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Bifurcation and Sensitivity Analysis of a Malaria Model with Isolated Drug Resistant Population

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ABSTRACT. A malaria model with isolated drug resistant population after the first line of treatment is presented using six systems of first order nonlinear differential equations. The disease free equilibrium point and the basic reproduction number are determined. Local stability of the disease free equilibrium is determined and the conditions for the existence of endemic equilibrium. Bifurcation analysis reveals the existence of backward bifurcation. Sensitivity analysis is used to determine the impact of the model parameter on the basic reproduction number. Early detection and using correct dosage will go a long way to prevent drug resistance.

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Malaria is caused by the protozoan parasites of genus Plasmodium. In humans it is caused by Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax. Of these, P.falciparum is the most common cause of infection in Africa and South East Asia (Mandal *et al.*, 2011). The symptoms of malaria includes chills, fever, vomiting and headache. The first mathematical model of malaria was developed by Sir Ronald Ross, while serving at the Indian Medical Service in 1890's. He developed a simple mathematical model now known as the classical "Ross model" which explained the relationship between the number of mosquitoes and incidence of malaria in humans. Over the years, various mathematical models have developed to effectively understand the dynamics of malaria (Olaniyi *et al.*, 2014 and Ngwa *et al.*, 2000). Drug resistance occurs due to genetic mutation that allows the organism to survive treatment. As a result, the drug becomes less effective and infections persist in the body, increasing the risk of spread to others. Improper use of drugs and taking smaller than recommended doses are among the major causes of drug resistance. According to the world health organization, coordinated action is needed to reduce the emergence and spread of antimicrobial resistance.

Most research work on this subject involves non isolated drug resistant population (Okosun *et al.*, 2011, Cai *et al.*, 2013 and Ronoh *et al.*, 2016). Here, we propose a model where those with initial drug resistance are isolated and cannot transmit the disease during this period until they are effectively treated.

MATERIALS AND METHOD

The model divides the total human population into susceptible humans S_h, infected humans I_h, isolated drug resistant humans R_s, and recovered humans R_h. The vector population is divided into susceptible mosquitoes S_m, and infected mosquitoes R_m. The exposed stage is omitted in both human and vector population because we assumed that they will progress to the infectious stage. The dynamics of the model is such that susceptible individual are recruited into the human population at input rate Λ_h. Every class of human population is decreased by natural death μ_h except for the infectious class and isolated drug resistant class which has a per capita disease induced death rate δ_1 and δ_2 respectively . A susceptible human becomes infected after being bitten by an infectious mosquito with contact rate b and transmission rate β_h. After the first line of treatment, those that respond to treatment move to the recovered class while the ones who do not respond move to the isolated drug resistant class for further treatment. However, the recovered humans develop a temporary acquired immunity against the disease and later loses this immunity to become susceptible again at per capita rate c. Mosquitoes are recruited into the population at rate Λ_m but decreased through interaction with infectious humans with transmission rate β_m. Both the susceptible and infectious

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mosquitoes are decreased by natural death μ_m while the infectious mosquitoes are further reduced as a result of the parasite at rate δ_m. The following systems of first order differential equations describe the model.

$$S_h' = \Lambda_h - \frac{d\beta_h S_h I_m}{N_h} - \mu_h S_h + cR_h \qquad (1)$$

$$I_h' = \frac{d\beta_h S_h I_h}{N_h} - (\mu_h + \sigma + a + \delta_1) I_h \qquad (2)$$

$$R_s' = \sigma I_h - (\mu_h + b + \delta_2) R_s \qquad (3)$$

$$R_h' = aI_h - (\mu_h + c) R_h + bR_s \qquad (4)$$

$$S_m' = \Lambda_m - \frac{d\beta_m S_m I_m}{N_m} - \mu_m S_m \qquad (5)$$

$$I_m' = \frac{d\beta_m S_m I_h}{N_m} - (\mu_m + \delta_m) I_m \qquad (6)$$

Table 1. The description of the state variables and parameters of the model.

Definition	Symbol
Recruitment term of the susceptible humans	Λ_h
Recruitment term of the susceptible mosquitoes	Λ_m
Transmission probability from mosquito to human	β_h
Transmission probability from human to mosquito	β_m
Effective treatment rate of drug resistant humans	b
Effective treatment rate of infectious humans	a
Disease induced death due of infectious humans	δ_1
Disease induced death due of drug resistance humans	δ_2
Disease induced death of mosquitoes	δ_m
Progression rate of infectious human to drug resistant humans	σ
Per capita transition rate of recovered humans	c
Natural death rate of humans	μ_h
Natural death rate of mosquitoes	μ_m
Biting rate	d

RESULTS AND DISCUSSIONS

Theorem 1: *(Invariant region).* The feasible region $\mathcal{R}$ defined by $\left\{S_h(t), I_h(t), R_s(t), R_h(t), S_m(t), I_m(t), \in R_+^6 : N_h(0) \le N_h(t) \le \frac{\Lambda}{\mu}, N_m(0) \le N_m(t) \le \frac{\Lambda_m}{\mu_m}\right\}$ with initial conditions $S_h(0) \ge 0, I_h(0) \ge 0, R_s(0) \ge 0, R_h(0) \ge 0, S_m(0) \ge 0, I_m(0) \ge 0$ is positive invariant for system $(1) - (6)$.

Proof: The total human population size is given by

$$N_h(t) = S_h(t) + I_h(t) + R_s(t) + R_h(t).$$

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \delta_1 I_h - \delta_2 R_s$$

$$\frac{dN_h}{dt} \le \Lambda_h - \mu_h N_h$$

Solving above gives $0 \le N_h(t) \le \left(N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t})\right)$

As $t \to \infty, 0 \le N_h \le \frac{\Lambda_h}{\mu_h}$, If $N(0) \le \frac{\Lambda_h}{\mu_h}$ then $N(t) \le \frac{\Lambda}{\mu}$. Hence,

$$N_h(0) \le N_h(t) \le \frac{\Lambda_h}{\mu_h}$$

Using similar argument,

$N_m(0) \le N_m(t) \le \frac{\Lambda_m}{\mu_m}$

Thus, $\mathcal{R}$ is a positivity invariant set under the model. Hence it is sufficient to consider the dynamics of model $(1) - (6)$ in region $\mathcal{R}$.

Disease-free equilibrium point: The disease-free equilibrium points of system $(1) - (6)$ is given by,

$$\pi_o = \left(\frac{\Lambda_h}{\mu_h}, 0,0,0, \frac{\Lambda_m}{\mu_m}, 0\right) \qquad (7)$$

Basic reproduction number: The next generation matrix approach by Driessche and Watmough (2002) is applied to obtain the basic reproduction number.

The nonlinear terms with the new infection $\mathcal{F}$ and the outflow term $\mathcal{V}$ of system $(1) - (6)$ are given by

$$\mathcal{F} = \begin{pmatrix} \frac{d\beta_h S_h I_m}{N_h} \\ 0 \\ \frac{d\beta_m S_m I_h}{N_m} \end{pmatrix} \qquad (8)$$

$$\mathcal{V} = \begin{pmatrix} (\mu_h + \sigma + a + \delta_1) I_h \\ -\sigma_h I_h + (\mu_h + b + \delta_2) R_s \\ (\mu_m + \delta_m) I_m \end{pmatrix} \qquad (9)$$

The linearized matrices F and V, computed at the disease-free equilibrium from (8) and (9) above give

$$\mathrm{F} = \begin{pmatrix} 0 & 0 & d\beta_h \\ 0 & 0 & 0 \\ d\beta_m & 0 & 0 \end{pmatrix}$$

And

$$V = \begin{pmatrix} (\mu_h + \sigma + a + \delta_1) & 0 & 0 \\ -\sigma_h & (\mu_h + \mathrm{b} + \delta_2) & 0 \\ 0 & 0 & (\mu_m + \delta_m) \end{pmatrix}$$

The basic reproduction R_0 is given by $\rho(FV^{-1})$ where ρ is the spectral radius. Thus,

$$R_0 = \sqrt{\frac{d^2\beta_h\beta_m}{(\mu_h+\sigma+\alpha+\delta_1)(\mu_m+\delta_m)}} \qquad (10)$$

Local stability of disease-free equilibrium: One of the most important concerns in the analysis of epidemiological models is the determination of the asymptomatic behaviour of their solutions which is usually based on the stability of the associated equilibrium.

Theorem 2: (Local stability of disease-free equilibrium). The disease-free equilibrium for the system $(1)-(6)$ is locally asymptomatically stable if $R_0 < 1$ and unstable otherwise.

Proof: The Jacobian matrix evaluated at the disease-free is given by

$$J(\pi_0) = \begin{pmatrix} -\mu_h & 0 & 0 & c & 0 & -d\beta_h \\ 0 & -(\mu_h+\sigma+a+\delta_1) & 0 & 0 & 0 & d\beta_h \\ 0 & \sigma & -(\mu_h+b+\delta_2) & 0 & 0 & 0 \\ 0 & a & b & -(\mu_h+c) & 0 & 0 \\ 0 & -d\beta_m & 0 & 0 & -\mu_m & 0 \\ 0 & d\beta_m & 0 & 0 & 0 & -(\mu_m+\delta_m) \end{pmatrix}$$

Some of the roots of the characteristic equation are $-\mu_h$, $-\mu_m$, $-(\mu_h+$ c) and $-(\mu_h+b+\delta_2)$. The other roots can be obtained from the sub matrix given below.

$$J_1(\pi_0) = \begin{pmatrix} -(\mu_h+\sigma+a+\delta_1) & d\beta_h \\ d\beta_m & -(\mu_m+\delta_m) \end{pmatrix}$$

The remaining roots are the solution to the following equations

$$\begin{vmatrix} -(\mu_h+\sigma+a+\delta_1) & d\beta_h \\ d\beta_m & -(\mu_m+\delta_m) \end{vmatrix} = 0$$

This leads to the characteristic equation: $(\mu_h+\sigma+a+\delta_1)(\mu_m+\delta_m) - d^2\beta_h\beta_m = 0$. It is obvious from the equation that two negative real roots or two conjugate complex roots with negative real roots can be obtained if $R_0 < 1$.

Theorem 3: (Existence of endemic equilibrium). The model under consideration has an endemic equilibrium when $R_0 > 1$ and $Z < 1$ or $R_0 < 1$ and $Z > 1$

Proof: Let $E_e^* = (S_h^*, I_h^*, R_s^*, R_h^*, S_m^*, I_m^*)$ be a equilibrium of the model $(1)-(6)$. The model at steady state becomes

$$S_h^* = \frac{(d\beta_m I_h^* + \Lambda_m)\Lambda_h}{\mu_h\Lambda_m R_0^2}$$

$$R_s^* = \frac{\sigma I_h^*}{(\mu_h+b)}$$

$$R_h^* = \frac{[a(\mu_h+b+\delta_2)+\sigma b]I_h^*}{(\mu_h+b+\delta_2)(\mu_h+b)}$$

$$S_m^* = \frac{\Lambda_m^2}{d\beta_m I_h^*\mu_m + \Lambda_m\mu_m}$$

$$I_m^* = \frac{R_{0m}\Lambda_m I_h^*}{d\beta_m I_h^* + \Lambda_m}$$

$$I_h^* = \frac{(\mu_h+\text{c})(\mu_h+b+\delta_2)\Lambda_h\Lambda_m(1-R_0^2)}{Z}$$

Where

$$R_{0m} = \frac{d\beta_m}{\mu_m+\delta_m},$$

$$Z = c\Lambda_m R_0^2[a(\mu_h+b)+\sigma b] - d(\mu_h+\text{c})(\mu_h+b)\Lambda_m\beta_h R_{0m} + \Lambda_h\beta_m$$

This shows the possibility of an existence of backward bifurcation.

Bifurcation Analysis: To demonstrate the possibility of the co-existence of the equilibria of the model $(1)-(6)$ at $R_0 < 1$ but near $R_0 = 1$, the centre manifold theory described in (Chavez *et al.,* 2004) is applied. This theory can be used to establish the local stability of the endemic equilibrium near the threshold parameter $R_0 = 1$. Model $(1)-(6)$ can be written in the vector form as $\frac{dX}{dt} = F(X)$

Where $X = \left(x_1, x_2, x_3, x_4, x_5, x_6\right)^T$ and

$$F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$$

So that

$$S_h = x_1, I_h = x_2, R_s = x_3,$$

$R_h = x_4$, $S_m = x_5$ and $I_m = x_6$. The model $(1) - (6)$ becomes

$$x_1' = \Lambda_h - \frac{d\beta_h x_1 x_6}{N_h} - \mu_h x_1 + c x_4 \qquad (11)$$

$$x_2' = \frac{d\beta_h x_1 x_6}{N_h} - (\mu_h + \sigma + a + \delta_1)x_2 \quad (12)$$

$$x_3' = \sigma x_2 - (\mu_h + b + \delta_2)x_3 \qquad (13)$$

$$x_4' = a x_2 - (\mu_h + c)x_4 + b x_3 \qquad (14)$$

$$x_5' = \Lambda_m - \frac{d\beta_m x_5 x_2}{N_m} - \mu_m x_5 \qquad (15)$$

$$x_6' = \frac{d\beta_m x_5 x_2}{N_m} - (\mu_m + \delta_m)x_6 \qquad (16)$$

Let β_h be a bifurcation parameter such that $\beta_h = \beta_h^*$ when $R_0 = 1$.Then β_h^* can be obtained from (10) as

$$\beta_h = \frac{(\mu_h + \sigma + \alpha + \delta_1)(\mu_m + \delta_m)}{d^2 \beta_h \beta_m}$$

The Jacobian matrix of $(11) - (16)$ evaluated at disease-free equilibrium is

$$\begin{pmatrix} -\mu_h & 0 & 0 & c & 0 & -d\beta_h^* \\ 0 & -(\mu_h + \sigma + a + \delta_1) & 0 & 0 & 0 & d\beta_h^* \\ 0 & \sigma & -(\mu_h + b + \delta_2) & 0 & 0 & 0 \\ 0 & a & b & -(\mu_h + c) & 0 & 0 \\ 0 & -d\beta_m & 0 & 0 & -\mu_m & 0 \\ 0 & d\beta_m & 0 & 0 & 0 & -(\mu_m + \delta_m) \end{pmatrix}$$

The linearized system has a simple zero eigenvalue and all other eigenvalues have negative real parts. Hence, the center manifold theory can be applied to the model. The component of the right eigenvector is given as $w = [w_1, w_2, w_3, w_4, w_5, w_6]^T$ and

$$w_1 = \frac{(\mu_m + \delta_m)}{\mu_h d\beta_m}\left(\frac{c}{(\mu_h + c)(\mu_h + b + \delta_2)}[a(\mu_h + b + \delta_2) + b\sigma] - (\mu_h + \sigma + a + \delta_1)\right) w_6$$

$$w_2 = \frac{(\mu_m + \delta_m)w_6}{(\mu_h + \sigma + a + \delta_1)}$$

$$w_3 = \frac{\sigma(\mu_m + \delta_m)w_6}{d(\mu_h + b + \delta_2)}$$

$$w_4 = \frac{(\mu_m + \delta_m)}{d\beta_m(\mu_h + c)(\mu_h + b + \delta_2)}[a(\mu_h + b + \delta_2) + b\sigma]w_6$$

$$w_5 = -\frac{(\mu_m + \delta_m)w_6}{\mu_m}$$

The component of the left eigenvector is given as $v = [v_1, v_2, v_3, v_4, v_5, v_6]^T$ and

$$v_1 = 0, v_2 = \frac{d\beta_m v_6}{(\mu_h + \sigma + a + \delta_1)}, v_3 = 0, v_4 = 0, v_5 = 0.$$

All the second order partial derivative at π_o and β_h^* are zero except for $\frac{\partial^2 f_2}{\partial x_2 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_2} = \frac{\partial^2 f_2}{\partial x_3 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_3} = \frac{\partial^2 f_2}{\partial x_4 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_4} = -\frac{d\beta_h \mu_h}{\Lambda_h}$

$$\frac{\partial^2 f_6}{\partial x_2 \partial x_6} = \frac{\partial^2 f_6}{\partial x_6 \partial x_2} = -\frac{d\beta_h \mu_h}{\Lambda_h} \text{ and } \frac{\partial^2 f_2}{\partial x_6 \partial \beta_h} = d$$

Using the definition of a_1 and b_1 from (Chavez *et al.,* 2004) and solving gives $a_1 < 0$ and $b_1 > 0$.

We conclude that the model $(1) - (6)$ exhibits a backward bifurcation (Chavez *et al.,* 2004).

Sensitivity analysis: Sensitivity analysis is used to determine dependencies between input parameters and results of the model. The normalised forward sensitivity index of a variable,w, that depends on a parameter, q, is defined as:

$$\Gamma_q^w = \frac{\partial w}{\partial q} \times \frac{q}{w}$$

Sensitivity index of the basic reproduction number of the basic reproduction number with respect to the model parameters are computed below:

Table 2. Sensitivity index

Parameter	$\Gamma_{parameter}^{R_0}$
d	1
β_h	$\frac{1}{2}$
β_m	$\frac{1}{2}$

μ_h	$\frac{-\mu_h}{2(\mu_h+\sigma+a+\delta_1)}$
σ	$\frac{\sigma}{2(\mu_h+\sigma+a+\delta_1)}$
μ_m	$\frac{-\mu_h}{2(\mu_m+\delta_m)}$
δ_m	$\frac{-\delta_m}{2(\mu_m+\delta_m)}$

$\Gamma_{R_0}^{d}$= 1 revealed that a 10 percent in transmission rate corresponds to 10 percent increase in the basic reproduction number. The negative sign of the sensitivity analysis shows inverse proportionality between the parameter and the basic reproduction number.

*Conclusion***:** We present a mathematical model for malaria dynamics with isolated drug resistant population after the first line of treatment. The basic reproduction number of the model and the local stability of the disease free equilibrium are determined. The model is found to exhibit a backward bifurcation which implies that keeping the basic reproduction number below unity is not sufficient for the eradication of the disease. The contribution of the model parameters on the basic reproduction number were also highlighted through sensitivity analysis.

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