Nigerian Research Journal of Engineering and Environmental Sciences 6(1) 2021 pp. 38-60

Nigerian Research Journal of Engineering and Environmental Sciences
Journal homepage: www.rjees.com

Original Research Article

Malaria-Dengue Co-Infection Transmission Dynamics with Malaria Prior Immunity

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ARTICLE INFORMATION

Article history:
Received 02 May, 2021
Revised 23 May, 2021
Accepted 24 May, 2021
Available online 30 Jun, 2021

Keywords:
Backward bifurcation
Co-infection
Dengue
Malaria
Prior immunity
Treatment

ABSTRACT

A new deterministic mathematical model to assess the impact of malaria prior immunity on dengue as well as treatment on the dynamics of malaria-dengue co-infection in a human population is presented. The malaria-dengue co-infection model does undergo the phenomenon of backward bifurcation due to the presence of five parameters: the reduced probability of re-infection by recovered individuals due to malaria prior acquired immunity, the slower rate of treatment of individuals infected with malaria, the susceptibility of malaria-infected individuals to dengue infection, the probability of effective transmission of malaria from infectious humans to susceptible Anopheles vectors, and the probability of effective transmission of dengue infection from infectious humans to Aedes aegypti vectors. The co-infection model was numerically simulated to investigate the impact of various treatment strategies for singly infected and co-infected individuals with and without malaria prior immunity. It was observed that previous exposure to malaria infection does not affect co-infected individuals but has impact on singly infected individuals with malaria. The study also revealed that with high treatment rates the incidence of the co-infection can be reduced if not totally eliminated.

1. INTRODUCTION

Malaria and dengue are two of the most important diseases spread by mosquitoes which are affecting humans. According to Bhatt *et al.* (2013) and WHO (2016), approximately 584,000 and 12,000 people die annually from malaria and dengue respectively while another 198 million and 96 million are estimated to fall ill from malaria and dengue respectively. It is quite important to note that although the *Anopheles* mosquito (for malaria) and the *Aedes* mosquito (for dengue), occupy different ecological niches, considerable geographical overlap in disease risk exists for the 3.3 and 4 billion people who live in an area endemic for malaria and dengue respectively (Brady *et al.*, 2012; WHO, 2016). Both diseases also share

many common clinical features which includes, fever, headache, body aches and fatigue (but the treatment of these two illnesses is different) (Ward, 2006). This makes one disease easily mistaken for the other.

Malaria-dengue co-infection is a situation where both malaria and dengue exists in a patient at the same time. According to Arya *et al.* (2005) and Charrel *et al.* (2005), the first reports of co-infection occurred in 2005 and most subsequent reports describe only individual patients and rely on serological methods for diagnosing dengue virus (DENV) infection. The majority of reports originate from India and Pakistan, West Africa (Charrel *et al.*, 2005), French Guiana (Carme *et al.*, 2009; Epelboin *et al.*, 2012), Brazil (Magalhães *et al.* (2014), Malaysia (Yong and Koh, 2013), Bangladesh (Faruque *et al.*, 2012, Swoboda *et al.*, 2014), East Timor (Ward, 2006), Thailand (Issaranggoon *et al.*, 2014) and Indonesia (Yong and Koh, 2013). The report by Carme *et al.* (2009) in French Guiana revealed that the specific rate of malaria-dengue co-infection from overall febrile patients was equal to 0.99. Malaria-dengue co-infection tends to be more severe than single infection (Epelboin *et al.*, 2012). The biological influence of dengue virus which affects the endothelium which is a major protagonist of severe malaria pathophysiology has an effect on the severity on *falciparum* malaria. Co-infected patients present deep thrombocyloperia, anaemia and low platelet than single infected patients (Carme *et al.*, 2009). Though dengue and malaria are difficult to clinically differentiate, the treatment of the co-infections is very different. As stated by Ward (2006), a delay in instituting an appropriate management can be fatal. In fact, clinical and biological pictures of co-infected cases are different from single infection and bivariate comparisons show more differences between malaria-dengue and dengue than between malaria-dengue and malaria (Epelboin *et al.*, 2012). Both dengue and malaria are reported to co-exist in thrombocytopenic patients, especially those presenting with acute febrile illness, as reported from study elsewhere (Yasir, *et al.*, 2014). However, malaria can be chronic in contrast to dengue. The triads of haematological findings: a typical lymphocytosis, haemoconcentration and thrombocytopaenia, might be a clue for differential diagnosis of dengue infection rather than other tropical infections, including malaria (Wiwanitkit, 2011). However, a more specific diagnosis of either condition is advised (Sinniah and Lye, 2000). Any suspicion of malaria in disease-endemic areas must be excluded with microscopy (Ward, 2006).

Mathematical models have become important tools in analyzing the spread and control of infectious diseases (Hethcote, 2000). The model formulation process clarifies assumptions, variables, and parameters; moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, etc. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Epidemiology modeling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in forecasts (Hethcote, 2000). The co-infection of malaria and dengue has the propensity to be more severe than single malaria or single dengue infection (Epelboin *et al.*, 2012). This is of serious concern to health authorities and critical stakeholders who reside in such geographical areas where these two diseases are endemic and overlap (Issaranggoon *et al.*, 2014).

Several mathematical models to understand the infection transmission dynamics of malaria have been formulated (Ngwa and Shu, 2000; Chiyaka *et al.*, 2008; Niger and Gumel, 2008; Nwankwo, 2020). Several authors have also contributed to the literature on dengue transmission dynamics (Garba *et al.*, 2008; Phaijoo and Gurung, 2015). A lot of work has also been done by some authors in terms of malaria co-infection with several other diseases, namely: HIV co-infection with malaria (Abu-Raddad *et al.*, 2006; Mukandavire *et al.*, 2009), malaria co-infection with meningitis (Lawis *et al.*, 2011), malaria co-infection with typhoid (Mutua *et al.*, 2015), malaria co-infection with cholera (Okosun and Makinde, 2014), malaria co-infection with schistosomiasis (Bakare and Nwozo, 2016). Other authors have also contributed to dengue co-infection

with other diseases and with itself, such as dengue-chikunguya co-infection (Aldila and Agustin, 2018) and co-infection of two serotypes of dengue (Kawabuchi *et al.*, 2000). These aforementioned contributions have presented solutions which serve to advice health authorities and critical stakeholders in the decision-making process as to how best to tackle such epidemiological challenges in their domain. To the best of the authors' knowledge, no work has been done to investigate malaria-dengue co-infection in the presence of malaria prior immunity. Therefore, the aim of this study is to formulate a deterministic mathematical model to investigate the impact of malaria-dengue co-infection on a human population in the presence of malaria prior immunity.

2. METHODOLOGY

2.1. Model Formulation

The total human population at time *t*, denoted by $N_h(t)$, was divided into the following epidemiological subgroups: wholly susceptible individuals (S_w), infectives with malaria (I_m), infectives with dengue (I_d), malaria infected-dengue infected (I_{mwd}), malaria infected-dengue recovered (I^M_{mwd}), malaria recovered-dengue infected (I^D_{mwd}), malaria recovered (R_m), dengue recovered (R_d), susceptible with prior immunity (S_r), malaria infectives with prior immunity (I_{mr}), malaria infectives with prior immunity-dengue infectives (I_{mrd}), malaria infectives with prior immunity and dengue recovered (I^D_{mrd}), and malaria recovered with prior immunity (R_{mr}). Thus:

$$N_h(t) = S_w(t) + S_r(t) + I_m(t) + I_{mr}(t) + I_d(t) + I_{mwd}(t) + I_{mrd}(t) + I^M_{mwd}(t) + I^M_{mrd}(t) + I^D_{mwd}(t) + I^D_{mrd}(t) + R_m(t) + R_{mr}(t) + R_d(t) \quad (1)$$

The vector (anopheles mosquito) population at time *t*, denoted by $N_m(t)$ was divided into susceptible *Anopheles* mosquitoes $M_s(t)$ and infectious anopheles mosquitoes $M_i(t)$, so that:

$$N_m(t) = M_s(t) + M_i(t) \quad (2)$$

Similarly, the vector (*Aedes aegypti*) population at time *t*, denoted by $N_d(t)$ was divided into susceptible *Aedes aegypti* $D_s(t)$ and infectious *Aedes* aegypti $D_i(t)$, so that:

$$N_d(t) = D_s(t) + D_i(t) \quad (3)$$

Thus, the total vector population at time *t*, denoted by $N_v(t)$ is given by:

$$N_v(t) = N_m(t) + N_d(t) \quad (4)$$

2.1.1. Transmission by Malaria and Dengue infected individuals

Individuals acquire malaria infection allowing effective contact with infected *Anopheles* mosquitoes (M_i) at a rate given by:

$$\lambda_m = \beta_m \frac{b_m M_i}{N_h} \quad (5)$$

Where β_m is the transmission rate per bite and b_m is the per capital biting rate of anopheles mosquitoes. Similarly, individuals acquire dengue infection following effective contact with infected *Aedes aegypti* (D_i) at a rate given by:

$$\lambda_d = \beta_d \frac{b_d D_i}{N_h} \tag{6}$$

Where β_d is the transmission rate per bite and b_d is the per capita biting rate of *Aedes aegypti*.

2.1.2. Transmission by vectors

The population of susceptible anopheles mosquitoes $\left(M_s(t)\right)$ acquires malaria infection following effective contacts with humans at a rate:

$$\lambda_{hm} = \frac{\emptyset_7 \beta_{vm} b_m (I_m + I_{mwd} + \gamma_1 I_{mr} + \gamma_2 I_{mrd})}{N_h} \tag{7}$$

where β_{vm} is the transmission rate of malaria infection, b_m is the biting rate of anopheles mosquitoes. The parameters γ_1 and γ_2 accounts for reduction in infectiousness due to development of partial immunity to malaria after reinfection in the I_{mr} and I_{mrd} classes respectively. The population of susceptible *Aedes aegypti* $\left(D_s(t)\right)$ acquires dengue infection following effective contacts with humans at a rate:

$$\lambda_{hd} = \frac{\emptyset_8 \beta_{vd} b_d (I_d + I_{mwd})}{N_h} \tag{8}$$

Where β_{vd} is the transmission rate of dengue infection and b_d is the biting rate of *Aedes aegypti*.

2.1.3. Derivation of model equations

The wholly susceptible human population, $S_w(t)$, is generated by the recruitment of individuals (assumed susceptible) into the population at a rate Λ_h. The population of susceptible individuals is reduced due to malaria and dengue infections at the rate λ_m and λ_d respectively. The population is further reduced by natural death (natural death occurs in all epidemiological compartments at this rate) at a rate μ_h. Thus:

$$\frac{dS_w}{dt} = \Lambda_h - (\lambda_m + \lambda_d + \mu_h) S_w \tag{9}$$

The population of individuals infected by malaria is increased by those who acquire malaria infection at a rate λ_m and those infected by malaria after recovery from dengue infection. This population is reduced by progression to the malaria-recovered class at the rate γ_m, those who get infected with dengue at the rate λ_d, by natural mortality and disease-induced mortality at the rates μ_n and d_m, respectively. Thus:

$$\frac{dI_m}{dt} = \lambda_m S_w + \lambda_m R_d - (\lambda_d + \gamma_m + \mu_h + d_m) I_m \tag{10}$$

The population of individuals infected by dengue is increased by those who acquire dengue infection at a rate λ_d but diminished by the progression of these individuals to the dengue-recovered class, at the rate γ_d, by those who get infected with malaria at the rate λ_m, by natural death and disease-induced mortality at the rates μ_h and d_1 respectively. Hence:

$$\frac{dI_d}{dt} = \lambda_d S_w - (\lambda_m + \gamma_d + \mu_h + d_1) I_d \tag{11}$$

The population of malaria recovered individuals is generated by individuals who recover from malaria infection at a rate γ_m and the malaria infected-dengue recovered individuals who recover from malaria at a

rate $\theta_m \gamma_m$ (θ_m is a modification parameter for slower rate in recovery). This population is reduced by progression to the susceptible class with prior immunity at a rate Ψ_m (which accounts for the rate of loss of immunity) and by natural mortality μ_n. Thus:

$$\frac{dR_m}{dt} = \gamma_m I_m + \theta_m \gamma_m I_{mwd}^M - (\Psi_m + \mu_h) R_m \tag{12}$$

The population of dengue recovered individuals is generated by individuals who recover from dengue infection at a rate γ_d. This population is reduced following infection from anopheles mosquito at a rate λ_m and natural mortality. So that:

$$\frac{dR_d}{dt} = \gamma_d I_d - (\lambda_m + \mu_h) R_d \tag{13}$$

The dually infected individuals are generated following malaria infection of dengue infected individuals at a rate λ_m and dengue infection of malaria infected individuals at a rate λ_d. This population is decreased by treatment of malaria and dengue at the rate τ_m and τ_d respectively. This population is further decreased by natural mortality, malaria-induced mortality rate and dengue induced mortality rate at the rates μ_m, d_m and d_1 respectively. Thus:

$$\frac{dI_{mwd}}{dt} = \lambda_d I_m + \lambda_m I_d - (\tau_d + \tau_m + \mu_h + d_m + d_1) I_{mwd} \tag{14}$$

The population of malaria infected-dengue recovered individuals is increased by those who recover from dengue following treatment at the rate τ_d. The population is decreased by progression to the malaria recovered class at a rate $\theta_m \gamma_m$, by natural death and by disease-induced death rate given by μ_h and d_{mw} respectively. Thus:

$$\frac{dI_{mwd}^M}{dt} = \tau_d I_{mwd} - (\theta_m \gamma_m + \mu_h + d_{mw}) I_{mwd}^M \tag{15}$$

The population of malaria recovered-dengue infected individuals is increased by those who recover from malaria due to malaria treatment at the rate τ_m. This population is reduced by progression to the susceptible class with prior immunity at a rate $\theta_d \gamma_d$ (where θ_d is a modification parameter which accounts for slower rate of recovery from dengue infection), by progression to the class of malaria infectives with prior immunity-dengue infected individuals at the rate $\emptyset_1 \lambda_m$ ($\emptyset_1$ is a modification parameter which accounts for susceptibility to malaria infection) by natural death rate and disease-induced death rate at μ_h and d_2 respectively. Thus:

$$\frac{dI_{mwd}^D}{dt} = \tau_m I_{mwd} - (\theta_d \gamma_d + \emptyset_1 \lambda_m + \mu_h + d_2) I_{mwd}^D \tag{16}$$

The population of malaria infectives with prior immunity-dengue infected individuals is generated by progression from the population of malaria recovered-dengue infected individuals at a rate $\emptyset_1 \lambda_m$. This population is decreased following treatment of malaria and dengue infection at the rates $\emptyset_2 \tau_m$ and $\emptyset_3 \tau_d$ (where $\emptyset_2$ and $\emptyset_3$ are modification parameters which account for slower response rate to treatment), by natural death rate, malaria-induced death rate and dengue induced death rate given by μ_h, d_{mr} and d_2 respectively. Thus:

$$\frac{dI_{mrd}}{dt} = \emptyset_1 \lambda_m - (\emptyset_3 \tau_d + \emptyset_2 \tau_m + \mu_h + d_{mr} + d_2) I_{mrd} \tag{17}$$

The population of malaria infectives with prior immunity and dengue recovered individuals is generated by the progression of malaria infectives with prior immunity-dengue infectives at a rate $\emptyset_4\tau_d$. This population is decreased by progression to malaria recovered class with prior immunity at the rate $\emptyset_{mr}\gamma_{mr}$, by natural death and malaria-induced death rate given by μ_h and d_{mr} respectively. So that:

$$\frac{dI^M_{mrd}}{dt} = \emptyset_4\tau_d I_{mrd} - (\emptyset_{mr}\gamma_{mr} + \mu_h + d_{mr})I^M_{mrd} \tag{18}$$

The population of malaria recovered with prior immunity and dengue infected individuals is increased by progression from the malaria infectives with prior immunity-dengue infected individuals at a rate $\emptyset_5\tau_m$. This population is decreased by progression to the susceptible class with immunity at the rate γ_{dr}, by natural death and dengue induced death rate at the rates μ_h and d_3 respectively. Thus:

$$\frac{dI^D_{mrd}}{dt} = \emptyset_5\tau_m I_{mrd} - (\gamma_{dr} + \mu_h + d_3)I^D_{mrd} \tag{19}$$

The population of susceptible individuals with prior immunity is generated following progression from individuals who recover from malaria, dually infected individuals who recover from both diseases, malaria infectives with prior immunity-dengue recovered individuals and malaria recovered with prior immunity dengue infected individuals at the rates $\Psi_m, \Psi_{mr}, \theta_d\gamma_d$, and γ_{dr} respectively. This population is decreased following infection and natural death at the rates $\emptyset_6\lambda_m$, μ_h respectively. The parameter $\emptyset_6$ acccounts for the reduced probability of re-infection by recovered individuals due to malaria prior acquired immunity. Thus:

$$\frac{dS_r}{dt} = \Psi_m R_m + \Psi_{mr}R_{mr} + \theta_d\gamma_d I^D_{mwd} + \gamma_{dr}I^D_{mrd} - (\emptyset_6\lambda_m + \mu_h)S_r \tag{20}$$

The population of infected individuals with prior immunity is increased by malaria infection at a rate λ_m. This population is decreased as a result of recovery from malaria, natural death rate and malaria induced death rate given by μ_h and d_{mr} respectively. So that:

$$\frac{dI_{mr}}{dt} = \emptyset_6\lambda_m S_r - (\gamma_{mr} + \mu_h + d_{mr})I_{mr} \tag{21}$$

The population of recovered individuals with prior immunity is increased by individuals who recover from malaria with prior immunity at the rate γ_{mr}, individuals who recover from dengue and malaria infection at the rate $\theta_{mr}\gamma_{mr}$. This population is decreased by natural death at the rate μ_h.

$$\frac{dR_{mr}}{dt} = \gamma_{mr}I_{mr} + \theta_{mr}\gamma_{mr}I^M_{mrd} - (\Psi_{mr} + \mu_h)R_{mr} \tag{22}$$

The susceptible malaria population is generated by recruitment of mosquitoes into the population at a rate Λ_m. This population is decreased following effective contact with infected individuals at a rate λ_{hm} and by natural death at the rate μ_m. Thus:

$$\frac{dM_s}{dt} = \Lambda_m - (\lambda_{hm} + \mu_m)M_s \tag{23}$$

The infected malaria population is increased by susceptible vectors that get infected with malaria infection at a rate λ_{hm} and decreased as a result of natural death at a rate μ_m. So that:

$$\frac{dM_i}{dt} = \lambda_{hm}M_s - \mu_m M_i \tag{24}$$

The susceptible *Aedes aegypti* population is generated by recruitment of *Aedes aegypti* into the population at a rate Λ_d. This population is decreased following effective contact with infected individuals at rate λ_{hd} and by natural death μ_d. Thus:

$$\frac{dD_s}{dt} = \Lambda_d - (\lambda_{hd} + \mu_d)D_s \tag{25}$$

The infected *Aedes aegypti* population is increased by susceptible vectors that get infected with dengue infection at a rate λ_{hd} and decreased as a result of natural death at a rate μ_d. Thus:

$$\frac{dD_i}{dt} = \lambda_{hm}D_s - \mu_d D_i \tag{26}$$

On the basis of the foregoing, the malaria-dengue co-infection model with prior immunity to malaria infection in a population is given by the following system of eighteen non-linear ordinary differential equations:

$$\begin{aligned}
\frac{dS_w}{dt} &= \Lambda_h - (\lambda_m + \lambda_d + \mu_h)S_w \\
\frac{dS_r}{dt} &= \Psi_m R_m + \Psi_{mr} R_{mr} + \theta_d \gamma_d I^D_{mwd} + \gamma_{dr} I^D_{mrd} - (\emptyset_6 \lambda_m + \mu_h)S_r \\
\frac{dI_m}{dt} &= \lambda_m S_w + \lambda_m R_d - (\emptyset_1 \lambda_d + \gamma_m + \mu_h + d_m)I_m \\
\frac{dI_{mr}}{dt} &= \emptyset_6 \lambda_m S_r - (\gamma_{mr} + \mu_h + d_{mr})I_{mr} \\
\frac{dI_d}{dt} &= \lambda_d S_w - (\emptyset_2 \lambda_m + \gamma_d + \mu_h + d_1)I_d \\
\frac{dI_{mwd}}{dt} &= \emptyset_1 \lambda_d I_m + \emptyset_2 \lambda_m I_d - (\tau_d + \tau_m + \mu_h + d_m + d_1)I_{mwd} \\
\frac{dI_{mrd}}{dt} &= \emptyset_3 \lambda_m - (\emptyset_4 \tau_d + \emptyset_5 \tau_m + \mu_h + d_{mr} + d_2)I_{mrd} \\
\frac{dI^M_{mwd}}{dt} &= \tau_d I_{mwd} - (\theta_m \gamma_m + \mu_h + d_{mw})I^M_{mwd} \\
\frac{dI^D_{mwd}}{dt} &= \tau_m I_{mwd} - (\theta_d \gamma_d + \emptyset_3 \lambda_m + \mu_h + d_2)I^D_{mwd} \\
\frac{dI^M_{mrd}}{dt} &= \emptyset_4 \tau_d I_{mrd} - (\theta_{mr} \gamma_{mr} + \mu_h + d_{mr})I^M_{mrd} \\
\frac{dI^D_{mrd}}{dt} &= \emptyset_5 \tau_m I_{mrd} - (\gamma_{dr} + \mu_h + d_3)I^D_{mrd} \\
\frac{dR_m}{dt} &= \gamma_m I_m + \theta_m \gamma_m I^M_{mwd} - (\Psi_m + \mu_h)R_m \\
\frac{dR_{mr}}{dt} &= \gamma_{mr} I_{mr} + \theta_{mr} \gamma_{mr} I^M_{mrd} - (\Psi_{mr} + \mu_h)R_{mr} \\
\frac{dR_d}{dt} &= \gamma_d I_d - (\lambda_m + \mu_h)R_d \\
\frac{dM_s}{dt} &= \Lambda_m - (\lambda_{hm} + \mu_m)M_s \\
\frac{dM_i}{dt} &= \lambda_{hm} M_s - \mu_m M_i
\end{aligned} \tag{27}$$

$$\frac{dD_s}{dt} = \Lambda_d - (\lambda_{hd} + \mu_d)D_s$$
$$\frac{D_i}{dt} = \lambda_{hd}D_s - \mu_d D_i$$

The associated variables and parameters and described in Table 1 and Table 2 respectively.

Table 1: Description of variables in model

Variables	Interpretation
$S_w(t)$	Wholly susceptible
S_r(t)	Susceptible with prior immunity
$I_m(t)$	Malaria infective
$I_{mr}(t)$	Malaria infective with prior immunity
$I_d(t)$	Dengue infective
$I_{mwd}(t)$	Malaria infected and dengue infected
$I_{mrd}(t)$	Malaria infective with prior immunity and dengue infective
$I^M_{mwd}(t)$	Malaria infected and dengue recovered
$I^M_{mrd}(t)$	Malaria infected with prior immunity and dengue recovered
$I^D_{mwd}(t)$	Malaria recovered and dengue infected
$I^D_{mrd}(t)$	Malaria recovered with prior immunity and dengue infected
$R_m(t)$	Malaria recovered
$R_{mr}(t)$	Malaria recovered with prior immunity
$R_d(t)$	Dengue recovered
$M_s(t)$	Susceptible anopheles mosquitoes
$M_i(t)$	Infected *Anopheles* mosquitoes
$D_s(t)$	Susceptible *Aedes aegypti*
$D_i(t)$	Infected *Aedes aegypti*

2.2. Model Analysis

2.2.1. Basic properties of the model

For model (Equation 27) to be epidemiologically meaningful, it is pertinent to show that all its state variables are non-negative for all time, *t*. In other words, since model (Equation 27) monitors the human population, all associated state variables and parameters are non-negative for all time $t \geq 0$. Thus, the solutions of model (Equation 27) with positive initial data will remain positive for all $t \geq 0$.

Table 2: Description of the parameters in model

Parameter	Interpretation
Λ_h	Recruitment rate of humans
Λ_m	Recruitment rate of anopheles mosquitoes
Λ_d	Recruitment rate of *Aedes aegypti*
μ_h	Death rate of humans
μ_d	Death rate of *Aedes aegypti*
μ_m	Death of anopheles mosquitoes
λ_m	Infectious rate of anopheles mosquito
λ_d	Infectious rate of *Aedes aegypti*
β_{vm}	Transmission rate from humans to malaria vectors
β_{vd}	Transmission rate from humans to dengue vectors
β_m	Transmission rate from malaria vectors to humans
β_d	Transmission rate from dengue vectors to humans
b_m	Biting rate of anopheles mosquitoes

Parameter	Interpretation
b_d	Biting rate of *Aedes aegypti*
$\mathfrak{l}_1, \mathfrak{l}_2$	Modification parameter for reduction in infectiousness due to prior immunity to malaria infection
$\gamma_{i(i=m,mr)}$	Recovery rate of malaria infectious humans without (i=m), and with (i=mr) prior immunity
γ_d	Recovery rate of dengue infected humans
$\tau_{i(i=m,mr)}$	Treatment rates for malaria infective without (i=m) and with (i=mr) prior immunity
τ_d	Treatment rate for dengue infective
$d_{i(i=m,mw,mr)}$	Malaria induced death rate without (i=m, mw) and with (i:mr) prior immunity
$d_{i(i=1,2,3)}$	Dengue induced death rate for single and co-infected classes
Ψ_m, Ψ_{mr}	Transmission rate of recovered individuals into the partially immune class
$\theta_{i(i=m,mr)}$	Slower rate of recovery from malaria infection without (i=m) and with (i=mr) prior immunity to malaria
θ_d	Modification parameter for slower rate of recovery from dengue due to co-infection
$\emptyset_2, \emptyset_3$	Modification parameter that account for slower rate of treatment of individuals infected with malaria and dengue respectively
$\emptyset_1$	Modification parameter that accounts for susceptibility of malaria infected individuals to dengue infection
$\emptyset_4, \emptyset_5$	Modification parameters that account for slower recovery in the malaria infected-dengue recovered and the malaria recovered-dengue infected classes respectively
$\emptyset_6$	Modification parameter that accounts for the reduced probability of re-infection by recovered individuals due to malaria prior acquired immunity
$\emptyset_7, \emptyset_8$	Modification parameters that account for the probability of effective transmission of infection from the malaria infected and infected-dengue individuals respectively to the susceptible *Anopheles* and *Aedes aegypti* vectors respectively

Lemma 1: The feasible region

$$\Omega = \begin{cases} (S_w, S_r, I_m, I_{mr}, I_d, I_{mwd}, I_{mrd}, I^M_{mwd}, I^D_{mwd}, I^M_{mrd}, I^D_{mrd}, R_m, R_{mr}, R_d) \epsilon \mathbb{R}^{14}_+ : \mu_h \leq \dfrac{\Lambda_h}{\mu_h} \\ (M_s, M_i) \epsilon \mathbb{R}^2_+ : \mu_m \leq \dfrac{\Lambda_m}{\mu_m} \\ (D_s, D_i) \epsilon \mathbb{R}^2_+ : \mu_d \leq \dfrac{\Lambda_d}{\mu_d} \end{cases} \tag{28}$$

is positively invariant and attracting for model (Equation 27)

Proof: Adding the first fourteen equations, the fifteenth and sixteenth equations as well as the last two equations gives the following result:

$$\begin{aligned} \frac{dN_h}{dt} = \Lambda_h - \mu_h N_h \\ - [d_m I_m + d_r I_{mr} + d_1 I_d + (d_m + d_1) I_{mwd} + (d_{mr} + d_2) I_{mrd} \\ + d_{mw} I^M_{mwd} + d_2 I^D_{mwd} + d^D_{mrd} + d_3 I^D_{mrd}] \end{aligned} \tag{29}$$

$$\frac{dN_m}{dt} = \Lambda_m - \mu_m N_m \tag{30}$$

$$\frac{dN_d}{dt} = \Lambda_d - \mu_d N_d \tag{31}$$

Solving this differential inequality that arises from Equation (29) (i.e., $\frac{dN_h}{dt} + \mu_h N_h \leq \Lambda_h$) gives:

$N_h(t) \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t})$.

Similarly, $N_m(t) \leq N_m(0)e^{-\mu_m t} + \frac{\Lambda_m}{\mu_m}(1 - e^{-\mu_m t})$ and $N_d(t) \leq N_d(0)e^{-\mu_d t} + \frac{\Lambda_d}{\mu_d}(1 - \mathrm{e}^{-\mu_\mathrm{d} \mathrm{t}})$.

In particular:

$$N_h(t) \leq \frac{\Lambda_h}{\mu_h}, \quad if \quad N_h(0) \leq \frac{\Lambda_h}{\mu_h} \quad and \quad N_m(t) \leq \frac{\Lambda_m}{\mu_m}, \quad if \quad N_m(0) \leq \frac{\Lambda_m}{\mu_m}$$

$$N_m(t) \leq \frac{\Lambda_m}{\mu_m}, \quad if \quad N_m(0) \leq \frac{\Lambda_m}{\mu_m} \; and \; N_d(t) \leq \frac{\Lambda_d}{\mu_d}, \quad if \quad N_d(0) \leq \frac{\Lambda_d}{\mu_d}$$

For all $t > 0$.

Thus, Ω is positively invariant under the flow described by the model. The solutions with initial condition in Ω remain in Ω with respect to the model. Thus, it is sufficient to consider the dynamic of the flow generated by model (Equation 27) in Ω. The model is mathematically and epidemiologically well posed in the region Ω (Hethcote, 2000).

Theorem 2: The system Ω (Equation 27) preserves positivity of solutions. This implies that the solution with positive initial conditions will remain positive for all time $t > 0$.

Proof: Suppose

$$t_1 = Sup\{\, t > 0 : S_w(t) > 0, S_r(t) > 0, I_m(t) > 0, I_{mr}(t) > 0, I_d(t) > 0, I_{mwd}(t) > 0, I_{mrd}(t) > 0, I^M_{mwd}(t) > 0, I^D_{mwd}(t) > 0, I^M_{mrd}(t) > 0, I^D_{mrd}(t) > 0, R_m(t) > 0, R_{mr}(t) > 0, R_d(t) > 0, M_s(t) > 0, M_i(t) > 0, D_s(t) > 0, D_i(t) > 0\} > 0$$

From the first equation of the model, it follows that:

$$\frac{dS_w}{dt} = \Lambda_h - (\lambda_m + \lambda_d + \mu_h)S_w$$

Solving this equation gives:

$$\begin{aligned} S_w(t_1) = S_w(0)exp\left[-\mu_h t_1 - \int_0^{t_1} \big(\lambda_m(\tau) + \lambda_d(\tau)\big)d(\tau)\right] \\ + \left\{exp\left[-\mu_h t_1 - \int_0^{t_1} \big(\lambda_h(\tau) + \lambda_d(\tau)\big)d(\tau)\right\}\right. \\ \times \int_0^{t_1} \Lambda\left[\exp\left(\mu_h y + \int_0^{y} \big(\lambda_m(\tau) + \Lambda_d(\tau)\big)\right)dy > 0\right] \end{aligned} \tag{32}$$

Similarly, using the same approach, we can show that all other state variables of model will remain positive for all time $t > 0$.

2.2.2. The disease-free equilibrium of the Malaria-Dengue co-infection model

The malaria-dengue model (27) has a disease-free equilibrium (DFE), obtained by setting the right-hand sides of the equations in the model to zero, which is given by

$$\begin{aligned}&\varepsilon_0\\&=\left(S_w^{**},S_r^{**},I_m^{**},I_{mr}^{**},I_d^{*},I_{mwd}^{**},I_{mrd}^{**},I_{mwd}^{M^{**}},I_{mwd}^{D^{**}},I_{mrd}^{M^{**}},I_{mrd}^{D^{**}},R_m^{**},R_{mr}^{**},R_d^{**},M_s^{**},M_i^{**},D_s^{**},D_i^{**}\right)\\&=\left(\frac{\Lambda_h}{\mu_h},0,0,0,0,0,0,0,0,0,0,0,0,0,0,\frac{\Lambda_m}{\mu_m},0,\frac{\Lambda_d}{\mu_d}\right)\end{aligned}\tag{33}$$

The linear stability of ε_0 can be established using the next generation operator method in van den Driessche and Watmough (2002) on the model. It follows that the effective reproduction number of the malaria-dengue model denoted by R_{md}, is given by:

$$R_{md}=\max(R_{om},R_{od})\tag{34}$$

Where:

$$R_{om}=\sqrt{\frac{\emptyset_7\beta_{vm}\beta_m b_m^2\Lambda_m\mu_h}{\Lambda_h\mu_m^2(\gamma_m+\mu_h+d_m)}}\tag{35}$$

R_{om} is the effective reproduction number of the malaria-only component of R_{md}, while

$$R_{od}=\sqrt{\frac{\emptyset_8\beta_d\beta_{vd}{b_d}^2\Lambda_d\mu_h}{\Lambda_h{\mu_d}^2(\gamma_d+\mu_h+d_1)}}\tag{36}$$

R_{od} is the effective reproduction number of the dengue-only component of R_{md}. From Theorem 2 in van den Driessche and Watmough (2002), the following result is claimed.

Lemma 3: *The disease-free equilibrium of the malaria-dengue model (27) given by (33) is locally asymptotically stable (LAS) if* $R_{md}<1$ *and unstable if* $R_{md}>1$.

The implication of this is that the malaria-dengue co-infection can be eliminated from the population whenever $R_{md}<1$. When $R_{md}<1$, then, averagely an infected person produces less than one newly infected person over the entire period of his infectiousness and malaria-dengue co-infection dies out. For R_{md} to be less than one, then $\beta_d,\beta_m,\beta_{vm},\beta_{vd},b_m$ and b_d must decrease without bounds. Otherwise, if $R_{md}>1$, then each infected person produces less, averagely more than one new infection and the malaria-dengue co-infection can invade the population.

Theorem 4: The malaria-dengue co-infection model does undergo backward bifurcation at $R_{md}=1$.

Proof: The proof is based on using the center manifold theory on the malaria-dengue model. Let $S_w=x_1^*,\ S_r=x_2^*,\ I_m=x_3^*,\ I_{mr}=x_4^*,I_d=x_5^*,\ I_{mwd}=x_6^*,\ I_{mrd}=x_7^*,\ I_{mwd}^M=x_8^*,\ I_{mwd}^D=x_9^*,\ I_{mrd}^M=x_{10}^*,\ I_{mrd}^D=x_{11}^*,\ R_m=x_{12}^*,R_{mr}=x_{13}^*,R_d=x_{14}^*,M_s=x_{15}^*,M_i=x_{16}^*,D_s=x_{17}^*,D_i=x_{18}^*$. Furthermore, we use the eigenvector notation

$$x^*=(x_1^*,x_2^*,x_3^*,x_4^*,x_5^*,x_6^*,x_7^*,x_8^*,x_9^*,x_{10}^*,x_{11}^*,\ x_{12}^*,\ x_{13}^*,\ x_{14}^*,\ x_{15}^*,\ x_{16}^*,\ x_{17}^*,\ x_{18}^*)^T$$

The model is re-written in the form:

$$\frac{dx}{dt}=F^*(x)$$

With $F^*=(f_1^*,f_2^*,f_3^*,f_4^*,f_5^*,f_6^*,f_7^*,f_8^*,f_9^*,f_{10}^*,f_{11}^*,f_{12}^*,f_{13}^*,\ f_{14}^*,\ f_{15}^*,\ f_{16}^*,\ f_{17}^*,\ f_{18}^*)^T$ as:

$$\begin{aligned}
\frac{dx_1^*}{dt} &= f_1^* = \Lambda_h - (\lambda_m + \lambda_d + \mu_h)x_1^* \\
\frac{dx_2^*}{dt} &= f_2^* = \Psi_m x_{12}^* + \Psi_{m1} x_{13}^* + \theta_d \gamma_d x_9^* + \gamma_{dr} x_{11}^* - (\emptyset_6 \lambda_m + \mu_h)x_2^* \\
\frac{dx_3^*}{dt} &= f_3^* = \lambda_m x_1^* + \lambda_m x_{14}^* - (\gamma_m + \emptyset_1 \lambda_d + \mu_h + d_m)x_3^* \\
\frac{dx_4^*}{dt} &= f_4^* = \emptyset_6 \lambda_m x_2^* - (\gamma_{mr} + \mu_h + d_{mr})x_4^* \\
\frac{dx_5^*}{dt} &= f_5^* = \lambda_d x_1^* - (\lambda_m + \gamma_d + \mu_h + d_1)x_5^* \\
\frac{dx_6^*}{dt} &= f_6^* = \lambda_m \emptyset_2 x_5^* + \lambda_d \emptyset_1 x_3^* - (\tau_d + \tau_m + \mu_h + d_m + d_1)x_6^* \\
\frac{dx_7^*}{dt} &= f_7^* = \emptyset_3 \lambda_m x_9^* - (\emptyset_4 \tau_d + \emptyset_5 \tau_m + \mu_h + d_{mr} + d_2)x_7^* \\
\frac{dx_8^*}{dt} &= f_8^* = \tau_d x_6^* - (\theta_m \gamma_m + \mu_h + d_{mw})x_8^* \\
\frac{dx_9^*}{dt} &= f_9^* = \tau_m x_6^* - (\emptyset_3 \lambda_m + \theta_d \gamma_d + \mu_h + d_2)x_9^* \\
\frac{dx_{10}^*}{dt} &= f_{10}^* = \emptyset_4 \tau_d x_7^* - (\theta_{mr} \gamma_{mr} + \mu_h + d_{mr})x_{10}^* \\
\frac{dx_{11}^*}{dt} &= f_{11}^* = \emptyset_5 \tau_m x_7^* - (\gamma_{dr} + \mu_h + d_3)x_{11}^* \\
\frac{dx_{12}^*}{dt} &= f_{12}^* = \gamma_m x_3^* + \theta_m \gamma_m x_8^* - (\Psi_m + \mu_h)x_{12}^* \\
\frac{dx_{13}^*}{dt} &= f_{13}^* = \gamma_{mr} x_4^* + \theta_{mr} \gamma_{mr} x_{11}^* - (\Psi_m + \mu_h)R_{mr} \\
\frac{dx_{14}^*}{dt} &= f_{14}^* = \gamma_d x_5^* - (\lambda_m + \mu_h)x_{14}^* \\
\frac{dx_{15}^*}{dt} &= f_{15}^* = \Lambda_m - (\lambda_{hm} + \mu_m)x_{15}^* \\
\frac{dx_{16}^*}{dt} &= f_{16}^* = \lambda_{hm} x_{15}^* - \mu_m x_{16}^* \\
\frac{dx_{17}^*}{dt} &= \Lambda_d - (\lambda_{hd} + \mu_d)x_{17}^* \\
\frac{dx_{18}^*}{dt} &= \lambda_{hd} x_{17}^* - \mu_d x_{18}^*
\end{aligned} \tag{37}$$

With:

$\lambda_m = \frac{\beta_m b_m x_{16}^*}{N_H}$, $\lambda_d = \frac{\beta_d b_d x_{18}^*}{N_H}$, $\lambda_{hm} = \frac{\emptyset_7 \beta_{vm} b_m (x_3^* + x_6^* + \gamma_1 x_4^* + \gamma_2 x_7^*)}{N_H}$

and

$\lambda_{hd} = \frac{\emptyset_8 \beta_{vd} b_d (x_5^* + x_6^*)}{N_H}$

The Jacobian of Equation 37 at the DFE (ξ_0) denoted by $J(\varepsilon_0)$ is given by:

$$\mathrm{J}(\varepsilon_0) = \begin{bmatrix} \mathrm{T}_{11(9x9)} & \mathrm{T}_{12(9x9)} \\ \mathrm{T}_{21(9x9)} & \mathrm{T}_{22(9x9)} \end{bmatrix} \tag{38}$$

Where:

$$\mathrm{T}_{11}=\begin{bmatrix}-\mu_h & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & -\mu_h & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_d\theta_d\\ 0 & 0 & -J_1 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & -J_2 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & -J_3 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & -J_4 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & -J_5 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & \tau_d & 0 & -J_6 & 0\\ 0 & 0 & 0 & 0 & 0 & \tau_m & 0 & 0 & -J_7\end{bmatrix}, \mathrm{T}_{12}$$

$$=\begin{bmatrix}0 & 0 & 0 & 0 & 0 & 0 & -b_m\beta_m & 0 & -b_d\beta_d\\ 0 & \gamma_{\mathrm{dr}} & \psi_m & \psi_{\mathrm{mr}} & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & b_m\beta_m & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & b_d\beta_d\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\end{bmatrix}$$

$$\mathrm{T}_{21}=\begin{bmatrix}0 & 0 & 0 & 0 & 0 & 0 & \tau_d\phi_4 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & \tau_m\phi_5 & 0 & 0\\ 0 & 0 & \gamma_m & 0 & 0 & 0 & 0 & \gamma_m\theta_m & 0\\ 0 & 0 & 0 & \gamma_{\mathrm{mr}} & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & \gamma_d & 0 & 0 & 0 & 0\\ 0 & 0 & -J_{12} & -J_{13} & 0 & -J_{12} & -J_{14} & 0 & 0\\ 0 & 0 & J_{12} & J_{13} & 0 & J_{12} & J_{14} & 0 & 0\\ 0 & 0 & 0 & 0 & -J_{15} & -J_{15} & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & J_{15} & J_{15} & 0 & 0 & 0\end{bmatrix},$$

$$\mathrm{T}_{22}=\begin{bmatrix}-J_8 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & -J_9 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & -J_{10} & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & \gamma_{\mathrm{mr}}\theta_{\mathrm{mr}} & 0 & -J_{11} & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & -\mu_h & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & -\mu_m & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_m & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_d & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_d\end{bmatrix}$$

Where:

$$J_1^*=\gamma_m+\mu_h+d_m,\quad J_2^*=\gamma_{mr}+\mu_h+d_r,\quad J_3^*=\gamma_d+\mu_h+d_1$$
$$J_4^*=\tau_d+\tau_m+\mu_h+d_m+d_1,\quad J_5^*=\phi_4\tau_d+\phi_5\tau_m+\mu_h+d_{mr}+d_2$$
$$J_6^*=\theta_m\gamma_m+\mu_h+d_{mw},\ J_7^*=\theta_d\gamma_d+\mu_h+d_2,\ J_8^*=\theta_{mr}\gamma_{mr}+\mu_h+d_{mr}$$
$$J_9^*=\gamma_{dr}+\mu_h+d_3,\quad J_{10}^*=\Psi_m+\mu_h,$$
$$J_{11}^*=\Psi_{mr}+\mu_h,\quad J_{12}^*=\frac{\emptyset_7\beta_{vm}b_m\Lambda_m\mu_h}{\mu_m\Lambda_h},$$
$$J_{13}^*=\frac{\emptyset_7\gamma_1\beta_{vm}b_m\Lambda_m\mu_h}{\mu_m\Lambda_h},\quad J_{14}^*=\frac{\emptyset_7\gamma_2\beta_{vm}b_m\Lambda_m\mu_h}{\mu_m\Lambda_h},\quad J_{15}^*=\frac{\emptyset_8\beta_{vd}b_d\Lambda_d\mu_h}{\mu_d\Lambda_h}$$

(39)

It follows that $J(\varepsilon_0)$ of (Equation 27) at DFE has eigenvalues in which the real parts are negative. For convenience, recall, from Equations 35 and 36:

$$R_{od} = \sqrt{\frac{\emptyset_8 \beta_d \beta_{vd} b_d^2 \Lambda_d \mu_h}{\Lambda_h \mu_d^2 (\gamma_d + \mu_h + d_1)}} \qquad and \qquad R_{om} = \sqrt{\frac{\emptyset_7 \beta_m \beta_{vm} b_m^2 \Lambda_m \mu_h}{\Lambda_h \mu_m^2 (\gamma_m + \mu_h + d_m)}} \ .$$

Consider the case when $R_{md} = 1$ $(i.e\ R_{om} < R_{od} = 1)$. Suppose that $\beta_d = \beta^*$ is chosen as a bifurcation parameter. Solving for β_d from $R_{od} = 1$, gives:

$$\beta_d = \beta^* = \frac{\Lambda_h \mu_d^2 (\gamma_d + \mu_h + d_1)}{\emptyset_8 \beta_{vd} b_d^2 \Lambda_d \mu_h} \tag{40}$$

The Jacobian $J(\varepsilon_0)$ of Equation 27 at $\beta_d = \beta^*$ written as $J_{\beta^*}(\varepsilon_0)$ has right eigenvector given by:

$w_1{}^* = (w_1^*, w_2^*, w_3^*, w_4^*, w_5^*, w_6^*, w_7^*, w_8^*, w_9^*, w_{10}^*, w_{11}^*, w_{12}^*, w_{13}^*, w_{14}^*, w_{15}^*, w_{16}^*, w_{17}^*, w_{18}^*)^T$

Where:

$$w_1{}^* = \frac{-(\beta_m b_m w_{16}^* + \beta_d b_d w_{18}^*)}{\mu_h},$$

$$w_2^* = \frac{\Psi_m \gamma_m w_3^*}{J_{10}^* \mu_h}, w_3^* = w_3^* > 0, \qquad w_4^* = 0,$$

$$w_5^* = w_5^* > 0,$$

$$w_6^* = w_7^* = w_8^* = w_9^* = w_{10}^* = w_{11}^* = w_{12}^* = w_{13}^* = 0 \tag{41}$$

$$w_{14}^* = \frac{\gamma_d w_5^*}{\mu_h}, \qquad w_{15}^* = \frac{-J_{12}^* w_{18}^*}{\mu_m}, \qquad w_{16}^* = w_{16}^* > 0, \qquad w_{17}^* = -w_{18}^*, w_{18}^* = w_{18}^* > 0.$$

Similarly, $J_{\beta^*}(\varepsilon_0)$ of (27) has left eigenvector

$V^* = (V_1^*, V_2^*, V_3^*, V_4^*, V_5^*, V_6^*, V_7^*, V_8^*, V_9^*, V_{10}^*, V_{11}^*, V_{12}^*, V_{13}^*, V_{14}^*, V_{15}^*, V_{16}^*, V_{17}^*, V_{18}^*)$, satisfying $V^*.w^* = 1$, with

$$V_1^* = 0, \quad V_2 = 0, \quad V_3^* = V_3^* > 0,$$

$$V_4^* = \frac{J_{13}^* V_{16}^*}{J_2^*}, \qquad V_5^* = V_5^* > 0, \qquad V_6^* = \frac{J_{12}^* V_{16}^* + J_{15}^* V_{18}^*}{J_4^*}, \qquad V_7^* = \frac{J_{14}^* V_{16}^*}{J_5^*},$$

$$V_8^* = V_9^* = V_{10}^* = V_{11}^* = V_{12}^* = V_{13}^* = V_{14}^* = V_{15}^* = 0, \tag{42}$$

$$V_{16}^* = V_{16}^* > 0, \qquad V_{17}^* = 0, \qquad V_{18}^* = V_{18}^* > 0.$$

Applying the centre manifold theory, we have that the associated bifurcation coefficients *a* and *b*, defined by (Carr, 1981; Castillo-Chavez and Song, 2004).

$$a = \sum_{k,i,j=1}^{n} V_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \qquad and \qquad b = \sum_{k,i=1}^{n} V_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) \tag{43}$$

The associated bifurcation coefficients are computed to be, after several algebraic manipulations:

$$
\begin{aligned}
a = {} & \frac{2\beta_m b_m \mu_h}{\Lambda_h}[\emptyset_6 V_4^* w_2^* w_{16}^* + \emptyset_2 V_6^* w_5^* w_{16}^*] + \frac{2\beta_d b_d \mu_h}{\Lambda_h}[\emptyset_1 V_6^* w_3^* w_{18}^*] \\
& + \frac{2\beta_{vd} b_d \mu_h}{\Lambda_h}[\emptyset_8 V_{17}^* w_5^* w_{18}^*] \\
& + \frac{2\beta_{vd} b_d \Lambda_d \mu_h^2}{\mu_d \Lambda_h^2}[\emptyset_8 V_{17}^* w_5^* (w_2^* + w_3^* + w_5^* + w_{12}^* + w_{14}^*)] \\
& + \frac{2\mu_h}{\Lambda_h^2}(\beta_m b_m w_{16}^* + \beta_d b_d w_{18}^*)\left[\frac{\beta_{vm} b_m \Lambda_m}{\mu_m}\emptyset_7 V_{16}^* w_3^* \right. \\
& \left. + \frac{\beta_{vd} b_d \Lambda_d}{\mu_d}\emptyset_8 V_{18}^* w_5^*\right] \\
& - \frac{2\beta_m b_m \mu_h}{\Lambda_h}[V_3^* w_{16}^* (w_2^* + w_3^* + w_5^* + w_{12}^*) + V_5^* w_5^* w_{16}^*] \\
& - \frac{2\beta_d b_d \mu_h}{\Lambda_h}[\emptyset_1 V_2^* w_3^* w_{18}^* + V_5^* w_{18}^* (w_2^* + w_3^* + w_5^* + w_{12}^* + w_{14}^*)] \\
& - \frac{\beta_{vm} b_m \Lambda_m}{\mu_m}[\emptyset_7 V_{16}^* w_3^* \{\frac{\Lambda_m \mu_h}{\Lambda_h}(w_2^* + w_3^* + w_5^* + w_{12}^* + w_{14}^*) \\
& + \frac{\emptyset_7 \beta_{vm} b_m \Lambda_m \mu_h w_{18}^*}{\mu_m \Lambda_h}\}] \\
& - \frac{\beta_{vd} b_d \Lambda_d}{\mu_d}[\emptyset_8 V_{17}^* w_5^* (\beta_m b_m w_{18}^* + \beta_d b_d w_{16}^*)]
\end{aligned} \tag{44}
$$

and

$$b = V_5 w_{18} b_d > 0 \tag{45}$$

Obviously $b > 0$ for all biologically feasible parameter values. Thus, backward bifurcation occurs if and only if the following five parameters: (1.) the reduced probability of re-infection by recovered individuals due to malaria prior acquired immunity ($\emptyset_6$), (2.) the slower rate of treatment of individuals infected with malaria ($\emptyset_2$), (3.) the susceptibility of malaria-infected individuals to dengue infection ($\emptyset_1$), (4.) the probability of effective transmission of malaria from infectious humans to susceptible *Anopheles* vectors ($\emptyset_7$) and (5.) the probability of effective transmission of dengue infection from infectious humans *Aedes* a*egypti* vectors ($\emptyset_8$), are large enough such that $a > 0$. This, therefore, implies that the effective reproduction number then becomes a necessary and sufficient tool for promoting control measures that will lead to disease eradication.

Consequent upon the results obtained above, the following is claimed.

Theorem 5: (Non-existence of backward bifurcation) The model (27) (or (37)) does not experience backward bifurcation at the point $\mathcal{R}_{md} = 1$, whenever $\emptyset_6 = \emptyset_2 = \emptyset_1 = \emptyset_7 = \emptyset_8 = 0$.

Proof: Consider the unique case of the model (27) with negligible parameters responsible for the existence of the backward bifurcation phenomenon (i.e., $\emptyset_6 = \emptyset_2 = \emptyset_1 = \emptyset_7 = \emptyset_8 = 0$). Then the backward bifurcation coefficient, a, in (44) reduces to:

$$
\begin{aligned}
a = {} & -\frac{2\mu_h}{\Lambda_h}[\beta_m b_m w_{16}^* \{V_3^* (w_2^* + w_3^* + w_5^* + w_{12}^*) + V_5^* w_5^*\}] \\
& - \frac{2\mu_h}{\Lambda_h}[\beta_d b_d V_5^* w_{18}^* (w_2^* + w_3^* + w_5^* + w_{12}^* + w_{14}^*)]\} < 0
\end{aligned} \tag{46}
$$

Thus, this study has confirmed that the presence of the following five parameters: (1.) the reduced probability of re-infection by recovered individuals due to malaria prior acquired immunity ($\emptyset_6$), (2.) the slower rate of

treatment of individuals infected with malaria ($\emptyset_2$), (3.) the susceptibility of malaria-infected individuals to dengue infection ($\emptyset_1$), (4.) the effective transmission of malaria from infectious humans to susceptible *Anopheles* vectors ($\emptyset_7$) and (5.) the effective transmission of dengue infection from infectious humans *Aedes* a*egypti* vectors ($\emptyset_8$) activate backward bifurcation phenomenon in the epidemic dynamics of malaria co-infection with dengue.

2.2.3. Effect of Malaria on Dengue infection

In this section, the effect of malaria on dengue infection is analyzed. This is done by expressing the effective reproduction number of malaria on dengue (that is, expressing R_{od} in terms of R_{om}).

$$R_{om} = \sqrt{\frac{\emptyset_7\beta_{vm}\beta_m b_m^2\Lambda_m\mu_h}{\Lambda_h\mu_m^2(\gamma_m+\mu_h+d_m)}} \tag{47}$$

$$R_{om}^2 = \frac{\emptyset_7\beta_{vm}\beta_m b_m^2\Lambda_m\mu_h}{\Lambda_h\mu_m^2(\gamma_m+\mu_h+d_m)} \tag{48}$$

$$R_{om}^2\Lambda_h\mu_m^2(\gamma_m+d_m)+R_{om}^2\Lambda_h\mu_m^2\mu_h = \emptyset_7\beta_{vm}\beta_m b_m^2\Lambda_m\mu_h$$

Let

$$F_1=\Lambda_h\mu_m^2,\ F_2=\emptyset_7\beta_{vm}\beta_m b_m^2\Lambda_m,\ R_{om}\ F_3=R_{om}^2F_1(\gamma_m+d_m),\ R_{om}F_4=R_{om}^2F_1$$

Then:

$$R_{om}^2F_1(\gamma_m+d_m)=F_2\mu_h-R_{om}^2F_1$$

$$\mu_h=\frac{F_3R_{om}}{F_2-R_{om}F_4} \tag{49}$$

Recall that

$$R_{od}=\sqrt{\frac{\emptyset_8\beta_{vd}\beta_d b_d^2\Lambda_d\mu_h}{\Lambda_h\mu_d^2(\gamma_d+\mu_h+d_1)}} \tag{50}$$

Substituting μ_h into Equation 50 gives:

$$R_{od}^2=\frac{\emptyset_8\beta_{vd}\beta_d b_d^2\Lambda_d F_3R_{om}}{\Lambda_h\mu_d^2\big((F_2-R_{om}F_4)(\gamma_d+d_1)+F_3R_{om}\big)} \tag{51}$$

Differentiating R_{od}^2 with respect to R_{om} gives:

$$\frac{\partial R_{od}^2}{\partial R_{om}}=\frac{\emptyset_8\beta_{vd}\beta_d b_d^2\Lambda_d\Lambda_h\mu_d^2F_2F_3(\gamma_d+d_1)}{(\Lambda_h\mu_d^2[(F_2-R_{om}F_4)(\gamma_d+d_1)+F_3R_{om}])^2}>0 \tag{52}$$

Since, from the definition of R_{om}^2, we have that:

$$F_2-R_{om}F_4=\emptyset_7\beta_{vm}\beta_m b_m^2\Lambda_m\mu_h-\Lambda_h\mu_m^2\mu_h=R_{om}^2\Lambda_h\mu_m^2(\gamma_m+d_m)>0$$

The result shows that Equation 52 is greater than zero which implies that an increase in malaria infection would result in an increase in dengue infection in the community. Thus, malaria infection has a significant effect on the transmission dynamics of dengue.

2.2.4. Effect of Dengue on Malaria infection

Similarly, to establish the effect of dengue on malaria infection, R_{om} is expressed in terms of R_{od}.

$$R_{od} = \sqrt{\frac{\emptyset_8 \beta_{vd} \beta_d b_d^2 \Lambda_d \mu_h}{\Lambda_h \mu_d^2 (\gamma_d + \mu_h + d_1)}} \tag{53}$$

Rearranging the Equation (53) gives:

$$R_{od}^2 \Lambda_h \mu_d^2 \mu_h - \emptyset_8 \beta_{vd} b_d b_d^2 \Lambda_d \mu_h = R_{od}^2 \Lambda_h \mu_d^2 (\gamma_d + d_1) \tag{54}$$

Let:

$$R_{od} G_1 = R_{od}^2 \Lambda_h \mu_d^2 (\gamma_d + d_1), R_{od} G_2 = R_{od}^2 \Lambda_h \mu_d^2, G_3 = \emptyset_8 \beta_{vd} \beta_d b_d^2 \Lambda_d$$

So that:

$$\mu_h = \frac{G_1 R_{od}}{G_3 - R_{od} G_2} \tag{55}$$

Recall that

$$R_{om} = \sqrt{\frac{\emptyset_7 \beta_{vm} \beta_m b_m^2 \Lambda_m \mu_h}{\Lambda_h \mu_m^2 (\gamma_m + \mu_h + d_m)}} \tag{56}$$

Substituting μ_h into (56) gives:

$$R_{om}^2 = \frac{\emptyset_7 \beta_{vm} \beta_m b_m^2 \Lambda_m G_1 R_{od}}{\Lambda_h \mu_m^2 [(G_3 - R_{od} G_2)(\gamma_m + d_m) + G_1 R_{od}]} \tag{57}$$

Differentiating R_{om}^2 with respect to R_{od} gives:

$$\frac{\partial R_{om}^2}{\partial R_{od}} = \frac{\emptyset_7 \beta_{vm} \beta_m b_m^2 \Lambda_m \mu_h \Lambda_h \mu_m^2 G_1 G_3 (\gamma_m + d_m)}{\Lambda_h \mu_m^2 [(G_3 - R_{od} G_2)(\gamma_m + d_m) + G_1 R_{od}]^2} \tag{58}$$

Since, from the definition of R_{od}^2, it is clear that:

$$G_3 - R_{od} G_2 = \emptyset_8 \beta_{vd} b_d b_d^2 \Lambda_d \mu_h - R_{od}^2 \Lambda_h \mu_d^2 \mu_h = R_{od}^2 \Lambda_h \mu_d^2 (\gamma_d + d_1) > 0$$

The result also shows that (Equation 58) is greater than zero which implies that an increase in dengue infection would result in an increase in malaria infection in the community. This shows that dengue infection has a significant impact on the transmission dynamics of malaria. This corresponds with the study done in Carme *et al.* (2009), where it was asserted that dengue virus is a major protagonist of severe malaria and has an effect on the severity of *falciparum* malaria. This result shows that one disease affects the other as both diseases have the same signs and symptoms such that one disease can be mistaken for another.

2.3. Numerical Simulation

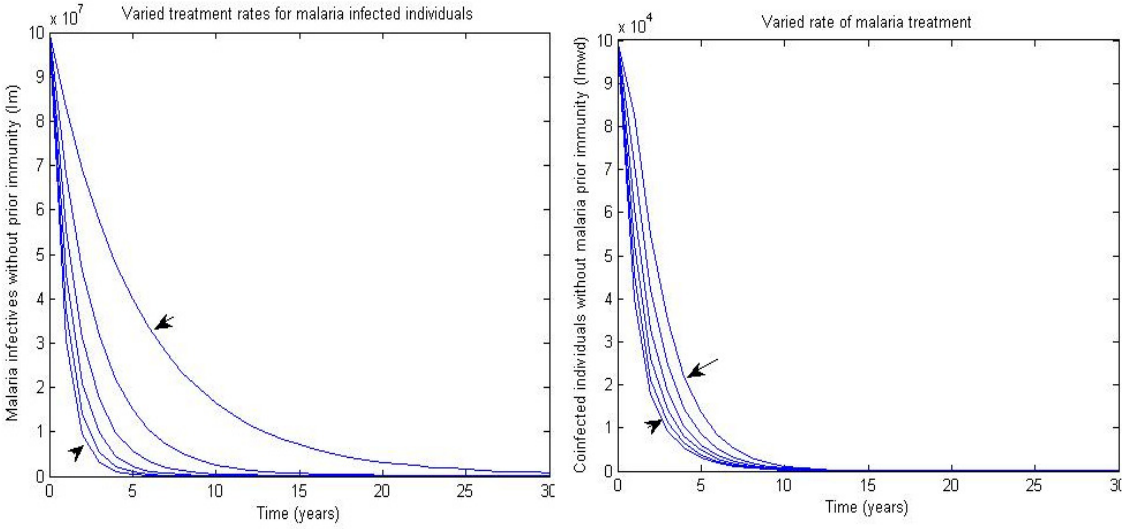
The malaria-dengue model was numerically simulated to illustrate the effect of varying some key parameters related to treatment of malaria with and without malaria prior immunity. The parameter values listed in Table 3 were used for the simulations, otherwise specific parameter values (especially the transmission rate, β) used for the simulations are stated in the caption of Figures 1, 2 and 3. For the simulation in this section, demographic parameters relevant to Nigeria were chosen. Since the total population of Nigeria in 2015 is estimated to be 199,707,545 (Worldometer, 2019), it follows that, at the disease free equilibrium, Λ_h/μ_h=199,707,545. Moreover, the average mortality rate in Nigeria is μ_h= 0.02041 per year (UNAIDS, 2014) so that the average recruitment rate is Λ_h = 4,076,031 per year, and the total malaria incidence in Nigeria was estimated to be 100,000,000 in 2019 (WHO, 2019). Similarly, the total dengue incidence in Nigeria is estimated to be between 40,000,000 - 80,000,000 (NCDC, 2019).

Table 3: Baseline values and ranges of the parameters of the Malaria-dengue model, with the total population (N_h) of Nigeria as of 3rd of August 2019 estimated at 199,707,545 (Worldometer, 2019).

Parameters	Baseline values	Ranges	References
Λ_h	4,076,031 year^{-1}	[4,000,000, 4,500,00]	Worldometer (2019)
Λ_m	10,000,000 year^{-1}	[8,000,000, 12,000,000]	Blayneh *et al.* (2009)
Λ_d	10,000,000 year^{-1}	[8,000,000, 12,000,000]	Garba *et al.* (2008)
μ_h	0.02041 year^{-1}	[0.0143, 0.03]	UNAIDS (2014)
μ_m	0.75year^{-1}	[0.5, 0.8]	Labadin *et al.* (2009)
μ_d	0.365year^{-1}	[0.2, 0.4]	Blayneh *et al.* (2009)
β_{vm}	0.5 year^{-1}	[0.2. 0.8]	Labadin *et al.* (2009)
β_{vd}	0.09 year^{-1}	[0.05, 0.5]	Garba *et al.* (2008)
β_m	0.75 year^{-1}	[0.5, 0.9]	Olaniyi and Obabiyi (2013)
β_d	0.833 year^{-1}	[0.5, 0.9]	Garba *et al.* (2008)
b_m	0.13 year^{-1}	[0.09, 0.5]	Olaniyi and Obabiyi (2013)
b_d	0.12 year^{-1}	[0.08, 0.5]	Assumed
γ_m	0.499 year^{-1}	[0.1, 0.8s]	Blayneh *et al.* (2009)
γ_{mr}	0.1 year^{-1}	[0.08, 0.5]	Assumed
γ_{dr}	0.428 year^{-1}	[0.1, 0.6]	Assumed
γ_d	2.5 year^{-1}	[2, 3]	Garba *et al.* (2008)
Ψ_m	0.00457 year^{-1}	[0.001, 0.01]	Blayneh *et al.* (2009)
Ψ_{mr}	0.00017year^{-1}	[0.0001, 0.001]	Niger and Gumel (2008)
τ_m	0.56 year^{-1}	[0.2, 0.9]	Labadin *et al.* (2009)
τ_d	0.44 year^{-1}	[0.2, 0.9]	Assumed
d_m	0.001 year^{-1}	[0.0009, 0.005]	Assumed
d_{mw}	0.01 year^{-1}	[0.005, 0.002]	Labadin *et al.* (2009)
d_{mr}	0.002 year^{-1}	[0.001, 0.005]	Assumed
d_1	0.0365 year^{-1}	[0.01, 0.05]	Assumed
d_2	0.01 year^{-1}	[0.005, 0.02]	Assumed
d_3	0.02 year^{-1}	[0.01, 0.05]	Assumed
$\theta_m, \theta_{mr}, \theta_d$	0-1	[0, 1]	Assumed
$\emptyset_6$	0.5 year^{-1}	[0.1, 0.9]	Niger and Gumel (2008)
$\emptyset_3$	0.3 year^{-1}	[0.1, 0.9]	Niger and Gumel (2008)
$\emptyset_1, \emptyset_2, \emptyset_4, \emptyset_5, \emptyset_7, \emptyset_8$	0-1	[0, 1]	Assumed
γ_1	0.6 year^{-1}	[0.1, 0.9]	Niger and Gumel (2008)
γ_2	0.5 year^{-1}	[0.1, 0.9]	Niger and Gumel (2008)

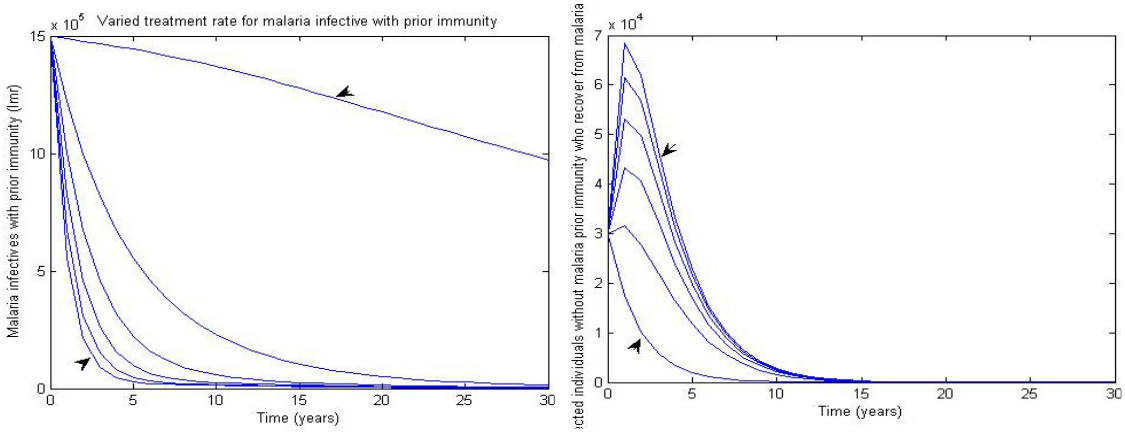
3. RESULTS AND DISCUSSION

In this work, the treatment rate for singly infected and co-infected individuals, the rate of treatment for co-infected individuals with malaria prior immunity and the parameter for reduction in infectiousness due to malaria prior immunity were varied. Figure 1 shows the number of malaria infected individuals and co-infected individuals without malaria prior immunity as the rate of malaria treatment (γ_m and τ_m) for singly infected individuals and co-infected individuals respectively was varied. The simulations revealed that varying the treatment rate for singly infected and co-infected individuals, the number of infected individuals (single and co-infected) reduced. Figure 2 shows the number of malaria infected individuals and co-infected individuals with malaria prior immunity as we vary the rate of malaria treatment (γ_{mr} and τ_m $with$ $\emptyset_5 = 1$) for singly infected individuals and coinfected individuals respectively. The simulation reveals that much effect is not attained if the treatment rate is 1 but increasing the rate of treatment to 5 would lead to a reduction of single infected individuals who have prior immunity to malaria infection. Similarly varying the rate of treatment for co-infected individuals with malaria prior immunity will reduce the population of co-infected individuals with malaria prior immunity.



(a) (b)

Figure 1: Plots of the number of malaria infected and co-infected individuals without malaria prior immunity. (a) the treatment rate (γ_m) is varied from 1 to 5. (b) malaria treatment rate (τ_m) for co-infected individuals is varied from 0 to 1



(a) (b)

Figure 2: Plots of the number of malaria infected and co-infected individuals with malaria prior immunity. (a) the treatment rate (γ_{mr}) is varied from 1 to 5. (b) the malaria treatment rate (τ_m) for coinfected individuals is varied from 0 to1 with the modification parameter ($\emptyset_5$) = 1

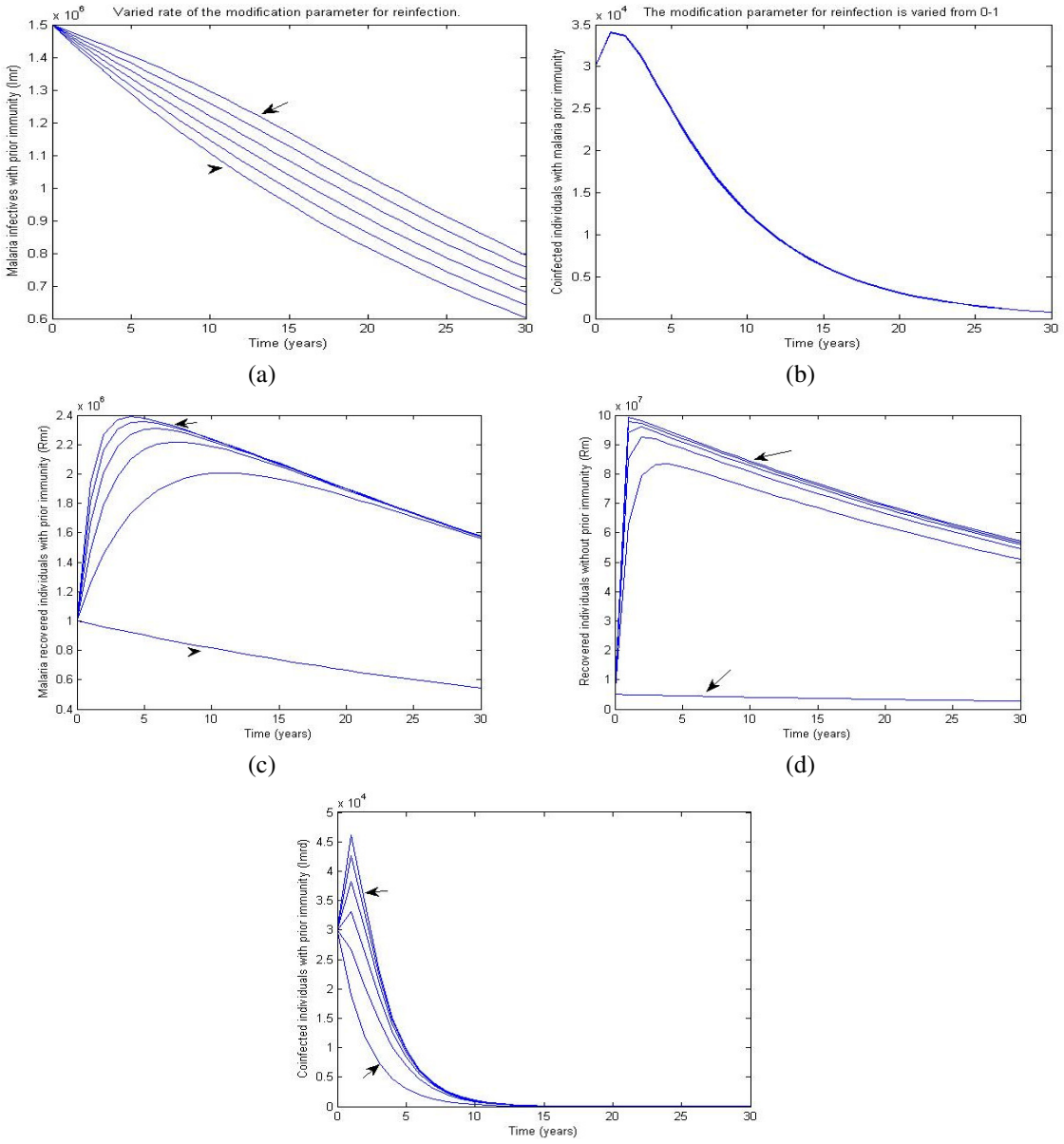


Figure 3: Plots of the number of malaria infected individuals with prior immunity, recovered individuals with and without malaria prior immunity and coinfected individuals with malaria prior immunity. (a) the rate of reduction in infectiousness due to ($\emptyset_6$) is varied from 0 to 1. (b) the modification parameter for reinfection is varied from 0-1 (c) The malaria treatment rate (γ_{mr}) for infected individuals is varied from 0 to1. (d) The malaria treatment rate (γ_m) is varied from 1 to 5. (e) Treatment rate for malaria infection (τ_m) varied from 0-1 with the modification parameter ($\emptyset_5$) set at 1

Figure 3(a) revealed that varying the parameter for reduction in infectiousness due to malaria prior immunity will lead to reduction of malaria infectives with prior immunity. Varying the modification parameter for re-infection for co-infected individuals with malaria prior immunity has no effect on the population of co-infected individuals with high treatment rates as shown in Figure 3(b). Similarly, varying the parameter for

treatment of infected individuals with prior immunity increases the population of recovered individuals with prior immunity as seen in Figure 3(c). A treatment rate of unity decreases the population of recovered individuals which implies that for effective increase of recovered individuals with prior immunity to be achieved, the recovery rate should be very high as seen in Figure 3(d). In the same vein, if the treatment rate for infected individuals is 1, then there would be no effect on the population of recovered individuals without prior immunity. Figure 3(e) shows that the population of co-infected individuals with malaria prior immunity will decrease as the rate of treatment for malaria is increased.

A pertinent feature of malaria disease is that, in regions where malaria is endemic, humans develop natural immunity to malaria after several exposures; and such immunity has a large effect on how the disease spreads. Low exposure to malaria is a vaccination, and leads to the development of immunity to the disease. The findings in our numerical simulations shows with low rate of treatment the population of recovered individuals with prior immunity will decrease but increasing the rate of treatments for recovered individual will increase this population. Niger and Gumel (2008) had opined that there were three aspects of immunity that are acquired at different rates: loss of infectivity, increase in recovery and decrease in ability to be detected. This strengthens the results obtained from the simulation of recovered individuals due to malaria prior immunity. The results also revealed that if high rate of malaria treatment is applied to the co- infected population with or without malaria prior immunity, the co-infection can be reduced if not totally eliminated overtime. Furthermore, the results from this study have shown that if re-infection occurs for the individuals in the susceptible class who have had prior immunity, there would be reduction in infectiousness due to the immunity developed before and according to Niger and Gumel (2008), the infectivity will be reduced. This implies that continuous exposure to malaria infection overtime in endemic areas builds a measure of immunity to the disease and this has a far reaching effect on the transmission dynamics of malaria-dengue co-infection.

4. CONCLUSION

A new mathematical model for the transmission dynamics of malaria-dengue co-infection in a population is designed and used to assess the impact of treatment of malaria on single and co-infected individuals with and without malaria prior immunity on the co-endemicity of both diseases in a population. Qualitative analysis revealed that both diseases enhance each other. This result shows that one disease affects the other as both diseases have the same signs and symptoms such that one disease can be mistaken for another. Furthermore, the qualitative analysis of the model revealed that the model does undergo the phenomenon of backward bifurcation due to the presence of the reduced probability of re-infection by recovered individuals due to malaria prior acquired immunity, the slower rate of treatment of individuals infected with malaria, the susceptibility of malaria-infected individuals to dengue infection, the probability of effective transmission of malaria from infectious humans to susceptible *Anopheles* vectors, and the probability of effective transmission of dengue infection from infectious humans *Aedes* a*egypti* vectors. Numerical study of model was carried out to assess the impact of various treatment strategies for malaria on the dynamics of both diseases in the population. Results from this study revealed that the specific class of infected individuals whose malaria treatment is varied is of great importance if the co-infection is to be reduced significantly. In particular, the numerical results show that concentrating treatment on infected individuals with and without malaria prior immunity (singly or dually infected with dengue) will go a long way reducing the co-infection, as well as the incidence of dengue in the population. The results of this work have revealed that the prospect of effectively controlling the spread of malaria-dengue co-infection in a population, where treatment of malaria for individuals who have prior immunity to malaria infection and those who have not been infected before, is very bright.

5. ACKNOWLEDGMENT

The authors wish to acknowledge the assistance and contributions of the members of the Mathematical, Computational and Statistical Biology Research Group, Department of Mathematics, University of Benin, Benin City, Nigeria, towards the success of this work.

6. CONFLICT OF INTEREST

There is no conflict of interest associated with this work.

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