Mathematical Model with Relapse and the Effect of Ivermectin on Malaria Transmission Dynamics

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Abstract: **Malaria is an infectious disease transmitted to humans through bites from infected mosquito that kills millions of people on a yearly basis. Despite over a century of enormous research with all existing intervention programs to control and eliminate malaria, yet it remains a global threat. A new and promising tool which is being given current attention is an endectocide known as ivermectin (IVM). In this study, we develop a mathematical model for the control of this disease in the presence of relapse with IVM drug as a mosquitocidal tool. The model is developed using ordinary differential equation from which we obtained the basic reproduction number, R_0 and then investigate the existence and stability of the disease-free equilibrium(DFE). Numerical simulations of the model shows that treatment alone in the presence of relapse is not sufficient to bring down malaria burden to a reasonable level. But for control purpose, the result suggests that the human recovery rate should be increased while effort be made strongly to avoid relapse. Adding the effect of IVM through additional mortality of the mosquitoes made a great difference in the human and mosquito population in terms of malaria burden and the vector abundance. The outcome from further suggests that IVM has the potential of bringing down the vector population thereby reducing transmission intensity.**

Keywords: **Malaria, basic reproduction number, ivermectin, relapse, mosquitocidal, endectocide.**

I. INTRODUCTION

One of the diseases that has been greatly explored and still requires more exploration using mathematical models is the dynamics of malaria, an infectious parasitic disease that is transmitted by a bite of the female Anopheles mosquito. In terms of morbidity and mortality, malaria is considered to be one of the world's most significant infectious diseases. The disease is endemic in 91 countries with the highest burden in sub-Saharan Africa [23]. According to WHO [25] report, the estimated cases of malaria that occurred showed an increase from 210,000-211,000 cases from the year 2014-2015 and then to 216 million symptomatic cases in 2016. Subsequently, an estimate of 219 million cases of malaria occurred in 2017 with 435 000 malaria related death out of which 92% of the cases and 93% of the deaths was from WHO African region [26]. Five countries in that region were reported to be responsible for nearly half of these cases worldwide, these are: Nigeria (25%), the Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%).

Treatment is one way of controlling malaria with various antimalarial drugs being available but almost all have been found with the problem of parasite resistance to the drug. At present, Artemisinin-combination therapy (ACT) is the first-line therapy in the treatment of malaria infection and it rapidly clears asexual parasites and developing gametocytes but leaves mature P.falciparum gametocytes largely unaffected; a proportion of patients may transmit malaria after successful ACT treatment [18] and may also be at risk of evolution of parasite resistance.

The dynamics of malaria as regard transmission and control have been greatly explored and still require more exploration using mathematical models. A treatment malaria model whereby recovered humans return to the susceptible class due to loss of immunity and infectious class due to relapse of parasite among the recovered individuals was introduced in [5] using system of ordinary differential equations . The result of their analysis suggests that complete and adequate treatment should be given to symptomatic patients rather than asymptomatic infection. Notwithstanding, for the asymptomatic patients, the outcome of their study strongly recommend the need for the government to control the relapse rate strictly to be able to control and eradicate the malaria. The relapse rate explained in [11] is a condition whereby symptoms reappear after the parasites had been eliminated from blood but persist as dormant hypnozoites in liver cells. This occurrence takes place usually between 8–24 weeks and is said to be commonly seen with *P. vivax* and *P. ovale* infections. An SEIRS-SEI epidemic malaria transmission models with regards to human recovery rate was formulated and analysed in [17]. The outcome of their analyses showed that increase in the human recovery rate leads to a decline in the number of infected human and mosquito populations suggesting that with time, the disease will disappear from the population. In 2015, a deterministic model of malaria transmission with standard incidence rate and treatment was presented in [4].

Despite over a century of enormous research with all existing intervention programs to control and eliminate malaria, yet it remains a global threat. A new and promising tool which is being given current attention is an endectocide known as ivermectin (IVM). According to WHO, it is said to be an anti-helminthic drug that is being used for the control of several neglected tropical diseases (NTDs) and has been

found to kill *Anopheles* mosquitoes that ingest it in a blood meal [24]. Several earlier studies ([2],[7],[8]) recorded higher mortality rate for vectors that feed on human or animal hosts that have recently taken IVM. In addition, it is also said to cause possible reductions in sporogony and delayed re-feeding frequency ([7], [8]) with mosquitocidal impact that is thought to last for about 6 day after host ingestion [21]. It is also on record that the drug has brought about huge success in driving the two most devastating and disfiguring neglected tropical diseases (NTD), lymphatic filariasis and onchocersiasis to the brink of elimination [14]. The drug also bestows immeasurable non-target benefits, increasing the health and socioeconomic prospects of all communities where mass drug administration (MDA) has been carried out. In an earlier study carried out in[19], the potential impact of combining artemisinin-combination therapy (ACT) and IVM in MDA campaigns was highlighted. An explicit vector mortality model where IVM was added as a control measure was developed by the authors and the outcome of the model indicated that adding IVM during individual malaria treatment leads to a minimal additional transmission suppression effect while an accelerated time to elimination was an indication when IVM MDA is added to anti-malarial MDA. Nevertheless, it allows for elimination in settings where antimalarial MDA alone would not achieve it. In [15] another study on the efficacy and safety of the mosquitocidal impact of IVM on malaria transmission was carried out. The study was based on a double-blind, placebo-controlled trial that involved 120 participants who were asymptomatic carriers of *plasmodium falciparum* parasite. The outcome from the analysis of the study certify the safety use of the drug in combination with AL and that IVM has the likelihood of reducing malaria transmission through the shortening of mosquito lifespan as it feeds on bloodmeal with the drug. With the drug proven to be extremely safe for human use makes the prospects to currently look highly promising considering its potential to bring down mosquito abundance, prevent onward transmission of parasites ingested following a bite taken on a malaria-infected individual and as a result could bring down malaria burden to a significant level with the possibility of elimination.

This current paper is similar to that of [5]where the role of both the relapse and recovery rate were considered but further incorporates the effect of IVM by adding a compartment that consists of susceptible humans administered with the drug and its resulting effect on the mosquito population.

II. The Model Equation

In this section, we formulate a compartmental mathematical model for the transmission and control of malaria in which individuals move between, susceptible without IVM, S_H, or susceptible with IVM, P_H, infected, I_H, and recovered (immune), R_H classes. Since mosquitoes are assumed not to recover from the parasites, we therefore have the mosquito population divided into two epidemiological classes: the susceptible, S_V and infected, I_V. The total human population at time $t$is given by $N_H(t) = S_H(t) + P_H(t) + I_H(t) + R_H(t)$ while that of the mosquito population is $N_V(t) = S_V(t) + I_V(t)$. The model equation is a coupled system of nonlinear ordinary differential equations provided in Equation (1).

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= (1-\psi)\lambda_h - \frac{abS_H I_V}{N_H} + (1-\theta)\rho_1 R_H - \mu_h S_H \\
\frac{dP_H}{dt} &= \psi\lambda_h + \theta\rho_1 R_H - \frac{abP_H I_V}{N_H} - \mu_h P_H \\
\frac{dI_H}{dt} &= \frac{abS_H I_V}{N_H} + \frac{abP_H I_V}{N_H} + \rho_2 R_H - (r+\delta+\mu_h) I_H \\
\frac{dRH}{dt} &= rI_H - (\rho_1+\rho_2+\mu_h) R_H \\
\frac{dS_V}{dt} &= \lambda_v - \frac{\mathrm{c}\, bS_V I_H}{N_H} - \frac{\beta bS_V R_H}{N_H} - (\mu_v + zP_H) S_V \\
\frac{dI_V}{dt} &= \frac{\mathrm{c}\, bS_V I_H}{N_H} + \frac{\beta bS_V R_H}{N_H} - (\mu_v + zP_H)\,\mathrm{I}_V
\end{aligned}\right\} \quad (1)$$

where $\frac{abS_H I_V}{N_H}$, $\frac{\beta bS_V R_H}{N_H}$ and $\frac{\mathrm{c}\, bS_V I_H}{N_H}$ denote the force of infection from infected and recovered human to susceptible mosquitoes and from infected mosquito to susceptible human respectively.

Table 1: Model Parameters and Description

Parameter	Description
λ_h	Human birth rate
λ_v	Mosquito birth rate
a	Probability of transmission to susceptible human
b	Mosquito biting rate
c	Probability of transmission to susceptible mosquito
z	Mortality in mosquitoes due to IVM ingestion
r	Human recovery rate
ρ_1	Human loss of immunity rate
ρ_2	Relapse rate
μ_h	Per capital natural death rate of human
μ_v	Per capital natural death rate of mosquito
θ	Fraction of Susceptibles moving to IVM class
ψ	Fraction of new birth from IVM users
δ	Disease induced death rate
β	Probability of transmission from recovered human

III. Analysis of the model

3.1. Basic Properties: Invariant Region:

From Equation (1), we have that

$$\left.\begin{aligned}\frac{dN_H}{dt} &= \lambda_h - \mu_h N_H - \delta I_H \\ \frac{dN_V}{dt} &= \lambda_v - (\mu_v + \mathrm{zP}_H) N_V\end{aligned}\right\} (2).$$

In the absence of the disease in both the human and vector population, the total human and mosquito population size respectively approaches $N_H \le \lambda_h / \mu_h$ and $N_V \le \lambda_v / \mu_v$, the carrying capacity and the region of biological interest is

$$\Omega = \left\{ \begin{aligned} &(\mathrm{S}_H(t), \mathrm{P}_H(t), \mathrm{I}_H(t), \mathrm{R}_H(t), \mathrm{I}_V(t)) \in \Re_+^5 : \mathrm{S}_H(t), \mathrm{P}_H(t), \mathrm{I}_H(t), \mathrm{R}_H(t), \mathrm{I}_V(t) \ge 0, \\ &\mathrm{S}_H(t) + \mathrm{P}_H(t) + \mathrm{I}_H(t) + \mathrm{R}_H(t) \le N_H, N_H \le \frac{\lambda_h}{\mu_h}, N_V \le \frac{\lambda_v}{\mu_v} \end{aligned} \right\} \quad (3)$$

which can be shown to be positively-invariant with respect to Equation (1) where $\Re_+^5$ is the nonnegative cone of $\Re^5$ with its lower dimensional faces. The boundary and the interior of Ω are denoted by $\partial\Omega$ and $\hat{\Omega}$ respectively.

3.2 Disease-Free Equilibrium (DFE) Point and the Basic Reproduction Number:

The DFE point is a steady state solution in a malaria-free human population and mosquito population free of *Plasmodium* parasite. We need to verify that this equilibrium point exists when the population of the diseased groups, $I_H = R_H = I_V = 0$. Note also that at DFE, it is assumed that there are no IVM users which implies that $\psi = \theta = 0$ and so the model has a disease-free equilibrium givenby $\mathrm{E}_0 = \{\mathrm{S}_H, \mathrm{P}_H, \mathrm{I}_H, \mathrm{R}_H, \mathrm{S}_V, \mathrm{I}_V\} = \{\lambda_h/\mu_h, 0, 0, 0, \lambda_v/\mu_v, 0\}$. To be able to analyze the stability of system (1) we need to first obtain the basic reproduction number which is a threshold condition for the establishment of the disease. This will be obtained using the next generation operator method developed in[22]. Rearranging the system (1) beginning with the infected infected classes, we have:

$$\left.\begin{aligned}\frac{dI_H}{dt} &= \frac{abS_H I_V}{N_H} + \frac{abP_H I_V}{N_H} + \rho_2 R_H - (r + \delta + \mu_h) I_H \\ \frac{dR_H}{dt} &= rI_H - (\rho_1 + \rho_2 + \mu_h) R_H \\ \frac{dI_V}{dt} &= \frac{\mathrm{c}\,bS_V I_H}{N_H} + \frac{\beta b S_V R_H}{N_H} - (\mu_v + \mathrm{zP}_H)\,\mathrm{I}_V \\ \frac{dS_H}{dt} &= (1-\psi)\lambda_H - \frac{abS_H I_V}{N_H} + (1-\theta)\rho_1 R_H - \mu_h S_H \\ \frac{dP_H}{dt} &= \psi\lambda_h + \theta\rho_1 R_H - \frac{abP_H I_V}{N_H} - \mu_h P_H \\ \frac{dS_V}{dt} &= \lambda_v - \frac{\mathrm{c}\,bS_V I_H}{N_H} - \frac{\beta b S_V R_H}{N_H} - (\mu_v + \mathrm{zP}_H) S_V\end{aligned}\right\} (4)$$

We now obtain the Jacobian matrices F as new infection terms and V, the transfer terms by linearizing the infected compartments about the DFE from the partial derivatives of f and v with respect to the infected classes as below:

$$f = \begin{pmatrix} \frac{abS_H I_V}{N_H} + \frac{abP_H I_V}{N_H} \\ 0 \\ \frac{\mathrm{c}\,bS_V I_H}{N_H} + \frac{\beta b R_H S_V}{N_H} \end{pmatrix}, \quad v = \begin{pmatrix} (r + \delta + \mu_h)\,\mathrm{I}_H - \rho_2 R_H \\ (\rho_1 + \rho_2 + \mu_h)\,\mathrm{R}_H - rI_H \\ (\mu_v + \mathrm{zP}_H)\,\mathrm{I}_V \end{pmatrix}.$$

Differentiating with respect to the infected classes and then evaluating at the DFE yields

$$F = \begin{pmatrix} 0 & 0 & ab \\ 0 & 0 & 0 \\ \frac{cb\lambda_v\mu_h}{\mu_v\lambda_h} & \frac{\beta b\lambda_v\mu_h}{\mu_v\lambda_h} & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} r + \delta + \mu_h & -\rho_2 & 0 \\ -r & \rho_1 + \rho_2 + \mu_h & 0 \\ 0 & 0 & \mu_v \end{pmatrix}$$

Applying the next generation operator method, we obtain the dominant eigenvalue corresponding to the spectral radius $\rho(FV^{-1})$ of the matrix FV^{-1} as the reproduction number given by

$$R_0 = \frac{b\sqrt{a\lambda_h\lambda_v\mu_h AB}}{\lambda_h\mu_v A}$$

where

$A = \left(\delta\mu_h + \delta\rho_1 + \delta\rho_2 + r\mu_h + r\rho_1 + \mu_h^2 + \mu_h\rho_1 + \mu_h\rho_2\right)$

and $B = \left(\beta r + c\mu_h + c\rho_1 + c\rho_2\right)$.

3.3 Local Stability of the Disease-Free Equilibrium

The local stability of the disease-free equilibrium can be analyzed using the Jacobian matrix of the malaria model of Equation (1) at the disease free equilibrium point. The Jacobian matrix is computed by differentiating each equation in the system with respect to the state variables $S_H, P_H, I_H, R_H, S_V, I_V$. The model Equation (1) is then defined as

$$\left.\begin{aligned}
F_1 &= (1-\psi)\lambda_h - \frac{abS_H I_V}{N_H} + (1-\theta)\rho_1 R_H - \mu_h S_H \\
F_2 &= \psi\lambda_h + \theta\rho_1 R_H - \frac{abP_H I_V}{N_H} - \mu_h P_H \\
F_3 &= \frac{abS_H I_V}{N_H} + \frac{abP_H I_V}{N_H} + \rho_2 R_H - (r+\delta+\mu_h) I_H \\
F_4 &= rI_H - (\rho_1+\rho_2+\mu_h) R_H \\
F_5 &= \lambda_v - \frac{\mathrm{c}\, bS_V I_H}{N_H} - \frac{\beta bS_V R_H}{N_H} - (\mu_v + zP_H) S_V \\
F_6 &= \frac{\mathrm{c}\, bS_V I_H}{N_H} + \frac{\beta bS_V R_H}{N_H} - (\mu_v + zP_H)\, \mathrm{I}_V
\end{aligned}\right\} \quad (5)$$

At the steady states, the Jacobian $F_1, F_2, F_3, F_4, F_5, F_6$ with respect to $S_H, P_H, I_H, R_H, S_V, I_V$ evaluated at the disease free equilibrium point E_0 is given by the matrix of Equation (6).

$$E_0 = \begin{pmatrix}
-\mu_h & 0 & 0 & (1-\theta)\rho_1 & 0 & -\dfrac{ab\lambda_h}{\mu_h N_H} \\
0 & -\mu_h & 0 & \theta\rho_1 & 0 & 0 \\
0 & 0 & -(r+\delta+\mu_h) & \rho_2 & 0 & \dfrac{ab\lambda_h}{\mu_h N_H} \\
0 & 0 & r & -(\rho_1+\rho_2+\mu_h) & 0 & 0 \\
0 & \dfrac{-z\lambda_v}{\mu_v} & -\dfrac{cb\lambda_v}{\mu_v N_H} & \dfrac{-\beta b\lambda_v}{\mu_v N_H} & -\mu_v & 0 \\
0 & 0 & \dfrac{cb\lambda_v}{\mu_v N_H} & \dfrac{\beta b\lambda_v}{\mu_v N_H} & 0 & -\mu_v
\end{pmatrix} \quad (6)$$

Theorem 1: The disease free equilibrium point for system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$ ([9], [22]).

Proof: The eigenvalues of the Jacobian matrix, *J* of the malaria model (1) evaluated at the disease-free equilibrium point are the solutions of the characteristic equation $\left|J_{(E_0)} - \lambda I\right| = 0$.

$$\text{i.e.} \left|J_{(E_0)} - \lambda I\right| = \begin{pmatrix}
-\mu_h - \lambda & 0 & 0 & (1-\theta)\rho_1 & 0 & -\dfrac{ab\lambda_h}{\mu_h N_H} \\
0 & -\mu_h - \lambda & 0 & \theta\rho_1 & 0 & 0 \\
0 & 0 & -(r+\partial+\mu_h) - \lambda & \rho_2 & 0 & \dfrac{ab\lambda_h}{\mu_h N_H} \\
0 & 0 & r & -(\rho_1+\rho_2+\mu_h) - \lambda & 0 & 0 \\
0 & \dfrac{-z\lambda_v}{\mu_v} & -\dfrac{cb\lambda_v}{\mu_v N_H} & \dfrac{-\beta b\lambda_v}{\mu_v N_H} & -\mu_v - \lambda & 0 \\
0 & 0 & \dfrac{cb\lambda_v}{\mu_v N_H} & \dfrac{\beta b\lambda_v}{\mu_v N_H} & 0 & -\mu_v - \lambda
\end{pmatrix} = 0 \quad (7)$$

Since the 5th and 2nd and 1st column contain only the diagonal terms which gives the eigenvalue $-\mu_h, -\mu_h \text{ and } -\mu_v$, all negative, as shown below. The other three eigenvalues can be obtained from the sub-matrix $J_{1(E_0)}$ formed by excluding the 1st, 2nd and 5th row and column of $J_{(E_0)}$, Hence we have

$$(-\mu_h-\lambda_1)(-\mu_v-\lambda_5)(-\mu_h-\lambda_2)\left|J_{1(E_0)}\right|=0 \quad (8)$$

Hence,

$$\left|J_{1(E_0)}-\lambda I\right|=\begin{vmatrix} J_{11}-\lambda & J_{12} & J_{13} \\ J_{21} & J_{22}-\lambda & J_{23} \\ J_{31} & J_{32} & J_{33}-\lambda \end{vmatrix}=0 \quad (9)$$

where

$$J_{11}=-\left(r+\delta+\mu_h\right), J_{12}=\rho_2, J_{13}=\frac{ab\lambda_h}{\mu_h N_H}, J_{21}=r,$$

$$J_{22}=-\left(\rho_1+\rho_2+\mu_h\right), J_{31}=\frac{cb\lambda_v}{\mu_h N_H}, J_{32}=\frac{\beta b\lambda_v}{\mu_v N_H}, J_{33}=-\mu_v$$

The eigenvalues of the matrix $J_{1(E_0)}$ are the roots of the characteristic equation

$$A_3\lambda^3+A_2\lambda^2+A_1\lambda^1+A_0=0 \quad (10)$$

Where

$$A_3=1 \quad (11)$$

$$A_2=-(J_{11}+J_{22}+J_{33}) \quad (12)$$

$$A_1=(J_{11}J_{22}+J_{11}J_{33}-J_{12}J_{21}-J_{13}J_{31}+J_{22}J_{33}) \quad (13)$$

$$A_0=(-J_{11}J_{22}J_{33}+J_{12}J_{21}J_{33}-J_{13}J_{21}J_{32}+J_{31}J_{13}J_{22}) \quad (14)$$

i.e.

$$A_0=\left\{\left(-r-\delta_h-\mu_h\right)\left(-\rho_1-\rho_2-\mu_h\right)\mu_v-\rho_2 r\mu_v-\frac{ab^2\lambda_h r\beta\lambda_v}{\mu_h N_H^2\mu_v}+\frac{ab^2\lambda_h\left(-\rho_1-\rho_2-\mu_h\right)c\lambda_v}{\mu_h N_H^2\mu_v}\right\}$$

which gives

$$\left(\delta\mu_h+\delta\rho_1+\delta\rho_2+r\mu_h+r\rho_1+\mu_h^2+\mu_h\rho_1+\mu_h\rho_2\right)\mu_v-\frac{ab^2\lambda_h\lambda_v\left(r\beta+c\mu_h+c\rho_1+c\rho_2\right)}{\mu_h N_H^2\mu_v} \quad (15)$$

Further manipulation of A_0 in terms of the reproduction number R_0, yields

$$\begin{pmatrix}\delta\mu_h+\delta\rho_1+\delta\rho_2+r\mu_h+\\ r\rho_1+\mu_h^2+\mu_h\rho_1+\mu_h\rho_2\end{pmatrix}\mu_v-\frac{\lambda_h^2}{\mu_h N_H^2\mu_v}\begin{pmatrix}\delta\mu_h+\delta\rho_1+\delta\rho_2+r\mu_h+\\ r\rho_1+\mu_h^2+\mu_h\rho_1+\mu_h\rho_2\end{pmatrix}\mu_v R_0^2 \quad (16)$$

and since $\frac{\lambda_h}{\mu_h}=N_H$, factorizing (16) yields

$$\left(\delta\mu_h+\delta\rho_1+\delta\rho_2+r\mu_h+r\rho_1+\mu_h^2+\mu_h\rho_1+\mu_h\rho_2\right)\mu_v\left(1-R_0^2\right) \quad (17)$$

Alternatively, If we let

$B_1=\left(r+\delta+\mu_h\right)$, $B_2=\left(\rho_1+\rho_2+\mu_h\right)$ and $B_3=\mu_v$,

the eigenvalues of $J_{1(E_0)}$ are the roots of the characteristic equation (corresponding to Equation (10)) given below

$$\left(r+\delta+\mu_h+\lambda\right)\left(\rho_1+\rho_2+\mu_h+\lambda\right)\left(\mu_v+\lambda\right)-K=0 \quad (18)$$

Thus we have

$$\left(B_1+\lambda\right)\left(B_2+\lambda\right)\left(B_3+\lambda\right)-K=0 \quad (19)$$

which when expanded also yields

$$A_3\lambda^3+A_2\lambda^2+A_1\lambda^1+A_0=0 \quad (20)$$

where A_0, A_1, A_2, A_3 are the coefficients of $\lambda's$ in terms of $B_i's$ given by

$$A_3=1 \quad (21)$$

$$A_2=B_1+B_2+B_3 \quad (22)$$

$$A_1=B_1B_2+B_1B_3+B_2B_3 \quad (23)$$

$$A_0=B_1B_2B_3-K \quad (24)$$

A similar manipulation of A_0 in terms of the reproduction number R_0, yields

$$\left(\delta\mu_h+\delta\rho_1+\delta\rho_2+r\mu_h+r\rho_1+\mu_h^2+\mu_h\rho_1+\mu_h\rho_2\right)\mu_v\left(1-R_0^2\right) \quad (25).$$

We employ the Routh-Hurwitz criterion on (18), which states that all roots of the polynomial (18) have negative real parts if and only if the coefficients A_i are positive and matrices $H_i>0$, for $i=0,1,2,3$. From (21) - (24), it is easy to see that $A_1>0,\ A_2>0,\ A_3>0$, Since all $B_i's$ in the above

expression (21) - (24) are positive. Moreover, if $R_0 < 1$, it follows from (25) that $A_0 > 0$. Also the Hurwitz matrices for the polynomial (18) are found to be positive. That is,

$$H_1 = (B_2) > 0 \qquad H_2 = \begin{pmatrix} B_2 & B_3 \\ B_0 & B_1 \end{pmatrix} > 0$$

$$H_3 = \begin{pmatrix} B_2 & B_3 & 0 \\ B_0 & B_1 & B_2 \\ 0 & 0 & B_0 \end{pmatrix} > 0$$

Therefore, all the eigenvalues of the Jacobian matrix $J_{(E_0)}$ have negative real parts when $R_0 < 1$, and the disease-free equilibrium point is locally asymptotically stable.

However, when $R_0 > 1,$, we observed that $A_0 < 0$, and by Descartes' rule of signs [16] there is exactly one sign change in the sequence, A_3, A_2, A_1, A_0 of coefficients of the polynomial (20). So, there is one eigenvalue with positive real part and the disease free equilibrium point is unstable.

IV. Numerical Result and Discussion

The dynamics of malaria within the human and mosquito population with the role played by some key epidemiological parameters is investigated based on numerical simulations obtained by a fourth-order Runge-Kutta numerical scheme in Matlab using the parameter values provided on Table 2. The initial conditions hypothetically assumed for the human and mosquito populations are as follows:

$S_H(0) = 90, P_H(0) = 10, I_H(0) = 20, R_H(0) = 20$ for the human population and $S_V(0) = 80, I_V(0) = 20$ for the mosquito population. To start with, we considered the case where treatment of infected human is the only control measure in the presence of relapse among the recovered individuals.

Table 2: Parameter Values and References

Parameter	Values	References
λ_h	100/day	[6]
λ_v	1000/day	[6]
a	0.034	[12]
b	0.1	[13]
c	0.8333	[10]
r	1/730	[6]
ρ_1	1/(60x365)/day	[1]
ρ_2	0.004	[5]
μ_h	0.0000548	[13]
μ_v	0.04	[3]
θ	0.2	Assumed
ψ	0.2	Assumed
δ	0.05	[20]
β	0.08333	[5]

In [19], the vector daily mortality rate base on the time of bloodmeal post MDA was represented in Figure 2C of their work. There it was assumed that the vectors considered were Anopheles gambiae with IVM dose of $150\mu g / kg$. The result on that Figure showed that the vector daily mortality falls between 0.2-0.4 for bloodmeal taken between 2-4 days post-MDA with 1 dose daily. In our work, we assume the value of daily vector mortality rate due to IVM to be 0.2445 which falls within the range obtained in [19] for bloodmeal taken between 2-4 days with 1 daily dose.

4.1 Treatment only:

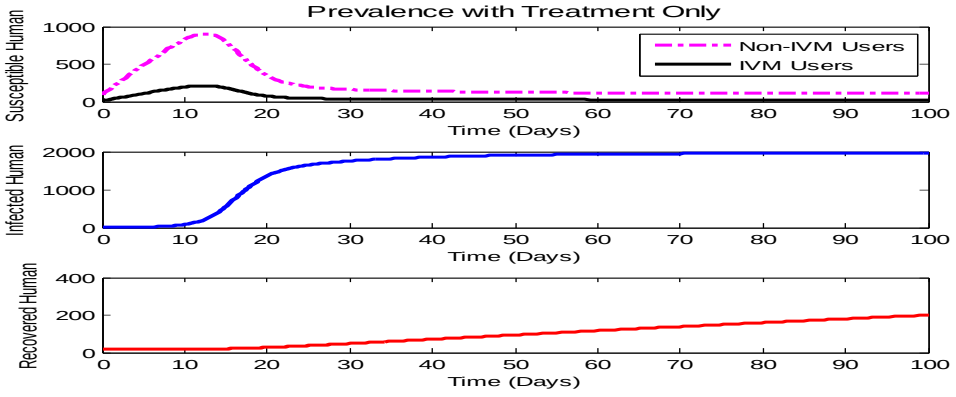

Figure 1: Malaria prevalence in the human population while considering only treatment of infected individual in the presence of relapse (ρ_2 = 0.0014) in the recovered class.

With the treatment of the infected human population as the only control measure, Figure 1 gives an illustration of the susceptible human population (IVM and non-IVM users) initially following an increasing trend for a period of time but later declines to an equilibrium. It can be observed from the plot that the time the infected population kicked up with an increasing flow in a way corresponds with the period of sudden decline of the susceptible individuals. As represented in our model of Equation (1), the relapse of infection among the recovered individuals contributes positively to the infected human population thereby reducing the number of individuals progressing to the susceptible class due to loss of immunity.

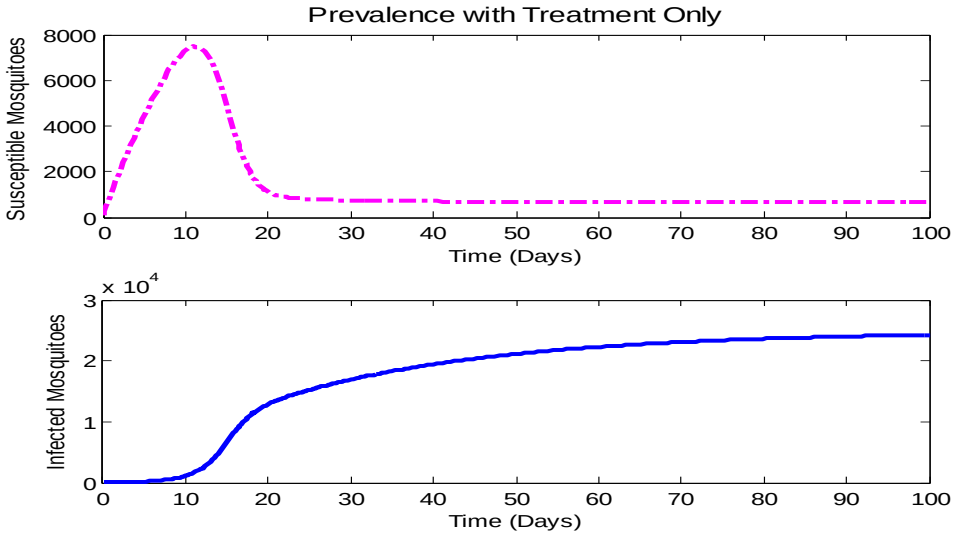

Figure 2: Malaria prevalence in the mosquito population while considering only treatment of infected human population in the presence of relapse (ρ_2 =0.0014) among the recovered class.

Similar observation is made with the mosquito population (Figure 2) where the infected population is on the increase as a result of the susceptible ones getting infected from the bite on both the infected and partly from recovered human. Despite treatment of the infected human, the disease is still sustained in both human and mosquito population with possibly high transmission rate.

4.2 Effect of Varying Recovery Rate on the Infected Human Population:

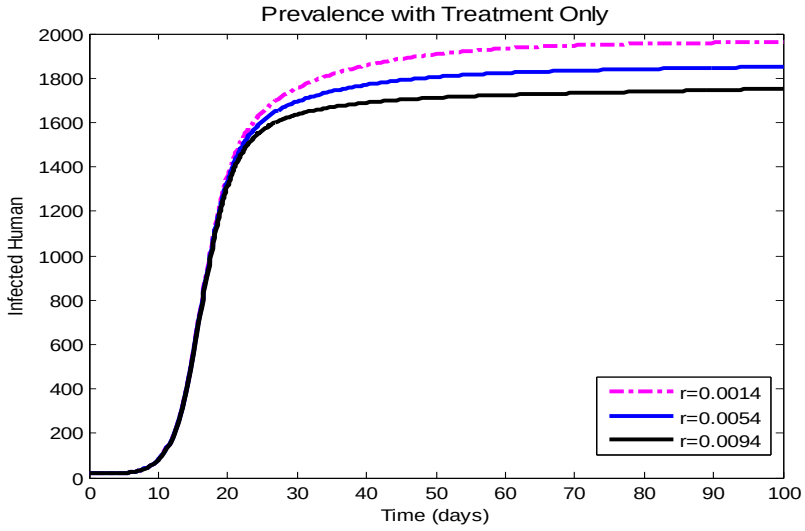

Figure 3: Representation of the changes in the infected human population while varying the recovery rate (r) in the case scenario where treatment of infected human is considered as the only control strategy.

As shown in Figure 3, as the recovery rate is increasing, the malaria infected human population is decreasing while the reverse is the case with varying the relapse rate as illustrated on Figure 4, where the infected population decreases with lower values of the relapse rate.

4.3 Effect of Varying Relapse Rate on the Infected Human Population:

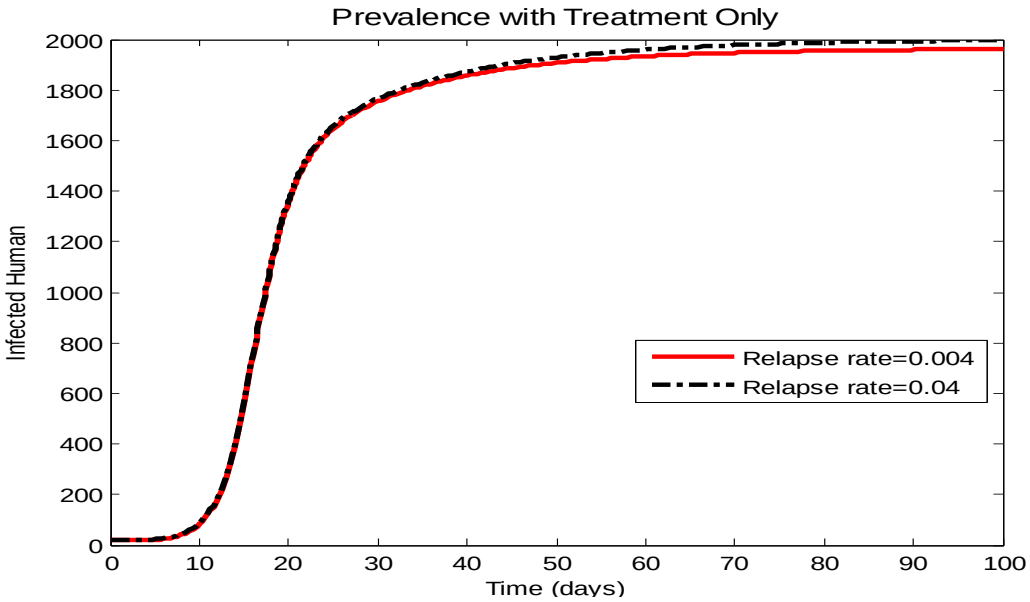

Figure 4: Representation of the changes in the infected human population while varying the relapse rate (ρ_2) in the case scenario where treatment of infected human is considered as the only control strategy.

The results of Figures 3 and 4 demonstrates low infection prevalence with high recovery rate and low relapse rate respectively which suggests that to control malaria in the human population, it is important to increase the recovery rate while proper care is taken to avoid relapse among the recovered human population.

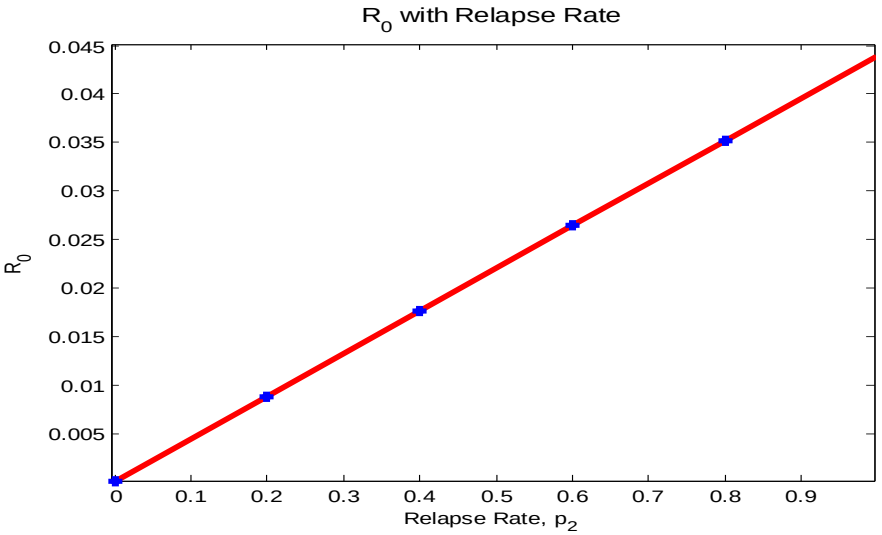

Figure 5: Relationship between the basic reproduction number, R_0 and relapse rate, ρ_2

The plot on Figure 5 further buttress our findings and discussion above as regard the role of relapse on the disease dynamics among the human and mosquito population. In conformity with the expectation, the transmission rate is shown to increase as the relapse rate increases. This is similar to the outcome of the numerical solutions in [6] where the

basic reproduction number, R_0 was shown to increase with respect to the relapse rate.

4.4 Treatment of Infected Human and the Effect of IVM as a Mosquitocidal Tool:

Here, we are considering the case where two control strategies are considered. This has to do with treatment of human and the use of IVM drug among a fraction of the susceptible human population, P_H . The use of this drug has direct effect on the mosquito population as a mosquitocidal tool that causes additional mortality of mosquitoes that ingest concentration of it from the blood meal where it is present. The impact is further felt in the human population positively as regards malaria burden. Since both the susceptible and infected mosquitoes feed on human blood, this makes the impact of additional mortality directly felt on both populations in similar manner. Figures 6 and 7 illustrate the effect of the drug on malaria burden among both the human and mosquito population. The additional control strategy based on the use of this drug resulted in the obvious decline of the infected and susceptible mosquito population with that of the infected human population. While the recovered human population is decreasing, an increasing trend is noticed with the susceptible population. In my opinion, the effect of IVM in a way silenced that of the relapse rate.

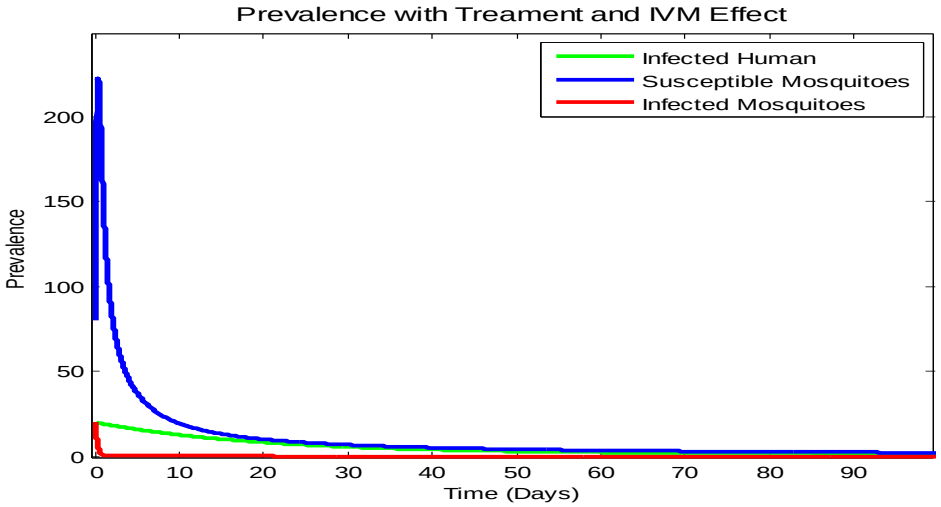

Figure 6: Prevalence of malaria in the population with treatment and IVM use as control strategies.

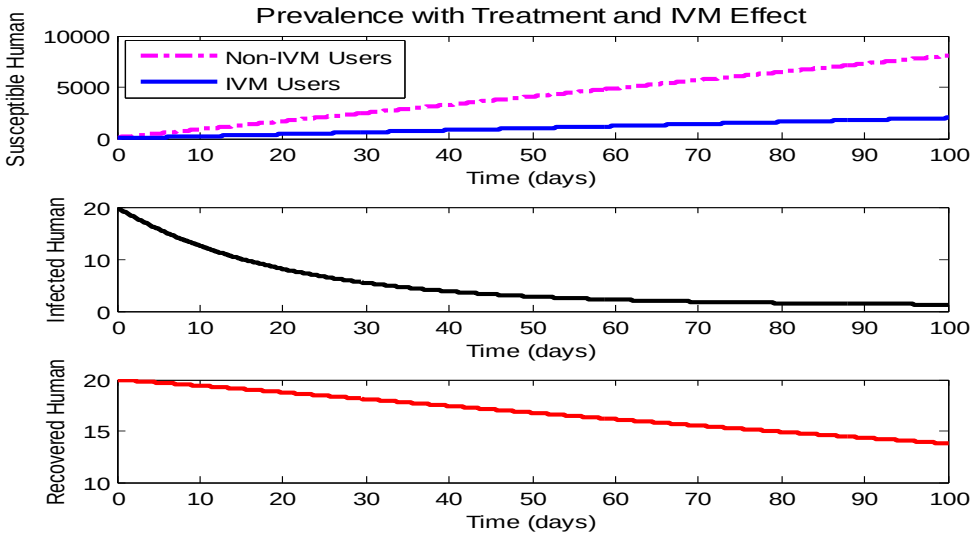

Figure 7: Prevalence of malaria in the population with treatment and IVM use as control strategies.

This strategy as compared to the case of treatment alone greatly brings down the vector population thereby blocking malaria transmission observed with the decline in the infected human and mosquito populations as depicted on Figures 6 and 7. Similar observation made in[23] also revealed that by including the use of IVM as one of the control strategy

increases the reductions in malaria parasite prevalence and also delayed the reemergence of parasites as compared to mass treatment only.

V. Conclusion

In this study, a deterministic model for the transmission of malaria disease that assumed relapse of the parasite among the recovered human andivermectin usage was derived and analyzed. The model's basic reproduction number was calculated and the existence and stability of the disease free equilibrium was investigated. As regard the control of malaria, treatment of infected human as the only strategy was first considered but showed not to be sufficient in bringing down the burden from the population. This was followed by the inclusion of ivermectin usage among a fraction of the susceptible human but acting as a mosquitocidal tool by an additional mortality in the vector population after ingesting bloodmeal from the ivermectin users and this proved to be a potential strategy that will interrupt transmission by bringing down the vector abundance and inturn causing great decline in the disease prevalence both in the human and vector population. As a matter of conclusion, to control and possibly eradicate malaria from the population, the outcome of this study strongly suggests:

1. That treatment of infected human alone is insufficient
2. That government should make every effort to increase the human recovery rate while ensuring that relapse rate goes down to zero or to a very minimal level
3. The inclusion of ivermectin in any control program that is aimed at achieving significant successand brightens the hope of the 2030 elimination target.

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