R_{eff} a Function of Drug Therapy and Treatment in the Mathematical Model of Malaria Disease Dynamics

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ABSTRACT

In this paper, we propose a mathematical model of malaria disease which involves Fractional Differential Equations (FDEs) introducing the effect of drug therapy and treatment rates. The effective reproduction number (R_{eff}) is obtained and computed using next generation method. The R_{eff} was analytically evaluated for its sensitivity in the model dynamics. It was proved that R_{eff} is a strict decreasing function of drug therapy and treatment parameters.

(Keywords: effective reproductive number, malaria disease, drug therapy, treatment, sensitivity)

INTRODUCTION

In biomathematics of epidemiological models, one of the most interesting parts is the behavior of basic reproduction number. The basic reproduction number denoted by R_0 is the expected number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible. According to Benya (2007), R_0 is the threshold quantity for many epidemiology models.

For a single infected individual or compartment R_0, is the product of the infection rate on mean duration of the infection. This implies that if μ is the death rate for a host population or individual, then the life expectancy is $1/\mu$ and δ is the death rate due to infection, the mean duration of infection is $1/\delta$. Similarly, if γ is the recovery rate, the period of recovery will be given by $1/\gamma$. In Ashezua, *et al.* (2015), the author reported that there are two commonly used methods for computing the basic reproduction number in Biomathematics. Ashezua (2017), pointed out that the first method is associated with models involving ordinary differential equations and the second method deals with infection-age and age-structured population models.

The authors of Abdulrahman, *et al.* (2013) and Abdulrahman (2014) ascertained that if $R_0 < 1,$ then on average, an infected individual produces less than one newly infected individual over the course of its infection period. In this case, the infection may die out in the long run. Conversely, if $R_0 > 1,$ each infected individual produces, on average, more than one new infection, the infection will be able to spread in a population. A large value of R_0 may indicate the possibility of a major epidemic. Similarly, the effective reproduction number, R_{eff} represents the average number of secondary cases generated by infected cell or individual if introduced into a susceptible host cell or population where control strategies are used (Hoppensteadt, *et al.,* 1974; Huang, *et al.,* 2012; Jinliang, *et al.,* 2015; Benya, 2008; Castillo-Chavez and Bruer, 2001; Chowell, *et al.,* 2004; Chitnis, *et al.,* 2008).

The mathematical accepted method for finding R_0 that reflect its biological meaning is the next generation operator approach described by Diekmann, *et al.* (1990) and subsequently analyzed in Driessche and Watmough (2002). The basic reproduction number is obtained by dividing the whole population into n compartments in which there are $m < n$ infected

compartments. Let $x_i, i = 1,2,3,...,m$ be the numbers of infected individuals in the i^{th} infected compartments at time t. The largest eigenvalue or spectral radius of FV^{-1} is the basic reproduction number of the model. $FV^{-1} = \left[\partial F_i\left(E^0\right)/\partial x_i\right]\left[\partial V_i\left(E^0\right)/\partial x_i\right]^{-1}$, where F_i is the rate of appearance of new infected in compartment i, V_i is the transfer of infections from one compartment i to another and E^0 is the disease-free equilibrium (Somma, *et al.,* 2017).

The basic reproduction number is normally affected by several factors including the duration of the infectivity of the affected patients, the infectiousness of the organisms, and the number of susceptible people which are the population that the affected patients get in contact with (Abah, *et al.,* 2015). However, on the other hand malaria is the third leading cause of death most especially for children under five years worldwide, after *pneumonia* and diarrheal disease.

Malaria disease is the second leading cause of death from infectious diseases in Africa, after HIV/AIDS. Almost 1 out of 5 deaths of children under 5 in Africa are due to malaria. Malaria disease is caused by *Plasmodium* parasites. The parasites are spread to people through the bites of an infected female *Anopheles* mosquito known as malaria vector. There are two forms of vector control insecticide with treated mosquito nets and indoor residual spraying is effective in a wide range to prevent the disease. *Anti-malarial* medicines can also be used to prevent malaria. According World Health Organization (WHO, 2016), malaria has been recognized as a disease of poverty with vulnerable groups facing several barriers to access *anti-malarial* interventions.

In this work, we present a deterministic mathematical model of malaria disease dynamics which is a system of Fractional Differential Equations (FDE) to investigate the behavior of effective reproduction number on drug therapy and treatment rate. We consider the probability of receiving treatment p at the time of acquiring infection rather than the time of infection, as an alternative way of capturing the proportion of infections that are treated. The total time to move from being infectious to becoming susceptible again is $(q+\tau)$ and hence the populations who receive drug therapy with probability p do so at a rate of $p \times 1/(q+\tau)$.

The populations that are infectious but remain untreated recovered naturally at the natural recovery rate $\left((1-p)/\delta\right)$. However, as pointed out in (Tatem and Smith, 2010; Driessche and Watmogh, 20002) an infection with malaria is a lifelong disease since the infected individual harbored the virus in the blood for at least more than a year. With malaria, infected individuals return to the susceptible class on recovery because the disease confers no immunity against re-infection. Some fractions of susceptible proportion, latent proportion and symptomatic proportion are placed on a regular time to seek drug therapy at an equal rate of σ_3. This is simply because 97 percent of Nigerians are infected with malaria virus from mosquito bites. And we assume that all infected individuals who recovered naturally at the rate $\left((1-p)/\delta\right)$, symptomatic individuals that do not access drug therapy and treatment at a rate $1/\alpha_0$ and those who only take drug therapy may enter latent compartment and can be considered as latently infected individuals. We allow the reproduction rate of malaria virus from the mosquitoes to enter the model. Therefore, susceptible individuals are allowed to be either under drug therapy or latent with certain probabilities.

MATERIAL AND METHODS

Formulation of the Model Equations

We formulate a mathematical model for malaria disease where the population is partitioned into six compartments of the Susceptible $S(t)$; Latent $L(t)$; Symptomatic $B(t)$; Infected $I(t)$; Drug therapy $Q(t)$; while the sixth class is the Treatment $T(t)$. Patients may seek drug therapy when symptoms have manifested as well as at the infectious stage, and a person may be re-infected once susceptible again.

The natural recovery period is assumed to be longer than the drug recovery period and the time to infectiousness. Probability of receiving treatment *p* is applied at the time of acquiring infection rather than during the infection. The classes susceptible, latent and symptomatic seek

drug therapy at a regular rate σ_3. After the drug therapy, individual may move to either susceptible, latent or treatment class depending on whether the malaria viruses are cleared, hidden or persist. Time to seek treatment after drug therapy is not equal time to seek treatment during infection; becoming susceptible again is the combined effects of treatment, drug therapy and recovery rate per infected individual. Reproduction rate of malaria virus and death removal rate are not equal.

Disease induced death rate is applicable to only infected class. Probability of receiving treatment *p* is applied during the infection, and those who recovered naturally δ without drug and treatment moved into latent class. We assumed the malaria virus is not cleared in their body and the influx of malaria virus reproduction at a rate β, natural death is applicable to all the compartments at a rate μ_0, disease induce death only to infectious class at a rate μ_1 and latent rate α_0 relative to infection by symptomatic class. The population N is compartmentalized into the proportions of susceptible, latent, symptomatic, infected, drug therapy, and treatment class.

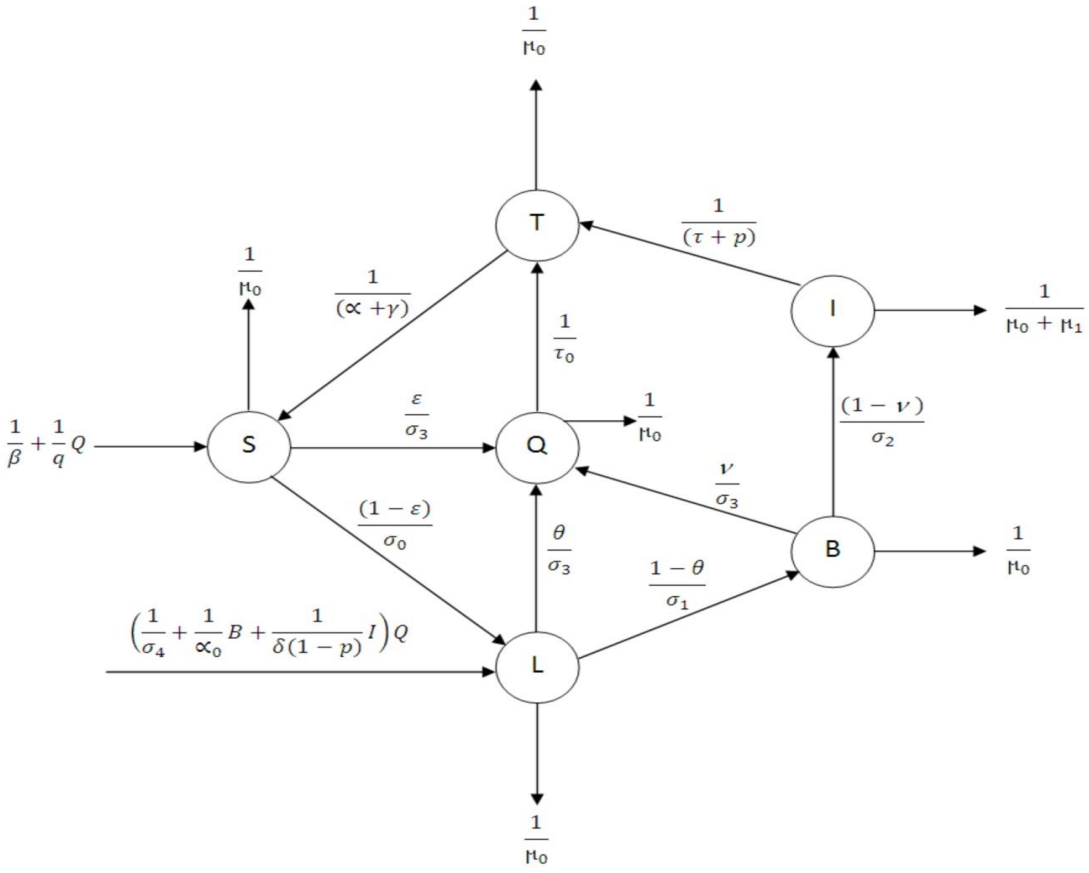

Figure 1: Model Flowchart.

Model Equations

$$\frac{dS}{dt} = \frac{1}{\beta} + \frac{1}{q}Q + \frac{1}{(\alpha+\gamma)}T - \left(\frac{1-\varepsilon}{\sigma_0} + \frac{\varepsilon}{\sigma_3} + \frac{1}{\mu_0}\right)S \quad \textbf{(1)}$$

$$\frac{dL}{dt} = \frac{1-\varepsilon}{\sigma_0} S + \left(\frac{1}{\delta(1-p)} I + \frac{1}{\alpha_0} B + \frac{1}{\sigma_4} \right) Q - \left(\frac{\theta}{\sigma_3} + \frac{1-\theta}{\sigma_1} + \frac{1}{\mu_0} \right) L \quad \textbf{(2)}$$

$$\frac{dB}{dt} = \frac{1-\theta}{\sigma_1} L - \left(\frac{\nu}{\sigma_3} + \frac{1-\nu}{\sigma_2} + \frac{1}{\mu_0} \right) B \quad \textbf{(3)}$$

$$\frac{dI}{dt} = \frac{1-\nu}{\sigma_2} B - \left(\frac{1}{(\tau + p)} + \frac{1}{(\mu_0 + \mu_1)} \right) I \quad \textbf{(4)}$$

$$\frac{dQ}{dt} = \frac{1}{\sigma_3} (\varepsilon S + \theta L + \nu B) - \left(\frac{1}{q} + \frac{1}{\tau_0} + \frac{1}{\sigma_4} + \frac{1}{\mu_0} \right) Q \quad \textbf{(5)}$$

$$\frac{dT}{dt} = \frac{1}{(\tau + p)} I + \frac{1}{\tau_0} Q - \left(\frac{1}{(\alpha + \gamma)} + \frac{1}{\mu_0} \right) T \quad \textbf{(6)}$$

$$S(0) \geq 0, L(0) \geq 0, B(0) \geq 0, I(0) \geq 0, Q(0) \geq 0, T(0) \geq 0.$$
$$S(t) + L(t) + B(t) + I(t) + Q(t) + T(t) = 1 \quad \textbf{(7)}$$

The model is defined in the subset $D \times [0, \infty)$ of $\Re_+^6$, where:

$$D = \left\{ (S, L, B, I, Q, T) \in \Re_+^6 : 0 \leq S, L, B, I, Q, T \leq 1, S + L + B + I + Q + T \leq 1 \right\}$$

Table 1: Definition of variables and parameter are represented as follows

Symbols	Description
$S(t)$	Susceptible individuals at time t
$L(t)$	Latent period at time t
$B(t)$	Symptomatic individuals at time t
$I(t)$	Infected period at time t
$Q(t)$	Drug therapy period at time t
$T(t)$	Treatment period at time t
σ_0	Period of susceptible
σ_1	Period of latent
σ_2	Time of infectiousness
σ_3	Time to seek drug therapy
σ_4	Latent period after drug therapy
τ_0	Time to seek treatment after drug therapy
τ	Time to seek treatment
β	Reproduction rate of malaria virus
μ_0	Natural death rate
μ_1	Death rate of Infected
α	Treatment rate
α_0	Latent rate relative to infection by symptomatic class
γ	Rate of recovery
ε	Susceptible proportions that seek drug therapy at σ_3
θ	Latent proportions that seek drug therapy at σ_3
ν	Symptomatic proportions that seek drug therapy at σ_3
q	Drug recovery period
δ	Natural recovery period
p	Probability of treatment
N	Population size
$\delta(1-p)$	Rate of moving from infected to latent when there is no drug therapy and treatment

The Effective Reproduction Number

We now compute the disease-free equilibrium state of the model. We begin this by setting the left hand sides of equations (1) to (7) to zero and get the disease-free equilibrium state as follows. The disease-free equilibrium state, $E_0 = (S_0, 0, 0, 0, Q_0, T_0)$.

Where,

$$S_0 = \frac{\left(\frac{1}{q}+\frac{1}{\tau_0}+\frac{1}{\sigma_4}+\frac{1}{\mu_0}\right)\sigma_3}{\beta\left(\frac{\left(\frac{1}{1-\varepsilon}+\frac{\varepsilon}{\sigma_3}+\frac{1}{\mu_0}\right)\left(\frac{1}{q}+\frac{1}{\tau_0}+\frac{1}{\sigma_4}+\frac{1}{\mu_0}\right)\sigma_3}{\varepsilon}-\frac{1}{(\alpha+\gamma)\tau_0\left(\frac{1}{\alpha+\gamma}+\frac{1}{\mu_0}\right)}-\frac{1}{q}\right)\varepsilon} \quad \textbf{(8)}$$

$$Q_0 = \frac{1}{\beta\left(\frac{\left(\frac{1}{1-\varepsilon}+\frac{\varepsilon}{\sigma_3}+\frac{1}{\mu_0}\right)\left(\frac{1}{q}+\frac{1}{\tau_0}+\frac{1}{\sigma_4}+\frac{1}{\mu_0}\right)\sigma_3}{\varepsilon}-\frac{1}{(\alpha+\gamma)\tau_0\left(\frac{1}{\alpha+\gamma}+\frac{1}{\mu_0}\right)}-\frac{1}{q}\right)} \quad \textbf{(9)}$$

$$T_0 = \frac{\left(\frac{1}{\tau_0}\right)\left(\frac{1}{\beta\left(\frac{\left(\frac{1}{1-\varepsilon}+\frac{\varepsilon}{\sigma_3}+\frac{1}{\mu_0}\right)\left(\frac{1}{q}+\frac{1}{\tau_0}+\frac{1}{\sigma_4}+\frac{1}{\mu_0}\right)\sigma_3}{\varepsilon}-\frac{1}{(\alpha+\gamma)\tau_0\left(\frac{1}{\alpha+\gamma}+\frac{1}{\mu_0}\right)}-\frac{1}{q}\right)}\right)}{\frac{1}{\alpha+\gamma}+\frac{1}{\mu_0}} \quad \textbf{(10)}$$

Remark 1: For SEIR models, the rate of appearance of new infections is given by the new infection terms in the latent compartment (Heffeman, 2005; Ameh, 2009; Hsu, 2005). From the equations (1) to (7) of the model, we have the following: The vector $F(x)$ of the rates of new infections in compartments $L(t)$, $B(t)$ and $I(t)$ is given by:

$$F(x) = \begin{pmatrix} \frac{1-\varepsilon}{\sigma_0}S + \left(\frac{1}{\delta(1-p)}I + \frac{1}{\alpha_0}B + \frac{1}{\sigma_4}\right)Q \\ 0 \\ 0 \end{pmatrix} \quad \textbf{(11)}$$

Also, the remaining transfer terms in compartments L, B and I is given by Equation (12).

$$V(x) = \begin{pmatrix} \left(\frac{\theta}{\sigma_3}+\frac{1-\theta}{\sigma_1}+\frac{1}{\mu_0}\right)L \\ -\frac{1-\theta}{\sigma_1}L + \left(\frac{\nu}{\sigma_3}+\frac{1-\nu}{\sigma_2}+\frac{1}{\mu_0}\right)B \\ -\frac{1-\nu}{\sigma_2}B + \left(\frac{1}{(\tau+p)}+\frac{1}{(\mu_0+\mu_1)}\right)I \end{pmatrix} \quad \textbf{(12)}$$

The matrix of partial derivatives of $F(x)$ at DFE State $\bar{x} = E_0 = (S_0, 0, 0, 0, Q_0, T_0)$ is given by:

$$F_x(E_0) = \begin{pmatrix} 0 & \frac{1}{\alpha_0} Q_0 & \frac{1}{\delta(1-p)} Q_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \textbf{(13)}$$

Where,

$$Q_0 = \frac{1}{\beta\left(\frac{\left(\frac{1}{1-\varepsilon}+\frac{\varepsilon}{\sigma_3}+\frac{1}{\mu_0}\right)\left(\frac{1}{q}+\frac{1}{\tau_0}+\frac{1}{\sigma_4}+\frac{1}{\mu_0}\right)\sigma_3}{\varepsilon} - \frac{1}{(\alpha+\gamma)\tau_0\left(\frac{1}{\alpha+\gamma}+\frac{1}{\mu_0}\right)} - \frac{1}{q}\right)} \quad \textbf{(14)}$$

And the matrix of partial derivatives of $V(x)$ at DFE State $\bar{x} = E_0 = (S_0, 0, 0, 0, Q_0, T_0)$ is:

$$V_x(E_0) = \begin{pmatrix} \frac{\theta}{\sigma_3}+\frac{1-\theta}{\sigma_1}+\frac{1}{\mu_0} & 0 & 0 \\ -\frac{1-\theta}{\sigma_1} & \frac{\nu}{\sigma_3}+\frac{1-\nu}{\sigma_2}+\frac{1}{\mu_0} & 0 \\ 0 & -\frac{1-\nu}{\sigma_2} & \frac{1}{\tau+p}+\frac{1}{\mu_0+\mu_1} \end{pmatrix} \quad \textbf{(15)}$$

It follows that the effective reproduction number R_{eff} is given by Equation (16).

$$R_{eff} = \rho\left(F_x V^{-1}\right) \quad \textbf{(16)}$$

$$R_{eff} = \frac{(1-\theta)Q_0}{\alpha_0\sigma_1\left(\frac{\theta}{\sigma_3}+\frac{1-\theta}{\sigma_1}+\frac{1}{\mu_0}\right)\left(\frac{\nu}{\sigma_3}+\frac{1-\nu}{\sigma_2}+\frac{1}{\mu_0}\right)} + \frac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\frac{\theta}{\sigma_3}+\frac{1-\theta}{\sigma_1}+\frac{1}{\mu_0}\right)\left(\frac{\nu}{\sigma_3}+\frac{1-\nu}{\sigma_2}+\frac{1}{\mu_0}\right)\left(\frac{1}{\tau+p}+\frac{1}{\mu_0+\mu_1}\right)} \quad \textbf{(17)}$$

Theorem 1: R_{eff} is a strictly decreasing function of $\sigma_3, \theta, \tau, \nu, p \in (0,1)$.

Proof: The partial derivative of R_{eff} with respect to $\sigma_3, \theta, \tau, \nu$ and p is given by (18) to (22).

$$\frac{\partial R_{eff}}{\partial \sigma_3} = -\frac{\sigma_3\left(\begin{array}{l}\dfrac{(1-\theta)Q_0\theta}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)^2\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\sigma_3^2}+\dfrac{(1-\theta)Q_0\nu}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)^2\sigma_3^2}\\ +\dfrac{(1-\theta)(1-\nu)Q_0\theta}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)^2\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)\sigma_3^2}\\ +\dfrac{(1-\theta)(1-\nu)Q_0\nu}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)^2\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)\sigma_3^2}\end{array}\right)}{\left(\begin{array}{l}\dfrac{(1-\theta)Q_0}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)}+\\ \dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)}\end{array}\right)} < 0 \quad \textbf{(18)}$$

$$\frac{\partial R_{eff}}{\partial \theta} = -\frac{\theta\left(\begin{array}{l}\dfrac{Q_0}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)}-\dfrac{(1-\theta)Q_0\left(\dfrac{1}{\sigma_3}-\dfrac{1}{\sigma_1}\right)}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)^2\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)}\\ +\dfrac{(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)}\\ -\dfrac{(1-\theta)(1-\nu)Q_0\left(\dfrac{1}{\sigma_3}-\dfrac{1}{\sigma_1}\right)}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)^2\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)}\end{array}\right)}{\left(\begin{array}{l}\dfrac{(1-\theta)Q_0}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)}+\\ \dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)}\end{array}\right)} < 0 \quad \textbf{(19)}$$

$$\frac{\partial R_{eff}}{\partial \tau} = -\frac{\tau Q_0\left((1-\theta)(1-\nu)\right)}{\left(\begin{array}{l}\left(\dfrac{(1-\theta)Q_0}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)}\right.\\ \left.+\dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)}\right)\\ \delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)^2(\tau+p)^2\end{array}\right)} < 0 \quad \textbf{(20)}$$

$$\frac{\partial R_{eff}}{\partial \nu} = -\frac{\left(\nu\left(\begin{array}{c} -\dfrac{(1-\theta)Q_0\left(\dfrac{1}{\sigma_3}-\dfrac{1}{\sigma_1}\right)Q_0}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)^2}+ \\ \dfrac{(1-\theta)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)} \\ -\dfrac{(1-\theta)(1-\nu)Q_0\left(\dfrac{1}{\sigma_3}-\dfrac{1}{\sigma_1}\right)}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)^2\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)} \end{array}\right)\right)}{\left(\begin{array}{c} \dfrac{(1-\theta)Q_0}{\alpha_0\sigma_1\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)}+ \\ \dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)} \end{array}\right)} < 0 \quad \textbf{(21)}$$

$$\frac{\partial R_{eff}}{\partial p} = -\frac{\left(p\left(\begin{array}{c} \dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)^2\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)} \\ +\dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)^2(\tau+p)^2} \end{array}\right)\right)}{\left(\begin{array}{c} \dfrac{(1-\theta)Q_0}{\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)} \\ +\dfrac{(1-\theta)(1-\nu)Q_0}{\delta(1-p)\sigma_1\sigma_2\left(\dfrac{\theta}{\sigma_3}+\dfrac{1-\theta}{\sigma_1}+\dfrac{1}{\mu_0}\right)\left(\dfrac{\nu}{\sigma_3}+\dfrac{1-\nu}{\sigma_2}+\dfrac{1}{\mu_0}\right)\left(\dfrac{1}{\tau+p}+\dfrac{1}{\mu_0+\mu_1}\right)} \end{array}\right)} < 0 \quad \textbf{(22)}$$

RESULTS AND DISCUSSION

Therefore, R_{eff} is a strictly decreasing function of $\sigma_3, \theta, \tau, \nu$ and p as shown in Equations (18) to (22). The results we obtained by using this technique show that the malaria disease can be eliminated if R_{eff} is below unity. From the analysis of the model, the study suggests a proportionate combination of drug therapy and treatment for each infected individual as a better control strategy.

CONCLUSION

The effective reproduction number (R_{eff}) represents the average number of secondary cases generated by an infected cell or individual if introduced into a susceptible host cell or population where control strategies are used. In the analysis, the results show that effective reproduction number is a decreasing function of both drug therapy and treatment rates. We observed that the optimal control of malaria disease is the availability of *anti-malaria* known as drug therapy and its clinical treatment.

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