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Modeling the Effect of Misdiagnosis in the Co-circulation and Co-infection of Dengue and Zika Virus Disease

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Abstract

Dengue and Zika are flavivirus diseases that spread through bites of Aedes aegypti, a mosquito in the Aedes family. There have been emerging reports of co-infection of these two diseases in humans and Aedes aegypti in the areas where the two diseases are prevalent. More so, the two diseases are known to manifest similar characteristic symptoms, which makes misdiagnosis and wrong treatment possible. Therefore, this paper models the co-circulation and co-infection of dengue and Zika virus diseases in human and mosquito populations with a system of non-linear ordinary differential equations. It is shown that the disease-free equilibrium of the model may not be globally asymptotically stable due to the re-infection of infected humans and mosquitoes by the other disease. The impact of misdiagnosis of the diseases is investigated, which shows that misdiagnosis would increase the spread of the diseases if the proportion of humans that are accurately diagnosed and treated is more than the rate of recovery of humans that are wrongly diagnosed and treated. Positive constants are obtained, which give the rates at which the spread of one disease affects the spread of the other. Plots are given to visualize these important results.

Keywords: Dengue, Zika virus disease, Aedes aegypti, co-infection; Misdiagnosis
2010 MSC: 92B05, 93A30, 34D20

1. Introduction

One of the vector-borne diseases predominant in the tropics and subtropics is dengue fever caused by Flavivirus, which is transmitted to humans by the Aedes aegypti mosquito. The disease is characterized by four serotypes with the common symptom as fever, which is usually associated with severe body pains. When an individual infected with one type of fever is infected with another serotype, the individual conditions become complicated, which could result in death[1]. Moreover, a person's recovery from one particular dengue serotype leads to permanent immunity to the same serotype and partial or temporary immunity to the other serotypes [2]. Dengue viral infection has recently been estimated to be around 50 million cases yearly, of which 500,000 are admitted to hospitals for medical care, and about 12,500 death cases are recorded in the world. The disease is currently

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common in urban and semi-urban environments and spreads faster in tropical regions, becoming one of the leading causes of death [3]. Zika virus disease is another emerging Flavivirus disease that is transmitted by the same Aedes aegypti mosquito. The clinical presentation of Zika virus disease is extremely complex and can be easily misdiagnosed to be other infectious illnesses like dengue. The disease is known to be associated with mild sickness until the outbreak in French Polynesia that occurred during 2013-2014 with severe neurological complications [4]. Zika virus has been detected in serum, urine, and semen, and Zika virus infection in some pregnant women has been associated with congenital brain abnormalities in the newborn and Guillain-Barré Syndrome in adults[5, 6, 7, 8]. This made the World Health Organization declare the Zika epidemic a Public Health Emergency of International Concern in February 2016[9]. Symptoms of Zika virus disease are similar to other viral diseases transmitted through mosquito bites, such as dengue, malaria, and chikungunya. Several documented experimental reports have been on the co-infection of dengue and Zika virus disease in humans in the areas where the two diseases are co-circulating [10, 11, 12]. For instance, co-infection of Dengue and Zika virus disease has been identified in two patients in New Caledonia after undergoing a series of tests[16]. Several cases may exist in a similar environment where the two diseases are common, particularly in Southern America. Co-circulation of dengue and Zika virus disease makes their diagnoses and treatment a challenge to health professionals, especially due to their similar clinical manifestations. A majority of co-infected individuals reported symptoms of myalgia, headache, fever, exanthema, and arthralgia, and a minority of them reported conjunctival hyperemia, abdominal pain, and vomiting [13, 14]. Due to the similarity of their symptoms, it has been advised that drugs such as aspirin, ibuprofen, naproxen, and other non-steroidal anti-inflammatory drugs are not to be taken for Zika virus disease until infection with dengue is completely ruled out to avoid the risk of bleeding [15]. A couple of mathematical models have been proposed to understand the co-infection dynamics of the two diseases in human and mosquito populations[16, 17]. However, the model we propose in this work includes the simultaneous transmission of viruses from co-infected humans and mosquitoes to susceptible mosquitoes and humans, respectively. In addition, we introduce compartments of humans that are misdiagnosed with one disease as the other. This will enable us to determine the impact of misdiagnoses on the spread of the diseases. The remaining part of this work is organized as follows: in section two, the models are presented, which include the sub-models for dengue and Zika virus disease dynamics and the full co-infection model, with their analyses. In section 3, we have the impact of misdiagnosis on the transmission of the diseases, and in section 4, we presented the impact of the spread of one disease on the other. Section 5 has a simulation of the model, discussion, and conclusion of the work.

2. Model Formulation and Analysis

Three models are formulated in this section. These are the Zika-only sub-model, the dengue-only sub-model, and the full co-infection model, a combination of the sub-models. The models are formulated based on the assumption that humans, under certain probability, may contract any of the diseases or both when bitten by mosquitoes infected with Zika virus, dengue virus, or both. In the same way, mosquitoes contract any diseases when they bite humans infected with dengue, Zika virus disease, or both.

2.1. *Zika-only Model*

Here, we present Zika-only model which describes the dynamics of Zika virus disease in human and mosquito population. We propose a five-compartment model for humans which are the susceptible(S_h), Humans infectious with Zika virus disease(I_{hz}), infectious humans receiving dengue treatment due to mis-diagnosis(T_d), infectious humans receiving treatment for Zika virus disease(T_{hz}), infectious humans who have recovered from Zika virus infection(R_h). In the aedes aegypti mosquito population, we have two compartments namely, mosquitoes that are susceptible to Zika virus disease(S_m) and mosquitoes that are infectious with Zika virus disease(I_{mz}). Based on these compartments as shown in fig. 1, we have the following system of nonlinear ordinary differential equations,

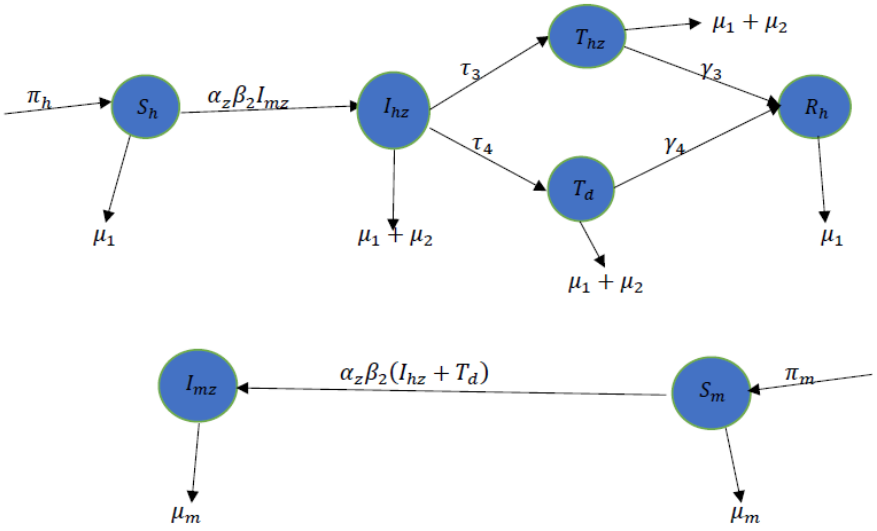

Figure 1: Zika-only Flow Diagram

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \pi_h - \alpha_z\beta_2 I_{mz} S_h(t) - \mu_1 S_h,\\
\frac{dI_{hz}(t)}{dt} &= \alpha_z\beta_2 I_{mz} S_h(t) - (\tau_3+\tau_4+\mu_1+\mu_2) I_{hz},\\
\frac{dT_{hz}(t)}{dt} &= \tau_3 I_{hz} - (\gamma_3+\mu_1+\mu_2) T_{hz}(t),\\
\frac{dT_d(t)}{dt} &= \tau_4 I_{hz} - (\gamma_4+\mu_1+\mu_2) T_d(t),\\
\frac{dR_h(t)}{dt} &= \gamma_4 T_d + \gamma_3 T_{hz} - \mu_1 R_h(t),\\
\frac{dS_m(t)}{dt} &= \pi_m - (\alpha_z\beta_2 I_{hz} + \alpha_z\beta_2 T_d) S_m(t) - \mu_m S_m,\\
\frac{dI_{mz}(t)}{dt} &= (\alpha_z\beta_2 I_{hz} + \alpha_z\beta_2 T_d) S_m(t) - \mu_m I_{mz}.
\end{aligned}
\tag{2.1}
$$

Let the initial solution to the system (2.1) be given as $X_0 = (S_h^0, I_{hz}^0, T_{hz}^0, T_d^0, R_h^0, S_m^0, I_{mz}^0)$. We assume that the system has a unique positive solution $X(t)$ which passes through X_0. In the above model, humans and mosquitoes are recruited into the susceptible humans and susceptible mosquitoes, respectively, at the rates π_h and π_m. The parameter, α_z represents the transmission probability of Zika virus from infectious mosquito to human and vice versa, while β_2 is the biting rate of mosquitoes that carry Zika virus disease. Furthermore, τ_3 is the proportion of infectious humans that are receiving treatment for Zika virus disease, and τ_4 is the proportion of infectious humans that are receiving wrong treatment for Zika virus disease. The rate of recovery for humans that are receiving treatment for Zika virus disease is γ_3, while γ_4 is the recovery rate humans that are being treated wrongly. The natural mortality rates for all humans and mosquitoes are μ_1 and μ_m, respectively, while μ_2 is the Zika-induced mortality rate for all the infected humans.

2.1.1. Zika-free Equilibrium and Basic Reproduction Number of Zika Virus Disease

The Zika-only sub-model has Zika-free equilibrium $E_0^z = \left(\frac{\pi_h}{\mu_1}, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}, 0\right)$, obtained by solving $f(X(t)) = 0$ when the populations are free of Zika infection. That is when $I_{hz} = T_{hz} = T_d = I_{mz} = 0$. The basic reproduction number, $\mathcal{R}_{0z}$ of Zika virus disease is the average number of persons that can be infected by an index case of the disease when introduced in a Zika-free environment. This important number determines the ability of Zika virus disease to spread quickly in the population or to die out gradually. The next generation matrix method determines basic reproduction number as the spectral radius of the next generation matrix(FV^{-1}), where F and V are $n \times n$ Jacobian matrices obtained from the model equations, and n is the number of infected classes in the model[18]. Using the next generation matrix method, the matrices F and V are

$$F_z = \begin{pmatrix} 0 & 0 & 0 & \frac{\alpha_z \beta_2 \pi_h}{\mu_1} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\alpha_z \beta_2 \pi_m}{\mu_m} & 0 & \frac{\alpha_z \beta_2 \pi_m}{\mu_m} & 0 \end{pmatrix}$$

,

$$V_z = \begin{pmatrix} \tau_3 + \tau_4 + \mu_1 + \mu_2 & 0 & 0 & 0 \\ -\tau_3 & \gamma_3 + \mu_1 + \mu_2 & 0 & 0 \\ -\tau_4 & 0 & \gamma_4 + \mu_1 + \mu_2 & 0 \\ 0 & 0 & 0 & \mu_m \end{pmatrix}.$$

The next generation matrix is therefore

$$F_z V_z^{-1} = \begin{pmatrix} 0 & 0 & 0 & \frac{\alpha_z \beta_2 \pi_h}{\mu_1 \mu_m} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\alpha_z \beta_2 \pi_m}{\mu_m(\tau_3+\tau_4+\mu_1+\mu_2)} + \frac{\alpha_z \beta_2 \pi_m \tau_4}{\mu_m(\tau_3+\tau_4+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2)} & 0 & \frac{\alpha_z \beta_2 \pi_m}{\mu_m(\gamma_4+\mu_1+\mu_2)} & 0 \end{pmatrix},$$

with the eigenvalues $0, 0, \pm\sqrt{\frac{\alpha_z^2\beta_2^2\pi_h\pi_m(\gamma_4+\mu_1+\mu_2+\tau_4)}{\mu_1\mu_m^2(\gamma_4+\mu_1+\mu_2)(\tau_3+\tau_4+\mu_1+\mu_2)}}$. Therefore, the basic reproduction number of Zika virus is

$$\mathcal{R}_{0z}^2 = \frac{\alpha_z^2\beta_2^2\pi_h\pi_m}{\mu_1\mu_m^2(\tau_3+\tau_4+\mu_1+\mu_2)} + \frac{\alpha_z^2\beta_2^2\pi_h\pi_m\tau_4}{\mu_1\mu_m^2(\gamma_4+\mu_1+\mu_2)(\tau_3+\tau_4+\mu_1+\mu_2)}, \tag{2.2}$$

The term, $\frac{\alpha_z^2\beta_2^2\pi_h\pi_m\tau_4}{\mu_1\mu_m^2(\gamma_4+\mu_1+\mu_2)(\tau_3+\tau_4+\mu_1+\mu_2)}$, in (2.2) is the average number of humans and mosquitoes that can be infected due to mis-diagnosis and and wrong treatment.

2.1.2. Local Asymptotic Stability of Zika-free Equilibrium

The Jacobian matrix of Zika-only sub-model evaluated at the Zika-free equilibrium is

$$J(E_0^z) = \begin{pmatrix} -\mu_1 & 0 & 0 & 0 & 0 & 0 & -\frac{\alpha_z\beta_2\pi_h}{\mu_1} \\ 0 & -(\tau_3+\tau_4+\mu_1+\mu_2) & 0 & 0 & 0 & 0 & \frac{\alpha_z\beta_2\pi_h}{\mu_1} \\ 0 & \tau_3 & -(\gamma_3+\mu_1+\mu_2) & 0 & 0 & 0 & 0 \\ 0 & \tau_4 & 0 & -(\gamma_4+\mu_1+\mu_2) & 0 & 0 & 0 \\ 0 & 0 & \gamma_3 & \gamma_4 & -\mu_1 & 0 & 0 \\ 0 & -\frac{\alpha_z\beta_2\pi_m}{\mu_m} & 0 & -\frac{\alpha_z\beta_2\pi_m}{\mu_m} & 0 & -\mu_m & 0 \\ 0 & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & 0 & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & 0 & 0 & -\mu_m \end{pmatrix}.$$

The Zika-free equilibrium, E_0^z, is locally asymptotically stable if all the eigenvalues of $J(E_0^z)$ have negative real parts. If we remove the rows and the columns that contain the eigenvalues $-\mu_1, -\mu_1, -\mu_m, -(\gamma_3+\mu_1+\mu_2)$ we obtain 3×3 submatrix

$$J_1(E_0^z) = \begin{pmatrix} -(\tau_3+\tau_4+\mu_1+\mu_2) & 0 & \frac{\alpha_z\beta_2\pi_h}{\mu_1} \\ \tau_4 & -(\gamma_4+\mu_1+\mu_2) & 0 \\ \frac{\alpha_z\beta_2\pi_m}{\mu_m} & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & -\mu_m \end{pmatrix}.$$

Observe that the submatrix, $-J_1(E_0^z)$ has Z-pattern. That is, the elements of $-J_1(E_0^z)$ satisfy $-a_{ik} \leqslant 0,\ \forall\ i \neq k$. A matrix with Z-pattern is called a non-singular M-matrix if all its principal leading minors are positive, and all eigenvalues of a non-singular M-matrix are positive or have positive real parts[19]. The principal leading minors of $-J_1(E_0^z)$ are $\tau_3+\tau_4+\mu_1+\mu_2 > 0, (\tau_3+\tau_4+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2) > 0$ and $\mu_m(\tau_3+\tau_4+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2)(1-\mathcal{R}_{0z}^2)$, which are all positve if $\mathcal{R}_{0z}^2 < 1$. This indicates that all eigenvalues of $-J_1(E_0^z)$ are positive if $\mathcal{R}_{0z} < 1$. This means that all the eigenvalues of $J_1(E_0^z)$ are negative if $\mathcal{R}_{0z} < 1$. This shows that E_0^z is locally asymptotically stable if $\mathcal{R}_{0z} < 1$, and unstable if $\mathcal{R}_{0z} > 1$. This implies that in the absence of dengue, Zika virus disease can be eradicated when $\mathcal{R}_{0z} < 1$, if the initial size of the compartments are in the basin of attraction of the Zika-free equilibrium[20].

2.1.3. Existence of Endemic Equilibrium

Let $E_1 = (S_h^*, I_{hz}^*, T_d^*, T_{hz}^*, R_h^*, S_m^*, I_{mz}^*)$ be an arbitrary equilibrium point of (1), where $S_h^* = \frac{\pi_h}{\alpha_z\beta_2 I_{mz}^*+\mu_1}, I_{hz}^* = \frac{\alpha_z\beta_2 I_{mz}^* S_h^*}{\tau_3+\tau_4+\mu_1+\mu_2}, T_d^* = \frac{\tau_4 I_{hz}^*}{\gamma_4+\mu_1+\mu_2}, T_{hz}^* = \frac{\tau_3 I_{hz}^*}{\gamma_3+\mu_1+\mu_2}, R_h^* = \frac{\gamma_3 I_{hz}^*+\gamma_4 T_d^*}{\mu_1}, S_m^* =$

$\frac{\pi_m}{\alpha_z\beta_2(I^*_{hz}+T^*_d)+\mu_m}$,
$I^*_{mz} = \frac{\alpha_z\beta_2(I^*_{hz}+T^*_d)S^*_m}{\mu_m}$. That is E_1 solves the system

$$\begin{aligned}
\pi_h - \alpha_z\beta_2 I^*_{mz}S^*_h - \mu_1 S^*_h &= 0, && (2.3)\\
\alpha_z\beta_2 I^*_{mz}S^*_h - (\tau_3+\tau_4+\mu_1+\mu_2)I^*_{hz} &= 0, && (2.4)\\
\tau_3 I^*_{hz} - (\gamma_3+\mu_1+\mu_2)T^*_{hz} &= 0, && (2.5)\\
\tau_4 I^*_{hz} - (\gamma_4+\mu_1+\mu_2)T^*_d &= 0, && (2.6)\\
\gamma_4 T^*_d + \gamma_3 T^*_{hz} - \mu_1 R^*_h &= 0, && (2.7)\\
\pi_m - (\alpha_z\beta_2 I^*_{hz} + \alpha_z\beta_2 T^*_d)S^*_m - \mu_m S^*_m &= 0, && (2.8)\\
(\alpha_z\beta_2 I^*_{hz} + \alpha_z\beta_2 T^*_d)S^*_m - \mu_m I^*_{mz} &= 0, && (2.9)
\end{aligned}$$

Substitution of E_1 into (2.4), and arranging gives the equation
$\frac{\alpha_z^2\beta_2^2\pi_h\pi_m(\gamma_4+\mu_1+\mu_2+\tau_4)I^*_{hz}}{\mu_1\mu_m^2(\gamma_4+\mu_1+\mu_2)+\mu_1\mu_m\alpha_z\beta_2(\gamma_4+\mu_1+\mu_2+\tau_4)I^*_{hz}+\alpha_z^2\beta_2^2\pi_m(\gamma_4+\mu_1+\mu_2+\tau_4)} - (\tau_3+\tau_4+\mu_1+\mu_2)I^*_{hz} = 0$,
which can be written in the form

$$I^*_{hz}(A_1 - A_2 I^*_{hz}) = 0, \qquad (2.10)$$

where $A_1 = \mu_1\mu_m^2(\tau_3+\tau_4+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2)(\mathcal{R}^2_{0z}-1), A_2 = \alpha_z\beta_2(\tau_3+\tau_4+\mu_1+\mu_2)(\mu_1\mu_2+\alpha_z\beta_2\pi_m)$
The trivial solution $I_{hz} = 0$ to (2.10) gives the Zika-free equilibrium already proved to be locally asymptotically stable when $\mathcal{R}_{0z} < 1$. Since $A_2 > 0$, the remaining solution to (2.10) would be positive if $A_1 > 0$, or precisely if $\mathcal{R}_{0z} > 1$. This shows that the model has a unique endemic equilibrium which exists if $\mathcal{R}_{0z} > 1$. This rules out possible occurrence of backward bifurcation in the model, since backward bifurcation requires at least two endemic equilibria, to occur. Epidemiologically, this means that having $\mathcal{R}_{0z} < 1$, is a necessary and sufficient condition for eradicating Zika virus disease in the population.

2.2. Dengue-only sub-Model

We assume that dengue infection follows similar transmission dynamics as Zika virus disease. There are five compartments for humans namely the susceptible(S_h), Humans infectious with dengue(I_{hd}), infectious humans receiving Zika treatment due to mis-diagnosis(T_z), infectious humans receiving treatment for dengue(T_{hd}), infectious humans who have recovered from dengue(R_h). On the other hand, in the aedes aegypti population, we have two compartments namely, mosquitoes that are susceptible to dengue(S_m), and mosquitoes that are infectious with dengue, (I_{md}). The level of recruitment of humans into the susceptible class is π_h. The infectious mosquitoes bite humans at the rate β_1 , and transmit dengue virus with probability, α_d. We assume that the proportion τ_1 of the infectious humans receive treatment for dengue, while the proportion τ_2 receive treatment for Zika due to mis-diagnosis. The rates of recovery for (T_{hd}) and (T_z) are put at γ_1 and γ_2, respectively. Also,μ_1 and μ_m are the natural mortality rates for humans and mosquitoes, respectively, while μ_2 is the dengue-induced mortality rate for all the infected humans. In the mosquito population, the level of recruitment of mosquitoes into the susceptible class is π_m. The susceptible class of mosquitoes contracts dengue virus with the

probability α_d, when they bite humans in the infectious classes I_{hd} and T_z at the biting rate β_1. The above assumptions on the transmission dynamics of dengue leads to the following system of nonlinear ordinary differential equations with the flow diagram shown in fig. 2

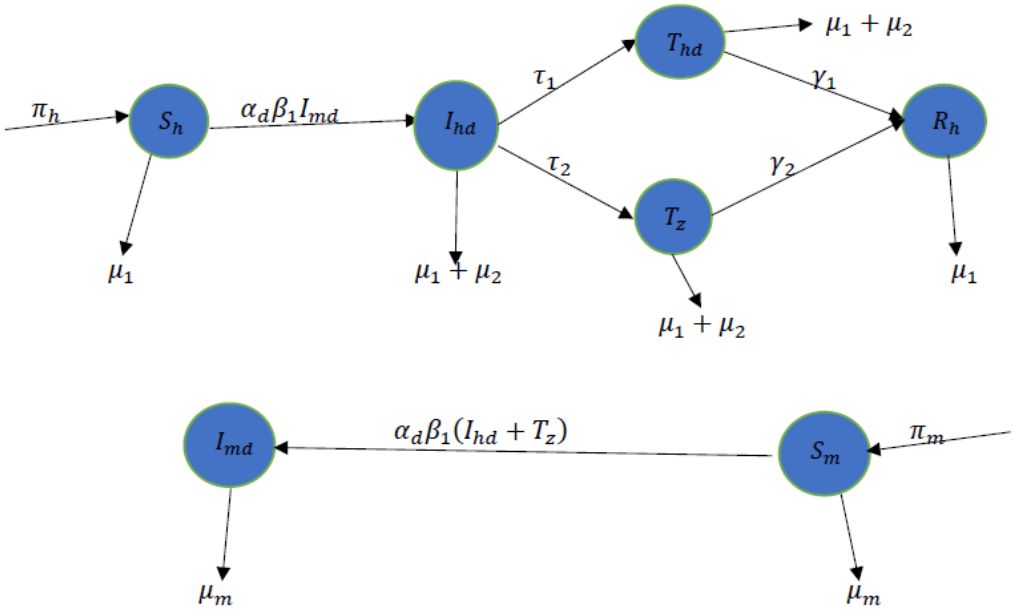

Figure 2: Dengue-only Flow Diagram

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \pi_h - \alpha_d\beta_1 I_{md} S_h(t) - \mu_1 S_h, \\
\frac{dI_{hd}(t)}{dt} &= \alpha_d\beta_1 I_{md} S_h(t) - (\tau_1 + \tau_2 + \mu_1 + \mu_2) I_{hd}, \\
\frac{dT_{hd}(t)}{dt} &= \tau_1 I_{hd} - (\gamma_1 + \mu_1 + \mu_2) T_{hd}(t), \\
\frac{dT_z(t)}{dt} &= \tau_2 I_{hd} - (\gamma_2 + \mu_1 + \mu_2) T_z(t), \\
\frac{dR_h(t)}{dt} &= \gamma_2 T_z + \gamma_1 T_{hd} - \mu_1 R_h(t), \\
\frac{dS_m(t)}{dt} &= \pi_m - \alpha_d\beta_1 (I_{hd} + T_z) S_m(t) - \mu_m S_m, \\
\frac{dI_{md}(t)}{dt} &= \alpha_d\beta_1 (I_{hd} + T_z) S_m(t) - \mu_m I_{md},
\end{aligned}
\tag{2.11}
$$

Let the initial solution to the system (2.11) be given as $Y_0 = (S_h^0, I_{hd}^0, T_{hd}^0, T_z^0, R_h^0, S_m^0, I_{md}^0)$. We assume that the system (2.11) has a unique positive solution $Y(t)$ which passes through Y_0.

2.2.1. Dengue-free Equilibrium and Basic Reproduction Number of Dengue

The next generation matrix for dengue-only model is

$$F_d V_d^{-1} = \begin{pmatrix} 0 & 0 & 0 & \frac{\alpha_d \beta_1 \pi_h}{\mu_1 \mu_m} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\alpha_d \beta_1 \pi_m}{\mu_m(\tau_1+\tau_2+\mu_1+\mu_2)} + \frac{\alpha_d \beta_1 \pi_m \tau_2}{\mu_m(\tau_1+\tau_2+\mu_1+\mu_2)(\gamma_2+\mu_1+\mu_2)} & 0 & \frac{\alpha_d \beta_1 \pi_m}{\mu_m(\gamma_2+\mu_1+\mu_2)} & 0 \end{pmatrix}.$$

Hence, the basic reproduction number for dengue infection is

$$\mathcal{R}_{0d} = \sqrt{\frac{\alpha_d^2 \beta_1^2 \pi_h \pi_m}{\mu_1 \mu_m^2(\tau_1+\tau_2+\mu_1+\mu_2)} + \frac{\alpha_d^2 \beta_1^2 \pi_h \pi_m \tau_2}{\mu_1 \mu_m^2(\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)}}.$$

As in the case of Zika-sub model, the term $\frac{\alpha_d^2 \beta_1^2 \pi_h \pi_m \tau_2}{\mu_1 \mu_m^2(\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)}$ is the average number of humans and mosquitoes that would be infected due to the proportion, τ_2 of infected humans that are wrongly treated.

2.2.2. Local Asymptotic Stability of dengue-free Equilibrium

The Jacobian matrix of dengue-only sub-model evaluated at the dengue-free equilibrium is

$$J(E_0^d) = \begin{pmatrix} -\mu_1 & 0 & 0 & 0 & 0 & 0 & -\frac{\alpha_d \beta_1 \pi_h}{\mu_1} \\ 0 & -(\tau_1+\tau_2+\mu_1+\mu_2) & 0 & 0 & 0 & 0 & \frac{\alpha_d \beta_1 \pi_h}{\mu_1} \\ 0 & \tau_1 & -(\gamma_1+\mu_1+\mu_2) & 0 & 0 & 0 & 0 \\ 0 & \tau_2 & 0 & -(\gamma_2+\mu_1+\mu_2) & 0 & 0 & 0 \\ 0 & 0 & \gamma_1 & \gamma_2 & -\mu_1 & 0 & 0 \\ 0 & -\frac{\alpha_d \beta_1 \pi_m}{\mu_m} & 0 & -\frac{\alpha_d \beta_1 \pi_m}{\mu_m} & 0 & -\mu_m & 0 \\ 0 & \frac{\alpha_d \beta_1 \pi_m}{\mu_m} & 0 & \frac{\alpha_d \beta_1 \pi_m}{\mu_m} & 0 & 0 & -\mu_m \end{pmatrix}.$$

The dengue-free equilibrium E_0^d is locally asymptotically stable if all the eigenvalues of $J(E_0^d)$ have negative real part. It is easy to see that the eigenvalues of $J(E_0^d)$ are $-\mu_1, -\mu_1, -\mu_m, -(\gamma_1+\mu_1+\mu_2)$, and the eigenvalues of the sub-matrix

$$J_1(E_0^d) = \begin{pmatrix} -(\tau_1+\tau_2+\mu_1+\mu_2) & 0 & \frac{\alpha_d \beta_1 \pi_h}{\mu_1} \\ \tau_2 & -(\gamma_2+\mu_1+\mu_2) & 0 \\ \frac{\alpha_d \beta_1 \pi_m}{\mu_m} & \frac{\alpha_d \beta_1 \pi_m}{\mu_m} & -\mu_m \end{pmatrix}.$$

The matrix, $-J_1(E_0^d)$, has Z-pattern, and its principal leading minors are $\tau_1+\tau_2+\mu_1+\mu_2 > 0, (\tau_1+\tau_2+\mu_1+\mu_2)(\gamma_2+\mu_1+\mu_2) > 0$ and $\mu_m(\tau_1+\tau_2+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2)(1-\mathcal{R}_{0d}^2)$. Hence, -$J_1(E_0^d)$ is a non-singular M-matrix if $\mathcal{R}_{0d} < 1$. This implies that all the eigenvalues of $J_1(E_0^d)$ are negative or have negative real part if $\mathcal{R}_{0d} < 1$. Therefore, the dengue-free equilibrium, E_0^d is locally asymptotically stable if $\mathcal{R}_{0d} < 1$, and unstable if $\mathcal{R}_{0d} > 1$.

It can also be shown, using the same method for Zika-only model that dengue-only model has a unique endemic equilibrium if $\mathcal{R}_{0d} > 1$. Hence, backward bifurcation does not happen in the dengue-only sub-model..

2.3. The Co-infection Model

The full model is derived by combining the two sub-models, and including the compartments of humans and mosquitoes that are co-infected with dengue and Zika virus disease. It is assumed that at the beginning ($t = 0$), there is no coinfection. To be precise, the class, I_{hdz}, of humans who are infected with both dengue and Zika, and the class, T_{hdz}, of humans receiving treatment for co-infection are added to the human population. Similarly, the class, I_{mdz}, of mosquitoes that are infected with both dengue and Zika is added to the mosquito population. It is assumed that when mosquitoes in the class I_{mdz} bites susceptible humans, they transmit either dengue virus, Zika virus or both viruses, with probabilities α'_d, α'_zor α_{dz}, respectively, where $\alpha'_d < \alpha_d$ and $\alpha'_z < \alpha_z$, with biting rate β_3. On the other hand, humans that are co-infected with dengue and Zika virus disease transmits dengue, Zika, or both to susceptible mosquitoes with the same probabilities, α'_d, α'_z or α_{dz}. The proportion τ_5 of I_{hdz} receive treatment for both dengue and Zika virus disease at the rate γ_5. Further, co-infection can also occur when humans in the class, I_{hz}, transmit Zika virus to mosquitoes in the class, I_{md}, and when mosquitoes in the class, I_{md}, transmit dengue virus to humans in the class I_{hz}, and they become co-infected with dengue and Zika virus disease. The same scenario occurs between the classes, I_{hd} and I_{mz}. It is to be noted that in the human population, the classes T_z and T_d also have the capacities to transmit dengue and Zika virus disease respectively to susceptible mosquitoes, since they are receiving wrong treatments due to mis-diagnosis.

Taking $f_1 = (\alpha_d\beta_1 I_{md} + \alpha'_d\beta_3 I_{mdz})S_h(t), f_2 = (\alpha_z\beta_2 I_{mz} + \alpha'_z\beta_3 I_{mdz})S_h(t), f_3 = \alpha_z\beta_2 I_{mz} I_{hd}$, $f_4 = \alpha_d\beta_1 I_{md} I_{hz}, f_5 = \alpha_z\beta_2 I_{hz} I_{md}, f_6 = \alpha_d\beta_1 I_{hd} I_{mz}, f_7 = (\alpha_d\beta_1 I_{hd} + \alpha'_d\beta_3 I_{hdz} + \alpha_d\beta_1 T_z)S_m(t), f_8 = (\alpha_z\beta_2 I_{hz} + \alpha'_z\beta_3 I_{hdz} + \alpha_z\beta_2 T_d)S_m(t)$, then the coinfection flow is set up in fig. 3.

We now have the following system of ordinary differential equations that describes the dynamics of co-circulation and co-infection of the two diseases as

$$
\begin{aligned}
\frac{dS_h(t)}{dt} &= \pi_h - (\alpha_d\beta_1 I_{md} + \alpha_z\beta_2 I_{mz} + \alpha'_d\beta_3 I_{mdz} + \alpha'_z\beta_3 I_{mdz} + \alpha_{dz}\beta_3 I_{mdz})S_h(t) - \mu_1 S_h,\\
\frac{dI_{hd}(t)}{dt} &= \alpha_d\beta_1 I_{md} S_h(t) + \alpha'_d\beta_3 I_{mdz} S_h - \alpha_z\beta_2 I_{mz} I_{hd} - (\tau_1 + \tau_2 + \mu_1 + \mu_2)I_{hd},\\
\frac{dI_{hz}(t)}{dt} &= \alpha_z\beta_2 I_{mz} S_h(t) + \alpha'_z\beta_3 I_{mdz} S_h - \alpha_d\beta_1 I_{md} I_{hz} - (\tau_3 + \tau_4 + \mu_1 + \mu_2)I_{hz},\\
\frac{dI_{hdz}(t)}{dt} &= \alpha_{dz}\beta_3 I_{mdz} S_h(t) + \alpha_d\beta_1 I_{md} I_{hz} + \alpha_z\beta_2 I_{mz} I_{hd} - (\tau_5 + \mu_1 + \mu_2)I_{hdz},\\
\frac{dT_{hd}(t)}{dt} &= \tau_1 I_{hd} - (\gamma_1 + \mu_1 + \mu_2)T_{hd}(t),\\
\frac{dT_z(t)}{dt} &= \tau_2 I_{hd} - (\gamma_2 + \mu_1 + \mu_2)T_z(t),\\
\frac{dT_{hdz}(t)}{dt} &= \tau_5 I_{hdz} - (\gamma_5 + \mu_1 + \mu_2)T_{hdz}(t),\\
\frac{dT_{hz}(t)}{dt} &= \tau_3 I_{hz} - (\gamma_3 + \mu_1 + \mu_2)T_{hz}(t),
\end{aligned}
\tag{2.12}
$$

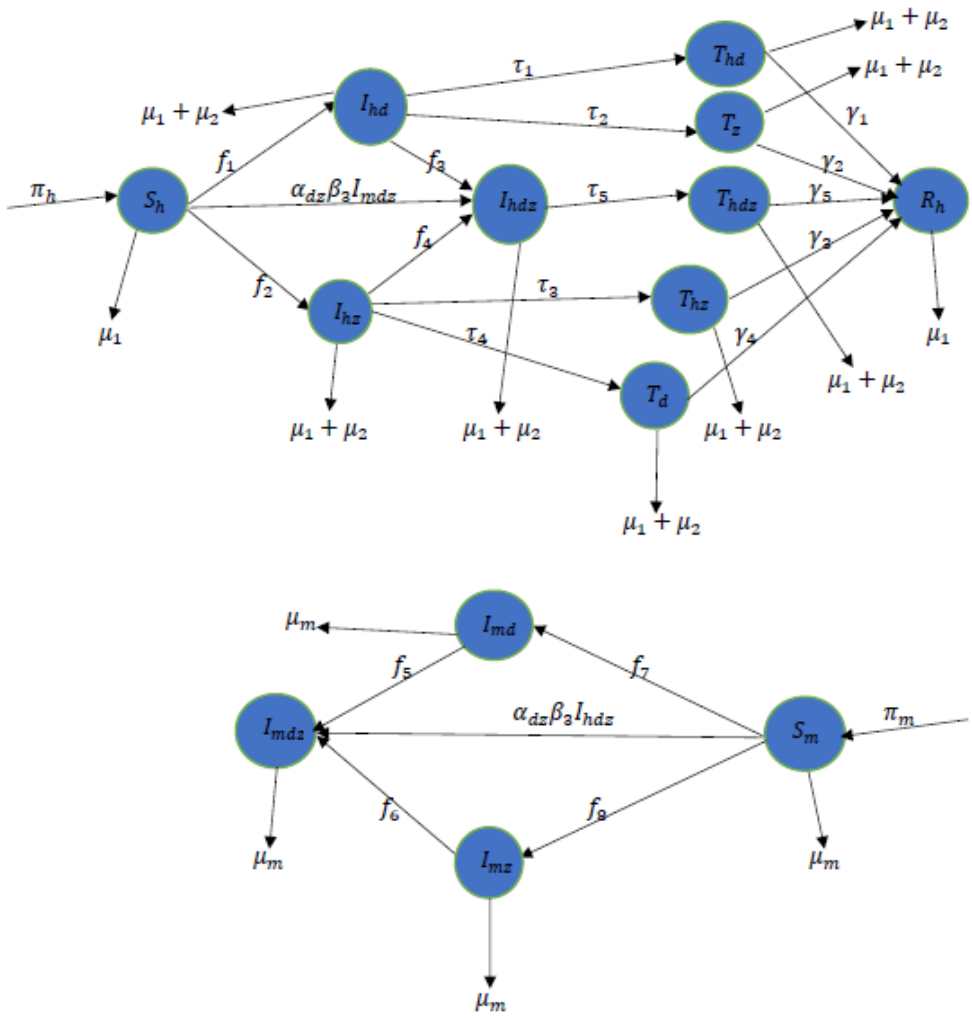

Figure 3: Coinfection Flow Diagram

$$\frac{dT_d(t)}{dt} = \tau_4 I_{hz} - (\gamma_4 + \mu_1 + \mu_2)T_d(t),$$

$$\frac{dR_h(t)}{dt} = \gamma_2 T_z + \gamma_1 T_{hd} + \gamma_3 T_{hz} + \gamma_4 T_d + \gamma_5 T_{hdz} - \mu_1 R_h(t),$$

$$\frac{dS_m(t)}{dt} = \pi_m - (\alpha_d\beta_1 I_{hd} + \alpha_z\beta_2 I_{hz} + \alpha'_z\beta_3 I_{hdz} + \alpha'_d\beta_3 I_{hdz} + \alpha_{dz}\beta_3 I_{hdz} + \alpha_d\beta_1 T_z)S_m(t) + \alpha_z\beta_2 T_d S_m(t) - \mu_m S_m,$$

$$\frac{dI_{md}(t)}{dt} = (\alpha_d\beta_1 I_{hd} + \alpha'_d\beta_3 I_{hdz} + \alpha_d\beta_1 T_z)S_m(t) - \alpha_z\beta_2 I_{hz} I_{md} - \mu_m I_{md},$$

$$\frac{dI_{mz}(t)}{dt} = (\alpha_z\beta_2 I_{hz} + \alpha'_z\beta_3 I_{hdz} + \alpha_z\beta_2 T_d)S_m(t) - \alpha_d\beta_1 I_{hd} I_{mz} - \mu_m I_{mz},$$

$$\frac{dI_{mdz}(t)}{dt} = \alpha_{dz}\beta_3 I_{hdz} S_m(t) + \alpha_d\beta_1 I_{hd} I_{mz} + \alpha_z\beta_2 I_{hz} I_{md} - \mu_m I_{mdz},$$

with initial solution, $Z_0 = (S_h^0, I_{hd}^0, I_{hz}^0, I_{hdz}^0, T_{hd}^0, T_z^0, T_{hdz}^0, T_{hz}^0, T_d^0, R_h^0, S_m^0, I_{md}^0, I_{mz}^0, I_{mdz}^0)$. The total human population, $N_h(t)$ and total mosquito population $N_m(t)$ in (2.12) satisfy the following differential equations

$$\begin{aligned} \frac{dN_h(t)}{dt} &= \pi_h - \mu_1 N_h(t) - \mu_2 N_h^*(t) \\ \frac{dN_m(t)}{dt} &= \pi_m - \mu_m N_m(t) \end{aligned} \tag{2.13}$$

where $N_h^*(t) = I_{hd}(t) + I_{hz}(t) + I_{hdz}(t) + T_{hd}(t) + T_z(t) + T_{hdz}(t) + T_{hz}(t) + T_d(t)$ is the total number of humans that are infected with any of the diseases or both. We assume that a unique solution, $Z(t)$, to the system, which passes through Z_0 exists in the region defined by $\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_m$, where
$\mathcal{D}_h = \{(S_h, I_{hd}, I_{hz}, I_{hdz}, T_{hd}, T_z, T_{hdz}, T_{hz}, T_d, R_h(t)) \in \mathbb{R}^{10} : N_h \leqslant \frac{\pi_h}{\mu_1}\}$,
and $\mathcal{D}_m = \{(S_m, I_{md}, I_{mz}, I_{mdz}) \in \mathbb{R}^4 : N_m \leqslant \frac{\pi_m}{\mu_m}\}$.

2.3.1. Positivity of Solutions

Lemma: Given that the initial solution $(S_h^0, S_m^0) > 0, (I_{hd}^0, I_{hz}^0, I_{hdz}^0, T_{hd}^0, T_z^0, T_{hdz}^0, T_{hz}^0, T_d^0, R_h^0, I_{md}^0, I_{mz}^0, I_{mdz}^0) > 0$ lies in the region, $\mathcal{D}$, then the solution set $(S_h(t), I_{hd}(t), I_{hz}(t), I_{hdz}(t), T_{hd}(t), T_z(t), T_{hdz}(t), T_{hz}(t), T_d(t), R_h(t), S_m(t), I_{md}(t), I_{mz}(t), I_{mdz}(t))$ to the system is positive $\forall$ t.

Proof: We see from the first equation in (2.12) that $\frac{dS_h(t)}{dt} \geqslant -\mu_1 S_h(t)$, which solves to give $S_h(t) \geqslant S_h^0 e^{-\mu_1 t}$.
Also, from the second equation, we have $I_{hd}(t) \geqslant I_{hd}^0 e^{-(\tau_1+\tau_2+\mu_1+\mu_2)t}$.
Therefore, given positive initial condition, the solutions $S_h(t)$ and $I_{hd}(t)$ remain positive for all t. The positivity of other components of the solution set can be demonstrated similarly. Hence, the solution to the model system remains positive at all times provided the initial solution set is positive.

2.3.2. Invariant Region

Lemma: No solution to the model system lies outside the region $\mathcal{D}$.

Proof: We want to prove that the region, $\mathcal{D}$ is positively invariant by showing that all the component solutions to the model system enter and remain in $\mathcal{D}$.
Let $(S_h, I_{hd}, I_{hz}, I_{hdz}, T_{hd}, T_z, T_{hdz}, T_{hz}, T_d, R_h) \in \mathbb{R}^{10}$, be any solution to the human-only component of the system, with non-negative initial solution. Then, from (2.13), we have $\frac{dN_h(t)}{dt} < \pi_h - \mu_1 N_h(t)$, whose solution is $N_h(t) < \frac{\pi_h}{\mu_1} + \left(N(0) - \frac{\pi_h}{\mu_1}\right) e^{-\mu_1 t}$. This shows that as $t \to \infty$, we have $0 < N_h \leqslant \frac{\pi_h}{\mu_1}$. Thus, all feasible solutions to the human-only component of the model system enter the region
$\mathcal{D}_h = \left\{(S_h, I_{hd}, I_{hz}, I_{hdz}, T_{hd}, T_z, T_{hdz}, T_{hz}, T_d, R_h) \in \mathbb{R}^{10} : N_h \leqslant \frac{\pi_h}{\mu_1}\right\}$. Using the same procedure, we can show that all feasible solutions to the mosquito-only component of the equation enter and remain in the region $\mathcal{D}_h = \left\{(S_m, I_{md}, I_{mz}, I_{mdz}) \in \mathbb{R}^4 : N_m \leqslant \frac{\pi_m}{\mu_m}\right\}$.
Thus, all possible solution to the system will enter and stay in the region $\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_m$. Hence, the region, $\mathcal{D}$ is positively invariant with respect to the flow generated by the model system of equations. Therefore, the system can be considered to be epidemiologically and mathematically well-posed in the region, $\mathcal{D}$. This makes it sufficient to analyze the system in this feasible region.

2.3.3. Basic Reproduction Number of the Co-circulation

The disease-free equilibrium of (2.12) is the steady state of the co-infection model in the absence of dengue, Zika virus disease or both. This is given by $E_0^{dz} = \left(\frac{\pi_h}{\mu_1}, 0, 0, 0, 0, 0, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}, 0, 0, 0\right)$. The basic reproduction number of the Zika-dengue co-circulation is the average number of persons that can be infected with dengue, Zika virus disease or both when an index case of dengue, Zika virus disease or both is introduced in a purely susceptible human and mosquito population. Using the same method of next generation matrix, we see that the matrices F and V for the co-infection are given by

$$F_{dz} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\alpha_1\beta_1\pi_h}{\mu_1} & 0 & \frac{\alpha_d'\beta_3\pi_h}{\mu_1} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\alpha_z\beta_2\pi_h}{\mu_1} & \frac{\alpha_z'\beta_3\pi_h}{\mu_1} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\alpha_{dz}\beta_3\pi_h}{\mu_1} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\alpha_d\beta_1\pi_m}{\mu_m} & 0 & \frac{\alpha_d'\beta_3\pi_m}{\mu_m} & \frac{\alpha_d\beta_1\pi_m}{\mu_m} & 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & \frac{\alpha_z'\beta_3\pi_m}{\mu_m} & 0 & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & 0 & 0 & 0 \\ 0 & 0 & \frac{\alpha_{dz}\beta_3\pi_m}{\mu_m} & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

$$V_{dz} =$$

$$\begin{pmatrix} \tau_1+\tau_2+\mu_1+\mu_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \tau_3+\tau_4+\mu_1+\mu_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \tau_5+\mu_1+\mu_2 & 0 & 0 & 0 & 0 & 0 \\ -\tau_2 & 0 & 0 & \gamma_2+\mu_1+\mu_2 & 0 & 0 & 0 & 0 \\ 0 & -\tau_4 & 0 & 0 & \gamma_4+\mu_1+\mu_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \mu_m & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \mu_m & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_m \end{pmatrix},$$

respectively. The basic reproduction number of Zika-dengue co-circulation is

$$\mathcal{R}_0 = \rho(F_{dz}V_{dz}^{-1}) = \max(\mathcal{R}_{0d}, \mathcal{R}_{0z}, \mathcal{R}_{0dz}),$$

where $\mathcal{R}_{0z}$ and $\mathcal{R}_{0d}$ are as defined in subsection (2.1.1) and subsection (2.2.1), respectively, and $\mathcal{R}_{0dz} = \sqrt{\frac{\alpha_{dz}^2\beta_3^2\pi_h\pi_m}{\mu_1\mu_m^2(\tau_5+\mu_1+\mu_2)}}$ is the average number of persons and mosquitoes that can be infected with Zika, dengue or both if one co-infected human or mosquito is placed in an environment free of these diseases.

2.3.4. Local Stability Analysis of Disease-free Equilibrium in the Co-circulation Model

The Jacobian matrix of the co-infection full model, evaluated at the disease-free equilibrium E_0^{dz} is

$$J(E_0^{dz}) =$$

$$\begin{pmatrix}
-\mu_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{\alpha_d\beta_1\pi_h}{\mu_1} & -\frac{\alpha_z\beta_2\pi_h}{\mu_1} & -G_1 \\
0 & -f_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\alpha_1\beta_1\pi_h}{\mu_1} & 0G_2 & \\
0 & 0 & -f_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\alpha_z\beta_2\pi_h}{\mu_1} & G_3 \\
0 & 0 & 0 & -f_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & G_4 \\
0 & \tau_1 & 0 & 0 & -f_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \tau_2 & 0 & 0 & 0 & -f_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \tau_5 & 0 & 0 & -f_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \tau_3 & 0 & 0 & 0 & 0 & -f_7 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \tau_4 & 0 & 0 & 0 & 0 & 0 & -f_8 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \gamma_1 & \gamma_2 & \gamma_5 & \gamma_3 & \gamma_4 & -\mu_1 & 0 & 0 & 0 & 0 \\
0 & -Q_1 & -Q_2 & -Q_3 & 0 & -Q_4 & 0 & 0 & -Q_5 & 0 & -\mu_m & 0 & 0 & 0 \\
0 & R_1 & 0 & R_2 & 0 & R_3 & 0 & 0 & 0 & 0 & 0 & -\mu_m & 0 & 0 \\
0 & 0 & T_1 & T_2 & 0 & 0 & 0 & 0 & T_3 & 0 & 0 & 0 & -\mu_m & 0 \\
0 & 0 & 0 & U_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_m
\end{pmatrix}.$$

where $Q_5 = \frac{\alpha_z\beta_2\pi_m}{\mu_m}$, $Q_4 = \frac{\alpha_d\beta_1\pi_m}{\mu_m}$, $Q_3 = \frac{(\alpha'_d+\alpha'_z+\alpha_{dz})\beta_3\pi_m}{\mu_m}$, $Q_2 = \frac{\alpha_z\beta_2\pi_m}{\mu_m}$, $Q_1 = \frac{\alpha_d\beta_1\pi_m}{\mu_m}$
$R_1 = \frac{\alpha_d\beta_1\pi_m}{\mu_m}$, $R_2 = \frac{\alpha'_d\beta_3\pi_m}{\mu_m}$, $R_3 = \frac{\alpha_d\beta_1\pi_m}{\mu_m}$, $T_1 = \frac{\alpha_z\beta_2\pi_m}{\mu_m}$, $T_2 = \frac{\alpha'_z\beta_3\pi_m}{\mu_m}$, $T_3 = \frac{\alpha_z\beta_2\pi_m}{\mu_m}$, $U_1 = \frac{\alpha_{dz}\beta_3\pi_m}{\mu_m}$,
$G_1 = \frac{(\alpha'_d+\alpha'_z+\alpha_{dz})\beta_3\pi_h}{\mu_1}$, $G_2 = \frac{\alpha'_d\beta_3\pi_h}{\mu_1}$, $G_3 = \frac{\alpha'_z\beta_3\pi_h}{\mu_1}$, $G_4 = \frac{\alpha_{dz}\beta_3\pi_h}{\mu_1}$, $f_1 = \tau_1+\tau_2+\mu_1+\mu_2$,
$f_2 = \tau_3+\tau_4+\mu_1+\mu_2, f_3 = \tau_5+\mu_1+\mu_2, f_4 = \gamma_1+\mu_1+\mu_2, f_5 = \gamma_2+\mu_1+\mu_2, f_6 = \gamma_5+\mu_1+\mu_2$,
$f_7 = \gamma_3+\mu_1+\mu_2, f_8 = \gamma_4+\mu_1+\mu_2$. The eigenvalues of $J(E_0^{dz})$ are -μ_m, $-\mu_1(twice)$, $-(\gamma_1+\mu_1+\mu_2)$, $-(\gamma_3+\mu_1+\mu_2)$, and $-(\gamma_5+\mu_1+\mu_2)$, and the eigenvalues of the sub-matrix

$$J_1(E_0^{dz}) = \begin{pmatrix}
-f_1 & 0 & 0 & 0 & 0 & \frac{\alpha_1\beta_1\pi_h}{\mu_1} & 0 & \frac{\alpha'_d\beta_3\pi_h}{\mu_1} \\
0 & -f2 & 0 & 0 & 0 & 0 & \frac{\alpha_z\beta_2\pi_h}{\mu_1} & \frac{\alpha'_z\beta_3\pi_h}{\mu_1} \\
0 & 0 & -f_3 & 0 & 0 & 0 & 0 & \frac{\alpha_{dz}\beta_3\pi_h}{\mu_1} \\
\tau_2 & 0 & 0 & -f_5 & 0 & 0 & 0 & 0 \\
0 & \tau_4 & 0 & 0 & -f_8 & 0 & 0 & 0 \\
\frac{\alpha_d\beta_1\pi_m}{\mu_m} & 0 & \frac{\alpha'_d\beta_3\pi_m}{\mu_m} & \frac{\alpha_d\beta_1\pi_m}{\mu_m} & 0 & -\mu_m & 0 & 0 \\
0 & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & \frac{\alpha'_z\beta_3\pi_m}{\mu_m} & 0 & \frac{\alpha_z\beta_2\pi_m}{\mu_m} & 0 & -\mu_m & 0 \\
0 & 0 & \frac{\alpha_{dz}\beta_3\pi_m}{\mu_m} & 0 & 0 & 0 & 0 & -\mu_m
\end{pmatrix}.$$

Observe that the matrices, F_{dz}, V_{dz} and $J_1(E_0^{dz})$ are related by $F_{dz} - V_{dz} = J_1(E_0^{dz})$. In Van Den Driessche and Watmough[21], it is shown that all the eigenvalues of $F_{dz} - V_{dz}$ or equivalently, of $J_1(E_0^{dz})$ have negative real parts if $\rho(F_{dz}V_{dz}^{-1}) < 1$. Therefore, the equilibrium point, E_0^{dz}, is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

2.3.5. Possible Backward Bifurcation in the Full Model

The nature of the model equations would not allow investigation of existence of endemic equilibrium by using known standard methods. We therefore, conduct global stability analysis of disease-free equilibrium to ascertain if the model has a unique endemic equilibrium. If the disease-free equilibrium is globally asymptotically stable, then the

model has a unique endemic equilibrium that is stable when $\mathcal{R}_0 > 1$. Otherwise, the model has more than one endemic equilibrium and consequently, backward bifurcation takes place in the model. The method described in Castillo-Chavez et al.[22] shall be adopted in investigating the global stability of the disease-free equilibrium. It requires splitting of the model system of equations into the system for uninfected compartments and infected compartments. Hence, the model system can be written as

$$\frac{dX}{dt} = F(X, Y) \tag{2.14}$$

$$\frac{dY}{dt} = G(X, Y), \tag{2.15}$$

where $X = (S_h, T_{hd}, T_{hdz}, T_{hz}, R_h, S_m)$ and $Y = (I_{hd}, I_{hz}, I_{hdz}, T_z, T_d, I_{md}, I_{mz}, I_{mdz})$ are the uninfected and infected compartments, respectively,

$$F = \begin{pmatrix} \pi_h - (\alpha_d\beta_1 I_{md} + \alpha_z\beta_2 I_{mz} + \alpha'_d\beta_3 I_{mdz} + \alpha'_z\beta_3 I_{mdz} + \alpha_{dz}\beta_3 I_{mdz})S_h(t) - \mu_1 S_h, \\ \tau_1 I_{hd} - (\gamma_1 + \mu_1 + \mu_2)T_{hd}(t), \\ \tau_5 I_{hdz} - (\gamma_5 + \mu_1 + \mu_2)T_{hdz}(t), \\ \tau_3 I_{hz} - (\gamma_3 + \mu_1 + \mu_2)T_{hz}(t), \\ \gamma_2 T_z + \gamma_1 T_{hd} + \gamma_3 T_{hz} + \gamma_4 T_d + \gamma_5 T_{hdz} - \mu_1 R_h(t), \\ \pi_m - (\alpha_d\beta_1 I_{hd} + \alpha_z\beta_2 I_{hz} + \alpha'_z\beta_3 I_{hdz} + \alpha'_d\beta_3 I_{hdz} + \alpha_{dz}\beta_3 I_{hdz} + \alpha_d\beta_1 T_z)S_m(t) + \alpha_z\beta_2 T_d S_m(t) - \mu_m S_m, \end{pmatrix}$$

and

$$G = \begin{pmatrix} \alpha_d\beta_1 I_{md} S_h(t) + \alpha'_d\beta_3 I_{mdz} S_h - \alpha_z\beta_2 I_{mz} I_{hd} - (\tau_1 + \tau_2 + \mu_1 + \mu_2)I_{hd}, \\ \alpha_z\beta_2 I_{mz} S_h(t) + \alpha'_z\beta_3 I_{mdz} S_h - \alpha_d\beta_1 I_{md} I_{hz} - (\tau_3 + \tau_4 + \mu_1 + \mu_2)I_{hz}, \\ \alpha_{dz}\beta_3 I_{mdz} S_h(t) + \alpha_d\beta_1 I_{md} I_{hz} + \alpha_z\beta_2 I_{mz} I_{hd} - (\tau_5 + \mu_1 + \mu_2)I_{hdz}, \\ \tau_2 I_{hd} - (\gamma_2 + \mu_1 + \mu_2)T_z(t), \\ \tau_4 I_{hz} - (\gamma_4 + \mu_1 + \mu_2)T_d(t), \\ (\alpha_d\beta_1 I_{hd} + \alpha'_d\beta_3 I_{hdz} + \alpha_d\beta_1 T_z)S_m(t) - \alpha_z\beta_2 I_{hz} I_{md} - \mu_m I_{md}, \\ (\alpha_z\beta_2 I_{hz} + \alpha'_z\beta_3 I_{hdz} + \alpha_z\beta_2 T_d)S_m(t) - \alpha_d\beta_1 I_{hd} I_{mz} - \mu_m I_{mz}, \\ \alpha_{dz}\beta_3 I_{hdz} S_m(t) + \alpha_d\beta_1 I_{hd} I_{mz} + \alpha_z\beta_2 I_{hz} I_{md} - \mu_m I_{mdz}, \end{pmatrix}$$

In (2.14), it is required that the disease-free equilibrium $\left(\frac{\pi_h}{\mu_1}, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}\right)$ for the system $\frac{dX}{dt} = F(X, 0)$ is globally asymptotically stable. That is $(S_h, T_{hd}, T_{hdz}, T_{hz}, R_h, S_m) \to \left(\frac{\pi_h}{\mu_1}, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}\right)$ as $t \to \infty$. In the system (2.15), it is required that $\hat{G}(X, Y) := BY - G(X, Y) \geqslant 0$, where B is the Jacobian matrix of $G(X, Y)$ evaluated at the disease-free

equilibrium of the model. The solution to $\frac{dX}{dt} = F(X,0)$ is obtained as

$$\begin{aligned}
S_h(t) &= \frac{\pi_h}{\mu_1} + \left(S_h(0) - \frac{\pi_h}{\mu_1}\right) e^{-\mu_1 t} \\
T_{hd}(t) &= T_{hd}(0)e^{-(\gamma_1+\mu_1+\mu_2)t} \\
T_{hdz}(t) &= T_{hdz}(0)e^{-(\gamma_5+\mu_1+\mu_2)t} \\
T_{hz}(t) &= T_{hz}(0)e^{-(\gamma_3+\mu_1+\mu_2)t} \\
R_h(t) &= R_h(0)e^{-\mu_1 t} + \frac{\gamma_1 T_{hd}(0)}{\gamma_1+\mu_2}\left(e^{-\mu_1 t} - e^{-(\gamma_1+\mu_1+\mu_2)t}\right) + \frac{\gamma_3 T_{hz}(0)}{\gamma_3+\mu_2}\left(e^{-\mu_1 t} - e^{-(\gamma_3+\mu_1+\mu_2)t}\right) \\
&\quad + \frac{\gamma_5 T_{hdz}(0)}{\gamma_5+\mu_2}\left(e^{-\mu_1 t} - e^{-(\gamma_5+\mu_1+\mu_2)t}\right) \\
S_m(t) &= \frac{\pi_m}{\mu_m} + \left(S_m(0) - \frac{\pi_m}{\mu_m}\right) e^{-\mu_m t}.
\end{aligned} \tag{2.16}$$

We see that as $t \to \infty, (S_h(t), T_{hd}(t), T_{hdz}(t), T_{hz}(t), R_h(t), S_m(t)) \to \left(\frac{\pi_h}{\mu_1}, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}\right)$ irrespective of the sizes of initial populations. Therefore, the disease-free equilibrium, $\left(\frac{\pi_h}{\mu_1}, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}\right)$ of the system, $\frac{dX}{dt} = F(X,0)$, is globally asymptotically stable. For the second condition, note that the matrix B is the same as the Jacobian matrix $J_1(E_0^{dz})$. Therefore,

$$\hat{G}(X,Y) = \begin{pmatrix}
\alpha_z\beta_2 I_{mz} I_{hd} + (\alpha_d\beta_1 I_{md} + \alpha'_d\beta_3 I_{mdz})\left(\frac{\pi_h}{\mu_1} - S_h(t)\right) \\
\alpha_d\beta_1 I_{md} I_{hz} + (\alpha_z\beta_2 I_{mz} + \alpha'_z\beta_3 I_{mdz})\left(\frac{\pi_h}{\mu_1} - S_h(t)\right) \\
-(\alpha_d\beta_1 I_{md} I_{hz} + \alpha_z\beta_2 I_{mz} I_{hd}) + \alpha_{dz}\beta_3 I_{mdz}\left(\frac{\pi_h}{\mu_1} - S_h(t)\right) \\
0 \\
0 \\
\alpha_z\beta_2 I_{hz} I_{md} + (\alpha_d\beta_1 I_{hd} + \alpha_d\beta_1 T_z + \alpha'_d\beta_3 I_{hdz})\left(\frac{\pi_m}{\mu_m} - S_m(t)\right) \\
\alpha_d\beta_1 I_{hd} I_{mz} + (\alpha_z\beta_2 I_{hz} + \alpha_z\beta_2 T_d + \alpha'_z\beta_3 I_{hdz})\left(\frac{\pi_m}{\mu_m} - S_m(t)\right) \\
-(\alpha_d\beta_1 I_{mz} I_{hd} + \alpha_z\beta_2 I_{md} I_{hz}) + \alpha_{dz}\beta_3 I_{hdz}\left(\frac{\pi_m}{\mu_m} - S_m(t)\right)
\end{pmatrix}$$

From (2.16), we see that $S_h(t) \leqslant \frac{\pi_h}{\mu_1}$, and $S_m(t) \leqslant \frac{\pi_m}{\mu_m}$. Hence, we are certain of non-negativity of all but the 3^{rd} and the 8^{th} rows. This indicates that E_0^{dz} may not be globally stable. Therefore, it is possible to have backward bifurcation occur in the model. Note that if $\alpha_d\beta_1 I_{md} I_{hz} + \alpha_z\beta_2 I_{mz} I_{hd} = 0$ and $(\alpha_d\beta_1 I_{mz} I_{hd} + \alpha_z\beta_2 I_{md} I_{hz}) = 0$, then we have $\hat{G}(X,Y) \geqslant 0$, and the disease-free equilibrium becomes globally asymptotically stable. This means that the global instability of the disease-free equilibrium or backward bifurcation is as a result of re-infection of infected humans and mosquitoes with the other disease.

3. Impact of Wrong Diagnoses on the Spread of the Diseases

We can determine the impact of wrong diagnoses on the spread of the two diseases by calculating the sensitivities of the their reproduction numbers with respect to the pro-

portion of humans that are wrongly diagnosed. By definition, the normalized forward sensitivity index of $\mathcal{R}_0$ that depends on the parameter p is given by

$$\mathcal{S}_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0} \tag{3.1}$$

The sensitivity index of $\mathcal{R}_{0d}$ with with respect to τ_2 is

$$\begin{aligned} \frac{\partial \mathcal{R}_{0d}}{\partial \tau_2} \times \frac{\tau_2}{\mathcal{R}_{0d}} &= \frac{\alpha_d^2 \beta_1^2 \pi_h \pi_m (\gamma_2 + \mu_1 + \mu_2)(\tau_1 - \gamma_2)}{2\sqrt{\frac{\alpha_d^2 \beta_1^2 \pi_h \pi_m (\gamma_2+\mu_1+\mu_2+\tau_2)}{\mu_1 \mu_m^2 (\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)}}} \times \frac{\tau_2}{\mathcal{R}_{0d}} \\ &= \frac{\alpha_d^2 \beta_1^2 \pi_h \pi_m (\gamma_2 + \mu_1 + \mu_2)(\tau_1 - \gamma_2)\tau_2}{2\mathcal{R}_{0d}^2} \end{aligned} \tag{3.2}$$

The sensitivity index is positive if $\tau_1 - \gamma_2 > 0$, irrespective of value of τ_2. Also, the sensitivity index of $\mathcal{R}_{0z}$ with with respect to τ_4 is

$$\frac{\partial \mathcal{R}_{0z}}{\partial \tau_4} \times \frac{\tau_4}{\mathcal{R}_{0z}} = \frac{\alpha_z^2 \beta_2^2 \pi_h \pi_m (\gamma_4 + \mu_1 + \mu_2)(\tau_3 - \gamma_4)\tau_4}{2\mathcal{R}_{0z}^2}. \tag{3.3}$$

The sensitivity index is positive if $\tau_3 - \gamma_4 > 0$, irrespective of value of τ_4. The sensitivity indices show that an increase in the proportion of humans that are wrongly diagnosed of the two diseases would increase the spread of the diseases since it is obvious that the proportion of those that are receiving accurate treatment is more than the recovery rate of people that are receiving wrong treatment. The sensitivity indices of $\mathcal{R}_{0d}$ and $\mathcal{R}_{0z}$ with respect to other parameters in their expressions are shown in table 1 and table 2 respectively. The parameters with positive sensitivity indices are the parameters whose values must be reduced in order to reduce the spread of the diseases. On the other hand, the parameters with negative sensitivity indices indicates the parameters whose values must be increase if the spread of the diseases are to be curtailed.

Table 1: sensitivity indices of parameters of dengue-only model

parameter	π_h	π_m	α_d	μ_m	β_1	γ_2	τ_1	τ_2	μ_1	μ_2
initial v	0.5	0.5	1	-1	1	-0.11	-0.2	0.04	-0.5	-0.2

Table 2: sensitivity indices of parameters of Zika-only model

parameter	π_h	π_m	α_z	μ_m	β_2	γ_4	τ_3	τ_4	μ_1	μ_2
initial v	0.5	0.5	1	-1	1	-0.04	-0.02	0.008	-0.5	-0.2

4. Impact of Dengue on Zika and Vice Versa

The impact of dengue on Zika, and vice versa can be investigated by expressing the basic reproduction number of one as a function of the other, and taking partial derivatives.

From $\mathcal{R}_{0d}$, we have that

$$\mu_1\mu_m^2 = \frac{\alpha_d^2\beta_1^2\pi_h\pi_m(\gamma_2+\mu_1+\mu_2+\tau_2)}{\mathcal{R}_{0d}^2(\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)}$$

Substituting this in the expression for $\mathcal{R}_{0z}^2$ gives

$$\mathcal{R}_{0z} = \sqrt{\frac{\alpha_z^2\beta_2^2(\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2+\tau_4)}{\alpha_d^2\beta_1^2(\gamma_2+\mu_1+\mu_2+\tau_2)(\gamma_4+\mu_1+\mu_2)(\tau_3+\tau_4+\mu_1+\mu_2)}}\mathcal{R}_{0d} \tag{4.1}$$

Taking partial derivative of $\mathcal{R}_{0z}$ with respect to $\mathcal{R}_{0d}$ shows that dengue increase spread of Zika virus disease at the constant rate $\left(\frac{\alpha_z^2\beta_2^2(\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2+\tau_4)}{\alpha_d^2\beta_1^2(\gamma_2+\mu_1+\mu_2+\tau_2)(\gamma_4+\mu_1+\mu_2)(\tau_3+\tau_4+\mu_1+\mu_2)}\right)^{\frac{1}{2}}$. Conversely, by expressing $\mathcal{R}_{0d}$ in terms of $\mathcal{R}_{0z}$, and taking partial derivative we see that Zika virus disease increase the spread of dengue at the constant rate, $\left(\frac{\alpha_z^2\beta_2^2(\gamma_2+\mu_1+\mu_2)(\tau_1+\tau_2+\mu_1+\mu_2)(\gamma_4+\mu_1+\mu_2+\tau_4)}{\alpha_d^2\beta_1^2(\gamma_2+\mu_1+\mu_2+\tau_2)(\gamma_4+\mu_1+\mu_2)(\tau_3+\tau_4+\mu_1+\mu_2)}\right)^{-\frac{1}{2}}$. This result is true since the two diseases are spread by the same mosquitoes. An increase in the spread of one disease is an indication that there are many aedes aegypti mosquitoes present in the area, which also spread the other disease.

5. Simulation of the Model and Discussion

Simulation of the dengue-Zika full model is carried out in this section to graphically illustrate some of the results obtained in this work. The simulation is carried out in MATLAB© R2010a, where fourth-order Runge-Kutta integration scheme is used to obtain numerical solution to the non-linear system. The initial values of the state variables and the parameter values used in the simulation can be found in Table 3 and Table 4, respectively.

Table 3: Initial Values

variables	S_h	I_{hd}	I_{hz}	I_{hdz}	T_{hd}	T_z	T_{hdz}	T_{hz}	T_d	R_h	S_m	I_{md}	I_{mz}	I_{mdz}
initial values	500	100	100	0	15	20	0	15	10	0	1000	500	300	0

The value of some of the parameters were obtained from the literature, while others are assumed to be within a reasonable and realistic range for the purpose of the simulation.

The result of the simulation exercise are presented in Figures(4-6). Figure 4 shows the dynamics of the two diseases and their co-infection in human and mosquito populations. We see that the population of humans and mosquitoes that are co-infected with dengue and Zika virus disease is higher than those that are infected with the individual diseases. This means that in an environment where the two diseases are co-circulating, it is possible to have more people who are co-infected with the two diseases than those who are singly-infected with any of the diseases. This is because as assumed in this model, co-infection

Table 4: Parameter Values used in this model

Parameter	*Value*	*Source*	*Parameter*	*Value*	*Source*
π_h	100	assumed	α_z'	0.00015	assumed
π_m	1000	assumed	τ_1	0.017	assumed
α_d	0.0002	[23]	τ_2	0.015	assumed
α_z	0.0002	[5]	μ_1	0.0005	[24]
μ_m	0.03008	[17]	μ_2	0.0085	assumed
β_1	0.375	[25]	τ_3	0.002	assumed
β_2	0.175	[16]	τ_4	0.35	assumed
β_3	0.15	assumed	τ_5	0.15	assumed
α_{dz}	0.2	[16]	γ_1	0.2	[23]
α_d'	0.0002	assumed	γ_2	0.01	assumed
γ_3	0.28	[17]	γ_4	0.001	assumed
γ_5	0.08	assumed			

of humans and mosquitoes occurs in two ways. Firstly, humans and mosquitoes infected with one disease could be re-infected with the other disease by infected mosquitoes and humans, respectively. Secondly, susceptible humans and mosquitoes could be doubly-infected with the two diseases by co-infected mosquitoes and humans, respectively. This surely increases the number of humans and mosquitoes that are co-infected with dengue and Zika virus disease. The effects of mis-diagnoses on the spread of dengue and Zika virus disease as derived in (3.2) and (3.3) are depicted in Figure 5. The figures confirm that for $\tau_1 > \gamma_2$ and $\tau_3 > \gamma_4$, an increase in τ_2 and τ_4 leads to an increase in the spread of dengue and Zika virus disease, respectively. Figure 6 shows the impact of spread of one disease on the spread of the other. As obtained in section 4, an increase in the spread of one disease leads to an increase in the spread of the other when the two diseases co-circulate. This is shown by plotting the graph of humans infected with dengue against humans infected with Zika virus disease and vice-versa, which shows that the two diseases have direct relationships with each other.

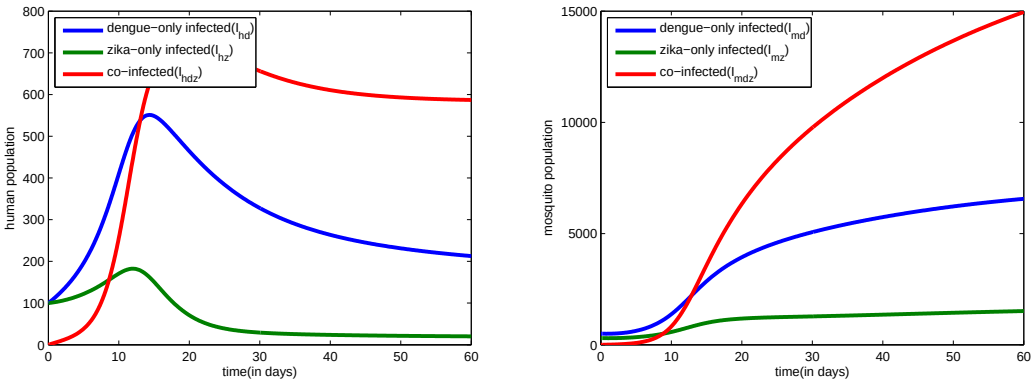

Figure 4: (i) infected humans (ii)infected mosquitoes

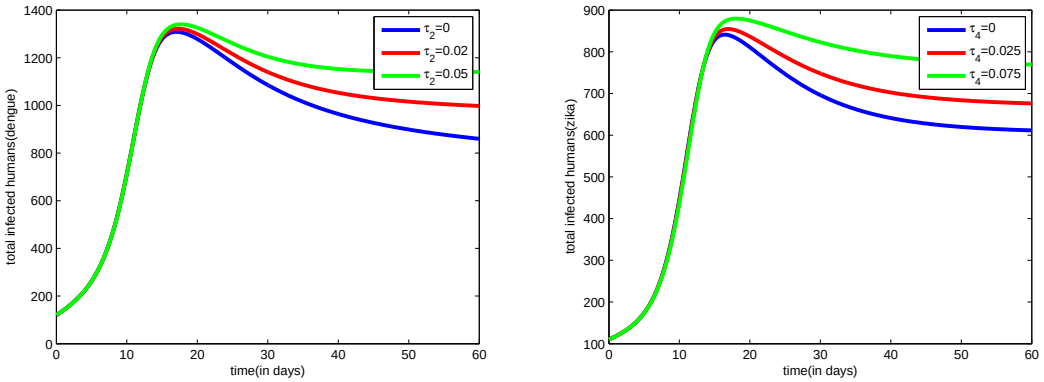

Figure 5: (i)dengue-infected humans for increasing τ_2 (ii) Zika-infected humans for increasing τ_4

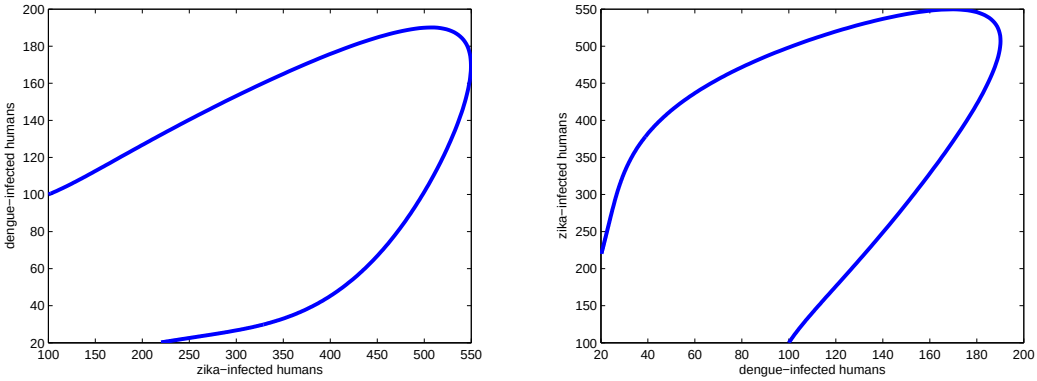

Figure 6: (i)Graph of I_{hd} vs I_{hz} (ii) Graph of I_{hz} vs I_{hd}

6. Summary

Co-circulation and co-infection of dengue and Zika virus disease has been modeled in this paper. The model is a system of non-linear ordinary differential equations that describe the dynamics of the two diseases when they co-circulate in human and Aedes aegypti populations. The disease-free equilibrium of the co-infection model is shown to be locally asymptotically stable when the basic reproduction number of the co-infection is less than one. However, with reinfection of infected humans and mosquitoes with another disease, the disease-free equilibrium fails to be globally asymptotically stable when $\mathcal{R}_0 < 1$. The global instability of the disease-free equilibrium indicates that the model does not possess a unique endemic equilibrium that is locally asymptotically stable when $\mathcal{R}_0 > 1$. Hence, backward bifurcation takes place in the model. The occurrence of backward bifurcation in the model is indicative that having $\mathcal{R}_0 < 1$, is not sufficient enough to eradicate the two diseases and their co-infection in the population. The impact of misdiagnosis of each of the diseases is discussed. The result is that an increase in the proportion of those wrongly diagnosed with the other disease would increase the spread of the disease if the proportion of those who are properly diagnosed is more than the recovery rate of those

wrongly diagnosed. The effect of the spread of one disease on the spread of the other is also investigated, which shows a positive relationship between the spread of the two diseases. Plots from the numerical experiments show that where dengue and Zika virus disease are co-circulating, more humans and mosquitoes are likely to be co-infected with the two diseases than single diseases. This is because apart from re-infection of infected humans and mosquitoes with the other disease, humans and mosquitoes co-infected with the two diseases can transmit the two diseases to susceptible mosquitoes and humans, respectively.

7. Conclusion

In conclusion, based on the results obtained in this paper, it can be concluded that wrong diagnosis plays a major role in the spread of dengue and Zika virus diseases. Therefore, it is important not to treat infected humans based only on their present symptoms. A distinguishing test should always be conducted on people suspected of being infected with the two diseases to avoid a wrong diagnosis. Furthermore, since the disease-free equilibrium is not globally asymptotically stable, extra effort should be adopted to bring the reproduction number below $\mathcal{R}_0'$, such that $\mathcal{R}_0' < \mathcal{R}_0 < 1$, to eradicate the two diseases.

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