A mathematical model for Zika virus transmission with Optimal Control

Santosh Kumar Sharma *[1] and Nawin Kumar Agrawal[2]

[1]Department of Mathematics, K. L. S. College, Nawada, Magadh University, Bodh Gaya, Bihar-805110, India
[2]Department of Mathematics, L N Mithila University, Darbhanga Bihar 846008, India

October 16, 2023

Abstract

In this research, we developed a mathematical model to study the co-interaction of the Zika virus (a vector-borne disease). We qualitatively analyzed the model and established the necessary conditions under which disease-free and endemic equilibria are asymptotically stable. We qualitatively analyzed the model and established the necessary conditions under which disease-free and endemic equilibria are asymptotically stable. There are only two possible equilibrium points in our system, two of which are endemic and one of which is devoid of disease. The disease-free equilibrium is shown by the theoretical study to be both locally and globally asymptotically stable if the basic reproduction number is less than one. The most sensitive factors of the analyzed Zika model are the number of times susceptible (infected) individuals were bitten by susceptible (infected) mosquitoes, the host population's awareness rate, and the recovery rates of susceptible (infected) humans. The World Health Organisation has classified the current Zika virus (ZIKV) pandemic as a worldwide public health emergency. Concerns include the lack of effective diagnostic tests and vaccinations, the wide geographic range of mosquito species that can spread the virus, and the lack of population immunity in recently impacted nations.

Keywords: Zika virus, Reproduction number, Optimal control, Stability analysis, equilibrium point.

1 Introduction

Zika is a mosquito-borne virus that was initially discovered in a Rhesus macaque monkey in Uganda in 1947. Infection and sickness in people were then discovered

*Corresponding author. Email: santoshmumath@gmail.com

in other African nations in the 1950s. Between the 1960s and the 1980s, isolated cases of human infections were reported from Asia and Africa. However, since 2007, epidemics of the Zika virus infection have been documented in Africa, the Americas, Asia, and the Pacific. When the Zika virus first emerged in the Americas, a link between infection and microcephaly (a smaller-than-normal head size) was first noticed.

The WHO declared a Public Health Emergency of International Concern (PHEIC) in relation to microcephaly, other neurological disorders, and the Zika virus as soon as the link between the Zika virus and congenital malformations was confirmed. In India, Zika virus epidemic activity was discovered in 2021. Although 89 nations and territories have yet to report evidence of Zika virus infection brought on by mosquitoes, worldwide surveillance is still insufficient. Symptoms of the Zika virus in most infected individuals are rare. If they develop, they often begin 3–14 days after infection, are minor in nature, include rash, fever, conjunctivitis, muscle and joint pain, malaise, and headache, and last 2–7 days on average. In tropical and subtropical areas, Aedes (Stegomyia) genus mosquitoes, especially Aedes aegypti, are the major vectors of Zika virus transmission.

In the course of the day, Aedes mosquitoes typically bite. Along with transmitting urban yellow fever, these mosquitoes also spread dengue and chikungunya. People who experience rashes, fevers, or joint discomfort should obtain plenty of rest, drink lots of water, and use antipyretics and/or analgesics to relieve their symptoms. Patients should seek medical attention and counseling if their symptoms get worse. Pregnant women who live in Zika transmission regions or who exhibit signs of the virus should consult a doctor for clinical treatment, laboratory testing, education, and other services. Protection against mosquito bites throughout the day and early evening is a vital step in avoiding Zika virus infection, especially among pregnant women, women who are trying to get pregnant, and young children. Examples of personal safety precautions include dressing in clothing that covers as much of the body as possible and is ideally light in color;

Recent studies, how the human and mosquito populations how the virus spreads. The study by Ali et al [2], According to the studies by Gonalez-Parra Gilberto, et al [9], The Zika virus can be contained more effectively with the help of educational programs and pesticide use. The study by Bernhauerov et al [4], provided a numerical characterization of in vitro ZIKV infection and contributed to a better understanding of the dynamics of ZIKV-host cell interactions. A mathematical model and cost-effectiveness analysis to compare different control strategies and emphasize the need for accurate implementation of optimal control measures. by the studies, Wanget al. [18], In the study of Aldila et al. [1], it was discovered that when R_0 is greater than 1, a local asymptote, or endemic equilibrium point, exists. Reducing the impact of Zika on the neighborhood may be possible with the addition of a class of asymptomatic carriers and the use of control measures. The studies of Khan et al. [11], According to Bonyah et al. [6], studied the best strategies to control a co-infection model while using the center manifold theory to examine the dynamics of a system.

Transmission dynamics between humans and mosquitoes, the impact of vaccination, and the effectiveness of different control strategies. In the study by Sharma et al [16], The ideal control system employing prevention, treatment, and pesticide spraying is determined by the stability analysis of the model's fixed points. By the studies, Alzahrani et al [3], By the studies, Biswas et al. [5] provide calculations and analysis to comprehend the dynamics of the virus in populations of both humans and mosquitoes. Rezapour et al. [15] found that the fractional-order Caputo derivative is what transmits the Zika virus between people and mosquitoes. According to the study, Nwalozie et al. [13] better preventative, control, and management measures are needed to decrease the consequences of the Zika virus on world health. Studies by Mello et al. [7] show that baculovirus expression technology is used in insect cell cultures to create vaccines against arboviruses, such as ZIKV.

These techniques are being used by WHO to stop the Zika virus. who It assists nations in confirming epidemics, offers technical assistance and direction for the efficient control of disease outbreaks brought on by mosquitoes, looks into the development of new tools, such as pesticide products and application technology, develops evidence-based strategies for managing attacks and solutions, and assists nations in confirming epidemics with the assistance of its network of cooperating laboratories.

Two areas where mathematical models have a big impact are the dynamics of infectious diseases and the development of improved techniques to halt their spread in the future. Using mathematical models, the dynamic is anticipated, and this helps to create more efficient techniques for stopping its spread in the future.

The numerical findings of our study were produced using built-in MATLAB functions since we were more concerned with analyzing the qualitative dynamical behaviors of the model under discussion than with the precision, rate of convergence, etc. of the generated numerical solutions. Additionally, we have created an optimum control issue for the system, where the objectives are to reduce immunization and boost revenue.

In this study, we proposed epidemiological models for the Zika virus that consider the virus' antigenic changes. In the models for transmission, specifics on changes to the amino acid sequences of the HA proteins at epitope regions were included. First, using the sequencing data, we calculated the rate of time-varying antigenic change for each Zika virus subtype. Finally, we demonstrated how changes in viral antigenicity may drastically influence the dynamics of Zika virus transmission at the population level. In light of this, we suggested epidemiological models for the Zika viruses. We therefore proposed epidemiological models for the Zika virus.

The article is organized as follows. In part 2, which is the section after this one, we create the mathematical model. Fundamental characteristics like well-posedness, nonnegativity, boundedness, etc. are examined in Section 3. Analysis of equilibrium and stability is discussed in Section 4. Section 5 presents the topic of best control.The discussion in Section 6 concludes the essay.

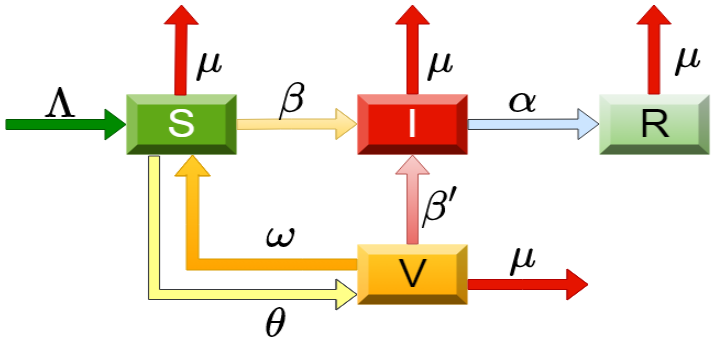

Figure 1: Schematic diagram of the model (1)

2 Formulation of Zika Virus Epidemic Model

The transmission model with media coverage is given by the following deterministic system of nonlinear ordinary differential equations

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda + \omega V - \frac{\beta SI}{1+pI} - (\mu+\theta)S, \\
\frac{dI}{dt} &= \frac{\beta SI}{1+pI} + \frac{\beta' VI}{1+pI} - (\mu+\alpha)I, \\
\frac{dV}{dt} &= \theta S - (\mu+\omega)V - \frac{\beta' VI}{1+pI}, \\
\frac{dR}{dt} &= \alpha I - \mu R. \qquad (1)
\end{aligned}$$

where the initial conditions are

$$S = S_0, \quad I = I_0, \quad V = V_0, \quad R = R_0. \qquad (2)$$

In this model, Λ is the constant production, ω is the [], β is Transmission rate, p is Haf saturation constant, μ is Death rate, θ is Rate of vacillation, α is Rate of infected, and β' is Disseses transmission after vacillation.The schematic explanation of our proposed model is displayed in Figure 1. The values of the parameters of the model (1) are given in Table (1).

3 Stability of the equilibrium states

(A) The disease-free equilibrium of the system (1) is given by

$$E^0 = (S^0,\ I^0,\ V^0,\ R^0) = \left(\frac{\Lambda(\mu+\omega)}{\mu(\mu+\omega+\theta)},\ 0,\ \frac{\Lambda\theta}{\mu(\mu+\omega+\theta)},\ 0\right). \qquad (3)$$

(B) The endemic equilibrium of the system (1) is given by

$$E^* = (S^*,\ I^*,\ V^*,\ R^*),$$

It satisfies $S^* > 0,\ I^* > 0,\ V^* > 0,\ R^* > 0$ and

$$\begin{aligned} S^* &= \frac{Y_1 - (\Lambda + \omega V^*)}{(\mu + \theta)}, \\ I^* &= \frac{(Y_1 + Y_2)}{(\mu + \alpha)}, \\ V^* &= \frac{(\theta S^* - Y_2)}{(\mu + \alpha)}, \\ R^* &= \frac{\alpha I^*}{\mu}. \end{aligned} \tag{4}$$

where,

$$Y_1 = \frac{\beta S^* I^*}{(1 + pI^*)} \ \ and \ \ Y_2 = \frac{\beta' V^* I^*}{(1 + pI^*)}.$$

Substituting the above into the second equation at equilibrium will yield the expression for I after some rearrangement. For illustration,

4 Basic reproduction number of the model

The local stability of the system E^0 is governed by the basic reproduction number $R_0 < 1$. The basic reproduction number is the average number of new secondary infections in entirely susceptible Zika virus produced by a single infected Zika virus. With the help of the next generation method [17], we can calculate the basic reproduction number. For this method, we consider the model variables in such a manner that the compartments reflect only infected individuals. By this assumption, we have $y = (S, I, V, R)$, where I are the infected compartments. Furthermore, $\mathcal{G}_H$ denotes the set of all infection-free states—that is,

$$\mathcal{X}_H = \{X \geq 0 : X_i, i = 1, 2\}. \tag{5}$$

System (1) is rewritten as

$$X'_i = h_i(X) = \mathcal{F}_i(X) - \mathcal{G}_i(X),\ i = 1, 2, \tag{6}$$

where $\mathcal{F}_i(X)$ describes the rate of appearance of new infections in compartment i. Moreover,

$$\mathcal{Y}_i(X) = \mathcal{G}_i^-(X) - \mathcal{G}_i^+(X), \tag{7}$$

$\mathcal{Y}_i^+(X)$ is the transmission rate into the compartment i, and $\mathcal{Y}_i^-(X)$ is the rate of transmission out of this compartment. The subsequent norms are to be modeled.

(B_1) $\mathcal{F}_i(X) \geq 0, \quad \mathcal{G}_i^-(X) \geq 0, \quad \mathcal{G}_i^+(X) \geq 0, \quad for \quad any \quad X \geq 0;$

(B_2) If $X_i = 0$, then $\quad \mathcal{G}_i^- = 0;$

(B_3) $\mathcal{F}_i = 0$, for $i = 2;$

(B_4) If $X \in \mathcal{X}_H$, then $\mathcal{F}_i(X) = 0, \quad \mathcal{G}_i^+(X) = 0$, for $i = 1, 2;$

(B_5) For the disease-free equilibrium (DFE) X_0, the Jacobi matrix $Dh(X_0)$ constrained to the subspace $h = 0$ has all negative eigenvalues.

To formulate the next generation matrix FG^{-1} [17] from matrices of partial derivatives of $\mathcal{F}_i$ and $\mathcal{G}_i$. Specifically,

$$F = \left[\frac{\partial \mathcal{F}_i(X_0)}{\partial X_j}\right], \quad G = \left[\frac{\partial \mathcal{G}_i(X_0)}{\partial X_j}\right], \tag{8}$$

where $i, j = 1, 2$. Here, F, G are two-dimensional squared matrices and $R_0 = \varrho(FG^-)$ (ϱ denotes a spectral radius of the matrix). For model (1), we have

$$\mathcal{F} = \begin{pmatrix} \frac{\beta SI}{1+pI} + \frac{\beta' VI}{(1+pI)} \\ 0 \end{pmatrix}, \quad \mathcal{G} = \begin{pmatrix} (\mu+\alpha)I \\ -\alpha I + \mu R \end{pmatrix}. \tag{9}$$

Next, we are setting that the entry-wise non-negative new infection matrix is F. Let the non-singular Metzler matrix [12] define the transitions of Zika virus infection between the infection compartments and the matrices, which are given as follows.

$$F = \begin{pmatrix} \frac{\beta S}{(1+pI)^2} + \frac{\beta' V}{(1+pI)^2} & 0 \\ 0 & 0 \end{pmatrix}, \quad G = \begin{pmatrix} \mu+\alpha & 0 \\ -\alpha & \mu \end{pmatrix},$$

$$G^{-1} = \begin{pmatrix} \frac{1}{(\mu+\alpha)} & 0 \\ \frac{\alpha}{\mu(\mu+\alpha)} & \frac{1}{\mu} \end{pmatrix}.$$

We observe that G^{-1} is also an entry-wise non-negative matrix and thus FG^{-1} is an entry-wise non-negative next-generation matrix showing the expected number of new infections which is given by

$$\begin{aligned} FG^{-1} &= \begin{bmatrix} \frac{\beta S}{(1+pI)^2} + \frac{\beta' V}{(1+pI)^2} & 0 \\ 0 & 0 \end{bmatrix} \times \begin{bmatrix} \frac{1}{(\mu+\alpha)} & 0 \\ \frac{\alpha}{\mu(\mu+\alpha)} & \frac{1}{\mu} \end{bmatrix}, \\ &= \begin{bmatrix} \frac{\beta S+\beta' V}{(1+pI)^2(\mu+\alpha)} & 0 \\ 0 & 0 \end{bmatrix}. \end{aligned} \tag{10}$$

Table 1: Parameters and their associated sensitivity indices along with the relative percentage impact on the threshold quantity (R_0)

Parameter	Definition	Value	Reference
Λ	Birth rate		
ω			
β	Transmission rate		
p	Haf sauration costant		
μ	Death rate		
θ	Rate of vacillation		
α	Rate of infected		
β'	Disseses transmission after vacillation		

Using the spectral radius of the next-generation matrix [10, 17], for the system (1), we find the basic reproduction number R_0, which is the largest eigenvalue of FG^{-1} at E^0. Thus,

$$\begin{aligned} \mathcal{R}_0 &= \frac{\beta S + \beta' V}{(\mu+\alpha)}, \\ &= \frac{\beta S\mu(\mu+\omega+\theta)+\beta'\Lambda\theta}{\mu(\mu+\alpha)(\mu+\omega+\theta)}. \end{aligned} \tag{11}$$

Theorem 1. *The system* (1) *describes the spreading kinetics of Zika virus infection, which has a threshold parameter basic reproduction number* $R_o = \frac{\beta S\mu(\mu+\omega+\theta)+\beta'\Lambda\theta}{\mu(\mu+\alpha)(\mu+\omega+\theta)}$. *at* E^0. *For* $R_0 > 1$, *the system* (1) *has a unique positive endemic steady state.*

5 Local stability of the disease-free equilibrium

Theorem 2. *The disease-free equilibrium* E^0 *is locally asymptotically stable if* $R_0 < 1$, *and unstable if* $R_0 > 1$.

Proof. The Jacobian of the system (1) evaluated at E^0 is given by

$$J_{E^0} = \begin{pmatrix} -(\mu+\theta) & -\beta S & \omega & 0 \\ 0 & \beta S + \beta' V - (\mu+\alpha) & 0 & 0 \\ \theta & -\beta' V & -(\mu+\omega) & 0 \\ 0 & \alpha & 0 & -\mu \end{pmatrix}. \tag{12}$$

Here the eigenvalues are $[\lambda = -\mu,\ \{(\beta S + \beta' V) - (\mu+\alpha)\}]$ and the other two eigenvalues are determined from the given equation

$$\begin{vmatrix} -(\mu+\theta)-\lambda & \omega \\ \theta & -(\mu+\omega)-\lambda \end{vmatrix} = 0 \tag{13}$$

and the characteristic equation for (13) is

$$A_0\lambda^2 + A_1\lambda + A_2\lambda \quad = \quad 0. \tag{14}$$

where,

$$A_0 \quad = \quad 1 > 0, \quad A_1 = (\omega + \theta + 2\mu), \quad A_2 = (\mu^2 + \mu\theta + \mu\omega).$$

Now, it is easy to note that $A_0 \geq 0$, and $A_1 > 0$. If $A_0 > 0$, then all the roots of Equation (4) will be negative (Section 3.3 in [10]). If $A_2 > 0$, then we have threshold criteria to determine the stability condition at the infection-free point E^0. We have the condition $\mu_1 + 2\frac{p\hat{H}_S}{H_T} < \nu < \frac{\mu_2\mu_3}{\beta_1\hat{H}_S}$, which implies that $R_0 < 1$ and results in the eradication of infection. □

5.1 Local stability of the endemic equilibrium:

Theorem 3. *The system* (1) *around* E^* *is locally asymptotically stable (LAS) if* $R_0 > 1$.

Proof. We already established that the equilibrium E^* is feasible when $R_0 > 1$. Now, the Jacobi matrix around E^* is

$$|J_{E^*} - \lambda| \quad = \quad \begin{pmatrix} a_{11} - \lambda & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} - \lambda & 0 & 0 \\ a_{31} & a_{32} & a_{33} - \lambda & 0 \\ 0 & a_{42} & 0 & a_{44} - \lambda \end{pmatrix}. \tag{15}$$

where,

$$\begin{aligned} a_{11} &= -\frac{\beta I}{(1+pI)} - (\mu + \theta), \; a_{12} = -\frac{\beta S}{(1+pI)^2}, \\ a_{21} &= \frac{\beta I}{(1+pI)}, \; a_{22} = \frac{\beta S + \beta' V}{(1+pI)^2} - (\mu + \alpha), \\ a_{32} &= -\frac{\beta' V}{(1+pI)^2}, \; a_{33} = -(\mu + \omega) - \frac{\beta' I}{(1+pI)}, \\ a_{13} &= \omega, \quad a_{31} = \theta, \quad a_{42} = \alpha, \quad a_{44} = \mu. \end{aligned}$$

At E^*, the characteristic equation is

$$\lambda^4 - x_1\lambda^3 + x_2\lambda^2 + x_3\lambda^+ x_4\lambda^0 \quad = \quad 0. \tag{16}$$

where,

$$\begin{aligned} x_1 &= (a_{33} + a_{44} + a_{11} + a_{22}), \\ x_2 &= (a_{33}a_{44} + a_{11}a_{33} + a_{22}a_{44} + a_{11}a_{22}), \\ x_3 &= (a_{33}a_{44} - a_{11}a_{22}a_{33} - a_{11}a_{22}a_{44}), \\ x_4 &= (a_{11}a_{22}a_{33}a_{44}). \end{aligned}$$

By the Routh-Hurwitz criteria at the endemic equilibrium E^*, the system (1) is LAS if $R_0 > 1$. □

6 Global Stability

Theorem 4. *The system is globally asymptotically stable (GAS) when* $R_0 < 0$.

Proof. We consider the Lyapunov function as follows:

$$L_1 = \xi_1 I + \xi_2 V + \xi_3 R. \tag{17}$$

Differentiating the Lyapunov function $L_1(17)$ with respect to t,we find

$$\begin{aligned} \frac{dL_1}{dt} &= \xi_1 \frac{dI}{dt} + \xi_2 \frac{dR}{t} \\ &= \xi_1 \left[\frac{\beta SI}{(1+pI)} + \frac{\beta' VI}{(1+pI)} - (\mu+\alpha)I \right] + \xi_2(\alpha I - \mu R) \end{aligned} \tag{18}$$

When $R_0 < 1$, we have $\frac{dL_1}{dt} < 0$ and $\frac{dL_1}{dt} = 0$ implies that $R = 0$. From the model (1), we can say that $I = 0$ when $R = 0$ in the limit $t \to 0$. Hence, according to the Lyapunov–LaSalle theorem, the system is globally asymptotically stable when $R_0 < 1$. This completes the proof. □

Theorem 5. *The endemic equilibrium* E^* *is globally asymptotically stable (GAS) if* $R_0 > 1$.

Proof. Let us consider the Dulac function:

$$D(S,\ I,\ V,\ R) = \frac{1}{(S\ I\ V\ R)}, \tag{19}$$

and denote the R.H.S of equations in the system (1) as

$$\begin{aligned} Z_1 &= \Lambda + \omega V - \frac{\beta SI}{1+pI} - (\mu+\theta)S, \\ Z_2 &= \frac{\beta SI}{1+pI} + \frac{\beta' VI}{1+pI} - (\mu+\alpha)I, \\ Z_3 &= \theta S - (\mu+\omega)V - \frac{\beta' VI}{1+pI}, \\ Z_4 &= \alpha I - \mu R. \end{aligned} \tag{20}$$

Then, from (20), we have

$$\begin{aligned} \frac{\partial(DZ_1)}{\partial S} &= -\frac{1}{S^2IVR}\left[\Lambda + \omega V - \frac{\beta SI}{(1+pI)} - (\mu+\theta)S\right] \\ &\quad + \frac{1}{SIVR}\left[-\frac{\beta I}{(1+pI)} - (\mu+\theta)\right], \\ &= -\frac{(\Lambda+\omega V)}{S^2IVR} < 0, \end{aligned} \tag{21}$$

$$\begin{aligned}\frac{\partial(DZ_2)}{\partial I} &= -\frac{1}{SI^2VR}\left[\frac{\beta SI+\beta' VI}{(1+pI)}-(\mu+\alpha)I\right]\\ &\quad +\frac{1}{SIVR}\left[\frac{\beta S+\beta' V}{(1+pI)^2}-(\mu+\alpha)\right],\\ &\quad -\frac{p(\beta S+\beta' V)}{SVR(1+pI)^2}<0, \end{aligned} \tag{22}$$

$$\begin{aligned}\frac{\partial(DZ_3)}{\partial I} &= -\frac{1}{SIV^2R}\left[\theta S-(\mu+\omega)V-\frac{\beta' VI}{(1+pI)}\right]\\ &\quad +\frac{1}{SIVR}\left[-(\mu+\omega)-\frac{\beta' I}{(1+pI)}\right],\\ &\quad -\frac{\theta S}{SIV^2R}<0, \end{aligned} \tag{23}$$

$$\begin{aligned}\frac{\partial(DZ_4)}{\partial I} &= -\frac{1}{SIVR^2}(\alpha I-\mu R)+\frac{1}{SIVR}(-\mu),\\ &\quad -\frac{\alpha I}{SIVR^2}<0. \end{aligned} \tag{24}$$

From the inequalities (21)-(24), we find

$$\frac{\partial(DZ_1)}{\partial S}+\frac{\partial(DZ_2)}{\partial I}+\frac{\partial(DZ_3)}{\partial V}+\frac{\partial(DZ_4)}{\partial R}<0. \tag{25}$$

Thus, every positive solution of the system (1) tends to the endemic equilibrium E^* when $R_0>1$. According to the Dulac–Bendixson theorem, there exists no periodic orbit for (1), and hence the system is globally asymptotically stable for E^*. □

7 The optimal control model

Control theoretic study plays a pivotal role in the minimization of different infectious diseases. We use optimization techniques to develop an optimal control mechanism that minimizes the transmission of the novel Zika virus. We have incorporated the combination of two control parameters/variables as symbolized by $u(t)$ and define it as $u(t)=\{u_1(t),u_2(t)\}$. Physically or biologically these control measures represent the reverse transcript inhibitor, and the control minimizing the reservoir contribution to the virus. We place the control functions

into the model (1) which leads to the following state system:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda + \omega V - \frac{\beta SI}{\{1+(1-u_2)pI\}} - \{\mu + (1-u_1)\theta\}S, \\
\frac{dI}{dt} &= \frac{\beta SI}{\{1+(1-u_2)pI\}} + \frac{\beta' VI}{\{1+(1-u_2)pI\}} - (\mu+\alpha)I, \\
\frac{dV}{dt} &= (1-u_1)\theta S - (\mu+\omega)V - \frac{\beta' VI}{\{1+(1-u_2)pI\}}, \\
\frac{dR}{dt} &= \alpha I - \mu R. \qquad (26)
\end{aligned}$$

where the initial conditions are

$$S = S_0, \quad I = I_0, \quad V = V_0, \quad R = R_0. \qquad (27)$$

We define the objective cost function as follows:

$$J[u,x] = \int_0^{t_f} (Au_1^2 + Bu_2^2 + CI^2)dt \qquad (28)$$

Here the main aim is to minimize the cost function subject to the state system (26).

In the objective function described by (28), where $x = (S, I, V, R)$ and A, B and C, are the positive constants called weight constants. The weighting constants I are the relative costs of infection and virus, while A and B are the weighting constants that measure the associated cost of the control variables $u_1(t)$ *and* $u_2(t)$ respectively.

We have to find the optimal control function represented by (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \min\{J(u_1, u_2),\ u_i \in \mathcal{U},\ \text{for } i = 1, 2\}, \qquad (29)$$

subject to the state system (26) and the control set $\mathcal{U}$ is described as:

$$\mathcal{U} = \{(u_1, u_2,) : u_i \text{ is Lebesgue measurable and } \ 0 \le u_i(t) \le 1,\ i = 1, 2\}. \quad (30)$$

where $\mathcal{U}$ is the control set. The basic concept of an optimal control problem is to prove the existence of optimal control through an optimality system [14]. Here we prove the existence condition of optimal control problem by using the approach of Fleming and Rishel [8].

Further to proceed, the existence of such control measures variables will be shown. The existence of a system is subjected to the boundedness of the controls as well as Lebesgue measurable, and the initial data non-negativity. Thus the control problem may take the form:

$$\frac{dX}{dt} = PX + Q(X). \qquad (31)$$

where $X = (S, I, V, R)'$, and the matrices P and $Q(X)$ respectively containing the linear and nonlinear bounded coefficients are given by the following:

Theorem 6. *There exists an optimal solution* $u^* = (u_1^*, u_2^*) \in \mathcal{U}$ *to the control problem* (42).

Proof. Clearly, the state and control variables have non-negative values. Furthermore, the set of control $\mathcal{U}$ is closed and convex. Moreover, the boundedness of the control system leads to its compactness. The integral functional (28) is also convex. Therefore, optimal controls exist. □

7.1 Methodology

Let the control input $u^*(t)$ denote the quantity of the drug dose at time t. The cost function (28) subject to the system of ODE (26) represents the necessary conditions for which an optimal control and corresponding states must satisfy Pontryagin's Maximum Principle. To determine the optimal control $u_1^*(t)$ and $u_2^*(t)$, we use Pontryagin's maximum principle [14]. With the aid of this principle, we change the system (42) and the cost function (28) into a minimizing problem by constructing the Hamiltonian function H with respect to $(u_1(t), u_2(t))$.

We find the optimal values to the problem described by (28) subject to the control system (26). For that, the Lagrangian, as well as the Hamiltonian associated with the control problem, will be defined. Therefore, we take the state variable x and control variable u to define the Lagrangian ($\mathcal{L}$) as

$$\mathcal{L} = Au_1^2 + Bu_2^2 + CI. \tag{32}$$

Using the adjoint variables together with the state variables, the Hamiltonian is constructed as follows:

$$\begin{aligned}
\mathcal{H} = {} & Au_1^2 + Bu_2^2 + CI^2 \\
& + \lambda_1 \left[\Lambda + \omega V - \frac{\beta SI}{\{1 + (1-u_2)pI\}} - \{\mu + (1-u_1)\theta\} S \right] \\
& + \lambda_2 \left[\frac{\beta SI}{\{1 + (1-u_2)pI\}} + \frac{\beta' VI}{\{1 + (1-u_2)pI\}} - (\mu + \alpha) I) \right] \\
& + \lambda_3 \left[(1-u_1)\theta S - (\mu + \omega) V - \frac{\beta' VI}{\{1 + (1-u_2)pI\}} \right]. \\
& + \lambda_4 (\alpha I - \mu R).
\end{aligned} \tag{33}$$

Here, $\xi_i,\ i = 1, 2, 3, 4$ denote the adjoint variables, P and Q are the weight constants, and A represents the penalty multiplier.

From (33), we have

$$
\begin{aligned}
\frac{\partial \mathcal{H}}{\partial S} &= \frac{\beta I}{\{1+(1-u_2)pI\}}(\lambda_2-\lambda_1)-\lambda_1\{\mu+(1-u_1)\theta\}+\lambda_3(1-u_1)\theta,\\
\frac{\partial \mathcal{H}}{\partial I} &= 2CI+\frac{\beta S}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_1)+\frac{\beta' V}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_3)-\lambda_2(\mu+\alpha)+\lambda_4(\alpha),\\
\frac{\partial \mathcal{H}}{\partial V} &= \lambda_1\omega+\frac{\beta' I}{\{1+(1-u_2)pI\}}(\lambda_2-\lambda_3)-\lambda_3(\mu+\omega),\\
\frac{\partial \mathcal{H}}{\partial R} &= \lambda_4(-\mu),\\
\frac{\partial \mathcal{H}}{\partial u_1} &= 2Au_1+\theta S(\lambda_1-\lambda_3),\\
\frac{\partial \mathcal{H}}{\partial u_2} &= 2Bu_2+\frac{\beta S p I^2}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_1)+\frac{\beta' V p I^2}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_3). \qquad (34)
\end{aligned}
$$

281 According to Pontryagin's minimum principle, the adjoint variables satisfy,

$$
\frac{d\xi}{dt}=-\frac{\partial \mathcal{H}}{\partial x}. \qquad (35)
$$

282 Therefore, using (35), the adjoint system evaluated at optimal controls input
283 $(u_1(t), u_2(t))$ and corresponding to the model state variables (S, I, V, R) is ob-
284 tained as:

$$
\begin{aligned}
\frac{d\lambda_1}{dt} &= -\left[\frac{\beta I}{\{1+(1-u_2)pI\}}(\lambda_2-\lambda_1)-\lambda_1\{\mu+(1-u_1)\theta\}+\lambda_3(1-u_1)\theta\right],\\
\frac{d\lambda_2}{dt} &= -\left[2CI+\frac{\beta S}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_1)+\frac{\beta' V}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_3)-\lambda_2(\mu+\alpha)+\lambda_4(\alpha)\right],\\
\frac{d\lambda_3}{dt} &= -\left[\lambda_1\omega+\frac{\beta' I}{\{1+(1-u_2)pI\}}(\lambda_2-\lambda_3)-\lambda_3(\mu+\omega)\right],\\
\frac{d\lambda_4}{dt} &= -\left[\lambda_4(-\mu)\right]. \qquad (36)
\end{aligned}
$$

285 The transversality conditions are $\lambda_1(t_f)=0,\ \lambda_2(t_f)=0,\ \lambda_3(t_f)=0,\ \lambda_4(t_f)=$
286 0. Now Pontryagin's Maximum Principle [14] states that the unconstrained op-
287 timal control $u^*(t)$ satisfies

$$
\frac{\partial H}{\partial u(t)} = 0. \qquad (37)
$$

288 This gives,

$$\begin{aligned}
\frac{\partial \mathcal{H}}{\partial u_1} &= 2Au_1 + \theta S(\lambda_1 - \lambda_3) = 0, \\
\frac{\partial \mathcal{H}}{\partial u_2} &= 2Bu_2 + \frac{\beta SpI^2}{\{1+(1-u_2)pI\}^2}(\lambda_2 - \lambda_1) \\
&\quad + \frac{\beta' VpI^2}{\{1+(1-u_2)pI\}^2}(\lambda_2 - \lambda_3) = 0. \qquad (38)
\end{aligned}$$

Solving (38) these for optimal control, we obtain

$$\begin{aligned}
u_1^*(t) &= \frac{(\lambda_3 - \lambda_1)\theta S}{2A}, \\
u_2^*(t) &= \frac{(\lambda_1 - \lambda_2)K - (\lambda_2 - \lambda_3)K'}{2B}, \qquad (39)
\end{aligned}$$

where,

$$K = \frac{\beta SpI^2}{\{1+(1-u_2)pI\}^2}, \quad K' = \frac{\beta' VpI^2}{\{1+(1-u_2)pI\}^2}.$$

Since the standard control is bounded, we conclude for the control $u_1(t),\ u_2(t)$:

$$u_1^*(t) = \begin{cases} 0, & \frac{(\lambda_3-\lambda_1)\theta S}{2A} < 0, \\ \frac{(\lambda_3-\lambda_1)\theta S}{2A}, & 0 < \frac{(\lambda_3-\lambda_1)\theta S}{2A} < 1, \\ 1, & \frac{(\lambda_3-\lambda_1)\theta S}{2A} > 1. \end{cases} \qquad (40)$$

$$u_2^*(t) = \begin{cases} 0, & \frac{(\lambda_1-\lambda_2)K-(\lambda_2-\lambda_3)K'}{2B} < 0, \\ \frac{(\lambda_1-\lambda_2)K-(\lambda_2-\lambda_3)K'}{2B}, & 0 < \frac{(\lambda_1-\lambda_2)K-(\lambda_2-\lambda_3)K'}{2B} < 1, \\ 1, & \frac{(\lambda_1-\lambda_2)K-(\lambda_2-\lambda_3)K'}{2B} > 1. \end{cases} \qquad (41)$$

Hence the compact form of $u_1^*(t)$ is

$$u_1^*(t) = max\left(min\left(1, \frac{(\lambda_3 - \lambda_1)\theta S}{2A}\right), 0\right).$$

Similarly, we can obtain the compact form of $u *_2 (t)$ in the form of.

$$u_2^*(t) = max\left(min\left(1, \frac{(\lambda_1 - \lambda_2)K - (\lambda_2 - \lambda_3)K'}{2B}\right), 0\right).$$

Utilizing the equation and taking the state system along with the adjoint system, and the transversality conditions, we have the following optimal system:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda + \omega V - \frac{\beta SI}{\{1+(1-u_2)pI\}} - \{\mu + (1-u_1)\theta\}S, \\
\frac{dI}{dt} &= \frac{\beta SI}{\{1+(1-u_2)pI\}} + \frac{\beta' VI}{\{1+(1-u_2)pI\}} - (\mu+\alpha)I, \\
\frac{dV}{dt} &= (1-u_1)\theta S - (\mu+\omega)V - \frac{\beta' VI}{\{1+(1-u_2)pI\}}, \\
\frac{dR}{dt} &= \alpha I - \mu R, \\
\frac{d\lambda_1}{dt} &= -\left[\frac{\beta I}{\{1+(1-u_2)pI\}}(\lambda_2-\lambda_1) - \lambda_1\{\mu+(1-u_1)\theta\} + \lambda_3(1-u_1)\theta\right], \\
\frac{d\lambda_2}{dt} &= -\left[2CI + \frac{\beta S}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_1) + \frac{\beta' V}{\{1+(1-u_2)pI\}^2}(\lambda_2-\lambda_3) - \lambda_2(\mu+\alpha) + \lambda_4(\alpha)\right], \\
\frac{d\lambda_3}{dt} &= -\left[\lambda_1\omega + \frac{\beta' I}{\{1+(1-u_2)pI\}}(\lambda_2-\lambda_3) - \lambda_3(\mu+\omega)\right], \\
\frac{d\lambda_4}{dt} &= -\left[\lambda_4(-\mu)\right]. \qquad (42)
\end{aligned}
$$

with the initial conditions as: $S(0) > 0,\ I(0) > 0,\ V(0) > 0,\ R(0) > 0$. and boundary conditions as: $\lambda_i(t_f) = 0,\ \ i = 1, 2, 3, 4$.

8 Conclusion

In this study, we focused on the role during Zika-virus-Infection in our investigation. Furthermore, a deterministic SEIVR Zika epidemic model is created, investigated, and analysed, utilising nonlinear stability and optimal control theory. Hier, the proposed model's positivity and boundedness are examined. Using a next-generation matrix approach, we were able to determine the fundamental reproduction number. The steady-state analysis demonstrates that, if the basic reproduction number R'_o is smaller than unity, the disease-free equilibrium (DFE) ist globally asymptotically stable. Endemic equilibrium is locally asymptotically stable, if the fundamental reproduction number R'_0 is bigger than 1. It is a requirement that the reproduction number be fewer than one, in order to eradicate the zikavirus from the populace. Of course, we cannot take into account all such considerations in order to avoid complexity. However, we plan to consider these options in our future work.

References

[1] D Aldila, K Rasyiqah, G Ardaneswari, and H Tasman. A mathematical model of zika disease by considering transition from the asymptomatic to symptomatic phase. In *Journal of Physics: Conference Series*, volume 1821, page 012001. IOP Publishing, 2021.

[2] Aatif Ali, Saeed Islam, M Riaz Khan, Saim Rasheed, FM Allehiany, Jamel Baili, Muhammad Altaf Khan, and Hijaz Ahmad. Dynamics of a fractional order zika virus model with mutant. *Alexandria Engineering Journal*, 61(6):4821–4836, 2022.

[3] Ebraheem O Alzahrani, Wisal Ahmad, Muhammad Altaf Khan, and Sharaf J Malebary. Optimal control strategies of zika virus model with mutant. *Communications in Nonlinear Science and Numerical Simulation*, 93:105532, 2021.

[4] Veronika Bernhauerová, Veronica V Rezelj, and Marco Vignuzzi. Modelling degradation and replication kinetics of the zika virus in vitro infection. *Viruses*, 12(5):547, 2020.

[5] Sudhanshu Kumar Biswas, Uttam Ghosh, and Susmita Sarkar. Mathematical model of zika virus dynamics with vector control and sensitivity analysis. *Infectious Disease Modelling*, 5:23–41, 2020.

[6] Ebenezer Bonyah, Muhammad Altaf Khan, Kazeem Oare Okosun, and JF Gómez-Aguilar. On the co-infection of dengue fever and zika virus. *Optimal Control Applications and Methods*, 40(3):394–421, 2019.

[7] Renata Gois de Mello, Thaissa Consoni Bernardino, Luis Giovani Oliveira Guardalini, Renato Mancini Astray, Marta Maria Antoniazzi, Simone Gonçalves Silva Jared, Eutimio Gustavo Fernández Núñez, and Soraia Attie Calil Jorge. Zika virus-like particles (vlps) produced in insect cells. *Frontiers in Pharmacology*, 14:1181566, 2023.

[8] Wendell H Fleming and Raymond W Rishel. *Deterministic and stochastic optimal control*, volume 1. Springer Science & Business Media, 2012.

[9] Gilberto González-Parra, Miguel Díaz-Rodríguez, and Abraham J Arenas. Optimization of the controls against the spread of zika virus in populations. *Computation*, 8(3):76, 2020.

[10] Jane M Heffernan, Robert J Smith, and Lindi M Wahl. Perspectives on the basic reproductive ratio. *Journal of the Royal Society Interface*, 2(4):281–293, 2005.

[11] MA Khan, Syed Wasim Shah, Saif Ullah, and JF Gómez-Aguilar. A dynamical model of asymptomatic carrier zika virus with optimal control strategies. *Nonlinear Analysis: Real World Applications*, 50:144–170, 2019.

[12] Kumpati S Narendra and Robert Shorten. Hurwitz stability of metzler matrices. *IEEE Transactions on Automatic Control*, 55(6):1484–1487, 2010.

[13] Rhoda Nwalozie, Roseanne Adah Ikpeama, Brenda Anyakwe Nnokam, and Rose Mary Kaiso Esiere. A review on zika virus: Epidemiology, pathogenesis and clinical outcomes. *International Journal of Pathogen Research*, 12(3):35–41, 2023.

[14] Lev Semenovich Pontryagin. *Mathematical theory of optimal processes*. CRC press, 1987.

[15] Shahram Rezapour, Hakimeh Mohammadi, and Amin Jajarmi. A new mathematical model for zika virus transmission. *Advances in difference equations*, 2020(1):1–15, 2020.

[16] Naveen Sharma, Ram Singh, Jagdev Singh, and Oscar Castillo. Modeling assumptions, optimal control strategies and mitigation through vaccination to zika virus. *Chaos, Solitons & Fractals*, 150:111137, 2021.

[17] Pauline Van den Driessche and James Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1-2):29–48, 2002.

[18] Xia Wang, Mingwang Shen, Yanni Xiao, and Libin Rong. Optimal control and cost-effectiveness analysis of a zika virus infection model with comprehensive interventions. *Applied Mathematics and Computation*, 359:165–185, 2019.