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Comparative Transmission Dynamics and Optimal Controls for Chikungunya, Dengue and Zika Virus Infections: A Case Study of Mexico

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In this study, we used a simple epidemic model and 2015–16 outbreak data of Chikungunya, Dengue and Zika viruses, arthropod mediated infections that are transmitted by the common mosquito vector *Aedes aegypti*, from Mexico to quantify the transmission rates (humans-to-mosquitoes and mosquitoes-to-humans) of the three diseases. The transmission rates are estimated for the observed data and consequently the basic reproduction number R_0 is calculated 6.740, 2.904 and 12.6283 for Chikungunya, Dengue and Zika infection, respectively. Using the estimated parameters for the three diseases, we evaluated self-imposed controls measures by the population as a result of fear-driven behavior changes often seen during an outbreak. Furthermore, the sensitivity analysis reveals that the parameter 'mosquitoes death rate' is the most sensitive one for R_0 . Simulations of controlled basic reproduction number are also performed for all considered control measures. This study is likely to enrich the understanding about transmission of such viral infections and control strategies.

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1 Introduction

The mosquito mediated infections are major contributors in the infectious diseases (PAHO, 2017). Some common mosquito transmitted diseases are Chikungunya, Dengue, Zika, Yellow fever, Saint Louis encephalitis, Japanese encephalitis and West-Nile virus. Chikungunya virus (CHIKV), Dengue virus (DENV), Zika virus (ZIKV) infections are transmitted by a common female mosquito, *Aedes aegypti* and *Aedes albopictus*. Co-circulation and co-infection with these viruses are reported due to the common vector in many geographical regions of the world including Asia (Okuneye et al., 2017). The differential diagnosis of the three infections is sometimes difficult because they share similar clinical manifestations (Cardoso et al., 2017; Dupont-Rouzeyrol et al., 2015; Furuya-Kanamori et al., 2016). However, other modes of transmission have been reported for ZIKV such as sexual transmission, maternal-foetal and blood transmission. Furthermore, transmission of ZIKV via these mediums is marginal as compared to the vector borne one. Thus, we neglected the transmission of ZIKV via these mechanisms in present model and considered that infection is transmitted via mosquito only.

Mathematical modeling is a preferred tool to explore and predict the progression dynamics of an infection in the given population. Many scientists have investigated several mathematical modeling techniques based on different architecture including compartmental modeling, spatial model, meta-population model, network model, individual-based model, etc., (Wiratsudakul et al., 2018). Homogeneous mixing of humans and mosquitoes is one of the most important hypotheses in the mathematical modeling of vector transmitted infections (Johansson et al., 2011; Andraud et al., 2012; Reiner Jr et al., 2013). Out of them, the compartmental modeling is one of the important technique in which the whole population is subdivided into mutually exclusive classes, categorized based on the infectious status of the individuals. For instance, in SIR model, the whole population is divided into three mutually exclusive classes namely, susceptible (S, healthy individuals but susceptible to the infection), infected (I, individuals contagious to the infection) and recovered (R, immune individuals). During the course of an infection, the health status of individuals may change to another compartment. Other types of compartmental models also exist for instance SI, SIS,

SIRS, SEIR, SEIRS, MSIR, MSIRS, etc. Choice of the model depends upon the characteristics of the disease for which it is to be developed (Hethcote, 2000).

Elucidation of disease progression dynamics can be associated towards development of control measures to prevent the epidemics. Involvement of parameters in the mathematical model is decided by a strategy regarding epidemic control (Kumar and Srivastava, 2017; Gupta and Rink, 1973; Lashari and Zaman, 2012; Yan et al., 2007). There are several studies regarding optimization of the control measures for different infections such as Chikungunya (Moulay et al., 2012), Dengue (Rodrigues et al., 2014; De Castro Medeiros et al., 2011; Rodrigues et al., 2012), Zika (Chaikham and Sawangtong, 2017) and HIV (Kirschner et al., 1997). These reports have described the theoretical analysis of model with controlling factors but the results of these papers do not correlate with the real data of outbreaks and the authors have also not done the sensitivity analysis in these papers. The correlation with the outbreak data and knowing the situation of controlling factors specifying any outbreak data is novelty of the present manuscript. Another interesting feature of the present paper is that we have also carried out the sensitivity analysis of the controlling factors that has not been reported earlier. These optimal control studies might assist in mitigating the disease progression in a population (Ding et al., 2016). In addition, these investigations will also contribute towards the cost reduction in implementing control strategy. Control measures for prevention of mosquito borne infections include mosquito elimination using insecticides, reduction of contact with the infected individuals and use of insect repellents or mosquito nets (Rodrigues et al., 2014; Thomé et al., 2010; Aldila et al., 2013).

Other previous reports have described mathematical model for progression of multiple infectious diseases that have similar transmission mechanism (Da Cruz Ferreira et al., 2017; Guzzetta et al., 2016). We have investigated the quantitative transmission dynamics of the three mosquito borne infections (CHIKV, DENV and ZIKV) in a given geographical region through mathematical modeling. The main aim of this study is to incorporate optimal control measures against the above three infections in the given mathematical model. The control parameters used for the model include vector elimination, vector-to-human contact reduction, and human-to-human contact reduction. The mathematical model consisting of vector mediated transmission of ZIKV is taken from previous study (Kumar et al., 2017). We have used the same model for CHIKV and DENV using different values of parameters, since all these three infections have similar mode of transmission. The control model has been generated by including control parameters into the model system, then model has been analysed by using optimal control theory. The necessary conditions that an optimal control and corresponding state must satisfy are determined by using Pontryagin's maximum principle (Pontryagin and Boltyanskii, 1962). We also estimate the values of factors which are responsible for infections and reproduction number for real data. Interestingly, the simulations reveal information about the quantitative characteristics of control measures to prevent disease transmission in the given population. Finally, we carried out the sensitivity analysis of parameters that provides information about the factors that are primarily responsible for disease transmission in the given human population. The study may be beneficial to investigate the progression dynamics of co-circulation and co-infection of CHIKV, DENV and ZIKV to formulate model for control measures.

2 Mathematical Modeling

2.1 Simple Epidemic Model

Our understanding in viral infections is based on compartmental modeling, where individuals in the population are divided into mutual exclusive classes. Chikungunya, Dengue and Zika viral infections spread in human population but their transmission occurs mostly through mosquito bite. These are also called vector-borne infectious diseases. In the framework of our modeling, we have considered classes of susceptible (S_b), exposed (E_b), infected (I_b) and recovered (R_b) for human population and susceptible (S_v), exposed (E_v) and infected (I_v) for mosquito population (vector population). Here we consider a mathematical model presented by the system of equations (1a–1g), that is similar to earlier study (Kumar et al., 2017) which is based on the ZIKV infection. We assume the same mathematical model for Dengue and Chikungunya because the transmission mechanism of Dengue and Chikungunya is similar to the Zika virus. However, the values of the assumed parameters will be different because the transmission characteristics are different for all three diseases (CHIKV, DENV, ZIKV). Although, model construction remains same due to the similar mechanism occurred during the progression dynamics of disease.

$$\frac{dS_b}{dt} = -\alpha_b S_b I_v \quad (1a)$$

$$\frac{dE_b}{dt} = \alpha_b S_b I_v - \beta_b E_b \quad (1b)$$

$$\frac{dI_b}{dt} = \beta_b E_b - \gamma_b I_b \quad (1c)$$

$$\frac{dR_b}{dt} = \gamma_b I_b \quad (1d)$$

$$\frac{dS_v}{dt} = \mu_v N_v - \mu_v S_v - \alpha_v I_b S_v \quad (1e)$$

$$\frac{dE_v}{dt} = -\mu_v E_v - \beta_v E_v + \alpha_v I_b S_v \quad (1f)$$

$$\frac{dI_v}{dt} = \beta_v E_v - \mu_v I_v \quad (1g)$$

The model is constructed under the following assumptions (i) homogeneous mixing of humans and mosquito population (ii) constant population of humans and mosquitoes (iii) no direct transmission between ‘human to human’ and ‘mosquito to mosquito’ (iv) no consideration of infection recovery in mosquito population. The letters S, E, I, R are used for susceptible, exposed, infected, and recovered population, while the subscripts h, v are used for human population, mosquito population, respectively. The parameters α_b, β_b and γ_b are the transfer rates from susceptible to exposed, exposed to infected and infected to recovered in human population, respectively. Similarly, the parameters α_v, β_v are the transfer rates in mosquito population from susceptible to exposed, exposed to infected, respectively. The variables N_h and N_v represent the total population of humans and mosquitoes in the given region. The parameter μ_v denotes the birth (or death) rate of the mosquitoes.

The rate at which susceptible human becomes infected is $\alpha_b = a \times b \times m$ whereas the rate at which susceptible mosquitoes become infected is $\alpha_v = a \times c$, where a is mosquito biting rate per mosquito per day. The parameters ‘mosquito biting rate per mosquito per day (a)’, ‘transmission probability from mosquito to human per bite (b)’, ‘transmission probability from human to mosquito (c)’, ‘recovery rate for human infection (γ_b)’, ‘mosquito death rate (μ_v)’ and ‘average mosquito rate per human (m)’ for all three infections (CHIKV, DENV, ZIKV) have been taken from previous studies (Gao et al., 2016; De Castro Medeiros et al., 2011; Kucharski et al., 2016; Gourinat et al., 2015; Chikaki and Ishikawa, 2009; Andraud et al., 2012; Musso et al., 2015). The basic reproduction number (R_0) is also a resultant from the mathematical model which provides number of secondary infections produced by a single infected individual in a wholly susceptible population. It is an important threshold parameter which tell us whether the infection will spread or not in the given population. To compute R_0 , we adopted the same methodology as given in the papers (Van den Driessche and Watmough, 2002) and (Kumar et al., 2017) for ZIKV infection. It is expressed by equation (2). This will also be useful to compute R_0 for CHIKV and DENV infection for a specific region.

$$R_0 = \sqrt{\frac{\alpha_b \alpha_v \beta_v}{\gamma_b \mu_v (\mu_v + \beta_v)}} \quad (2)$$

2.2 Model formulation under controlling factors

The formulation of mathematical models for progression of infectious diseases are governed by several factors that may affect their transmission. In this section, we formulate a corresponding control problem by assuming controlling factors in human population. Some controlling factors proposed by WHO are prevention from mosquito biting, anticipation from the infection, avoidance from traveling in high risk zone of infection, segregation/isolation of exposed or infected humans, avoidance of sexual relation with infected individuals (PAHO, 2017; WHO, 2009; Patterson et al., 2016). Out of these, there are two factors; namely (i) isolation of exposed and infected humans (ii) self-protection of susceptible humans; are most significant. These control interventions are being described in the following paragraph in detail. We incorporate these two factors in model (1a–1g) and consequently, newly formulated model becomes

$$\frac{dS_b}{dt} = -\alpha_b(1 - \tau(t))S_b I_v \quad (3a)$$

$$\frac{dE_b}{dt} = \alpha_b(1 - \tau(t))S_b I_v - \beta_b E_b - \varepsilon_1(t)E_b \quad (3b)$$

$$\frac{dI_b}{dt} = \beta_b E_b - \gamma_b I_b - \varepsilon_2(t)I_b \quad (3c)$$

$$\frac{dR_b}{dt} = \gamma_b I_b + \varepsilon_1(t)E_b + \varepsilon_2(t)I_b \quad (3d)$$

$$\frac{dS_v}{dt} = \mu_v N_v - \mu_v S_v - \alpha_v I_b S_v \quad (3e)$$

$$\frac{dE_v}{dt} = -\mu_v E_v - \beta_v E_v + \alpha_v I_b S_v \quad (3f)$$

$$\frac{dI_v}{dt} = \beta_v E_v - \mu_v I_v \quad (3g)$$

Here, we have assumed that $\tau(t)$ is the self-protection coefficient in susceptible human population, whereas $\varepsilon_1(t), \varepsilon_2(t)$ are isolation coefficients in exposed and infected human population respectively. We are considering that $\tau(t), \varepsilon_1(t), \varepsilon_2(t)$ are time

dependent controlled parameters because the value of control measure is absolutely based on the compartmental population dynamics. The value of these control parameters lie between 0 and 1.

Isolation of exposed and infected humans The vaccines for these three infections are not available. The tetravalent vaccine for dengue has been approved by FDA and licensed in many countries but there are many disadvantages of this vaccine. Therefore isolation of exposed and infected individuals may be a technique to prevent the spread of infection in the human population. However, a crucial question is that what *weight* and also *when* the isolation of exposed and infected should be followed by the human population, so that maximum population is isolated with minimum cost incurred. Keeping in mind the social and economical structure, it is not advisable to isolate exposed and infected humans at a constant rate throughout the outbreak.

Self-protection of susceptible human population The other measurement for control of disease is self-protection as proposed by WHO such as mosquito repellent or spray, wearing full-sleeved cloths and long trousers, use of screened or air-conditioned rooms, use of mosquitoes nets, etc. Increase of self-protection in the human population decreases the risk of the infection in the population. Therefore, we also treat this self-protection in susceptible population at a variable rate with respect to time and denote it by $\tau(t)$. The value of $\tau(t)$ lies between 0 (no protection) to 1 (total protection). Self-protection is correlated with the mosquito biting rate (a) that further affect α_b , because it is product of a , b and c . Thus, $(1 - \tau)$ will be multiplicative coefficient of α_b and it has been incorporated in the system of equations (3a–3g). Our goal is to find optimal values for these control variables with minimum cost incurred in this self-protection measure.

2.2.1 Optimum control problem

In this section, we formulate a corresponding control problem by assuming isolation of exposed and infected humans, and self protection of susceptible humans. The control parameters $\tau(t)$, $\varepsilon_1(t)$, $\varepsilon_2(t)$ lie in the set $\Gamma = \{(\tau(t), \varepsilon_1(t), \varepsilon_2(t)) \mid 0 \leq \tau(t), \varepsilon_1(t), \varepsilon_2(t) \leq 1, t \in [0, T]\}$. The parameters $\tau_1(t)$, $\varepsilon_1(t)$, $\varepsilon_2(t)$ are bounded and measurable, and T is the final time for intervention policy namely isolation and self-protection. The upper limit for $\tau(t)$, $\varepsilon_1(t)$, $\varepsilon_2(t)$ is one, which is feasible. Therefore there may exist some $\tau_{max}(t)$, $\varepsilon_{1,max}(t)$, $\varepsilon_{2,max}(t)$ such that $\tau(t) \leq \tau_{max}(t)$, $\varepsilon_1(t) \leq \varepsilon_{1,max}(t)$, $\varepsilon_2(t) \leq \varepsilon_{2,max}(t)$. The values of $\tau_{max}(t)$, $\varepsilon_{1,max}(t)$, $\varepsilon_{2,max}(t)$ and final time (T) depend on the disease and its characteristics in a given geographical region.

First, we define the cost function for the control problem which is to be minimize over the set Γ .

$$\min \mathcal{J}[\tau(t), \varepsilon_1(t), \varepsilon_2(t)] = \int_0^T [A_1 E_b^2(t) + A_2 I_b^2(t) + B_1 \tau^2(t) + B_2 \varepsilon_1^2(t) + B_3 \varepsilon_2^2(t)] dt$$

The cost function contains the weighted sum of the variables $E_b, I_b, \tau(t)$ and $\varepsilon_2(t)$ having weights A_1, A_2, B_1, B_2 and B_3 , respectively. These weights represent costs incurred corresponding to unit value of the associated variables. For example, A_1 is cost due to single exposed human and A_2 is cost due to single infected human. Therefore, $A_1 E_b$ represents the total cost due to all exposed humans and $A_2 I_b$ represents the total cost due to all infected humans at time t . In rest of the work, we consider the notations $\tau(t) = \tau$, $\varepsilon_1(t) = \varepsilon_1$ and $\varepsilon_2(t) = \varepsilon_2$ for convenience.

As we know, Lagrange equation (Pontryagin and Boltyanskii, 1962; Pontryagin, 2018) for the controlling problem can be written as

$$L = A_1 E_b^2(t) + A_2 I_b^2(t) + B_1 \tau^2(t) + B_2 \varepsilon_1^2(t) + B_3 \varepsilon_2^2(t)$$

and, Hamiltonian equation will be written as

$$H = L + \sum_{i=1}^7 \lambda_i g_i(t, p, u)$$

where,

$$\sum_{i=1}^7 \lambda_i g_i(t, p, u) = [\lambda_1 S_b'(t) + \lambda_2 E_b'(t) + \lambda_3 I_b'(t) + \lambda_4 R_b'(t) + \lambda_5 S_v'(t) + \lambda_6 E_v'(t) + \lambda_7 I_v'(t)]$$

with $p = (S_b, E_b, I_b, R_b, S_v, E_v, I_v)$, $u = (\tau, \varepsilon_1, \varepsilon_2)$. In given expression, $\lambda_i, i = 1, 2, 3, \dots, 7$ are adjoint functions. Let p^* and u^* are the solutions of the problem then by Pontryagin Maximum Principle (Pontryagin, 2018; Lenhart and Workman, 2007), the necessary condition for optimal solution may be written as

$$p'(t) = \frac{\partial H(t, p^*, u^*, \lambda)}{\partial \lambda} \quad (4a)$$

$$\lambda'(t) = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial p} \quad (4b)$$

$$\frac{\partial H(t, p^*, u^*, \lambda)}{\partial u} = 0 \quad (4c)$$

Theorem 2.1. If the model (3a–3g) has the optimal control $u^* = (\tau^*, \varepsilon_1^*, \varepsilon_2^*)$ and solution $S_b^*, E_b^*, I_b^*, R_b^*, S_v^*, E_v^*, I_v^*$, then there exist adjoint functions $\lambda_i; i = 1, 2, 3, \dots, 7$ satisfying the following adjoint conditions:

$$\frac{d\lambda_1}{dt} = \alpha_b(1 - \tau)(\lambda_1 - \lambda_2)I_v \quad (5a)$$

$$\frac{d\lambda_2}{dt} = -2A_1E_b + \beta_b(\lambda_2 - \lambda_3) + \varepsilon_1(\lambda_2 - \lambda_4) \quad (5b)$$

$$\frac{d\lambda_3}{dt} = -2A_1I_b + (\gamma_b + \varepsilon_2)(\lambda_3 - \lambda_4) + \alpha_vS_v(\lambda_5 - \lambda_6) \quad (5c)$$

$$\frac{d\lambda_4}{dt} = 0 \quad (5d)$$

$$\frac{d\lambda_5}{dt} = \alpha_vI_b(\lambda_5 - \lambda_6) + \lambda_6\mu_v\beta_v \quad (5e)$$

$$\frac{d\lambda_6}{dt} = \beta_v(\lambda_6 - \lambda_7) + \mu_v(\lambda_6 - \lambda_7) \quad (5f)$$

$$\frac{d\lambda_7}{dt} = \mu_v(\lambda_7 - \lambda_5) + \alpha_b(1 - \tau)S_b\lambda_1 \quad (5g)$$

having transversality conditions $\lambda_i(T) = 0; i = 1, 2, 3, \dots, 7$. Moreover the control $u^* = (\tau^*, \varepsilon_1^*, \varepsilon_2^*)$ may be identified as

$$\tau^*(t) = \min\{\max\{0, (\lambda_2 - \lambda_1)(\alpha_bS_b^*I_v^*)/(2B_1)\}, 1\} \quad (6a)$$

$$\varepsilon_1^*(t) = \min\{\max\{0, (\lambda_2 - \lambda_4)E_b^*/(2B_2)\}, 1\} \quad (6b)$$

$$\varepsilon_2^*(t) = \min\{\max\{0, (\lambda_4 - \lambda_3)I_b^*/(2B_3)\}, 1\} \quad (6c)$$

Proof: From the necessary conditions (4a–4c), we have

$$\frac{d\lambda_1}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial S_b} = \alpha_b(1 - \tau)(\lambda_1 - \lambda_2)I_v \quad (7a)$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial E_b} = -2A_1E_b + \beta_b(\lambda_2 - \lambda_3) + \varepsilon_1(\lambda_2 - \lambda_4) \quad (7b)$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial I_b} = -2A_1I_b + (\gamma_b + \varepsilon_2)(\lambda_3 - \lambda_4) + \alpha_vS_v(\lambda_5 - \lambda_6) \quad (7c)$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial R_b} = 0 \quad (7d)$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial S_v} = \alpha_vI_b(\lambda_5 - \lambda_6) + \lambda_6\mu_v\beta_v \quad (7e)$$

$$\frac{d\lambda_6}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial E_v} = \beta_v(\lambda_6 - \lambda_7) + \mu_v(\lambda_6 - \lambda_7) \quad (7f)$$

$$\frac{d\lambda_7}{dt} = -\frac{\partial H(t, p^*, u^*, \lambda)}{\partial I_v} = \mu_v(\lambda_7 - \lambda_5) + \alpha_b(1 - \tau)S_b\lambda_1 \quad (7g)$$

Let $S_b = S_b^*, E_b = E_b^*, I_b = I_b^*, R_b = R_b^*, S_v = S_v^*, E_v = E_v^*, I_v = I_v^*$ then necessary conditions $\frac{\partial H(t, p^*, u^*, \lambda)}{\partial u(\tau, \varepsilon_1, \varepsilon_2)} = 0$ with transversality conditions $\lambda_i(T) = 0; i = 1, 2, 3, \dots, 7$ yield

$$\frac{\partial H}{\partial \tau} = 0 \implies \tau(t) = (\lambda_2 - \lambda_1)(\alpha_bS_b^*I_v^*)/(2B_1) \quad (8a)$$

$$\frac{\partial H}{\partial \varepsilon_1} = 0 \implies \varepsilon_1(t) = (\lambda_2 - \lambda_4)E_b^*/(2B_2) \quad (8b)$$

$$\frac{\partial H}{\partial \varepsilon_2} = 0 \implies \varepsilon_2(t) = (\lambda_4 - \lambda_3)I_b^*/(2B_3) \quad (8c)$$

Then corresponding optimum control will be

$$\tau^*(t) = \min\{\max\{0, (\lambda_2 - \lambda_1)(\alpha_bS_b^*I_v^*)/(2B_1)\}, 1\} \quad (9a)$$

$$\varepsilon_1^*(t) = \min\{\max\{0, (\lambda_2 - \lambda_4)E_b^*/(2B_2)\}, 1\} \quad (9b)$$

$$\varepsilon_2^*(t) = \min\{\max\{0, (\lambda_4 - \lambda_3)I_b^*/(2B_3)\}, 1\} \quad (9c)$$

2.3 Basic reproduction number of proposed model

As we have discussed in Section 2.1, the reproduction number is an important resultant for every formulated mathematical model of infectious diseases. Therefore, the derivation of reproduction number for a newly proposed model with control measures (controlled basic reproduction number, R_0^c) is as follows.

The model (3a–3g) at infection free stage ($E_b = I_b = R_b = 0$ and $E_v = I_v = 0$) can be written in the following form:

$$\frac{dE_b}{dt} = \alpha_b(1 - \tau)S_bI_v - \beta_bE_b - \varepsilon_1E_b \quad (10a)$$

$$\frac{dI_b}{dt} = \beta_bE_b - \gamma_bI_b - \varepsilon_2I_b \quad (10b)$$

$$\frac{dE_v}{dt} = -\mu_vE_v - \beta_vE_v + \alpha_vI_bS_v \quad (10c)$$

$$\frac{dI_v}{dt} = \beta_vE_v - \mu_vI_v \quad (10d)$$

Taking the population in proportion such that ($s_b = \frac{S_b}{N_b}, e_b = \frac{E_b}{N_b}, i_b = \frac{I_b}{N_b}, r_b = \frac{R_b}{N_b}, s_v = \frac{S_v}{N_v}, e_v = \frac{E_v}{N_v}, i_v = \frac{I_v}{N_v}$) and ($n_b = \frac{N_b}{N_b} = 1, n_v = \frac{N_v}{N_v} = 1$), the subsystem of equations (10a–10d) can be written in the following manner

$$\frac{de_b}{dt} = \alpha_b(1 - \tau)s_b i_v - \beta_b e_b - \varepsilon_1 e_b \quad (11a)$$

$$\frac{di_b}{dt} = \beta_b e_b - \gamma_b i_b - \varepsilon_2 i_b \quad (11b)$$

$$\frac{de_v}{dt} = -\mu_v e_v - \beta_v e_v + \alpha_v i_b s_v \quad (11c)$$

$$\frac{di_v}{dt} = \beta_v e_v - \mu_v i_v \quad (11d)$$

At infection-free stage, $e_b = i_b = r_b = 0$ imply $s_b = n_b = 1$, and $e_v = i_v = 0$ imply $s_v = n_v = 1$. Then resulting linearized sub-system of model (11a–11d), at infection-free stage will be

$$\frac{de_b}{dt} = \alpha_b(1 - \tau)i_v - \beta_b e_b - \varepsilon_1 e_b \quad (12a)$$

$$\frac{di_b}{dt} = \beta_b e_b - \gamma_b i_b - \varepsilon_2 i_b \quad (12b)$$

$$\frac{de_v}{dt} = -\mu_v e_v - \beta_v e_v + \alpha_v i_b \quad (12c)$$

$$\frac{di_v}{dt} = \beta_v e_v - \mu_v i_v \quad (12d)$$

Subsystem (12a–12d) can be written in matrix form, $\frac{dX}{dt} = (F + V)X$; where

$$F = \begin{bmatrix} 0 & 0 & 0 & \alpha_b(1 - \tau) \\ 0 & 0 & 0 & 0 \\ 0 & \alpha_v & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}; \quad V = \begin{bmatrix} -(\beta_b + \varepsilon_1) & 0 & 0 & 0 \\ \beta_b & -(\gamma_b + \varepsilon_2) & 0 & 0 \\ 0 & 0 & -(\mu_v - \beta_v) & 0 \\ 0 & 0 & \beta_v & -\mu_v \end{bmatrix}; \quad X = \begin{bmatrix} e_b \\ i_b \\ e_v \\ i_v \end{bmatrix}$$

The next-generation matrix is computed,

$$G = -FV^{-1} = \begin{bmatrix} 0 & 0 & \frac{\alpha_b \beta_v (1 - \tau)}{\mu_v (\beta_v + \mu_v)} & \frac{\alpha_b (1 - \tau)}{\mu_v} \\ 0 & 0 & 0 & 0 \\ \frac{\alpha_v \beta_b}{(\beta_b + \varepsilon_1)(\gamma_b + \varepsilon_2)} & \frac{\alpha_v}{(\gamma_b + \varepsilon_2)} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

Therefore, the control basic reproduction number, $R_0^c =$ spectral radius of matrix $G, \rho(G) = R_0^c = \sqrt{\frac{\alpha_b \alpha_v \beta_b \beta_v (1 - \tau)}{\mu_v (\beta_b + \varepsilon_1)(\gamma_b + \varepsilon_2)(\mu_v + \beta_v)}}$.

3 Simulation Results

3.1 Parameter Estimates

First we discuss primary model given in Section 2.1, described by the system of equations (1a–1g), for CHIKV, DENV, ZIKV transmission followed by simulation of the model with incorporation of control measures. The values of certain parameters needed for the simulation of the primary model (1a–1g), are either taken from literature or are estimated using the software System Biology Toolbox (Schmidt and Jirstrand, 2005) in MATLAB. The number of cases of CHIKV, DENV and ZIKV are taken from W.H.O. website during 2015-16 outbreaks in Mexico. The initial values for the simulation are taken according to this data. The data have been taken for 44 epidemiological weeks starting from week 42 of 2015 to week 33 of 2016. We consider the confirmed cases only given by week-wise. Total cumulative cases in the above duration for CHIKV, DENV and ZIKV have been reported as 2365, 12246 and 1951, respectively. Whereas, the maximum number of cases for CHIKV, DENV and ZIKV has been reported as 524, 920 and 265 in 4th, 5th and 43th epidemiological weeks, respectively. The plot of actual number of cases for all the three infections is shown in Figure 1a. We have simulated our primary model given by the system of equations (1a–1g) with the real data using ode45 function in MATLAB and System Biology Toolbox (Schmidt and Jirstrand, 2005) in MATLAB. During the simulation process, we have estimated the values of parameters through best fitting with collected data. The values of β_b for CHIKV, DENV and ZIKV are estimated as 0.0228, 0.0331 and 4.813×10^{-4} , respectively. Similarly, the values of β_v for CHIKV, DENV and ZIKV are estimated as 0.1104, 0.0087 and 0.0113, respectively.

The actual cumulative data for CHIKV, DENV and ZIKV is shown in dotted curves whereas cumulative data calculated by the model are presented by solid line curves in Figures 1b, 1c and 1d, respectively. The estimated and calculated values of parameters are given in Table 1. The values of basic reproduction number (R_0) for CHIKV, DENV and ZIKV are calculated as 6.740, 2.904 and 12.6283 for the given parameters in Table 1. The highest value of R_0 for ZIKV suggests that the infection is spreading rapidly in the given population. In contrast the value of R_0 for DENV is minimal suggesting a lower rate of its transmission in the given population. The simulation of the primary model estimates the values of parameters for the selected population in that region during that particular time. This data will assist in understanding the progression dynamics of the compartmental population with varying initial conditions.

3.2 Optimal controls for the three diseases

In the next part of the simulation the value of control measures with respect to time for all the three infections are presented in Figure 2. The values of parameters used for this simulation are taken from the above mentioned analysis. We assume weights $A_1 = 0.2$, $A_2 = 0.2$, $B_1 = 0.5$, $B_2 = 0.5$ and $B_3 = 0.5$ in the cost function for the optimum control during the simulation as mentioned in previous studies (Yan et al., 2007). The maximum level of control measures (ε_1), (ε_2) and (τ) are assumed to be between 0 to 95% during the simulation. The control measures ε_1 , ε_2 and τ are plotted with respect to time in Figure 2a, Figure 2b and Figure 2c for CHIKV, DENV and ZIKV, respectively.

The parameters ε_1 and ε_2 remain constant upto eight weeks, whereas τ remains constant up to the fourth week for CHIKV infection in Figure 2a. The value of ε_1 is greater than ε_2 during its initial steady state phase (ε_1 is almost twice than ε_2). Thereafter, the value of control parameters (ε_1 , ε_2 and τ) decreases rapidly in the next ten weeks from its initial steady states and approach to zero. The control parameters (ε_1 , ε_2 and τ) remain constant initially for twelve weeks for DENV which is represented in Figure 2b. These variables vanish in next six weeks (12 to 18 weeks) for DENV infection. Here also, ε_1 is greater than ε_2 in its initial steady state. In Figure 2c, the control parameters (ε_1 , ε_2 and τ) for ZIKV infection reduce exponentially from its initial state and tend to zero approximately after 40 weeks. This analysis suggests that the isolation of exposed human population is more effective than the isolation of infected human population to prevent transmission of all the three infections. However, isolation of both the categories of the population are important. It is observed that higher rate of isolation and self-protection is needed to control DENV as compared to CHIKV and ZIKV infection in the given population at that particular time. The rearrangement has been made of Figure 2 in Figure 3. Each plot in the rearrangement is comparing all the three infections for any specific control measure. Figure 3a, interprets that self-protection is required for higher number of weeks for DENV disease than the CHIKV and ZIKV. Figures 3b & 3c, quantify the effect of isolation of exposed and infected population respectively. These two graphs have almost similar pattern for all the three diseases. Thus it can be concluded that CHIKV, DENV and ZIKV are in decreasing order in terms of number of days required for protection of disease. This analysis reveals that initially all protection will be consistently applicable on DENV than CHIKV and ZIKV.

The effect of control measures on the controlled basic reproduction number (R_0^c) for CHIKV, DENV, ZIKV infection in human population is shown in Figures 4, 5 and 6, respectively. The value of R_0^c is less than one when the value of control measure is greater than its critical value. All critical values for control parameters are summarized in Table 2. In Figures 4a, 5a and 6a, R_0^c is plotted with respect to ε_1 , when $\varepsilon_2 = \tau = 0$. This figure depicts that R_0^c decreases rapidly by changing the value of ε_1 for all three infections. When the values of ε_1 is greater than 0.8, 0.022 and 0.95 for CHIKV, DENV and ZIKV respectively then R_0^c is less than 1 for all the three infections. The Figures 4b, 5b and 6b shows the reciprocal behavior between R_0^c and ε_2

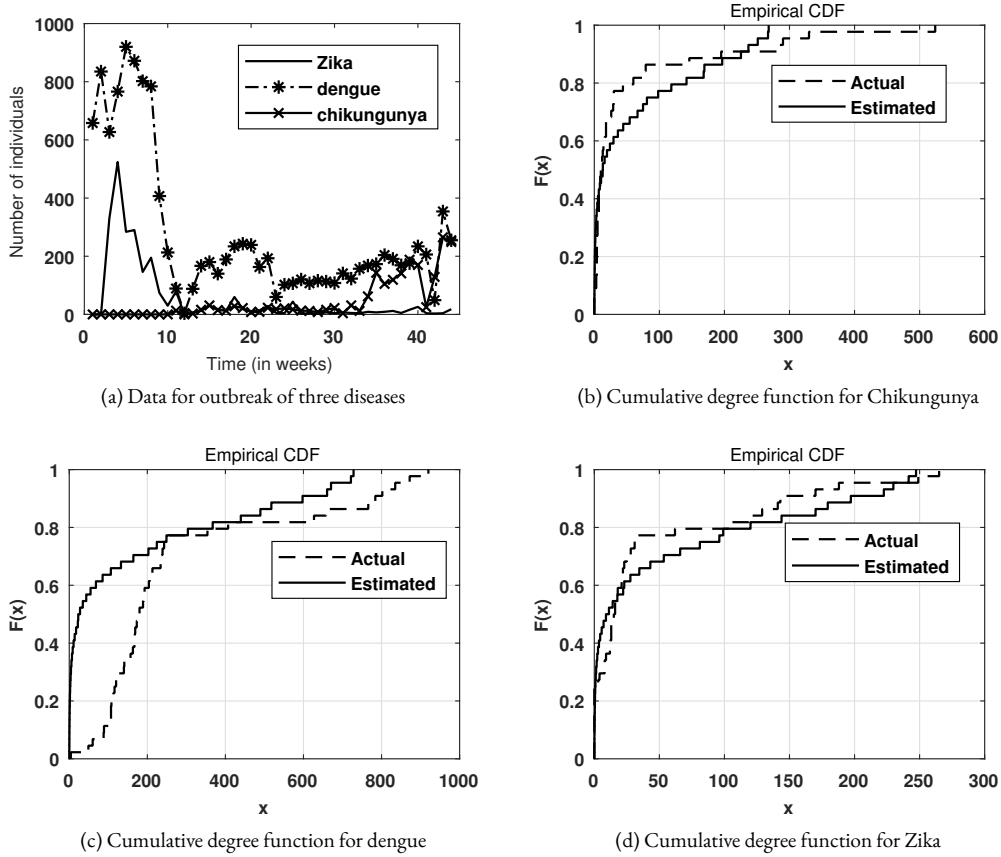


Figure 1: Data and cumulative degree function with model estimate for all three diseases (CHIKV, DENV, ZIKV) outbreak in the Mexico during 2015–16

(when $\varepsilon_1 = \tau = 0$). The critical values of ε_2 are 0.85 and 0.99 for DENV and ZIKV infections. However, we could not obtain any value of ε_2 for which R_0^c is less than 1.

Figures 4c, 5c and 6c show the relationship between R_0^c and τ (when $\varepsilon_1 = \varepsilon_2 = 0$) and the critical values for τ are 0.99, 0.9, 0.99 for CHIKV, DENV and ZIKV infections, respectively. The combined effect of ε_1 and ε_2 on R_0^c for CHIKV, DENV and ZIKV infections are shown via three dimensional surface curves in Figures 4d, 5d and 6d, respectively.

The simulation related to controlled basic reproduction number is carried out for different values of control measures. This analysis suggests that the value of R_0^c is decaying exponentially to 1 with respect to ε_1 and ε_2 , whereas R_0^c is decaying almost linearly with respect to τ .

3.3 Sensitivity Sensitivity Analysis of the R_0

Sensitivity analysis is a crucial tool to check the robustness the prediction of a model with respect to the input variables (Chitnis et al., 2008). Using this analysis, important input parameters can be identified for the outcome variables of the model. It also measures the change in the output variables related to the input variables. The magnitude of sensitivity index describes the relative importance of that variable with respect to the basic reproduction number (R_0), whereas the sign represents proportional (for positive) or reciprocal (for negative) relationship. We have calculated normalized sensitivity index (Gao et al., 2016) for basic reproduction number (R_0) with respect to the involved parameters in its expression (Table 3). This analysis reveals that the parameter ‘mosquitoes death rate (μ_v)’ is most sensitive one. Furthermore, the largest negative index has been found for μ_v . This suggests that when mosquito death rate (μ_v) decreases then the basic reproduction number increases, leading to the disease progression in that area. Other two parameters ‘rate at which susceptible human becomes infected (α_h)’ and ‘rate at which susceptible mosquito becomes infected (α_v)’ are equally important and have positive sensitivity index of magnitude 0.5. The parameter ‘recovery rate of human from infection (γ_h)’ is similar to (α_h) and (α_v) but opposite in sign. Thus, all these three parameters have equal impact on R_0 . The parameter ‘rate from exposed to infected mosquito (β_v)’ has the minimum impact on R_0 and shows the positive sign.

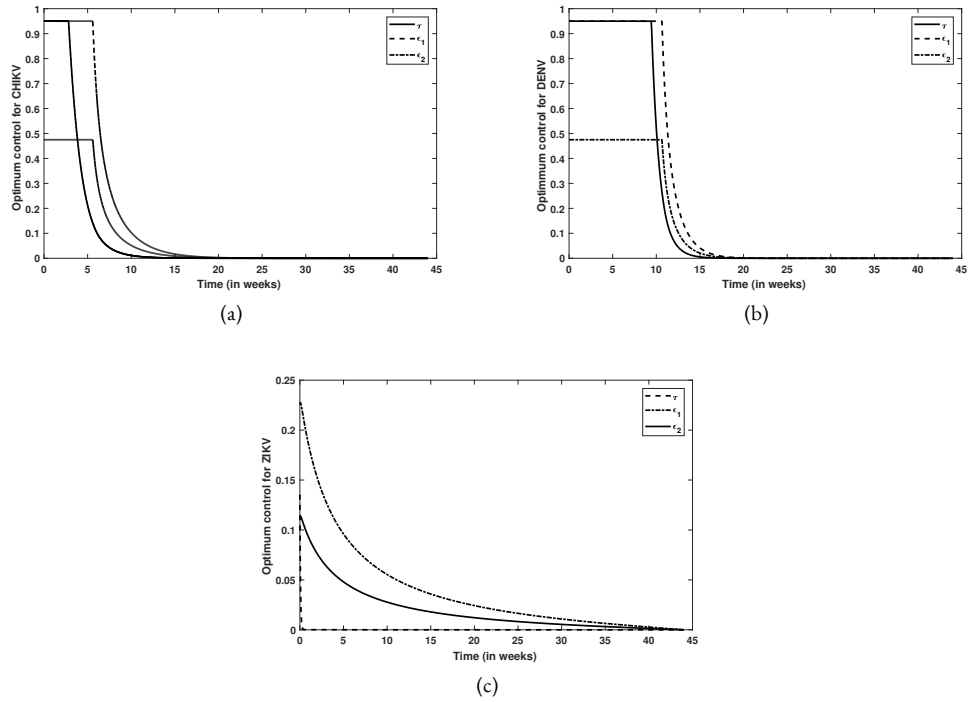


Figure 2: Optimum control in human population with respect to time for all three infection.

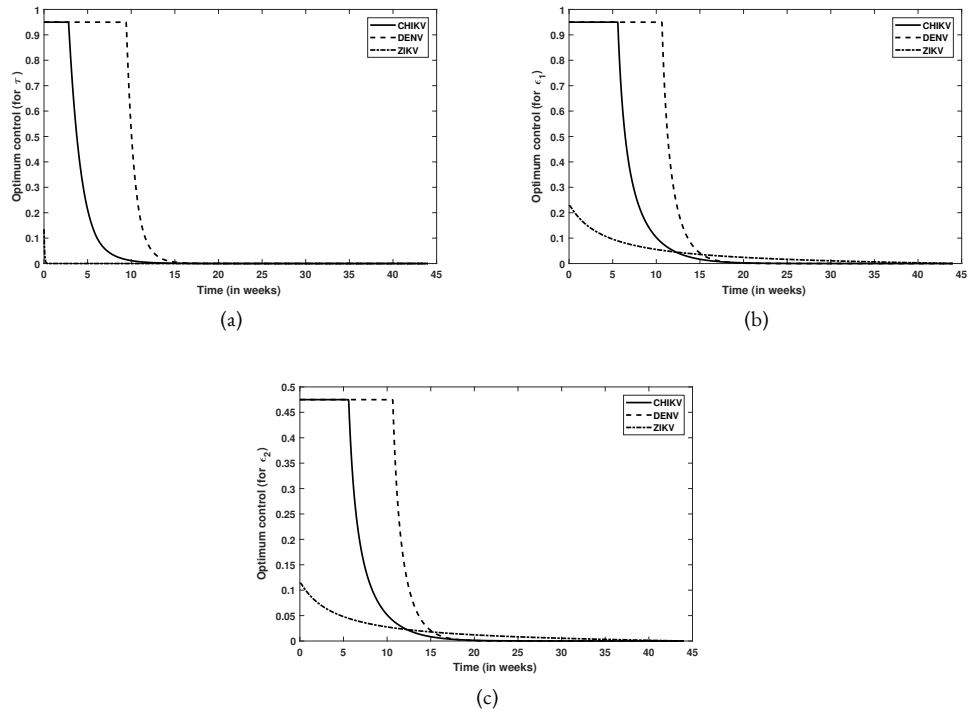


Figure 3: Comparison plot for control measures dynamics of all three infections.

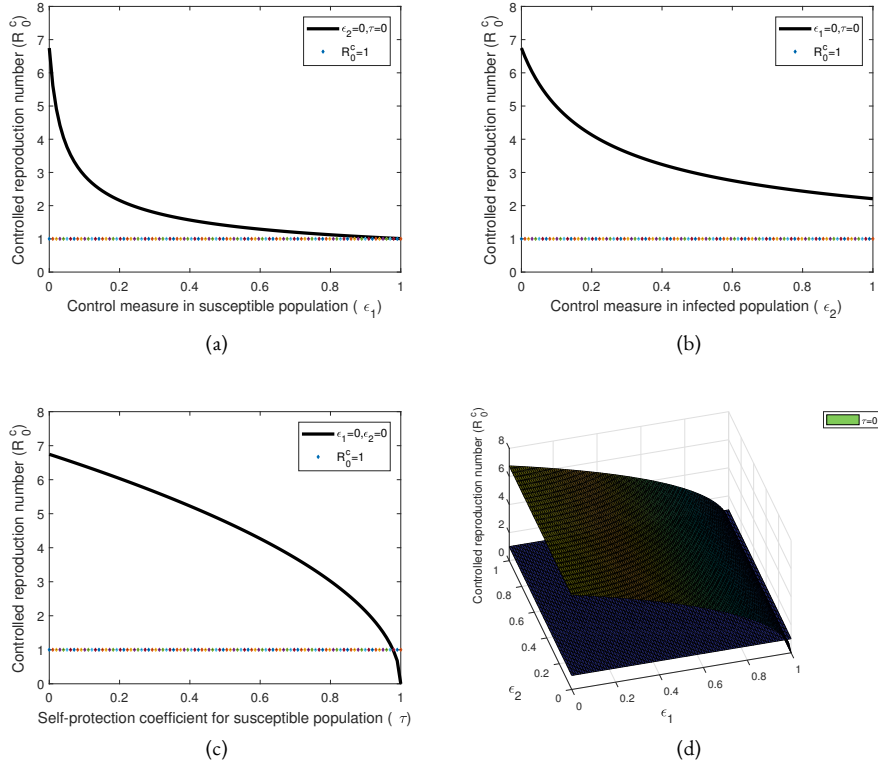


Figure 4: Profile of controlled basic reproduction number (R_0^c) measured with controlling parameters in CHIKV infected human population.

4 Discussion

The work in this article has been bifurcated in two parts. One is related to the transmission rates and its analysis of the proposed model. Other part deals with the optimal control in relation to the comparison between the three diseases. First of all, we have considered the model for the three disease dynamics which was done earlier only for ZIKV. But, during the analysis of the model, we found that the model correctly fits the observed data, as anticipated during the model construction. The fitted data was found best for all the assumed disease with varying their parameter values. Thus, the result show that the transmission process is similar in all three diseases, except that the rate of transmission were different.

The implementation of control strategies in the existing model can provide us useful insights about the invasion of disease during the outbreak, which can directly benefit the society. The measurement of optimization of the control strategies redirects to minimize cost of implementation during the invasion of the disease during the outbreak. The study in the article gives us values of parameters for the outbreak and optimal control during the outbreak. The calculation of reproduction number is well validating models and estimation of parameters. It has also been found that the reproduction number of control measurements is highly correlated with the values of control measure. This again validates control strategies based on the newly developed model. Thus, the model and implementation of control strategies are a really helpful to society and state.

5 Conclusions

We have formulated a new model by incorporating control measures in the existing model. The simulation analysis accomplished a newly formulated model with estimated parameters from the data obtained from the outbreak of CHIKV, DENV and ZIKV infections in Mexico during 2015-16. These estimated parameters might assist in the evaluation of infectious disease dynamics in near future at Mexico city. Isolation and self-protection factors had played a major role in DENV rather than CHIKV and ZIKV infection during the initial phase of this outbreak in Mexico during this period. Finally, we determined the mosquito death rate as the most sensitive parameter for all three infections during this outbreak. In future perspective, the model has a scope for improvement for more parametric analysis and incorporation of more control measures. This model can also be adopted for similar diseases in other geographical regions as well.

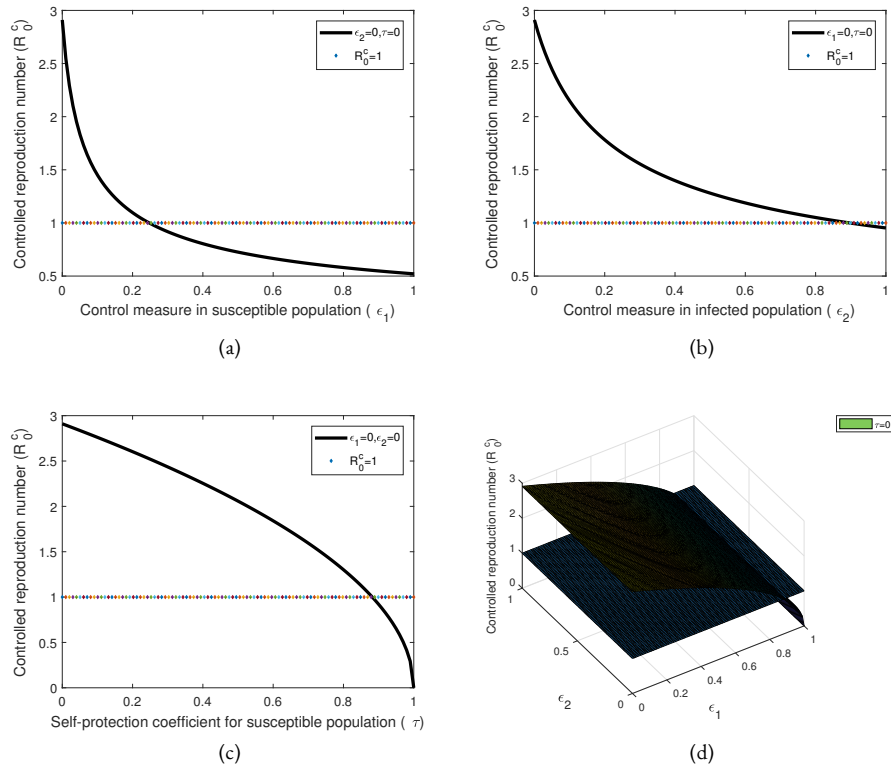


Figure 5: Profile of controlled basic reproduction number (R_0^c) measured with controlling parameters in DENV infected human population.

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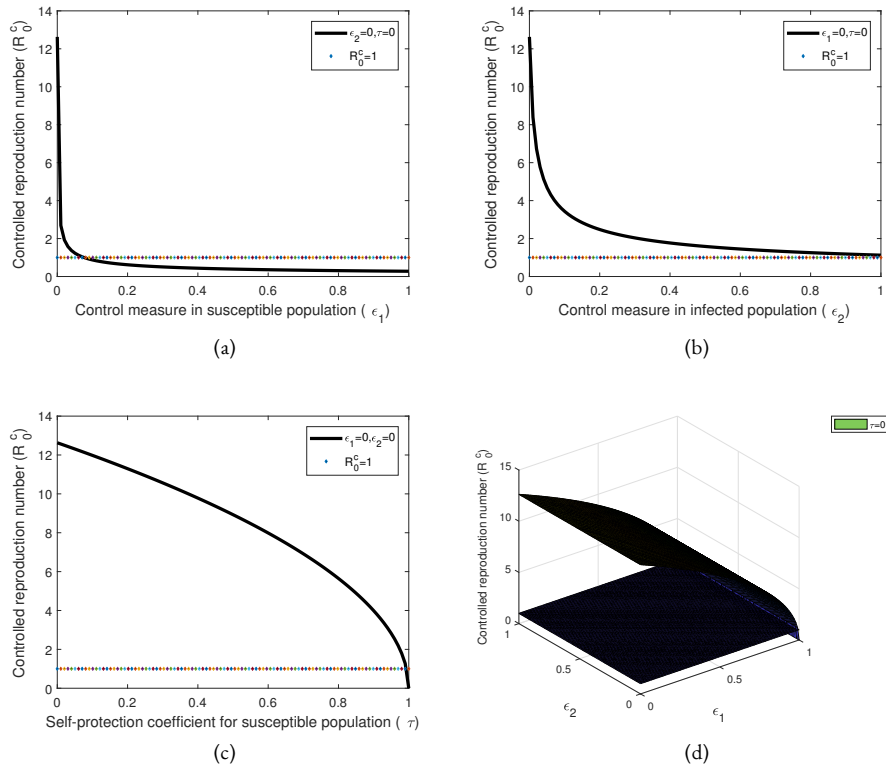


Figure 6: Profile of controlled basic reproduction number (R_0^c) measured with controlling parameters in ZIKV infected human population.

Table 1: Table of parameters with their notation, description, range and used values in simulation

Parameter	Description	Range	CHIKV	DENV	ZIKV	References
a	Mosquito biting rate (per mosquito per day)	0.3–1	0.6	0.6	0.6	Andraud et al., 2012
b	Probability of transmission from infectious mosquito to susceptible human per bite	0.1–0.75	0.4	0.4	0.4	Andraud et al., 2012
c	Probability of transmission from infected human to susceptible mosquito per bite	0.3–0.75	0.4	0.4	0.4	Chikaki and Ishikawa, 2009
γ_b	Rate from infected human population to recovered human population	0.035–0.071	0.12	0.12	0.008	Gourinat et al., 2015; Musso et al., 2015
β_b	Rate from Exposed human population to infected human population	0–0.03	0.0228	0.0331	4.813×10^{-4}	Estimated
β_v	Rate from exposed to infected mosquito	0.03–0.13	0.1104	0.0087	0.0113	Estimated
$1/\mu_v$	Life span of mosquitoes (in days)	4–35	15	15	15	Andraud et al., 2012; Chikaki and Ishikawa, 2009
m	Average ratio of mosquitoes to human	1–10	10	10	10	De Castro Medeiros et al., 2011

Table 2: Table of critical values for control parameters $\varepsilon_1, \varepsilon_2$ and τ .

Control parameter	CHIKV	DENV	ZIKV
ε_1 (when $\varepsilon_2 = \tau = 0$)	0.8	0.022	0.1
ε_2 (when $\varepsilon_1 = \tau = 0$)	No value	0.85	0.99
τ (when $\varepsilon_1 = \varepsilon_2 = 0$)	0.99	0.9	0.99

Table 3: Sensitivity analysis of basic reproduction number R_0 with respect to different parameters

Parameters	Sensitive index	CHIKV	DENV	ZIKV
α_b	0.5	0.5	0.5	0.5
α_v	0.5	0.5	0.5	0.5
β_v	$0.5(1 - \beta_v)$	0.44448	0.49565	0.49435
γ_b	-0.5	-0.5	-0.5	-0.5
μ_v	$-0.5\mu_v$	-7.5757	-7.5757	-7.5757

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