Transmission dynamics of recent outbreaks: Ebola and Zika virus

Thesis submitted in partial fulfillment of the requirement for the award of the degree of

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Submitted by
Jasmine Caur
301503009

Under the guidance of
Dr. Parimita Roy
(Assistant Professor)

Thapar University
Patiala-147004, Punjab
India

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Certificate

I hereby certify that the work which is being presented in the thesis entitled "**Transmission dynamics of recent outbreaks: Ebola and Zika virus**" in partial fulfilment of the requirements for the award of degree of Master of Science, School of Mathematics, Thapar University, Patiala is an authentic record of my own work carried out under the supervision of Dr. Parimita Roy.

The material submitted in this thesis has not been submitted for the award of any other degree of this or any other university.

(Jasmine Caur)
301503009

This is to certify that the above statement made by the candidate is correct and true to the best of my knowledge.

Dr. Parimita Roy
Assistant Professor (SoM)
Thapar University
Patiala

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Abstract

The spread of infectious diseases has always been a major cause of misery, sickness and death in humans and animals world-wide. It has caused serious problems for the survival of human beings and other species, and for the economic and social development of the human society. To prevent and to control infectious diseases more effectively, it is important to understand the mechanism of the spread transmission dynamics of the diseases, and then provide useful predictions and guidance so that better strategies can be established. Dynamic modeling of infectious diseases has contributed greatly to this end (Anderson and May, 1991). Dynamical complexity of ecological and epidemiological systems has motivated many researchers to find out the hidden realities of the biological interactions. Epidemiology is now necessary for outbreak investigations, surveillance, hypothesis testing, and generating follow-up activities necessary to perform a complete and proper epidemiologic analysis. Therefore, mathematical models are designed and explored. In this work, we explore the interplay of infectious diseases and human-animal interactions.

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Chapter 1

INTRODUCTION AND LITERATURE REVIEW

"If you are trying to get information across to someone, your ability to create a compelling introduction may be the most important single factor in the later success of your mission."
John Medina

1.1. General Introduction

Emerging infectious diseases are considered as active cause of global change that represents compelling challenges in agriculture, public health, and wildlife management (Blower and McLean, 1991; Keeling *et al*., 2001; Binder *et al*., 1999). While the role of mathematics in understanding and predicting certain sciences is self-explanatory, the usefulness of certain mathematical models in the field of epidemiology is often not so clear. Predicting the spread of an infectious disease depends on profound understanding of the dynamics of an epidemic model. A fundamental challenge in mathematical epidemiology is to determine how the structure of a population influences disease transmission. Epidemiologists are still contemplating a list of basic questions about how and why the infectious diseases like Ebola and Zika have been spreading through populations across the world. Some other issues that needed to be addressed are:

(i) What is the time period between infection and the onset of infectiousness?
(ii) For how long do patients remain infectious?
(iii) How many infections will each patient produce further?
(iv) How many people will get infected during the epidemic?
(v) Are the current public health guide-lines enough to bring these diseases under control?

The epidemiology is difficult, in part because of the variable responses by individuals, institutions, and governments to a new and dangerous disease. Moreover, about 60% of newly emerging infections in humans originate from wildlife (Jones et al., 2008; Taylor et al., 2001). Therefore, it is important to understand how infectious agents spread in wildlife, how they lead to changes in the dominance in some species rather than others and how they can ultimately increase infections in humans. Ecological field and experimental studies are starting to emerge suggesting that infection dynamics in wildlife communities is influenced

by ecological interactions in fundamental ways. A central question in conservation biology which is needed to be addressed is to understand how a parasite affects biodiversity and ecosystem. Mathematical representation and analysis of infectious disease has been central to infectious disease epidemiology since its inception as a discipline more than a century ago. Mathematical analysis and models have been successful in explaining previous observations and have played a vital role in structuring public health strategies in many countries.

Ecological models are very useful in simulating and analyzing long-term dynamics and stability properties of a complex ecological system. They allow integrating data from different disciplines as well as interpreting, analyzing and understanding field observations. Ecosystem models have applications in a wide variety of disciplines, such as natural resource management, ecotoxicology and environmental health, disease control or the adaptations to the impact of climate change, agriculture, and wildlife conservation. This provides a basis for developing tools for management support and policy advice purpose.

Among many infectious diseases, mosquito-borne diseases are notoriously difficult to control. A little-known mosquito-borne pathogen such as Zika virus causes a sudden outbreak accompanied by deadly side effects, mathematical models that stimulate the spread of mosquito-borne diseases can provide important guidance and insight to questions such as (i) how far and how quickly will the disease spread?, (ii) how many people will the outbreak potentially infect?, (iii) how can we best slow or prevent the outbreak and protect vulnerable population?.

Another disease which caused a devastating effect recently, is Ebola. The origin of the Ebola virus is somewhat obscure. There have been three major known outbreaks of the Ebola virus, and all have happened in West Central African countries. Ebola is a unique member of the ribonucleic acid virus family that has no known natural reservoir. The onset of Ebola is characterized by severe fever, headaches, bloody diarrhoea, malaise, vomiting, and rash. Ebola is frequently misdiagnosed as typhoid and malaria and hence diagnosis of Ebola can be difficult. Currently there is no treatment of Ebola. The mortality rate of Ebola is anywhere from 50-90%. Ebola is transmitted through primary contact with health workers who are in direct contact with body fluids from the infected.

In this work we are interested in developing new, robust numerical methodologies that deepen our understanding on the temporal dynamics of infectious diseases. The general objective of our work is to study and establish epidemiological models to get some insight about the recent Zika and Ebola outbreak. This work attempts to address some challenges of the future like (i) the preservation of biodiversity, and (ii) understanding the travelling waves of infections like in Zika and Ebola.

1.1.1. A brief review of mathematical models in epidemiology

Modeling in the field of epidemiology has had its roots in the early twentieth century. Sir Ronald Ross (1857-1932) studied and developed a model for spread of malaria and gave an important idea that one didn't need to eradicate all mosquitoes to eliminate the disease. Modern epidemiology has its theoretical roots founded on modeling the spread of a disease and showing that if certain conditions are met, then a disease will go extinct. Kermack and McKendrick (1927) formulated a well-recognized SIR compartmental model in 1927, to study the outbreak of the Great Plague in London during 1665-1666, and the outbreak of plague in Mumbai in 1906. They examined a series of models based on healthy, infected, and immune individuals in a constant population (no births or deaths). Basically, these epidemic models partition the population into several distinct classes, accounting for the individuals that may catch the disease (S), those that already are infected and can spread the infection (I), and those that are recovered from the infection (R). Many dynamical models for infectious diseases were proposed based on model given by Kermack and McKendrick (1927, 1932). An overwhelming majority of disease models are based on a compartmentalization of individuals or hosts according to their disease status. Initially, almost all work used nonparametric methods to search for chaos and other nonlinear phenomena in time series of notified cases (Schaffer and Kot, 1985; Olsen and Schaffer, 1990; Sugihara et al., 1990; Ellner, 1991; Nychka et al., 1992; Grenfell, 1992; Tidd et al., 1993; Ellner and Turchin, 1995). More recently, semi-mechanistic (Ellner et al., 1998) and mechanistic approaches (Finkenst and Grenfell, 2000) have been used to confront dynamical models with time series data. The SIRS model with simple mass action was first used to describe the spread of the disease in predator population (Auger et al., 2009). The dynamic behaviours of the SIR epidemic model and a lot extension are well investigated by many scholars (Shulgin et al., 1998; Stone et al., 2000; McCluskey, 2010; Ackleh and Allen, 2003; Earn et al., 2000). The SEIR epidemic model has also been extensively studied by many researchers (Li et al., 1999; Li and Jin, 2005; Al-Sheikh, 2012; Li and Muldowney, 1995; Li et al., 2006; Zhang and Ma, 2003) and references therein.

1.2. Biological preliminaries

(i) Endemic

It is the continuous presence of a disease or an infectious agent within a given geographic area or population group. It is the usual or expected frequency of disease within a population. For example, chickenpox is endemic (steady state) in the UK, but malaria is not.

(ii) Epidemic

An epidemic is a disease that spreads rapidly among many people in a community at the same time. For example, in 2003, the severe acute respiratory syndrome (SARS) epidemic took the lives of nearly 800 people worldwide.

(iii) Incubation period

Incubation period is the interval between effective exposure of the susceptible host to an infectious agent and the appearance of signs and clinical symptoms of the disease in that host. During this time, viral genomes replicates and the host responds by producing cytokines such as interferon that can have global effects, leading to the classical symptoms of an acute infection (e.g., fever, malaise, aches, pains, and nausea). These symptoms are called the prodrome, to distinguish them from those characteristic of infection (e.g. paralysis for poliovirus, hemorrhagic fever for Ebola viruses, rash for measles virus). Whether or not an infected person is shedding virus during the incubation period depends on the virus. For example, Ebola virus infected patients do not pass the virus on to others during the incubation period.

(iv) Susceptible population

This class includes those units of population which are free from infections i.e. they are healthy but have an active potential threat of infection by the infective agent at any point of time.

(v) Exposed population

This class includes the units that have been infected but are not yet infectious. It means that the person has had contact with an infected individual but he himself is not infectious.

(v) Infected population

This class includes the units that have been infected and who have the potential to transmit the infectious disease to the rest of population on having adequate contacts with the susceptible class of the populations.

(vi) Recovered population

This class includes those individuals who have ceased to be infectious and have acquired immunity, which may be permanent or temporary based on whether they remain in this class forever or move back to the susceptible class.

(vii) Basic reproductive number (R_0)

R_0 is the expected number of secondary cases resulting from a single infected person in a fully susceptible population. The stability or instability of a disease free equilibrium is determined by the basic reproduction number. If $R_0 < 1$, then the disease free equilibrium is locally asymptotically stable. If $R_0 > 1$, the disease free equilibrium is unstable and the introduction of an infected individual will result in an outbreak. In the early stages of an epidemic R_0 is the key quantity of interest.

1.3. Tools of analysis

(i) Definition of Stability

The mathematical models or equations that describe physical phenomena are in most cases ordinary differential equations of the form $x' = F(t , x)$ with the initial data $x(t_0) = x_0$.

Definition 1: The solution $x(t)$ is said to be stable if, for each $\varepsilon > 0$, there exists a $\delta = \delta(\varepsilon) > 0$ such that for any solution $\bar{x}(t) = x(t , t_0 , \bar{x}_0)$ of the given equation , the inequality $\| \bar{x}_0 - x \| < \delta \Rightarrow \| \bar{x}(t) - x(t) \| < \varepsilon \ \forall \ t > t_0$.

Definition 2: The solution $x(t)$ is said to be asymptotically stable if it is stable and if $\exists$ a $\delta_0 > 0$, such that $\| \bar{x}_0 - x \| < \delta_0 \Rightarrow \| \bar{x}_0(t) - x(t) \| \to 0$ as $t \to \infty$.

(ii) Hurwitz theorem

A necessary and sufficient condition for the negativity of the real parts of all the roots of the polynomial

$$L(\lambda) = \lambda^n + a_1 \lambda^{n-1} + \ldots\ldots\ldots + a_n$$

with real coefficients is the positivity of all the principal diagonals of the minors of the Hurwitz matrix

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & 0 & 0 & 0 & \cdots & a_n \end{pmatrix}$$

It should be noted that the principal diagonal of the matrix H_n exhibits the coefficients of the polynomial $L(\lambda)$ in the order of their numbers from a_1 to a_n. The principal diagonal minors of the matrix by

$$D_1 = |a_1|, D_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix}, \ldots, D_n = |H_n|$$

This theorem becomes impractical for large '*n*'. To observe this, let us apply it to polynomials of the second, third and fourth degrees:

1. $\lambda^2 + a_1\lambda + a_2$

   The Hurwitz conditions reduce to $a_1 > 0$ and $a_2 > 0$.

2. $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$

   The Hurwitz conditions reduce to $a_1 > 0$, $a_2 > 0$, $a_3 > 0$ and $a_1a_2 - a_3 > 0$

3. $\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$

   The Hurwitz conditions reduce to $a_1 > 0$, $a_2 > 0$, $a_3 > 0$, $a_4 > 0$ and $a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$

From the Hurwitz conditions it follows that all the $a_i > 0$, $i = 1, 2, 3.....n$; however, the positivity of all the coefficients is not enough for the real part of all the roots of $L(\lambda)$ to be negative.

1.4. Problem description and solution strategies

The goal of this work is to implement a framework for Ebola and Zika virus risk prediction that is robust to temporal changes, being validated on historical information, and able to anticipate future outbreak. Mathematical models which are both structurally and dynamically complex are designed and the following questions are answered

1. Which variables contribute to virus spread?
2. What effect mobility and precaution measures have on disease spread?

3. How past changes to the virus can be used to inform future risk predictions?

The thesis output can inform about the identification of future research priorities and the proactive definition of conservation interventions, to anticipate and prevent future outbreak. An improved understanding of how risk to biodiversity can be monitored cost effectively, and how early-warning signals can be systematically identified and addressed, which in turn will allow us to anticipate future outbreak and will shed light on the potential future effects of current policy decisions.

Chapter 2

Prevention and Control of Ebola virus: A Mathematical Modelling Analysis

"At any time we can have another epidemic.
It's very important now to be able to fight the ebola virus
anytime, anywhere it appears."
Dr. Samel Edzang

Introduction

A CNN news reporter Christensen writes about how Ebola spreads "*Imagine – the largest Ebola epidemic in history began with the simple act of caring for a child. Soon, it spreads from the child's remote village in Guinea. And now, the infection has wiped out entire families, created thousands of orphans in its wake, and left people terrified from Dubreka, Guinea, to Dallas, Texas. Scientists predict as many as 1.4 million people could be infected if nothing is done to help*" (Christensen, 2014). Ebola viruses are highly transmissible by direct contact with infected blood, secretions, tissues, organs and other bodily fluids from dead or living infected persons (Colebunders and Borchert, 2000), it can also transmit via inanimate objects contaminated with infected bodily fluids (fomites) (Bausch et al., 2007). Airborne transmission has not been documented (Colebunders and Borchert, 2000). Burial ceremonies and handling of dead bodies play an important role in transmission (http://www.who.int/mediacentre/factsheets/fs103/en/). The mode of transmission is important for two reasons: (i) it determines the probable response of the disease to control, and (ii) to predict what will happen when pathogen is introduced into a system in which it does not currently exist (Pech and Hone, 1988; Anderson et al., 1981). Controlling an outbreak requires rigorous assessment and follow-up of exposed cases. This requires identifying all people who may have been exposed to a person with Ebola and checking for signs of illness every day for 21 days – the maximum number of days of Ebola's incubation period. Providing basic health surveillance can play a key role in controlling the outbreak if done carefully with proper safety precautions and adequate supervision. This is extremely important in the early stages of an epidemic, when pharmaceutical interventions are not often possible because treatment or vaccine options are not yet developed. Towers et al. (2014) indicated that enforced quarantine may not be effective control measure. Aylward et al.

(2014) suggested that without drastic improvement in control measures, the number of cases and deaths from Ebola will continue to increase from hundreds to thousands per week. Recently, Yamin et al. (2015) examined the potential for targeted interventions to eliminate the disease and evaluated the contribution of disease progression and case fatality on transmission. Agusto et al. (2015) designed a mathematical model and assessed the impact of basic non-pharmaceutical control measures on the 2014 Ebola outbreaks. Fast et al. (2015) introduced a model of the joint diffusion of social response and disease through a population during disease outbreak. Due to social differences, epidemic trajectories and uptake of control measure can vary widely between populations (Bauch and Galvani, 2013). To better understand and characterize the transmission of the Ebola virus and to improve control strategies, we have made an attempt by constructing a SEIR model of infectious disease outbreak.

In this chapter, we propose a mathematical model to describe the development of the Ebola outbreak to date, examine the potential impact of several interventions, and provide short term projections for its future development. We use parameter values estimated in the past and inspect carefully the extent to which the designed model prediction agrees with the pattern of spread seen in West Africa. We employ sensitivity analysis to determine the extent to which the predictions could have improved by better parameterization. This allows us to examine the state of the patterns seen and discuss implications for the control of future pandemics.

2.1. Formulation of Epidemic Model

An SEIR model is an epidemiological model that computes the theoretical number of people infected with a contagious illness in a closed population over time. The name of this class of models derives from the fact that they involve coupled equations relating the number of susceptible people *S*, number of people exposed to the infection *E*, number of infected people *I*, and number of people who have recovered *R*.

Many data-driven epidemic models for Ebola have been proposed, however only a few, tackle the behaviour of diseases at the global scale. Althus (2014) used an SEIR mathematical model to estimate the basic reproduction number in the absence and presence of control interventions. Maximum likelihood estimates of the parameters were obtained by fitting the data of the 2014 Ebola outbreak in West Africa. Upadhyay & Roy (2016) proposed a mathematical model to describe the development of the Ebola outbreak to date, provide short term projections for its future development, and examine the potential impact of several

interventions. They have considered factors like (i) the movement of individual populations (including patients), those are not infected with Ebola virus, seeking and providing assistance in health-care facilities, (ii) the movements of individuals taking care of patients infected with Ebola virus not admitted to hospital, and (iii) the population attending the traditional funeral ceremony and involving in social rituals as the main factors contributing to the geographical spread of Ebola in West Africa.

Our SEIR model is based on the following assumptions:

1. The infection is spread directly by contact of infected individuals to other individual (termed "adequate contact") and in no other way.
2. Any non-immune individual in the group, after such contact with an infectious individual in a given period, will develop the infection and will be infectious to others only within the following time period; in subsequent time periods, he is wholly and permanently immune.
3. Every individual has a fixed likelihood of coming into adequate contact with any other specified individual in the group within one time interval, and this probability is the same for every individual of the group.
4. The individuals are wholly isolated from others outside the group. (It is a closed population.)
5. These conditions remain constant during the epidemic.

The infection force $\lambda(t)$ is given by $\lambda(t) = pM\frac{I}{N}$, where M is the contact number of one susceptible with all individuals per unit time, $\frac{MI}{N}$ gives the number of infectious contacts from those contacts, and p is the valid transmission probability under $\frac{MI}{N}$ infectious contacts. It should be noted that the increase of infection cases can motivate people to use better protection measures. Thus, the transmission probability p is a decreasing function of infective number I. In the present paper, we assume that $p = \frac{p_0}{1+hI}$ with positive constants p_0 and h. Then, $\lambda(t) = M\frac{p_0 I}{(1+hI)N}$. Next, we assume that the contact numbers $M = k_1 mN$ where k_1 is a proportional constant and m denotes the intensity of population mobility. Then,

$\lambda(t) = \frac{mk_1 p_0 I}{1 + hI}$. Consider parameter *m* is influenced by economic benefits of mobility and infection risk. Without epidemic infections, mobility of population is only determined by economic benefits, which means that the social capacity of population mobility in the context of economics is *b/a*. With the occurrence of epidemics, the benefit of mobility is decreased by infection.

In view of the above assumptions, the SEIR model is given by:

$$\begin{aligned}
\frac{dS}{dt} &= A - \mu S - \frac{\beta mIS}{1+nI} \\
\frac{dE}{dt} &= \frac{\beta mIS}{1+nI} - (\mu + \sigma) E \qquad (2.1) \\
\frac{dI}{dt} &= \sigma E - (\gamma + \mu) I \\
\frac{dR}{dt} &= (1-f)\gamma I - \mu R
\end{aligned}$$

Here the initial conditions are: *S(t=0) = N ;E(t=0) = 0 ;I(t=0) = 0 ;R(t=0) = 0.* All parameters involved in the model are positive and their description is given in Table 2.1.

Table 2.1: Previously published estimates of parameters for Ebola

Parameter	Description	Value	Reference
A	Recruitment rate of susceptible population.	0.2	Assumed
μ	Death rate	0.003	Assumed
β	Per capita infection rate	0.27	Althaus (2014)
m	Intensity of population mobility	0.025	Assumed
n	Precaution constant	10.9	Assumed
σ	Average time-span of an infected individual in exposed class	0.085	Upadhyay & Roy (2016)
γ	Recovery rate	0.1751	Upadhyay & Roy (2016)
f	Fatality rate	0.74	Althaus (2014)

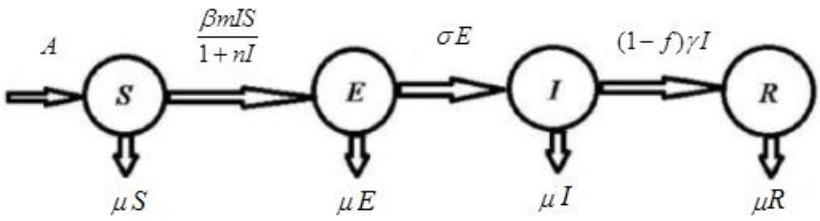


Figure 1: Flow diagram for proposed Ebola model.

2.2. Analysis of behaviour of the Epidemic Model

In this section, we calculate all feasible steady states and basic reproduction number for the Ebola epidemic model.

2.2.1. Possible equilibria and its existence criteria

To find the equilibrium point, we solve the following equations simultaneously

$$A-\mu S-\frac{\beta mIS}{1+nI}=0$$

$$\frac{\beta mIS}{1+nI}-(\mu+\sigma)E=0$$

$$\sigma E-(\gamma+\mu)I=0$$

$$(1-f)\gamma I-\mu R=0$$

and obtain two solutions:

Solution (a): $Q^0(S,E,I,R)$, where $S = \frac{A}{\mu}$, $E = 0$, $I = 0$, $R = 0$; This is a disease free equilibrium.

Solution (b): $Q^*(S^*, E^*, I^*, R^*)$, where $S^* = \frac{An\sigma+(\mu+\gamma)(\mu+\sigma)}{\sigma(m\beta+n\mu)}$,

$E^* = \frac{Am\beta\sigma-\mu(\mu+\gamma)(\mu+\sigma)}{\sigma(m\beta+n\mu)(\mu+\sigma)}$, $I^* = \frac{Am\beta\sigma-\mu(\mu+\gamma)(\mu+\sigma)}{(m\beta+n\mu)(\mu+\sigma)(\gamma+\mu)}$,

$R^* = \frac{\gamma(f-1)[Am\beta\sigma-\mu(\mu+\gamma)(\mu+\sigma)]}{\mu(\gamma+\mu)(m\beta+n\mu)(\mu+\sigma)}$; This is an endemic equilibrium.

Theorem 1: The Ebola epidemic model (2.1) has

1. No endemic equilibrium (EE), if $m\beta\sigma(Am\beta\sigma-\mu(\gamma+\mu)(\mu+\sigma))\le 0$,
2. Unique endemic equilibrium if $m\beta\sigma(Am\beta\sigma-\mu(\gamma+\mu)(\mu+\sigma))>0$.

2.3. Basic Reproduction Number

The basic reproduction number, R_0 is defined as the expected number of secondary cases produced by a single infection in a completely susceptible population. This is useful because it helps to determine whether or not an infectious disease will spread through the population. Following, Van den Driessche and Watmough (2002), we calculate the basic reproduction number. Let $x = (E, I)$, then from Ebola epidemic (2.1), it follows:

$$\frac{dx}{dt}=F-V,$$

where, $F = \begin{bmatrix} \frac{\beta mIS}{1+nI} \\ 0 \end{bmatrix}$ and $V = \begin{bmatrix} (\mu+\sigma)E \\ -\sigma E + (\gamma+\mu)I \end{bmatrix}$.

We obtain F_1 = Jacobian of F at DFE = $\begin{bmatrix} 0 & \frac{m\beta S}{(1+nI)} - \frac{m\beta SI}{(1+nI)^2} \\ 0 & 0 \end{bmatrix}$, and V_1 = Jacobian of V at DFE = $\begin{bmatrix} (\mu+\sigma) & 0 \\ -\sigma & (\gamma+\mu) \end{bmatrix}$.

The next generation matrix for the epidemic model is given by $K = F_1V_1^{-1}$

i.e. $$K = \begin{bmatrix} \frac{S\beta m\sigma}{(\sigma+\mu)(\gamma+\mu)(1+nI)^2} & \frac{S\beta m}{(\mu+\gamma)(1+nI)^2} \\ 0 & 0 \end{bmatrix}.$$

The basic reproduction number, R_0 is defined as the spectral radius of the next generation matrix $K = F_1V_1^{-1}$. Thus, basic reproduction for the model (2.1) is given as

$$R_0 = \frac{A\beta m\sigma}{\mu(\sigma+\mu)(\gamma+\mu)}. \quad (2.2)$$

2.4. Stability analysis of Epidemic Model

Now, we are in a position to perform the stability analysis of the model system. To analyse the stability of our model, we construct the Jacobian (***J***) of equations in (2.1) and then substitute both the solutions to obtain the characteristic equations.

The general form of the Jacobian is:

$$\boldsymbol{J} = \begin{pmatrix} -\mu - \frac{\beta Im}{(1+nI)} & 0 & \frac{m\beta S}{(1+nI)^2} & 0 \\ \frac{\beta Im}{(1+nI)} & -\sigma-\mu & \frac{-m\beta S}{(1+nI)^2} & 0 \\ 0 & \sigma & -\mu-\gamma & 0 \\ 0 & 0 & -\gamma(f-1) & -\mu \end{pmatrix}$$

2.4.1. Local stability analysis of our SEIR model around the Disease free Equilibrium

In this section, we explore the local stability of the model system (2.1) around the disease-free equilibrium.

Theorem 2: The disease free equilibrium is locally asymptotical if R_0 >1, and unstable if R_0 < 1.

Proof: The Jacobian matrix around disease free equilibrium is given by:

$$\boldsymbol{J_0} = \begin{pmatrix} -\mu & 0 & \frac{-Am\beta}{\mu} & 0 \\ 0 & -\sigma-\mu & \frac{Am\beta}{\mu} & 0 \\ 0 & 0 & -\mu-\gamma & 0 \\ 0 & 0 & -\gamma(f-1) & -\mu \end{pmatrix}$$

The characteristic polynomial of $\boldsymbol{J_0}$ is given as

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0.$$

Where, $a_1 = \gamma + 4\mu + \sigma$,

$$a_2 = 6\mu^2 - \frac{Am\beta\sigma}{\mu} + 3\mu\sigma + \gamma(3\mu+\sigma),$$

$$a_3 = -2Am\beta\sigma + \mu(3\gamma\mu + 4\mu^2 + 2\gamma\sigma + 3\mu\sigma),$$

$$a_4 = \mu(-Am\beta\sigma + \mu(\gamma+\mu)(\mu+\sigma)).$$

The eigen values of J_0 are:

$\lambda_1 =$ -μ,

$\lambda_2 =$ -μ,

$$\lambda_3 = \frac{-\sqrt{\mu}(\gamma+2\mu+\sigma) - \sqrt{\mu(\gamma-\sigma)^2 + 4Am\beta\sigma}}{2\sqrt{\mu}},$$

$$\lambda_4 = \frac{-\sqrt{\mu}(\gamma+2\mu+\sigma) + \sqrt{\mu(\gamma-\sigma)^2 + 4Am\beta\sigma}}{2\sqrt{\mu}}.$$

Clearly if R_0 < 1, then all the four eigen values of J_0 have negative real parts. If R_0 > 1, then two eigen values of J_0 have negative real parts and two eigen value has positive real part. Hence, DFE is locally asymptotically stable, if R_0 < 1 and unstable, if R_0 > 1. At R_0 = 1, DFE Q^0 = (A/μ, 0, 0, 0) is a non hyperbolic equilibrium point. Thus, if R_0 < 1, all the nearby

trajectories of the system states, starting from various initial conditions approach Q^0. Thus, to maintain disease-free situation, the basic reproduction number, R_0 must be made less than one. This can be done through (i) a decrease in the probability of disease transmission rate, β, (ii) through increase in natural death rate, μ and (iii) through an increase in the recovery rate, γ by medication or control measures. The second option seems unrealistic to focus upon, so we must concentrate on the other two options to fight from this deadly disease.

2.4.2. Local stability analysis of our SEIR model around the Endemic Equilibrium

Theorem 3: The endemic equilibrium is locally asymptotically stable if $b_1 > 0$, $b_2 > 0$, $b_3 > 0$, $b_4 > 0$ and $b_1b_2b_3 - b_3^2 - b_1^2b_4 > 0$, where b_1, b_2, b_3 and b_4 are given in the proof.

Proof: The Jacobian matrix of solution (b) is given by:

$$J_* = \begin{pmatrix} -\mu - \dfrac{I^*\beta m}{(1+nI^*)} & 0 & \dfrac{m\beta S^*}{(1+nI^*)^2} & 0 \\ \dfrac{I^*\beta m}{(1+nI^*)} & -\sigma-\mu & \dfrac{-m\beta S^*}{(1+nI^*)^2} & 0 \\ 0 & \sigma & -\mu-\gamma & 0 \\ 0 & 0 & -\gamma(f-1) & -\mu \end{pmatrix}$$

The characteristic polynomial is given as:

$$P(\lambda) = \lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 = 0.$$

Where $b_1 = \dfrac{\mu(\gamma+\mu)(\gamma+3\mu) + Am\beta\sigma + (An+\gamma+\mu)(\gamma+4\mu)\sigma + (An+\gamma+\mu)\sigma^2}{An\sigma + (\gamma+\mu)(\mu+\sigma)}$,

$$b_2 = \frac{-n\mu(\gamma+\mu)^2(\mu+\sigma)^2 + Am^2\beta^2\sigma(\gamma+3\mu+\sigma) + m\beta(\gamma^2\mu(\mu+\sigma))}{m\beta(An\sigma+(\gamma+\mu)(\mu+\sigma))}$$

$$+ \frac{\gamma(3\mu+\sigma)(An\sigma+\mu(\mu+\sigma)) + \mu(2\mu+\sigma)(3An\sigma+\mu(\mu+\sigma)))}{m\beta(An\sigma+(\gamma+\mu)(\mu+\sigma))},$$

$$b_3 = \frac{-2n\mu^2(\gamma+\mu)^2(\mu+\sigma)^2 - m\beta\mu(\mu^2(\gamma+\mu)^2 + \mu(2(\gamma+\mu)^2 - An(3\gamma+4\mu))\sigma)}{m\beta(An\sigma+(\gamma+\mu)(\mu+\sigma))}$$

$$- \frac{(((\gamma+\mu)^2 - An(2\gamma+3\mu))\sigma^2) + Am^2\beta^2\sigma(\gamma(2\mu+\sigma)+\mu(3\mu+2\sigma))}{m\beta(An\sigma+(\gamma+\mu)(\mu+\sigma))},$$

$$b_4 = -\frac{\mu(\gamma+\mu)(m\beta+n\mu)(\mu+\sigma)(-Am\beta\sigma+\mu(\gamma+\mu)(\mu+\sigma))}{m\beta(An\sigma+(\gamma+\mu)(\mu+\sigma))}.$$

By following Routh-Hurwitz criterion for the polynomial *P*, the equilibrium is locally asymptotically stable if $b_1 > 0$, $b_2 > 0$, $b_3 > 0$, $b_4 > 0$ and $b_1b_2b_3 - b_3^2 - b_1^2b_4 > 0$.

2.5. Global stability of Disease free Equilibrium

In this section, we analyze the global stability of the disease-free steady states by using the method developed by Castillo-Chavez and Song (2004). Since the variable *R* of system (2.1) does not appear in the first three equations, in the subsequent analysis, we only consider the subsystem:

$$\frac{dS}{dt} = A - \mu S - \frac{\beta mIS}{1+nI} = f_1(S,E,I) \tag{2.3}$$

$$\frac{dE}{dt} = \frac{\beta mIS}{1+nI} - (\mu+\sigma)E = f_2(S,E,I) \tag{2.4}$$

$$\frac{dI}{dt} = \sigma E - (\gamma+\mu)I = f_3(S,E,I) \tag{2.5}$$

Now, we state two conditions which guarantee the global stability of the disease-free state. Rewriting the epidemic model system (2.3)–(2.5) as

$$\begin{aligned} \frac{dX}{dt} &= F(X,Z), \\ \frac{dZ}{dt} &= G(X,Z), G(X,0) = 0 \end{aligned} \tag{2.6}$$

where $X = (S)$ and $Z = (E, I)$, where $X \in R$ denotes the number of uninfected individuals and $Z \in R^2$ denotes the number of infected individuals including the latent and the infectious. The disease-free equilibrium is now denoted by $Q_0 = (X_0, 0)$. The following conditions (H1) and (H2) must be met to guarantee a local asymptotic stability: (H1) For $\frac{dX}{dt} = F(X,0), X_0$ is globally asymptotically stable, (H2) $G(X,Z) = BZ - \tilde{G}(X,Z)$, where $\tilde{G}(X,Z) \geq 0$, for $(X,Z) \in \Gamma$, where $B = D_Z G(X_0,0)$ is an *M*-matrix (the off-diagonal elements of *B* are non-negative) and Γ is the region where the epidemic model makes biological sense. Then, we state the following lemma.

Lemma 1: *The* fixed point $Q_0 = (X_0, 0)$ is a globally asymptotically stable equilibrium of model system (2.6) provided that $R_0 < 1$ and that assumptions (H1) and (H2) are satisfied.

Theorem 4: Suppose $R_0 < 1$, then the disease-free equilibrium Q_0 is globally asymptotically stable.

Proof: Let $X = (S)$ and $Z = (E, I)$, here $Q_0 = (X_0, 0)$, where $X_0 = \frac{A}{\mu}$. Then, we have

$$\frac{dX}{dt} = F(X, Z) = A - \mu X - \frac{\beta m I X}{1 + nI}$$

At $X = X_0$, $F(X, 0) = 0$. Now, $\frac{dX}{dt} = F(X, 0) = A - \mu X$, as $t \to \infty$, $X \to X_0$. Hence, $X = X_0$ is globally asymptotically stable. Thus, condition (H1) is satisfied. Now, from equations (2.3)–(2.5), we obtain

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

$$= \begin{pmatrix} -\mu - \sigma & \beta m N \\ \sigma & -\gamma - \mu \end{pmatrix} \begin{pmatrix} E \\ I \end{pmatrix} - \begin{pmatrix} \beta m I (N - \frac{X}{1 + nI}) \\ 0 \end{pmatrix}$$

$$= BZ - \tilde{G}(X, Z)$$

Clearly, B is an M-matrix. For $I \geq 0$, $N \geq S \geq 0$, $\tilde{G}(X, Z) \geq 0$. Thus, both the conditions (H1) and (H2) are satisfied, therefore by Lemma 1, the DFE Q_0 is globally asymptotically stable, if $R_0 < 1$.

2.6. Sensitivity analysis

In order to determine how best we can reduce human morbidity and mortality due to Ebola virus, it is necessary to know the relative importance of the different parameters responsible for its transmission and prevalence. Initially, disease transmission and prevalence are directly related to the basic reproduction number, R_0, and the endemic equilibrium point Q^*, specifically to the magnitude of I^*, respectively. We calculate the sensitivity indices of the reproductive number, R_0, and the endemic equilibrium point Q^*, to the parameters in the model. These indices indicate how crucial each parameter is to disease transmission and prevalence. Here, we use it to find parameters that have a high impact on R_0 and Q^*, and should be targeted by intervention strategies. In order to find sensitivity indices, we use similar methodology as suggested by Chitinis *et al.* (2008).

Definition: The normalised forward sensitivity index of a variable, *w* that depends on a parameter *p*, is defined as $\gamma_p^w = \frac{\partial w}{\partial p} \times \frac{p}{w}$

2.6.1. Sensitivity indices of R_0

In this section, our aim is to determine the uncertainty of R_0 based on the uncertainty of the input parameters. Some of the parameters even change their values on the basis of natural history of Ebola. The values of these parameters thus need a statistical analysis to examine the impact of their uncertainties. Since we already derived an explicit formula for R_0 given in equation (2.2), we evaluate the sensitivity indices at the baseline parameter values given in Table 2.1. The resulting sensitivity indices of R_0 to the eight different parameters in the model are also shown in the Table below.

Table 2.6.1: The sensitivity indices, $\gamma_{p_j}^{R_0} = \frac{\partial R_0}{\partial p_j} \times \frac{p_j}{R_0}$, of the basic reproduction number R_0 to the parameters p_j, for baseline parameter values given in Table 2.1.

Parameters (p_j)	A	β	μ	σ	γ	n	m
Sensitivity index of R_0	1	1	-1.0509	0.0340	-0.9831	0	1

The most influential parameter in determining the value of R_0 is the death rate of the infected human population. Decreasing (or increasing) the value of this parameter by 10% increases (or decreases) the value of R_0 by 10.5%. The second most influential parameters are recruitment rate (A), the transmission rate (β) and the intensity of population mobility (m) as shown in Table 2.6.1. Decreasing (or increasing) the value of these parameters by 10% decreases (or increases) the value of R_0 by 10%.

2.6.2. Sensitivity indices of Q^*

We now perform sensitivity analysis of the state variable I^* with respect to the model parameters. Sensitivity indices of the state variable I^* at endemic equilibrium are shown in Table 2.6.2. From this table, we observe that all the parameters have positive impact on I^*

except μ, n and γ. In this study, we have identified the most important parameters that drive the transmission mechanism of Ebola. The identification of these parameters is vital in formulating control strategies effective for fighting the disease. The result of sensitivity analysis suggest that a strategy which reduces the recruitment rate (A) of human and the transmission rate (β) of Ebola infection in the community and the strategy which increases the recovery rate (γ_h) would be quite effective in restricting the spread of the disease.

Table 2.6.2: The sensitivity indices, $\gamma_{p_j}^{I^*} = \frac{\partial I^*}{\partial p_j} \times \frac{p_j}{I^*}$, of the variable I^* at the endemic equilibrium with respect to the parameter p_j, for baseline parameter values given in Table 2.1.

Parameters (p_j)	A	β	μ	σ	γ	n	m
Sensitivity index of I^*	1.6941	1.5230	-1.6093	0.0577	-1.6656	-0.8288	1.5230

2.7. Numerical Simulation

The global dynamical behavior of Ebola epidemic model system is investigated numerically. The ODEs were integrated using Runge-Kutta method in the MATLAB R2017a software environment. We have considered the starting point of the simulation from May 27, 2014 and have taken, the initial population sizes as: $S(0)$ = 6205382; $E(0)$ = 16; $I(0)$ = 5; $R(0)$ = 0, (Althaus 2014)

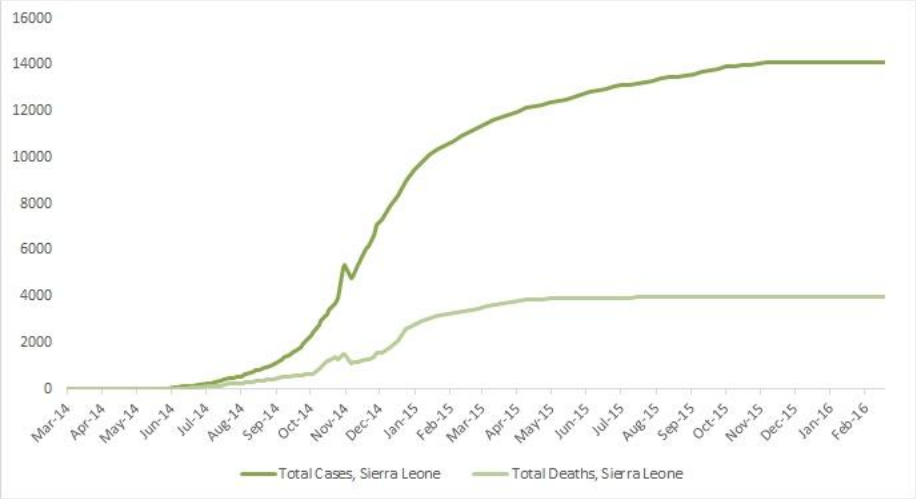


Figure 2(a): Total number of cases and total number of deaths due to Ebola virus in Sierra Leone (West Africa).

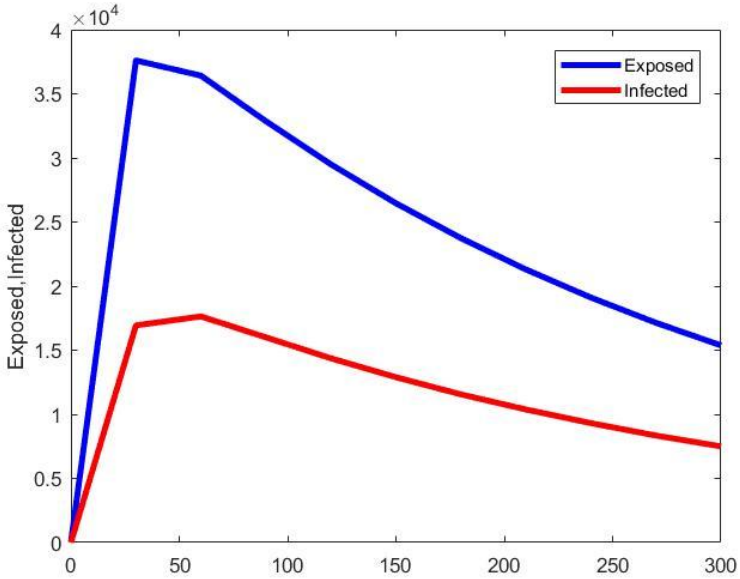
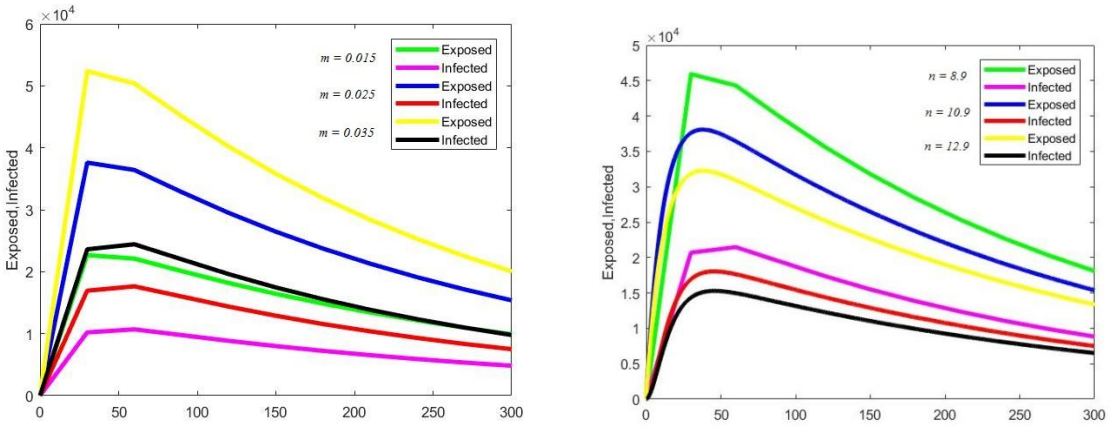


Figure 2(b): Exposed and infected cases of population at Sierra Leone for the parameter values given in Table 2.1

Figure 2(a) gives us an overview of the actual number of cases that were reported by WHO for surveillance purpose. From Figure 2(b), we observe that our model suggests that the epidemic will reach its peak in about 50 days. The correspondence between the predicted and observed appears quite good and shows similar time series and in accordance with the data published by WHO. There is still a tremendous amount of work needed to be done guiding researches and policy makers in targeting prevention with maximum effectiveness. Since, there is a similarity between the natures of both the figures, indicating that our model assumptions are close to reality.

2.7.1. Effect of change in parameters



(i) (ii)

Figure 3: Time series of Exposed and Infected population for different values of (i) *m* and (ii) *n*

In this section we observe the impact of population mobility (*m*) and precaution constant (*n*) in determining the number of people that are affected by the disease. We can see that as we increase the intensity of population mobility (*m*), there is a drastic increase in the exposed and infected population. On the other hand, if we increase the precaution constant (*n*), there is a decrease in the exposed and infected population. This can also be inferred from the sensitivity analysis given in Table 2.6.2, *m* has a positive and *n* has a negative effect on I^*.

This simulation result suggests that to decrease the spread of the disease we should (i) limit our contact with other people as it spreads through contact with bodily fluids such as (urine, saliva, sweat, urine, vomit, breast milk, semen, and vaginal fluids), (ii) take

precautions such as washing our hands with soap and water or an alcohol-based hand sanitizer, (iii) avoid funeral or burial rituals that require handling the body of someone who has died from Ebola, (iv) isolate patients with Ebola from other patients and practice proper infection control and sterilization measures.

2.8. Discussion and Conclusion

The worst outbreak of the virus has seen nearly 9,000 deaths in a year – almost all of them are in the Liberia, Guinea and Sierra Leone - and sparked a major health fright worldwide. An SEIR Ebola epidemic model is proposed and analyzed using nonlinear stability theory. The model exhibits two biological feasible equilibria, the disease free and endemic equilibrium. The finding in this work can be used to predict the number of future Ebola cases which can be controlled. A model of infectious diseases has been developed to assess the interdependencies of critical infrastructures placed under stress by disease outbreaks and to instruct recommendations regarding control measures. The results of sensitivity analysis show that the sensitive inputs to the infectious disease model match our prior expectations – recruitment rate, transmission rate and population mobility.

In this work, we find that use of non-pharmaceutical interventions helps us to mitigate disease burden from the environment by lowering the level of infectious individuals. Controlling the Ebola epidemic wherever it occurs is not only a humanitarian duty but also a matter of crude self-interest. These findings suggest that if disaster is to be prevented and if we want to end the epidemic soon there was a need for improved control measures including restricting mobility between individuals.

Our model is a simplified representation of reality and is limited to (i) the non-granular nature of the data available for model parameterization in this particular outbreak, (ii) the epidemic is ongoing in multiple geographic locations and no model can capture the complex geographical patterns of spread in the region, and (iii) the parameters are dependent on the environmental conditions, so they are rarely constant. But for simplification of our model, we have assumed that the parameters are constant. Despite of the above mentioned limitations, our findings are useful to demonstrate that the cases will steadily grow and will go down in mid of year 2015. Our model study is a small step towards the goal of identifying the parameters of interest and understanding the spatial spread of Ebola virus. Instead of panicking about Ebola, we should be working to combat it, along with other gruesome diseases. We must address these kinds of issues for what they are, not what we perceive them to be.

Chapter 3

Zika virus: Risk for India?

"Our number one priority is our patients,
and the hope is that our care and research
will also lead to new developments in the effort
to fight this potentially devastating disease."
William May

Introduction

Zika virus (ZIKV) received little attention until a surge in microcephaly cases was reported after 2015 outbreak in Brazil. The virus was initially isolated from a rhesus monkey in the Zika forest of Uganda in 1947, and later isolated from humans in Nigeria in 1954. Subsequently, only sporadic confirmed human cases were reported from Africa and Southeast Asia. In April 2007, the first documented ZIKV outbreak outside traditionally affected areas occurred on Yap Island, Federated States of Micronesia, in the North Pacific. In October 2013, a severe ZIKV outbreak was reported in French Polynesia, South Pacific, with an estimated 28,000 cases.

Zika is primarily spread by the female *Aedes aegypti* mosquito, which is active mostly in the daytime. The disease of Zika virus is transmitted from infected *Aedes* mosquitoes to humans through mosquito bites. Most cases have no symptoms, but when present they are usually mild and can resemble dengue fever. Symptoms may include fever, red eyes, joint pain, headache, and a maculopapular rash. Symptoms generally last less than seven days. There are no specific treatments currently. Zika virus has been detected in serum, saliva, urine, and semen. It has also been detected in urine and semen even after it disappears from blood and in one convalescent case it was detected in semen 27 and 62 days after onset of febrile illness. Recent studies show that it can also be transmitted via sexual contact. Zika virus is a cause of complications such as microcephaly (a birth defect where a baby's head and/or brain is smaller than expected) and Guillain-Barre syndrome (a neurological disorder that could lead to paralysis and death).

The ongoing outbreak, which began in April 2015 in Brazil, has rapidly spread to many other countries in South and Central America and the Caribbean with more than 140,000 suspected and confirmed cases by the end of February 2016. Nearly 6,000 suspected cases of microcephaly (including 139 deaths) among newborns might be linked to ZIKV infections in Brazil between October 2015 and February 2016. The WHO declared the epidemic a Public Health Emergency of International Concern (PHEIC) on February 1, 2016,

and the U.S. CDC's Emergency Operations Centre has moved to the highest level of activation on February 3, 2016. Based on the reported dengue data from 2015, WHO estimated that up to four million people in the Americas could be infected by ZIKV in 2016.

A recent study published in 'The Lancet' says that India is at high risk for the spread of Zika, as it hosts over 67,000 travellers from areas where there is an active circulation of the virus. An estimated 1.2 billion people are susceptible to Zika virus exposure at the time of peak seasonal risk in India. More than 67,000 air travellers arrive every year – and four other countries (Philippines, China, Thailand and Indonesia) were most at risk for year-round transmission of the Zika virus. Further, other studies have shown that India has the perfect climate for the virus to spread exponentially.

Scientists trying to predict the future path of Zika say that 2.6 billion people living in parts of Asia and Africa could be at risk of infection, based on a new analysis of travel, climate and mosquito patterns in those regions. Some of the most vulnerable countries include India, China, the Philippines, Indonesia, Nigeria, Vietnam, Pakistan and Bangladesh, according to the research. It is an urgent awakening call for policy-makers and health planners, one that gently push them yet again, to invest in primary and preventive healthcare ahead of tertiary healthcare, well before an epidemic breaks out.

3.1. Formulation of Zika Epidemic Model

Mathematical models are powerful tools for gaining acute observation into the transmission and control of infectious diseases, and can be used to address important issue. Kucharski *et.al.* (2016) has used a compartmental mathematical model to simulate vector-borne transmission. Both human population and mosquitoes were modelled using a susceptible-exposed-infectious-removed (SEIR) framework. The model incorporated delays as a result of the intrinsic (human) and extrinsic (vector) incubation periods. Andraud *et.al.* (2012) developed a global R_0 model for ZIKV that explicitly includes two vector species and one host and considers the influence of climate dynamically. They extended a recently developed two-vector mathematical framework for an animal VBD to ZIKV and parameterize the model using some published estimates. They also drive the model using global observation-based historical climate data to derive global and seasonal estimates of the R_0 of ZIKV that describe transmission risk by one, the other, and both vectors where they co-occur. Olaniyi & Obabiyi (2013) considered transmission of ZikV between human-mosquito and human-human. They found that increasing the recovery to a very high rate has significant effect of reducing infection and isolation of infected individuals also reduces the transmission

of the ZikV infection. Also, the rate of human-induced deaths of mosquito should be increased. This can be achieved by reducing mosquito population through source reduction.

In this section, we will formulate an epidemic model for transmission of Zika virus motivated from the above work. To construct the model, we consider the following assumptions:

(i) The population is interacting homogeneously and well mixing.

(ii) Under high-risk total human population (N) is divided into four mutually exclusive classes, namely, a susceptible class (those at risk of contracting the disease) of size (S), exposed class (infected but not yet infectious) (E), Infected class (showing symptoms of Zika and capable of transmitting the disease) (I) and recovered class (infectious people who have cleared or recovered from Ebola) (R) and $N = S + E + I + R$.

Consequently, incorporating the adaptive behaviour of population mobility becomes

$$
\begin{aligned}
\frac{dS_h}{dt} &= A - \frac{\beta_h I_m}{1 + hI_m} S_h - \mu_h S_h = f_1, \\
\frac{dE_h}{dt} &= \frac{\beta_h I_m}{1 + hI_m} S_h - (\sigma_h + \mu_h) E_h = f_2, \\
\frac{dI_h}{dt} &= \sigma_h E_h - (\gamma_h + \mu_h) I_h = f_3, \\
\frac{dR_h}{dt} &= (1 - f)\gamma_h I_h - \mu_h R_h = f_4, \\
\frac{dS_m}{dt} &= M - \beta_m I_h S_m - \mu_m S_m = f_5, \\
\frac{dE_m}{dt} &= \beta_m I_h S_m - (\sigma_m + \mu_m) E_m = f_6, \\
\frac{dI_m}{dt} &= \sigma_m I_m - \mu_m I_m = f_7.
\end{aligned}
\tag{3.1}
$$

Table 3.1: Previously published estimates of parameters used for numerical simulations of Zika

Parameter	Description	Value	Reference
A	Recruitment rate of infected humans	0.0154	Kucharski *et.al.* (2016)
β_h	Transmission rate	0.0885	Dantas *et.al.* (2017)
μ_h	Death rate of humans	0.001	Assumed
σ_h	Incubation period of humans	0.2	De Castro Medeiros *et.al*. (2011)
h	Precaution constant	10.9	Assumed
γ_h	Recovery rate of humans	0.64	Kucharski *et.al.* (2016)
f	Fatality	0.5	Assumed
M	Recruitment rate of infected mosquitoes	0.07	Olaniyi & Obabiyi (2013)
β_m	Transmission rate	0.116	Dantas *et.al.* (2017)
μ_m	Death rate of mosquitoes	0.028	Andraud *et.al.* (2012), Chikaki & Ishikawa (2009)
σ_m	Incubation period of mosquitoes	0.0833	Andraud *et.al.* (2012), Boorman & Poterfield (1956)

3.2. Dynamical behaviour of the Zika Epidemic Model

In this section, we calculate all feasible steady states and basic reproduction number for the Zika epidemic model.

3.2.1. Possible equilibria and its existence criteria

There are only two equilibria exists for the epidemic model (3.1) namely, disease free (Q^0) and endemic equilibrium (Q^*).

(i) The system has disease free equilibrium (DFE) $Q^0 = \left(\frac{A}{\mu_h}, 0, 0, 0, \frac{M}{\mu_m}, 0, 0\right)$.

(ii) The system (3.1) also has an interior equilibrium called endemic equilibrium $Q^* = \left(S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*\right)$ exists; if and only if there is a positive solution to the following equations: $f_1 = 0$; $f_2 = 0$; $f_3 = 0$; $f_4 = 0$; $f_5 = 0$; $f_6 = 0$; $f_7 = 0$ given by

$$S_h^* = \frac{(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m) + A\beta_m\sigma_h(hM\sigma_m + \mu_m(\mu_m + \sigma_m))}{\beta_m\sigma_h(M\beta_h\sigma_m + \mu_h(\mu_m^2 + (hM + \mu_m)\sigma_m))},$$

$$E_h^* = \frac{AM\beta_h\beta_m\sigma_h\sigma_m - \mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m)}{\beta_m\sigma_h(\mu_h + \sigma_h)(M\beta_h\sigma_m + \mu_h(\mu_m^2 + (hM + \mu_m)\sigma_m))},$$

$$I_h^* = \frac{AM\beta_h\beta_m\sigma_h\sigma_m - \mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m)}{\beta_m(\gamma_h + \mu_h)(\mu_h + \sigma_h)(M\beta_h\sigma_m + \mu_h(\mu_m^2 + (hM + \mu_m)\sigma_m))},$$

$$R_h^* = \frac{(-1 + f)\gamma_h(-AM\beta_h\beta_m\sigma_h\sigma_m + \mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m))}{\beta_m\mu_h(\gamma_h + \mu_h)(\mu_h + \sigma_h)(M\beta_h\sigma_m + \mu_h(\mu_m^2 + (hM + \mu_m)\sigma_m))},$$

$$S_m^* = \frac{(\gamma_h + \mu_h)(\mu_h + \sigma_h)(M\beta_h\sigma_m + \mu_h(\mu_m^2 + (hM + \mu_m)\sigma_m))}{(h\mu_h(\gamma_h + \mu_h)\mu_m(\mu_h + \sigma_h) + \beta_h(A\beta_m\sigma_h + (\gamma_h + \mu_h)\mu_m(\mu_h + \sigma_h)))\sigma_m},$$

$$E_m^* = \frac{AM\beta_h\beta_m\sigma_h\sigma_m - \mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m)}{(A\beta_h\beta_m\sigma_h + (\gamma_h + \mu_h)(\beta_h + h\mu_h)\mu_m(\mu_h + \sigma_h))\sigma_m(\mu_m + \sigma_m)},$$

$$I_m^* = \frac{A\beta_h\beta_m M\sigma_h\sigma_m - \mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m)}{\mu_m(A\beta_h\beta_m\sigma_h + (\gamma_h + \mu_h)(\beta_h + h\mu_h)\mu_m(\mu_h + \sigma_h))(\mu_m + \sigma_m)}.$$

Theorem 1: The Zika epidemic model (3.1) has

(i) No endemic equilibrium (EE), if $\frac{\sqrt{A}\sqrt{M}\sqrt{\beta_h}\sqrt{\beta_m}\sqrt{\sigma_h}\sqrt{\sigma_m}}{\sqrt{\mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m)}} < 1.$

(ii) Unique endemic equilibrium if $\frac{\sqrt{A}\sqrt{M}\sqrt{\beta_h}\sqrt{\beta_m}\sqrt{\sigma_h}\sqrt{\sigma_m}}{\sqrt{\mu_h(\gamma_h + \mu_h)\mu_m^2(\mu_h + \sigma_h)(\mu_m + \sigma_m)}} > 1.$

3.3. Basic Reproduction Number

The basic reproduction number R_0 is defined as the expected number of secondary cases produced by a single infection in a completely susceptible population (van den Driessche & Watmough, 2002; Diekmann, 1990). This is useful because it helps to determine whether or not an infectious disease will spread through the population. Following, Driessche and Watmough (2002), we calculate the basic reproduction number.

Let *x = (E; I),* then from Zika epidemic (3.1), it follows:

$$\frac{dx}{dt} = F - V\ .$$

We obtain F_1 = Jacobian of F at DFE= $\begin{pmatrix} 0 & 0 & 0 & \frac{A\beta_h}{\mu_h} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{M\beta_m}{\mu_m} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$ and V_1 = Jacobian of V at

DFE= $\begin{pmatrix} \mu_h + \sigma_h & 0 & 0 & 0 \\ -\sigma_h & \gamma_h + \mu_h & 0 & 0 \\ 0 & 0 & \mu_m + \sigma_m & 0 \\ 0 & 0 & -\sigma_m & \mu_m \end{pmatrix}$

The next generation matrix for the epidemic model is given by $K = F_1 V_1^{-1}$

i.e. $K = \begin{pmatrix} 0 & 0 & \frac{A\beta_h\sigma_m}{\mu_h\mu_m(\mu_m+\sigma_m)} & \frac{A\beta_h}{\mu_h\mu_m} \\ 0 & 0 & 0 & 0 \\ \frac{M\beta_m\sigma_h}{(\gamma_h+\mu_h)\mu_m(\mu_h+\sigma_h)} & \frac{M\beta_m}{(\gamma_h+\mu_h)\mu_m} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$

The basic reproduction number, R_0, is defined as the spectral radius of the next generation matrix $K = F_1 V_1^{-1}$, i.e., $R_0 = \rho(F_1 V_1^{-1})$. Thus basic reproduction for the model (3.1) is given as $R_0 = \dfrac{\sqrt{A}\sqrt{M}\sqrt{\beta_h}\sqrt{\beta_m}\sqrt{\sigma_h}\sqrt{\sigma_m}}{\sqrt{\mu_h(\gamma_h+\mu_h)\mu_m^2(\mu_h+\sigma_h)(\mu_m+\sigma_m)}}$. (3.2)

3.4. Stability analysis of Zika Epidemic Model

Now, we are in a position to perform the stability analysis of the model system. The Jacobian matrix of the model system (3.1) is

$$\boldsymbol{J} = \begin{pmatrix} -\frac{I_m\beta_h}{1+hI_m} - \mu_h & 0 & 0 & 0 & 0 & 0 & -\frac{S_h\beta_h}{(1+hI_m)^2} \\ \frac{I_m\beta_h}{1+hI_m} & -\mu_h - \sigma_h & 0 & 0 & 0 & 0 & \frac{S_h\beta_h}{(1+hI_m)^2} \\ 0 & A\sigma_h & -\gamma_h - \mu_h & 0 & 0 & 0 & 0 \\ 0 & 0 & -(-1+f)\gamma_h & -\mu_h & 0 & 0 & 0 \\ 0 & 0 & -S_m\beta_m & 0 & -I_h\beta_m + \mu_m & 0 & 0 \\ 0 & 0 & S_m\beta_m & 0 & I_h\beta_m & -\mu_m - \sigma_m & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_m & -\mu_m \end{pmatrix}$$

3.4.1. Local stability of Disease free Equilibrium

In the section, we explore the local stability of the model system (3.1) around the disease-free equilibrium.

Theorem 2: The disease-free equilibrium (DFE) Q^0 is

(i) Locally asymptotically, if $R_0 < 1$; and unstable, if $R_0 > 1$.

(ii) Non hyperbolic equilibrium point at $R_0 = 1$.

Proof: The proof follows from definition of reproduction number R_0.

For example: for the system parameters $A = 0.0154$, $\beta_h = 0.0885$, $\mu_h = 0.001$, $\sigma_h = 0.2$, $h = 10.9$, $\gamma_h = 0.64$, $f = 0.5$, $M = 0.07$, $\beta_m = 0.116$, $\mu_m = 0.028$, $\sigma_m = 0.0833$, $R_0 = 4.04$, no disease free equilibrium exists only endemic equilibrium i.e. $S_h^* = 2.5936$, $E_h^* = 0.0637$, $I_h^* = 0.0198$, $R_h^* = 6.3613$, $S_m^* = 2.3097$, $E_m^* = 0.0478$, $I_m^* = 0.1423$ exists. Whereas, for the system parameters $A = 0.0154$, $\beta_h = 0.0885$, $\mu_h = 0.001$, $\sigma_h = 0.2$, $h = 10.9$, $\gamma_h = 0.64$, $f = 0.5$, $M = 0.07$, $\beta_m = 0.116$, $\mu_m = 0.28$, $\sigma_m = 0.0833$, $R_0 = 0.22$, only disease free equilibrium i.e $S_h = 2.5$, $E_h = 0$, $I_h = 0$, $R_h = 0$, $S_m = 15.4$, $E_m = 0$, $I_m = 0$ exists.

Thus, if $R_0 < 1$, all the nearby trajectories of the system starting from various initial conditions approach Q^0.

3.5. Sensitivity analysis

In order to determine how best we can reduce human morbidity and mortality due to Zika virus, it is necessary to know the relative importance of the different parameters responsible for its transmission and prevalence. Initially, disease transmission and prevalence are directly related to the basic reproduction number, R_0, and the endemic equilibrium point Q^*, specifically to the magnitude of I_h and I_m respectively. We calculate the sensitivity indices of the reproductive number, R_0, and the endemic equilibrium point I^* (I_h and I_m), to the parameters in the model.

These indices indicate how crucial each parameter is to disease transmission and prevalence. Here, we use it to find parameters that have a high impact on R_0 and Q^*, and should be targeted by intervention strategies.

Definition: The normalised forward sensitivity index of a variable, w that depends on a parameter p, is defined as $\gamma_p^w = \frac{\partial w}{\partial p} \times \frac{p}{w}$

3.5.1. Sensitivity indices of R_0

In this section, our aim is to determine the uncertainty of R_0 based on the uncertainty of the input. As we have an explicit formula for R_0 given in equation (3.2), we can derive an analytic expression for the sensitivity of R_0 as $\gamma_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}$ for each parameter. Here, we evaluate the sensitivity indices at the baseline parameter values given in Table 3.1. The resulting sensitivity indices of R_0 to the nine different parameters in the model are shown in this table.

Table 3.5.1: The sensitivity indices, $\gamma_{p_j}^{R_0} = \frac{\partial R_0}{\partial p_j} \times \frac{p_j}{R_0}$, of the basic reproduction number R_0 to the parameters, p_j.

Parameters (p_j)	A	β_h	μ_h	σ_h	γ_h	M	β_m	μ_m	σ_m
Sensitivity index of R_0	0.5	0.5	-0.5032	0.0024	-0.4992	0.5	0.5	-1.1257	0.1257

The most influential parameter is the death rate of mosquitoes μ_m. Since $\gamma_{\mu_m}^{R_0}$ = - 1.1257, increasing (decreasing) μ_m by 10% decreases (or increases) the value of R_0 by 11.27%. Similarly, the second most influential parameter in determining the value of R_o are transmission rates β_m, β_h and recruitment rates *M, A,* as shown in Table 3.5.1. Since $\gamma_{\beta_h,\beta_m,M,A}^{R_0}$= 0.5, increasing (decreasing) β_h, β_m, M, A by 10% increases (or decreases) the value of R_0 by 5%.

3.5.2. Sensitivity indices of Q^*

Again we perform sensitivity analysis of the state variables (I_h and I_m) with respect to the model parameters. Sensitivity indices of the state variable (I_h and I_m) at endemic equilibrium are shown in Table 3.5.2 and 3.5.3. From these table, we observe that all the parameters have positive impact on I_h and I_m except μ_h, μ_m and γ_h. In this study, we have identified the most important parameters that drive the transmission mechanism of disease in Brazil. The identification of these parameters is vital in formulating control strategies effective for fighting the disease. The result of sensitivity analysis suggest that a strategy which reduces the recruitment rate of human (*A*) and the transmission rate (β_h) of Zika infection in the community and the strategy which increases the recovery rate (γ_h) would be quite effective in restricting the spread of the disease in Brazil. We also observe that the increased death rate of mosquitoes will reduce the disease. Women should avoid becoming pregnant while travelling in areas with active Zika virus transmission. Prevent mosquito breeding around houses and use mosquito killing spray.

Table 3.5.2: The sensitivity indices, $\gamma_{p_j}^{I_h} = \frac{\partial I_h}{\partial p_j} \times \frac{p_j}{I_h}$, of I_h to the parameters, p_j.

Parameters (p_j)	A	β_h	μ_h	σ_h	γ_h	M	β_m	μ_m	σ_m
Sensitivity index of I_h	1.064	0.179	-0.186	0.005	-1.064	0.070	0.064	-0.152	0.017

Table 3.5.3: The sensitivity indices, $\gamma_{p_j}^{I_m} = \frac{\partial I_m}{\partial p_j} \times \frac{p_j}{I_m}$, of I_m to the parameters, p_j.

Parameters (p_j)	A	β_h	μ_h	σ_h	γ_h	M	β_m	μ_m	σ_m
Sensitivity index of I_m	0.983	0.165	-0.172	0.004	-0.982	1.064	0.983	-2.316	0.267

3.6. Numerical Simulation

The ODEs were integrated using Runge–Kutta method in the MATLAB R2017a software environment. The first case for the current Brazil epidemic of Zika virus disease was reported in May 2015. Therefore, we have considered the starting point of the simulation from this date. We have used the value of parameter from past in such a way that the basic reproduction number, R_0, matches with early estimates of R_0. We have taken the initial condition as: $S_h(0) = 2095670$; $E_h(0) = 70$; $I_h(0) = 50$; $R_h(0) = 0$; $S_m(0)= 1000$; $E_m(0)= 50$; $I_m(0)= 5$.

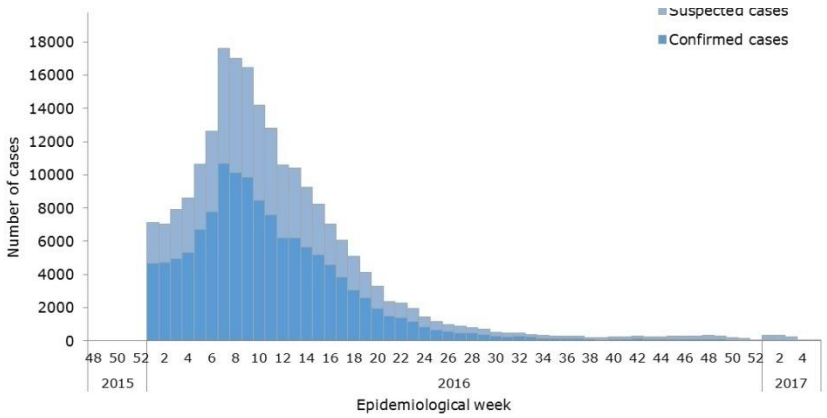


Figure 1(a): Suspected and confirmed cases of Zika virus in Brazil (Data is not available for 2015 because Zika disease was not made a reportable disease by the Brazil Ministry of Health until February 17, 2016).

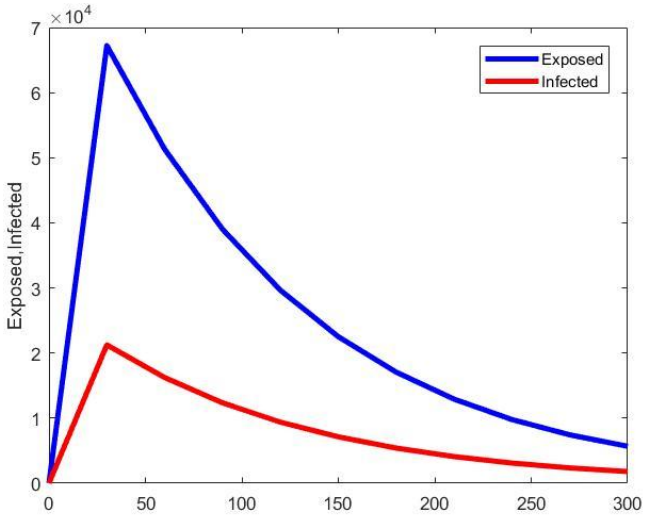


Figure 1(b): Exposed and infected cases of population at Brazil for the parameter values given in Table 3.1

This section compares the model prediction simulations to the observed data available from CDC. The correspondence between predicted and observed appears quiet good for Brazil. Simulation result for Brazil in Figure 1(b) shows only one wave, roughly in agreement with the recently available data presented in Figure 1(a). From Figure 1(b) one can observe that the simulated peak month of infection is March 2016, and will decline after approximately one year.

3.6.1. If Zika comes to India?

On 15 May 2017, the Ministry of Health and Family Welfare-Government of India (MoHFW) reported three laboratory-confirmed cases of Zika virus disease in Bapunagar area, Ahmedabad District, Gujarat, State, India. As per various scientists, the mosquito which are responsible for the diseases, become stronger during summer and the hotter it gets the better it carries the virus, making India more suitable place for the growth and prevalence of Zika virus. Since India provides fertile climate for the *Aedes* mosquito to grow and multiply, there is the potential of an outbreak situation in the country. The mosquito also carries dengue and chikungunya viruses that claim 100s of lives and infect 1000s every year. There could be a lack of population immunity against the virus in newly affected areas. We fed our model the initial conditions of Zika transmission to get an overview of what might come if it arrives to India. The following graph shows that it might take more than 300 days before we get rid of the disease.

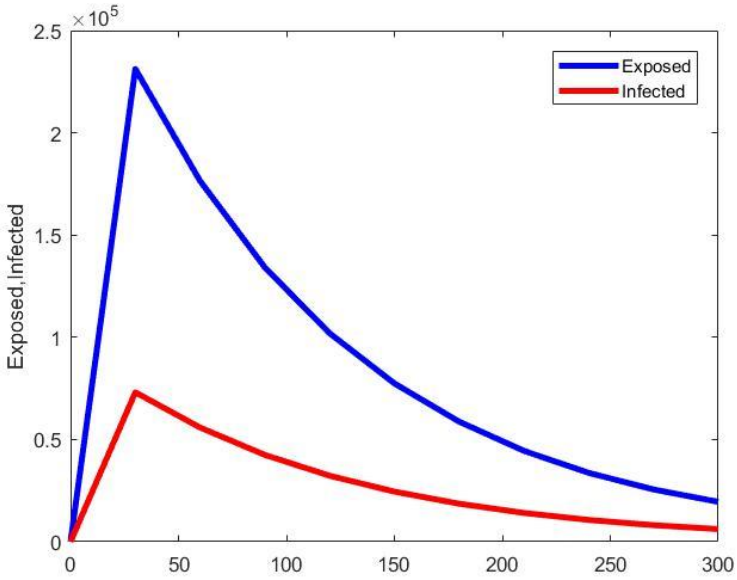


Figure 2: Simulated exposed and infected cases in Ahmedabad for the parameter values given in Table 3.1.

Recently, according to a report (http://www.brazilgovnews.gov.br/news/2017/03/brazil-sees-significant-drop-in-dengue-chikungunya-and-zika-cases), the number of Zika incidence cases in Brazil has observed a drop of about 97.6% in the first few months of this year as compared with the same period last year due to awareness and use of control measures. In our model, we have taken *h* as a precaution constant which denotes the control measures being taken. We can see that as we increase *h*, there is a significant drop in the number of exposed and infected population. This figure indicates that practical interventions to address the ongoing Zika epidemic may have beneficial impact on public health, but they will not result in immediate halting, or even obvious slowing of the epidemic. A long term commitment of resources and support is necessary to address Zika outbreak. This simulation result also shows how control and prevention can slow down and eventually stop the epidemic by end of July 2018.

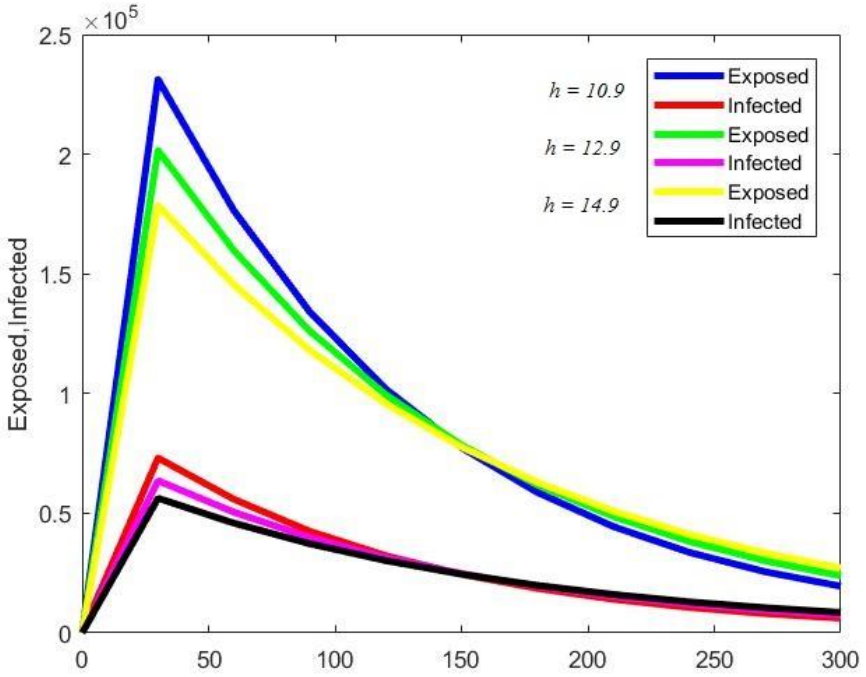


Figure 3: Exposed and Infected population if precaution constant *h* is increased.

3.7. Discussion and Conclusion

Zika is a multidimensional global public health concern. Concerns about the potential emergence of Zika into currently uninfected countries are justified in light of the 2016 outbreak of Zika in Brazil. Prevention and control relies on reducing mosquitoes through source reduction (removal and modification of breeding sites), and reducing contacts between mosquitoes and people.

Mathematical models for transmission dynamics of mosquito-borne diseases can be useful in providing better insights into the behaviour of this disease. The models have played great roles in influencing the decision making processes regarding intervention strategies for preventing and controlling the insurgence of mosquito-borne diseases. Global change dynamics involving increased interconnectivity via air-passenger travel and alterations in environmental conditions due to climate change are reinforcing the concern for high resource setting in temperate areas more than ever before. An SEIR Zika epidemic model is proposed and analyzed using nonlinear stability theory. The model exhibits two biological feasible equilibria, the disease free and endemic equilibrium. The finding in this work can be used to predict the number of future Zika cases which can be controlled. A model of infectious diseases has been developed to assess the interdependencies of critical infrastructures placed under stress by disease outbreaks and to instruct

recommendations regarding control measures. The results of sensitivity analysis show that the sensitive inputs to the infectious disease model match our prior expectations – death rate of mosquitoes and the transmission rates.

Chapter 4

SUMMARY AND CONCLUSIONS

"A conclusion is simply the place where you got tired of thinking."
Dan Chaon

The thesis consists of four chapters in which second and third chapter discusses the mathematical models for human infectious disease Ebola and Zika and shows the impact of control measure if implemented.

Chapter 2 attempts to model the Ebola virus dynamics using an SEIR model to better understand and characterize the transmission trajectories of the Ebola outbreak. In Chapter 3, we try to model the dynamics of Zika virus by again using an SEIR model to identify the most important parameters that drive the transmission mechanism of the disease.

Both models are analyzed using different tools of dynamical system theory, namely, Routh-Hurwitz criteria, etc. Epidemic threshold like basic reproduction number (R_0) is calculated for the model. It is observed that in the system, the disease-free equilibrium is locally asymptotically stable if associated control reproduction is less than unity.

Numerical experimentation is performed for the proposed systems taking biologically relevant parametric values to support our analytical findings. Furthermore, sensitivity analysis result in Chapter 2 and 3 showed that transmission rate, recruitment rate and population mobility are the most sensitive parameters. The model indicates that the disease will decline after peaking up if multinational efforts to control the spread of infection are maintained. Also, the model in Chapter 3 indicates that if the Zika virus hits India, there is a potential of an outbreak in the country. It would take more than 300 days to get rid of the disease. Therefore, we need to take precautions and control measures if we want to avoid an epidemic.

One aspect overlooked in both chapters is that the changes in incident rate can be a function of the factors that are extrinsic to the infection, such as host behavioral change or seasonal change in climate. Seasonal change can further complicate patterns of incidence. Furthermore, our knowledge of the values of many parameters in the transmission process is poor and therefore it is difficult to promise absolute accuracy. Accurate quantitative

prediction of parameters is practically impossible, particularly given the potential complexities of dynamic wildlife host population as mentioned above.

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