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Mathematical analysis of the role of hospitalization/isolation in controlling the spread of Zika fever

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ABSTRACT

The Zika virus is transmitted to humans primarily through Aedes mosquitoes and through sexual contact. It is documented that the virus can be transmitted to newborn babies from their mothers. We consider a deterministic model for the transmission dynamics of the Zika virus infectious disease that spreads in, both humans and vectors, through horizontal and vertical transmission. The total populations of both humans and mosquitoes are assumed to be constant. Our models consist of a system of eight differential equations describing the human and vector populations during the different stages of the disease. We have included the hospitalization/isolation class in our model to see the effect of the controlling strategy. We determine the expression for the basic reproductive number R_0 in terms of horizontal as well as vertical disease transmission rates.

An in-depth stability analysis of the model is performed, and it is consequently shown, that the model has a globally asymptotically stable disease-free equilibrium when the basic reproduction number $R_0 < 1$. It is also shown that when $R_0 > 1$, there exists a unique endemic equilibrium. We showed that the endemic equilibrium point is globally asymptotically stable when it exists. We were able to prove this result in a reduced model. Furthermore, we conducted an uncertainty and sensitivity analysis to recognize the impact of crucial model parameters on R_0. The uncertainty analysis yields an estimated value of the basic reproductive number $R_0 = 1.54$. Assuming infection prevalence in the population under constant control, optimal control theory is used to devise an optimal hospitalization/isolation control strategy for the model. The impact of isolation on the number of infected individuals and the accumulated cost is assessed and compared with the constant control case.

1. Introduction

The Zika virus spreads among humans primarily through an infected mosquito bite, which has been increasing at an alarming incidence rate worldwide over the past few years (Dick et al., 1952). It belongs to the family of flaviviruses which includes more than fifty viruses, such as dengue, yellow fever, and the West Nile virus.

This virus was first identified in the Zika forests of Uganda and East Africa during the investigations on the ecology of the yellow fever (Anderson et al., 2016). The first isolation was made in April of 1947 from the serum of pyrexia rhesus monkey caged. The second isolation was made in 1947 in the same forest (Dick et al., 1952). Just a year later, in 1948, the virus was recovered from mosquito Aedes Africanus from the Zika forest. The first human case of Zika fever was reported in Uganda in 1952. The first outbreak of Zika fever was reported in 2007 on the Pacific island of Yap, this outbreak caused 108 symptomatic cases. Another epidemic outbreak occurred in French Polynesia between 2012 and 2014. During this time, it was estimated that about 28,000 people were reported to have Zika like symptoms (Anderson et al., 2016).

Recently a large and sustained epidemic in Brazil was confirmed in April 2015. Thousands of symptomatic cases have been reported. Brazilian authorities have indeed confirmed that over 500 cases with flu-like symptoms were due to the Zika virus. Thus, owing to its recent spread outside Africa and Pacific Asia, the Zika virus can be considered an emerging pathogen. The Pan American Health Organization (PAHO), reported more than 100,000 cases of Zika virus by the end of 2016. Only 9 deaths were reported in that period (Pan American Health Organization, 2018).

Brazil was by far the country that was most affected by this

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epidemic, reporting the most cases of people infected with the Zika virus worldwide. In 2016, the state of Rio de Janeiro alone reported over 71,000 probable Zika virus infections, however, this number dropped to only 2210 cases in 2017.

Sexual transmission of the Zika virus has also been reported from both males and females to their partners (CDC, 2018; ECDC, 20185; Hastings and Fikrig, 2003; Summers and Acosta, 2015). Zika virus can be sexually transmitted from a person who is infected by the virus, even while they are not symptomatic. Furthermore, it has been suggested that Zika virus can be transmitted from a pregnant woman to her fetus during pregnancy. Zika virus can be transferred horizontally as well as vertically. During the Zika epidemic, Brazilian health officials reported an increase in the number of cases of microcephaly disease, a condition in which a baby's head is smaller than normal in Zika affected areas.

The main symptoms of Zika fever include a fever, the Maculopapular rash often spreading from the face to the body, joint and muscle pain, vomiting, or bilateral non-purulent conjunctivitis (ECDC). The first well-documented case of Zika fever was reported in 1964 and started with a mild headache with later development of a maculopapular rash, fever, and back pain (Hayes, 2009). The symptoms of Zika fever are thus quite similar to those of Dengue fever and there is a strong possibility of misdiagnosis in regions where Dengue virus is common.

The incubation period for the Zika virus is between 3 and 14 days (Krow-Lucal et al., 2017). Disease-related symptoms are developed within one week of infection for 50% of the infected individuals and within 2 weeks among 99% (Krow-Lucal et al., 2017) of the infected individuals. The vast majority of infections are not contagious from person to person; however, it may be passed person to person during sex. The virus infection is usually diagnosed by a blood test. The disease symptoms are usually mild and short lasting (17 days), and infection may go unrecognized or be misdiagnosed as Dengue fever (ECDC).

Unfortunately, there is no vaccine, antiviral drug, or other modality available to prevent or treat the Zika virus infection. Zika fever is a preventable but not a curable disease. Thus, the only means of controlling the Zika virus is to control the mosquitoes that spread the disease and protection during sex.

In the past several years, a number of deterministic models for the transmission dynamics of the Dengue virus have been studied and analyzed (Esteva and Vargas, 1998, 1999, 2003; Ferguson et al., 1999; Garba et al., 2008, 2010; Kautner et al., 1997; Wearing and Rohani, 2006). After the Zika outbreak, models for Zika transmission have been developed (Agustoa et al., 2017; Maxiana et al., 2017; Wiratsudakul et al., 2018) and analyzed. In these models, the authors included the effect of sexual transmission of the disease.

In this work, we formulate and study a deterministic model for Zika virus transmission including vertical and horizontal transmission of the disease. Although Esteva (Esteva and Vargas, 2000) discussed vertical disease transmission it was among vectors in a Dengue transmission.

Our deterministic model for Zika virus transmission includes horizontal and vertical transmission in both humans and vectors. As stated previously, it has been suggested that Zika virus can spread to newborns from their mothers, and we therefore feel that an accurate model must include the vertical transmission. Our work is an extension of our previous model (Imran et al., 2017) by including a population group that is using controlling measures. In the previous work, we considered death due to the infection and the total human and vector populations were functions of time. The previous model did not possess global stability for both disease-free and endemic equilibriums. We showed a backward bifurcation phenomenon. The current model has constant population size. Since death cases reported from Zika fever were negligible, we take disease-induced mortality to be zero. There is no backward bifurcation and the steady states results are global. Since the only way to control the disease is to isolate patients who have been infected with the Zika virus, we included a new population compartment consisting of hospitalized individuals. We have calculated the basic reproductive number associated with our model that guarantees the elimination of the disease. Finally, using optimal control techniques, we also propose and analyze the control strategies for decrease infected individuals while minimizing the costs and resources simultaneously.

The rest of this paper is organized as follows, the proposed model is presented in Section 2. Basic properties and a detailed steady-state analysis of the model are presented in Section 3. In Section 4, we perform a sensitivity and uncertainty analysis of the model parameters and reproductive number associated with our model. Section 5 uses ideas from optimal control theory to propose various controlling strategies to overcome Zika are proposed. Finally, Section 6 presents our conclusions and contains a brief discussion of our results.

2. Model formulation

We consider two types of populations in this model one for the humans and for the mosquitoes. The total human and mosquitoes populations at time t, denoted by N_h and N_v, are constant. The human population is divided into five mutually exclusive groups, susceptible humans $S_h(t)$, exposed humans $E_h(t)$, infected humans $I_h(t)$, isolated or hospitalized individuals $H_h(t)$ and recovered humans $R_h(t)$. The total vector population is divided into three mutually exclusive classes comprising of susceptible vectors $S_v(t)$, exposed vectors $E_v(t)$ and infected vectors $I_v(t)$. The model assumes that the susceptible human population $S_h(t)$ has a recruitment rate $\mu_h N_h$, where N_h is total human population and μ_h is the natural birth rate of humans. We assume that the birth rate of human population is same as the natural death rate. Susceptible individuals get infected with Zika fever virus (due to contact with infected vectors) at a rate λ_h and thus enter the exposed class E_h. In order to consider vertical transmission in our model, we make the assumption (see, e.g., Li et al., 2001) that a fraction of newborn individuals from parents in the $E_h(t)$ and $I_h(t)$ classes will be infected, and thus remain in E_h class before becoming infectious. We have assumed that the hospitalized individuals do not contribute to vertical transmission. Population in each class is removed at the natural death rate μ_h. We assumed a lifelong immunity for humans who recovered from Zika virus. The exposed individuals who got an infection, move to infectious class at a rate ξ. The infected population recovers from the Zika fever at a rate θ_I and some infected individuals are transferred to hospitalized class at a rate τ. The hospitalized population recovered at a rate of θ_H.

The susceptible vector population $S_v(t)$ has a recruitment rate $\mu_v N_v$, and μ_v is a natural death rate of vector population. A fraction of offsprings in the $E_v(t)$ and $I_v(t)$ classes will be infected, and thus remain in E_h class before becoming infectious. Because of this vertical transmission, a fraction of susceptible individuals will enter the exposed class. Susceptible vectors are infected with Zika virus (due to effective contact with infected humans) at a rate of λ_v and thus move to the exposed vector class E_v. The susceptible, exposed and infected vectors have natural death rate μ_v. In addition, exposed vectors develop symptoms and move to the infected vector class I_v at a rate of σ_v. It is assumed that infected vectors do not recover, and die at the natural death rate of μ_v.

As mentioned earlier there is no vaccine available for Zika fever. The only way to control this disease is to reduce the contact rate either by killing the mosquitoes or using the protective measure like mosquito repellents, nets etc. The effective contacts will be further reduced by isolating the infected humans. Isolation of individuals with disease

symptoms constitutes what is probably the first infection control measure since the beginning of recorded human history (Hethcote, 2000). Over the decades, these control measures have been applied, with varying degrees of success, to combat the spread of some emerging and re-emerging diseases such as leprosy, plague, cholera, typhus, yellow fever, smallpox, diphtheria, tuberculosis, measles, Ebola, pandemic influenza and, more recently, severe acute respiratory syndrome (Gumel et al., 2003; Imran et al., 2013; Lipsitch et al., 2003; Lloyd-Smith et al., 2003). Chavez et al. analyzed a SAIQR model in detail, to investigate the effect of isolation on influenza (Vivas-Barber et al., 2015). They used the isolation (quarantine) I-Q model, where the infected population is isolated. We have included epidemiological factors like permanent or partial immunity after recovery as well as intervention control measures through the inclusion of a hospitalized (or isolated) class, H_h.

$$\begin{aligned}
\frac{dS_h}{dt} &= N_h\mu_h - p\mu_h E_h - q\mu_h I_h - \lambda_h S_h - \mu_h S_h\\
\frac{dE_h}{dt} &= \lambda_h S_h + p\mu_h E_h + q\mu_h I_h - (\xi + \mu_h)E_h\\
\frac{dI_h}{dt} &= \xi E_h - (\theta_I + \tau + \mu_h)I_h\\
\frac{dH_h}{dt} &= \tau I_h - (\theta_H + \mu_h)H_h\\
\frac{dR_h}{dt} &= \theta_I I_h + \theta_H H_h - \mu_h R_h\\
\frac{dS_v}{dt} &= N_v\mu_v - r\mu_v E_v - s\mu_v I_v - \lambda_v S_v - \mu_v S_v\\
\frac{dE_v}{dt} &= r\mu_v E_v + s\mu_v I_v + \lambda_v S_v - (\sigma_v + \mu_v)E_v\\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v.
\end{aligned} \tag{1}$$

In this case both the total host population and the vector population are constant.

The forces of infection λ_h and λ_v are given as (Garba et al., 2008):

$$\lambda_h = \frac{C_{hv}}{N_h} I_v \quad \text{and} \quad \lambda_v = \frac{C_{hv}}{N_h}(I_h + \eta H_h).$$

Here we assumed that an individual in H class still can transmit the disease but with lower rate. The value of modification parameter $0 \le \eta < 1$.

Fig. 1 presents schematic diagram of the model (1).

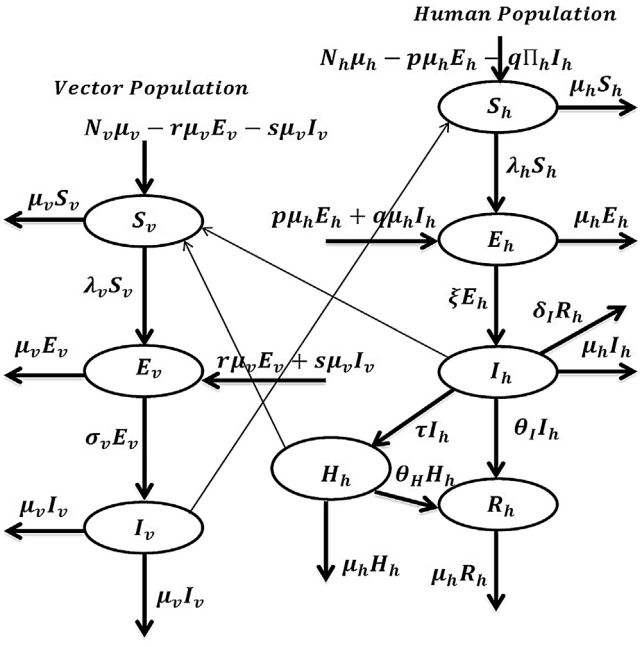


Fig. 1. Schematic diagram of the model (1).

Table 1
Description of the variables of the model (1).

Variable	Description
N_h	Total human population
N_v	Total vector population
S_h	Population of susceptible humans
E_h	Population of exposed humans
I_h	Population of infected humans
H_h	Population of hospitalized humans
R_h	Population of recovered humans
S_v	Population of susceptible vectors
E_v	Population of exposed vectors
I_v	Population of infected vectors

Table 2
Description of the parameters of the model (1).

Parameter	Description
μ_h	Natural death rate of humans
μ_v	Natural death rate of vectors
p	Fraction of new born from exposed humans
q	Fraction of new born from infected humans
r	Fraction of offsprings from exposed vectors
s	Fraction of offsprings from infected vectors
θ_I	Recovery rate of infected humans
θ_H	Recovery rate of hospitalized humans
ξ	Progression rate of humans from exposed to infected class
τ	Hospitalization rate of infected individuals
σ_v	Progression rate of vectors from exposed to infected class
C_{hv}	Effective contact rate
η	Modification parameter for relative infectiousness of hospitalized humans

A description of the variables and parameters of the model (1) is given in Tables 1 and 2 respectively.

The model (1) will be studied on the closed set:

$$\mathcal{B} = \{(S_h, E_h, I_h, H_h, R_h, S_v, E_v, I_v) \in \mathbb{R}^8_+ : S_h + E_h + I_h + H_h + R_h = N_h;\ S_v + E_v + I_v = N_v\}.$$

$\mathcal{B}$ is positively invariant and attracting with respect to the model (1). It can be seen that the solutions are always positive. The right sides of (1) are smooth, so that initial value problems have unique solutions that exist on maximal intervals. Since paths cannot leave $\mathcal{B}$, solutions exist for all positive time. Thus the model is mathematically and epidemiologically well posed.

3. Basic reproductive number and steady states analysis

In this section, we will perform a detailed steady state and stability analysis of the Zika fever model presented in Section 2.

3.1. Basic reproductive number and local stability of disease free equilibrium

The model (1) has a disease free equilibrium (DFE) given by

$$\mathcal{E}_0 = (S_h^*, E_h^*, I_h^*, H_h^*, R_h^*, S_v^*, E_v^*, I_v^*) = (N_h, 0, 0, 0, 0, N_v, 0, 0)$$

In order to investigate the local stability of the DFE ($\mathcal{E}_0$), the next generation operator method (van den Driessche and Watmough, 2002) will be used. Following the notation of van den Driessche and Watmough (2002), the matrix F (for the new infection terms) and the matrix V (of the transition terms) are given, respectively, by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & C_{hv} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{C_{hv}}{N_h}S_v^* & \frac{C_{hv}}{N_h}\eta S_v^* & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} -p\mu_h + K_1 & -q\mu_h & 0 & 0 & 0 \\ -\xi & K_2 & 0 & 0 & 0 \\ 0 & -\tau & K_3 & 0 & 0 \\ 0 & 0 & 0 & -r\mu_v + K_4 & -s\mu_v \\ 0 & 0 & 0 & -\sigma_v & K_5 \end{pmatrix}$$

where $K_1 = \xi + \mu_h$, $K_2 = \theta_I + \tau + \mu_h$, $K_3 = \theta_H + \mu_h$, $K_4 = \sigma_v + \mu_v$, and $K_5 = \mu_v$.

The basic reproduction number R_0 for our model is given by

$$R_0 = \rho(FV^{-1}) = \sqrt{\frac{C_{hv}^2 N_v \xi \sigma_v (K_3 + \eta\tau)}{N_h K_3[(K_1 - p\mu_h)K_2 - q\mu_h\xi][(K_4 - r\mu_v)K_5 - s\mu_v\sigma_v]}}$$
$$= \sqrt{\frac{C_{hv}^2 N_v \xi \sigma_v (K_3 + \eta\tau)}{N_h[K_2\mu_h(1-p) + \xi(\theta_I + \tau + \delta_I + \mu_h(1-q))][K_5\mu_v(1-r) + \sigma_v(\delta_v + \mu_v(1-s)}}]>0. \quad (2)$$

When $p = q = 0$, vertical transmission is not present in the model; the above R_0 reduces to the basic reproduction number R_0 of a SEIR model for a vector disease (Garba et al., 2008).

To get a better understanding of the basic reproduction number R_0 in (2), we rewrite it using Taylor expansion about p and q:

$$R_0^2 = \frac{C_{hv}^2 N_v \xi \sigma_v}{N_h K_1 K_2 K_3 K_4 K_5}[1 + \frac{K_2 p\mu_h + q\mu_h\xi}{K_1K_2} + \frac{K_5 r\mu_v + s\mu_v\sigma_v}{K_4K_5} + (R)^2 + \cdots],$$
$$= R_c[1 + \frac{K_2 p\mu_h + q\mu_h\xi}{K_1K_2} + \frac{K_5 r\mu_v + s\mu_v\sigma_v}{K_4K_5} + (R)^2 + \cdots],$$
$$= R_c(1 + R + R^2 + \cdots),$$

where

$$R_c = \frac{C_{hv}^2 N_v \xi \sigma_v (K_3 + \eta\tau)}{N_h K_1 K_2 K_3 K_4 K_5} \quad \text{and} \quad R = \frac{p\mu_h K_2 + q\mu_h K_1}{K_1K_2} + \frac{K_5 r\mu_v + s\mu_v\sigma_v}{K_4K_5}.$$

Now

$$R = R_p + R_q + R_r + R_s = \frac{p\mu_H}{K_1} + \frac{q\mu_H\xi}{K_1K_2} + \frac{r\mu_V}{K_4} + \frac{s\mu_V\sigma_v}{K_4K_5}.$$

Note that R_c is the basic reproductive number for horizontal transmission (Khan et al., 2014). The square root means that the two generations required for an infected vector or host to reproduce itself (van den Driessche and Watmough, 2002). $R_p + R_q$ is the sum of the number of infected individuals during the mean latent period and the number of infected individuals during the mean infectious period. Similarly, $R_r + R_s$ is the sum of the number of infected vector offsprings during the mean latent period and the number of infected vector offsprings during the mean infectious period. The expression $R = R_cR_p + R_cR_q + R_cR_r + R_cR_s$) represents the total contribution to the infective class made by the exposed and infective individuals of first generation (Li et al., 2001). The local stability of the disease free equilibrium follows directly from van den Driessche and Watmough (2002). We have following result about local and global stability of disease free state:

Lemma 3.1. *The DFE ($\mathcal{E}_0$) of the model (2.1), is locally-asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

Theorem 3.2. *The DFE, $\mathcal{E}_0 = (N_h, 0, 0, 0, 0, N_v, 0, 0)$, of the model (1) is globally-asymptotically stable in $\mathcal{B}$ whenever $R_0 < 1$.*

Proof. Let $x(t) = (S_h(t), E_h(t), I_h(t), H_h, R_h(t), S_v(t), E_v(t), I_v(t))$ be a solution of (1) with $x_0 = x(0)$.

A comparison theorem will be used for the proof. The equations for the infected components of (1) can be written as (where the prime denotes the derivative with respect to time),

$$\begin{pmatrix} E_h' \\ I_h' \\ H_h' \\ E_v' \\ I_v' \end{pmatrix} = (F - V)\begin{pmatrix} E_h \\ I_h \\ H_h \\ E_v \\ I_v \end{pmatrix} - (1 - \tfrac{S_h}{N_h})\begin{pmatrix} 0 & 0 & 0 & 0 & C_{hv} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} E_h \\ I_h \\ H_h \\ E_v \\ I_v \end{pmatrix}$$
$$- (1 - \tfrac{S_v}{N_v})\begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{C_{hv}S_v^*}{N_h} & \frac{\eta C_{hv}S_v^*}{N_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} E_h \\ I_h \\ H_h \\ E_v \\ I_v \end{pmatrix}$$
$$\le (F - V)\begin{pmatrix} E_h \\ I_h \\ H_h \\ E_v \\ I_v \end{pmatrix}$$

Lemma 3.1 established the local asymptotic stability of the DFE when $R_0 < 1$, or equivalently, $\rho(FV^{-1}) < 1$, which is equivalent to all eigenvalues of $F - V$ having negative real parts when $R_0 < 1$ (van den Driessche and Watmough, 2002). Also, $F - V$ has all off-diagonal entries non negative. Then $E_h(t)$; $I_h(t)$; $H_h(t)$; $E_v(t)$; $I_v(t) \to 0$ as $t \to \infty$ (see Corollary B.2. in [38]). Substituting $E_h = I_h = H_h = E_v = I_v = 0$ into the model (1) gives $S_h \to N_h$, $R_h \to 0$ and $S_v \to N_v$ as $t \to \infty$. This means that the Omega limit set of x_0, $\omega(x_0)$, is contained in the disease-free space. But, on the other hand, it is straightforward to check that every solution with the initial condition in the disease-free space converges to $\mathcal{E}_0$. Hence $\mathcal{E}_0 \in \omega(x_0)$. This implies that, in fact, $\omega(x_0) = \mathcal{E}_0$ (because N_0 is asymptotically stable). Thus, $x(t) \to \mathcal{E}_0$ as $t \to 0$, which completes the proof. □

The epidemiological implication of the above result is that the disease can be eliminated from the population if the basic reproduction number R_0 can be brought down to a value less than unity (that is, the condition $R_0 < 1$ is sufficient and necessary for disease elimination) irrespective of the size of the initial populations in each class. The stability of the DFE is demonstrated in Fig. 2a. If $R_0 > 1$ the DFE is unstable in this case and the solutions are attracted to an (apparently unique and stable) endemic equilibrium, as depicted in Fig. 2b.

3.2. Existence of endemic state

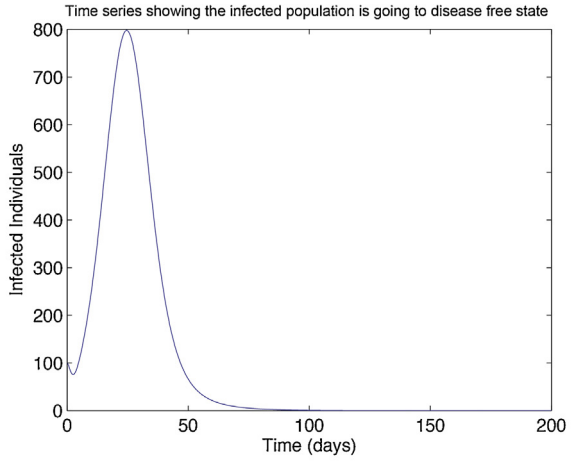
In this section, the existence and stability of endemic equilibrium (EE) of the model (1) will be discussed. We define endemic equilibrium to be those fixed points of the system (1) in which at least one of the infected compartments of the model are non-zero.

Theorem 3.3. *The Endemic State, $\mathcal{E}_1$, of the model (1) exists whenever $R_0 > 1$.*

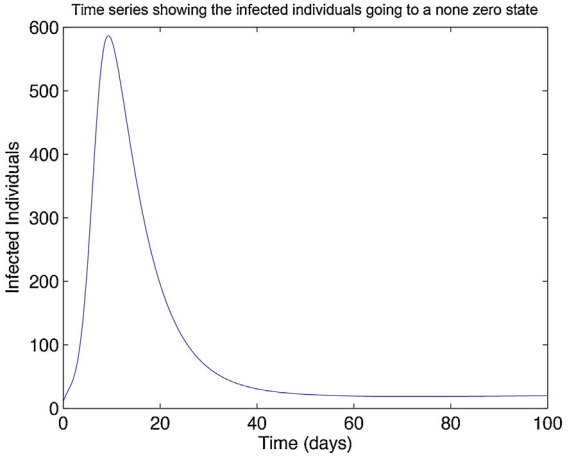
Proof. Let $\mathcal{E}_1 = (S_h^\varnothing, E_h^\varnothing, I_h^\varnothing, H_h^\varnothing, R_h^\varnothing, S_v^\varnothing, E_v^\varnothing, I_v^\varnothing)$ denote an arbitrary endemic equilibrium of the model (1). Also, let

$$\lambda_h^\varnothing = \frac{C_{hv}I_v^\varnothing}{N_h}, \quad \lambda_v^\varnothing = \frac{C_{hv}(I_h^\varnothing + \eta H_h^\varnothing)}{N_h} \quad (3)$$

Solving the equations of the model (1) for steady-state by setting right hand asides of the model (1) equal to zero yields



(a) The population is approaching Disease-free Equilibrium: $R_0 = 0.73$, $C_{hv} = 0.17$



(b) The infected population is converging to endemic equilibrium: $R_0 = 1.13$, $C_{hv} = 0.22$

Fig. 2. (a and b) Time series of the model (1) converging to possible steady states.

$$
\begin{aligned}
S_h^{\varrho} &= \frac{N_h\mu_h m_1}{m_1(\lambda_h^{\varrho}+\mu_h)+p\lambda_h^{\varrho}\mu_h K_2+q\lambda_h^{\varrho}\mu_h\xi};\\
E_h^{\varrho} &= \frac{\lambda_h^{\varrho}N_h\mu_h K_2}{m_1(\lambda_h^{\varrho}+\mu_h)+p\lambda_h^{\varrho}\mu_h K_2+q\lambda_h^{\varrho}\mu_h\xi};\\
I_h^{\varrho} &= \frac{\xi\lambda_h^{\varrho}N_h\mu_h}{m_1(\lambda_h^{\varrho}+\mu_h)+p\lambda_h^{\varrho}\mu_h K_2+q\lambda_h^{\varrho}\mu_h\xi};\\
H_h^{\varrho} &= \frac{\tau\xi\lambda_h^{\varrho}N_h\mu_h}{K_3(m_1(\lambda_h^{\varrho}+\mu_h)+p\lambda_h^{\varrho}\mu_h K_2+q\lambda_h^{\varrho}\mu_h\xi)};\\
R_h^{\varrho} &= \frac{\xi\lambda_h^{\varrho}N_h\mu_h(\theta_I+\theta_H}{K_3\mu_h(m_1(\lambda_h^{\varrho}+\mu_h)+p\lambda_h^{\varrho}\mu_h K_2+q\lambda_h^{\varrho}\mu_h\xi)};\\
S_v^{\varrho} &= \frac{N_v\mu_v m_2}{m_2(\lambda_v^{\varrho}+\mu_v)+r\lambda_v^{\varrho}\mu_v K_4+q\lambda_v^{\varrho}\mu_v\sigma_v};\\
E_v^{\varrho} &= \frac{\lambda_v^{\varrho}N_v\mu_v K_4}{m_2(\lambda_v^{\varrho}+\mu_v)+r\lambda_v^{\varrho}\mu_v K_4+s\lambda_v^{\varrho}\mu_v\sigma_v};\\
I_v^{\varrho} &= \frac{\sigma_v\lambda_v^{\varrho}N_v\mu_v}{m_2(\lambda_v^{\varrho}+\mu_v)+r\lambda_v^{\varrho}\mu_v K_4+s\lambda_v^{\varrho}\mu_v\sigma_v}.
\end{aligned}
\tag{4}
$$

Where $m_1 = K_2(K_1 - p\mu_h) - q\mu_h\xi$, $m_2 = K_5(K_4 - r\mu_v) - s\mu_v\sigma_v$ and all $K's$ are defined above. Substituting (4) in (3) and simplifying gives,

$$
\lambda_h^{\varrho} = \frac{C_{\mathrm{hv}}\sigma_v\lambda_v^{\varrho}N_v\mu_v\mu_h}{N_h\mu_h[m_2(\lambda_v^{\varrho}+\mu_v)+r\lambda_v^{\varrho}\mu_v K_4+s\lambda_v^{\varrho}\mu_v\sigma_v]} \tag{5}
$$

Also,

$$
\lambda_v^{\varrho} = \frac{C_{\mathrm{hv}}\lambda_h^{\varrho}\xi\mu_h(K_3+\eta\tau)}{K_3[m_1(\lambda_h^{\varrho}+\mu_h)+p\lambda_h\mu_h K_2+q\lambda_h\mu_h\xi]} \tag{6}
$$

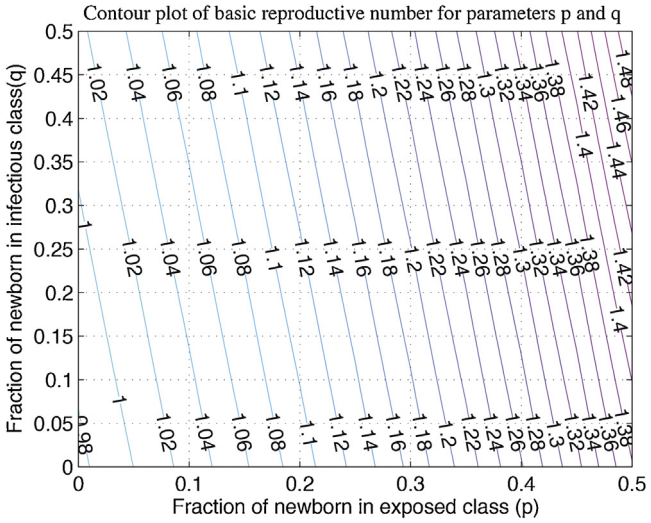


Fig. 3. Simulation of the model (1) showing the contour plot of R_0 as a function of fraction of newborn exposed individuals (p) and newborn infected individuals (q).

Substitute (6) into (5), we have the following equation in λ_h^{ϱ}

$$
\begin{aligned}
\lambda_h^{\varrho} = {} & \frac{m_1 m_2\mu_h\mu_v K_3(R_0^2-1)}{N_h\mu_h[m_2K_3C_{\mathrm{hv}}\xi\mu_h + m_2\mu_v K_3A + (r\mu_v K_4 + q\mu_v\sigma_v)(K_3C_{\mathrm{hv}}\xi\mu_h}\\
& + \eta\tau\xi\mu_h N_h\mu_h)]
\end{aligned}
\tag{7}
$$

where $A = m_1 + p\mu_h K_2 + q\mu_v\sigma_v$. Clearly the model (1) has no endemic state if $R_0 < 1$ and one unique endemic state when $R_0 > 1$. □

Fig. 3 shows the variation in R_0 with the relative fraction of newborn exposed individuals (p) and newborn infected individuals (q). We notice that no less than %5 of newborn exposed individuals (p) and no more than 25% of the fraction of newborn infected individuals to bring R_0 less than 1:

Fig. 4 shows the effect of hospitalization rate τ of infected individuals on the basic reproductive number R_0. From this figure, we can see that effective isolation will help to reduce the basic reproductive number. About 25% of infected individuals should be effectively isolated to bring the basic reproductive number to less than 1. This plot shows that the effective isolation is helpful in controlling the epidemic of Zika virus.

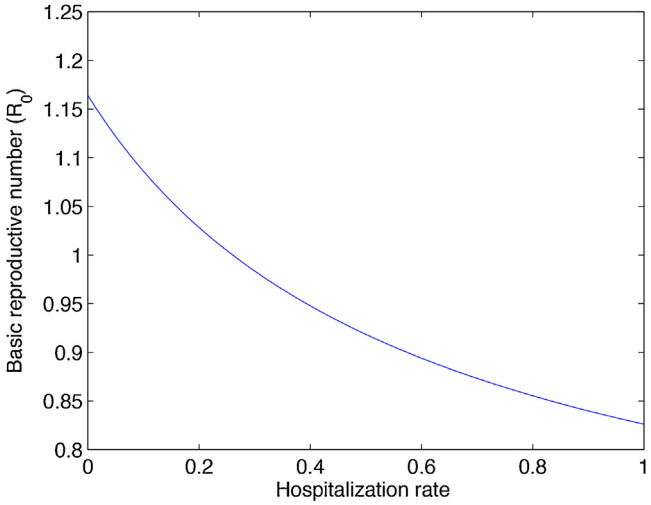


Fig. 4. The effect of hospitalization rate τ of infected individuals versus basic reproductive number R_0 for the model (1).

3.2.1. Uniform persistence

Let $\mathcal{I} = (E_h, I_h, H_h, E_v, I_v)$. Then $(\mathcal{I})'(t) = A(x(t))\mathcal{I}(t)$, where

$$A(x) = \begin{pmatrix} -K_1 + p\mu_h & q\mu_h & 0 & 0 & \frac{C_{hv}}{N_h}S_h \\ \xi & -K_2 & 0 & 0 & 0 \\ 0 & 0 & -K_3 & 0 & 0 \\ 0 & \frac{C_{hv}}{N_h}S_v & \frac{\eta C_{hv}}{N_h}S_v & -K_4 + r\mu_v & s\mu_v \\ 0 & 0 & 0 & \sigma_v & -K_5 \end{pmatrix}, \tag{8}$$

denote by $s(A)$ the spectral bound of matrix A. Let $\rho: \mathbb{R}^8_+ \to \mathbb{R}_+$,

$$\rho(x) = \min_{i=1}^{4} \mathcal{I}_i. \tag{9}$$

Theorem 3.4. *If $R_0 > 1$ then the disease is strongly uniformly ρ-persistent: $\exists \varepsilon > 0$ such that*

$$\liminf_{t\to\infty} \rho(x(t)) > \varepsilon, \tag{10}$$

whenever $\rho(x(0)) > 0$. Where $x(t) = (S_h(t), E_h(t), I_h(t), H_h(t), R_h(t), S_v(t), E_v(t), I_v(t)$ be a solution of model (1). In this case there exists an endemic steady state.

Proof. Let $X = \{x \in \mathbb{R}^8_+ | \rho(x(t)) = 0 \ \forall \ t \geq 0\}$. Then $X = \{x \in \mathbb{R}^8_+ | E_h = I_h = H_h = R_h = E_v = I_v = 0\}$ (that is, X is the disease-free subspace). Note that X, as well as $\mathbb{R}^7_+ \backslash X$, are positively invariant. Also, all solutions originating in X converge to N_0 as $t \to \infty$. N_0 is asymptotically stable in X. Hence N_0 is isolated in X. Corollary 4.7 in Salceanu (2011) (where $M = B \cap X$, $\Omega(M) = \{N_0\}$, $T = 1$, $P(1, N_0)$ is $e^{A(N_0)}$)), together with Proposition 4.1 and Lemma 3.1 in Salceanu (2011), imply that $\{N_0\}$ is also uniformly weakly repelling. Then, from Theorem 8.17 in Smith and Thieme (2011) we have that the semiflow generated by (2.4) is uniformly weakly ρ-persistent. From the positive invariance of $\mathcal{B}$, we have that (2.4) is point dissipative. Then, according to Theorem 2.28 in Smith and Thieme (2011), there exists a compact attractor of points for (1). This, together with uniformly weakly ρ-persistent imply (10) (see Smith and Thieme, 2011, Theorem 5.2). In this case there exists an endemic steady state (Smith and Thieme, 2011). □

3.3. Stability of endemic state

The local stability of the endemic steady state $\mathcal{E}_1$ of the model (1) is given in the lemma below.

Theorem 3.5. *If $R_0 > 1$, then the endemic state of the model (1) is locally asymptotically stable in for model (1).*

for the proof of this above local stability theorem see Imran et al. (2017).

For the global stability of the endemic steady state $\mathcal{E}_1$, we consider the (1) with no hospitalization and a small incubation period so that we can assume that susceptible individuals after infection move to infected class.

In this case, it is easily seen that both for the host population and for the vector population the corresponding total population sizes are asymptotically constant. We assumed that in our model the total population is constant. Previous results (Thieme, 1992) imply that the dynamics of systems (1) is qualitatively equivalent to the dynamics of system given by:

$$\begin{aligned} \frac{dS_H}{dt} &= \Pi_H - q\Pi_H I_H - \lambda_H S_H - \mu_H S_H \\ \frac{dI_H}{dt} &= \lambda_H S_H + q\Pi I_H - (\theta + \mu_H) I_H \\ \frac{dI_V}{dt} &= \lambda_V (\frac{\Pi_V}{\mu_V} - I_V) - \mu_V I_V \end{aligned} \tag{11}$$

We study the following feasible region of the new system (11):

$$\mathcal{D} = \left\{(S_H, I_H, I_V) \in \mathbb{R}^3_+ : S_H + I_H \leq \frac{\Pi_H}{\mu_H}; \ I_V \leq \frac{\Pi_V}{\mu_V}.\right\}$$

Denote the interior of $\mathcal{D}$ by $\mathcal{D}^o$.

Theorem 3.6. *If $R_0 > 1$, then the endemic state of (11) is globally asymptotically stable in $\mathcal{D}^o$.*

Proof. We will use geometric approach to global-stability method given in Li et al. (2001). Let $x = (S, I_H, I_V)$ and $f(x)$ denote the vector field of (11). The Jacobian matrix

$$J = \begin{bmatrix} C_H I_V - \mu_H & -q\Pi & -C_H S_H \\ C_H I_V & -\theta - \mu_H & C_H S_H \\ 0 & C_V(\frac{\Pi_V}{\mu_V} - I_V) & -\mu_H - C_V I_H \end{bmatrix}$$

and its second additive compound matrix $J^{[2]}$ is (see Li et al., 2001):

$$J^{[2]} = \begin{bmatrix} C_H I_V - 2\mu_H - \theta & C_H S_H & C_H S_H \\ C_V(\frac{\Pi_V}{\mu_V} - I_V) & -C_H I_V - C_V I_H - \mu_H - \mu_V & -q\Pi_H \\ 0 & C_H I_V & -C_V I_H - \mu_H - \mu_V - \theta \end{bmatrix}$$

.

Here $C_H = C_V = C_{HV}\frac{\mu_H}{\Pi_H}$. Take the function $P(x)$ as:

$$P(x) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & (1 - a_2)\frac{I_H}{I_V} & 0 \\ 0 & 0 & \frac{I_H}{I_V} \end{bmatrix}$$

where

$$a_2 = \begin{cases} 0 & \text{if } \theta \geq \Pi_H \\ 1 - \frac{\theta}{q\Pi_H} & \text{if } \theta < \Pi_H. \end{cases}$$

$$P(x) = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix}$$

where $B_{11} = -C_H I_V - 2\mu_H - \theta + q\Pi_H$, $B_{12} = (C_H\frac{S_H I_V}{I_H},)C_H\frac{S_H I_V}{I_H})$, $B_{21} = (C_V\frac{I_H}{I_V}(\frac{\Pi_V}{\mu_V} - I_H), 0)^t$ and

$$B_{22} = \begin{bmatrix} \frac{I'_H}{I_H} - \frac{I'_V}{I_V} - C_H I_V - C_V I_H - \mu_H & -(1 - a_2)q\Pi_H \\ -\mu_V + q\Pi_H & \\ C_H I_V & \frac{I'_H}{I} - \frac{I'_V}{I_V} - C_V I_H - \mu_H - \mu_V - \theta \end{bmatrix}$$

$\mu(B) \leq \sup\{g_1, g_2\}$

where

$g_1 = \mu(B_{11}) + |B_{12}|, \quad g_2 = |B_{21}| + \mu(B_{22}).$

$$\begin{aligned} \mu(B_{22}) &= \frac{I'_H}{I_H} - \frac{I'_V}{I_V} - C_V I_H - \mu_H - \mu_V + \max\{0, q\Pi_H - \theta\} \\ &\leq \frac{I'_H}{I_H} - \frac{I'_V}{I_V} - C_V I_H - \mu_H - \mu_V. \end{aligned}$$

Therefore,

$$q_1 = C_H I_V - \theta - 2\mu_H + C_H\frac{S_H I_V}{I_H} \tag{12}$$

$$g_2 = C_V \frac{I_H}{I_V}\left(\frac{\Pi_V}{\mu_V} - I_V\right) - C_V I_H - \mu_H - \mu_V + \frac{I'_H}{I_H} - \frac{I'_V}{I_V}. \quad (13)$$

Now from the system (11), we can write second and third equation,

$$C_H \frac{S_H I_V}{I_H} = (\theta + \mu_H) + \frac{I'_H}{I_H}$$
$$C_V \Pi_V \frac{I_H}{\mu_V I_V} = \mu_V + I_H + \frac{I'_V}{I_V}.$$

$$q_1 \leq \frac{I'_H}{I_H} - \mu_H \quad (14)(15)$$

4. Sensitivity analysis

The variation in the values of the parameters of our model (1) is a source of uncertainty and sensitivity. In this section, we carry out a parameter base global uncertainty and sensitivity analyses on R_0. There are a lot of reasons for the sensitivity of the parameters, for example, inadequate data, lack of information about the vertical transmission. We use the Latin-hypercube sampling based method to quantify the uncertainty and the sensitivity of R_0 as a function of the model parameters.

We use the Latin-hypercube sampling based method to quantify the uncertainty and the sensitivity of R_0 as a function of 13 model parameters, namely μ_h, μ_v, θ_I, θ_H, ξ, σ_v, p, q, r, s, C_{hv}, τ, η. The Partial Rank Correlation Coefficient (PRCC) measures the impact of the parameters on the output variable using the rank transformation of the data to reduce the effects of nonlinearity. The uncertainty analysis (Figs. 5 and 6) yields an estimated value of $R_0 = 1.54$ with 95% CI (1.3491, 1.7669) for the Zika fever.

The sensitivity analysis suggests that R_0 is highly sensitive to the parameters C_{hv}, θ_I, θ_H, μ_v, τ. The accuracy and precision in the values of these parameters is vital for the accurate predictions of the model.

The estimated parameters are presented in Table 3.

5. Optimal control for the isolation model (1)

One of the goals of this study is to come up with a time-dependent hospitalization/isolation strategy that would minimize the infected population while keeping the costs to a minimum at the same time.

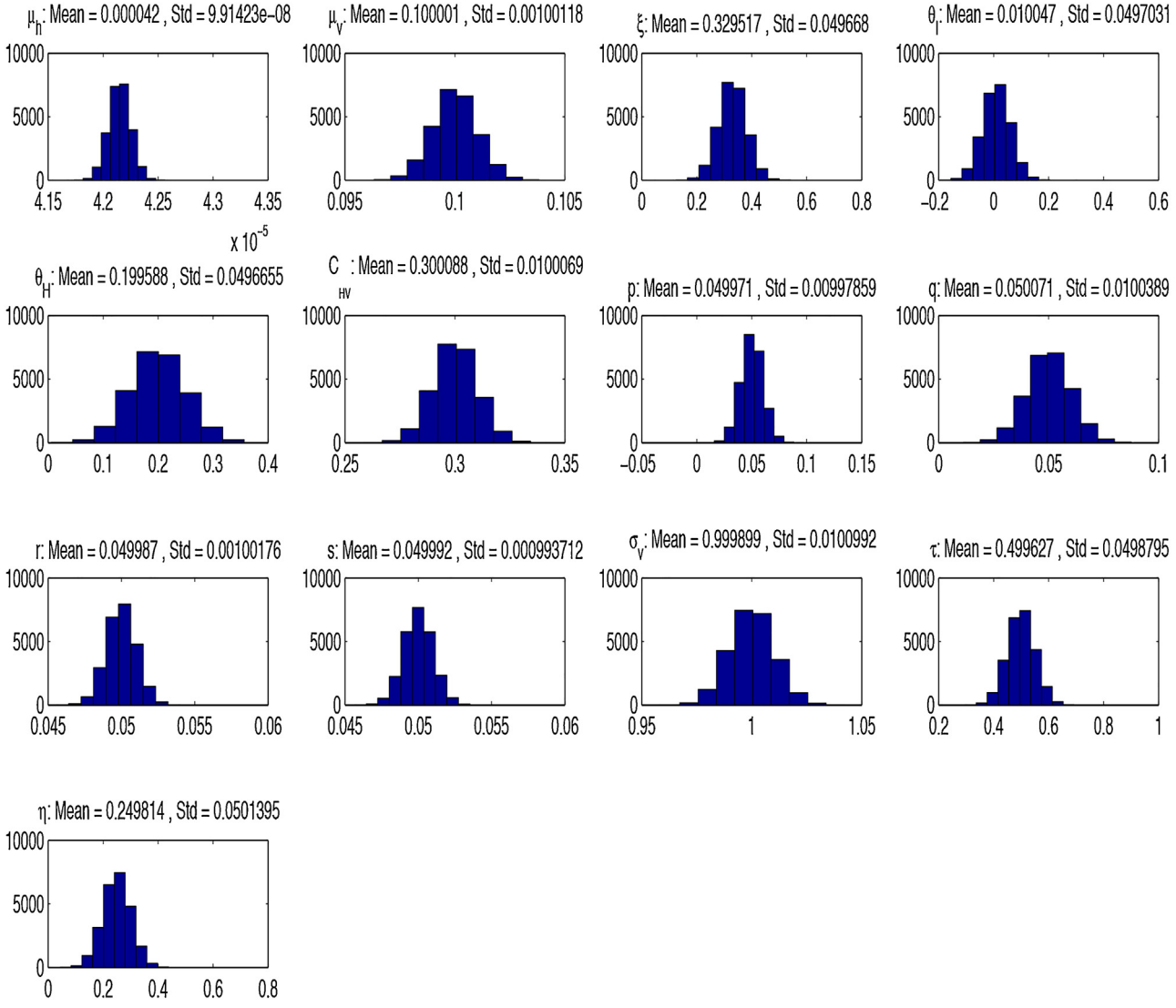


Fig. 5. Uncertainty analysis.

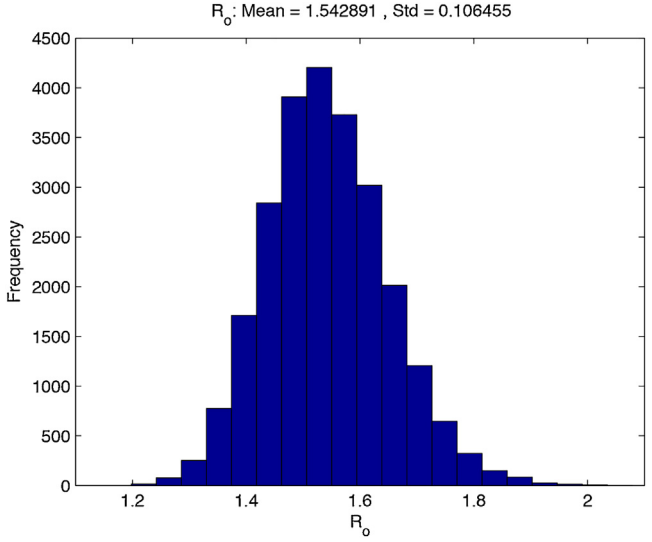


Fig. 6. Uncertainty analysis.

Table 3
Mean values of the model parameters with their assigned distributions. *N* and *G* represents the normal and gamma distribution respectively.

Parameter	Mean, Std.Dev	Distribution
μ_h	(0.000042, 9.91365e08)	*N*
μ_v	(0.100011, 0.00100085)	*N*
C_{hv}	(0.200012, 0.0100131)	*G*
ξ	(0.329517, 0.049668)	*N*
p	(0.049971, 0.00997859)	*N*
q	(0.050071, 0.0100389)	*N*
r	(0.049987, 0.00100176)	*N*
s	(0.049992, 0.000993712)	*N*
θ_I	(0.500184, 0.0497701)	*N*
θ_H	(0.010047, 0.0497031)	*N*
τ	(0.499627, 0.0498795)	*N*
η	(0.249814, 0.0501395)	*N*
σ_v	(0.999899, 0.0100992)	*N*

Optimal control is a very useful mathematical technique that can help us to address these questions. Here our goal is to put down infection from the population by increasing the recovered class and to minimize the required resources to control Zika fever infection using isolation or hospitalization.

The optimal control algorithm we use is based on Pontrygain's Maximum Principle which appends the original model to an adjoint system of differential equations with terminal conditions. The optimal objective system, which characterizes the optimal controls, consists of differential equations of the original model (state system) along with the adjoint differential equations (the adjoint system). The number of equations in the adjoint system is same as that of in the state system. The detailed mechanism of forming the necessary conditions for the adjoint and optimal controls are discussed in Fleming and Rishel (1975) and Pontryagin and Boltyanskii (1980).

An important decision while formulating an optimal control problem is deciding how and where to introduce the control in the system of differential equations. The form of the optimal control primarily depends on the system being analyzed and the objective function to be optimized. In this paper, we will propose various strategies to eradicate Zika fever using optimal control techniques.

5.1. Hospitalization control

The first step is to find an optimal hospitalization schedule that minimizes the number of infectious individuals and the overall cost of hospitalization during a fixed time. We define the control set as $\mathbf{U} = \{\tau(t) : 0 \le \tau(t) \le \zeta,\ 0 \le t \le T,\ 0 < \zeta \le 1,\ \tau(t)$ is Lebesgue measurable$\}$. Here ζ is a positive number and is defined as the maximum value attained during optimal control procedure. Our aim is to minimize the associated cost function which is given as:

$$J[\tau] = \int_0^T \left[A_I I_h + A_N N_v + \frac{1}{2} W\tau^2(t)\right] \mathrm{dt} \tag{15}$$

Here A_I and A_N are positive constants used to balance in the size of $I(t)$ and $N_v(t)$. Further, we used a nonlinear cost function in order to accommodate the impact of variety of factors associated with hospitalization, documented widely in literature, see for instance Kirschner et al. (1997). W is weight associated with quadratic cost due to hospitalization. Moreover a linear function has been chosen for cost incurred by infected individuals and the mosquitoes population. Our objective is to find an optimal control for hospitalization rate $\tau^*(t)$ such that $J[\tau^*] = \min_{\tau \epsilon U} J[\tau]$. The Lagrangian of the optimization problem is given by $L = A_I I_h + \frac{1}{2} W\tau^2(t)$. The associated "Hamiltonian" is given by

$$H^* = A_I I_h + \frac{1}{2} W\tau^2(t) + \sum_{i=1}^{8} \phi_i k_i \tag{16}$$

where k_i represents the right hand side of the ith equation in our original model. W depends on the relative importance of the control measures in mitigating the spread of the disease as well as the cost incurred (such as material resources and human effort) during the implementation of control measure per unit time. Pontrayagin's Maximum Principal converts model (1) and objective function (16) into minimizing the Hamiltonian (17) with respect to τ. Now we prove the following theorem to elicit the effect of optimal control of hospitalization.

Theorem 5.1. *There exists a unique optimal control $\tau^*(t)$ which minimizes J over* **U**. *Also, there exists an adjoint system of ϕ_i's such that the optimal treatment control is characterized as*

$$\tau^*(t) = \min\left[\zeta, \max\left(0, \frac{I_h(\phi_3 - \phi_4)}{W}\right)\right] \tag{17}$$

for some positive number ζ. The adjoint system is given as

$$\begin{aligned}
\frac{d\phi_1}{\mathrm{dt}} &= \left(\frac{C_{hv} I_v}{N_h} + \mu_h\right)\phi_1 - \frac{C_{hv} I_v}{N_h}\phi_2 \\
\frac{d\phi_2}{\mathrm{dt}} &= p\mu_h\phi_1 - p\mu_h\phi_2 + (\xi + \mu_h)\phi_2 - \xi\phi_3 \\
\frac{d\phi_3}{\mathrm{dt}} &= -A_I + q\mu_h\phi_1 - q\mu_h\phi_2 + (\theta_I + \tau + \delta_I + \mu_h)\phi_3 - \tau\phi_4 - \theta_I\phi_5 \\
&\quad + \frac{C_{hv} S_v}{N_h}\phi_6 - \frac{C_{hv} S_v}{N_h}\phi_7 \\
\frac{d\phi_4}{\mathrm{dt}} &= (\theta_H + \delta_H + \mu_h)\phi_4 - \theta_h\phi_5 + \frac{\eta C_{hv} S_v}{N_h}\phi_6 - \frac{\eta C_{hv} S_v}{N_h}\phi_7 \\
\frac{d\phi_5}{\mathrm{dt}} &= \mu_h\phi_5
\end{aligned} \tag{18}$$

The above adjoint system also satisfies the transversality condition, $\{\phi_i(T) = 0 : i = 1, b, \ldots, 8\}$.

Proof. We can easily verify that the integrand of J is convex with respect to $\tau(t)$. Also, the solutions of our model are bounded above. In addition, it is verifiable that the model has the Lipschitz property with respect to the state variables. Using the properties mentioned above along with corollary 4.1 of Fleming and Rishel (1975), the existence of an optimal control is established.

Now using the Pontryagin's Maximum Principle, we obtain

$$\begin{aligned}
\frac{d\phi_1}{\mathrm{dt}} &= -\frac{\partial H^*}{\partial S_h}, \quad \phi_1(T) = 0 \\
\frac{d\phi_2}{\mathrm{dt}} &= -\frac{\partial H^*}{\partial E_h}, \quad \phi_2(T) = 0 \\
&\vdots \quad \vdots \quad \vdots \\
\frac{d\phi_8}{\mathrm{dt}} &= -\frac{\partial H^*}{\partial I_v}, \quad \phi_8(T) = 0
\end{aligned}$$

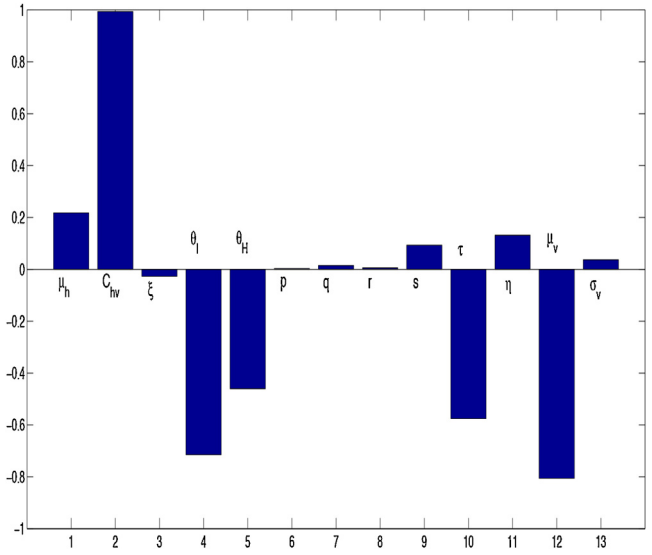


Fig. 7. Sensitivity analysis.

evaluated at the optimal control which results in the above stated adjoint system. The optimality condition is $\frac{\partial H}{\partial \tau} = 0$. Therefore on the set $\{T: 0 < \tau^*(T) < \zeta\}$ we obtain

$$\tau^*(t) = \frac{I_h(\phi_3 - \phi_4)}{W}$$

Now, we discuss the numerical solutions of the optimality system and the corresponding optimal control obtained using $\zeta = 0.5$. The optimal strategy is obtained by solving the optimal system consisting of both the state system as well as the adjoint system. Since there are initial conditions present for the state equations, we start solving them with a guess for τ using the fourth-order forward Runge-Kutta method. The adjoint equations are then solved using the fourth-order backward Runge-Kutta method because of the presence of final conditions. Then, the controls are updated by using a convex combination of the previous control and the value from the characterization given above. This process is repeated until we obtain a desired accuracy of convergence (Fig. 7).

Fig. 8 represents the optimal isolation(hospitalization) strategy to be employed to minimize the cost and the infected population. Considering the practical constraints, an upper bound of 0.5 was chosen for the optimal hospitalization control. The figure shows that initially, the optimal level remains at the upper bound of 0.5 after which it declines steadily to 0. This implies that in the early phase of the endemic breakout, keeping the control at the upper bound would help in

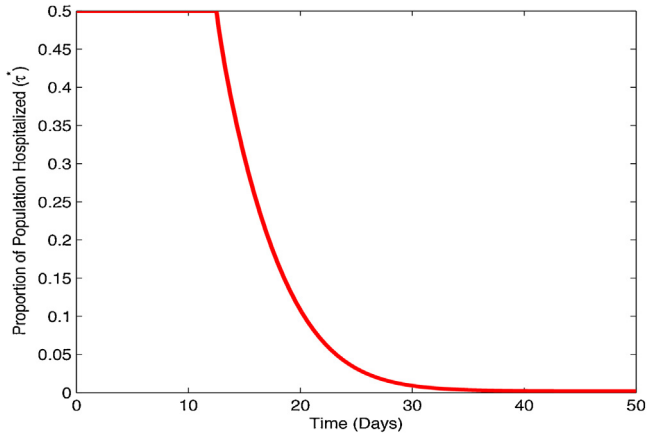


Fig. 8. Optimal hospitalization control.

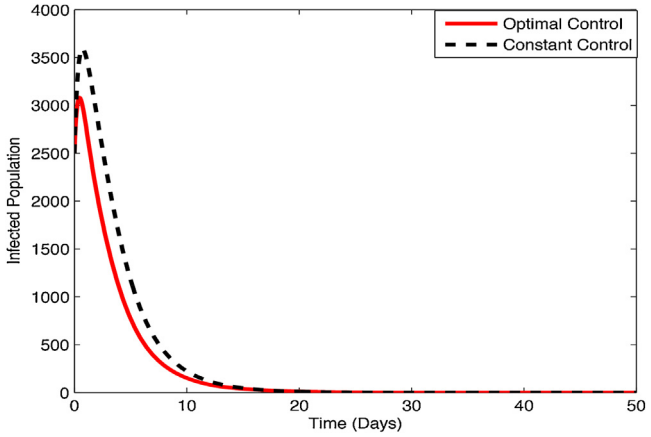


Fig. 9. Comparison of total infected host population under optimal and constant control.

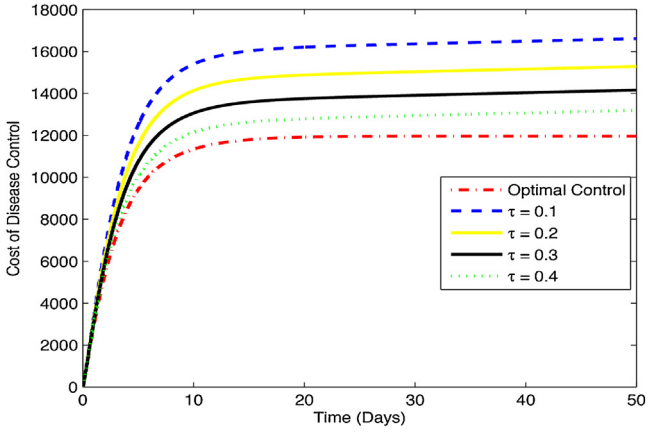


Fig. 10. Comparison of associated costs under optimal and constant control.

decreasing the number of infected individuals.

Fig. 9 captures the dynamics of the infected population (I_H) by virtue of a comparison between the infected host population under optimal control and constant control. It can be seen that the decrease in the number of infected individuals is greater with optimal control as compared to that with constant control. Furthermore, in contrast with a constant control, the infected population remains lower when an optimal control is applied.

Fig. 10 shows a comparison between the costs associated with optimal and different constant control strategies. It is clear that the cost associated with different control strategies is higher as compared to that of optimal control. It is important to note that high constant isolation rate ($\tau = 0.4$) incurs almost the same cost as the of optimal control. However, practically it is highly unlikely to implement these high constant controls primarily due to the lack of required resources and facilities. Fig. 11 captures the effect of the change in effective contact rate over the optimal control strategy. It is clear from the simulation that an increase in the contact rate may or may not lead to higher rates of hospitalization.

6. Discussion

In this paper, we have presented a Zika fever epidemic model comprising of eight compartments consists of vector and human population. The dynamics of Zika fever epidemic model have been considered. Furthermore, using optimal control theory, we proposed control strategies to eliminate the infection from the population.

A vertical and horizontal transmission model for Zika fever is

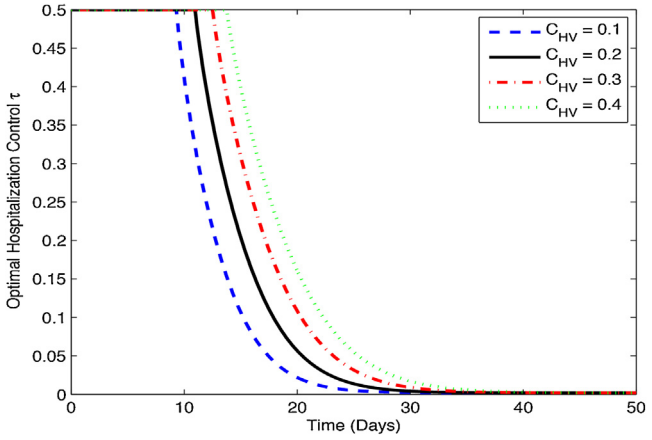


Fig. 11. Optimal hospitalization control for different values of effective contact rate C_{hv}.

constructed in the form of a system of ordinary differential equations. This model features the study of Zika fever by considering vertical transmission in both humans as well as vectors. The basic reproductive number R_0 is formulated by using a next-generation matrix. This reproductive number is simplified in order to better understand the effect of vertical transmission parameters. It is shown that the disease-free steady state is globally asymptotically stable when the basic reproductive number (R_0) is less than 1. The model has a unique endemic equilibrium when the reproduction number R_0 exceeds unity. This equilibrium is shown to be globally asymptotically stable when the reproduction number R_0 exceeds unity under the reduced model. It is locally asymptotically stable when we consider a full model.

We performed a parameter based global uncertainty and sensitivity analysis on R_0. The uncertainty analysis yields an estimated value of the basic reproductive number $R_0 = 1.54$ with 95% confidence interval (1.3491, 1.7669). This estimated value of R_0 is close to the calculated value of basic reproductive using real data (Villela et al., 2017). Our previous model had an estimated basic reproductive number $R_0 = 1.31$ with 95% confidence interval (1.23, 1.39) given in Imran et al. (2017). Our sensitivity analysis on the Zika model parameters showed that the most influential parameters are the effective contact rates, the recovery rate of the infected individuals and the birth rate of mosquitoes.

We proposed an optimal controlling strategy to eliminate Zika fever from the population. We observed that optimal control strategy is most effective in terms of eliminating infection as it minimizes our cost and resources at the same time. Moreover, the control measures themselves may take time to implement, once the outbreak has been realized. Despite these points, our analysis can help public health authorities to determine quasi-optimal strategies they might want to adopt, especially as our work highlights the relative effectiveness of different control strategies.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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