Effective and ineffective treatment in a malaria model for humans in an endemic region

B. A. Danquah[a], F. Chirove[a] and Jacek Banasiak[b]

[a]University of Kwazulu Natal, School of Mathematics, Statistics and Computer Science, P.M.B X01, Pietermaritzburg, South Africa; [b]Department of Mathematics and Applied Mathematics, University of Pretoria, South Africa

ABSTRACT

A mathematical model for malaria in humans was developed to explore the effect of treatment on the transmission and control of malaria. The model incorporates effective antimalarial and substandard drugs as treatment for infectious humans. The reproduction number R_0 is evaluated, and shown to increase due to the presence of partially recovered humans. The disease free equilibrium is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. The model exhibits backward, imperfect or transcritical bifurcation depending on the value of the disease induced death rate and R_0. The numerical simulations, local and global sensitivity analysis suggest that the combination of effective control measures and the prompt use of effective antimalarial drugs that clear parasites quickly and give a long post-treatment prophylaxis may not only prevent transmission of infection to mosquitoes, but significantly reduce the number of infectious humans and the overall sources of infection.

KEYWORDS

Malaria; recrudescence; treatment; bifurcation; simulation

1. Introduction

Malaria is a deadly infectious disease caused in humans by five species of the *Plasmodium* and transmitted by females of the *Anopheles* mosquito species. The most lethal malaria parasite is *Plasmodium falciparum*, which accounted for 99.7% of the estimated malaria cases and 93% of the malaria deaths in the WHO African Region in 2017 [37]. The most susceptible groups to malaria infection are children under five years and pregnant mothers [37]. According to the World Health Organization estimates, massive progress has been made in combating malaria, with, malaria case incidence reducing by 41% and malaria mortality rates by 62% between 2000 to 2015 [35]. In 2017, governments of malaria endemic countries and international partners invested about US$ 3.1 billion, allowing for an expansion in malaria prevention, diagnostic testing and treatment program [37].

One of the strategies recommended by World Health Organization(WHO) for the treatment of uncomplicated *Plasmodium falciparum* malaria infection is the use of artemisinin based combination therapy (ACT). The primary advantage of the combination is that the artemisinin quickly and drastically reduces the majority of malaria parasites and the partner drug clears the small number of parasites that remain [37].

CONTACT B. A.Danquah. Email: babghans@gmail.com

The overall efficacy rates of ACT is greater than 95% [37]. ACT give clinical cure and provide a period of post treatment prophylaxis [34]. Despite these benefits, many people, mostly from poorer communities, still opt for the other unapproved drugs [4, 18, 19, 26] which may lead to recrudescence, disease transmission, drug resistance or death [6, 25, 34]. To recall, the recrudescence occurs when the *Plasmodium falciparum* parasites, that remain in the red blood cells after an episode of malaria, start multiplying and cause the recurrence of clinical symptoms due to, for an example, treatment failure [34]. The treatment failure may result from the drug resistance or an inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual, or substandard medicines [34].

Artemisinin resistance typically refers to the slow clearance of malaria parasites from the bloodstream following treatment with an artesunate monotherapy or ACT. This places greater demand on the partner drug to clear a larger parasite mass. However, it is also possible for partner drug resistance to emerge independently from artemisinin resistance. Unlike artemisinin resistance, the presence of partner drug resistance brings a high risk of treatment failure.

In most malaria endemic settings, malaria in non-immune individuals usually starts with fever, sometimes accompanied by chills, sweats, headache or other symptoms that resemble other febrile illnesses, trigger diagnostic testing and use of drugs for treatment [37]. Uncomplicated malaria in the patients with low or no immunity may progress to a severe malaria, which can lead to death, if an effective treatment is not administered early [34]. On the other hand, some semi-immune individual can be cured by treatment regimens that are ineffective but WHO recommends that a full course of a highly effective ACT must be used, like in the case of non-immune individuals [34].

To eliminate malaria by the year 2030 (Sustainable Development Goals 3), more research on the disease prevention, control, vulnerable groups, efficacy of treatment, vaccines, etc. is needed to aid in the effective policy making. Some studies have considered recrudescence and recovery on the malaria transmission in humans. The study in [32] proposed a SIR-SI model for human and mosquito populations, that allowed the fully recovered humans to return to the susceptible class. Their results showed the availability of susceptibles which makes malaria more endemic. The model developed in [21] incorporated repeated reinfections, and found the possibility of backward bifurcation to exist (at $R_0 = 1$), but this does not occur if the immunity is complete and the force of infection is modelled by the mass action law. In [7], the authors assessed the role played by the partial immunity to reinfection in the infective class on the dynamics of malaria in the human population. Here, the results also indicated that backward bifurcation is not present if the mass action is used. The reinfection and infectiousness of recovered humans were considered in [12]. They found that the disease-free equilibrium of the model is globally asymptotically stable if $R_0 \leq 1$, and the system is uniformly persistent if $R_0 > 1$. Other works [2, 9, 10, 20] that considered the infectiousness of partially immune humans who are infectious to feeding mosquitoes, found that, such models show forward bifurcation at $R_0 = 1$ and the presence of the partially immune population have some effects on the endemicity of malaria in the community.

In this work, we extend the existing models [2, 7, 9, 10, 12, 20] by formulating ordinary differential equations that describe malaria transmission and control in non-immune individuals. The model incorporates full recovery due to use of an effective treatment, partial recovery due to use of an inadequate or ineffective treatment, and, the infectiousness and recrudescence of partially recovered individuals. We note that understanding such a model will facilitate efforts to promote the use of safe and effective malaria treatments [34], and, ultimately, malaria control and elimination.

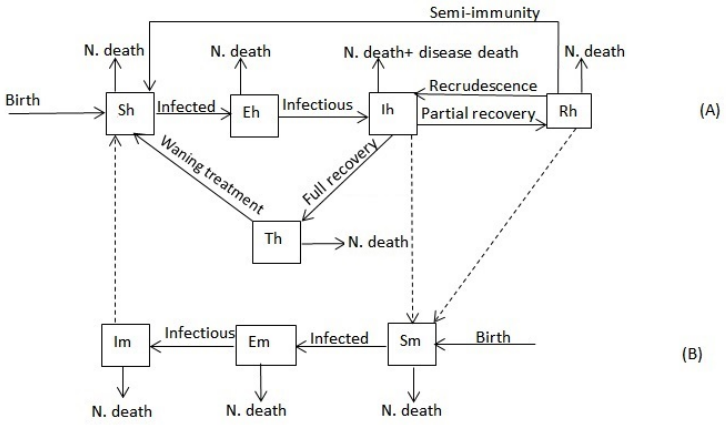


Figure 1. Schematic diagram of malaria transmission: (A)Humans and (B)females of the *Anopheles* mosquito spp.

The paper is organized as follows. In Section 2, we briefly describe the model. A mathematical analysis of the model is presented in Section 3, the numerical simulations are given in Section 4 and the sensitivity analysis in Section 5. The discussion of the results is done in Section 6.

2. Model formulation

The transmission model for *P. falciparum* malaria is formulated with the total human population at time t, $N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t) + T_h(t)$, where S_h, E_h, I_h, R_h and T_h denote the susceptible, exposed, infectious, partially recovered and fully recovered epidemiological classes, and the total mosquito population at a given time t is $N_m(t) = S_m(t) + E_m(t) + I_m(t)$ where S_m, E_m and I_m represent the susceptible, exposed and infectious classes. The flow between the classes is shown in Figure 1.

We note that the partially recovered humans are asymptotic individuals, who show no clinical symptoms, but maintain low levels of parasites due to semi-immunity in the case of semi-immune individual, drug resistance or unapproved drug use in the case of non-immune individuals. They can recrudesce into the infectious class or become susceptible (in the case of semi-immune individuals), and can transmit the infection to the susceptible mosquitoes. The fully recovered humans are infectious humans who have rid their bloodstream of parasites due to the use of effective antimalarial drugs. When the treatment (partner drug) wanes, the fully recovered humans become susceptible to the new infection. Also, the mosquitoes do not recover from the infection because of their short life cycle.

For the mosquito population, we consider a constant per capita birth rate α_m, and the death rate of the form $f_m(N_m) = \mu_{m1} + \mu_{m2}N_m$ [20]. Thus, in the absence of malaria, the population has the carrying capacity $K_m = \frac{r_m}{\mu_{m2}}$, with $r_m = \alpha_m - \mu_{m1} > 0$. For the human population, a constant total birth rate α_h and a constant per capita death rate $\mu_h > 0$ are considered; so that the carrying capacity of the disease free human population is given by $K_h = \frac{\alpha_h}{\mu_h}$.

The use of artemisinin combination therapy provides a period of post treatment prophylaxis. For this study, we use a per capita loss of post treatment prophylaxis rate given by $\phi = \frac{1}{D}$, where D is the average duration of the post treatment prophy-

laxis period (i.e. number of days until the effective treatment wanes allowing for the individual to be susceptible).

The size of the human susceptible class increases due to births at the total constant rate α_h, the loss of the post treatment prophylaxis by the fully recovered individuals at the per capita rate ϕ and the loss of the semi-immunity by the partially recovered individuals at the per capita rate θ. It decreases due to the natural deaths at the per capita rate μ_h and due to infections with the per capita rate given by the force of infection λ_h. In this paper, λ_h is given as the product of the average number of mosquito bites per human per day, a, and the transmission probability β_h (probability that a bite by an infectious mosquito on a susceptible human results in transmission of the disease given that a contact occurred between them). Thus, the rate of change of the susceptible humans class is given by,

$$\frac{dS_h}{dt} = \alpha_h + \phi T_h + \theta R_h - (\lambda_h + \mu_h)S_h, \tag{1a}$$

where

$$\lambda_h = \frac{a\beta_h}{N_h} I_m. \tag{1b}$$

The size of the exposed humans class increases due to the infections of the susceptible humans. It decreases due to deaths at the per capita rate μ_h and due to the development of the full infection in exposed individuals with the per capita transition rate ν_h. Hence,

$$\frac{dE_h}{dt} = \lambda_h S_h - (\nu_h + \mu_h)E_h. \tag{2}$$

The infectious humans class is generated by the transition of the exposed humans to the infectious class and the recrudescence in the partially recovered humans occurring at the per capita rate ξ. Its size decreases due to partial recovery at the per capita rate of η, the full recovery at the per capita rate γ, the disease induced deaths at the per capita rate δ_h and the natural deaths at the rate μ_h. Thus

$$\frac{dI_h}{dt} = \nu_h E_h + \xi R_h - (\eta + \gamma + \delta_h + \mu_h)I_h. \tag{3}$$

The partially recovered humans class is generated by the partial recovery of the infectious humans at the per capita rate η, while its size decreases due to the recrudescence at rate ξ, loss of semi-immunity at the per capita rate θ and the natural deaths at the per capita rate μ_h. Therefore,

$$\frac{dR_h}{dt} = \eta I_h - (\xi + \theta + \mu_h)R_h. \tag{4}$$

The fully recovered humans class is generated by the full recovery due to effective treatment of the infectious humans at the per capita rate γ, while it is reduced due to the loss of post treatment prophylaxis loss at the per capita rate ϕ and the natural

Table 1. Description of the state variables for the malaria model (1-8).

Variable	Description
S_h	Number of susceptible humans
E_h	Number of exposed humans
I_h	Number of infectious humans
R_h	Number of partially recovered humans
T_h	Number of fully recovered humans
S_m	Number of susceptible mosquitoes
E_m	Number of exposed mosquitoes
I_m	Number of infectious mosquitoes

deaths at the rate μ_h. Hence

$$\frac{dT_h}{dt} = \gamma I_h - (\phi + \mu_h)T_h. \tag{5}$$

For the mosquito population, the susceptible female anopheles mosquitoes are recruited from the pupa stage at the rate α_m and die at the per capita natural death rate $\mu_{m1} + \mu_{m2}N_m$. The susceptible mosquitoes are infected by the infectious and partially recovered humans at the per capita rate given by the force of infection $\lambda_m = \frac{a\beta_m}{N_h}(I_h + \rho R_h)$. Here, β_m is the probability that a bite by a susceptible mosquito on an infectious or partially recovered human results in the transmission of the gametocytes to the mosquito. The parameter ρ $(0 \leq \rho \leq 1)$ determines the degree of infectivity of a partially recovered human. When $\rho = 0$, then there is no infectivity, and $\rho = 1$ implies the same infectivity as of an infectious human, [7]. Thus,

$$\frac{dS_m}{dt} = \alpha_m N_m - (\lambda_m + \mu_{m1} + \mu_{m2}N_m)S_m. \tag{6}$$

The number of the exposed mosquitoes increases due to the infections of the susceptible mosquitoes and decreases due to the natural deaths at the per capita death rate $\mu_{m1} + \mu_{m2}N_m$ as well as due to the transition of the exposed mosquitoes to the infectious mosquitoes at the per capita rate $\nu_m > 0$. Therefore

$$\frac{dE_m}{dt} = \lambda_m S_m - (\nu_m + \mu_{m1} + \mu_{m2}N_m)E_m. \tag{7}$$

The number of infectious mosquitoes increases due to the transition of the exposed mosquitoes to the infected class and decreases due to the natural deaths at the per capita rate $\mu_{m1} + \mu_{m2}N_m$; that is,

$$\frac{dI_m}{dt} = \nu_m E_m - (\mu_{m1} + \mu_{m2}N_m)I_m. \tag{8}$$

The state variables and the parameters of the malaria model are shown in Tables 1 and 2 respectively.

Table 2. Description of the parameters for the malaria model (1-8).

Parameter	Description	Value/Range	Unit	References
β_h	The probability of transmission of infection from an infectious mosquito to a susceptible human given that a contact occured	0.015		[31]
β_m	The probability of transmission of infection from an infectious or partially recovered human to a susceptible mosquito given that a contact occured	0.475		[11]
ρ	The degree of infectivity of partially recovered humans	0.2/[0,1]		Assumed
a	The number of mosquito bites per human	11/[1-34]	day^{-1}	[5, 13, 30, 31]
α_h	The total birth rate of humans	0.031	day^{-1}	[36]
ν_h	The per capita transition rate of exposed humans to infectious humans	0.0833/[0.06 - 0.11]	day^{-1}	[10]
η	The per capita partial recovery rate of infectious humans	0.07143/[0.0357 - 0.333]	day^{-1}	[15, 22, 34]
γ	The per capita full recovery rate of infectious humans	0.07143/[0.0357 - 0.333]	day^{-1}	[15, 22, 34]
ξ	The per capita rate of recrudescence of partially recovered humans	0.07143/[0.0357 - 0.143]	day^{-1}	[34]
ϕ	The per capita rate of loss of post treatment prophylaxis for fully recovered humans	0.033/[5.48×10^{-4}- 0.071]	day^{-1}	[34]
θ	The per capita rate of loss of semi-immunity for some partially recovered humans	0.002740[$\frac{1}{30}$- $\frac{1}{1800}$]	day^{-1}	Assumed
μ_h	The natural death rate of humans	4.2808×10^{-5}	day^{-1}	[36]
δ_h	The per capita disease induced death rate of humans	[9×10^{-5}–1×10^{-4}]	day^{-1}	[37]
α_m	The per capita birth rate of mosquitoes	0.13	day^{-1}	[27]
ν_m	The per capita transition rate of exposed mosquitoes to infectious mosquitoes	0.091	day^{-1}	[27]
μ_{m1}	The density independent death rate of mosquitoes	0.033	day^{-1}	[27]
μ_{m2}	The density dependent death rate of mosquitoes	2×10^{-5}	$mosquitoes^{-1}\times day^{-1}$	[27]

3. Model analysis

3.1. Feasible region

The first step in showing that the malaria model (1)-(8) makes sense epidemiologically is to prove that the populations remain non-negative; that is, that all the solutions of system (1-8) with positive initial conditions will remain positive for all time $t > 0$. Given that typical initial conditions of system (1)-(8) at the beginning of the outbreak are

$$\begin{aligned} &S_h(0) > 0, E_h(0) \geq 0, I_h(0) \geq 0, R_h(0) = 0, T_h(0) = 0, \\ &S_m(0) > 0, E_m(0) \geq 0, I_m(0) \geq 0, \end{aligned} \tag{9}$$

with $E_h(0) + I_h(0) + E_m(0) + I_m(0) > 0$, we define a feasible region Ω, such that,

$$\Omega = \{(S_h, E_h, I_h, R_h, T_h, S_m, E_m, I_m) \in \Re^8_+ : 0 < N_h \leq K_h; 0 < N_m = K_m\}.$$

Theorem 3.1. *The feasible region Ω with initial conditions (9) is positively invariant and attracting.*

Proof. The proof is classical. The right hand side of system (1)-(8) is continuous with continuous partial derivatives in Ω (note that $N_h, N_m > 0$ in Ω so that the infection force is well defined). Thus the Picard theorem gives the existence of solu-

tions at least on some (maximum) interval $[0, \tau)$ (where τ can depend on the initial data). It can be seen that $S_h^{'} \geq 0$ if $S_h = 0$, $E_h^{'} \geq 0$ if $E_h = 0$, $I_h^{'} \geq 0$ if $I_h = 0$, $R_h^{'} \geq 0$ if $R_h = 0$, $T_h^{'} \geq 0$ if $T_h = 0$, $S_m^{'} \geq 0$ if $S_m = 0$, $E_m^{'} \geq 0$ if $E_m = 0$ and $I_m^{'} \geq 0$ if $I_m = 0$. Therefore, given the initial conditions (9), the solutions $S_h(t), E_h(t), I_h(t), R_h(t), T_h(t), S_m(t), E_m(t), I_m(t)$ are nonnegative on $[0, \tau)$. Adding equations (1)-(5) and equations (6)-(8) gives, respectively,

$$\frac{dN_h}{dt} = \alpha_h - \mu_h N_h - \delta_h I_h \leq \alpha_h - \mu_h N_h; \tag{10}$$

that is,

$$\alpha_h - (\mu_h + \delta_h) N_h \leq \frac{dN_h}{dt} \leq \alpha_h - \mu_h N_h, \tag{11}$$

and

$$\frac{dN_m}{dt} \quad = \quad r_m N_m - \mu_{2m} N_m^2 = r_m N_m \left(1 - \frac{N_m}{K_m}\right). \tag{12}$$

Solving the inequality (11) and equation (12) gives

$$N_h(0) e^{-(\mu_h + \delta_h)t} + \frac{\alpha_h}{\mu_h + \delta_h} \left(1 - e^{-(\mu_h + \delta_h)t}\right) \leq N_h(t) \leq K_h + (N_h(0) - K_h) e^{-\mu_h t}$$

and

$$N_m(t) \quad = \quad \frac{K_m N_m(0)}{N_m(0) + [K_m - N_m(0)] e^{-r_m t}}. \tag{13}$$

Thus we see that if $N_h(0) > 0$ and $N_m(0) > 0$, then neither N_h nor N_m can become 0 at any finite time (in particular, on $[0, \tau)$). Then, for $0 < N_h(0) < K_h$ and $0 < N_m(0) < K_m$, we see that on $[0, \tau)$

$$0 < N_h(t) < K_h, \quad 0 < N_m(t) < K_m$$

and thus, by the nonnegativity, the solution $(S_h, E_h, I_h, R_h, T_h, S_m, E_m, I_m)$ is a priori bounded and hence it is defined for all $t \geq 0$ and stays in Ω. In particular, taking the limit as $t \to \infty$ yields

$$\limsup_{t \to \infty} N_h(t) \quad \leq \quad K_h \tag{14}$$

and

$$\lim_{t \to \infty} N_m(t) \quad = \quad K_m. \tag{15}$$

Thus the region Ω is positively invariant. Further, if $N_h(0) > K_h$ and $N_m(0) > K_m$, then they are also isolated from zero and $N_h(t)$ either becomes smaller that K_h (and thus the solution enters Ω in a finite time), or approaches K_h, while $N_m(t)$ converges to K_m. Hence, the region Ω attracts the solutions in $\Re_+^8$ with $N_h(0) > K_h$ and $N_m(0) > K_m$. □

Since the region Ω is positively invariant and attracting, it is sufficient to consider the dynamics of the flow generated by the model in Ω.

3.2. Equilibrium points

Equating equations (1)-(8) to zero gives the equilibrium points the system. These are the disease-free equilibrium (DFE) and endemic equilibria (EE), which are denoted by E_0 and E_e respectively. At DFE, all the infected/infectious classes are zero i.e $E_h = I_h = R_h = E_m = I_m = 0$. At the endemic equilibrium, at least one of the infected/infectious classes should be non-zero.

The DFE of the model is given by

$$E_0 = (K_h, 0, 0, 0, 0, K_m, 0, 0). \tag{16}$$

3.2.1. The basic reproduction number

The local stability of E_0 is established using the next generation operator method [33] on the system (1)-(8). The matrices F and V, for the new infection terms and the remaining transfer terms, are, respectively, given by

$$\mathbf{F} = \begin{pmatrix} 0 & 0 & 0 & 0 & a\beta_h \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{a\beta_m K_m}{K_h} & \frac{a\beta_m \rho K_m}{K_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \mathbf{V} = \begin{pmatrix} -v_{11} & 0 & 0 & 0 & 0 \\ \nu_h & -v_{22} & \xi & 0 & 0 \\ 0 & \eta & -v_{33} & 0 & 0 \\ 0 & 0 & 0 & -v_{44} & 0 \\ 0 & 0 & 0 & \nu_m & -v_{55} \end{pmatrix} \tag{17}$$

where

$v_{11} = \nu_h + \mu_h$, $v_{22} = \eta + \gamma + \delta_h + \mu_h$, $v_{33} = \xi + \theta + \mu_h$, $v_{44} = \nu_m + \alpha_m$ and $v_{55} = \alpha_m$.

It follows that the basic reproduction number of the system denoted by R_0 and defined as the spectral radius of the next generation matrix (FV^{-1}) is given by

$$R_0 = \rho(FV^{-1}) = \sqrt{\frac{a^2\beta_h\beta_m\nu_m\nu_h(v_{33} + \rho\eta)K_m}{v_{11}(v_{22}v_{33} - \eta\xi)v_{44}v_{55}K_h}}. \tag{18}$$

R_0^2 is the number of susceptible humans that one infected human infects by generating infections in susceptible mosquitoes, assuming that we begin with human and mosquito populations only consisting of susceptible individuals, [9]. According to [9], since R_0 is positive, $R_0 < 1$ is equivalent to $R_0^2 < 1$; $R_0 = 1$ is equivalent to $R_0^2 = 1$; and $R_0 > 1$ is equivalent to $R_0^2 > 1$.

In the absence of the partially recovered humans (ineffectively treated and/or asymptomatic individuals), R_0 reduces to R_{01} which is given by

$$R_{01} = \sqrt{\frac{a^2\beta_h\beta_m\nu_m\nu_h K_m}{v_{11}v_{22}v_{44}v_{55}K_h}}. \tag{19}$$

From the formula in 18, if there are no partially recovered individuals within the population, then, $\frac{\rho\eta}{(v_{22}v_{33} - \eta\xi)} = 0$. This will mean that one reservoir of infection is

eliminated and the reproduction number will be significantly reduced given (19). Also, reducing the contact rate between mosquitoes and human (which is a squared term) will greatly reduce R_0. The transmission probabilities, the probability that an exposed mosquito will become infectious, the duration of the infectious lifetime of the mosquito, the proportion of the mosquitoes to humans, the probability that an exposed human will become an infectious human, duration of the infectious period of a human, the probability that an infectious human will partially recover, the duration of the partial recovery of a human, the probability that a partially recovered human will return to an infectious human, the per capita partial recovery rate of infectious humans and the degree of infectivity of the partially recovered human can lower transmission, infection in the population, recrudescence and reduce the value of R_0. To suggest efficient control strategies, it is important to know the magnitude to which a change in the model parameters will affect the reproduction number. Thus the need for sensitivity analysis (see Section 5).

Using Theorem 2 in [33], the following result is established on the local stability of E_0.

Lemma 1 The disease free equilibrium of the model E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3.3. Existence of endemic equilibrium

The conditions for the existence of an endemic equilibrium

$$E_e = (S_h^*, E_h^*, I_h^*, R_h^*, T_h^*, S_m^*, E_m^*, I_m^*) \tag{20}$$

for the model are explored. Equating (10) and (12) to zero gives

$$N_h^* = \frac{\alpha_h - \delta_h I_h^*}{\mu_h} \quad \text{and} \quad N_m^* = K_m.$$

Thus, an endemic equilibrium point exists if I_h lies between $(0, \frac{\alpha_h}{\delta_h})$. Hence, when malaria persists, the mortality due to the infections in humans is smaller than the birth rate of the population. At an endemic equilibrium, the forces of infection become

$$\lambda_h^* = \frac{a\beta_h I_m^*}{N_h^*} \quad \text{and} \quad \lambda_m^* = \frac{a\beta_m (I_h^* + \rho R_h^*)}{N_h^*}.$$

The endemic equilibrium E_e of the model is given in terms of λ_h^* and λ_m^* with

$$
\begin{aligned}
S_h^* &= \frac{\alpha_h v_{33}(\phi+\mu_h) + (\theta\eta(\phi+\mu_h) + \phi\gamma v_{33})I_h^*}{(\lambda_h^*+\mu_h)(\phi+\mu_h)v_{33}},\\
E_h^* &= \frac{\lambda_h^*\alpha_h(\phi+\mu_h) + \lambda_h^*\phi\gamma I_h^*}{(\lambda_h^*+\mu_h)(\phi+\mu_h)v_{11}},\\
I_h^* &= \frac{\lambda_h^*\nu_h\alpha_h(\phi+\mu_h)v_{33}}{(\lambda_h^*+\mu_h)(\phi+\mu_h)(v_{22}v_{33}-\xi\eta)v_{11} - \nu_h\lambda_h^*\gamma\phi v_{33}},\\
R_h^* &= \frac{\eta I_h^*}{v_{33}}, \quad T_h^* = \frac{\gamma I_h^*}{\phi+\mu_h}, \quad N_h^* = \frac{\alpha_h - \delta_h I_h^*}{\mu_h},\\
S_m^* &= \frac{\alpha_m K_m}{\lambda_m^*+\alpha_m}, \quad E_m^* = \frac{\lambda_m^*\alpha_m K_m}{(\lambda_m^*+\alpha_m)v_{44}}, \quad I_m^* = \frac{\nu_m\lambda_m^*\alpha_m K_m}{(\lambda_m^*+\alpha_m)v_{44}v_{55}}.
\end{aligned}
$$

Substituting λ_h^* and λ_m^* into I_h^* and I_m^* gives

$$
\begin{aligned}
I_h^* &= \frac{a\beta_h\nu_h\alpha_h(\phi+\mu_h)v_{33}I_m^*}{(a\beta_h I_m^* + \mu_h N_h^*)(\phi+\mu_h)(v_{22}v_{33}-\xi\eta)v_{11} - a\beta_h\nu_h\gamma\phi v_{33}I_m^*},\\
I_m^* &= \frac{a\beta_m\nu_m\alpha_m K_m(v_{33}+\rho\eta)I_h^*}{(a\beta_m(v_{33}+\rho\eta)I_h^* + \alpha_m v_{33}N_h^*)v_{44}v_{55}},
\end{aligned}
$$

and, finally, by substituting I_m^* into I_h^* we obtain

$$
I_h^*(AI_h^{*2} + BI_h^* + C) = 0, \tag{21}
$$

where

$$
\begin{aligned}
A &= \frac{\alpha_m\delta_h}{\mu_h}v_{11}v_{33}v_{44}v_{55}(\phi+\mu_h)(v_{22}v_{33}-\xi\eta)(\delta_h-\delta^*),\\
B &= a^2\beta_m\beta_h\nu_m\alpha_m K_m(v_{33}+\rho\eta)[v_{11}(\phi+\mu_h)(v_{22}v_{33}-\xi\eta) - \nu_h\phi\gamma v_{33}]\\
&\quad + \alpha_m v_{11}v_{33}v_{44}v_{55}K_h(\phi+\mu_h)(v_{22}v_{33}-\xi\eta)(\delta^*-2\delta_h),\\
&= \alpha_m v_{11}v_{33}v_{44}v_{55}K_h(\phi+\mu_h)(v_{22}v_{33}-\xi\eta)\times\\
&\qquad \left(R_0^2\left(\frac{v_{11}(v_{22}v_{33}-\xi\eta)}{\nu_h v_{33}} - \frac{\phi\gamma}{(\phi+\mu_h)}\right) + (\delta^*-2\delta_h)\right),\\
C &= \alpha_m\alpha_h v_{11}v_{33}v_{44}v_{55}K_h(\phi+\mu_h)(v_{22}v_{33}-\xi\eta)(1-R_0^2),\\
\delta^* &= \frac{a\beta_m\mu_h(v_{33}+\rho\eta)}{\alpha_m v_{33}}.
\end{aligned}
$$

Clearly, one of the roots of (21) is $I_h^* = 0$, which corresponds to the disease free equilibrium point E_0. The other roots are found from the remaining equation (22)

$$
f(I_h^*) = AI_h^{*2} + BI_h^* + C. \tag{22}
$$

It follows from (22) that $A > 0$ when $\delta_h > \delta^*$ and $C > 0$, whenever $R_0 < 1$. Therefore, the number of possible and exact positive real roots of (22) can be analyzed using Descartes' Rule of Signs, [3], and Sturm Theorem, [16], or simply by investigating the possible positions of the parabola. The various possibilities for the roots of (22) are tabulated in Table 3. Thus,

Table 3. The number of positive real roots of (22).

				Descartes' rule of signs	Sturm's Theorem
Cases	A	B	C	Possible positive real roots	Positive real roots
1	+	+	+ ($R_0 < 1$)	0	0
2	+	-	+ ($R_0 < 1$)	0 or 2	2 ($B^2 - 4AC > 0$)
3	-	+	+ ($R_0 < 1$)	1	1
4	-	-	+ ($R_0 < 1$)	1	1
5	+	+	- ($R_0 > 1$)	1	1
6	+	-	- ($R_0 > 1$)	1	1
7	-	+	- ($R_0 > 1$)	0 or 2	2 ($B^2 - 4AC > 0$)
8	-	-	- ($R_0 > 1$)	0	0

Using the various possibilities shown in Table 3, the following result is established on the existence of endemic equilibrium.

Theorem 3.2. *The model (1)-(8) has:*

(T1) a unique endemic equilibrium if $R_0 < 1$ *and* $\delta_h < \delta^*$, *(Case 3 and 4 in Table 3).*

(T2) a unique endemic equilibrium if $R_0 > 1$ *and* $\delta_h > \delta^*$, *(Case 5 and 6 in Table 3).*

(T3) two endemic equilibria if $R_0 < 1$, $\delta_h > \delta^*$, $B < 0$ *and* $B^2 - 4AC > 0$ *(Case 2 in Table 3).*

(T4) two endemic equilibria if $R_0 > 1$, $\delta_h < \delta^*$, $B > 0$ *and* $B^2 - 4AC > 0$ *(Case 7 in Table 3).*

(T5) no endemic equilibrium if $R_0 < 1$, $\delta_h > \delta^*$ *and* $B > 0$ *(Case 1 in Table 3).*

(T6) no endemic equilibrium if $R_0 > 1$, $\delta_h < \delta^*$ *and* $B < 0$ *(Case 8 in Table 3).*

Theorem 3.2 indicates the possibility of various bifurcations in the model when $\delta_h \neq 0$. Due to interdependence of the coefficients A, B and C a comprehensive analysis of all bifurcation patterns is very involved and outside the scope of this paper. We observe, however, that there are four clearly distinct cases, corresponding to the magnitude of the disease induced mortality rate δ_h. If $0 < \delta_h < \delta^*/2$, then $A < 0$ and $B > 0$. The latter inequality can be established by expanding the coefficients v_{11}, v_{22} and v_{33} to show that the first term of B is positive. The discriminant of the equations, $\Delta = B^2 - 4AC$, is positive for $C \geq 0$, hence for $0 < R_0 \leq 1$ but then, by continuity, $\Delta > 0$ for $R_0 \in (0, 1 + c)$ for some constant c. Note that this statement is valid even if changing R_0 changes some other parameters of the problem (apart from δ_h and δ^*). Thus, for $0 < R_0 < 1$ we have a coexistence of the DFE and EE and at $R_0 = 1$ a new EE emerges. Such a bifurcation is often termed an imperfect bifurcation, [28]. The other distinctive case is when δ_h is very large, large enough for $B < 0$ and $\delta_h > \delta^*$, so that $A > 0$. In such a case for $\Delta > 0$ we need $C \leq 0$ so that $\Delta > 0$ for $(1 - c, \infty)$. Both roots, however, will be positive as long as $C/A > 0$; that is, for $R_0 < 1$. If $R_0 > 1$, then we have only one positive root. Concluding, in this case we observe a backward bifurcation at $R_0 = 1$. Finally, we consider the intermediate range of δ_h. If $\delta_h < \delta^*$ but is not small enough so that $B > 0$, then we have the coexistence of a DFE and EE for $R_0 < 1$ with the EE disappearing for $R_0 > 1$. On the other hand, if $\delta_h > \delta^*$ but we still have $B > 0$, then for $R_0 < 1$ there only is a DFE and an EE appears while passing through $R_0 = 1$. In both latter cases we have a transcritical bifurcation at $R_0 = 1$ that is termed subcritical in the first case and supercritical in the second.

It is worth noting that from (22) there may be no dependence between the coeffi-

cients and R_0, and as such when $R_0 = 0$, the coefficients are nonzero (with $C > 0$), and a unique or two endemic equilibrium may exist.

3.4. Biological implications of the bifurcations

From the epidemiological point of view, elimination of the disease can be achieved if R_0 reduced below unity. This therefore makes the implication of these identified bifurcations on malaria infection in an area very important. The existence of the subcritical bifurcation means that the disease may not become epidemic if $R_0 > 1$ and $R_0 < 1$ is sufficient for disease elimination. The supercritical bifurcation means that malaria infection is established and endemic when $R_0 > 1$ but when $R_0 < 1$, the disease eventually dies out. On the other hand, the imperfect bifurcation means that there might be pockets of the disease for any $R_0 < 1$ but the disease will be well established if $R_0 > 1$.

On the other hand, when backward bifurcation exist (since the locally asymptotically stable DFE coexists with a locally asymptotically stable EE when $R_0 < 1$), getting $R_0 < 1$ is not sufficient for the infection to die out but, contrary to the subcritical case, there is a critical value of R_0, denoted by $R_{crit} \in (0, 1)$, such that if $R_0 < R_{crit}$, then no malaria will persist and the disease eliminated. Thus, for malaria to die out, there is need for constant monitoring and increase in control strategies, so that R_0 is always reduced below R_{crit} and no endemic equilibrium exists. If R_0 increases above R_{crit} (i.e. $R_{crit} < R_0 < 1$), malaria dynamics become complicated because infection tend to jump from DFE to persist at a high endemic level. This may result in a sudden boom in infection and reestablishment of the disease in the area where the infection may have otherwise been eliminated. We observe that the backward bifurcation occurs when $\Delta = B^2 - 4AC = 0$ so that to find R_{crit} this equation must be solved for the appropriate selection of the parameters.

Last but not least, the disease will be eliminated when $R_0 = 0$ (even in the case where the locally asymptotically stable DFE coexists with a locally asymptotically stable EE) because the disease induced mortality rate may be very large and hence, cause the infectious population to be maintained close to the DFE. Thus, infectious individuals die before they can successfully transmit the infection to susceptible humans. In the next section we present a series of numerical simulations to illustrate the impact of conditions T2 – T4 in Theorem 3.2. To recall, an endemic equilibrium exists for T2 – T4.

4. Numerical simulation

The numerical simulations of the system (1)-(8) are illustrated in Figures 2-7 for the parameter values shown in Table 2. The backward bifurcation diagram is shown in Figure 3. In addition, the effect of varying the partial recovery rate η, the full recovery rate γ, the recrudescence rate ξ and the loss of post treatment prophylaxis rate ϕ on the infectious population when an endemic equilibria exist (i.e. when one of the conditions T2 – T4 holds) is illustrated in Figures 4-7.

4.1. Parameter estimation

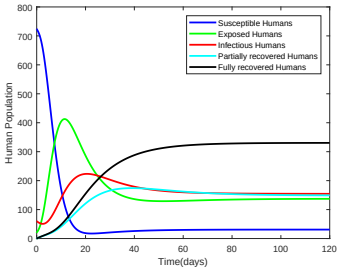
The numerical values of the parameters used for the simulation are given in Table 2. Most of the parameter values are taken from the literature on Ghana and other endemic regions. Other parameter values, not directly found in the literature, were estimated using the assumptions made during the model formulation and following literature indications. The value for μ_h is derived from the expected human life-span of sixty-four years [36]; that is, $\mu_h = 1/(64 \times 365)$. From the literature [15, 22, 34], the estimates of the partial recovery is to be within 3-28 days, so that we assume the average $\eta = 1/14$ and $\gamma = 1/14$. Again from [34], if the symptoms recur within 28 days of the initial treatment, then we say that there is the recrudescence. Therefore, similarly, the value of ξ is chosen as the average, $\xi = 1/14$. The value of ϕ is assumed to vary between 1/7 and 1/1800. The 7 days represent the shortest period of the duration of post treatment prophylaxis due to an effective treatment and 1800 days (5 years) is chosen to check for a long lasting post treatment prophylaxis. The value of θ is assumed to vary between 1/30 and 1/1800. The value of δ^* is calculated to be 0.0020645. To ensure the existence of the conditions T2 – T4 in Theorem 3.2, the value of δ_h is chosen to be 0.05 ($R_0 = 13.2467$), 15 ($R_0 = 1.2022$), 100 ($R_0 = 0.4666$) and 8.209×10^{-5} ($R_0 = 17.1311$) respectively, with, $\delta_h = 0.05$ and 15 showing Cases 5 and 6 in T2 respectively.

Figure 2 shows the numerical simulation of the malaria model (1)-(8) for the parameter values shown in Table 2. The initial conditions used are $S_h(0) = 724$, $E_h(0) = 20$, $I_h(0) = 60$, $R_h(0) = 0$, $T_h(0) = 0$, $S_m(0) = 4850$, $E_m(0) = 30$ and $I_m(0) = 100$. We choose $\delta_h = 8.209 \times 10^{-5}$, 0.05, 15 to illustrate the existence of an endemic equilibrium (where imperfect and supercritical bifurcations may occur) and $\delta_h = 100$ to illustrate disease free equilibrium (where backward bifurcation may occurs). In Figures 2(a) – (f), the simulations show the existence of an endemic equilibrium. The simulations in Figures 2(a)-(h) suggest that, as the value of δ_h increases, the size of the infected subpopulation (I_h, R_h, I_m) reduces. This makes sense also intuitively as a high disease induced mortality rate results in the depletion of the infected populations. Also, the endemic equilibrium disappears as δ_h increases from 15 to 100 (i.e at $\delta_h = 21.711$, $R_0 = 1$), also possibly due to the dying out of the infected classes. In Figures 2(g) and (h), the simulations show a locally asymptotically stable DFE. To show the existence of backward bifurcation, the backward bifurcation diagram for the malaria model (1-8) is depicted in Figure 3 with $\delta_h = 100$.

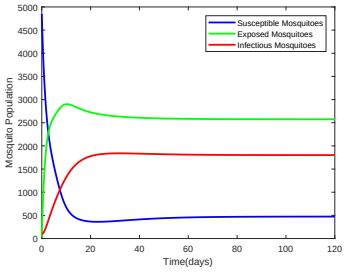
Figures 4 - 8 show the simulations of the evolution of the disease with varying rates of the partial recovery, recrudescence, loss of semi immunity, full recovery and loss of post treatment prophylaxis in the infected subpopulations for the parameter values in Table 2 and $\delta_h = 8.209 \times 10^{-5}, 0.05, 15$ and 100. The initial conditions used here are $S_h(0) = 724$, $E_h(0) = 20$, $I_h(0) = 60$, $R_h(0) = 0$, $T_h(0) = 0$, $S_m(0) = 4850$, $E_m(0) = 30$ and $I_m(0) = 100$.

As illustrated in Figure 4, an increase in partial recovery rate η from 0 to 1 results in a smaller equilibrium population of I_h. The decrease in the infectious equilibrium population in Figure 4(c-d) is more significant compared to Figure 4(a-b). Figure 4 illustrates that if it takes a short period for infectious humans to partially recover, then the size of the infectious population at the equilibrium will be small. However, if the disease induced death rate is very large, then, irrespective of the partial recovery rate, the infectious humans population will go extinct.

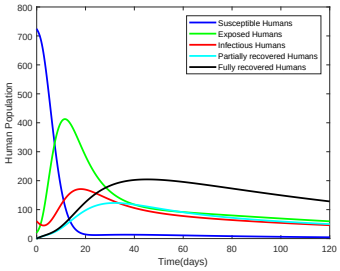
In Figure 5, we see that increasing the recrudescence rate ξ from 0 through to 1 causes an increase in the infectious human equilibrium population when $\delta_h = 8.209 \times$



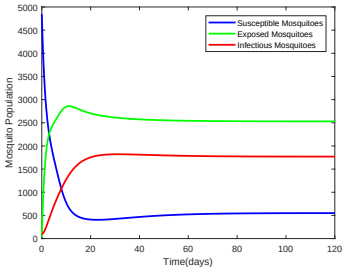
(a) Human population against time with $\delta_h = 8.209 \times 10^{-5}$.



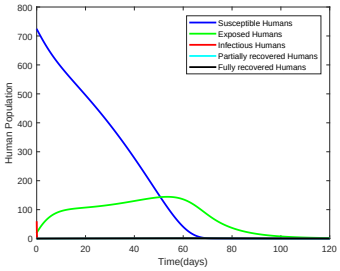
(b) Mosquito population against time with $\delta_h = 8.209 \times 10^{-5}$.



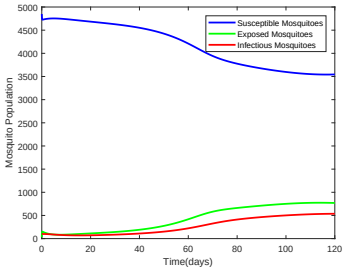
(c) Human population against time with $\delta_h = 0.05$.



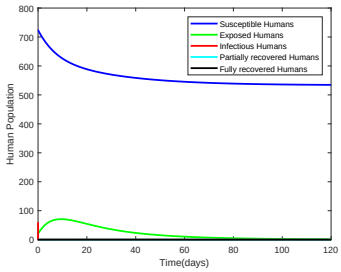
(d) Mosquito population against time with $\delta_h = 0.05$.



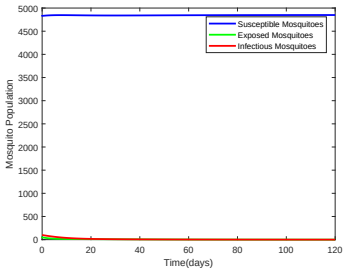
(e) Human population against time with $\delta_h = 15$.



(f) Mosquito population against time with $\delta_h = 15$.



(g) Human population against time with $\delta_h = 100$.



(h) Mosquito population against time with $\delta_h = 100$.

Figure 2. A numerical simulation of the malaria model (1–8) with initial conditions: $S_h = 724, E_h = 20, I_h = 60, R_h = 0, T_h = 0, S_m = 4850, E_m = 30, I_m = 100$. The parameters used are $\alpha_h = 0.031, \beta_h = 0.015, a = 11, \mu_h = 4.2808 \times 10^{-5}, \nu_h = 1/12, \alpha_m = 0.13, \mu_{m1} = 0.033, \mu_{m2} = 2 \times 10^{-5}, \beta_m = 0.475, \nu_m = 1/11, \rho = 0.2, \xi = 1/14, \phi = 1/30, \gamma = 1/14, \eta = 1/14, \theta = 1/365$ and **a,b** $\delta_h = 8.209 \times 10^{-5} (R_0 = 17.1311)$, **c,d** $\delta_h = 0.05 (R_0 = 13.2467)$, **e,f** $\delta_h = 15 (R_0 = 1.2022)$ and **g,h** $\delta_h = 100 (R_0 = 0.4666)$.

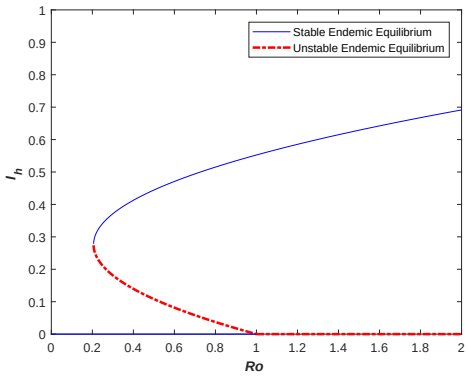


Figure 3. Backward bifurcation diagram for the infectious humans population for the following parameter values: $\alpha_h = 0.031, \beta_h = 0.015, a = 11, \mu_h = 4.2808 \times 10^{-5}, \nu_h = 1/12, \alpha_m = 0.13, \mu_{m1} = 0.033, \mu_{m2} = 2 \times 10^{-5}, \beta_m = 0.475, \nu_m = 1/11, \rho = 0.2, \xi = 1/14, \phi = 1/30, \gamma = 1/14, \eta = 1/14, \theta = 1/365$ and (a) $\delta_h = 100 (R_0 = 0.4666$ and $R_{crit} = 0.207)$.

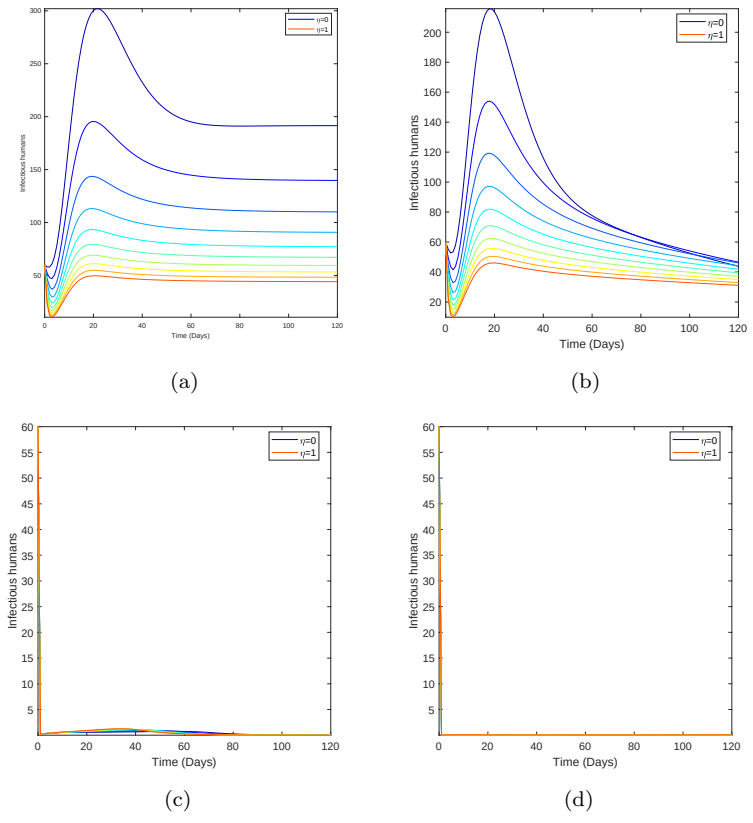


Figure 4. Graphs showing the effect of varying the partial recovery rate, η from 0 (blue line) to 1 (red line), on the long term behaviour of the infectious human population with (a) $\delta_h = 8.209 \times 10^{-5}$, (b) $\delta_h = 0.05$, (c) $\delta_h = 15$ and (d) $\delta_h = 100$.

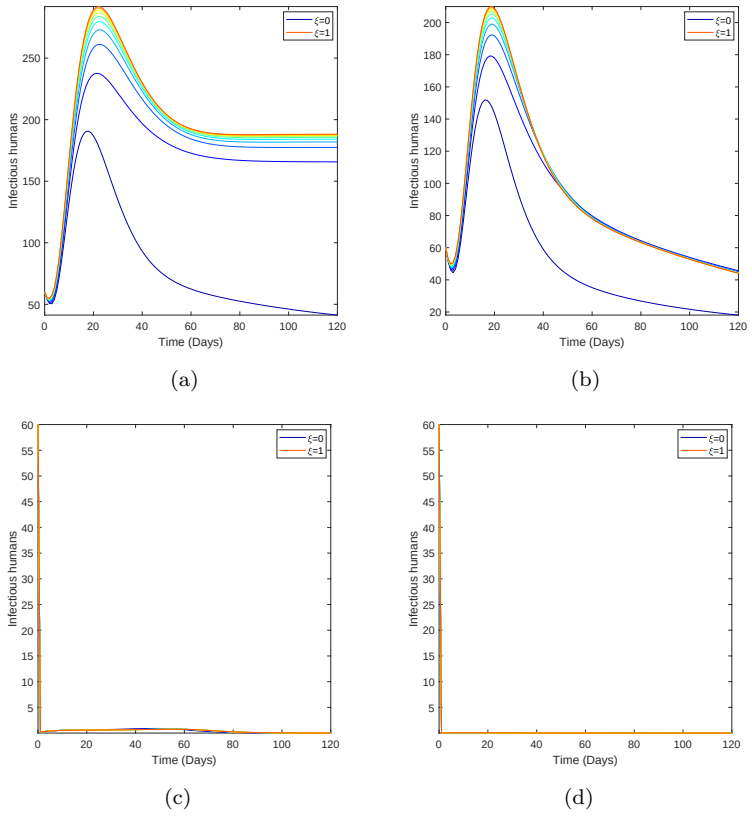


Figure 5. Graphs showing the effect of varying the recrudescence rate, ξ from 0 (blue line) to 1 (red line), on the long term behaviour of the infectious human population with (a) $\delta_h = 8.209 \times 10^{-5}$, (b) $\delta_h = 0.05$, (c) $\delta_h = 15$ and (d) $\delta_h = 100$.

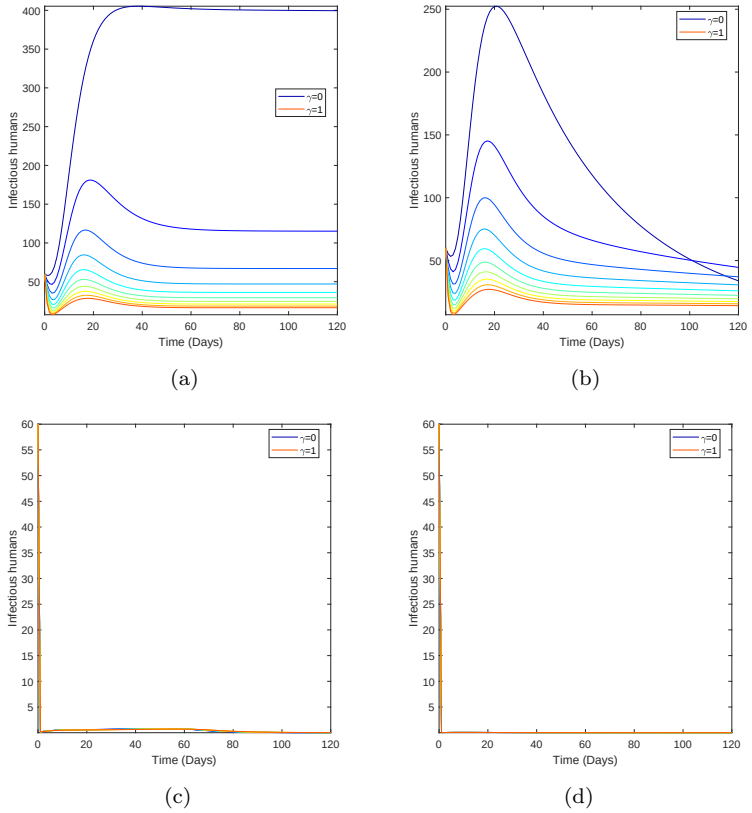


Figure 6. Graphs showing the effect of varying the full recovery rate, γ from 0 (blue line) to 1 (red line), on the long term behaviour of the infectious human population with (a) $\delta_h = 8.209 \times 10^{-5}$, (b) $\delta_h = 0.05$, (c) $\delta_h = 15$ and (d) $\delta_h = 100$.

10^{-5} and 0.05. This suggests that when the time it takes for the infection to recur is short, the number of infectious humans at equilibrium increases. The increase is more significant when the disease induced death rate is very small. Here, when $\xi = 0$, the population converges to zero. For Figures 5(c-d), no difference is observed in the infectious human equilibrium population as ξ is increased from 0 to 1 when $\delta_h = 15$ and 100. This may be because most humans, who become infectious, die before they get to recover.

In Figure 6 we see that varying the full recovery rate γ from 0 to 1 results in a significant decrease in infectious humans equilibrium population. This suggests that when treatment gives full recovery within the shortest period, the equilibrium of the infectious population reduces significantly. In Figure 6(c-d), we observe no difference in the infectious humans equilibrium population when γ is varied from 0 to 1 and $\delta_h = 15, 100$.

An increase in the loss of post treatment prophylaxis rate ϕ from 0 through to 1 increases the equilibrium of I_h, as seen in Figure 7(a-b). Here, when $\phi = 0$, the population converges to zero. Increasing ϕ from 0 to 1, when $\delta_h = 15, 100$, show no significant difference in the infectious humans population at equilibrium (Figure 7(c-d)). Figure 7 suggests that if it takes the longest period until an effective treatment wanes from the bloodstream, then the infectious population will go extinct in the long term, especially when the disease induced death rate is very small. However, when the disease induced death rate is very large, changing the loss of post treatment prophylaxis rate does not affect the infectious humans populations at equilibrium.

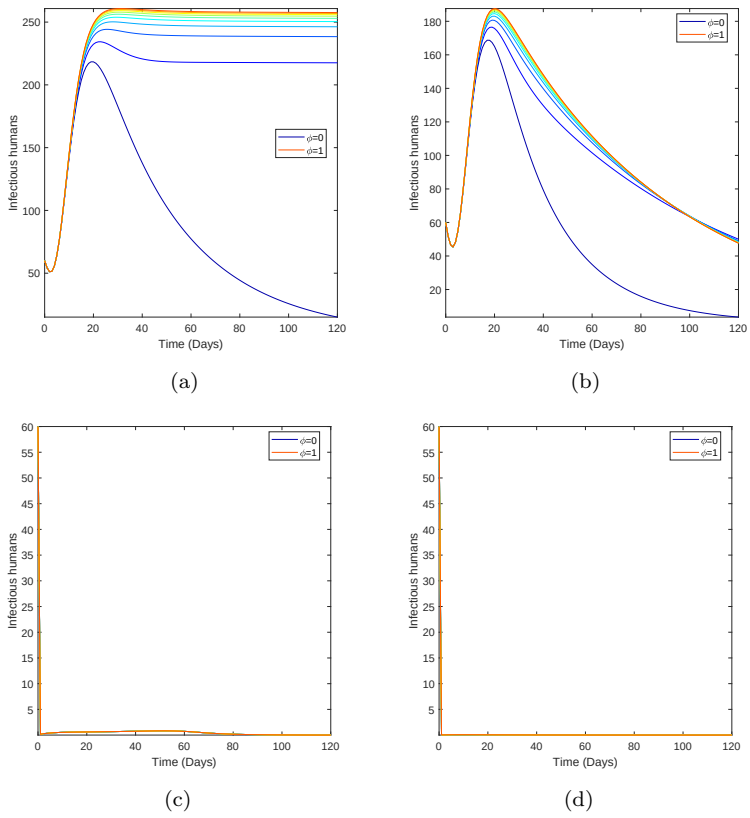


Figure 7. Graphs showing the effect of varying the loss of post treatment prophylaxis rate, ϕ from 0 (blue line) to 1 (red line), on the long term behaviour of the infectious human population with (a) $\delta_h = 8.209 \times 10^{-5}$, (b) $\delta_h = 0.05$, (c) $\delta_h = 15$ and (d) $\delta_h = 100$.

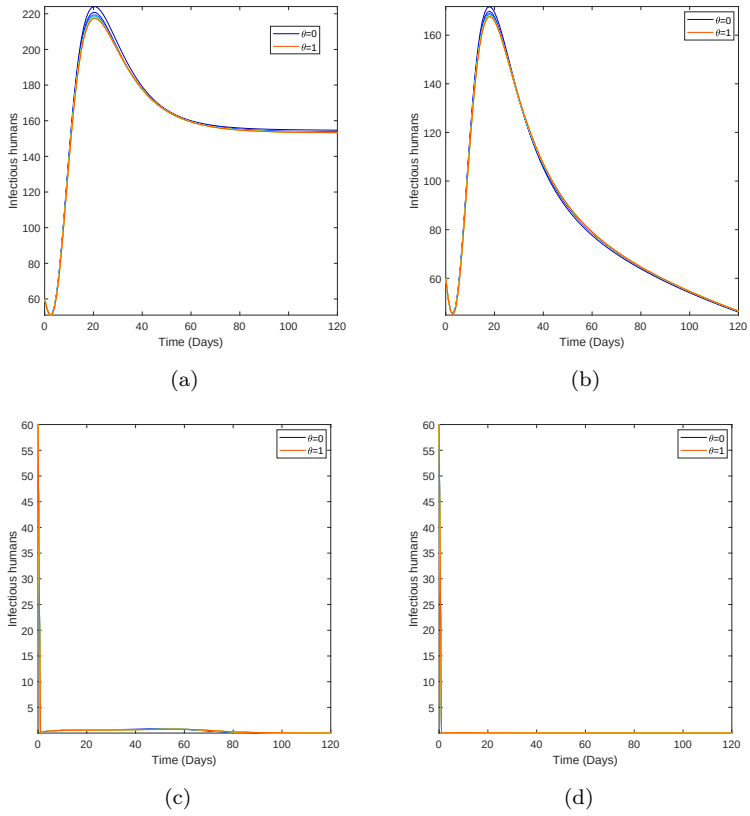


Figure 8. Graphs showing the effect of varying the loss of semi-immunity rate, θ from 0 (blue line) to 1 (red line), on the long term behaviour of the infectious human population with (a) $\delta_h = 8.209 \times 10^{-5}$, (b) $\delta_h = 0.05$, (c) $\delta_h = 15$ and (d) $\delta_h = 100$.

Table 4. Elasticity index of R_0 to parameters using parameter baseline values in Table 2 with $\delta_h = 8.209 \times 10^{-5}$, 0.05, 15 and 100.

	Elasticity indices of R_0			
Parameters	$\delta_h = 8.209 \times 10^{-5}$	$\delta_h = 0.05$	$\delta_h = 15$	$\delta_h = 100$
a	+1	+1	+1	+1
β_h	+0.5	+0.5	+0.5	+0.5
β_m	+0.5	+0.5	+0.5	+0.5
μ_h	-0.5	-0.5	-0.5	-0.5
α_h	-0.5	-0.5	-0.5	-0.5
μ_{m2}	-0.5	-0.5	-0.5	-0.5
ν_m	+0.29	+0.29	+0.29	+0.29
μ_{m1}	-0.17	-0.17	-0.17	-0.17
α_m	-0.12	-0.12	-0.12	-0.12
η	0.081	+0.081	+0.081	+0.081
ξ	-0.078	-0.078	-0.078	-0.078
ρ	+0.081	+0.081	+0.081	+0.081
ν_h	+0.00026	+0.00026	+0.00026	+0.00026
γ	-0.48	-0.29	-0.0024	-0.00036
δ_h	-0.00056	-0.201	-0.5	-0.5

An increase in the loss of semi-immunity rate θ from 0 through to 1 does not show significant difference on the infectious humans population at equilibrium (Figure 7(a-d)). We observe the infectious humans population at equilibrium converges to 0 for all the values of δ_h except $\delta_h = 8.209 \times 10^{-5}$. Figure 8 seem to suggest that the duration for the partially recovered to loss their semi-immunity may not impact the infectious population at equilibrium.

In general, Figures 4–8 seem to suggest that when δ_h is very large, then varying the rates of recovery, recrudescence, semi-immunity may not affect the infectious population, because, the population will eventually go extinct. However, when δ_h is very small, then the longest period until recrudescence occurs, an effective treatment that gives full recovery in the shortest time and longest post treatment prophylaxis period is crucial for the reduction of infection in the infectious population and control of malaria in the human population.

4.2. Sensitivity analysis of R_0

A local sensitivity analysis of R_0 is done by computing the elasticity index of the parameters [9]. This is derived by differentiating R_0 with respect to the model parameter p defined as

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}.$$

The parameter values in Table 2 and the values of $\delta_h = 8.209 \times 10^{-5}$, 0.05, 15, 100 are used to ensure the existence of imperfect, supercritical and backward bifurcation. The elasticity indices of R_0 to the model parameters for these four values of δ_h are given in Table 4. The + sign means that R_0 increases as the value of the parameter increases, while the − sign means that an increase in the value of the parameter decreases R_0.

From Table 4 we see that the most important parameter is the number of bites per person. The probabilities of transmission β_h (β_m), the per capita density dependent death rate for mosquitoes μ_{m2}, the birth rate α_h and natural death rate μ_h for humans have an equally strong impact on R_0 when all the bifurcations exist. The parameter ν_h has little effect on R_0. The parameters δ_h and γ have different effects on R_0. When

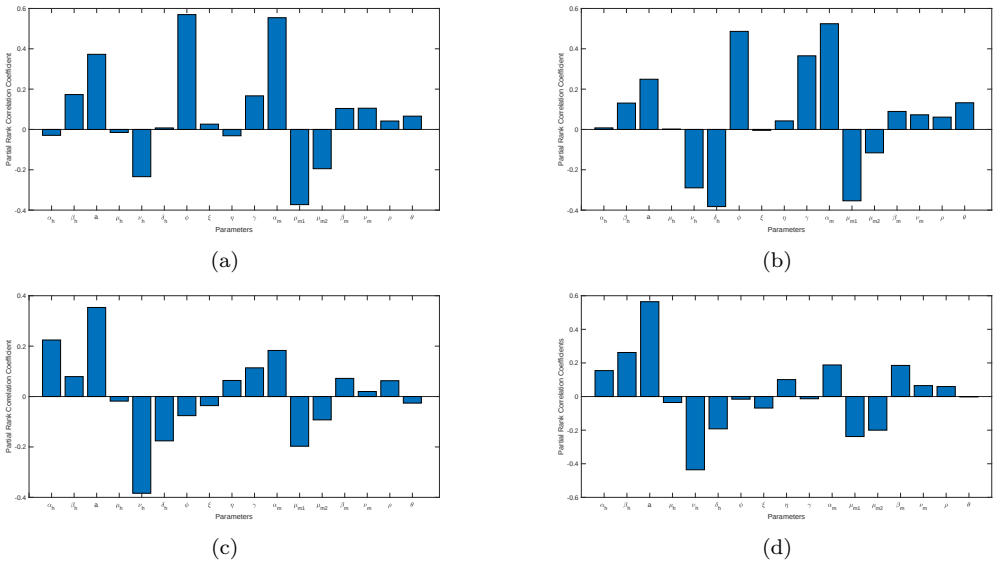


Figure 9. Global sensitivity analysis. Partial Rank Correlation Coefficients showing the ranking of parameters influence on the infectious humans population (I_h) with (a) $\delta_h = 8.209 \times 10^{-5}$, (b) $\delta_h = 0.05$, (c) $\delta_h = 15$ and (d) $\delta_h = 100$.

imperfect bifurcation occurs, γ has strong impact on R_0 while δ_h has a strong impact when supercritical (Case 6 in Table 3) and backward bifurcation exist.

The results suggest that depending on the bifurcation present, multiple interventions that combine all the significant parameters will effectively control the spread of malaria.

4.3. Sensitivity analysis of model parameters

A global sensitivity analysis [8] is done using the Latin Hypercube Sampling (LHS) with partial rank correlation coefficient index (PRCC). The parameter values in Table 2 and the values of $\delta_h = 8.209 \times 10^{-5}$, 0.05, 15, and 100 are used to ensure the existence of imperfect, supercritical and backward bifurcations respectively. The sets of input parameter values sampled using the LHS method were used to run 1000 simulations. The PRCC index of the model parameters on the infectious humans sub-population of the model (1)–(8) are calculated to show the parameters that significantly influence the growth or decline of it.

The results of the partial rank correlation coefficients show that when imperfect bifurcation occurs (Figure 9(a)), the per capita loss of post treatment prophylaxis ϕ and the per capita birth rate of mosquitoes α_m, have the highest influence on the infectious humans population reproduction followed by the number of mosquito bites per human a and the density independent death rate of mosquitoes μ_{m1}. In Figure 9(b), the parameters with the highest influence on the infectious humans population are the per capita loss of post treatment prophylaxis ϕ, the per capita birth rate α_m and the per capita full recovery rate γ. These are followed by the per capita disease induced death rate of humans δ_h and the density independent death rate of mosquitoes μ_{m1}. In Figure 9(c), the highest influence is from the per capita transition rate of exposed humans to infectious humans ν_h and the number of mosquito bites per human a. these are followed by the total birth rate of humans α_h. When backward bifurcation occurs, the results show that the number of mosquito bites per human a

and the per capita transition rate of exposed humans to infectious humans ν_h have the highest influence on the infectious humans population followed by the probability of transmission of infection from an infectious mosquito to a susceptible human β_h and the density independent death rate of mosquitoes μ_{m1} (Figure 9(d)). The contribution of other parameters are indicated in Figure 8.

In general, the birth rate of the mosquitoes and the number of mosquito bites per human are positively correlated to the infectious humans population while the density independent death rate of mosquitoes and the per capita transition rate of exposed humans to infectious humans are negatively correlated. We also find that the per capita rate of loss of post treatment prophylaxis is positively correlated to the infectious humans population only when imperfect or supercritical bifurcation ($\delta_h = 8.209 \times 10^{-5}$ or 0.05) occur. This seem to suggests that when the period for post treatment prophylaxis is very short, the infectious humans population increases. Thus increasing parameters that are positively correlated to the infectious humans population would result in the prevalence of malaria.

5. Discussion

A comprehensive deterministic model for *P. falciparum* malaria infection in humans was developed. The model included full recovery, partial recovery, recrudescence, a period of post treatment prophylaxis due to effective treatment and a period of semi-immunity in order to comprehensively understand the disease transmission dynamics to be able to control it and eliminate. We showed that the model is epidemiologically and mathematically well-posed. The basic reproduction number, R_0 and the equilibrium points of the model were derived. The model has a locally asymptotically stable disease free equilibrium when $R_0 < 1$.

We showed that the model could undergo imperfect, backward, transcritical (subcritical and supercritical) bifurcations depending on the value of the disease induced death rate and R_0. Most previous studies focused on the possible existence [7, 9, 21, 23] and removal [7, 21, 23] of backward bifurcation. In this study, we focused not only on backward bifurcation but also on supercritical and imperfect bifurcations, i.e. where at least an endemic equilibria exist for both $R_0 < 1$ and $R_0 > 1$. When a backward bifurcation exists, R_0 must be reduced below the threshold parameter (so that $B^2 - 4AC < 0$) through sustained control strategies; otherwise malaria may becomes endemic. From our analysis, reducing the disease induced death rate is crucial. One characteristics of malaria endemic areas is the large disease induced deaths in humans [37]. Thus, to reduce disease induced death the World Health Organisation recommends prompt diagnosis and the treatment of infected humans with effective antimalarials [15, 34, 37].

For the numerical simulations, sensitivity analysis and calculation of the partial rank correlation coefficient (PRCC), the parameter values from an endemic region were used. The numerical simulations suggested that a very high disease induced death rate drives the population to a stable disease free equilibrium. However, this control strategy is of course not acceptable. The simulations also suggest that time is of importance, even when an effective treatment is used. An effective treatment for malaria that gives full recovery within a short period and long period of post treatment prophylaxis seems the best choice for the removal of malaria in the population of humans. When backward bifurcation exists, attention must be given to especially the number of mosquito bites per human, the transition rate of exposed humans to

infectious, prompt diagnosis and use of effective treatment among others controls. Also, when backward bifurcation occurs there is need for constant monitoring of these control intervention to prevent sudden malaria outbreaks.

The sensitivity indices of R_0 showed that the ranking of all the parameters is similar when the different bifurcations exist except for the parameters, disease induced death rate and the per capita full recovery rate. The most important parameter when all the parameters are ranked was the average number of mosquito bites per person per day. Hence, being able to control the number of mosquito bites per day is very important for the control and elimination of malaria, regardless of the bifurcations present. Following the number of mosquito bites were the probabilities of transmission, the per capita density dependent death rate for mosquitoes, the total birth rate of humans, the natural death rate for humans and either the full recovery rate or the disease induced death, depending on the bifurcation present, with an equally strong impact on R_0.

The PRCC plots suggest that the per capita birth rate of mosquitoes α_m and the number of mosquito bites per human a were strongly positively correlated, while the density dependent death rate of mosquito μ_{m1} and the per capita transition rate of exposed humans ν_h were strongly negatively correlated, to I_h when all three types of bifurcations exist. Parameters β_h, ϕ_h, γ, δ_h, μ_{m1} and α_h were also correlated to I_h depending on the bifurcation present.

From the sensitivity analysis, an increase in the birth rate in mosquitoes (survival of eggs to pupa to larvae to adults) increased the prevalence of malaria, while the removal of the adult mosquitoes through death, climatic conditions and control strategies continually over a long period of time reduced malaria infection. In endemic regions, where the intrinsic growth rate of mosquitoes is always positive, [20], there is need for new and more economical methods that will lower the intrinsic growth rate of mosquitoes and indirectly control malaria. Methods such as destruction of breeding sites, the use of sterile insect technique [14], transgenes [17], indoor residual spraying and other larval or vector control techniques [27] have been suggested.

Summarizing, when the disease induced death is small, vector control methods and an effective treatments, that give full recovery within the shortest period and a long post treatment prophylaxis is better for reducing the disease burden. However, preventive methods such as reducing mosquito bite rates, transmission blocking drugs, intermittent prophylactic treatments, vector controls and the effective treatment will go a long way to reduce the burden of malaria in endemic areas where disease induced death are high.

The elimination of malaria will also require the prevention of use of ineffective treatments, and to make the effective drugs affordable and accessible.

It is worth noting that most of the control strategies have their inherent cost implications. The authors in [1, 2, 23, 27, 29] have recommended the levels of coverage and the impact of possible combinations of control strategies on the epidemiology of malaria, depending on the area. For future investigation, a cost benefit analysis of the current model, coupled with the suggested control strategies, will be performed to contribute to the effective allocation of scarce resources and efficient elimination programs in endemic areas. The effect of environment, weather and climate change have been found to impact the disease vector and the parasite [5, 13, 24, 30, 31]. This is another challenge in the quest of the malaria elimination.

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