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Optimal Control Strategies for the Transmission Dynamics of Zika Virus: With the Aid of Wolbachia-Infected Mosquitoes

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Abstract: In this paper, we looked at the potential of Wolbachia-infected mosquitoes to reduce Wolbachia-free mosquito populations and control Zika virus transmission which has garnered significant attention in recent years. This naturally occurring bacterium in many insect species has been shown to inhibit the replication of Zika and other mosquito-borne pathogens within infected mosquitoes. Therefore, this study presents a comprehensive mathematical model for Zika virus transmission dynamics by implementing vector control through Wolbachia-infected mosquitoes. The model incorporates various critical components and further carried out necessary analyses such as local stability analysis, determination of the basic reproduction number, global stability investigation, endemic equilibrium characterization, sensitivity analysis, and numerical simulations. The aim is to provide a holistic understanding of the Zika virus transmission dynamics and the potential impact of vector control strategies using Wolbachia-infected mosquitoes. Based on the result of the sensitivity analysis, the basic model of the Zika virus was extended to an optimal control model version by introducing four-time dependent controls, the use of condoms/avoidance of multiple sex partners, the screening/treatment of the infected humans, the boosting/enhancement of breeding Wolbachia mosquitoes and injection of Wolbachia infected mosquitoes into mosquito population. Our results show that the combination and implementation of these controls are very effective in reducing the number of infected individuals to almost zero before day 100 and eliminating the Aedes aegypti mosquitoes responsible for the spread of the Zika virus disease in the population. Finally, the results obtained through this mathematical modeling approach shed light on the promising effectiveness of such interventions in mitigating Zika virus outbreaks and contributing to the ongoing efforts in infectious disease control.

Keywords: Zika virus, mathematical modeling, Aedes aegypti mosquitoes, Wolbachia, sensitivity analysis, optimal control analysis.

1. Introduction

The Zika virus (ZIKV) outbreak, first discovered in Africa and named after the Zika forest in Uganda, has emerged as a significant global health concern [5]. This once-obscure virus has thrust itself into the limelight due to its rapid spread and its potential to cause severe health complications. While Zika virus disease remained relatively inconspicuous for many decades, outbreaks in various parts of the world, particularly in South and Central America, have elevated it to an international health crisis. The virus, transmitted primarily through the bite of infected Aedes mosquitoes, has been associated with devastating consequences, such as congenital disabilities and neurological disorders, underscoring the urgent need for effective control strategies [5].

The Zika virus is a member of the Flaviviridae family and is primarily transmitted through the bite of infected Aedes mosquitoes, mainly Aedes aegypti and Aedes albopictus [1,2]. This mosquito-borne virus was once regarded as a relatively mild infection, with symptoms often resembling other arboviral diseases like dengue and chikungunya. However, what distinguishes Zika is its association with severe congenital disabilities, notably microcephaly in infants born to infected mothers during pregnancy [6]. This link between Zika infection and birth abnormalities has catapulted the virus into the global spotlight. Zika virus infection can be asymptomatic in many cases, with up to 80% of infected individuals displaying no noticeable symptoms [1,5]. When symptoms do occur, they are typically mild and short-lived, including fever, rash, joint pain, and conjunctivitis. This makes Zika virus disease difficult to diagnose based on symptoms alone, as it shares similarities with other mosquito-borne illnesses. The challenges of identifying the virus's presence, especially in pregnant women, make it difficult to prevent the potential complications associated with congenital Zika syndrome. The primary transmission mode of the Zika virus is through the bite of infected Aedes mosquitoes. However, the virus can also be transmitted through sexual contact, blood transfusions, and from mother to child during pregnancy or childbirth. This

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multiplicity of transmission routes has heightened concerns about controlling the virus's spread. As of September 2023, no specific antiviral treatment for Zika virus disease [2,5]. Management primarily focuses on alleviating the symptoms, such as fever and pain, through rest, hydration, and over-the-counter medications. Given the potential for severe congenital disabilities, preventing Zika infection is of paramount importance. Strategies include mosquito control measures, the use of insect repellents, and the practice of safe sex to avoid sexual transmission, which are in place to control the virus [1].

1.1 Using Wolbachia-Infected Mosquitoes to Control Zika Virus Vectors

Mosquito-borne diseases, including malaria, dengue fever, Zika virus, and chikungunya, continue to be a global health threat, affecting millions of people each year. Traditional methods of controlling these diseases, such as insecticide use and bed nets, have had limited success in curbing their spread [9]. However, a novel and promising strategy has emerged in recent years – utilizing Wolbachia-infected mosquitoes. This groundbreaking approach, which involves the release of mosquitoes carrying the Wolbachia bacterium, can potentially revolutionize the fight against mosquito-borne diseases [7].

Wolbachia, a naturally occurring bacterium commonly found in arthropods, including mosquitoes, can remarkably inhibit the replication and transmission of several dangerous viruses within its insect hosts. When introduced into mosquito populations, Wolbachia effectively hinders the ability of mosquitoes to transmit diseases to humans. This unique method offers a more sustainable and environmentally friendly alternative to conventional mosquito control measures, such as chemical insecticides, which often lead to ecological concerns and the development of insecticide-resistant mosquito populations [7,10]. Wolbachia is a bacterium that can be introduced into mosquito populations, such as Aedes aegypti, the primary vector for Zika virus. When introduced, Wolbachia becomes a part of the mosquito's reproductive system. Wolbachia-infected male mosquitoes mate with both Wolbachia-infected and uninfected female mosquitoes; however, when an uninfected male mosquito mates with a Wolbachia-infected female mosquito, the eggs produced do not hatch successfully because of a phenomenon called cytoplasmic incompatibility, a reproductive barrier created by Wolbachia [8]. Over time, as Wolbachia-infected mosquitoes are released into the population, the prevalence of Wolbachia increases. This reduces the ability of mosquitoes to transmit the Zika virus because fewer mosquitoes can successfully reproduce. As the proportion of Wolbachia-infected mosquitoes in the population grows, there is a significant reduction in the transmission of Zika virus because fewer competent vectors (mosquitoes capable of transmitting the virus) are available.

Mathematical modeling represents real-world phenomena, systems, and problems using mathematical concepts and tools. This approach provides a structured framework for understanding, analyzing, and solving complex issues that arise in various fields, ranging from physics and biology to engineering and economics [11]. Several authors have applied mathematical models to infectious diseases. For zika virus disease especially using Wolbachia-infected mosquitoes to control the virus, the author [21] used Wolbachia-infected mosquitoes to fight zika virus disease considering the effect of cytoplasmic incompatibility on the mosquitoes' reproduction stages by giving the following.

- Wolbachia-free males mate with Wolbachia-free females to produce Wolbachia-free eggs.
- Wolbachia-free males mate with Wolbachia-infected females to produce Wolbachia-infected eggs.
- Wolbachia-infected males mate with Wolbachia-free females to produce non-viable eggs.
- Wolbachia-infected males mate with Wolbachia-infected females to produce Wolbachia-infected eggs.

A mathematical Zika virus transmission dynamics model with a time-dependent mosquito biting rate was examined [14]. Their model considered both human and vector populations and the influences of seasonal change on the Zika virus transmission dynamics through the varying rates of mosquito bites over time. They found a correlation between the time series of the estimated mosquito biting rate and the average temperature. There are many mathematical analyses to study the dynamics of these diseases, such as sensitivity analysis, stability analysis, and optimal control analysis. In particular, optimal control analysis is implemented in a model to examine the impact of control measures. It requires the recognition of a feasible scheme, control, policy, program, strategy, or campaign to arrive at a system's optimal possible outcome. It helps find controls for dynamic systems to optimize the objective function and minimize the number of infected humans. Several authors have implemented optimal control strategies for the dynamics of different infectious diseases, including monkeypox infection [36], fungal *Tinea capitis* [37], hepatitis B infection [39], and deadly Nipah virus infection [38]. For Zika virus disease, authors such as [35] considered the impact of asymptomatic carriers of the Zika virus on the disease with optimal control strategies, and [15] considered the effect of immigration on the virus in the presence of vaccination and screening. They found that vaccination and screening are indispensable control measures to halt the Zika virus. Models found in [16, 17, 18, 19, 20, 22] are beneficial for understanding the transmission dynamics of the Zika virus using mathematical modeling approaches. The work of [15] serves as motivation for this research; even though they carried out optimal control in their study, they did not incorporate Wolbachia-Infected Mosquitoes as a compartment in their work and control such as the boosting/enhancement of breeding and injection of Wolbachia infected mosquitoes' control into

mosquitoes' population was not also considered in their work. Hence, [15] is modified in this study by incorporating the Wolbachia mosquito population to control the Aedes aegypti mosquitoes responsible for the spread of the Zika disease to the barest minimum. This is achieved by carrying out quantitative analysis, Sensitivity analysis, and optimal control analysis, which has yet to be considered by other authors based on the literature we assessed.

The rest of the paper is divided into the following sections: Section 2 contains the model formulation, while Section 3 is the detailed mathematical analysis of the model. Section 4 considered the sensitivity analysis of the model, and Section 5 described the optimal control model and analysis and numerical simulations. Finally, Section 6 concludes the study.

2. Model Formulation

The model formulation involves the human Aedes aegypti mosquitoes and Wolbachia mosquito populations. The total human population, $N_H(t)$, at time t, is subdivided into four compartments viz susceptible human population, $S_H(t)$, exposed human population, $E_H(t)$, infected human population, $I_H(t)$, and recovered human population, $R_H(t)$. The total Aedes aegypti mosquito population, $N_M(t)$, at time, t, is subdivided into three groups namely, the susceptible Aedes aegypti mosquito, $S_M(t)$, exposed Aedes aegypti mosquito, $E_M(t)$, and infected Aedes aegypti mosquito, $I_M(t)$, subpopulations. Meanwhile, the mosquitoes with Wolbachia known as Wolbachia mosquitoes are used to control Aedes aegypti mosquitoes. The total Wolbachia mosquito population at time t is denoted as $N_W(t)$ and it is subdivided into susceptible wolbachia mosquito, $S_W(t)$, exposed wolbachia mosquito, $E_W(t)$, and infected Wolbachia mosquito together with non-Wolbachia mosquito infected with Wolbachia, $I_W(t)$, subpopulations. Let π_H be the constant recruitment rate of susceptible human population, $\lambda_H(t)$ represents the force of infection for human population with combination of source of transmission from infected Aedes mosquitoes and infected humans via sexual transmission. μ_H is the natural death rate for the human population and δ_H represents disease induced death rate for human. Exposed human progresses to infected human subpopulation at the rate α_H while the infected human recovered at the rate θ_H. We assume that the only means of transmission of this disease among humans is by mosquito bites or sexual transmission; vertical transmission is not considered in this work.

For the Aedes aegypti mosquito population, the recruitment rate for the susceptible Aedes mosquitoes is denoted as π_M. At the same time, the function $\lambda_M(t)$ represents the Aedes aegypti mosquito force of infection. In this proportion, $(1-\sigma)$ of the susceptible Aedes aegypti mosquito is being infected by the infected human via biting infected humans and progresses to the exposed Aedes aegypti mosquito, $E_M(t)$. In contrast, a proportion σ of the susceptible Aedes aegypti mosquito, $S_M(t)$, become infected with Wolbachia with the force of infection $\lambda_{W2}(t)$ through mating [54,56,57,59]. It is noted that only female Aedes aegypti mosquitoes bite and transmit the disease; the male mosquitoes do not bite; instead, they feed on nectar from flowers [5, 55]. The exposed Aedes aegypti mosquitoes become infectious at the rate of b_M, and the infected Aedes aegypti mosquito, $I_M(t)$, can be infected with Wolbachia with the force of infection $\lambda_{W2}(t)$ [8,54,56,57,59]. It is noteworthy to mention that we assumed that once an Aedes mosquito is infected (precisely the female) with Wolbachia (by infected male Wolbachia), then such mosquitos cease to hatch eggs that can lead to propagation of zika virus (cancellation of vertical transmission). It also ceases to be able to bite and infect humans with Zika virus. Given this transformation, we regarded the Aedes mosquito as suppressed and changed its status to that of infected Wolbachia carrier mosquitoes [54,56,59]. Hence, after transmission occurred, the reason for the progression to I_W. The parameter μ_M is the natural death rate for the Aedes aegypti mosquito. The constant π_W is the recruitment rate of Wolbachia mosquitoes. It is assumed that Wolbachia mosquitoes recruited into the subsisting Wolbachia population are boosted/enhanced, most precisely the male, for effectiveness and resilience to control the Aedes mosquito population and μ_W natural death rate of Wolbachia mosquito exposed Wolbachia mosquito progresses to infected class at the rate a_W where $\lambda_{W1}(t)$ is the Wolbachia mosquito force of infection transmission for non-infected Wolbachia mosquito population.

The force of infection for the three populations is defined as

$$\lambda_H(t) = \frac{\beta_1 \alpha_1 I_M + \beta_2 \alpha_2 I_H}{N_H}, \quad \lambda_M(t) = \frac{\beta_1 C_1 I_H}{N_H}, \quad \lambda_{W1}(t) = \frac{\alpha_3 \beta_3 I_W}{N_W}, \lambda_{W2}(t) = \frac{\alpha_4 \beta_3 I_W}{N_M}. \tag{1}$$

Other parameters and their descriptions are defined in Table 1.

The description of the parameters of the model and model flow diagram are displayed in Table 1 and Figure 1.

Table 1: Model Parameters and their descriptions.

Parameter	Description	Parameter	Description
π_H, π_M, π_W	The recruitment rate of human, non-Wolbachia, and Wolbachia mosquito populations, respectively	α_4	Transmission probability per mating of susceptible non-Wolbachia mosquito with infected Wolbachia mosquito
μ_H, μ_M, μ_W	The natural death rate of human, non-Wolbachia, and Wolbachia populations, respectively	β_2	Sexual contact rate between a susceptible human and an infected human
$\lambda_H, \lambda_M, \lambda_W$	Force of Infection for human, non-Wolbachia, and Wolbachia mosquito populations, respectively	α_H	Progression rate from exposed human to infected human
β_1, β_3	Mosquito biting rate and Mosquito mating rate, respectively	θ_H	The recovery rate of infected human
α_1, C_1	Transmission probability per biting of susceptible human with infected mosquito, and Transmission probability per biting of infected human by susceptible female Aedes mosquito, respectively	δ_H	Disease-induced death rate for the human population
α_2	Transmission probability per mating of susceptible human with infected human	b_M, σ	Progression from exposed non-Wolbachia mosquito to infected Aedes mosquito, and proportion of Aedes mosquitoes that progress to I_W after being infected with Wolbachia, respectively.
α_3	Transmission probability per mating of infected Wolbachia mosquito with susceptible Wolbachia mosquito	a_W	Progression from exposed Wolbachia to infected Wolbachia mosquito

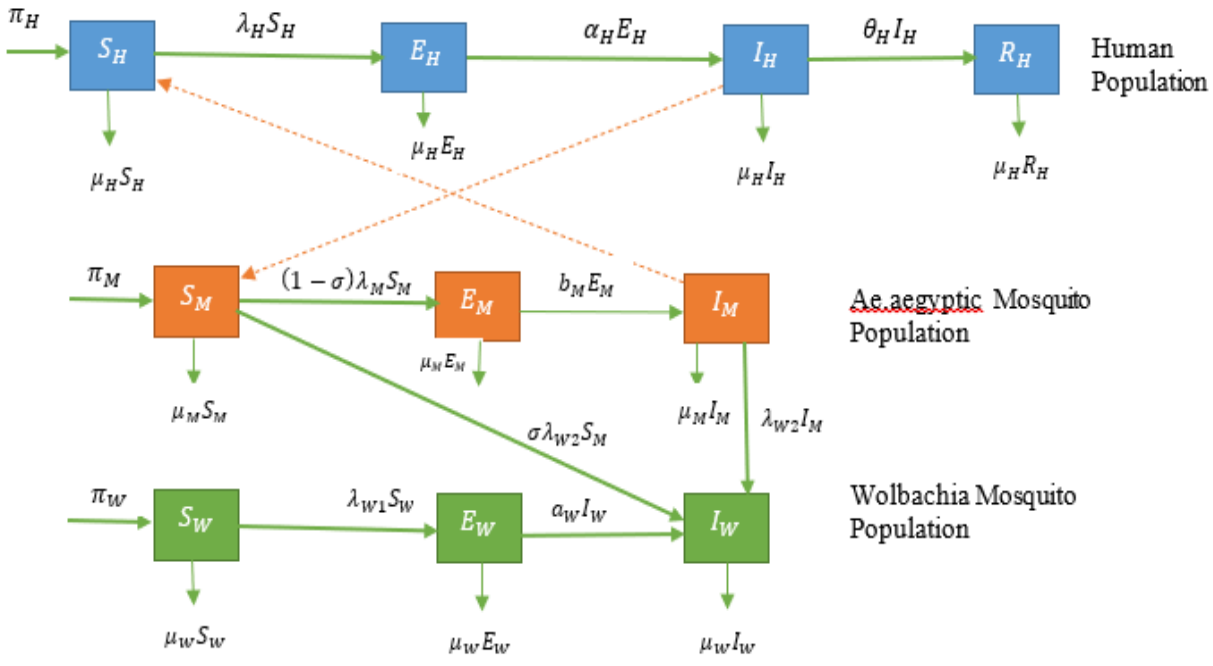


Fig. 1: Schematic diagram for the Zika virus model.

With the systemic diagram in Fig. 1 and parameter description in Table 1, the model equations are derived as a system of non-linear ordinary differential equations given as follows

$$\frac{ds_H}{dt} = \pi_H - (\mu_H + \lambda_H)s_H,$$
$$\frac{dE_H}{dt} = \lambda_H S_H - (\mu_H + \alpha_H)E_H,$$
$$\frac{dI_H}{dt} = \alpha_H E_H - (\mu_H + \delta_H + \theta_H)I_H,$$
$$\frac{dR_H}{dt} = \theta_H I_H - \mu_H R_H,$$
$$\frac{dS_M}{dt} = \pi_M - (\mu_M + (1-\sigma)\lambda_M + \sigma\lambda_{W2})S_M,$$
$$\frac{dE_M}{dt} = (1-\sigma)\lambda_M S_M - (\mu_M + b_M)E_M,$$
$$\frac{dI_M}{dt} = b_M E_M - (\mu_M + \lambda_{W2})I_M,$$
$$\frac{dS_W}{dt} = \pi_W - (\mu_W + \lambda_{W1})S_W,$$
$$\frac{dE_W}{dt} = \lambda_{W1} S_W - (\mu_W + a_W)E_W,$$
$$\frac{dI_W}{dt} = \alpha_W E_W + \sigma\lambda_{W2} S_M + \lambda_{W2} I_M - \mu_W I_W, \quad (2)$$

With

$$\lambda_H(t) = \frac{\beta_1\alpha_1 I_M + \beta_2\alpha_2 I_H}{N_H}, \quad \lambda_M(t) = \frac{\beta_1 c_1 I_H}{N_H}, \quad \lambda_{W1}(t) = \frac{\alpha_3\beta_3 I_W}{N_W}, \lambda_{W2}(t) = \frac{\alpha_4\beta_3 I_W}{N_M},$$

and the initial conditions,

$S_H(0) = S_{H0}, E_H(0) = E_{H0}, I_H(0) = I_{H0}, R_H(0) = R_{H0}, S_M(0) = S_{M0}, E_M(0) = E_{M0}, I_M(0) = I_{M0}, S_W(0) = S_{W0}, E_W(0) = E_{W0}, I_W(0) = I_{W0}.$
All the parameters are assumed to be positive.

3. Mathematical Analysis of the Zika Model

The basic properties of the model system (2) and the reproduction numbers are established in this section.

3.1 Invariant Region of the Zika Virus Model

The mathematical well-posedness of the model is proven in this subsection to show that the system (1) has epidemiological meaning. Defining

Theorem 1. *The solutions of themodel system (1) are feasible for all t > 0, if they enter the invariant region D, which is given by:*

$$D = \Big\{(S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_W, I_W): S_H > 0, E_H > 0, I_H > 0, R_H > 0, S_M > 0, E_M > 0, I_M > 0, S_W > 0, E_W > 0, I_W > 0, N_H \le \frac{\pi_H}{\mu_H}, N_M \le \frac{\pi_M}{\mu_M}, N_W \le \frac{\pi_W}{\mu_W}\Big\}.$$

Proof. By the definition of the total human population, $N_H(t)$, we have

$$N_H(t) = S_H(t) + E_H(t) + I_H(t) + R_H(t)$$

such that

$$N_H'(t) = S_H'(t) + E_H'(t) + I_H'(t) + R_H'(t) = \pi_H - N_H\mu_H - I_H\delta_H.$$

This can be written as

$$\frac{dN}{dt} \le \pi_H - \mu N_H \quad (3)$$

for the negligibility of $\delta_H \approx 0$.

Applying Birkhoff and Rota's theorem on the differential inequality (3), we obtain

$$N_H(t) \leq \frac{\pi_H}{\mu_H} + \left(N_H(0) - \frac{\pi_H}{\mu_H}\right) e^{-\mu_H t}$$

with the solution $0 \leq N_H \leq \frac{\pi_H}{\mu_H}$ as $t \to \infty$, where $N_H(0)$ is the initial total human population.

Using similar approach for the Aedes aegypti mosquito population and Wolbachia mosquito population, we obtain $0 \leq N_M \leq \frac{\pi_M}{\mu_M}$, $0 \leq N_W \leq \frac{\pi_W}{\mu_W}$ as $t \to \infty$.

Thus, the region, D is a positively invariant set under the flow described by the model system (2) such that solution path leaves the region, D [23]. With this, the Zika virus model with the human, Aedes aegypti mosquito and Wolbachia mosquito populations is epidemiologically and mathematically well-posed for further mathematical analysis.

3.2 Positivity of solution of the Zika virus model

It is necessary to prove that all solutions of the Zika virus model in system (1) are nonnegative for all time, t, for the model to be epidemiologically and mathematically well-posed in a feasible region D given by [23]:

$$D = \{(S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_W, I_W) \in R_+^{10}: S_H + E_H + I_H + R_H \leq N_H,\ S_M + E_M + I_M \leq N_M, S_W + E_W + I_W \leq N_W\}$$

This is done by proofing that $\{(S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_W, I_W) \geq 0 \in R_+^{10}\}$. We state the following Lemma.

Lemma 1: Let the initial data for the model (1) be $(S_H(0), E_H(0), I_H(0), R_H(0), S_M(0), E_M(0), I_M(0), S_W(0), E_W(0), I_W(0)) > 0$. Then the solutions $(S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_W, I_W)$ of the model (1) are positive for all time, $t > 0$.

Proof: *Let* $t = sup\{t > 0: S_H > 0, E_H > 0, I_H > 0, R_H > 0, S_M > 0, E_M > 0, I_M > 0, S_W > 0, E_W > 0, I_W > 0 \in [0, t]\}$. *Thus* $t > 0$.

From the first equation, we have that,

$$\frac{dS_H}{dt} = \pi_H - (\mu_H + \lambda_H)S_H \geq -(\mu_H + \lambda_H)S_H. \tag{4}$$

Integrating Equation (4) with the initial data, $S_H(0)$ yields

$$S_H(t) \geq S_H(0)e^{-(\mu_H + \lambda_H)t} \geq 0.$$

Since exponential functions are positive.

Similarly, it can be shown that $E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_W, I_W \geq 0$.

3.3 Existence of Disease-Free Equilibrium and Basic Reproduction Number of the Zika virus model

3.3.1 Disease-Free Equilibrium of the Zika Virus Model

The equilibrium state where there is no infection (or absence of the disease) in the population that is a state where $E_H = I_H = R_H = E_M = I_M = E_W = I_W = 0$ in the model (1) is called the disease-free equilibrium state (DFE) and it is given as;

$$\varepsilon_0 = \{S_H^0, E_H^0, I_H^0, R_H^0, S_M^0, E_M^0, I_M^0, S_W^0, E_W^0, I_W^0\} = \left\{\frac{\pi_H}{\mu_H}, 0, 0, 0, \frac{\pi_M}{\mu_M}, 0, 0, \frac{\pi_W}{\mu_W}, 0, 0\right\}. \tag{5}$$

3.3.2 Basic Reproduction Number of the Zika virus model

The basic reproduction number of Zika virus individuals denoted by R_0 is defined as the average number of secondary infections produced by a single Zika infectious individual introduced in a wholly susceptible population during his or her entire infectious period [24]. The basic reproduction number is calculated using the next-generation operator method on the dynamical system (1).

Hence, it follows that $R_0 = \rho(FV^{-1})$ where $\rho$is the dominant eigenvalue of FV^{-1}. F is the transmission matrix,

while the V is the transition matrix by other means except new infection. The details of the Next generation operator in [25]. We derived the following matrices from the Zika virus model:

$$F=\begin{bmatrix} 0 & \alpha_2\beta_2 & 0 & \alpha_1\beta_1 & 0 & 0 \\ 0 & \frac{(1-\sigma)\beta_1 C_1 \pi_M \mu_H}{\pi_H \mu_M} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_3\beta_3 \\ 0 & 0 & 0 & 0 & 0 & \sigma\alpha_4\beta_3 \end{bmatrix}, \quad V=\begin{bmatrix} P_1 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_H & P_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & P_3 & 0 & 0 & 0 \\ 0 & 0 & -b_M & \mu_M & 0 & 0 \\ 0 & 0 & 0 & 0 & P_4 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_W & \mu_W \end{bmatrix},$$

while the product of F and the inverse of V is given as

$$FV^{-1}=\begin{bmatrix} \frac{\beta_2\alpha_2\alpha_H}{P_1P_2} & \frac{\beta_2\alpha_2}{P_2} & \frac{\beta_1\alpha_1 b_M}{P_3\mu_M} & \frac{\beta_1\alpha_1}{\mu_M} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{(1-\sigma)\beta_1 C_1 \pi_M \mu_H \alpha_H}{\pi_H \mu_M P_1 P_2} & \frac{(1-\sigma)\beta_1 C_1 \pi_M \mu_H}{\pi_H \mu_M P_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\alpha_3\beta_3\alpha_W}{\mu_W P_4} & \frac{\alpha_3\beta_3}{\mu_W} \\ 0 & 0 & 0 & 0 & \frac{\sigma\alpha_4\beta_3\alpha_W}{\mu_W P_4} & \frac{\sigma\alpha_4\beta_3}{\mu_W} \end{bmatrix}.$$

Therefore from [25], the basic reproduction number of the Zika virus model is the positive and maximum eigenvalues of the matrix, FV^{-1}, which is given as

$$R_0 = max(R_0^{HM}, R_0^W)$$

where,

$$R_0^{HM}=\frac{\alpha_2\alpha_H\beta_2}{2P_1P_2}+\sqrt{\left(\frac{\alpha_2\alpha_H\beta_2}{2P_1P_2}\right)^2+\frac{(1-\sigma)\pi_M\alpha_H\alpha_1 b_M C_1\mu_H\beta_1^2}{\pi_H P_1P_2P_3\mu_M^2}}, \quad R_0^W=\frac{\alpha_3\beta_3\alpha_W}{\mu_W P_4}+\frac{\sigma\alpha_4\beta_3}{\mu_W},$$

With

$$P_1=(\mu_H+\alpha_H), P_2=(\mu_H+\theta_H+\delta_H), P_3=(\mu_M+b_M), P_4=(\mu_W+a_W). \tag{6}$$

R_0^{HM} is the reproduction number from humans and mosquitoes' interactions while R_0^W is the reproduction number from Aedes aegypti mosquito and Wolbachia mosquito mosquitoes' interactions.

3.4 Biological Impact of Reproduction Number on Zika Virus Transmission Dynamics

The reproduction number often denoted as (R_0), is a critical parameter in the mathematical modeling of infectious diseases, including the Zika virus. In the context of Zika virus transmission dynamics with vector control using Wolbachia-infected mosquitoes, having reproduction number, $R_0 < 1$ for the human population, Aedes aegypti mosquitoes, and Wolbachia-infected mosquitoes at disease-free equilibrium is indicative of effective control measures [24].

It is worth knowing that $R_0 < 1$ if $R_0^{HM} < 1$ or $R_0^W < 1$.

So,

$$R_0^{HM} < 1 \text{ if } \frac{\alpha_2\alpha_H\beta_2}{P_1P_2}+\frac{(1-\sigma)\pi_M\alpha_H\alpha_1 b_M C_1\mu_H\beta_1^2}{\pi_H P_1P_2P_3\mu_M^2} < 1, \tag{7}$$

while,

$$R_0^W < 1 \text{ if } \frac{\alpha_3\beta_3\alpha_W}{\mu_W P_4}+\frac{\sigma\alpha_4\beta_3}{\mu_W} < 1. \tag{8}$$

i. Human Population (Human-to-Human Transmission):

A reproduction number less than unity for the human population suggests that, on average, each infected individual is infecting fewer than one other person. This implies that the transmission of the Zika virus within the human population is being effectively suppressed. With proper vector control measures and potentially other intervention strategies such as vaccination or public health campaigns, the spread of the virus among humans can be mitigated [33].

ii. Aedes -aegypti Mosquitoes (Vector-to-Human Transmission):

Similarly, a reproduction number less than unity for the Ae. aegypti mosquitoes indicate that they are not effectively transmitting the virus to humans. This could be attributed to vector control measures such as insecticide spraying, larval source reduction, or environmental management aimed at reducing mosquito populations or interrupting their ability to transmit the virus. Keeping the reproduction number below unity for the mosquito population is crucial for preventing Zika virus outbreaks [34]

iii. Wolbachia-Infected Mosquitoes (Vector Control Strategy):

Introducing Wolbachia-infected mosquitoes as a vector control strategy aims to further reduce Zika virus transmission. The fact that the reproduction number for Wolbachia-infected mosquitoes is also less than unity signifies the effectiveness of this intervention. Wolbachia is a bacterium that can be introduced into mosquito populations to reduce their ability to transmit viruses like Zika. By reducing the vector competence of mosquitoes, Wolbachia-infected mosquitoes contribute to lowering the overall transmission potential of the virus, thus complementing other control measures [33, 34]

Therefore, maintaining reproduction numbers below unity for all relevant populations – humans, mosquitoes, and Wolbachia-infected mosquitoes is essential for effectively controlling Zika virus transmission dynamics. Achieving and sustaining these conditions requires comprehensive and integrated vector control strategies, along with continued surveillance and monitoring to assess the impact of interventions and adapt control measures as needed.

3.5 Local Asymptotic Stability of the Disease-Free Equilibrium of the Zika Virus Model

Theorem 2: *The disease-free equilibrium state of the Zika virus model is locally asymptotically stable (LAS) if* $R_0 < 1$, *and unstable if* $R_0 > 1$.

Theorem 3 [12]: *Assume that* $J(\varepsilon_0)$ *is an* $n \times n$ *matrix with constant entries and* $DetJ \neq 0$ *and* $J(\varepsilon_0)$ *has been obtained as a linearization method around the equilibrium* (ε_0), *then the equilibrium point is locally asymptotically stable if and only if*

Trace $J(\varepsilon_0) < 0$ and Determinant $J(\varepsilon_0) > 0$.

Proof: Using Jacobian matrix to prove the local stability of the disease-free equilibrium point.The Jacobian matrix associated with model (1) at the disease-free equilibrium state (ε_0) is calculated as

$$J(\varepsilon_0) = \begin{bmatrix} -\mu_H & 0 & -\beta_2\alpha_2 & 0 & 0 & 0 & -\beta_1\alpha_1 & 0 & 0 & 0 \\ 0 & -P_1 & \beta_2\alpha_2 & 0 & 0 & 0 & \beta_1\alpha_1 & 0 & 0 & 0 \\ 0 & \alpha_H & -P_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_H & -\mu_H & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\frac{(1-\sigma)\beta_1 c_1 \pi_M \mu_M}{\pi_H \mu_M} & 0 & -\mu_M & 0 & 0 & 0 & 0 & -\sigma\alpha_4\beta_3 \\ 0 & 0 & \frac{(1-\sigma)\beta_1 c_1 \pi_M \mu_M}{\pi_H \mu_M} & 0 & 0 & -P_3 & -\mu_M & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & b_M & -\mu_M & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_W & 0 & -\alpha_3\beta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -P_4 & \alpha_3\beta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_W & -\mu_W + \sigma\alpha_4\beta_3 \end{bmatrix} \quad (9)$$

To prove that the Zika virus-free equilibrium point $J(\varepsilon_0)$of the model is LAS, it is necessary to show that the eigenvalues of the Jacobian matrix, $J(\varepsilon_0)$of Equation (9) have negative real part. Thus, the first four eigenvalues are obtained as $-\mu_H$(multiplicity 2), $-\mu_M, -\mu_W$. The other six eigenvalues of the Jacobian matrix $J(\varepsilon_0)$ in Equation (3) can be obtained

from the following sub-matrix $J_1(\varepsilon_0)$ given by

$$J_1(\varepsilon_0) = \begin{bmatrix} -P_1 & \beta_2\alpha_2 & 0 & \beta_1\alpha_1 & 0 & 0 \\ \alpha_H & -P_2 & 0 & 0 & 0 & 0 \\ 0 & \frac{(1-\sigma)\beta_1 C_1 \pi_M \mu_M}{\pi_H \mu_M} & -P_3 & 0 & 0 & 0 \\ 0 & 0 & b_M & -\mu_W & 0 & 0 \\ 0 & 0 & 0 & 0 & -P_4 & \alpha_3\beta_3 \\ 0 & 0 & 0 & 0 & \alpha_W & -\mu_W + \sigma\alpha_4\beta_3 \end{bmatrix}. \quad (10)$$

Based on the Routh-Hurwitz conditions, the sub-matrix $J_1(\varepsilon_0)$expressed by Equation (10) has all its eigenvalues real and non-positive if the following two conditions are met:

i. Trace $J_1(\varepsilon_0) < 0$,

ii. Determinant $J_1(\varepsilon_0) > 0$.

We have that,

i. Trace $J_1(\varepsilon_0) = -\left(P_1 + P_2 + P_3 + \mu_M + P_4 + \mu_W\left(1 - \frac{\sigma\alpha_4\beta_3}{\mu_W}\right)\right) < 0$,

ii. Determinant $|J_1(\varepsilon_0)|$

$$|J_1(\varepsilon_0)| = \mu_M\mu_W P_1 P_2 P_3 P_4 \left(1 - \frac{\alpha_2\alpha_H\beta_2}{P_1P_2} - \frac{(1-\sigma)\pi_M\alpha_H\alpha_1 b_m C_1 \mu_H \beta_1^2}{\pi_H P_1 P_2 P_3 \mu_M^2}\right)\left(1 - \frac{\alpha_3\beta_1\alpha_W}{\mu_W P_4} - \frac{\sigma\alpha_4\beta_3}{\mu_W}\right). \quad (11)$$

Using Equations (7) and (8) implies that Equation (11) is positive if $R_0 < 1$, that is Determinant $|J_1(\varepsilon_0)| > 0$, if $R_0 < 1$. Also, Trace $J_1(\varepsilon_0) < 0$ if $R_0^W < 1$.

Consequently, all the eigenvalues of $J(\varepsilon_0)$ are real and negative implying that the Zika virus model (1) is locally asymptotically stable (LAS) if $R_0 < 1$and unstable otherwise [12, 27].

3.6 Global Asymptotic stability of the Zika virus model.

To investigate the global stability of the disease-free equilibrium, we use the technique implemented by Castillo-Chavez and Song [52]. To do this, we rewrite the equation in the uninfected class as

$$\frac{dX}{dt} = F(X,Z),$$

and the infected class as

$$\frac{dz}{dt} = G(X,Z),$$

where $X = (S_H, S_M, S_W, R) \in \mathbb{R}_+^4$ denotes the uninfected population and $Z = (E_H, I_H, E_M, I_M, E_W, I_W) \in \mathbb{R}_+^6$ denotes the infected population. $\varepsilon_0 = (X^*, 0)$ represent the disease-free equilibrium of the system.

So, the system is globally asymptotically stable if it satisfies the following conditions [26, 27]:

H_1: $\frac{dX}{dt} = F(X^*, 0)$, X^* is globally asymptotically stable,

H_2: $\frac{dZ}{dt} = D_Z G(X^*, 0)Z - \hat{G}(X,Z)$,

provided $\hat{G}(X,Z) \geq 0$ for all $(X,Z) \in D$and where $D_Z G(X^*, 0)$ is an M- matrix (i.e the diagonal elements are no-negative and it is equivalent to $D_Z G(X^*, 0) = F - V$. So, applying this to model (1), we have the following theorem.

Theorem 4: *The equilibrium point $\varepsilon_0 = (X^*, \mathbf{0})$ of the system (1) is globally asymptotically stable if $R_0 \leq 1$ otherwise it*

is unstable, where $X^* = \left\{\frac{\pi_H}{\mu_H}, 0, \frac{\pi_M}{\mu_M}, \frac{\pi_W}{\mu_W}\right\}$ *and* $\mathbf{0} = (0,0,0,0,0,0)$.

Proof: Using the technique by Castillo-Chavez and Song [52], we have

$$F(X,Z) = \begin{bmatrix} \pi_H - (\mu_H + \lambda_H)s_H \\ \theta_H I_H - \mu_H R_H \\ \pi_M - (\mu_M + \lambda_M)s_M \\ \pi_W - (\mu_W + \lambda_W)s_W \end{bmatrix}, \quad G(X,Z) = \begin{bmatrix} \frac{(\beta_1\alpha_1 I_M + \beta_2\alpha_2 I_H)S_H}{N_H} - P_1 E_H \\ \alpha_H E_H - P_2 I_H \\ \frac{(1-\sigma)\beta_1 C_1 I_H S_M}{N_H} - P_3 E_M \\ b_M E_M - \left(\mu_M + \frac{\alpha_4\beta_3 I_W}{N_M}\right) I_M \\ \frac{\alpha_3\beta_3 I_W S_W}{N_W} - P_4 E_W \\ \alpha_W E_W + \frac{\sigma\alpha_4\beta_3 I_W S_M}{N_M} + \frac{\alpha_4\beta_3 I_W I_M}{N_M} - \mu_W I_W \end{bmatrix}.$$

At disease free equilibrium, $\varepsilon_0 = (X^*, \mathbf{0})$ with $X^* = \left\{\frac{\pi_H}{\mu_H}, 0, \frac{\pi_M}{\mu_M}, \frac{\pi_W}{\mu_W}\right\}$ *and* $\mathbf{0} = (0,0,0,0,0,0)$,

$$H_1: \quad \begin{aligned} \frac{dS_H}{dt} &= \pi_H - \mu_H S_H, \\ \frac{dR}{dt} &= -\mu_H R_H, \\ \frac{dS_M}{dt} &= \pi_M - \mu_M S_M, \\ \frac{dS_W}{dt} &= \pi_W - \mu_W S_W, \end{aligned} \tag{12}$$

which is clear that the DFE, ε_0, is globally asymptotically stable since from Equation (12) that the Jacobian matrix, $J_{H_1}(\varepsilon_0)$, has negative eigenvalues, as given below,

$$J_{H_1}(\varepsilon_0) = \begin{bmatrix} -\mu_H & 0 & 0 & 0 \\ 0 & -\mu_H & 0 & 0 \\ 0 & 0 & -\mu_M & 0 \\ 0 & 0 & 0 & -\mu_W \end{bmatrix}$$

We have

$$H_2: \quad D_Z G(X^*, 0)Z = (F - V)Z = \begin{bmatrix} \beta_2\alpha_2 I_H + \beta_1\alpha_1 I_M - P_1 E_H \\ \alpha_H E_H - P_2 I_H \\ \frac{(1-\sigma)\beta_1 C_1 S_M^0 I_H}{N_H^0} - P_3 E_M \\ -\mu_M I_M + b_M E_M \\ \alpha_3\beta_3 I_W - P_4 E_W \\ \alpha_W E_W + \sigma\alpha_4\beta_3 I_W - \mu_W I_W \end{bmatrix},$$

where $\frac{S_M^0}{N_H^0} = \frac{\pi_M\mu_H}{\pi_H\mu_M}$.

Using the expression $\hat{G}(X,Z) = D_Z G(X^*,0)Z - G(X,Z)$, we get

$$\hat{G}(X,Z) = \begin{bmatrix} (\beta_2\alpha_2 + \beta_1\alpha_1)\left(\frac{S_H^0}{N_H^0} - \frac{S_H}{N_H}\right) \\ 0 \\ (1-\sigma)\beta_1 C_1 I_H\left(\frac{S_M^0}{N_H^0} - \frac{S_M}{N_H}\right) \\ 0 \\ \beta_3\alpha_3 I_W\left(\frac{S_W^0}{N_W^0} - \frac{S_W}{N_W}\right) \\ \sigma\beta_3\alpha_3 I_W\left(\frac{S_W^0}{N_W^0} - \frac{S_W}{N_W}\right) \end{bmatrix}.$$

Clearly, $\frac{S_H^0}{N_H^0} \geq \frac{S_H}{N_H}$, $\frac{S_M^0}{N_W^0} \geq \frac{S_M}{N_W}$ and $\frac{S_W^0}{N_H^0} \geq \frac{S_W}{N_H}$ and this implies that $\hat{G}(X,Z) \geq 0$. Therefore, the disease-free equilibrium of the Zika virus model (1) is globally asymptotically stable for $R_0 \leq 1$ since it satisfies the conditions of the technique by Castillo-Chavez and Song [52], otherwise it is unstable.

3.7 Endemic Equilibrium Point of the Model

The endemic equilibrium point is the steady state where there is persistence or prevalence of a disease in the population.

To obtain the endemic equilibrium, we set the right-hand side (RHS) of the differential equations in Equation (1) to zero and solve simultaneously for the state variables, $S_H, E_H, I_H, R_H, S_H, S_M, E_M, I_M, S_W, E_W, I_W$.

Thus, at the endemic equilibrium point, $\frac{dS_H}{dt} = \frac{dE_H}{dt} = \frac{dI_H}{dt} = \frac{dR_H}{dt} = \frac{dS_M}{dt} = \frac{dE_M}{dt} = \frac{dI_M}{dt} = \frac{dS_W}{dt} = \frac{dE_W}{dt} = \frac{dI_W}{dt} = 0$.

Let $\varepsilon^{**} = (S_H{}^{**}, E_H{}^{**}, I_H^{**}, R_H{}^{**}, S_M^{**}, E_M^{**}, I_M^{**}, S_W^{**}, E_W^{**}, I_W^{**})$ be the endemic equilibrium state.

We solve the endemic equilibrium state in terms of the force of infections in Equation (1) using the definition in Equation (6) such that

$$S_H^{**} = \frac{\pi_H}{\lambda_H^{**}+\mu_H}; \quad E_H^{**} = \frac{\pi_H \lambda_H^{**}}{(\lambda_H^{**}+\mu_H)P_1}, \quad I_H^{**} = \frac{\pi_H \lambda_H^{**} \alpha_H}{(\lambda_H^{**}+\mu_H)P_1 P_2}, \quad R_H^{**} = \frac{\pi_H \lambda_H^{**} \alpha_H \theta_H}{\mu_H(\lambda_H^{**}+\mu_H)P_1 P_2}, \quad S_M^{**} = \frac{\pi_M}{(1-\sigma)\lambda_M^{**}+\sigma\lambda_{W2}^{**}+\mu_M},$$

$$E_M^{**} = \frac{(1-\sigma)\pi_M \lambda_M^{**}}{\left((1-\sigma)\lambda_M^{**}+\sigma\lambda_{W2}^{**}+\mu_M\right)P_3}, \quad I_M^{**} = \frac{b_M E_M^{**}}{(\lambda_{W2}^{**}+\mu_M)}, \quad S_W^{**} = \frac{\pi_W}{\lambda_{W1}^{**}+\mu_W}, \quad E_W^{**} = \frac{\pi_W \lambda_{W1}^{**}}{(\lambda_{W1}^{**}+\mu_W)P_4},$$

$$I_W{}^{**} = \frac{\alpha_W E_W^{**} + (\sigma S_M^{**} + I_M^{**})\lambda_{W2}^{**}}{\mu_W}.$$

Due to the complexity of solving the endemic equilibrium state, we present it numerically in Figure 3 for the infected populations. The parameter values for the simulation are in Table 2.

Table 2: Parameter values of the model with their sources.

Parameters	Value	Source	Parameters	Value	Source
π_H	0.0647	[31]	α_2	0.16	Estimated
π_M	0.0471	Estimated	α_3	0.11	[18]
π_W	0.03645	Estimated	α_4	0.0000057	[22]
μ_H	0.00003	[30]	α_H	0.17	Estimated
μ_M	0.04	Estimated	θ_H	0.013	[22]
μ_W	0.000025	[30]	b_M	0.02070591	Estimated
β_1	0.45	[32]	α_W	0.0193	Estimated
β_2	0.37	Estimated	δ_H	0.0025	[18]
α_1	0.000006	[29]	C_1	0.12	Estimated
β_3	0.045	Estimated	σ	0.5	Estimated

4. Sensitivity Analysis of the Zika Virus Model

Sensitivity analysis, a fundamental tool in mathematical modeling, is crucial for model assessment, risk management, optimization, and decision-making. It plays a vital role in ensuring the reliability and utility of mathematical models in various fields, providing valuable insights into the behavior and reliability of mathematical validation and the verification of mathematical models.

The sensitivity index of the reproduction number of the Zika virus model, R_0, with respect to any parameter say p of R_0 is given by:

$$\Im_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}.$$

For the model (1), $R_0 = max(R_0^{HM}, R_0^W)$

where $R_0^{HM} = \frac{\alpha_2 \alpha_H \beta_2}{2P_1P_2} + \sqrt{\left(\frac{\alpha_2 \alpha_H \beta_2}{2P_1P_2}\right)^2 + \frac{(1-\sigma)\pi_M \alpha_H \alpha_1 b_M C_1 \mu_H \beta_1^2}{\pi_H P_1 P_2 P_3 \mu_M^2}}$, $R_0^W = \frac{\alpha_3 \beta_3 \alpha_W}{\mu_W P_4} + \frac{\sigma \alpha_4 \beta_3}{\mu_W}$,

we obtained the sensitivity indices of parameters of the R_0^{HM}, and R_0^W given in Figure 2 using the parameter values in Table 2.

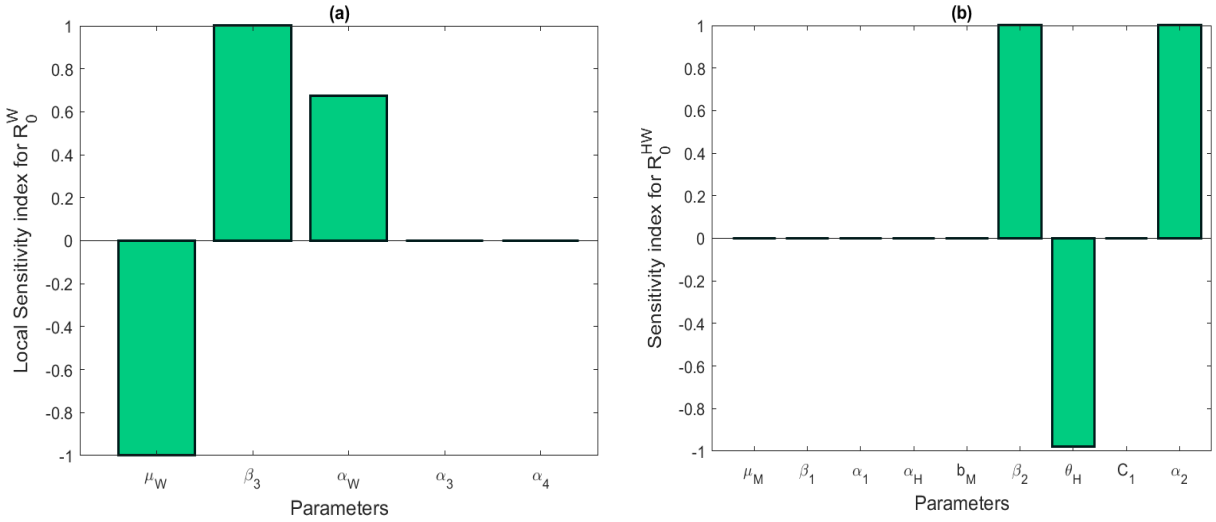


Fig. 2: Plot for local sensitivity index of R_0^{HM} and R_0^W using the parameter values in Table 2. (a) Sensitivity index for essential parameters of the reproduction number, R_0^W, and (b) Sensitivity index for essential parameters of the reproduction number, R_0^{HW}.

4.1 Sensitivity Plot of the Basic Reproduction Number

A sensitivity plot is a graphical representation used in epidemiology to visualize the impact of variations in model parameters, specifically those related to disease transmission and control, on the basic reproduction number (R_0). The basic reproduction number is a crucial epidemiological metric representing the average number of secondary infections generated by single infected individuals in a completely susceptible population [25]. Understanding how specific parameter changes influence R_0 is essential for effective disease control strategies. Sensitivity plots allow policymakers and epidemiologists to identify which parameters significantly influence R_0. They are used to predict the best method for disease control and are essential tools for decision-making in public health, especially during disease outbreaks and vaccination campaigns [23]. To interpret sensitivity results, parameters with positive sensitivity index value typically represent a factor that increases disease spread, while negative sensitivity index value parameters represent a factor that reduces disease spread. Figure 2 above reveals the sensitivity index of the R_0^{HM} and R_0^W with respect to their respective parameters. The effects on R_0^{HM} and R_0^W show how each parameter influences the basic reproduction number. The parameters with positive indices $(\beta_1, \beta_2, \alpha_2, \alpha_H, \alpha_1, C_1, \text{and } b_M)$ with $(\beta_2 \text{ and } \alpha_2)$ as the most significant parameters indicate that they tend to increase the disease in the population as their values rise on R_0^{HM} and R_0^M, respectively. This implies that the average number of secondary cases of infection increases in the population. However, the increase in the parameters $(\beta_3, \alpha_3, \alpha_4, \text{ and } \alpha_W)$ on R_0^W with β_3 and α_W as the most significant parameters will instead help in reducing the disease by reducing the disease potency in the Aedes mosquitoes that spread the disease, as Wolbachia is believed not to be harmful to human [53]. The parameters with negative indices, such as θ_H, and μ_M with θ_H, as the most significant on R_0^{HM} and R_0^M, will reduce the disease in society as the value of these parameters increases. An increase in μ_W may not be helpful as Wolbachia is being used as a suppression strategy to render Aedes mosquitoes impotent in spreading Zika disease.

5. The Optimal Control Model and Its Analysis

The basic model of the Zika virus in the system of Equations (1) is extended into the optimal control model version based on the sensitivity analysis results and the need to optimize some parameters such as $\beta_1, \beta_2, \mu_M, \alpha_2, \beta_3, \pi_W, \alpha_W, \mu_W, \theta_H$, which can influence the Zika reproduction number and, by implication, help control the spread of the disease. Therefore, the optimal control model is given as follows,

$$
\begin{aligned}
\frac{dS_H}{dt} &= \pi_H - \left(\frac{\beta_1(1-u_4(t))\alpha_1 I_M + \beta_2(1-u_1(t))\alpha_2 I_H}{N_H}\right) S_H - \mu_H S_H,\\
\frac{dE_H}{dt} &= \left(\frac{\beta_1(1-u_4(t))\alpha_1 I_M + \beta_2(1-u_1(t))\alpha_2 I_H}{N_H}\right) S_H - (\mu_H + \alpha_H) E_H,\\
\frac{dI_H}{dt} &= \alpha_H E_H - \left(\mu_H + \delta_H + \theta_H\left(1+u_2(t)\right)\right) I_H,\\
\frac{dR_H}{dt} &= \theta_H\left(1+u_2(t)\right) I_H - \mu_H R_H,\\
\frac{dS_M}{dt} &= \pi_M - \frac{(1-\sigma)\beta_1(1-u_4(t))c_1 I_H S_M}{N_H} - \frac{\sigma\beta_3(1+u_4(t))\alpha_4 I_W S_M}{N_M} - \mu_M\left(1+u_4(t)\right) S_M,\\
\frac{dE_M}{dt} &= \frac{(1-\sigma)\beta_1(1-u_4(t))c_1 I_H S_M}{N_H} - \left(\mu_M\left(1+u_4(t)\right) + b_M\right) E_M,\\
\frac{dI_M}{dt} &= b_M E_M - \mu_M\left(1+u_4(t)\right) I_M - \frac{\beta_3(1+u_4(t))\alpha_4 I_W I_M}{N_M},\\
\frac{dS_W}{dt} &= \pi_W\left(1+u_3(t)\right) - \left(\frac{\beta_3(1+u_4(t))\alpha_3 I_W}{N_W}\right) S_W - \mu_W\left(1-u_3(t)\right) S_W,\\
\frac{dE_W}{dt} &= \left(\frac{\beta_3(1+u_4(t))\alpha_3 I_W}{N_W}\right) S_W - \left(\mu_W\left(1-u_3(t)\right) + \alpha_W\right) E_W,\\
\frac{dI_W}{dt} &= \alpha_W E_W + \frac{\sigma\beta_3(1+u_4(t))\alpha_4 I_W S_M}{N_M} + \frac{\beta_3(1+u_4(t))\alpha_4 I_W I_M}{N_M} - \mu_W\left(1-u_3(t)\right) I_W,
\end{aligned}
\tag{13}
$$

with the initial conditions of the model (1).

Here, $u_1(t)$ is the use of condom/avoidance of multiple sex partners control, $u_2(t)$ is the screening/treatment of the infected humans, $u_3(t)$ is the boosting/enhancement of breeding Wolbachia mosquitoes' population, and $u_4(t)$ is the injection of infected Wolbachia mosquitoes' control into the mosquitoes population. The injection of Wolbachia-infected mosquitoes reduces the mosquito population, survival rate, and ability to transmit Zika disease [54]. The objective functional to be minimized is given as

$$
\begin{aligned}
J\left(u_1(t), u_2(t),\ u_3(t), u_4(t)\right) = \int_0^{tf} \Big(& AI_H + BN_M + CI_W + \frac{1}{2} m_1 u_1^2(t) + \frac{1}{2} m_2 u_2^2(t) - \\
& \frac{1}{2} m_3 u_3^2(t) + \frac{1}{2} m_4 u_4^2(t) \Big),
\end{aligned}
\tag{14}
$$

where the coefficient associated with the infected state variables, A, B, and C, where B is attached to all the Aedes population classes and the control weight coefficients, $m_1, m_2, m_3,$ and $m_4,$ are assumed positive. The quadratic form of the control variables, $\sum_{i=1}^{4} m_i u_i^2(t)$ in Equation (14), is due to the nonlinearity of the cost of controls and is also based on literature in optimal control of infectious diseases [40,41,42,43].

The optimal control model's objective is clear: to minimize the number of infected humans and mosquitoes while also minimizing the cost of implementing control measures. At the same time, the model aims to maximize the number of infected Wolbachia mosquitoes to depopulate them with the Zika virus, hence the reason for the negative attached to the control $u_3^*(t)$. So, we seek the optimal controls $u_1^*(t), u_2^*(t),\ u_3^*(t), u_4^*(t)$ such that

$$
J(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)) = \min_{\Phi_1} J\left(u_1(t),\ u_2(t),\ u_3(t),\ u_4(t)\right),
\tag{15}
$$

where,

$$
\Phi_1 = \left\{u_i(t), i = 1,2,3,4 \text{ are measurable with } u_i(t) \in [0,1], \text{for } 0 \le t \le t_f\right\}.
\tag{16}
$$

The state and control variables of equations (13) and (14) are nonnegative, as established in Subsection (3.1) and Equation (16), which implies that the set Φ_1 is closed, convex, and exists. By employing Corollary 4.1 of Pages 68-69 in [44] as implemented in [42,43,45,46], we state that the state and control variables of equations (13) and (14) are nonnegative. We therefore apply the Pontryagin maximum principle (PMP) [47] to the optimal control problem of the forward-backward sweep method with a two-point boundary value problem [48], which transforms Equations (13) and (14) into a problem of minimizing pointwise Hamiltonian H. The Hamiltonian H for the control problem consists of L, the inner product of the right-hand side of Equation (13), and the respective adjoint variables $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6,\ \lambda_7, \lambda_8, \lambda_9, \lambda_{10})$ of the state

variables, and it is presented as;

$$H(S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_M, I_W) = L\left(I_H, I_M, I_W, u_1(t),\ u_2(t),\ u_3(t), u_4(t)\right) + \lambda_1 \frac{dS_H}{dt} + \lambda_2 \frac{dE_H}{dt} + \lambda_3 \frac{dI_H}{dt} + \lambda_4 \frac{dR_H}{dt} + \lambda_5 \frac{dS_M}{dt} + \lambda_6 \frac{dE_M}{dt} + \lambda_7 \frac{dI_M}{dt} + \lambda_8 \frac{dS_W}{dt} + \lambda_9 \frac{dE_M}{dt} + \lambda_{10} \frac{dI_W}{dt}. \quad (17)$$

PMP is adopted to establish the necessary conditions for deriving the optimality system. Using a similar approach in [42,43,44,45], the following theorem is used to derive the optimality system.

Theorem Given an optimal control $u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)$ and corresponding state variables $S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_M, I_W$ that minimizes the objective functional $J\left(u_1(t),\ u_2(t),\ u_3(t), u_4(t)\right)$ over Φ_1, there exist non-trivial adjoint functions $\lambda_1, \ldots \lambda_{10}$ satisfying;

$$\frac{d\lambda_1}{dt} = (\lambda_1 - \lambda_2)(N_H - S_H)\left(\frac{\beta_1(1-u_4(t))\alpha_1 I_M + \beta_2(1-u_1(t))\alpha_2 I_H}{N_H^2}\right) + (\lambda_6 - \lambda_5)\frac{(1-\sigma)\beta_1(1-u_4(t))C_1 I_H S_M}{N_H^2} + \lambda_1\mu_H,$$

$$\frac{d\lambda_2}{dt} = (\lambda_2 - \lambda_1)\left(\frac{\beta_1(1-u_4(t))\alpha_1 I_M + \beta_2(1-u_1(t))\alpha_2 I_H}{N_H^2}\right) S_H + (\lambda_6 - \lambda_5)\frac{(1-\sigma)\beta_1(1-u_4(t))C_1 I_H S_M}{N_H^2} + (\lambda_2 - \lambda_3)\alpha_H + \lambda_2\mu_H,$$

$$\frac{d\lambda_3}{dt} = -A + (\lambda_1 - \lambda_2)\left(\frac{(N_H S_H - I_H S_H)\beta_2(1-u_1(t))\alpha_2 - \beta_1(1-u_4(t))\alpha_1 I_M S_H}{N_H^2}\right) + (\lambda_6 - \lambda_5)(N_H - I_H)\frac{(1-\sigma)\beta_1(1-u_4(t))C_1 S_M}{N_H^2} + (\lambda_3 - \lambda_4)\theta_H\left(1 + u_2(t)\right) + \lambda_3(\mu_H + \delta_H),$$

$$\frac{d\lambda_4}{dt} = (\lambda_2 - \lambda_1)\left(\frac{\beta_1(1-u_4(t))\alpha_1 I_M + \beta_2(1-u_1(t))\alpha_2 I_H}{N_H^2}\right) S_H + (\lambda_6 - \lambda_5)\frac{(1-\sigma)\beta_1(1-u_4(t))C_1 I_H S_M}{N_H^2} + \lambda_4\mu_H,$$

$$\frac{d\lambda_5}{dt} = -B + (\lambda_5 - \lambda_6)\frac{(1-\sigma)\beta_1(1-u_4(t))C_1 I_H}{N_H} + (\lambda_5 - \lambda_{10})(N_M - S_M)\frac{\sigma\beta_3(1+u_4(t))\alpha_4 I_W}{N_M^2} + (\lambda_{10} - \lambda_7)\frac{\beta_3(1+u_4(t))\alpha_4 I_W I_M}{N_M^2} + \lambda_5\mu_M\left(1 + u_4(t)\right),$$

$$\frac{d\lambda_6}{dt} = -B + (\lambda_{10} - \lambda_5)\frac{\sigma\beta_3(1+u_4(t))\alpha_4 I_W S_M}{N_M^2} + (\lambda_{10} - \lambda_7)\frac{\beta_3(1+u_4(t))\alpha_4 I_W I_M}{N_M^2} + (\lambda_6 - \lambda_7)b_M + \lambda_6\mu_M\left(1 + u_4(t)\right),$$

$$\frac{d\lambda_7}{dt} = -B + (\lambda_1 - \lambda_2)\frac{\beta_1(1-u_4(t))\alpha_1 S_H}{N_H} + (\lambda_{10} - \lambda_5)\frac{\sigma\beta_3(1+u_4(t))\alpha_4 I_W S_M}{N_M^2} + (\lambda_7 - \lambda_{10})(N_M - I_M)\frac{\beta_3(1+u_4(t))\alpha_4 I_W}{N_M^2} + \lambda_7\mu_M\left(1 + u_4(t)\right),$$

$$\frac{d\lambda_8}{dt} = (\lambda_8 - \lambda_9)(N_W - S_W)\left(\frac{\beta_3(1+u_4(t))\alpha_3 I_W}{N_W^2}\right) + \lambda_8\mu_W\left(1 - u_3(t)\right),$$

$$\frac{d\lambda_9}{dt} = (\lambda_9 - \lambda_8)\left(\frac{\beta_3(1+u_4(t))\alpha_3 I_W}{N_W^2}\right) S_W + (\lambda_9 - \lambda_{10})\alpha_W + \lambda_9\mu_W\left(1 - u_3(t)\right),$$

$$\frac{d\lambda_{10}}{dt} = -C + (\lambda_5 - \lambda_{10})\frac{\sigma\beta_3(1+u_4(t))\alpha_4 S_M}{N_M} + (\lambda_7 - \lambda_{10})\frac{\beta_3(1+u_4(t))\alpha_4 I_M}{N_M} + (\lambda_8 - \lambda_9)(N_W - I_W)\left(\frac{\beta_3(1+u_4(t))\alpha_3 S_W}{N_W^2}\right) + \lambda_{10}\mu_W\left(1 - u_3(t)\right), \quad (18)$$

with the transversality condition

$\lambda_i(t_f) = 0, i = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10$

and the controls $u_1^*(t)$, $u_2^*(t)$, $u_3^*(t), u_4^*(t)$ satisfying the optimality condition;

$$u_1^* = max\left\{0,\ min\left(\frac{\beta_2(\lambda_2 - \lambda_1)\alpha_2 I_H S_H}{m_1 N_H},\ 1\right)\right\},$$

$$u_2^* = max\left\{0,\ min\left(\frac{(\lambda_3 - \lambda_4)\theta_H I_H}{m_2},\ 1\right)\right\}, \quad (19)$$

$$u_3^* = max\left\{0,\ min\left(\frac{\lambda_8\pi_W+\lambda_8\mu_W S_W+\lambda_9\mu_W E_W+\lambda_{10}\mu_W I_W}{m_3},\ 1\right)\right\},$$

$$u_4^* = max\{0,\ min(M,\ 1)\},$$

where

$$M = \frac{1}{m_4}\left((\lambda_2-\lambda_1)J_1+(\lambda_6-\lambda_5)J_2+(\lambda_8-\lambda_9)J_3+(\lambda_5-\lambda_{10})J_5+(\lambda_7-\lambda_{10})J_6+J_4\right)$$

with,

$$J_1 = \frac{\beta_1\alpha_1 I_M S_H}{N_H},\quad J_2 = \frac{(1-\sigma)\beta_1 C_1 I_H S_M}{N_H},\quad J_3 = \frac{\beta_3\alpha_3 I_W S_W}{N_W},\quad J_5 = \frac{\sigma\beta_3\alpha_4 I_W S_M}{N_M},\quad J_6 = \frac{\beta_3\alpha_4 I_W I_M}{N_M},$$

$$J_4 = \lambda_5\mu_M S_M + \lambda_6\mu_M E_M + \lambda_7\mu_M I_M.$$

Proof. Employing PMP, the adjoint system (18) is obtained by differentiating Equation (17) with respect to their corresponding state variables, $S_H, E_H, I_H, R_H, S_M, E_M, I_M, S_W, E_W\ I_W$; this is evaluated at the optimal control functions $u_1(t), u_2(t),\ u_3(t), u_3(t)$ and negate. Then, the optimality condition equation (19) is obtained by solving for the controls, $u_1^*(t),\ u_2^*(t),\ u_3^*(t),\ u_4^*(t)$ at the respective steady states $\frac{\partial H}{\partial u_1(t)} = \frac{\partial H}{\partial u_2(t)} = \frac{\partial H}{\partial u_3(t)} = \frac{\partial H}{\partial u_4(t)} = 0$ on the interior of the control set. The proof is complete. Thus, the optimality system is Equation (18) and (19) substituted into (12).

5.1 The Optimal Control Problem Simulations

Numerical simulations of the optimality system are conducted to demonstrate the pictorial behaviors of the optimal control system with time using the fourth-order Runge-Kutta method with the aid of MATLAB R2007b. The parameter values used for the simulations are given in Table 2, and the initial conditions and weight coefficient values are as follows; $S_H(0) = 2000, E_H(0) = 1500, I_H(0) = 1300, R_H(0) = 1800,\ S_M(0) = 1000, E_M(0) = 800, I_M(0) = 900, S_W(0) = 1000,\ E_M(0) = 800,\ I_W(0) = 900, \mathrm{A}, \mathrm{B} = 10, \mathrm{C} = 20$,$m_1 = 9{,}000, m_2 = 10{,}000, m_3 = 50$ and $m_4 = 40{,}000$. At the same time, the values for the weight coefficients are chosen to balance the simulations and make the control variables feasible in the region, $u(t) \in [0,1]$.

The simulations are partitioned into four (4) possible cases with fifteen (15) different combination strategies

Combinations of all controls

- $u_1, u_2, u_3, u_4 \neq 0$ (use of condom/avoidance of multiple sex partners control+the screening/treatment of the infected humans+ the boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population).

Implementation of single control

- $u_1 \neq 0, u_2, u_3, u_4 = 0$ (use of condom/avoidance of multiple sex partners control)
- $u_2 \neq 0, u_1, u_3, u_4 = 0$ (screening/treatment of the infected humans)
- $u_3 \neq 0, u_1, u_2, u_4 = 0$ (boosting/enhancement of breeding Wolbachia mosquitoes' population)
- $u_4 \neq 0, u_1, u_2, u_3 = 0$ (injection of Wolbachia-infected mosquitoes' control into mosquitoes' population)

Implementation of double controls

- $u_1, u_2 \neq 0, u_3, u_4 = 0$ (use of condom/avoidance of multiple sex partners control+ screening/treatment of the infected humans)
- $u_1, u_3 \neq 0, u_2, u_4 = 0$ (use of condom/avoidance of multiple sex partners control+ boosting/enhancement of breeding Wolbachia infected mosquitoes' population)
- $u_1, u_4 \neq 0, u_2, u_3 = 0$ (use of condom/avoidance of multiple sex partners control+ injection of Wolbachia infected mosquitoe s' control into mosquitoes' population)
- $u_2, u_3 \neq 0, u_1, u_4 = 0$ (screening/treatment of the infected humans+ boosting/enhancement of breeding Wolbachia mosquitoes' population)

- $u_2, u_4 \neq 0, u_1, u_3 = 0$ (screening/treatment of the infected humans+ injection of Wolbachia infected mosquitoes' control into mosquitoes' population)
- $u_3, u_4 \neq 0, u_1, u_2 = 0$ (boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population)

Implementation of triple controls

- $u_1, u_2, u_3 \neq 0, u_4 = 0$ (use of condom/avoidance of multiple sex partners control+ screening/treatment of the infected humans+ boosting/enhancement of breeding Wolbachia mosquitoes' population)
- $u_1, u_2, u_4 \neq 0, u_3 = 0$ (use of condom/avoidance of multiple sex partners control+ screening/treatment of the infected humans + injection of Wolbachia infected mosquitoes' control into mosquitoes' population)
- $u_1, u_3, u_4 \neq 0, u_2 = 0$ (use of condom/avoidance of multiple sex partners control+ boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population)
- $u_2, u_3, u_4 \neq 0, u_1 = 0$ (screening/treatment of the infected humans+ boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population)
- The following notations are used in the simulation plots; $u_1, u_2 = u_1 + u_2$, $u_1, u_3 = u_1 + u_3$, $u_1, u_4 = u_1 + u_4$, $u_2, u_3 = u_2 + u_3$, $u_2, u_4 = u_2 + u_4$, $u_3, u_4 = u_3 + u_4$, $u_1, u_2, u_3 = u_1 + u_2 + u_3$, $u_1, u_2, u_4 = u_1 + u_2 + u_4$, $u_1, u_3, u_4 = u_1 + u_3 + u_4$, $u_2, u_3, u_4, = u_2 + u_3 + u_4$, $u_1, u_2, u_3, u_4 = u_1 + u_2 + u_3 + u_4$ (all controls).

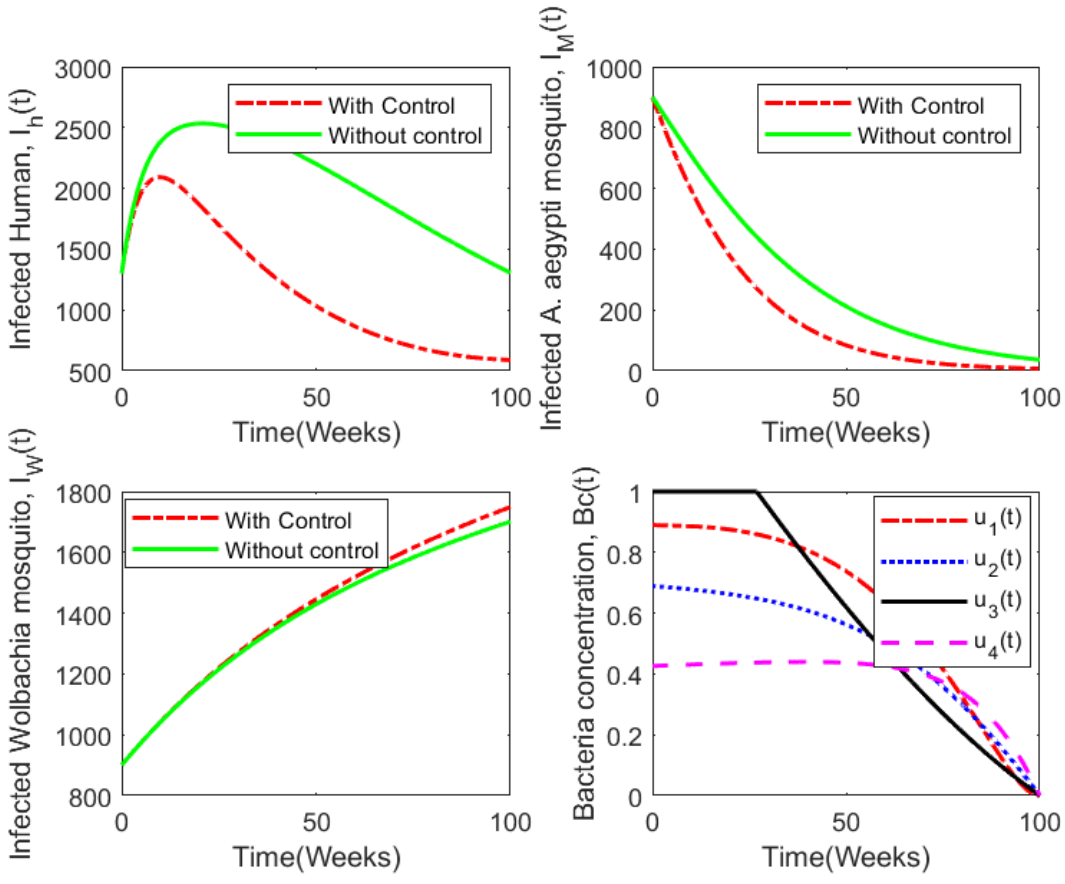


Fig. 3: Simulation plots for all controls implementation: Infected Humans, Infected mosquitoes (no Wolbachia), Infected Wolbachia mosquito and Control Profile for the Combined Implementation of All four controls.

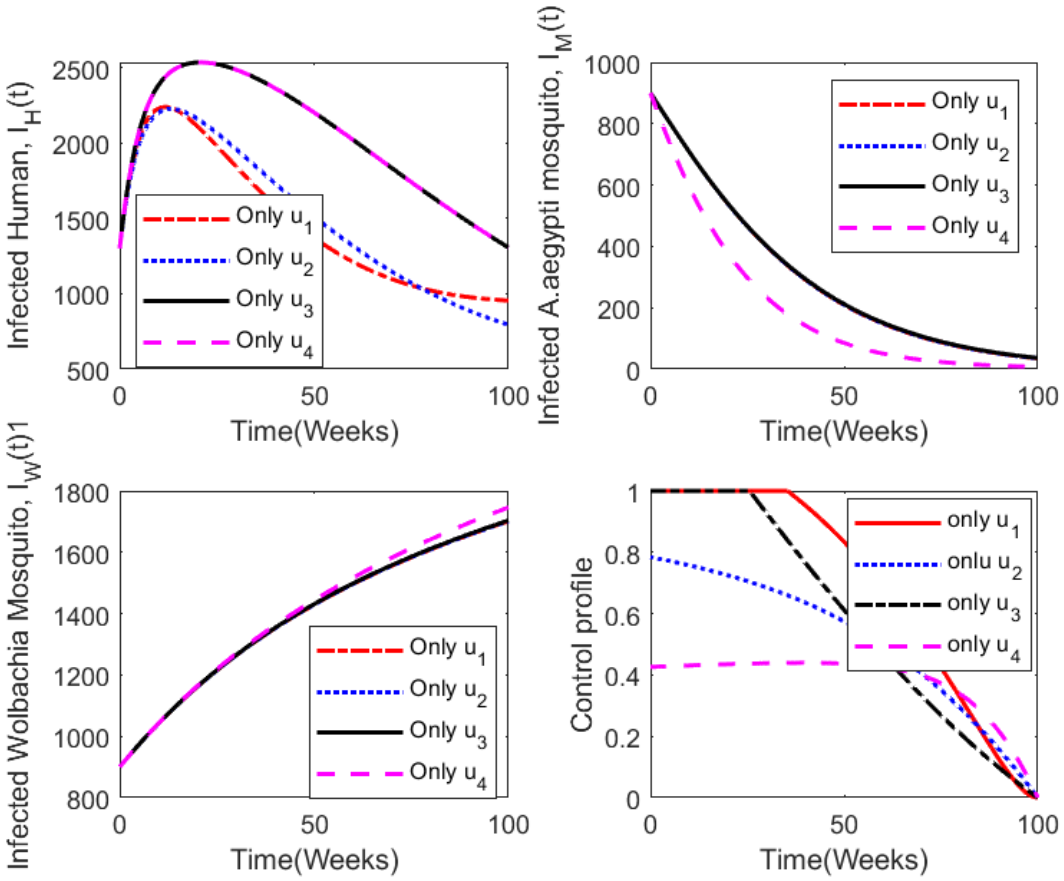
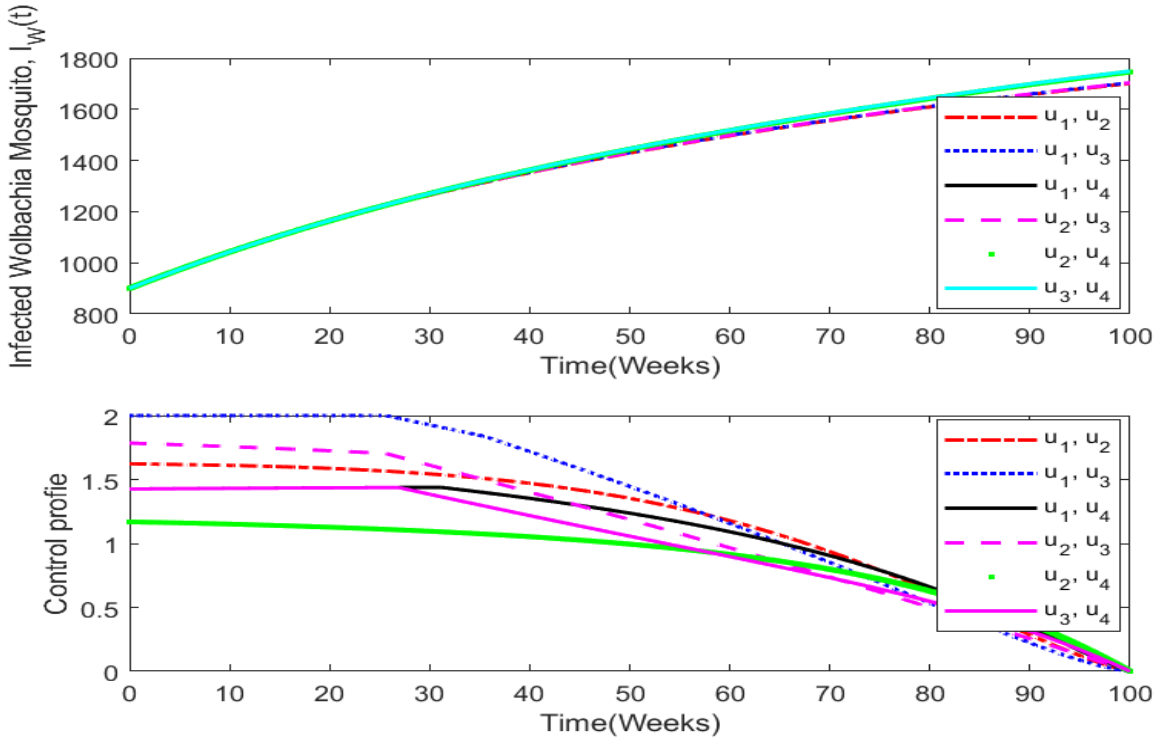


Fig. 4: Simulation plots for single implementation Control: Infected Humans, Infected mosquitoes (no Wolbachia), Infected Wolbachia mosquitoes, and Control Profile for the Combined Implementation of all Controls.



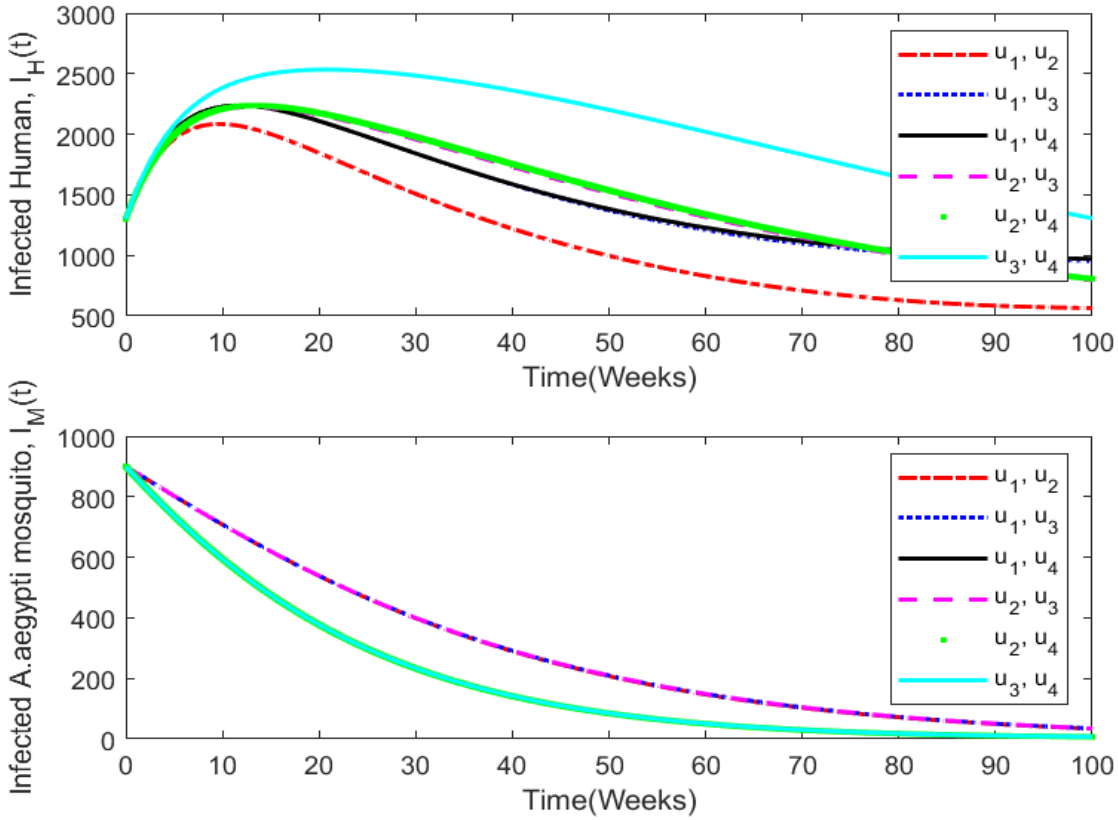
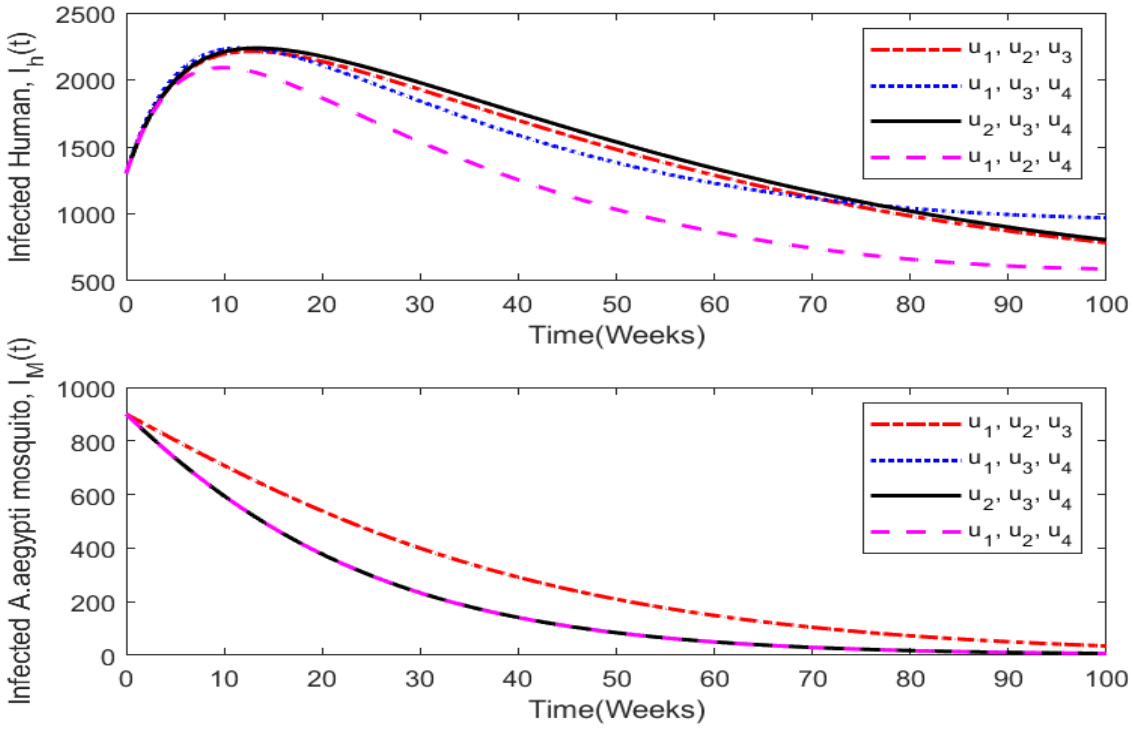


Fig. 5: Simulation plots for double implementation controls: Infected Humans, Infected mosquitoes (no Wolbachia), Infected Wolbachia mosquitoes and Control Profile for Combined Implementation of Double Controls.



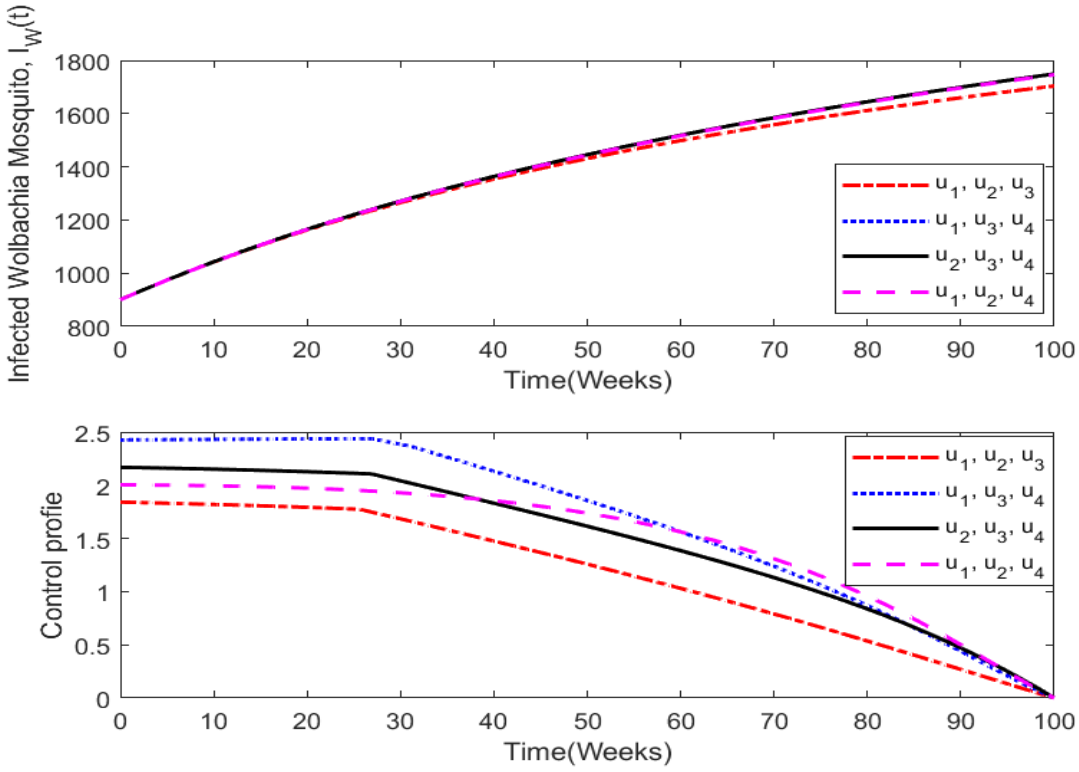


Fig. 6: Simulation plots for triple implementation controls: Infected Humans, mosquitoes (no Wolbachia), Infected Wolbachia mosquito and Control Profile for the Combined Implementation of Triple Controls.

5.2 Discussion

In Figure 3, the implementation of all the controls shows that infected humans increase to the maximum point of about 2050 on day 10 and start reducing from day 20 to almost zero at about day 90, while without control, the infected human population increases to about 2500 at day 20 and starts reducing gradually to the minimum point of about 1350. Also, with all the controls, the number of infected mosquitoes that spread the Zika virus has decreased from a maximum point of about 850 to almost zero at about day 85. In contrast, with no control, the number of mosquitoes started reducing from a maximum point of about 900 to a minimum point of about 55. This shows that the mosquitoes that transmit the Zika virus will be eliminated from the environment with controls. Also, with all the controls, infected Wolbachia mosquitoes, which fight other mosquitoes that transmit the Zika virus, keep increasing to a maximum of about 1750, while without control, the infected Wolbachia mosquitoes keep rising to a maximum point of about 1700. The control profile in Figure 3 shows how each control should be implemented to achieve the results on the infected humans and mosquitoes.

Figure 4 shows that $u_2(t)$, which is the screening/treatment of the infected humans, is the most effective in reducing the infected human population, followed by $u_1(t)$, the use of condoms/avoidance of multiple sex partners' control. In contrast, $u_4(t)$, which is the injection of Wolbachia-infected mosquitoes' control into the mosquitoes' population, is most effective in reducing infected mosquitoes with no Wolbachia (Aedes mosquitoes), which is almost eliminated at about day 80. Also, infected Wolbachia mosquitoes that fight other mosquitoes that transmit Zika virus keep increasing to a maximum point of about 1750 with the usage of control $u_4(t)$ which is the injection of Wolbachia infected mosquitoes' control into mosquitoes' population while the usage of $u_1(t)$ use of condom/avoidance of multiple sex partners control or $u_2(t)$ is the screening/treatment of the infected humans or $u_3(t)$ the boosting/enhancement of breeding Wolbachia mosquitoes' population increases the Infected Wolbachia to a maximum of 1700. The control profile represents the pattern in which the single control should be implemented.

Figure 5, which shows the implementation of double control strategies, shows that a combination of $u_1(t) + u_2(t)$ (use of condom/avoidance of multiple sex partners control + the screening/treatment of the infected humans) is the most effective strategy to reduce the population of infected humans compared to others. In contrast, a combination of $u_3(t) + u_4(t)$ (boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes'

control into mosquitoes' population) is the most effective control strategy to reduce the mosquitoes that transmit Zika virus to the barest minimum, followed by the strategy $u_2(t)+u_4(t)$. Also, the control strategy $u_3(t)+u_4(t)$ (boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population) is the most control implementation strategy that increases the number of infected Wolbachia mosquitoes to a maximum point of about1750, which can help to fight other mosquitoes that spread the Zika virus, followed by strategy $u_2(t)+u_4(t)$. The control profile shows how double control should be applied.

In Figure 6, the combination of $u_1(t)+u_2(t)+u_4(t)$ (use of condom/avoidance of multiple sex partners control + the screening/treatment of the infected humans+ injection of Wolbachia infected mosquitoes' control into mosquitoes' population) is the best strategy that reduces the infected human population to barest minimum before day 100, followed by the combination of $u_1(t)+u_2(t)+u_3(t)$ (use of condom/avoidance of multiple sex partners control + the screening/treatment of the infected humans+ boosting/enhancement of breeding Wolbachia mosquitoes' population). Also, the combined strategy is either $u_1(t)+u_3(t)+u_4(t)$ (use of condom/avoidance of multiple sex partners control + boosting/enhancement of breeding Wolbachia infected mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population) or $u_2(t)+u_3(t)+u_4(t)$ (the screening/treatment of the infected humans + boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population) or $u_1(t)+u_3(t)+u_4(t)$ (use of condom/avoidance of multiple sex partners control (the screening/treatment of the infected humans + injection of Wolbachia infected mosquitoes' control into mosquitoes' population) is the most effective and efficient strategy in reducing the mosquitoes that transmit Zika virus. The best control strategy to increase infected Wolbachia mosquitoes that fight other species of mosquitoes that spread Zika virus is either $u_1(t)+u_3(t)+u_4(t)$ (use of condom/avoidance of multiple sex partners control + boosting/enhancement of breeding Wolbachia mosquitoes' population + injection of Wolbachia infected mosquitoes' control into mosquitoes' population) or $u_2(t)+u_3(t)+u_4(t)$ or $u_1(t)+u_2(t)+u_4(t)$ (use of condom/avoidance of multiple sex partners control +the screening/treatment of the infected humans + injection of Wolbachia infected mosquitoes' control into mosquitoes' population). The control profile depicts the pattern in which the triple control should be applied.

6. Conclusion

This work examines a mathematical model for the dynamics of Zika virus disease by incorporating Wolbachia mosquitoes. The basic reproduction number, R_0, is derived and used to establish the local and global stability of the disease-free equilibrium when $R_0<1$. R_0 is further used to investigate the sensitivity analysis of model parameters. The sensitivity results for the parameters with sensitivity index values ≥ 0.5 have more impact on R_0 see details in [43, 49], even though others that are ≤ 0.5 also significantly influence the spread of the disease and cannot be underestimated. Hence, the optimal control model version with four time-dependent control measures is formulated and analyzed based on the critical assessment of the parameters that will influence the elimination of the disease. The incorporated controls include $u_1(t)$ use of condom/avoidance of multiple sex partners control, $u_2(t)$ the screening/treatment of the infected humans, $u_3(t)$ the boosting/enhancement of breeding Wolbachia mosquitoes' population, and $u_4(t)$, the injection of Wolbachia infected mosquitoes' control into mosquitoes' population. Our results show that the combination and implementation of these controls are very effective in reducing the number of infected individuals to almost zero before day 100 and eliminating the Aedes aegypti mosquitoes responsible for the spread of the Zika virus disease in the population. However, due to limited resources, implementation of the four controls at once may not be tenable; hence, for single control, $u_2(t)$, the screening/treatment of the infected humans is the most effective control in eliminating the disease from infected humans (see [15] which also align with this outcome). In contrast, $u_4(t)$, injection of Wolbachia-infected mosquitoes' control into the mosquito population is a suitable intervention for eliminating the Aedes aegypti mosquitoes responsible for the spread of the disease. For double control to be implemented, $u_1(t)$, the use of condoms/avoidance of multiple sex partners control, and $u_2(t)$, the screening/treatment of the infected humans, are the most effective control in eliminating the disease from infected humans; this conforms with [15], while either $u_3(t)$ the boosting/enhancement of breeding Wolbachia mosquitoes' population + $u_4(t)$, injection of Wolbachia infected mosquitoes' control into mosquitoes' population or $u_2(t)$ the screening/treatment of the infected humans + $u_4(t)$ injection of Wolbachia infected mosquitoes' control into mosquitoes' population is the suitable intervention for eliminating the Aedes aegypti mosquitoes responsible for the spread of the disease, see [7][8][50][51,58,59]. For the implementation of the combination of three control interventions,

$u_1(t) + u_2(t) + u_4(t)$ is the most appropriate combined intervention to use to reduce the infected humans wholly; this conforms with the outcome in [51, 15, 7, 8, 50,58,59] while either $u_1(t) + u_3(t) + u_4(t)$ or $u_2(t) + u_3(t) + u_4(t)$ or $u_1(t) + u_2(t) + u_4(t)$ is the most suitable intervention for eliminating the Aedes aegypti mosquitoes that spread the Zika virus disease; this aligns with the results in [51, 15, 7, 8, 50, 58, 59].

This work has limitations that will be considered for future research, such as the derivation of the model's endemic equilibrium state stability and the reliability of the parameter data. The model in this study can also be extended to include vaccination and vertical transmission among humans. Also, the cost-effectiveness analysis could be carried out due to limited resources, especially in the developing countries where this disease is domiciled.

Conflict of interest

The authors declare that they have no competing interests.

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Availability of data.

The data used in this study are referenced and presented in Table 2 above.

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