$$

The SEIR malaria model (1) will be analyzed in a biologically-feasible region as follows. This region should be feasible for both humans and mosquitoes populations. More precisely, we have Theorem 1.

Theorem 1

If $S_h(0), E_h(0), I_h(0), I_{dh}(0), R_h(0), S_v(0), E_v(0), I_v(0)$ are non negative then so are $S_h(t), E_h(t), I_h(t), I_{dh}(t), R_h(t), S_v(t), E_v(t)$ and $I_v(t)$ for all time $t > 0$ for all time $t > 0$. Moreover

$$\limsup_{t \rightarrow \infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h} \text{ and } \limsup_{t \rightarrow \infty} N_v(t) \leq \frac{\Lambda_v}{\mu_v}. \quad (1)$$

Furthermore, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$, and if $N_v(0) \leq \frac{\Lambda_v}{\mu_v}$, then $N_v(t) \leq \frac{\Lambda_v}{\mu_v}$. The feasible region for system (1) is therefore given by

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_v \subset \mathbb{R}_+^5 \times \mathbb{R}_+^3 \quad (2)$$

Where

$$\mathcal{D}_h = \{(S_h, E_h, I_h, I_{dh}, R_h) \in \mathbb{R}_+^5 : S_h + E_h + I_h + I_{dh} + R_h \leq \frac{\Lambda_h}{\mu_h}\}, \quad (4)$$

and

$$D_v = \{(S_v, E_v, I_v) \in \mathbb{R}_+^3 : S_v + E_v + I_v \leq \frac{\Lambda_v}{\mu_v}\} \tag{5}$$

D is positively invariant

Stability of the disease free equilibrium (DFE)

The DFE of the malaria Model (1) exists and is given by

$$\mathcal{E}_0 = \left(\frac{\lambda_h}{\mu_h}, 0, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0 \right)$$

The basic reproduction number of the Model (1), R is calculated by using the next generation matrix Driesshe and Watmough (2002). It is given by;

$$R = \sqrt{\frac{\alpha_1 \alpha_2 \lambda \Lambda_v \mu_h (\epsilon \phi)^2 \beta (\mu_h + \sigma + \psi + \eta \tau)}{\Lambda_h \mu_v^2 (\mu_h + \alpha_1) (\mu_h + \psi + \tau u_2) (\mu_v + \alpha_2) (\mu_h + \sigma + \psi)}} \tag{6}$$

The DFE is locally asymptotically stable if $R < 1$ and unstable if $R > 1$.

Existence of endemic equilibrium

Calculating the endemic equilibrium point, we obtain

$$\left\{ \begin{aligned} S_h^* &= \frac{(\Lambda_h + \kappa R_h^*)}{(\beta_m + \mu_h)} \\ E_h^* &= \frac{\beta_m S_h^*}{\alpha_1 + \mu_h} \\ I_h^* &= \frac{\alpha_1 E_h^*}{(b + \tau u_2 + \psi + \mu_h)} \\ I_{dh}^* &= \frac{u_2(1 - \rho)\tau I_h^*}{(\sigma + \psi + \mu_h)} \\ R_h^* &= \frac{\rho \tau u_2 I_h^*}{(\kappa + \mu_h)} \\ S_v^* &= \frac{\Lambda_v}{\mu_v + \lambda_v} \\ E_v^* &= \frac{\lambda_v S_v^*}{(\alpha_2 + \mu_v)} \\ I_v^* &= \frac{\alpha_2 E_v^*}{\mu_v} \end{aligned} \right. \tag{7}$$

The endemic equilibrium is $\beta_m = 0$ or

$$A(\beta_m^*)^2 + B(\beta_m^*) + C = 0, \tag{8}$$

where

$$A = \Lambda_h \mu_v (\alpha_2 + \mu_v) ((\kappa + \mu_h) (\mu_h + \sigma + \psi) (b + \mu_h + \psi + u_2 \tau)) + \alpha_1 (b (\mu_h + \sigma + \psi) + \kappa (\mu_h + \sigma + \psi + u_2 \tau) + (\mu_h + u_2 \tau) ((\kappa + \mu_h) \mu_v (\mu_h + \sigma + \psi) (b + \mu_h + \psi + u_2 \tau) + \alpha_1 (\mu_v (b (\mu_h + \sigma + \psi) + \kappa (\mu_h + \sigma + \psi + \tau) + (\mu_h + \sigma + \psi) (\mu_h + u_2 \tau) + \lambda (\kappa + \mu_h) (\mu_h + \sigma + \psi + \tau \eta))))),$$

$$B = \mu_h (\kappa + \mu_h) (2 \Lambda_h \mu_h^2 (\kappa + \mu_h) \mu_v^2 (\alpha_2 + \mu_v) ((\mu_h + \psi + \sigma))^2 ((b + \mu_h + \psi + u_2 \tau))^2 + \alpha_1 \mu_h (\mu_h + \psi + \sigma) (b + \mu_h + \psi + u_2 \tau) (\Lambda_h \mu_v^2 (2 \mu_v ((\kappa + \mu_h) (2 (b + \mu_h) + \psi) (\mu_h + \psi + \sigma) + (2 \mu_h (\mu_h + \psi + \sigma) + \kappa ((-\mu_h - \psi) (-2 + \rho) + \sigma)) u_2 \tau) + \beta \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) u_2 \tau \eta)) + \alpha_2 (- (\beta_1 \beta \Lambda_v \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) u_2 \tau \eta)) + \Lambda_h \mu_v (2 \mu_v ((\kappa + \mu_h) (2 (b + \mu_h) + \psi) (\mu_h + \psi + \sigma) + (2 \mu_h (\mu_h + \psi + \sigma) + \kappa ((-\mu_h - \psi) (-2 + \rho) + \sigma)) \tau u_2) + \beta \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) \tau u_2 \eta)))))) + \alpha_1^2 (\Lambda_h \mu_v^2 (\mu_h + \psi + \sigma) (b + \mu_h + \psi + \tau u_2) (2 \mu_v ((b + \mu_h) (\kappa + \mu_h) (\mu_h + \psi + \sigma) + ((\mu_h + \psi) (\kappa + \mu_h - \kappa \rho) + \mu_h \sigma) \tau u_2) + \beta \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) \tau u_2 \eta)) + (\alpha_2 (2 b^2 \Lambda_h (\kappa + \mu_h) \mu_v^2 (\mu_h + \psi + \sigma))^2 - \beta_1 \beta \Lambda_v \mu_h (\mu_h (\mu_h + \psi + \sigma) (\mu_h + \psi + \tau u_2) + \kappa (\mu_h + \psi) (\mu_h + \psi + \sigma + \tau u_2 - \rho \tau u_2)) (\mu_h + \psi + \sigma - (-1 + \rho) \tau u_2 \eta) + \Lambda_h \mu_v (\mu_h + \psi + \sigma) (\mu_h + \psi + \tau u_2) (2 \mu_v (\mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma) + ((\mu_h + \psi) (\kappa + \mu_h - \kappa \rho) + \mu_h \sigma) \tau u_2) + \beta \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) \tau u_2 \eta)) - b (\mu_h + \psi + \sigma) (\beta_1 \beta \Lambda_v \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) \tau u_2 \eta) - \Lambda_h \mu_v (2 \mu_v ((\kappa + \mu_h) (2 \mu_h + \psi) (\mu_h + \psi + \sigma) + (2 \mu_h (\mu_h + \psi + \sigma) + \kappa ((-\mu_h - \psi) (-2 + \rho) + \sigma)) \tau u_2) + \beta \mu_h (\kappa + \mu_h) (\mu_h + \psi + \sigma - (-1 + \rho) \tau u_2 \eta)))))),$$

$$C = C = \Lambda_h \mu_v^2 (\alpha_1 + \mu_h)^2 (\sigma + \psi + \mu_h)^2 (\alpha_2 + \mu_v)^2 (\kappa + \mu_h)^2 (b + \mu_h + \psi + u_2 \tau)^2 (1 - R^2).$$

The malaria model has:

THEOREM 2

1. A unique endemic equilibrium if $C < 0$, it implies that $R > 1$
2. A unique endemic equilibrium if $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$
3. Two endemic equilibrium if $C > 0$, $B < 0$ and $B^2 - 4AC > 0$
4. No endemic equilibrium otherwise.

The item (3) indicates the possibility of backward bifurcation in the model (1) when $R < 1$. This backward bifurcation is illustrated using a set of parameters values in Table 1. The result obtained is depicted in Figure 2.

Subsequently, we apply optimal control method using Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the impact of drug resistance on malaria disease.

ANALYSIS OF OPTIMAL CONTROL

To investigate the optimal level of efforts that would be needed to control the disease, we give the objective functional J , which is to minimize the number of human infective and the cost of applying the control ρ, U_2 .

$$J = \min_{\rho, u_2} \int_0^{t_f} mI_h + nI_{dh} + \frac{c\rho^2}{2} + \frac{du_2^2}{2} dt \tag{9}$$

where N, C, D are positive weights. We choose a quadratic cost on the controls, this is similar with what is in other literature on epidemic controls (Zaman et al., 2008; Marco and Takashi, 2001; Kbenesh et al., 2009; Rafikov et al., 2009). With the given objective function $J(\rho, U_2)$; our goal is to minimize the number of infected humans $I_H(T)$, while minimizing the cost of control $\rho(T)$ and $U_2(T)$. We seek an optimal control ρ^* and U_2^* such that

$$J(\rho^*, u_2^*) = \min\{J(\rho, u_2) | \rho, u_2 \in \mathcal{U}\} \tag{10}$$

where $U = \{(\rho, U_2) \text{ such that } \rho, U_2 \text{ measurable with } 0 \leq \rho \leq 1 \text{ and } 0 \leq U_2 \leq 1 \text{ for } T \in [0, T_f]\}$ is the control set. The necessary conditions that an optimal must satisfy come from the Pontryagin's Maximum Principle (Pontryagin, 1962). This principle converts Equations (1) to (9) into a problem of minimizing pointwise a Hamiltonian H , with respect to ρ and U_2

$$\begin{aligned} H = & mI_h + nI_{dh} + \frac{c\rho^2}{2} + \frac{du_2^2}{2} + \lambda_{S_h} \left\{ \Lambda_h - \frac{\beta I_v S_h}{N_h} - \mu_h S_h + \kappa R_h \right\} \\ & + \lambda_{E_h} \left\{ \frac{\beta I_v S_h}{N_h} - (\alpha_1 + \mu_h) E_h \right\} \\ & + \lambda_{R_h} \{ \rho \tau u_2 I_h + \sigma I_{dh} - (\kappa + \mu_h) R_h \} \\ & + \lambda_{S_v} \left\{ \Lambda_v - \frac{M_h S_v}{N_h} - \mu_v S_v \right\} \\ & + \lambda_{E_v} \left\{ \frac{M_h S_v}{N_h} - (\alpha_2 + \mu_v) E_v \right\} \\ & + \lambda_{I_v} \{ \alpha_2 E_v - \mu_v I_v \} \end{aligned} \tag{11}$$

where $\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{I_{dh}}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{E_v}$ and λ_{I_v} are the adjoint variables or co-state variables. By applying Pontryagin's maximum principle (Pontryagin et al., 1962) and the existence result for the optimal control from Fleming and Rishel (1975), we obtain.

Proposition 1

For the optimal control pair ρ^* and u_2^* that minimizes $J(\rho, u_2)$ over \mathcal{U} . There exist adjoint variables $\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{I_{dh}}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{E_v}, \lambda_{I_v}$ satisfying 12) and with transversality conditions

$$\begin{aligned} \lambda_{S_h}(t_f) = \lambda_{E_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{I_{dh}}(t_f) = \\ \lambda_{R_h}(t_f) = \lambda_{S_v}(t_f) = \lambda_{E_v}(t_f) = \lambda_{I_v}(t_f) \end{aligned} \tag{13}$$

$$\begin{aligned} \rho^* = \max \left\{ 0, \min \left(1, \frac{u_2 \tau (\lambda_{I_{dh}} - \lambda_{R_h})}{c} \right) \right\} \\ u_2^* = \max \left\{ 0, \min \left(1, \frac{\tau (\lambda_{I_h} - \lambda_{R_h})}{d} \right) \right\} \end{aligned} \tag{14}$$

PROOF

Corollary 4.1 of Fleming and Rishel (1975) gives the existence of an optimal control due to the convexity of the integrand of J with respect to ρ, U_2 , a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. By standard control arguments involving the bounds on the controls, we conclude

$$\begin{aligned} \rho^* = \begin{cases} 0 & \text{If } \varphi_1^* \leq 0 \\ \varphi_1^* & \text{If } 0 < \varphi_1^* < 1 \\ 1 & \text{If } \varphi_1^* \geq 1 \end{cases} \\ u_2^* = \begin{cases} 0 & \text{If } \varphi_2^* \leq 0 \\ \varphi_2^* & \text{If } 0 < \varphi_2^* < 1 \\ 1 & \text{If } \varphi_2^* \geq 1 \end{cases} \end{aligned}$$

where

$$\begin{aligned} \varphi_1^* = \frac{u_2 \tau (\lambda_{I_{dh}} - \lambda_{R_h})}{c} \\ \varphi_2^* = \frac{\tau (\lambda_{I_h} - \lambda_{R_h})}{d} \end{aligned}$$

Table 1. Description of bvariable and parameters of malaria model (1).

Baseline parameter	Description	Estimated value	References
β	Probability of human getting infected	0.8333	Assumed
λ	Probability of a mosquito getting	0.9	Kbenesh et al. (2009)
α_H	infected Natural death rate in humans	0.00004 day ⁻¹	Nakul et al. (2006)
α_V	Natural death rate in mosquitoes	0.1429 day ⁻¹	Nakul et al. (2006)
Λ_H	Human recruitment rate	100 day ⁻¹	Kbenesh et al. (2009)
Λ_V	Mosquitoes birth rate	1000 day ⁻¹	Kbenesh et al. (2009)
ϵ	Contact rate of vector per human per unit time	0.6 day ⁻¹	Nakul et al. (2006)
φ	Biting rate of vector per human per unit time	0.2	Kbenesh et al. (2009)
ψ	Disease induced death rate	0.05day ⁻¹	
α_1	Progression from exposed to infected human	1/17 day ⁻¹	Kbenesh et al. (2009)
α_2	Progression from exposed to infected mosquito	1/18 day ⁻¹	Kbenesh et al. (2009)
T	Drug efficacy	0.01 - 0.7	Assumed
K	Recovered individuals' loss of immunity	1/730 day ⁻¹	Kbenesh et al. (2009)

Due to the *a priori* boundedness of the state system, adjoint system and the resulting *Lipschitz* structure of the ODEs, we obtain the

uniqueness of the optimal control for small T_F . The uniqueness of

the optimal control follows from the uniqueness of the optimality system, which consists of (12) and (13) with characterization (14). There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction of the length on the time is due to the opposite time orientations of (12) and (13); the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems (Zaman et al., 2008; Kbenesh et al., 2009).

NUMERICAL RESULTS AND DISCUSSION

Here, we study numerically an optimal transmission parameter control for the malaria model. The optimal control is obtained by solving the optimality system, consisting state system and adjoint system. An iterative scheme is used for solving the optimality system. We start to solve the state equations with a guess for the controls over the simulated time using fourth order Runge-Kutta scheme. Because of the transversality conditions (13), the adjoint equations are solved by a backward fourth order Runge-Kutta scheme using the current iterations solutions of the state equation. Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (14). This process is repeated and iterations stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations (Lenhart and Workman, 2007). We examine a

deterministic model with drug resistance individuals and we study the effects of prevention and treatment on the spread of Malaria.

We investigate and compare numerical results, with the following scenario, (i) when control ρ was optimized

while treatment U_2 is set to zero, (ii) when treatment U_2 was optimized while we set ρ to zero, (iii) when both

controls were optimized. For the Figures 3 to 4, we assume that the weight factor, (C), associated with

control U_2 is greater than (N) and (D) which are associated with control ρ . This assumption is based on the facts that the cost associated with ρ will include the cost of screening and surveillance, and the cost

associated with treatment, U_2 , will include the cost of antimalarial drugs, medical examinations and hospitalization. We have chosen the same set of the weight factors, $N = 920$, $C = 25$ and $D = 50$ initial state variables $S_H(0) = 700$, $E_H(0) = 25$, $I_H(0) = 8$,

$S_V(0) = 950$, $E_V(0) = 120$, $I_V(0) = 50$ to illustrate the effect of different optimal control strategies on the spread of malaria in a population. Thus, we have considered the spread of malaria in an endemic population.

Optimal control of drug resistant and treatment of infective

With this strategy, the control ρ on individuals without

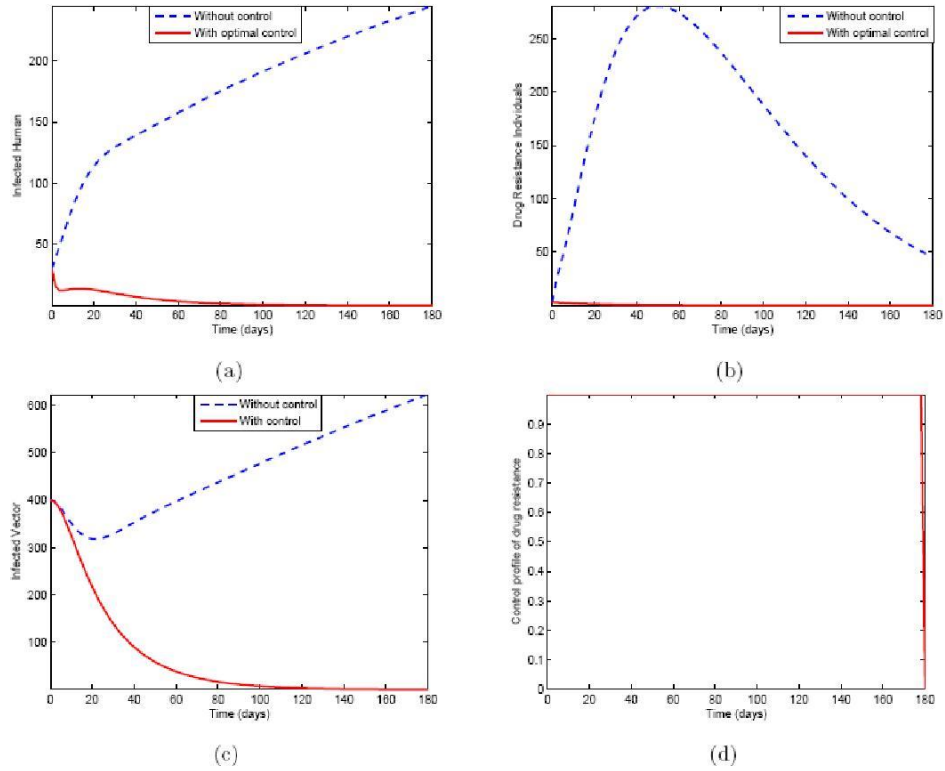


Figure 3. Simulations of the malaria model showing the effects of intervention strategies on the number of infectious humans and drug resistant individuals for $T = 0.35$.

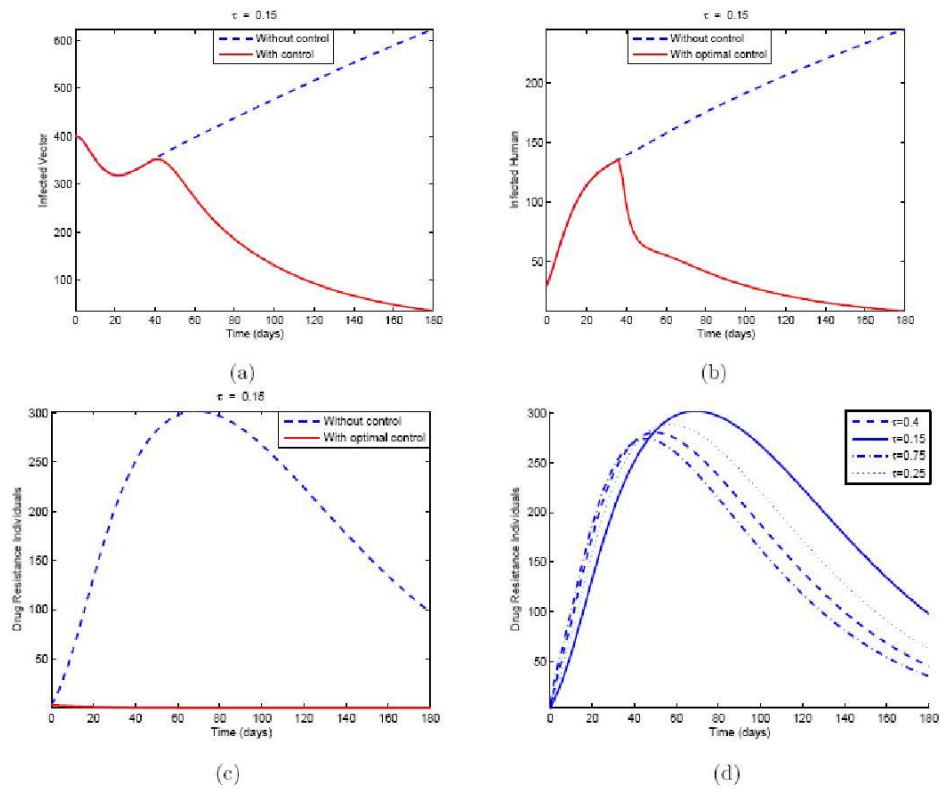


Figure 4. Simulations of the malaria model showing the effects of treatment on malaria transmission in (a) to (c), for $T = 0.15$, (d) shows the effect for various values of T .

drug resistant individuals and control U_2 on treatment are used to optimize the objective function J . Figure 3 shows a significant difference in the number of infected humans I_H , drug resistant individuals I_{DH} and infected mosquitoes I_V between the case with control and the case without. We observe in the Figures that an optimal control of individuals without drug resistant cases in the population will ensure that the community is disease free.

Conclusion

In this paper, we derived and analyzed a deterministic model for the transmission of malaria disease that includes the class of individuals with drug resistance and treatment measures. We calculated the basic reproduction number investigated the existence and stability of equilibria and performed optimal control analysis of the model. We found that the model exhibits backward bifurcation. Applying optimal control we derived and analyzed the conditions for optimal control of the disease with effective treatment regime and control of proportion of individuals who are drug resistant. From our numerical results we found that effective control of this proportion of individuals with drug resistance has a positive impact in reducing the spread of the disease.

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