A MATHEMATICAL MODEL FOR ZIKA VIRUS AND THE EFFECTS OF VARIABLE INFECTIVITY ON THE ASYMPTOMATIC AND SYMPTOMATIC INFECTED HUMAN

By

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El Zika es una enfermedad infecciosa desarrollada por el Virus del Zika (ZIKV por sus siglas en ingles), la cual ha estado, alertando a las regiones tropicales y subtropicales en los últimos años. La enfermedad es conocida como una infección que puede ser trasmitida por vía sexual o mediante un vector, en este caso un mosquito [4].

Es muy conocido que los síntomas son señales que permiten deducir el desarrollo de algún tipo de enfermedad. Sin embargo, no siempre el cuerpo humano produce síntomas cuando es atacado por un virus o bacteria. Este es el caso de enfermedades asintomáticas, pues son difíciles de diagnosticar y en consecuencia de tratar. Desafortunadamente, en muchos casos, las infecciones asintomáticas son detectadas cuando la enfermedad ya ha causado mucho daño de forma silenciosa.

El Zika es una enfermedad sintomática en el 20% de los casos y asintomática en el restante 80%. Debido a esto y con la motivación de trabajos anteriores, en esta investigación se estudia la dinámica de la transmisión vectorial y sexual del ZIKV considerando individuos infectados sintomáticos y asintomáticos. El modelo

propuesto incluye un parámetro de alteración de infecciosidad, el cual permitirá estudiar todos los posibles casos de infecciosidad desconocida al presente, analizar su efecto en la población y entender el rol de los asintomáticos, no solo bajo transmisión vectorial, si no también por transmisión sexual. Para esto, se formuló y estudió un modelo matemático epidemiológico compuesto de ocho estados. Los ocho estados representan las diferentes etapas que un humano y un mosquito con el ZIKV puede experimentar. Se obtiene el número reproductivo básico R_0, se realiza el análisis cualitativo y numérico del sistema para valores de parámetros tomados de la literatura, así como también, se realiza el análisis de sensibilidad de parámetros al R_0. Existen dos puntos de equilibrio en el sistema, el libre de Zika y el endémico. El análisis numérico predice una epidemia, donde el número de infectados (incidencia) puede crecer o decrecer dependiendo de los valores asignados a cada parámetro. Por lo tanto, esfuerzos para controlar una epidemia podrían enfocarse en reducir la tasa de infección de mosquito a humano, la tasa de transmisión sexual y controlar de manera oportuna la cantidad de individuos asintomáticos en la población. Cuando el numero reproductivo básico de transmisión vectorial es mas grande que el de transmisión sexual hay un retardo en el que el virus invada la población y bajo este escenario existen oportunidades para prevenir una epidemia del ZIKV con medidas preventivas como insecticidas, repelentes, condones, etc. R_0 es mas sensitivo a la tasa de mortalidad del mosquito y a la tasa de transmisión vectorial, por lo tanto la mejor manera de prevenir y controlar un brote del ZIKV es disminuyendo el número de mosquitos en la población e iniciando campañas para que cada individuo elimine los criaderos. Esta investigación también sugiere campañas para detectar los infectados (ya sea asintomáticos o sintomáticos) por el ZIKV y aislarlos, a tiempo.

Abstract of Dissertation Presented to the Graduate School
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Zika is an infectious disease developed by the Zika Virus (ZIKV), which has been alarming people during the last few years in tropical and subtropical regions. It is known as an infection that can be transmitted both sexually and through a vector, in this case a mosquito [4].

It is well known that symptoms are signals that allow to deduce the development of some type of disease. However, the human body does not always produce symptoms when attacked by a virus or bacterium. This is the case of asymptomatic diseases, a fact that makes them difficult to diagnose and, in consequence, to treat. Unfortunately, in many cases, the asymptomatic infected are detected when the disease has done much damage silently.

Zika is symptomatic in the 20% of cases and asymptomatic in the remaining 80%. Because of this and through the motivation of previous works, this research analyzes the dynamics of the vector and sexual transmissions of ZIKV in symptomatic and asymptomatic infected individuals. The model proposed includes a parameter of alteration of infectiousness that will allow to study all possible cases

of presently unknown infections, to analyze its effect on the population, and to understand the role of asymptomatic humans, not only under vector transmission but also considering sexual transmission. Thus, a mathematical epidemiological model composed of eight stages was formulated and studied. The eight stages represent the different phases that humans and mosquitoes with ZIKV may experience. The basic reproductive number R_0 was obtained and the qualitative and numerical analysis of the system were done for values of parameters taken from the literature, as well as the sensitivity analysis of parameters, thus obtaining two equilibrium points, the Zika-free equilibrium and the endemic equilibrium. The numerical analysis predicts an epidemic, where the number of infected can grow or decrease depending on the value of key parameters. Therefore, efforts to control an epidemic could focus on reducing the mosquito-to-human infection, sexual transmission rate, and the control, in a timely manner, of the number of asymptomatic individuals in the population. When the vector transmission ratio is larger than the sexual transmission ratio, there is a time delay for ZIKV to invade the population. Under this scenario there is a window of opportunities to prevent an epidemic of ZIKV with preventive measures, such as insecticide, repellents, condoms, among others. R_0 is more sensitive to the mosquito mortality rate and vector transmission rate; therefore, the best way to prevent and control an outbreak of the ZIKV is by decreasing the number of mosquitoes in the population and initiating campaigns for each individual to eliminate the breeding sites. This research also suggests campaigns to detect those infected-whether asymptomatic or symptomatic-with the ZIKV and isolate them on time.

To my parents, To the University of Puerto Rico, Mayagüez Campus

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LIST OF SYMBOLS

ZIKV	Zika Virus
DENV	Dengue Virus
CHIKV	Chikungunya Virus
CDC	Centers for Disease Control and Prevention
WHO	World Health Organization
SIR	Susceptible-Infected-Recovered
SEI	Susceptible-Exposed-Infected
R_0	Basic Reproductive Number
R_d	Direct transmission threshold
R_v	Vector transmission threshold
R_s	Basic Reproductive Number for Symptomatic Humans
R_a	Basic Reproductive Number for Asymptomatic Humans
DFE	Disease Free Equilibrium
HPV	Humans Papillomavirus
GBS	Guillain Barre syndrome
SI	Sensitivity Index

Chapter 1
INTRODUCTION

One of the main public health concerns are diseases of vector transmission which are organisms that transmit pathogens and parasites, such as mosquitoes, These diseases represent 17% of the estimated global burden of infectious diseases [34]. They are transmited from person to vector to person and from vector to person to vector. Some examples of vector borne diseases are **Zika**, dengue, schistosomiasis, lymphatic filariasis, yellow fever and malaria, among others. The most deadly being malaria, which caused an estimated 429000 deaths in 2015 worldwide [34]. On the other hand, currently there are more than 30 types of viruses, bacterias, and parasites which are transmitted through sexual contacts. The World Health Organization (WHO) reports that more than 1 million individuals get infected by some sexual transmission infection every day. Some of these sexually transmitted diseases are genital herpes, gonorrhea, HIV-AIDS, human papillomavirus (HPV), and syphilis, among others and now **Zika** [35].

Zika is an infectious disease that has turned emergency alarms in the last few years in tropical and subtropical regions. The Zika Virus (ZIKV) develops Zika fever or Zika disease. Its name comes from the Zika forest (in Uganda) where in 1947 this virus was first isolated [29]. In 2007, a major epidemic occurred in Yap Island, Micronesia; and more recent outbreaks ocurred, in 2013 in French Polynesia [29] and in 2016 in Puerto Rico. In March of 2017 the Puerto Rico Department of Health reported (for the years $2015-2017$), $39,984$ cumulative confirmed Zika cases

in the island. The reports also showed 3,448 cases from **pregnant women** (only) of whom 1,898 (55%) were symptomatic and 1,550 (45%) were asymptomatic. It was also reported that there were 415 (< 1%) hospitalized cases [13]. It is also known that ZIKV can be transmitted from a pregnant woman to her fetus [10]. In addition, serious defects are associated with children born of an infected mother [24]. According to WHO, in Brazil, the spread of ZIKV has been accompanied by an unprecedented rise in number of children being born with unusually small heads, know as microcephaly. Also in Brazil, WHO reported a steep increase in Guillain Barre Syndrome (GBS) a neurological disorder that could lead to paralysis and death. Thus, there is scientific consensus that ZIKV can cause microcephaly and Guillain Barre syndrome [36]. For example, the Puerto Rico Department of Health informed that in August 2017 there were 72 cases of GBS of which 53 of them had Zika [13].

ZIKV is ***now known as the first example of an infection that can be transmitted both sexually and through mosquitoes*** [4], as well as, perinatally and by blood-transfusions. The principal vector of Zika is the infected female mosquitoe of the flavivirus genus of name ***Aedes aegypti***, the same mosquito that transmits dengue [25] and chikungunya fever. ZIKV is the first flavivirus known to be of sexual transmission [8]. It was in February 2016 that the Centers for Disease Control and Prevention (CDC) first reported two confirmed cases of sexual transmission of ZIKV [32]. The CDC also informed that Zika has been found in the semen, vaginal fluids, urine and blood of those infected with the virus.

Figure 1–1 shows the cycle of the sexual and mosquito transmission of the ZIKV. An infected female mosquito bites a susceptible human, which may get infected with the virus, then the infected human can transmit the virus, through sexual contact to susceptible persons or to mosquitoes not infected through its bite.

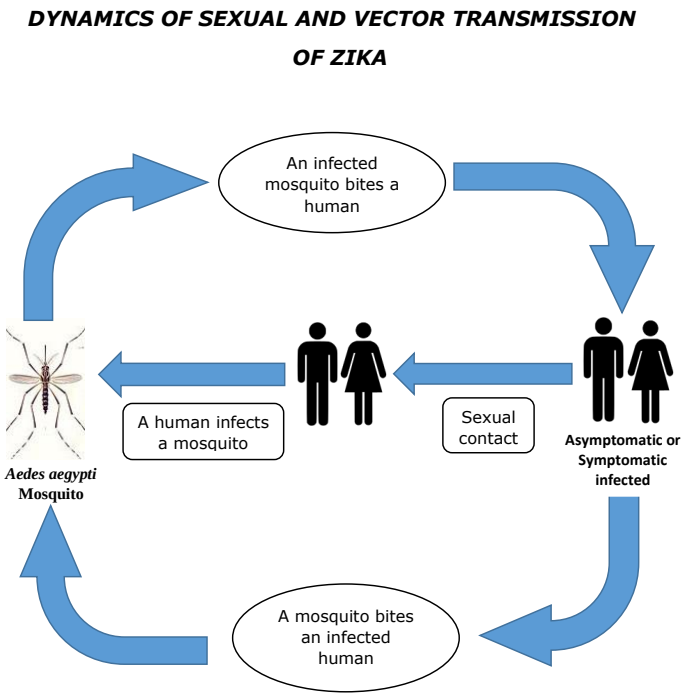

Figure 1–1: Dynamics of direct and vector transmission of Zika disease.

Zika is a disease of great scientific interest. It has no vaccine, no treatment, medicines that heal the patient's burden. But the medical school of the Medical Science Campus of the University of Puerto Rico, led by Dr. Jorge Santana, reported in October 2016 that they are in charge of the research study called *ZIKA 002*, which purpose is to evaluate the safety of a vaccine called *GLS -5700* for the prevention of infection caused by the Zika virus and if this vaccine produces an immune response to this disease [7]. Valega, W. and Rios-Soto, K. [33] developed studies from a mathematical model to understand the effects of a possible vaccine against Zika in a the spread of the virus through the population. Some ways to prevent the spread of Zika's disease are: avoiding conserved water in containers that can become mosquito breeding sites, use of mosquito repellents, and use of mosquito protection on windows and beds. Sexual transmission can be prevented through the use of condoms, taking preventive measures when traveling to areas with Zika.

1.1 Symptomatic versus asymptomatic infection and their infectivity

When detecting the presence of pathogens, the human body manifests a warning or signal that allows to deduce the development of some type of disease, which cause is the presence of this agent in the body. These signs are called symptoms. Therefore symptomatic infected individuals are the carriers of infectious agents and, hence, manifest symptoms. Symptoms indicate the type of infectious agent that is invading the human body (producing the disease) which allows to impose the infected symptomatic to some form of treatment, to cure or control the disease and, in some cases, to control a possible outbreak.

However the human body does not always, in the presence of an infectious agent, produce warnings or develops symptoms. This is called asymptomatic disease (without symptoms), where the carrier is called an asymptomatic infected individual. This makes it difficult to detect the presence of this pathogen. Unfortunately, in many cases, the asymptomatic infected are detected when the disease has done much damage silently, when it has developed completely, and it is too late to prevent the disease or its spread through the population.

Zika is a sexually and vector transmitted disease that in 20% of cases is symptomatic and in the remaining 80% is asymptomatic ([3],[26]), making Zika more difficult to diagnose and, in consequence, to treat. The most common symptoms of Zika are fever, rash, join pain, conjunctivitis (red eyes), muscle pain, and headache. The period of incubation of the virus in humans is 3 to 12 days while the symptoms appear from 2 to 7 days in symptomatic patients. A person acquires permanent immunity when he or she recovers from the disease.

According to the multilingual glossary of medical terms [21], infectivity refers to the ability of a infected individual to transmit and establish the infection in another susceptible individual. We can interpret this definition as in that if individual A is more infectious than B, it means that A has the power to infect more individuals

than B since contagion is more likely. An example that allows us to understand this concept, but does not relate to the content of the research, is: if two people, A and B, like to drink alcohol but the amount that A takes is much greater than the one that B takes, then, person A likes more alcohol than B, so it could be that A can influence more people to drink alcohol than B. Therefore A is more infectious than B.

In this research we study through a mathematical model, the dynamics of the vector and sexual transmissions of Zika under symptomatic and asymptomatic infected individuals. As described by, Moreno, V., et. al. [26], there is no full knowledge of the dynamics of Zika transmission. Thus, they assumed that symptomatic and asymptomatic humans are equally infectious. Other authors such as P. Padmanabhan [30] conducted their research under similar assumption. Therefore for our work and motivated by previous investigation, a parameter of alteration of infectiousness was added to the model allowing to study all possible cases of infections i.e a variable infectiveness (less, equal o greater) and to understand its effects on population. It will also focus on understanding the role of asymptomatic humans in an outbreak of Zika, not only under vector transmission, which Moreno et. al did not [26], but also considering direct transmission (sexual), which would broaden the knowledge about the ZIKV spread.

1.2 Objectives

The aim of this thesis work is to study the role that symptomatic and asymptomatic individuals have in the propagation of Zika Virus (ZIKV) under direct and vectorial transmission with infectious variability. For this we have proposed the following objectives:

- Formulate a mathematical model consisting of a system of non-linear ordinary differential equations to describe the spread of Zika virus in a population considering asymptomatic and symptomatic individuals under sexual and vector transmission.
- Compute the equilibria of the system and characterize their stability.
- To determine the basic reproductive number R_0 associated with the ZIKV disease.
- Perform numerical simulations to verify the theoretical results obtained.
- Perform sensitivity analysis to identify key parameters of the model.
- Analyze and interpret the epidemiological consequences of the results obtained.

Chapter 2
MATHEMATICAL MODELS OF ZIKA DISEASES

The use of mathematical models of infectious diseases has been of great interest to scientists and health professionals. Mathematical modeling is the formulation, for example through differential equations, of the relationships between variables or parameters of epidemics processes and to study the behaviors of infectious disease. Models can play an important role in the construction, planning and execution of programs for the detection, prevention and control of diseases.

The pioneer mathematical epidemic model was built by Kermack and McKendrick [23] and since then variations have been implemented throughout. There are four basic models of infectious diseases, although there are well known variations of these among the literature (see Hethcote H.W. (1994) "A Thousand and One Epidemic Models" [19]):

- SI: A susceptible-infected model describes when a susceptible individual (who may be infected by the infectious agent) has no immunity to the disease. When an individual is infected it becomes infectious and therefore can infect other individuals of the susceptible population.
- SIR: A susceptible-infected-recovered model is related with diseases that confer permanent immunity and describes when a susceptible individual is infected and gets recovered. An individual can go directly from S to R through artificial immunity, by vaccination or some other method.

- SIS: A susceptible-infected-susceptible model describes when a susceptible individual who is infected can be susceptible to infection again. This type of model is used in cases where the disease does not confer immunity.
- SIRS: A susceptible-infected-recovered -susceptible model is similar to the SIR model. But in this case the immunity is not permanent and an individual is again susceptible to infected (for example a common cold).
- SEIR: A susceptible-exposed-infected-recovered -susceptible model is similar to the SIR model. But in this case there is a new stage, the Exposed individual, which is when an individual acquires the virus but it is in an incubation period for a significant period of time, and typically not able to transmit the disease to others.

Numerous efforts have been made to understand sexually and vectorial transmitted diseases, in particular applying mathematical modeling. The follow is a selection of some important work relevant to this thesis.

In 1998 Lourdes Esteva and Cristobal Vargas formulated a mathematical model to analyze the dengue disease transmission in a constant human population and variable vector population. The authors studied the global stability of the endemic equilibrium and stability of periodic orbits and discussed the control measures of vector population, as well as through the basic reproductive number with some numerical simulations. The model consisted of 5 ordinary differential equations: 3 associated to the human population with a SIR type of behavior and 2 associated to the vectorial population with an SI behavior. The authors concluded that decreasing the carrying capacity of the environment for mosquitoes by frequent reduction of the vector breeding sites, seems to be the more effective way to control the disease. [17].

In June 2016, Gao D. et. al. [18] proposed a non-linear system of differential equations as a mathematical model to investigate the impact of mosquito-borne and

sexual transmission on the spread and control of ZIKV and calibrated the model to ZIKV epidemic data from Brazil, Colombia, and El Salvador. They considered that, an individual may progress from susceptible (S_h) to asymptomatically infected (A_h) to recovered (R_h), or from susceptible to exposed (E_h) to symptomatically infected (I_{h1}) to convalescent (I_{h2}) to recovered (R_h). On the other hand mosquitoes may progress from susceptible (S_v) to exposed (E_v) to infectious (I_v). In there model, Gao D et. al., assumed that mosquitoes can not be infected by biting asymptomatically ZIKV infected people. They estimated the basic reproductive number to be 2.005, perform a sensitivity analysis for it, obtaining that R_0 is most sensitive to the biting rate and mortality rate of mosquitoes. The author also concluded that if sexual transmission increases the risk of infection and epidemic size also increases, prolonging the outbreak. Prevention and control efforts against ZIKV should target both the mosquito-borne and sexual transmission routes.

Note that Gao D. et. al. considered that a mosquito can not be infected by an asymptomatic individual and also consider the immediate step from susceptible to asymptomatic. The model proposed in our research, considers that a mosquito can be infected by an asymptomatic individual and that the only difference between an asymptomatic and symptomatic individual is that the first one does not present symptoms but has the virus and the second has symptoms, this means, that both type of individual go through a state of exposition to ZIKV and progress thought the disease.

In August of 2016, Fred Brauer, et. al. [4], proposed and analyzed some models for epidemics of vector-transmitted diseases among them:

$$S' = -\beta S\frac{I_v}{N_v} - \alpha S\frac{I}{N}, \tag{2.1}$$

$$E' = \beta S\frac{I_v}{N_v} + \alpha S\frac{I}{N} - kE, \tag{2.2}$$

$$I' = kE - \gamma I, \tag{2.3}$$

$$S'_v = \mu N_v - \mu S_v - \beta_v S_v\frac{I}{N}, \tag{2.4}$$

$$E'_v = \beta_v S_v\frac{I}{N} - (\mu+\eta)E_v, \tag{2.5}$$

$$I'_v = \eta E_v - \mu I_v, \tag{2.6}$$

where $N = S + E + I$ and $N_v = S_v + E_v + I_v$ are constant populations.

The authors considered that sexual transmission of the ZIKV was possible, however according to the CDC and WHO the sexual transmission is now confirmed [4]. The model was analyzed to clarify the relationship between sexual and vector transmission. It was also formulated to assess epidemiological consequences and to provided qualitative and quantitative behavior including calculations of the basic reproductive number (R_0), all insights for better comprehension of the ZIKV. The basic reproductive number found by Brauer, et. al. was:

$$R_0 = \beta\beta_v\frac{\eta}{\mu\gamma(\mu+\eta)} + \frac{\alpha}{\gamma},$$

in which they identify $R_d = \dfrac{\alpha}{\gamma}$ as the vector transmission reproduction number and $R_v = \beta\beta_v\dfrac{\eta}{\mu\gamma(\mu+\eta)}$ as the direct transmission reproduction number, so that $R_0 = R_v + R_d$.

In October 2016, Baca-Carrasco D. and Velasco-Hernandez J. [5] proposed three mathematical models, in which vector transmission of the virus, sexual contact transmission and migration were considered. The first is a SEIR-Vector Model, the second is a two-sex SIR-Vector Model in where, they distinguish between the,

male and female populations. The third model the Two-Sex SIR-Vector Model that includes the role of migration in behavior of the virus when there is migration of the infected population. They performed numerical simulations of the model showing that sexual transmission influences the magnitude of the outbreaks and migration generates outbreaks over time.

Note that although different type of models are propose, none of these discussed consider the case of infected symptomatic and asymptomatic individual; and their infectiousness in general.

Moreno V. et. al. in December 2016, [26], proposed a model in which susceptible individual (S_h) become infected through a mosquito bite them becomes an exposed individual (E_h) of which, it passes to a state of asymptomatic individual ($I_{h,a}$) and symptomatic ($I_{h,s}$) which finally recover (R_h). On the other hand borne mosquitoes are susceptible (S_v) then become exposed (E_v) by stinging any of the humans infected with the ZIKV and the progressing to, infected mosquitoes (I_v). Note that the authors do not consider sexual transmission and assume that the infected symptomatic and asymptomatic have equal infectiousness. In our research, we consider the sexual transmission of the ZIKV and incorporate a parameter to account for the infectivity of the two types of infected individuals in the population, asymptomatic and symptomatic.

Chapter 3
MATHEMATICAL BACKGROUND

The analysis of the system of differential equations that models the Zika transmission dynamics considered in this work is basically done according to the theories, techniques, and methods developed in [6], [14] ,[15], [16], [20], [27], and [37] from which definitions, theorems, and sections have been taken to support the purpose of this work.

3.1 Definitions and Basic Theorems

In the development of this investigation, differential equations of the form

$$x'(t) = f(x), \tag{3.1}$$

are considered, where f is a vector field of **class** C^1, that is, f is a continuous function with continuous first partial derivatives in an open U set of $\mathbb{R}^n$. A differential equation of this class in which the function f does not explicitly depend of the independent variable t is called **autonomous**.

A **solution** of the Equation (3.1) in the interval $I \subset \mathbb{R}$ is a function $x(t)$

$$x : I \to \mathbb{R}^n,$$

continuously differentiable, which satisfies the Equation (3.1).

Theorem 1. ***Existence and Uniqueness****([20], Ch. 8, Sec. 2).*

Let U be an open subset of $\mathbb{R}^n$, x_0 a point in U, and f an application of class C^1 in U, then there exists an $a > 0$ such that the initial value problem

$$\begin{aligned} x' &= f(x), \\ x(0) &= x_0, \end{aligned} \tag{3.2}$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

Definition 3.1.1. *Let U be an open subset of $\mathbb{R}^n$ and f an application of class C^1 in U. For x_0 in U we denote $\phi(t, x_0)$ the solution of the Initial Value Problem (3.2) defined over a maximal interval of existence I. For t in I, the set of applications*

$$\phi_t : U \to U,$$

*defined as $\phi_t(x_0) = \phi(t, x_0)$, is called the **flux** of the differential equation, Equation (3.1).*

Definition 3.1.2. *Let U be an open set of $\mathbb{R}^n$, $f \in C^1(U)$, and $\phi_t : U \to U$ the flux of the Differential Equation (3.1) defined for all $t \in \mathbb{R}$. $\Omega \subset U$ is called **invariant** with respect to the flux if $\phi_t(\Omega) \subset \Omega$ for all $t \in \mathbb{R}$, and Ω is called **positively (or negatively) invariant** with respect to the flux if $\phi_t(\Omega) \subset \Omega$ for all $t \geq 0$ (or $t \leq 0$).*

One way to consider the qualitative analysis, locally, of the differential equation (3.1) is to use its linearization. This illustration is given below.

Definition 3.1.3. *Let $\overline{x}$ be a point in U. $\overline{x}$ is an **equilibrium point** of system (3.1) if $f(\overline{x}) = 0$, that is, if $\overline{x}$ is a root of the function f.*

Definition 3.1.4. *The equilibrium point $\overline{x}$ is **stable** if for all $\epsilon > 0$, there exists a $\delta > 0$ such that for all x in U with $||x - \overline{x}|| < \delta$ it is fulfilled that $||\phi_t(x) - \overline{x}|| < \epsilon$ for $t \geq 0$. If a $\delta > 0$ can be chosen such that for all x in U with $||x - \overline{x}|| < \delta$ it is fulfilled that*

$$\lim_{t \longrightarrow \infty} \phi_t(x) = \overline{x},$$

then $\overline{x}$ *is* ***asymptotically stable****. An equilibrium point* $\overline{x}$ *that is not stable is called* ***unstable****.*

Intuitively, a point of equilibrium is stable if all the solutions that start near the point of equilibrium remain closed to it for all future time, and it is asymptotically stable if all the solutions that start near the point of equilibrium are drawn closer to it for all future time; otherwise it is unstable.

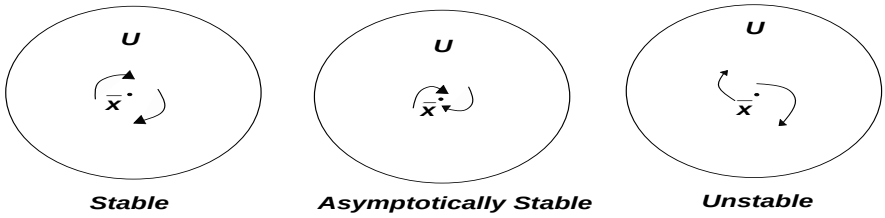

Figure 3–1: Stability of the equilibrium points.

Linearization Criteria

Let $\overline{x}$ be an equilibrium point of the differential equation system (3.1). We consider a disturbance of $\overline{x}$ given by

$$x = \overline{x} + y, \qquad \text{with } x \text{ in } U,$$

then developing f in the Taylor series around $\overline{x}$ we have

$$x' = \overline{x}' + y' = f(\overline{x} + y) = f(\overline{x}) + Df(\overline{x})y + N(\overline{x}, y),$$

with y in a neighborhood of the origin of $\mathbb{R}^n$, $N(\overline{x}, y)$ a nonlinear function such that

$$\lim_{||y|| \longrightarrow 0} \frac{N(\overline{x}, y)}{||y||} = 0,$$

and $Df(\overline{x})$ the derivative of f at $\overline{x}$ defined by

$$Df(\overline{x}) = \begin{pmatrix} \frac{\partial f_1(\overline{x})}{\partial x_1} & \frac{\partial f_1(\overline{x})}{\partial x_2} & \cdots & \frac{\partial f_1(\overline{x})}{\partial x_n} \\ \frac{\partial f_2(\overline{x})}{\partial x_1} & \frac{\partial f_2(\overline{x})}{\partial x_2} & \cdots & \frac{\partial f_2(\overline{x})}{\partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n(\overline{x})}{\partial x_1} & \frac{\partial f_n(\overline{x})}{\partial x_1} & \cdots & \frac{\partial f_n(\overline{x})}{\partial x_n} \end{pmatrix}.$$

This is known as **the Jacobian Matrix of** f in the point $\overline{x}$.

Given that $\overline{x}$ is an equilibrium point of f, then $f(\overline{x}) = 0$ and therefore

$$y' = Df(\overline{x})y + N(\overline{x}, y).$$

Under certain conditions the stability of the point $\overline{x}$ of System(3.1) is determined by the stability of the origin $y = 0$ of the linear system

$$y' = Df(\overline{x})y,$$

which is know as the **linearization** of system (3.1) around $\overline{x}$. We consider this below.

Definition 3.1.5. *Let $\overline{x}$ be an equilibrium point of (3.1), then*

- *If none of the eigenvalues of the matrix $Df(\overline{x})$ has real part equal to zero, $\overline{x}$ is a **hyperbolic equilibrium point**.*
- *If any eigenvalue of $Df(\overline{x})$ has real part equal to zero the equilibrium point is **non hyperbolic**.*

Definition 3.1.6. *Let $\overline{x}$ be a hyperbolic equilibrium point of the differential equation (3.1).*

- *$\overline{x}$ is a **sink** if all the eigenvalues of $Df(\overline{x})$ have negative real part.*
- *$\overline{x}$ is a **source** if all the eigenvalues of $Df(\overline{x})$ have positive real part.*
- *$\overline{x}$ is a **saddle** if $Df(\overline{x})$ has at least one eigenvalue with negative real part and one eigenvalue with positive real part.*

Definition 3.1.7. *Let $\overline{x}$ be an equilibrium point of the differential equation (3.1). $\overline{x}$ is a **center** if any eigenvalue of $Df(\overline{x})$ has real part equal to zero.*

Theorem 2. *([20], Ch. 9, Sec. 1-2).*

Let $\overline{x}$ be a hyperbolic equilibrium point of the differential equation system (3.1), then:

1. If $\overline{x}$ is a sink, then $\overline{x}$ is asymptotically stable.

2. If $\overline{x}$ is a source or a saddle, then $\overline{x}$ is unstable.

A result that directly relates the flux of the nonlinear system (3.1) with its linearization around an equilibrium point is the following:

Theorem 3. ***Hartman-Grobman.*** *([37], Ch. 2, Sec. 2.2D).*

Let U be an open subset of $\mathbb{R}^n$, f an application of class C^r, that is, a continuous function with continuous partial derivatives until order r, on U, $r \geq 1$, and $\overline{x}$ in U a hyperbolic equilibrium point of (3.1), then there exists a homeomorphism h defined in some neighborhood V of $\overline{x}$ that transforms locally the orbits of the nonlinear flux $\phi_t(x_0)$ of (3.1) in the orbits of the flux

$$e^{Df(\overline{x})t}h(x_0),$$

of the linear system

$$y' = Df(\overline{x})y.$$

The homeomorphism h preserves the direction of the orbits and can be selected in a way that preserves the orientation in the time.

3.2 Basic Reproductive Number

In this section, the concept of the basic reproductive number R_0 is presented, mathematically defined as the Next Generation Matrix method [6], [14]. [15].

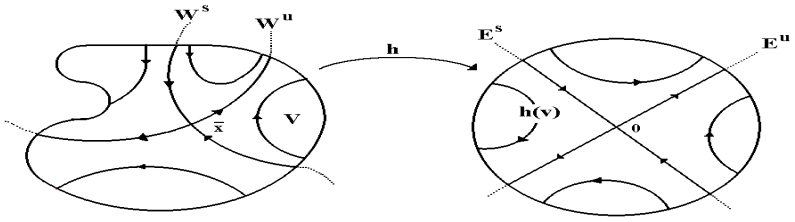

Figure 3–2: The Theorem of Hartman-Grobman.

Definition 3.2.1. *Considerer that the differential equation* (3.1) *describes the evolution of an infection in a healthy population in which a single infected individual is introduced. The* ***basic reproductive number****, denoted by* R_0*, is the average number of infected secondary individuals generated by the first infected individual during the period of infectivity in an entirely susceptible population.*

In addition, R_0 is the initial growth rate of an infection which refers only to the situation in which there is not regulation on the infected population. By its definition typically, if $R_0 < 1$, each infected individual generates, in average, less than one infected individual; in consequence, the infecion will tend to disappear from the population. On other hand, if $R_0 > 1$, each infected individual will infect, in average, more than one susceptible individual, causing the spread of the infection and this may result in an endemic state of disease. In the literature of mathematical biology, there is a method to calculate R_0 called *the Next Generation Matrix method*.

In addition, this method allows to interpret biologically the components of the matrix. It is assumed that the population can be classified into compartments where individuals from a given one are distinguishable from another. In detail, the parameters may vary from each compartment, but they are identical for all individuals within a given compartment. It is also assumed that the parameters do not depend on the time in which an individual remains in a compartment. The algorithm is based on a *system of ordinary differential equations* which describes the evolution of the number of individuals in each compartment. It is assumed that

from n compartments, m $(m > 1)$ correspond to the infected population, while the rest corresponds to individuals without infection [15]. The system of differential equations for the infection transmission model, which models the exchange rate x_i, where $x_i \geq 0$, is the number of individuals in the compartment i, can be written as:

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

$$X = \begin{pmatrix} x_1 \\ . \\ . \\ . \\ x_n \end{pmatrix}, \quad F(X) = \begin{pmatrix} f_1(X) \\ . \\ . \\ . \\ f_n(X) \end{pmatrix}, \quad V(X) = \begin{pmatrix} y_1^- - y_1^+ \\ . \\ . \\ . \\ y_n^- - y_n^+ \end{pmatrix},$$

where:

- $f_i(X)$ is the rate of appearance of new infections in the compartment i,
- y_i^+: transfer rate within the $i - th$ compartment based in other forms,
- y_i^-: transfer rate outside the $i - th$ compartment.

Note that $F(X)$ should only include new infections that are appearing, but should not include terms describing the transfer of infected individuals from one infected compartment to another.

Definition 3.2.2.

Consider the Jacobian matrix of F and V at the equilibrium point $\bar{x}$, this is,

$$DF(\bar{x}) = \left[\frac{\partial F_i(\bar{x})}{\partial x_j}\right], \quad DV(\bar{x}) = \left[\frac{\partial V_i(\bar{x})}{\partial x_j}\right], \quad i, j = 1, \ldots, m$$

*the **Next Generation Matrix** (NGM) is defined as the following product:*

$$(DF(\bar{x})).(DV(\bar{x})^{-1}).$$

Each component of the matrix $DF(\bar{x})$ represents the rate at which new infections are generated by infected individual . Each component $DV(\bar{x})^{-1}$ represents

the mean time in which the infected individual remains in the population of uninfected individuals. Thus, each component $(DF(\bar{x})).(DV(\bar{x})^{-1})$ denotes the expected number of new infections generated by the infected individual throughout the period of infectivity. Therefore, R_0 is established as the largest positive eigenvalue of the NGM.

Chapter 4
MODEL FOR ZIKA VIRUS DISEASES

To understand the dynamics of the Zika virus under vector and direct transmission and the effect of variable infectivity on the asymptomatic and symptomatic infected individual, a mathematical epidemiological model is built. The model is composed of eight ordinals equations differentials, representing the stages that human and a vector with ZIKV may experience (see Figure: 4–1). According to their epidemiological status, the total human and vector population are stratified into: $\bar{S}(t)$ represents the number of susceptibles humans, $\bar{E_h}(t)$ the number of exposed humans , $\bar{I}_s(t)$ the number of symptomatic infectious humans, $\bar{I}_a(t)$ the number of asymptomatic infectious humans, while $\bar{R}(t)$ represents the number of recovered humans, all at time t. The variable $\bar{S}_v(t)$ is the number of susceptibles vectors (mosquitoes), $\bar{E}_v(t)$ and $\bar{I}_v(t)$ is the number of exposed and infectious vectors (mosquitoes) respectively, all at time t.

Meanwhile, N_h and N_v are the total population of humans and vectors respectively. A human is considered susceptible ($\bar{S}$) when he or she may be infected by the ZIKV and has no immunity to the disease. The term $\mu_h N_h$ represents the recruitment rate or susceptibles human birth and because there are no official reports of deaths from Zika's disease alone, we do not assume death due to illness. The natural death rate of humans in the population is denoted by μ_h. Therefore, $\mu_h\bar{S}$, $\mu_h\bar{E_h}$, $\mu_h\bar{I}_s$, $\mu_h\bar{I}_a$ and $\mu_h\bar{R}$ represent the number of individuals who are susceptible, exposed, symptomatic infectious, asymptomatic infectious, and recovered per

unit of time, respectively. A susceptible individual can acquire the ZIKV by vector transmission with a transmission rate from vector to human $\beta_{hv} = af_{hv}$ where a is the biting rate of mosquitoes and f_{hv} is the probability that a bite transmits infection from vector to human. Therefore, $\beta_{hv}\bar{S}\dfrac{\bar{I}_v}{N_v}$ is the susceptible number that gets infected by the bite of a mosquito and progresses to an exposed stage. In our model, the ZIKV can be acquired by sexual transmission with a transmission rate α. In consequence, $\alpha\bar{S}\left(\dfrac{\bar{I}_s + \sigma\bar{I}_a}{N_h}\right)$ is the susceptible number that is infected by sexual contact with either symptomatic or asymptomatic individuals and progresses to the exposed class. Since the degree of infectivity of asymptomatic and symptomatic individuals is unknown, we defined a parameter σ to account for the infectivity [26]. Therefore, a *parameter of alteration of infectiousness* σ is suggested, which can represent all posible cases of infectiousness as follows:

- if $0 < \sigma < 1$, then I_a is less infectious that I_s,
- if $\sigma = 1$, then I_a and I_s are equally infectious,
- if $\sigma > 1$, then I_a is more infectious that I_s.

When a susceptible human acquires the ZIKV, it progresses to the exposed class symptomatically infectious with probability ρ at a rate k_h and asymptomatically infected with a probability $q = 1 - \rho$, also at a rate k_h. Thus, the parameter k_h represents the incubation period of ZIKV in humans. In consequence, $\rho k_h \bar{E}_h$ and $qk_h\bar{E}_h$ are the numbers of symptomatic and asymptomatic infected humans, respectively. An individual infected by the ZIKV can recover and acquire permanent immunity; the recovery rate are γ_s and γ_a for symptomatic and asymptomatic individuals, respectively. Thus, $\gamma_s\bar{I}_s$ and $\gamma_a\bar{I}_a$ are the numbers of symptomatic and asymptomatic recovered individuals, respectively.

The mosquito population becomes susceptible at a birth or recruitment rate given by $\mu_v N_v$. On the other hand, they die naturally at a rate μ_v; therefore, $\mu_v\bar{S}_v$, $\mu_v\bar{E}_v$ and $\mu_v\bar{I}_v$ are the susceptible, exposed, and infected number of mosquitoes that

leave the system by natural death. When a susceptible mosquito bites a symptomatic or asymptomatic infected human, it becomes infected at a transmission rate from human to vector given by $\beta_{vh} = a_v f_{vh}$ where, a_v is the biting rate and f_{vh} is the probability that a bite transmits infection from human to vector. Then $\beta_{vh}\bar{S}_v\frac{\bar{I}_s}{N_h}$ and $\beta_{vh}\bar{S}_v\frac{\sigma\bar{I}_a}{N_h}$ are the number of infected mosquitoes that get ZIKV by the bitting of a symptomatic or an asymptomatic infected human, respectively (notice the inclusion of the *parameter of alteration of infectiousness* in the asymptomatic population σ). When a mosquito in the exposed class develops the disease, it becomes infectious at a note k_v (k_v is the incubation rate). In consequence, $k_v\bar{E}_v$ is the numbers of infected mosquitoes that progress to become infections. A flow chart of the model is provided in Figure 4–1.

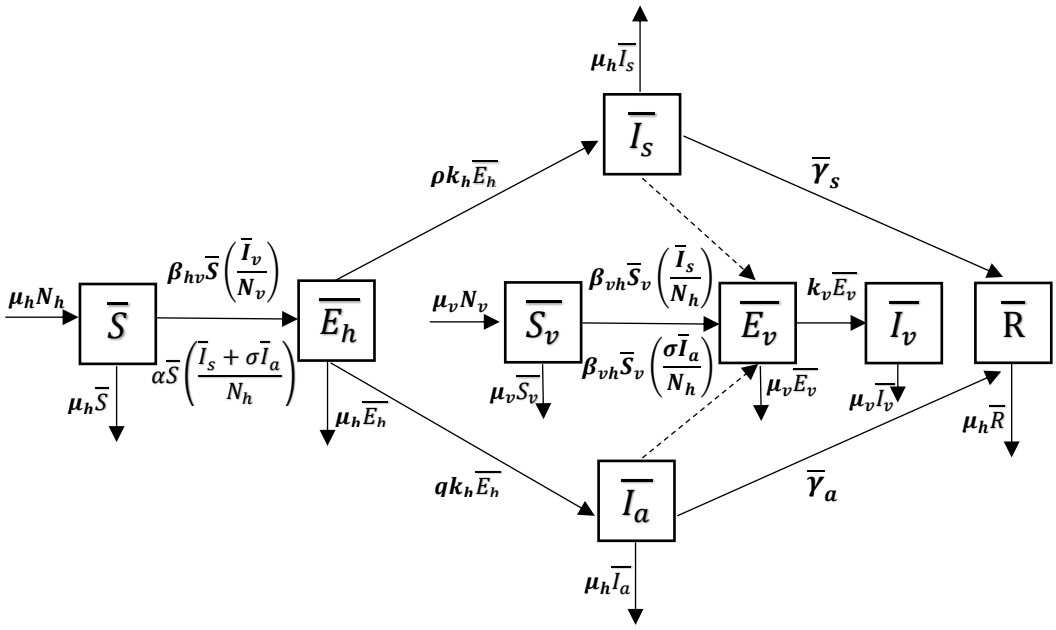

Figure 4–1: Compartmental Model for the Dynamics of ZIKA Disease, under the Inclusion of Symptomatic and Asymptomatic Infections Individuals.

The model is given by the following system of non-linear ordinary differential equations:

$$\frac{d\bar{S}}{dt} = \mu_h N_h - \beta_{hv}\bar{S}\frac{\bar{I}_v}{N_v} - \alpha\bar{S}\left(\frac{\bar{I}_s + \sigma\bar{I}_a}{N_h}\right) - \mu_h\bar{S}, \tag{4.1}$$

$$\frac{d\bar{E}_h}{dt} = \beta_{hv}\bar{S}\frac{\bar{I}_v}{N_v} + \alpha\bar{S}\left(\frac{\bar{I}_s + \sigma\bar{I}_a}{N_h}\right) - (\rho+q)k_h\bar{E}_h - \mu_h\bar{E}_h, \tag{4.2}$$

$$\frac{d\bar{I}_s}{dt} = \rho k_h\bar{E}_h - \gamma_s\bar{I}_s - \mu_h\bar{I}_s, \tag{4.3}$$

$$\frac{d\bar{I}_a}{dt} = qk_h\bar{E}_h - \gamma_a\bar{I}_a - \mu_h\bar{I}_a, \tag{4.4}$$

$$\frac{d\bar{R}}{dt} = \gamma_s\bar{I}_s + \gamma_a\bar{I}_a - \mu_h\bar{R}, \tag{4.5}$$

$$\frac{d\bar{S}_v}{dt} = \mu_v N_v - \beta_{vh}\bar{S}_v\left(\frac{\bar{I}_s + \sigma\bar{I}_a}{N_h}\right) - \mu_v\bar{S}_v, \tag{4.6}$$

$$\frac{d\bar{E}_v}{dt} = \beta_{vh}\bar{S}_v\left(\frac{\bar{I}_s + \sigma\bar{I}_a}{N_h}\right) - (k_v+\mu_v)\bar{E}_v, \tag{4.7}$$

$$\frac{d\bar{I}_v}{dt} = k_v\bar{E}_v - \mu_v\bar{I}_v, \tag{4.8}$$

where $q = 1-\rho$,

$$N_h = \bar{S} + \bar{E}_h + \bar{I}_s + \bar{I}_a + \bar{R},$$

and

$$N_v = \bar{S}_v + \bar{E}_v + \bar{I}_v.$$

Notice that

$$\frac{d\bar{S}}{dt} + \frac{d\bar{E}_h}{dt} + \frac{d\bar{I}_s}{dt} + \frac{d\bar{I}_a}{dt} + \frac{d\bar{R}}{dt} = \mu_h N_h - \mu_h(\bar{S} + \bar{E}_h + \bar{I}_s + \bar{I}_a + \bar{R}) = 0$$

and

$$\frac{d\bar{S}_v}{dt} + \frac{d\bar{E}_v}{dt} + \frac{d\bar{I}_v}{dt} = \mu_v N_v - \mu_v(\bar{S}_v + \bar{E}_v + \bar{I}_v) = 0.$$

In consequence the human and vector population are constants, that is $N_h(t) = N_h^0$ and $N_v(t) = N_v^0$ for all time t.

In the next section, we provide a qualitative analysis of the model where, the equilibria of the system are calculated, including a stability analysis. Finally, basic reproductive numbers associated with the model are compared.

4.1 Analysis of the Model Proposed

In order to analyze the model to be studied more easily, without modifying its qualities, the populations are rescaled into proportions.

4.1.1 Rescaled Model

Let the change of variables

$$S = \frac{\bar{S}}{N_h},\ \ E_h = \frac{\bar{E_h}}{N_h},\ \ I_s = \frac{\bar{I_s}}{N_h},\ \ I_a = \frac{\bar{I_a}}{N_h},\ \ R = \frac{\bar{R}}{N_h},\ \ S_v = \frac{\bar{S}_v}{N_v}, E_v = \frac{\bar{E}_v}{N_v} \text{ and } I_v = \frac{\bar{I}_v}{N_v},$$

where $S+E_h+I_s+I_a+R=1$, and $S_v+E_v+I_v=1$, since $R=1-(S+E_h+I_s+I_a)$ and $S_v=1-(E_v+I_v)$, we can reduce System 4 from seven to six equations a system, given by:

$$S' = \mu_h(1-S) - \beta_{hv} S I_v - \alpha S\left(I_s + \sigma I_a\right), \tag{4.9}$$

$$E_h' = \beta_{hv} S I_v + \alpha S\left(I_s + \sigma I_a\right) - (k_h + \mu_h)E_h, \tag{4.10}$$

$$I_s' = \rho k_h E_h - (\gamma_s + \mu_h) I_s, \tag{4.11}$$

$$I_a' = q k_h E_h - (\gamma_a + \mu_h) I_a, \tag{4.12}$$

$$E_v' = \beta_{vh}(1-(E_v+I_v))\left(I_s + \sigma I_a\right) - (k_v + \mu_v)E_v, \tag{4.13}$$

$$I_v' = k_v E_v - \mu_v I_v. \tag{4.14}$$

$$\tag{4.15}$$

4.1.2 Basic Reproductive Number R_0

In epidemiology, an important threshold condition value is called the basic reproductive number. It is denoted by R_0 and it is the expected number of secondary cases produced by a typical infective individual in a completely susceptible population. This metric is useful because it helps determine when an infectious disease can lead to an outbreak, or an epidemic in a population. The R_0 is calculated using *the Next Generation Matrix Method* (for detail see [14] and section 3.2).

Varied expressions for the basic reproductive number are allowed (Cushing and Diekmann [22]). We will choose the vector of new infections $\mathcal{F}$ in two different ways, obtaining two different representations of the basic reproductive number. In Subsection 4.1.3 we consider that the new infections are in the human populations, in which the process of human-vector-human infection is seen as a single generation, and in Subsection 4.1.4 we considered two types of new infection in the susceptible human population and in susceptible vectors, where the process of human-vector-human infection is observed as two generations.

4.1.3 Considering Only Human Infectious as New Infections

In the disease's development we can consider two different types of new infections caused by ZIKV, in the human population and in the mosquito population. In this subsubsection we consider that the infections process human to vector to human is only one generation of infections (for a recent discussion of this issue see Cushing and Diekmann [22]). Therefore, the new infections are only in the humans populations. Hence, the vector of new infections $\mathcal{F}$ contain the expression $\beta_{hv} S I_v + \alpha S \left(I_s + \sigma I_a\right)$ which is the term of contribution of new infections only in the infected humans population, where $\beta_{hv} S I_v$ is new infections by vector transmission and $\alpha S \left(I_s + \sigma I_a\right)$ by sexual transmission.

First, sort the system so that the first m differential equations correspond to infected states,that is:

$$E_h' = \beta_{hv} S I_v + \alpha S\left(I_s + \sigma I_a\right) - (k_h + \mu_h) E_h, \tag{4.16}$$

$$I_s' = \rho k_h E_h - (\gamma_s + \mu_h) I_s, \tag{4.17}$$

$$I_a' = q k_h E_h - (\gamma_a + \mu_h) I_a, \tag{4.18}$$

$$E_v' = \beta_{vh}(1 - (E_v + I_v))\left(I_s + \sigma I_a\right) - (k_v + \mu_v) E_v, \tag{4.19}$$

$$I_v' = k_v E_v - \mu_v I_v, \tag{4.20}$$

$$S' = \mu_h(1 - S) - \beta_{hv} S I_v - \alpha S\left(I_s + \sigma I_a\right). \tag{4.21}$$

The Zika free equilibrium of our model is then given by:

$$E_0 = (E_h^*, I_s^*, I_a^*, E_v^*, I_v^*, S^*) = (0, 0, 0, 0, 0, 1)$$

Let $\mathcal{F}$ the contribution of new infections to each compartment and the entries of the column vector $\mathcal{V}$ are the remaining terms that do not contribute to new infections, then

$$\mathcal{F} = \begin{pmatrix} \beta_{hv} S I_v + \alpha S\left(I_s + \sigma I_a\right) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (k_h + \mu_h) E_h \\ -\rho k_h E_h + (\mu_h + \gamma_s) I_s \\ -q k_h E_h + (\mu_h + \gamma_a) I_a \\ -\beta_{vh}(1 - (E_v + I_v))\left(I_s + \sigma I_a\right) + (k_v + \mu_v) E_v \\ -k_v E_v + \mu_v I_v \\ \mu_h(1 - S) - \beta_{hv} S I_v - \alpha S\left(I_s + \sigma I_a\right) \end{pmatrix}.$$

According to Lemma 1 of [14]

$$F = \begin{pmatrix} 0 & \alpha & \sigma\alpha & 0 & \beta_{hv} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu_h + k_h & 0 & 0 & 0 & 0 \\ -\rho k_h & \mu_h + \gamma_s & 0 & 0 & 0 \\ -q k_h & 0 & \mu_h + \gamma_a & 0 & 0 \\ 0 & -\beta_{vh} & -\sigma\beta_{vh} & k_v + \mu_v & 0 \\ 0 & 0 & 0 & -k_v & \mu_v \end{pmatrix}.$$

Let

$$b = \rho(\mu_h + \gamma_a) + \sigma q(\mu_h + \gamma_s)$$

and

$$c = (\mu_h + k_h)(\mu_h + \gamma_a)(\mu_v + k_v).$$

Thus,

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu_h + k_h} & 0 & 0 & 0 & 0 \\ \frac{k_h\rho}{(\mu_h + k_h)(\mu_h + \gamma_s)} & \frac{1}{\mu_h + \gamma_s} & 0 & 0 & 0 \\ \frac{k_h q}{(\mu_h + k_h)(\mu_h + \gamma_a)} & 0 & \frac{1}{\mu_h + \gamma_a} & 0 & 0 \\ \frac{k_h\beta_{vh}b}{(\mu_h + \gamma_s)c} & \frac{\beta_{vh}}{(\mu_h + \gamma_s)(\mu_v + k_v)} & \frac{\sigma\beta_{vh}}{(\mu_h + \gamma_a)(\mu_v + k_v)} & \frac{1}{(\mu_v + k_v)} & 0 \\ \frac{k_h k_v\beta_{vh}b}{\mu_v(\mu_h + \gamma_s)c} & \frac{\beta_{vh}k_v}{(\mu_h + \gamma_s)(\mu_v + k_v)} & \frac{\sigma k_v\beta_{vh}}{(\mu_h + \gamma_a)(\mu_v + k_v)} & \frac{k_v}{\mu_v(\mu_v + k_v)} & \frac{1}{\mu_v} \end{pmatrix}.$$

The Next Generation Matrix is then given by:

$$FV^{-1} = \begin{pmatrix} a_{11} & a_{12} & a_{13} & a_{14} & a_{15} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

where:

$$a_{11} = \frac{\alpha k_h \rho}{(\mu_h + k_h)(\mu_h + \gamma_s)} + \frac{\sigma \alpha k_h q}{(\mu_h + k_h)(\mu_h + \gamma_a)} + \frac{k_h k_v \beta_{vh} \beta_{hv} b}{\mu_v (\mu_h + \gamma_s) c},$$
$$a_{12} = \frac{\alpha}{\mu_h + \gamma_s} + \frac{\beta_{vh} \beta_{hv} k_v}{(\mu_h + \gamma_s)(\mu_v + k_v)},$$
$$a_{13} = \frac{\sigma \alpha}{\mu_h + \gamma_a} + \frac{\sigma k_v \beta_{vh} \beta_{hv}}{(\mu_h + \gamma_a)(\mu_v + k_v)},$$
$$a_{14} = \frac{k_v \beta_{hv}}{\mu_v (\mu_v + k_v)},$$
$$\text{and} \quad a_{15} = \frac{\beta_{hv}}{\mu_v}.$$

The eigenvalues of the characteristic equation from the matrix FV^{-1} are:

$$\lambda_1 = 0, \quad \lambda_2 = 0, \quad \lambda_3 = 0, \quad \lambda_4 = 0$$

and

$$\lambda_5 = \frac{\alpha \rho k_h}{(\mu_h + k_h)(\gamma_s + \mu_h)} + \frac{\sigma \alpha q k_h}{(\mu_h + k_h)(\gamma_a + \mu_h)} + \frac{\beta_{hv} \beta_{vh} k_h k_v b}{(\mu_h + \gamma_s) c \mu_v}$$

Thus, the basic reproductive number R_0 of Model (4.1.1) is $R_0 = \varphi(FV^{-1})$ defined by:

$$R_0 = \left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{vh}}{\mu_h + \gamma_s}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\left(\frac{\beta_{hv}}{\mu_v}\right) + \left(\frac{\sigma q k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{vh}}{\mu_h + \gamma_a}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\left(\frac{\beta_{hv}}{\mu_v}\right)$$
$$+ \left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\alpha}{\mu_h + \gamma_s}\right) + \left(\frac{q k_h}{\mu_h + k_h}\right)\left(\frac{\sigma \alpha}{\mu_h + \gamma_a}\right)$$

or equivalent to

$$R_0 = R^v_{I_s} + R^v_{I_a} + R^d_{I_s} + R^d_{I_a}$$

where:

1. $R^v_{I_s}$ is the contribution to R_0 by symptomatic individuals who acquire Zika through mosquito bites, which is equivalent to $\left[\left(\frac{\beta_{vh}}{\mu_h + \gamma_s}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\right]\left[\left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{hv}}{\mu_v}\right)\right]$.

$R^v_{I_s}$ describes the proportion of exposed humans that becomes symptomatic infected, this multiplied by the transmission rate from symptomatic individual to vectors, by the average time the symptomatic individuals spends with symptoms, multiplied by the proportion of mosquitoes that progress to infectious, times the transmission rate from vector to human multiply by the average life span a vector.

2. $R^v_{I_a}$ is the contribution to R_0 of asymptomatic individual that acquire Zika through mosquito bites, which is equivalent to $\left[\left(\frac{\beta_{vh}}{\mu_h+\gamma_a}\right)\left(\frac{k_v}{\mu_v+k_v}\right)\right]\left[\left(\frac{\sigma q k_h}{\mu_h+k_h}\right)\left(\frac{\beta_{hv}}{\mu_v}\right)\right]$. $R^v_{I_a}$ describes the proportion of exposed humans that becomes asymptomatic infected, this multiplied by the transmission rate from asymptomatic individual to vectors, by the average time the asymptomatic individuals spends in as asymptomatic, multiplied by the proportion of mosquitoes that progress to infectious, times the transmission rate from vector to human, multiply by the average life span of a vector.
3. $R^d_{I_s}$ is the contribution to R_0 by direct transmission of the symptomatic individuals that is $R^d_{I_s} = \left(\frac{\rho k_h}{\mu_h+k_h}\right)\left(\frac{\alpha}{\mu_h+\gamma_s}\right)$ describes the proportion of exposed humans that becomes symptomatic infected, multiplied by the direct transmission rate of a symptomatic individual times the average time the symptomatic individual spends with symptoms.
4. $R^d_{I_a}$ is the contribution to R_0 by direct transmission of the asymptomatic individuals that is $R^d_{I_a} = \left(\frac{q k_h}{\mu_h+k_h}\right)\left(\frac{\sigma\alpha}{\mu_h+\gamma_a}\right)$ describes the proportion of exposed humans that to becomes asymptomatic infected, multiplied by the direct transmission rate of an asymptomatic individual, length of time the average time the asymptomatic individual spends as asymptomatic.

Notice that R_0 can be rewritten as

$$R_v = R^v_{I_s} + R^v_{I_a} \quad \text{and} \quad R_d = R^d_{I_s} + R^d_{I_a},$$

where

$$R_0 = R_v + R_d.$$

Obtaining results similar to Brauer F., Castillo-Chavez C. [4] and Wencel V., Rios-Soto, K. [33] in which it is described that:

1. R_v is the vector transmission reproduction number, which is the contribution to R_0 by individuals who acquire Zika through mosquito bites.
2. R_d represents the direct transmission reproduction number, which is the contribution to R_0 by individuals who acquire Zika through sexual contact, either symptomatic or asymptomatic.

4.1.4 Considering Human and Mosquitoes Infectious as New Infections

Previously, in the calculation of the R_0, it was considered that the new infections only appear in humans. Now, we consider that the infections process human-to-vector-to-human are two generations of infections (for a recent discussion of this issue see Cushing and Diekmann [22]). Therefore we will consider that these arise both in humans and, in the mosquitoes and according to Next Generator Matrix Method [14], this produces only a change in vector $\mathcal{F}$ including the expressions $\beta_{hv} S I_v + \alpha S \left(I_s + \sigma I_a\right)$ and $\beta_{vh}(1 - (E_v + I_v)) \left(I_s + \sigma I_a\right)$ that are the terms of infections new for the human and vector population, respectively. In which $\beta_{hv} S I_v$ new infectious for humans is by sexual transmission and $\alpha S \left(I_s + \sigma I_a\right)$ is by vector transmission in the human papulation, where as $\beta_{vh}(1-(E_v+I_v)) \left(I_s + \sigma I_a\right)$ represent new infectious for mosquitoes from symptomatic and asymptomatic individuals.

$$\mathcal{F} = \begin{pmatrix} \beta_{hv} S I_v + \alpha S\left(I_s + \sigma I_a\right) \\ 0 \\ 0 \\ \beta_{vh}(1-(E_v+I_v))\left(I_s+\sigma I_a\right) \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (k_h+\mu_h)E_h \\ -\rho k_h E_h + (\mu_h+\gamma_s)I_s \\ -q k_h E_h + (\mu_h+\gamma_a)I_a \\ (k_v+\mu_v)E_v \\ -k_v E_v + \mu_v I_v \\ \mu_h(1-S) - \beta_{hv} S I_v - \alpha S\left(I_s+\sigma I_a\right) \end{pmatrix}.$$

According to Lemma 1 of [14]

$$F = \begin{pmatrix} 0 & \alpha & \sigma\alpha & 0 & \beta_{hv} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{vh} & \sigma\beta_{vh} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu_h+k_h & 0 & 0 & 0 & 0 \\ -\rho k_h & \mu_h+\gamma_s & 0 & 0 & 0 \\ -q k_h & 0 & \mu_h+\gamma_a & 0 & 0 \\ 0 & 0 & 0 & k_v+\mu_v & 0 \\ 0 & 0 & 0 & -k_v & \mu_v \end{pmatrix}.$$

Thus,

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu_h+k_h} & 0 & 0 & 0 & 0 \\ \frac{k_h\rho}{(\mu_h+k_h)(\mu_h+\gamma_s)} & \frac{1}{\mu_h+\gamma_s} & 0 & 0 & 0 \\ \frac{k_h q}{(\mu_h+k_h)(\mu_h+\gamma_a)} & 0 & \frac{1}{\mu_h+\gamma_a} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{(\mu_v+k_v)} & 0 \\ 0 & 0 & 0 & \frac{k_v}{\mu_v(\mu_v+k_v)} & \frac{1}{\mu_v} \end{pmatrix}.$$

The Next Generation Matrix is then given by:

$$FV^{-1} = \begin{pmatrix} \dfrac{\alpha k_h \rho}{(\mu_h + k_h)(\mu_h + \gamma_s)} + \dfrac{\sigma \alpha k_h q}{(\mu_h + k_h)(\mu_h + \gamma_a)} & \dfrac{\alpha}{\mu_h + \gamma_s} & \dfrac{\sigma\alpha}{\mu_h + \gamma_a} & \dfrac{k_v \beta_{hv}}{\mu_v(\mu_v + k_v)} & \dfrac{\beta_{hv}}{\mu_v} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \dfrac{k_h \rho \beta_{vh}}{(\mu_h + k_h)(\mu_h + \gamma_s)} + \dfrac{k_h q \sigma \beta_{vh}}{(\mu_h + k_h)(\mu_h + \gamma_a)} & \dfrac{\sigma \beta_{vh}}{\mu_h + \gamma_s} & \dfrac{\sigma \beta_{vh}}{\mu_h + \gamma_a} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

The eigenvalues of the characteristic equation from the matrix FV^{-1} are:

$$\lambda_1 = 0, \quad \lambda_2 = 0, \quad \lambda_3 = 0,$$

then

$$\lambda_4 = \frac{1}{2}\left(-\frac{\alpha k_h b}{(\mu_h + \gamma_s)(\mu_h + \gamma_a)(\mu_h + k_h)} + \sqrt{\left(\frac{\alpha k_h b}{(\mu_h + \gamma_s)(\mu_h + \gamma_a)(\mu_h + k_h)}\right)^2 + \frac{4 k_h k_v \beta_{vh} \beta_{hv} b}{\mu_v(\mu_h + \gamma_s)c}} \right),$$

$$\lambda_5 = \frac{1}{2}\left(\frac{\alpha k_h b}{(\mu_h + \gamma_s)(\mu_h + \gamma_a)(\mu_h + k_h)} + \sqrt{\left(\frac{\alpha k_h b}{(\mu_h + \gamma_s)(\mu_h + \gamma_a)(\mu_h + k_h)}\right)^2 + \frac{4 k_h k_v \beta_{vh} \beta_{hv} b}{\mu_v(\mu_h + \gamma_s)c}} \right).$$

Notice that λ_5 is equivalent to

$$\lambda_5 = \frac{1}{2}(R_d + \sqrt{(R_d)^2 + 4R_v}).$$

Thus, the basic reproductive number R_0^* of Model (4.1.1) is $R_0^* = \varphi(FV^{-1})$ defined by:

$$R_0^* = \frac{1}{2}(R_d + \sqrt{(R_d)^2 + 4R_v})$$

Notice that R_0^* can be understood as function of R_v and R_d,

$$R_0^*(R_v, R_d) = \frac{1}{2}\left(R_d + \sqrt{(R_d)^2 + 4R_v}\right).$$

Now, $R_0^*(R_v, R_d) = 1$ if only if $R_0 = R_v + R_d = 1$ and that:

- If there is no direct transmission ($\alpha = 0$) then $R_d = 0$ and

$$R_0^*(R_v, 0) = \sqrt{R_v},$$

that is, the R_0 with only vector transmission. Thus $R_0^*(R_v, R_d)$ is the combined effect of direct and vectorial transmission.

The basic reproductive number is an important parameter to understand disease spread, possible control measures, and prevention. Here, we show two different expressions for this number R_0 and R_0^*, both valid in the study of the modeling of infectious disease, but that we consider important to clarify. The value of R_0 provides a threshold condition when new infections are considered only for humans where as R_0^* provides a threshold condition for Zika virus spread when we consider mosquitoes with new infections as well. We have chosen to use R_0 for the basic reproductive number as it is a simpler expression of the process, in which the infection process human-vector-human is considered as one generation. It is because of this, that we only consider new infections in the susceptible humans only (as was also done in Brauer F. [4] and Wencel V., Rios-Soto, K. [33]).

4.1.5 Equilibrium Points of the Model

We use the system of algebraic equations associated to the system of differential equations, to explicitly find the Zika-free equilibrium and by using simple concepts such as the rule of Descartes Rule of sign, we deduce (from a quadratic polynomial that derives from the system) the existence of a second fixed point, the endemic equilibrium.

Theorem 4. *For the System (4.1.1), there exist an equilibrium point $E_1 = (1, 0, 0, 0, 0)$, the Zika-free equilibrium and is locally asymptotically stable provided that $R_0 \leq 1$. If $R_0 > 1$, there exists a unique Zika equilibrium, $E_2 = (S^*, E_h^*, I_s^*, I_a^*, E_v^*, I_v^*)$ (see the Figure 4–2).*

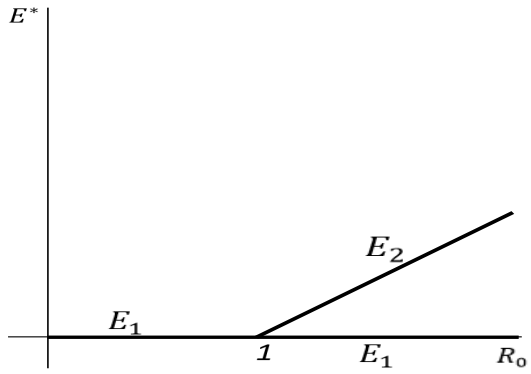

Figure 4–2: Existence of equilibrium points.

Proof. The equilibria of equations of System (4.1.1) are calculated by setting the equations equal to zero, thus obtaining the following algebraic system:

$$\mu_h(1-S^*) - \beta_{hv}S^*I_v^* - \alpha S^*\left(I_s^* + \sigma I_a^*\right) = 0, \tag{4.22}$$

$$\beta_{hv}S^*I_v^* + \alpha S^*\left(I_s^* + \sigma I_a^*\right) - (k_h+\mu_h)E_h^* = 0, \tag{4.23}$$

$$\rho k_h E_h^* - (\gamma_s+\mu_h)I_s^* = 0, \tag{4.24}$$

$$q k_h E_h^* - (\gamma_a+\mu_h)I_a^* = 0, \tag{4.25}$$

$$\beta_{vh}(1-(E_v^*+I_v^*))\left(I_s^* + \sigma I_a^*\right) - (k_v+\mu_v)E_v^* = 0, \tag{4.26}$$

$$\text{and} \quad k_v E_v^* - \mu_v I_v^* = 0. \tag{4.27}$$

Next we algebraically manipulate the system to determine the points that satisfy it.

From the Equations (4.24) and (4.25) we have:

$$E_h^* = E_h^*(I_s^*) = \frac{(\mu_h+\gamma_s)I_s^*}{\rho k_h}, \tag{4.28}$$

$$and \quad E_h^* = E_h^*(I_a^*) = \frac{(\mu_h+\gamma_a)I_a^*}{q k_h} \tag{4.29}$$

$$\tag{4.30}$$

respectively. Equating Equations (4.28) and (4.29), we obtain

$$I_s^*(I_a^*) = \frac{(\mu_h + \gamma_a)I_a^*\rho}{(\mu_h + \gamma_s)q}. \tag{4.31}$$

And adding σI_a^* to Equation (4.31) we have,

$$I_s^*(I_a^*) + \sigma I_a^* = \frac{bI_a^*}{q(\mu_h + \gamma_s)} \tag{4.32}$$

where

$$b = \rho(\mu_h + \gamma_a) + \sigma q(\mu_h + \gamma_s).$$

From the Equation (4.26)

$$E_v^* = \frac{\mu_v\beta_{vh}(I_s^* + \sigma I_a^*)}{(\beta_{vh}(I_s^* + \sigma I_a^*) + \mu_v)(k_v + \mu_v)},$$

and by Equation (4.32)

$$E_v^*(I_a^*) = \frac{\mu_v\beta_{vh}bI_a^*}{(\beta_{vh}bI_a^* + \mu_v q(\mu_h + \gamma_s))(k_v + \mu_v)}. \tag{4.33}$$

From Equation (4.27)

$$I_v^*(I_a^*) = \frac{k_v E_v^*}{\mu_v}$$

and by Equation (4.33)

$$I_v^* = \frac{k_v\beta_{vh}bI_a^*}{(\beta_{vh}bI_a^* + \mu_v q(\mu_h + \gamma_s))(k_v + \mu_v)} \tag{4.34}$$

From Equation (4.22)

$$S^* = \frac{\mu_h}{\mu_h + \beta_{hv}I_v^* + \alpha(I_s^* + \sigma I_a^*)} \tag{4.35}$$

and from Equation (4.23)

$$S^*(\beta_{hv}I_v^* + \alpha(I_s^* + \sigma I_a^*)) - (k_h + \mu_h)E_h^* = 0. \tag{4.36}$$

Finally, replacing Equations (4.29), (4.32), (4.34) and (4.35) into Equation (4.36), we obtain

$$\frac{\mu_h\left(\frac{k_v b\beta_{hv}\beta_{vh}I_a^*}{(\mu_v+k_v)(\beta_{vh}bI_a^*+\mu_v q(\gamma_s+\mu_h))}+\frac{\alpha bI_a^*}{q(\mu_h+\gamma_s)}\right)}{\mu_h+\left(\frac{k_v b\beta_{hv}\beta_{vh}I_a^*}{(\mu_v+k_v)(\beta_{vh}bI_a^*+\mu_v q(\gamma_s+\mu_h))}+\frac{\alpha bI_a^*}{q(\mu_h+\gamma_s)}\right)}-\frac{(\mu_h+k_h)(\mu_h+\gamma_a)I_a^*}{qk_h}=0$$

After some calculations, a cubic equation is obtained in terms of I_a^* given by:

$$I_a^*(a_2(I_a^*)^2+a_1I_a^*+a_0)=0$$

where

$$a_0=\mu_h q^2\mu_v(\mu_h+\gamma_s)^2c(R_0-1),$$

$$a_1=\mu_h q\beta_{vh}b(\mu_h+\gamma_s)c(R_d-1)-qb(\mu_h+k_h)(\mu_h+\gamma_a)(\mu_h+\gamma_s)(k_v\beta_{vh}\beta_{hv}+\alpha\mu_v(k_v+\mu_v)),$$

$$a_2=-c\alpha b^2\beta_{vh},$$

in which

$$c=(\mu_h+k_h)(\mu_h+\gamma_a)(\mu_v+k_v).$$

Then

$$I_a^*=0 \quad or \quad a_2(I_a^*)^2+a_1I_a^*+a_0,$$

in the case that $I_a^*=0$ and replacing in the Equations (4.29), (4.31), (4.33) and (4.35) we have the Zika-free equilibrium

$$E_1=(1,0,0,0,0).$$

On the other hand, if $I_a^*\neq 0$ then

$$a_2(I_a^*)^2+a_1I_a^*+a_0=0$$

Now we are going to determine the existence of nontrivial equilibria. Using Descartes' Rule of Signs, we find that the polynomial $f(I_a)=a_2I_a^2+a_1I_a+a_0$ has a unique

positive root I_a^*. Note that: a_2 is always negative, $I_{a_{MAX}} = -\dfrac{a_1}{2a_2}$ (since $f'(I_a) = 2a_2 I_a + a_1$) and that:

1. If $R_0 > 1$ then $f(0) = a_0 > 0$, while a_1 can be positive or negative. Therefore, the change of coefficient signs can be determined from the following table:

Table 4–1: Change of Signs Coefficient $f(I_a)$ for $R_0 > 1$

Case	a_2	a_1	a_0
I	$-$	$+$	$+$
II	$-$	$-$	$+$

In the two cases, there are two changes of signs then Descartes' rule, impliying the existence of only one positive root I_a^* (see Figure 4–3). Therefore, if $R_0 > 1$ in addition to E_1, there exists an infected equilibrium $E_2 = (S^*, E_h^*, I_s^*, I_a^*, E_v^*, I_v^*)$.

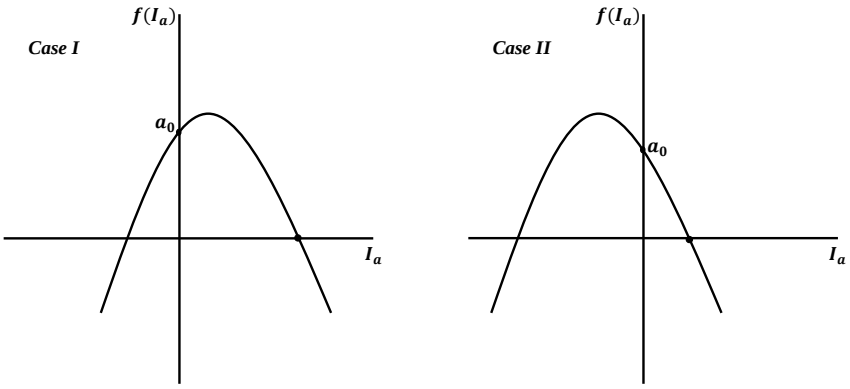

Figure 4–3: Graphic Illustration of the Existence of a Single Positive Root (Case I and II).

2. If $R_0 < 1$ then $f(0) = a_0 < 0$ and as $R_0 = R_v + R_d < 1$ thus $R_d < 1$ in consequence $a_1 < 0$. Therefore, we obtain the following table:

In the only case presented, we observe that there is not a change of sign then Descartes' rule implies the existence of zero positive roots (see Figure 4–4). Therefore, if $R_0 < 1$ there only exists the Zika-free equilibrium.

Table 4–2: Change of Signs Coefficient $f(I_a)$ for $R_0 < 1$

Case	a_2	a_1	a_0
I	−	−	−

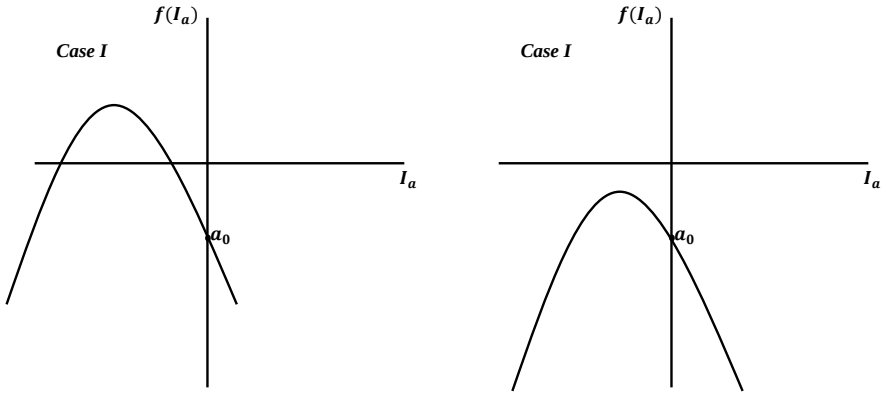

Figure 4–4: Graphic Illustration of the Absence of Real Roots Case I).

3. If $R_0 = 1$ then $f(0) = a_0 = 0$. Therefore $a_2(I_a^*)^2 + a_1 I_a^* = 0$ In consequence, $I_a^* = 0$ (E_1 equilibrium) or $I_a^* = \dfrac{a_1}{a_2}$ and as $R_0 = R_v + R_d = 1$ thus $R_d \leq 1$ then $a_1 < 0$ then $I_a^* = \dfrac{a_1}{a_2} < 0$ that does not have biological sense. Thus, if $R_0 = 1$ the Zika-free equilibrium is the only equilibrium.

□

4.1.6 Stability Analysis of the Equilibrium Points

In this section we discuss the local stability of the Zika-free equilibrium E_1 and of infected equilibrium, $E_2 = (S^*, E_h^*, I_s^*, I_a^*, E_v^*, I_v^*)$. For this, we will use results from the Second-Generation Matrix method described in the Theorem 2 of [14], and also perform a numerical analysis supported by the Hartman-Grobman theorem.

Theorem 5. *If $R_0 < 1$, then Zika-free equilibrium E_1 is locally asymptotically stable.*

Proof. We calculated R_0 using Next Generator Matrix method and according to Theorem 2 of [14] then, E_1 is locally asymptotically stable if $R_0 < 1$, but unstable if $R_0 > 1$. □

To determine the **local stability of the infected equilibrium**, we used a numerical analysis in which the real part of the eigenvalues associated with the Jacobian matrices evaluated at the equilibrium points E_1 and E_2, respectively, are presented for 1000 different values of R_0 with values taken from 5–1, as illustrated in Figure 4–5. Note that the red dots are the values of the real part of the eigenvalues associated with $R_0 > 1$ and the blue dots associated with $R_0 < 1$. In the figure it is shown that for these thousand values of R_0 the real part of the eigenvalues is negative. Consequently, it proves numerically that E_2 is locally asymptotically stable.

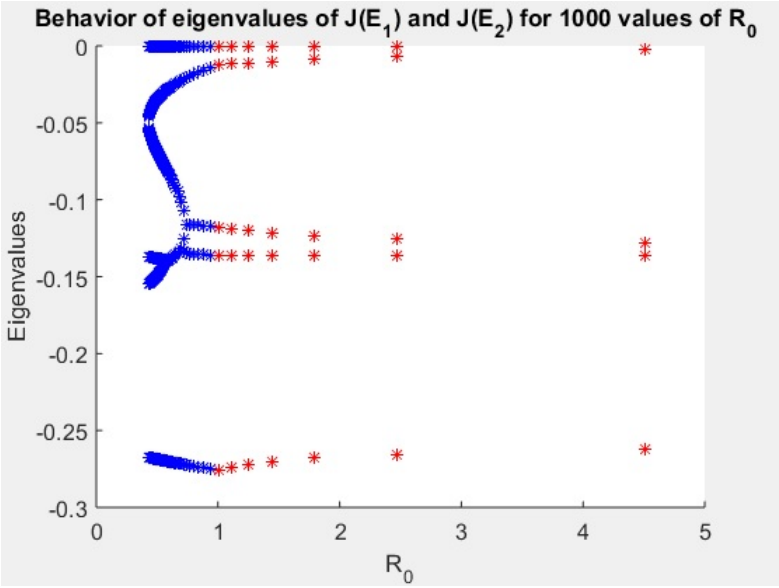

Figure 4–5: Graphic illustration of the Behavior of eigenvalues of $J(E_1)$ and $J(E_2)$ for 1000 values of R_0.

For example, for the particular values of the parameters gives in Table 4–3 in R_0,

Table 4–3: Values Table to the numerical stability of endemic equilibrium

Parameter	**Value**
μ_v	$1/20$
σ	1.5
γ_a	$1/9$
β_{hv}	0.15
β_{vh}	0.12
α	0.06
k_v	$1/9.5$
q	0.8
γ_s	$1/7$
ρ	0.2
μ_h	$1/(27 \times 365)$
k_h	$1/5$

We have that the basic reproductive number basic is $R_0 = 3.7044$, the endemic equilibrium is $E_2 = (S^*, E_h^*, I_s^*, I_a^*, E_v^*, I_v^*) = (0.2704, 0.0004, 0.0001, 0.0005, 0.0007, 0.0015)$. Thus, the Jacobian matrices evaluated at the equilibrium point E_2 provide all eigenvalues with negative real parts. Consequently, the endemic equilibrium E_2 is locally asymptotically stable, numerically.

Chapter 5
PARAMETER ESTIMATION AND NUMERICAL SOLUTIONS

5.1 Parameters Values and Estimation

All parameter descriptions and the estimation were done by reviewing the mathematical and epidemiological literature. In this section, we describe the baseline of parameter values used through the numerical simulation. Notice that ZIKV and DENV are virus of the same genus and have similar symptoms, high proportion of asymptomatic infections, duration of incubation, and infectiousness [5], [33], this as done in previous research. we take parameters values similar to dengue fever.

- μ_h and μ_v represent the recruitment and natural death rate of the human and vector populations in the system, respectively. The values that can take μ_h were taken from [5]. A person is sexually active in average between the ages of 18 and 50 years or age. Thus, in a life time is 18×365 and 50×365 days. Therefore, μ_h is in between $\left[\frac{1}{50 \times 365}, \frac{1}{18 \times 365}\right]$, and the average lifetime of a vector is between 4 and 35 days [18] in consequence μ_v is between $[1/4, 1/35]$.
- $\beta_{hv} = af_{hv}$ and $\beta_{vh} = af_{vh}$ represent the transmission rate from vector to human and human to vector, respectively, where a is the biting rate of mosquitoes and f_{hv} and f_{vh} are the probability that a bite transmits infection from vector to human and human to vector respectively. The biting rate for a mosquito is between 0.3 and 1 humans per day [18], and the probability of an effective

transmission f_{hv} for human is reported inside of the interval $[0.1, 0.75]$ [18]. On the other hand the probability f_{vh} that a mosquito gets infected from an infected human is taken freely between 0 and 1. Therefore, $\beta_{hv} \in [0.03, 0.75]$ and $\beta_{vh} \in [0, 1]$.

- α represents the sexual transmission rate of ZIKV. Tower, S. [28] estimated the basic reproductive number of the 2015 Zika outbreak in Barranquilla and found that the percent of cases due to sexual transmission may be as high as 47% with 95% confidence. Therefore, in a fraction between $[0.01, 0.47]$ Now the CDC reports [11] that in US for the period January 1, 2015 to March 22, 2017 (811 days), 5158 reported cases of Zika virus disease, of which 45 are due to sexual transmission. Hence, we have $\alpha = 0.055$ per day. In consequence, we will take $\alpha \in [0.01, 0.07]$ for the different simulations.
- k_h and k_v represent the incubation rate of ZIKV for human and vector, respectively. In the humans, the incubation period is between the 2 and 7 days and in the mosquitoes it is between 8 and 12 days [18]. Thus, were considered to be $k_h \in [1/7, 1/2]$ and $k_v \in [1/12, 1/8]$
- Zika is symptomatic and asymptomatic infectious disease. Then ρ and $q = 1 - \rho$ represent the population of exposed humans developing symptoms or not, respectively, but still infected with the virus. It is reported that 20% infected with ZIKV are symptomatic and the remaining 80% are asymptomatic [26], [1]. Therefore, $\rho = 0.2$ and $q = 0.8$ are chosen as fixed parameters values.
- An individual infected by the ZIKV can recover and acquire permanent immunity, γ_s and γ_a represents the recovery rate of symptomatic and asymptomatic infectious humans, respectively. Symptomatic individuals are slow to recover from 6 to 12 days, and the asymptomatic individuals between 5 and 10 days [18]. Thus $\gamma_s \in [1/12, 1/6]$ and $\gamma_a \in [1/10, 1/5]$.

- σ represents the parameter of alteration of infectiousness. For represents all posible cases of infectiousness:
  - if $0 < \sigma < 1$, then I_a is less infectious that I_s,
  - if $\sigma = 1$, then I_a and I_s are equally infectious,
  - if $\sigma > 1$, then I_a is more infectious that I_s,

  It is assumed that $\sigma \in (0, 2.5]$.

Table (5–1) summarizes the results of the estimated parameters.

Table 5–1: Description of Model Parameters.

Param.	**Definition**	**Range**	**Unit**	**Ref.**
μ_h	Recruitment and natural death rate of human sexually active	$[\frac{1}{50 \times 365}, \frac{1}{18 \times 365}]$	$days^{-1}$	[5]
μ_v	Recruitment and natural death rate of vector	$[1/4, 1/35]$	$days^{-1}$	[18]
a	Biting rate	$[0.3, 1]$	$days^{-1}$	[18]
f_{hv}	Probability that a bite transmits infection vector to human	$[0.1, 0.75]$	$unitles$	[18]
f_{vh}	Probability that a bite transmits infection human to vector	$[0, 1]$	$unitles$	Free
β_{hv}	Transmission rate vector to human	$[0.03, 0.75]$	$days^{-1}$	[18]
β_{vh}	Transmission rate human to vector	$[0, 1]$	$days^{-1}$	[18]
α	Sexual transmission rate	$[0.03, 0.07]$	$days^{-1}$	[11]
k_h	Humans' incubation rate	$[1/7, 1/2]$	$days^{-1}$	[18]
k_v	Vectors' incubation rate	$[1/12, 1/8]$	$days^{-1}$	[18]
ρ	Probability of an exposed human develop symptoms	0.2	$unitles$	[26]
q	Probability of an exposed human not develop symptoms	0.8	$unitles$	[26]
γ_s	Recovery rate of symptomatic	$[1/12, 1/6]$	$days^{-1}$	[5]
γ_a	Recovery rate of asymptomatic	$[1/10, 1/5]$	$days^{-1}$	[18]
σ	Parameter of alteration of infectiousness	$(0, 2.5]$	$unitles$	Est.

5.2 Numerical Analysis

Numerical simulations were made using the computer software Matlab with the function ODE45 based on an explicit Runge-Kutta (4,5) formula, in order to study the effects of different values R_d, R_v and R_0 or as well as the models solution for all epidemiological classes as parameter were varied. The simulations help us explain the dynamics of the disease and predict its future course. On the other hand, our initial conditions are set to: $(S(0), E_h(0), I_s(0), I_a(0), R(0), S_v(0), E_v(0), I_v(0)) = (0.98, 0.02, 0, 0, 0, 1, 0, 0)$, which represent the start of the infection, i.e., when a large percentage of the population are susceptible (98%) and a small percentage are exposed (2%). Note that in the population of vector we do not considered an initial number of infected mosquitoes that is $(I_v(0) = 0)$, since, the basic reproductive number was found from the fact of considering only humans as new infections.

First, we note that 8 different cases can be presented that illustrate the different values that can be taken of R_0 as a function of **the contribution to the basic reproductive number by direct and vector transmission R_d and R_v respectively**. In consequence, a diagram depicted by regions of the changes in R_0 as function of R_d and R_v in Figure 5–1 quadrant I is divided into two large regions: the region $R_0 \leq 1$, where these are two cases $R_d < R_v < 1$ or $R_v < R_d < 1$ where the existence of the Zika-free equilibrium is the only possible equilibrium. The second regions being when $R_0 > 1$ where there are two fixed points the Zika-free and the endemic equilibrium. The region in which $R_0 > 1$ is further divided into 4 subregions, where six different possible cases are considered for reproductive number of vectorial and direct transmission. These are $R_d < R_v < 1$, $R_v < R_d < 1$, $R_d < 1 < R_v$, $R_v < 1 < R_d$, $1 < R_d < R_v$ and $1 < R_v < R_d$. Note that there may be an endemic state of the disease even when the contribution to the basic reproductive number by direct and vector transmission is smaller than one ($R_i \leq \mathbb{R}_j < 1$ for $i, j \in v, d$

and $i \neq j$). The latter is an interesting case since, if in average, a mosquito and an infected individual infect through a bite and sexual transmission to less than one susceptible individual one average respectively, the combination of the two transmissions can generate an epidemic in the population. On the other hand, the case in which the contribution to the basic reproductive number for one ($R_i < 1 < \mathbb{R}_j$ for $i, j \in \{v, d\}$ and $i \neq j$) of the two contributions is less than one and in which the other contribution is greater than one, implies $R_0 > 1$, generating, an epidemic of the Zika virus. This case indicates that one of the two types of transmissions (sexual or vector) is sufficient to develop a Zika virus epidemic. In the last case, the contribution to the basic reproductive number due to the sexual and vectorial propagation of the ZIKV, is greater than one, consequently $R_0 > 1$. This is the case in which the two types of transmissions generate an epidemic, consequently the greatest amount of infected population occurs. For better understanding of the epidemic associated with these cases observed, refer to (Figure 5–2).

Figure 5–2 shows the simulations of the epidemic developed by the six possible variations (all $R_0 > 1$) of the contributions of the direct and vectorial transmission R_d and R_v respectively, to the basic reproductive number R_0 for the symptomatic population (Figure 5–2a.), asymptomatic (Figure 5–2b.) and the total number infected in the population (Figure 5–2c.) which is the sum of the two populations mentioned above, whose values are shown in Table 5–2. Figure 5–2a shows that the maximum number of symptomatic ZIKV infected that occur in the epidemic is: 0.045 reached at 40 days for the case in which $1 < R_v < R_d$, 0.033 reached at 45 days for the case in which $1 < R_d < R_v$, 0.025 reached the 50 days for the case in which $R_v < 1 < R_d$, 0.014 reached the 80 days for the case in which $R_d < 1 < R_v$ and 0.004 reached the 110 days for the case in which $R_d < R_v < 1$ and $R_v < R_d < 1$. Note that the proportional maxima of the epidemic are reached each time in greater number of days. Note that, in the case $R_v < 1 < R_d$ (purple color) in which the

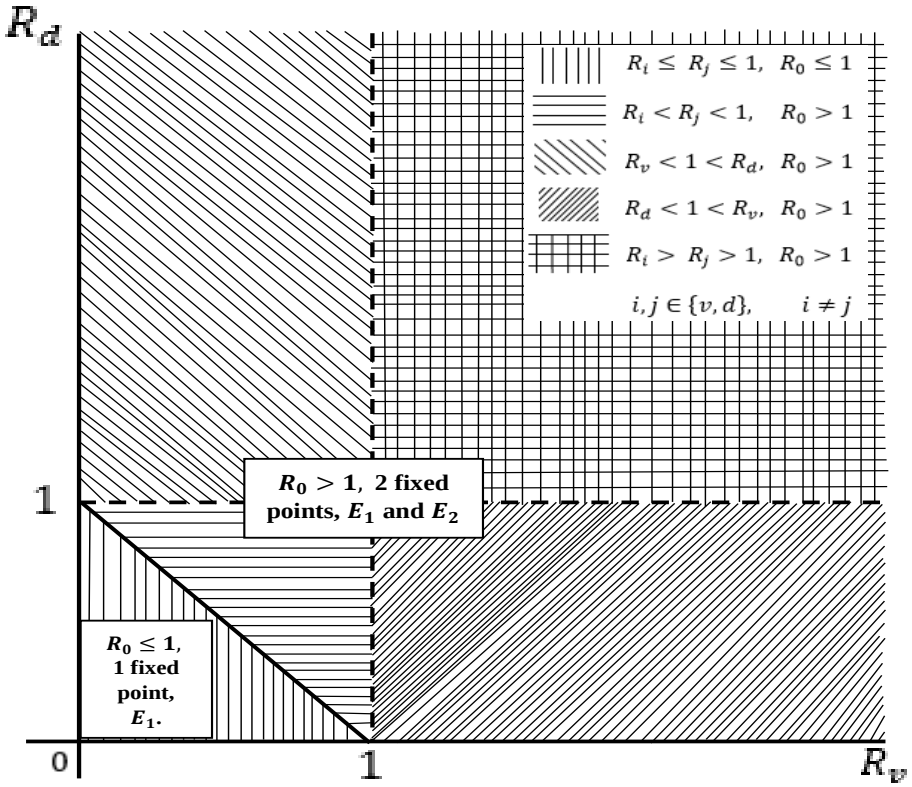

Figure 5–1: All the Possible Behavior of R_0 as a Function of R_d and R_v .

contribution to R_0 per vector transmission is less than one and for sexual transmission is greater than one, the maximum is reached in less days than in the case $R_v < 1 < R_d$ (green color) in which the contribution to R_0 per vector transmission is greater than one and for sexual transmission is less than one, indicating that the ZIKV is transmitted faster by having a sexual contact that leads to infection than by mosquito bite. A behavior and similar analysis are shown in Figure 5–2b, for the asymptomatic individuals (I_a) but note that the proportional maxima are different. The maxima associated to each case in the symptomatic population are 80% lower than those of the asymptomatic population. This is because from the beginning of

this investigation the reports were followed indicating that in an 80% of the infected population were asymptomatic and 20% symptomatic. Figure 5–2c is a summary of the Figures 5–2a and 5–2b but considering the total of the infectious population $(I_s + I_a)$. Note that the analysis of this graph is analogous to the analysis performed for the region associated with $R_0 > 1$ of Figure 5–1.

Table 5–2: Values for Figure 5–2.

Case	R_d	R_v	R_0
$R_v < R_d < 1$	0.7	0.6	1.3
$R_d < R_v < 1$	0.59	0.79	1.38
$R_v < 1 < R_d$	2.1	0.6	2.7
$R_d < 1 < R_v$	0.7	2.22	2.79
$1 < R_d < R_v$	2.1	2.99	5.09
$1 < R_v < R_d$	2.05	3.5	5.55

The parameter of alteration of infectiousness, the transmission rate from vector, to human and human to vector and the sexual transmission rate represented by σ, β_{hv}, β_{vh} and α respectively, are parameters that depending of values they take, can determine the free status of ZIKV or an endemic state. For example, the absence of vector and sexual transmission of the ZIKV would impede its propagation, determining the extinction of the disease, contrary to the presence of high values of these rates that would significant propagation allow of the ZIKV until potentially reaching an epidemic of the disease. Note that this can be verified in the value of R_0, in which these parameters appear in the numerators of the fractions indicating that they are directly influential in the extinction or progression of the disease. This fact will be corroborated and understood, in Chapter 6 of sensitivity analysis of R_0 to parameters. In consequence, the outcome of ZIKV infection depends mainly on the interplay of the parameters σ, β_{hv}, β_{vh}, and α. Numerical simulations are performed for different values of of σ, β_{hv}, β_{vh} and α and the values of some parameters are fixed as indicated in the Table 5–3.

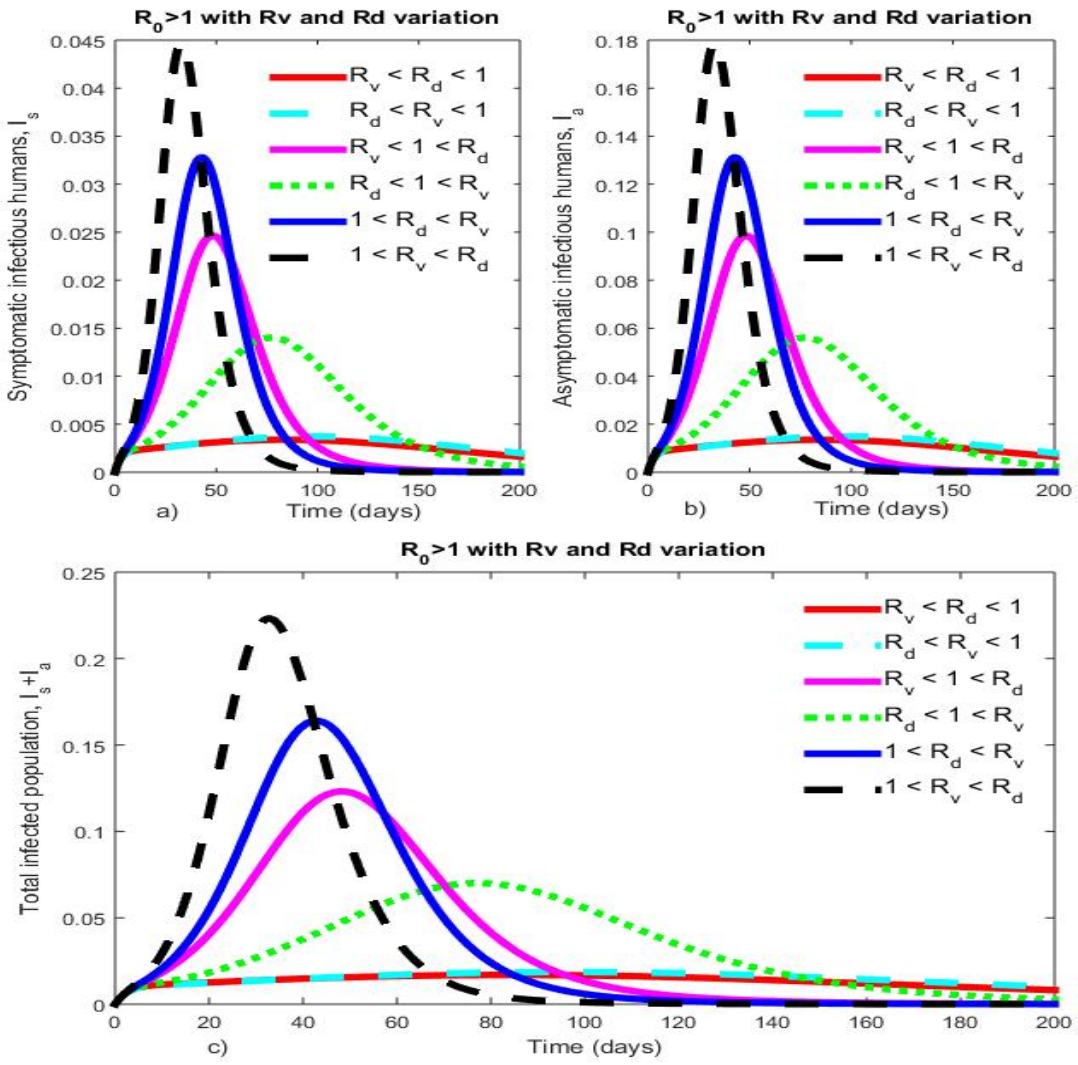

Figure 5–2: Temporal course of the infectious population all possible cases for the R_0 as function of R_d and R_v.

Table 5–3: Parameter with Fixed Values.

Param.	ρ	q	γ_a	γ_s	μ_h	μ_v	k_h	k_v
Valor	0.2	0.8	1/9	1/7	$1/(27 \times 365)$	1/20	1/5	1/9.5
Units	$Unitless$	$Unitless$	day^{-1}	day^{-1}	day^{-1}	day^{-1}	day^{-1}	day^{-1}

Figure 5–3 Shows the impact of the value of basic reproductive number (R_0) on Zika disease for value $R_0 < 1$. In any case, the solutions show the Zika free

equilibrium to be locally stable. Thus, the epidemic does not spread in the population, which means Zika dies out. Note that the population of susceptible mosquitoes reaches their maximum in less time (at 20 days) than the population of susceptible humans (at 90 days) because our model considers a recovered population and in the case of the Zika, the virus provides permanent immunity.

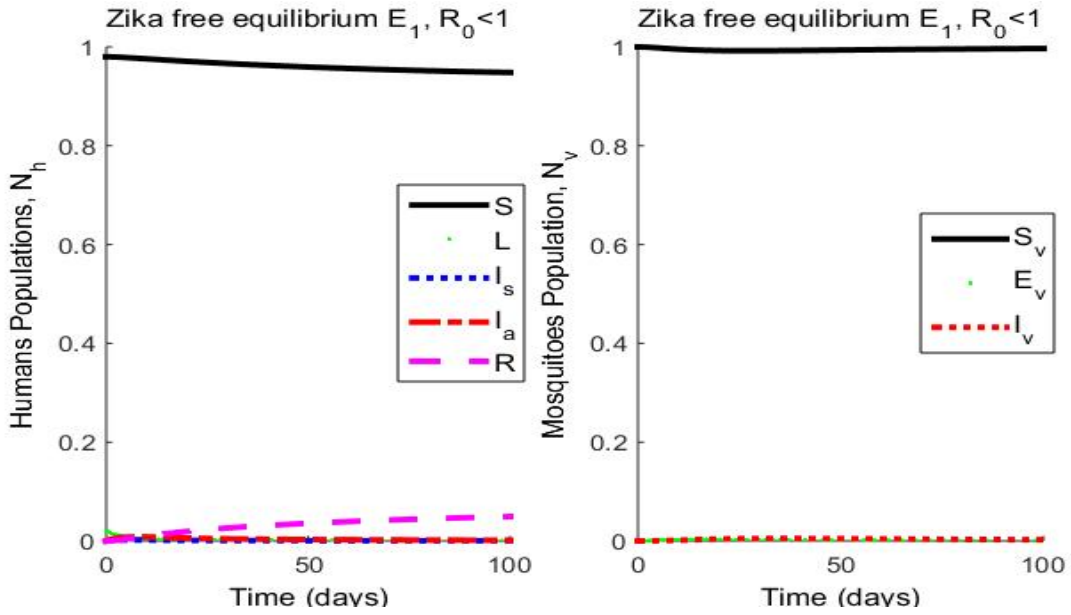

Figure 5–3: Model Solutions when $R_0 = 0.71 < 1$, the Epidemic Does Not Developed. This figure was created using the values from Table 5–3 with $\beta_{hv} = 0.035$, $\beta_{vh} = 0.07$ and $\alpha = 0.05$.

Figure 5–4 shows the impact of the basic reproductive number R_0 on Zika disease, for values of the parameters that provide $R_0 > 1$ (Table 5–3 with $\beta_{hv} = 0.15$, $\beta_{vh} = 0.12$ and $\alpha = 0.06$) . The simulations demonstrate that populations stabilize in an endemic equilibrium, as was demonstrated numerically. In this number of humans, susceptible and recovered per day are always larger than the number of infectious population (exposed, symptomatic and asymptomatic). Observe that approximately in the first 90 days, there is a growth of the infectious populations and consequently, a decrease in the susceptible ones. As the Zika disease produces

permanent immunity and no disease related deaths, there is growth of the recovered humans. After 90 days, the number of susceptible humans is less than the number of individuals recovered, where the number of infected by the virus decreases. This allows us to deduce that an epidemic of Zika virus would occur. But the permanent immunity achieved by infected individuals will cause that the number of infected in the population with the Zika virus will decrease, preventing the continued spread of this disease. Similarly, we note that the vector population has also reached the endemic equilibrium. Note that mosquitoes acquire the virus when they bite an infected human. This explains that approximately before 90 days there is a growth of infected vectors since in this same period of time, the number of infected humans is growing. But after 90 days, the population of infected mosquitoes decreases according to the population of infected people who are recovering.

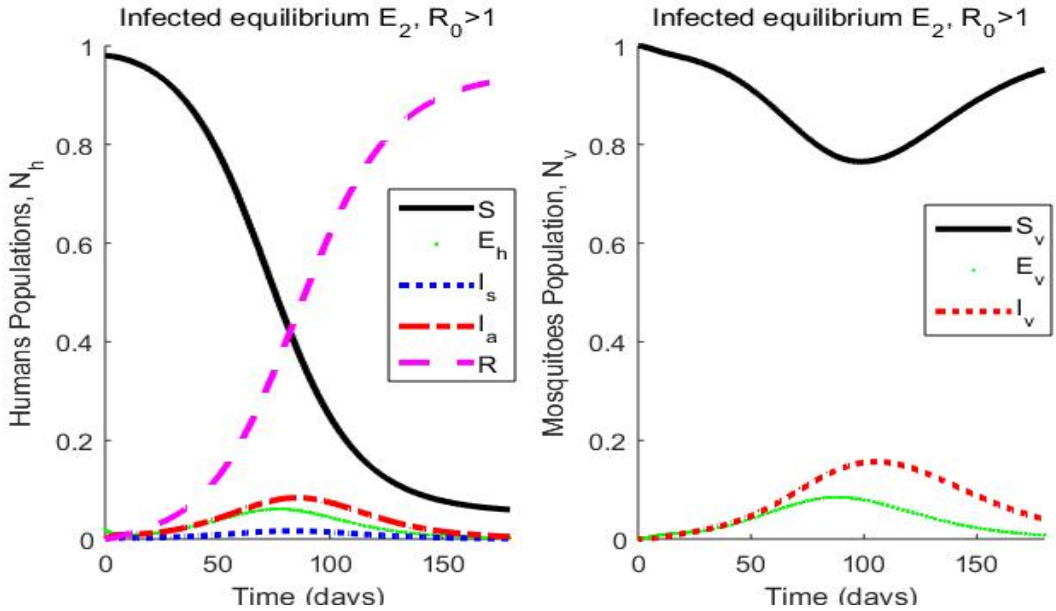

Figure 5–4: Model Solutions when $R_0 = 3.7 > 1$, the Infection Persists, Using the Values from Table 5–3 with $\beta_{hv} = 0.15$, $\beta_{vh} = 0.12$ and $\alpha = 0.06$.

Due to the scales that form the susceptible and recovered populations in the previous figures, it is difficult to observe the role of R_d, R_v and R_0. Consequently,

we present the solutions only for the infected individuals symptomatic and asymptomatic, which allow us to evaluate in more details the behavior of infection under these important parameters for this study.

In Figure 5–5, the graphs a, b, and c illustrate the behavior of the asymptomatic and symptomatic infected population, when the vector to human transmission rate β_{hv} variates. The maximums in proportion reached by the epidemic are: 0.03 and 0.006 for asymptomatic and symptomatic, respectively, in a time of 110 days for $\beta_{hv} = 0.1$ (Figure 5–5a.), 0.1 and 0.02 for asymptomatic and symptomatic individuals respectively, in a time of 70 days for $\beta_{hv} = 0.3$ (Figure 5–5b.), and 0.15 and 0.003 for asymptomatic and symptomatic respectively, in a time of 50 days for $\beta_{hv} = 0.5$ (Figure 5–5c.). These results show that when the vector to human transmission rate increases, the maximum number of cases at peak time (t peak) is reached in less days and the proportion of the maximum number of infected persons increases. The percentage difference of 80% of the number of asymptomatic and symptomatic infected persons is also preserved over time. Note the impact that the vector-to-human transmission rate has on the epidemic not only accelerates its growth, but also increases the infected population, and R_0 also grows by the direct relationship.

In Figure 5–6, the behavior of the two basic reproductive numbers R_0 (blue) and R_0^* (yellow) are analyzed as a function of the contribution by direct transmission and vector transmission R_d and R_v, respectively, and the constant plane $R_0 = 1$ (in red color). Recall that R_0 is the basic reproductive number considering humans as new infections and R_0^* is considering humans and mosquitoes as new infections. The graph indicates that two basic reproductive numbers share the same region of existence and stability for the equilibrium points.

Figure 5–7, a, b, and c illustrates the behavior of the asymptomatic and symptomatic infected population when the sexual transmission rate α varies. Notice the similar behavior that this figure has with the Figure 5–5 where the maximums in

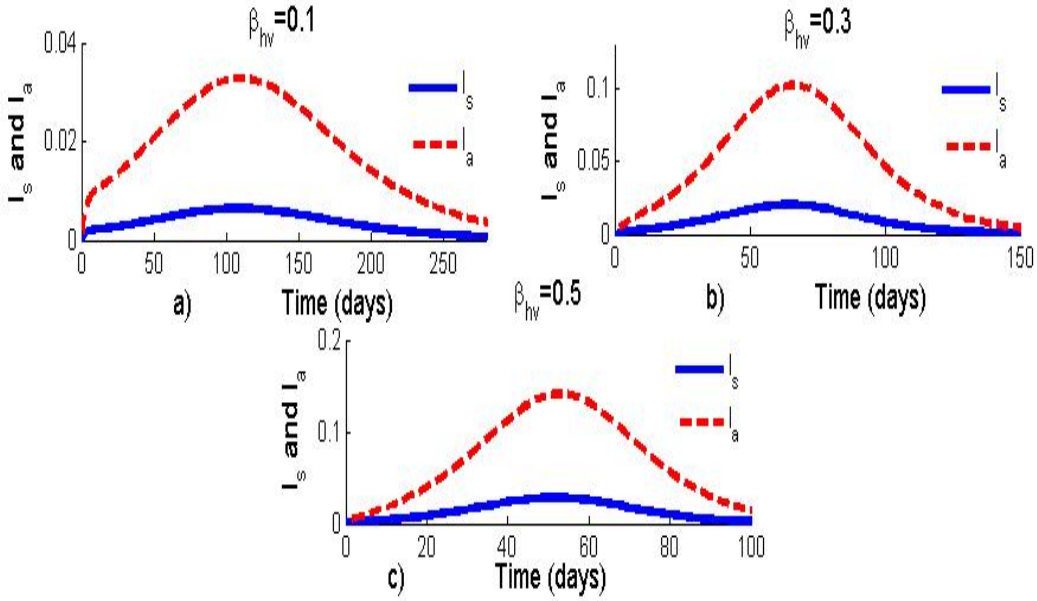

Figure 5–5: The graphs a, b, and c Represent the Behavior of the Symptomatic vs Asymptomatic Infectious Population when we varied β_{hv} for value $R_0 = 1.86$, $R_0 = 4.57$ and $R_0 = 7.29$, respectively. The parameter values are taken from Table 5–3 including $\sigma = 1.2$, $\beta_{vh} = 0.1$ and $\alpha = 0.05$

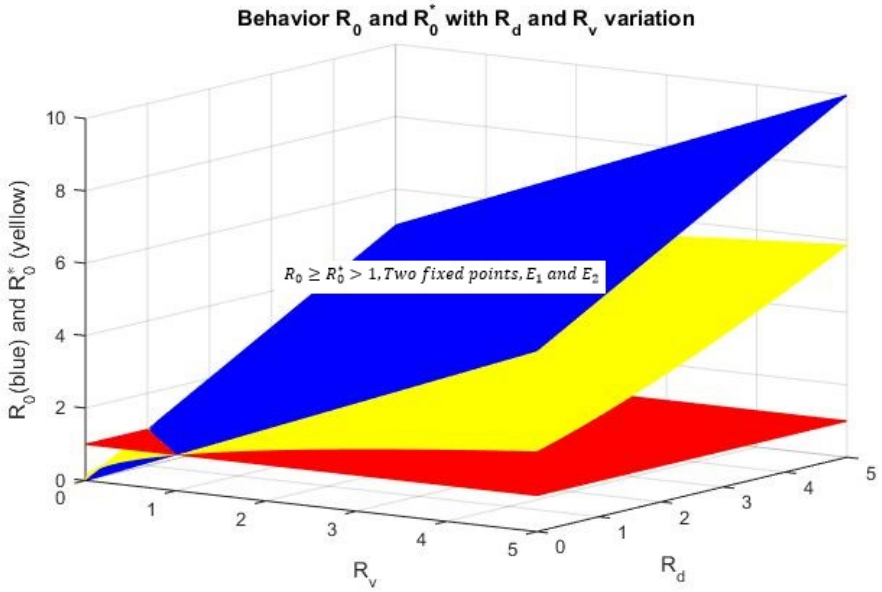

Figure 5–6: Behavior R_0 and R_0^* as a function of R_d and R_v.

proportion of humans reached by the epidemic are: 0.08 and 0.016 for asymptomatic and symptomatic, respectively, in a time of 80 days for $\alpha = 0.03$ (Figure 5–7a.), 0.09 and 0.018 for asymptomatic and symptomatic, respectively, in a time of 70 days for $\alpha = 0.05$ (Figure 5–7b.), and 0.1 and 0.02 for asymptomatic and symptomatic, respectively, in a time of 60 days for $\alpha = 0.07$ (Figure 5–7c.). The results show that when the sexual transmission rate increases, the maximum number of cases a time tpeak is reached in less days and the proportion of infected persons increases in the population. However, note that these maxima does not vary much compared to the maxima of Figure 5–5. Similarly, the percentage difference of 80% of the number of asymptomatic and symptomatic infected persons is preserved over time. If we compare the duration of the epidemic of this figure with those of the Figure 5–2, we corroborate the results obtained, in which the direct transmission causes a faster spread of the ZIKV than the vector transmission.

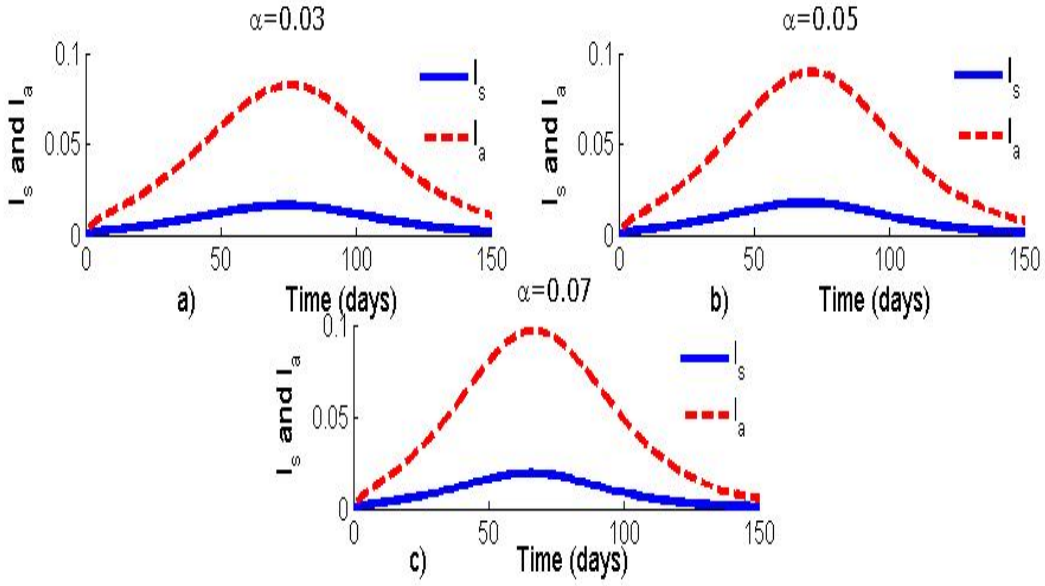

Figure 5–7: The graphs a, b and c represent the behavior of the symptomatic vs asymptomatic infectious populations by varying α with a $R_0 = 3.75$, $R_0 = 3.92$ and $R_0 = 4.09$, respectively. The parameter values are taken from Table 5–3 including $\sigma = 1$, $\beta_{vh} = 0.1$ and $\beta_{hv} = 0.3$

Figure 5–8 illustrates the behavior of the total infectious population ($I = I_a + I_s$) in which in graph a, the rate of vector-to-human transmission β_{hv} variates, while that of graph b is for the sexual transmission rate (α) variation. Summarizing illustrated in the Figures 5–5 and 5–7. In summary, the increase of the two rates has a relationship with the time taken to reach the maximum, that is, tpeak m of the infected population in an epidemic and a direct relationship with the growth of it. With the suggestion of the literature that β_{hv} is larger than α, the values of α are small compared to the of vector transmission, rate β_{hv}. Result shows that as both β_{hv} and α increase, the number of ZIKV cases also increases. However, the impact on the number of cases increases higher with larger values of β_{hv} that these of α.

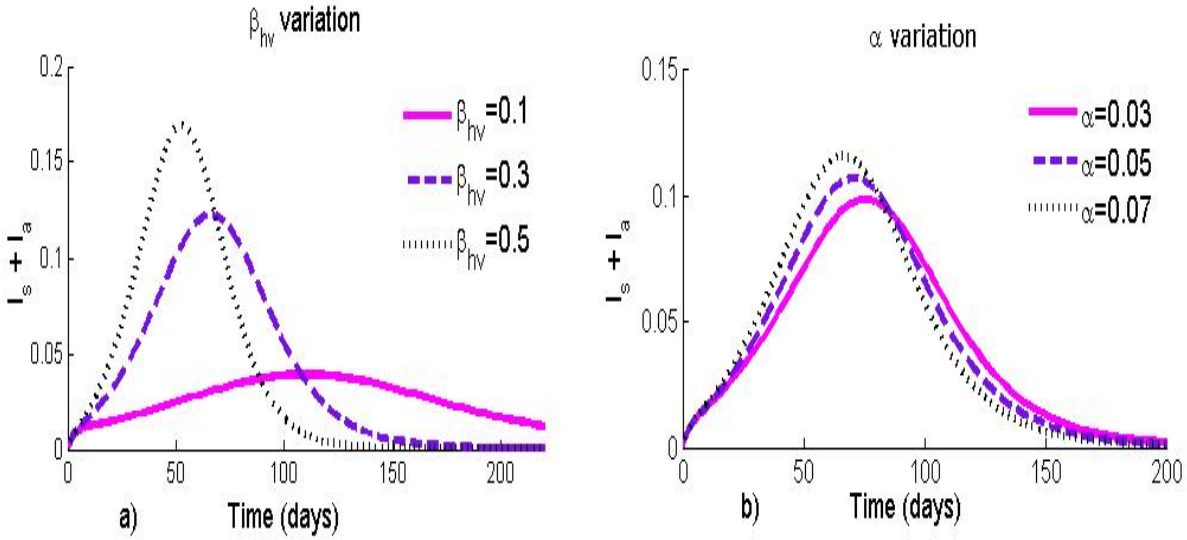

Figure 5–8: The graphs a and b represent the behavior of the infectious total population when β_{hv} and α variate, respectively. For β_{hv} equivalent to 0.1, 0.3 and 0.5, R_0 is 1.86, 4.57 and 7.29, respectively and for α equal to 0.03, 0.05 and 0.07, R_0 is 3.75, 3.92 and 4.09, respectively. For a and b the parameter values are taken from Table 5–3 including $\sigma = 1.2$, $\beta_{vh} = 0.1$ and $\alpha = 0.05$ for a and for b $\sigma = 1$, $\beta_{vh} = 0.1$ and $\beta_{hv} = 0.3$

Figure 5–9, shows behavior of the symptomatic and asymptomatic infected population under the variations of the probability of that exposed human not developing symptoms and developing symptoms, q and ρ, respectively. We observe that these two probabilities, unlike the vector and sexual transmission rates, only influence the number of infected people reached per day, but not the time tpeak since, for example, in the two graphs, we observe that the maximum is reached at 80 days in any of the cases of ρ and q. Note that if q grows, the population of infected asymptomatic grows and that of the symptomatic decreases.

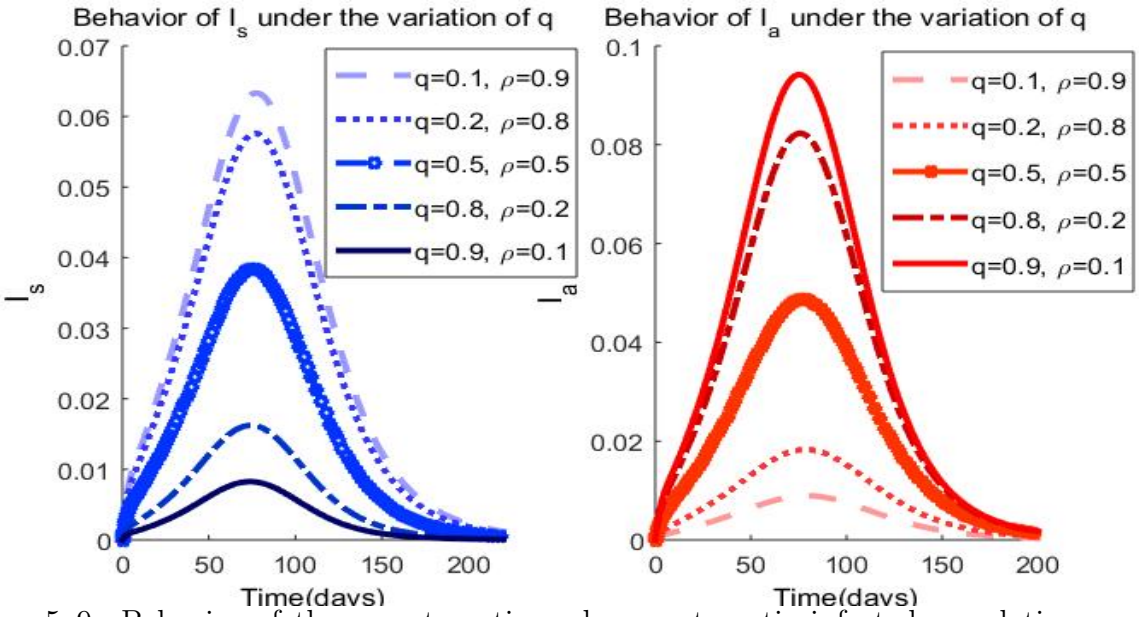

Figure 5–9: Behavior of the symptomatic and asymptomatic infected population under the variation of probability of that exposed human no developing symptoms and develop symptoms, q and ρ respectively .

In Figure 5–10 we observe the behavior of the basic reproductive number R_0 (blue color) as a function of β_{hv} and α, that is when the transmission rates of vector to human (β_{hv}) and of direct transmission (α) are varied. Here, the constant plane is $R_0 = 1$ is shown in red color. Note the direct relation between the indicated parameters and the basic reproductive number. On the other hand, the region where $R_0 \leq 1$ is represented by the bottom part of the intersection between the

plane of R_0 and the plane 1, is small in comparison with region $R_0 > 1$ indicating the strong impact of the direct and vectorial transmission rates on the development of the disease observe that the influence of β_{hv} is greater than that of α.

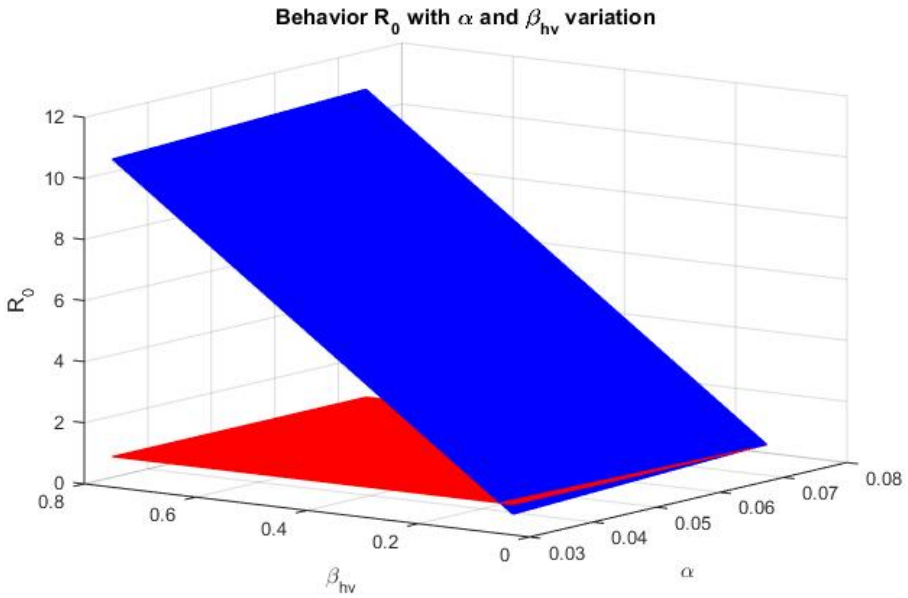

Figure 5–10: Behavior of the basic reproductive number R_0 when the transmission rates of vector a to human and of direct transmission β_{hv} and α are varied of blue color and the constant plane is $R_0 = 1$ of red color.

5.3 Role of the Parameter of Infectiousness (σ)

The infectiousness is understood as the measure to be able to spread with success an illness to a susceptible host, which means if the individual A is more infectious than B, then A has the power to spread more individuals than B. The study of the infectiousness in individuals affected by the virus, determines important information to know its role in the illness and, thereby, to enlarge the knowledge of it. For this, note that , R_0 can be written as:

$$R_0 = R_s + \sigma R_a, \tag{5.1}$$

where,

$$R_s = \left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{vh}}{\mu_h + \gamma_s}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\left(\frac{\beta_{hv}}{\mu_v}\right) + \left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\alpha}{\mu_h + \gamma_s}\right),$$

$$\text{and} \quad R_a = \left(\frac{q k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{vh}}{\mu_h + \gamma_a}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\left(\frac{\beta_{hv}}{\mu_v}\right) + \left(\frac{q k_h}{\mu_h + k_h}\right)\left(\frac{\alpha}{\mu_h + \gamma_a}\right),$$

therefore

$$R_a = \frac{1}{\sigma}(R_0 - R_s). \tag{5.2}$$

Similarly to Section 4.1.2, we can interpret R_s and R_a as the representation of the asymptomatic or symptomatic infectious reproduction numbers, which are a contribution to R_0 by individuals who are infectious asymptomatic and symptomatic to ZIKV, respectively.

Let us consider that R_a as a function of R_s for a fixed value of R_0, that is, it represents a segment with intercepts $\left(\frac{1}{\sigma}R_0, 0\right)$ and $(0, R_s)$ in the R_a and R_s plane, respectively. However, if we take $R_0 = 1$ the intercepts are $\left(\frac{1}{\sigma}, 0\right)$ and $(0, R_s)$. We obtain the segment that divides the $R_0 > 1$ and $R_0 < 1$ regions, as shown in Figure 5–11. In Figure 5–11b, we show that if σ grows (asymptomatic are lower infectious) then, $\frac{1}{\sigma}$ approaches 0 and the area of the region $R_0 < 1$ decreases as is illustrated by Figure 5–11a. Note that in this region there are all the values in which the basic reproductive number is less than 1, that is, where an infected individual infects less than one susceptible individual on average. Therefore, the disease does not develop and as it was verified mathematically in Section 4.1.5, when $R_0 < 1$ there is a Zika free equilibrium, which is asymptotically stable. Consequently, the disease does not progress. This region in which $R_0 < 1$ is called optimal region for the epidemic. Reciprocally, if σ decreases, then $\frac{1}{\sigma}$ take bigger values and the optimal region $R_0 < 1$ grows as is illustrated in Figure 5–11 c which verifies the impact

of the infectivity for the development or extinction of the disease of the infected population. In conclusion, if the parameter of infectivity alteration σ reaches values smaller than one, then the area of the region where the basic reproductive number is less than one increases, consequently increasing the probability of Zika's disease extinction.

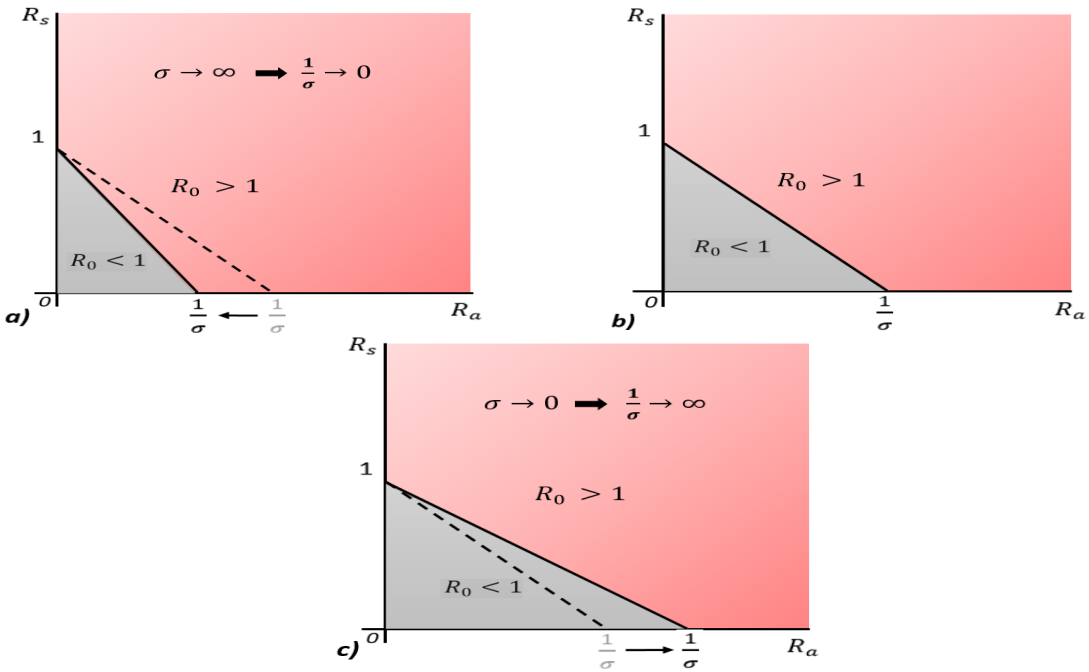

Figure 5–11: Regions of $R_0 < 1$ or $R_0 > 1$ as function of σ.

Figure 5–12 associated σ through Equation 5.1 shows the direct relationship between the basic reproductive numbers and the infectivity parameter (σ), corroborating the impact of this parameter on the spread of ZIKV. That is, there is a direct relationship between R_0 and σ, as σ increases (more infectivity for asymptomatic infected R_0 increases.

In Figure 5–13, the graphs a, b, and c illustrate the behavior of the asymptomatic and symptomatic infected populations, while Figure 5–13d illustrates the behavior of the total infected population. Notice the similar behavior that this figure

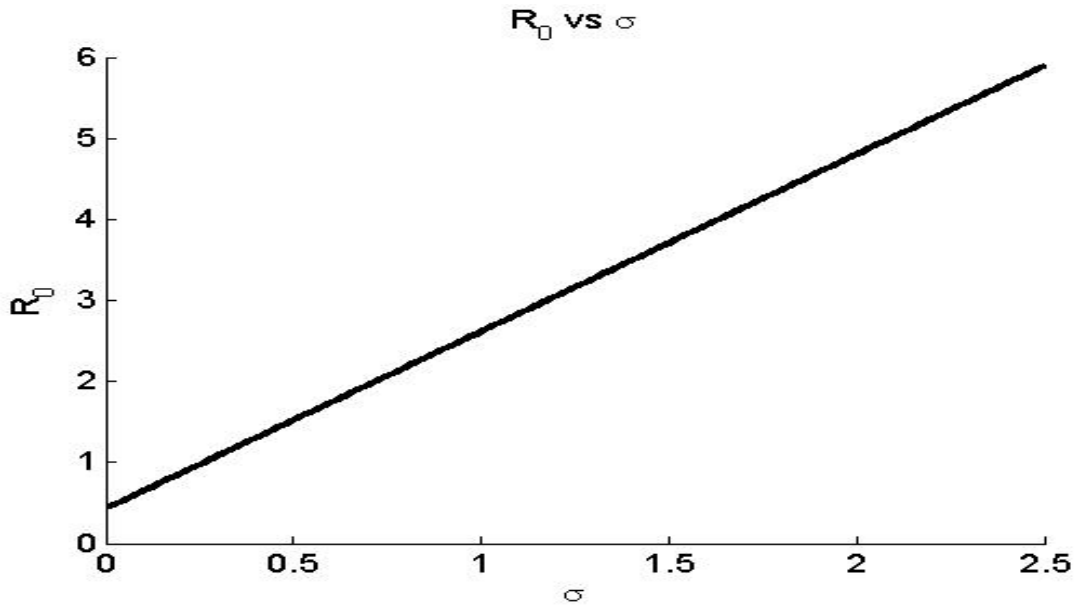

Figure 5–12: Behavior of basic reproductive number R_0 under the variation of parameter of alteration of infectiousness σ.

5–13 has with the Figure 5–5 and 5–7. Note that in Figure 5–13 a, b, and c the number of infected asymptomatic and symptomatic per day correspond to 80% and 20% of the total of the infected population shown in Figure 5–13d. The epidemic illustrated in Figure 5–13a occurs when the infectivity of asymptomatic infected persons is lower than that of symptomatic infected persons ($\sigma < 1$). At 100 days the maximum number of infected persons, is reached in a proportion of 0.025 and 0.006 for asymptomatic and symptomatic persons respectively. Figure 5–13b illustrates the development of an epidemic when the symptomatic and asymptomatic infected individuals have the same infectiousness ($\sigma = 1$), where the maximum number reached by the asymptomatic and symptomatic epidemic is 0.06 and 0.01 at the 80 day, respectively. On the other hand, Figure 5–13c occurs when the infected asymptomatic has greater infectiousness than the symptomatic ($\sigma > 1$), where the maximum in proportion is 0.12 and 0.03 for asymptomatic and symptomatic respectively at 60 days. Finally, Figure 5–13 d) illustrates the summary of Figures a, b, and c. An

epidemic of the total of the infected population ($I = I_s + I_a$) is illustrated. In summary, it is observed that when the infectivity of the asymptomatic individuals in comparison with the symptomatic ones grows, the maximum number of cases tpeak reached on the epidemic grows and the time in which it is reach (tpeak) decreases.

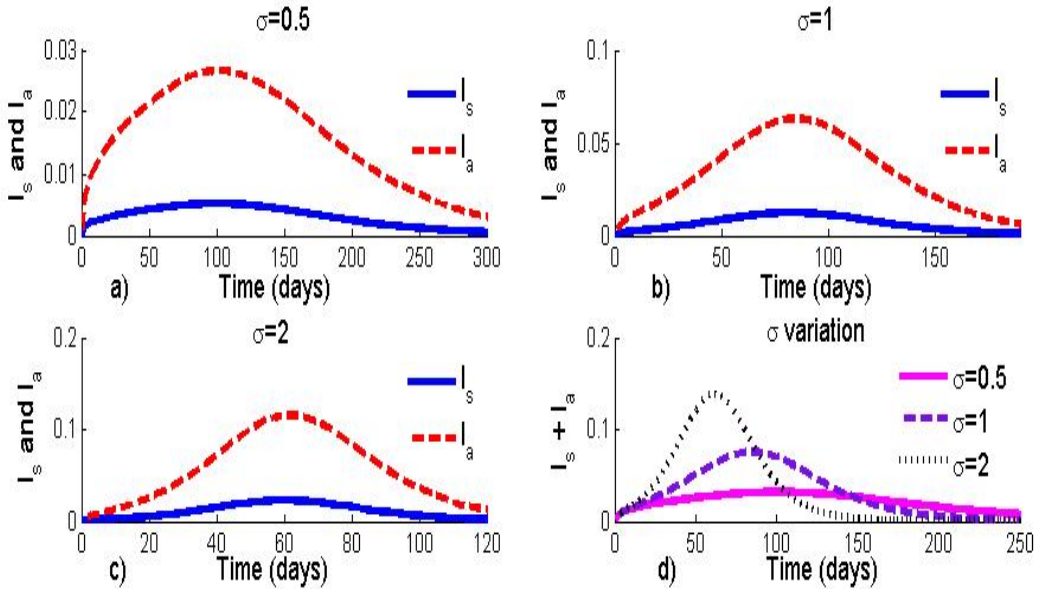

Figure 5–13: The graphs a, b and c represent the behavior of the symptomatic vs asymptomatic infectious population when σ is varied with a $R_0 = 1.63$, $R_0 = 2.80$ and $R_0 = 5.15$ respectively, and the graph d is the combination of all graphs for infectious total population. The parameter values are taken from Table 5–3 including $\alpha = 0.055$, $\beta_{vh} = 0.1$ and $\beta_{hv} = 0.2$.

Figure 5–14 illustrates the behavior at equilibrium for the populations of symptomatic and asymptomatic infected when the parameter of alteration of infectiousness σ varies for all possible cases of probability of being symptomatic ρ and asymptomatic q. Although, there is no bibliographic evidence of the case in which $\rho > q$.

Note that, Figure 5–14a illustrates the case supported by the literature that is, when the probability of being infected asymptomatic is greater than that of being symptomatically infected, the number of asymptomatic infected population at the equilibrium is always greater than that of the symptomatic. Observe that the

growth in the equilibrium of the symptomatic infected grows slowly in comparison with that of the asymptomatic ones; this is due to the fact that the infectivity of the asymptomatic grows and in the probability of being infected asymptomatic is greater than that of being infected symptomatic ($q > \rho$). Although there is no bibliographic evidence of this case, we present Figure 5–14b as a possible event when $\rho > q$, in which we note that at equilibrium the number of symptomatic remains greater than the number of asymptomatic in the population regardless of infectivity. This plot allows us to understand the role of the infectiousness in the populations since the quantity in the equilibrium of infected population of the two classes depends on who has the greater probability of infectivity, but the total number of the infected in the population (purple color) in the equilibrium is greater when the number of asymptomatic is greater than that of the symptomatic, indicating that, when the asymptomatic population is larger than the symptomatic, there are more cases of infections in the population than when the number of symptomatic individuals is greater than that of the asymptomatic. An explanation for this phenomenon that is happening in the infected population is that infected symptomatic are detected and therefore isolated to prevent the spread of the virus, while asymptomatic are not detected, they spread the virus silently. Note that when $\rho \leq q$ and if the infected symptomatic are more infectious than the asymptomatic $\sigma < 1$, the growth in the equilibrium of the two classes of infected populations is accelerated, while, when $\sigma > 1$ it slows down. (similarly for the case $\rho > q$).

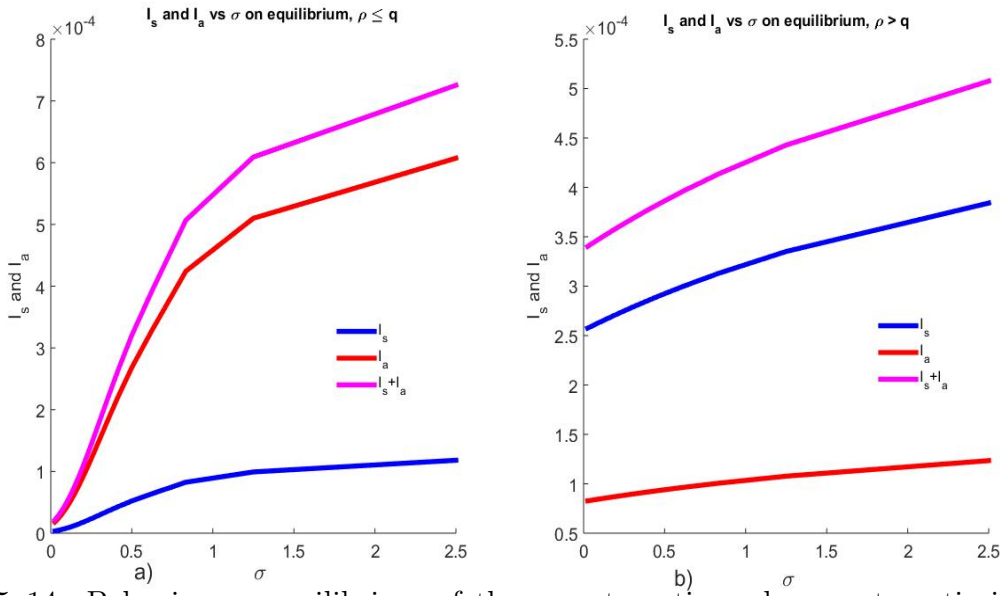

Figure 5–14: Behavior on equilibrium of the symptomatic and asymptomatic infected population with the σ variation, for all possible cases of ρ and q

Chapter 6
SENSITIVITY ANALYSIS FOR R_0

The parameter estimation provided baseline values or a range of values for the parameters involved in the model. But these have uncertainty that might affect the results obtained in Chapter 5. Sensitivity Analysis is a method that can be applied to quantify the effects of an input parameter in the uncertainties in the model's output solution [2]. The method consists of applying small perturbations to the parameters in order to quantify the change in the output solution (see Figure 6–1) and in consequence determine which parameters have most or least effect in the output.

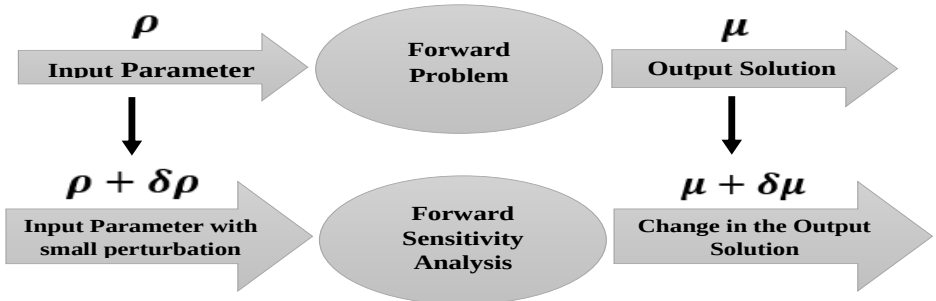

Figure 6–1: The forward problem with parameter ρ and output solution μ and small perturbations δ.

Leon Arriola and James M. Hyman [2] describes a forward problem as one that takes an input parameter ρ and produces the associated output solution μ. For

example given the Initial Value Problem:

$$\frac{d\overrightarrow{\mu}}{dt} = \overrightarrow{f}(\overrightarrow{\mu}, t; \rho), \quad \overrightarrow{\mu}(0) = \overrightarrow{\mu}_0,$$

then the forward sensitivity analysis consists of introducing small perturbations to the parameter $\delta\rho$ in order to quantify the output perturbations is,

$$\frac{d\overrightarrow{\mu} + \delta\overrightarrow{\mu}}{dt} = \overrightarrow{f}(\overrightarrow{\mu} + \delta\overrightarrow{\mu}, t; \rho + \delta\overrightarrow{\rho}).$$

It is said that a parameter is more sensitive, if small changes in it produce big changes in the solution output. Therefore, it relative size must be taken into account.

Leon Arriola and James M. Hyman [2] defined the normalized sensitivity index (SI) as

$$S_\rho = \lim_{\delta\rho\to 0} \frac{\frac{\delta\mu}{\mu}}{\frac{\delta\rho}{\rho}} = \frac{\rho}{\mu}\frac{\partial\mu}{\partial\rho} \quad \mu \neq 0.$$

If the sign of the number of the SI is positive then when the value of the parameter grows the output solution also grows. On the other hand, if the SI is negative: where the value of the parameter grows the output solution decreases [2] .

A classic example, for a better understanding of the sensitivity analysis is based on the SIR rescaled model by Kermack-McKendrick [23] given by:

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI - \mu S, \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I, \\ \text{and} \quad \frac{dR}{dt} &= \gamma I - \mu R, \end{aligned}$$

where μ is the recruitment and natural death rates of the population, β is the transmission rate, and γ is the recovered rate. The basic reproductive number

associated with the model is:

$$R_0 = \frac{\beta}{\gamma + \mu},$$

that is, the transmission rate times the total average time individuals spent as infectious. The basic reproductive number is the output solutions and the SI's for each parameters is given by:

$$\begin{aligned} S_\beta &= \frac{\beta}{R_0} \cdot \frac{\partial R_0}{\partial \beta} = 1, \\ S_\gamma &= \frac{\gamma}{R_0} \cdot \frac{\partial R_0}{\partial \gamma} = -\frac{\gamma}{\gamma + \mu}, \\ S_\mu &= \frac{\mu}{R_0} \cdot \frac{\partial R_0}{\partial \mu} = -\frac{\mu}{\gamma + \mu}. \end{aligned}$$

Using arbitrary parameter values we verified the impact in R_0 studying the sign of the SI of the parameters. If we take $\mu = 1/79$, $\gamma = 1/7$ and $\beta = 0.3$ then $R_0 = 1.92907$ and the SI value associated to every parameter is: $S_\mu = -0.081395$, $S_\gamma = -0.918604$ and $S_\beta = 1$ telling us that if we increase β by 1% then R_0 increases by 1% since the sign of S_β is positive. This is easily verified by increasing $\beta = 0.3$ to $\beta = 0.303$, which increase R_0 from 1.92907 to 1.94836 in consequence its growth represents a 1% increase in R_0, as estimated from the SI. Similarly since $S_\gamma = -0.918604$ is negative, if is γ increased by approximately 0.9186% then R_0 decrease approximately by 0.9186%. On the other hand, the parameters of greatest influence in the epidemic are β and γ, since, their SI magnitudes are the largest among the parameters. This result is to be expected since, when the rate of transmission increases, the infectious population grows and if the recovery rate increases then number of the infected individual decreases faster and in them decrease.

As mentioned before, the basic reproductive number R_0 is the expected number of secondary cases produced by a typical infective human in a completely humans

and vecotor susceptible population. In consequence, if $R_0 \leq 1$ the infection dies out while if $R_0 > 1$ the infection produced by the ZIKV remains, and the epidemic grows. Let us recall that in our case:

$$R_0 = \left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{vh}}{\mu_h + \gamma_s}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\left(\frac{\beta_{hv}}{\mu_v}\right) + \left(\frac{\sigma q k_h}{\mu_h + k_h}\right)\left(\frac{\beta_{vh}}{\mu_h + \gamma_a}\right)\left(\frac{k_v}{\mu_v + k_v}\right)\left(\frac{\beta_{hv}}{\mu_v}\right) + \left(\frac{\rho k_h}{\mu_h + k_h}\right)\left(\frac{\alpha}{\mu_h + \gamma_s}\right) + \left(\frac{q k_h}{\mu_h + k_h}\right)\left(\frac{\sigma\alpha}{\mu_h + \gamma_a}\right),$$

and shown in Section 4.1.2.

First we calculate the SI's of R_0 for the twelve parameters involved.

$$
\begin{aligned}
S_{\mu_h} &= -\frac{\mu_h}{R_0}\left[\frac{R_0}{\mu_h+k_h}+\frac{R_{I_s}^v+R_{I_s}^d}{\mu_h+\gamma_s}+\frac{R_{I_a}^v+R_{I_a}^d}{\mu_h+\gamma_a}\right],\\
S_{\mu_v} &= -\frac{\mu_v}{R_0}\left[\frac{R_v}{\mu_v+k_v}+\frac{R_v}{\mu_v}\right],\\
S_{\beta_{hv}} &= \frac{R_{I_s}^v+R_{I_a}^v}{R_0},\\
S_{\beta_{vh}} &= \frac{R_{I_s}^v+R_{I_a}^v}{R_0},\\
S_{\alpha} &= \frac{R_{I_s}^d+R_{I_a}^d}{R_0},\\
S_{k_h} &= \frac{\mu_h}{\mu_h+k_h},\\
S_{k_v} &= \frac{\mu_v R_v}{(\mu_v+k_v)R_0},\\
S_{\rho} &= \frac{R_{I_s}^v+R_{I_s}^d-\rho/q(R_{I_a}^v+R_{I_a}^d)}{R_0},\\
S_{q} &= \frac{\rho/q(R_{I_a}^v+R_{I_a}^d)-(R_{I_s}^v+R_{I_s}^d)}{R_0},\\
S_{\gamma_s} &= -\frac{\gamma_s}{R_0}\left[\frac{R_{I_s}^v+R_{I_s}^d}{\mu_h+\gamma_s}\right],\\
S_{\gamma_a} &= -\frac{\gamma_a}{R_0}\left[\frac{R_{I_a}^v+R_{I_a}^d}{\mu_h+\gamma_a}\right],\\
\text{and}\quad S_{\sigma} &= \frac{R_{I_a}^v+R_{I_a}^d}{R_0}.
\end{aligned}
$$

Table 6–1 shows the parameter that we chose from the literature as well as their corresponding SI's. From Table 6–1, we observe that the parameters with largest SI's (in magnitud), and in consequence, more influential to R_0 are μ_v and γ_a with negative SI follow by, σ, β_{hv} and β_{vh} with positive SI (See Figure 6–2). That is, if μ_v and γ_a increase by 0.9835% and 0.8364%, respectively, then R_0 decreasing by 0.9835% and 0.8364%, respectively. Similarly, if β_{hv}, β_{vh} and σ by 0.7440%, 0.7440% and 0.8372% respectively then R_0 also increases in the same percent. The recruitment and natural death rate vector (μ_v) cannot be change, naturally only through control measures. Now, if the death rate of mosquitoes grows, the basic reproductive

number decreases since these are transmitters of the infection. Therefore, once an epidemic occurs, efforts to control the epidemic should focus on the recovery rate of asymptomatic γ_a, the transmission rate from vector to human β_{hv}, the transmission rate human to vector β_{vh} and the parameter of greater interest based our research the parameter of alteration of infectiousness σ. For example if we increase the recovery rate of the asymptomatic infected γ_a then, considering that Zika is a disease with permanent immunity, we will have fewer propagation contacts that transmit infection consequently R_0 decreases, the vector transmission rates β_{hv} and β_{vh} have equal positive SI's value. The prevention of the vector contagion of the ZIKV whether by medical treatment, the use of repellents or a possible vaccine (see [33]), could reduce these transmission rates and speed up recovery, consequently decreasing R_0 with the possibility of reach the eradication of the disease (when $R_0 < 1$).

Table 6–1: Fixed parameter values to compute the SI's.

Parameter	**Value**
μ_v	$1/20$
σ	1
γ_a	$1/9$
β_{hv}	0.1
β_{vh}	0.15
α	0.07
k_v	$1/9.5$
q	0.8
γ_s	$1/7$
ρ	0.2
μ_h	$1/(27 \times 365)$
k_h	$1/5$

SI	**Value**
S_{μ_v}	-0.9835
S_{σ}	0.8372
S_{γ_a}	-0.8364
$S_{\beta_{hv}}$	0.7440
$S_{\beta_{vh}}$	0.7440
S_{α}	0.2560
S_{k_v}	0.2396
S_{q}	0.1859
S_{γ_s}	-0.1627
S_{ρ}	-0.0464
S_{μ_h}	-0.0013
S_{k_h}	0.0005071

On the other hand, note that the value of the SI associated with the parameters γ_a and σ are negative and positive ,respectively, and its absolute value are the largest of the rest of the parameters. Therefore, γ_a and σ are parameters most influential to among R_0. These two parameters are significantly related since if the parameter of alteration infectious increases (with $\sigma > 1$), then the infectious of the asymptomatic

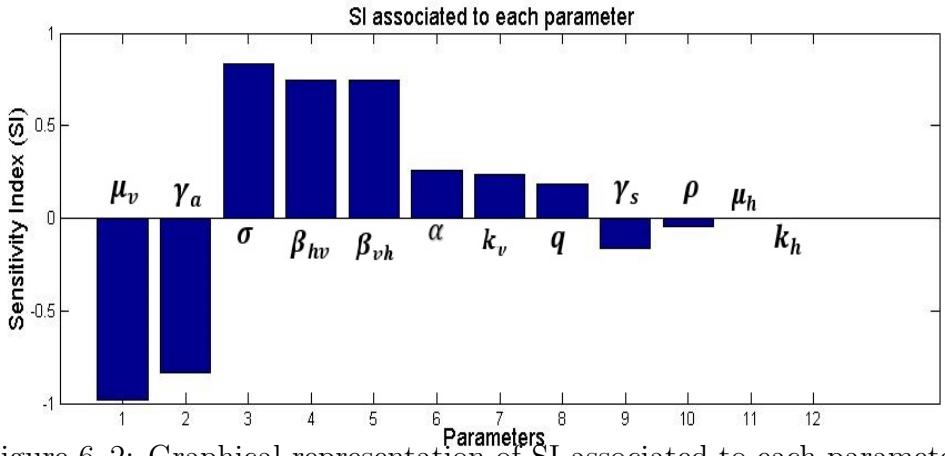

Figure 6–2: Graphical representation of SI associated to each parameter.

infected individuals is greater than that of symptomatic infected particularly considering 80% of individuals are asymptomatic. On the other hand, if the recovery rate of asymptomatic individuals decreases (γ_a), then there are more asymptomatic infectious individual without recovery and if the σ parameter is growing in consequence, a greater susceptible population are infected by asymptomatic individuals which increases R_0.

Now, we present the SI's for all possible combination of σ, ρ and q. SI's case for when the infectivity of the symptomatic infected is lower than that of the asymptomatic ($\sigma < 1$), the same than that of the asymptomatic ($\sigma = 1$) and greater than that of the asymptomatic ($\sigma > 1$) are show the Figure 6–3, 6–4 and 6–5 respectively. As a reminder, ρ is the probability that an individual infected by the ZIKV becomes symptomatic, while q is the probability that become asymptomatic, therefore R_0 is more sensitive to:

- μ_v, β_{hv}, and β_{vh} in the cases when $\rho = q$ and for all σ or when $\rho < q$ and $\sigma < 1$.
- μ_v, σ, and γ_a when $\rho < q$ and $\sigma \geq 1$.
- μ_v, γ_s, and β_{hv} when $\rho > q$ and $\sigma \leq 1$.
- μ_v, q and ρ when $\rho > q$ and $\sigma > 1$.

This can be summarized in Table 6–2:

Table 6–2: Sensitivity Analysis for General Cases

Param.	μ_v	β_{hv}	β_{vh}	σ	γ_a	γ_s	q	ρ
SI sign	-	+	+	+	-	-	+	-

Cases	$\rho < q$	$\rho = q$	$\rho > q$
$\sigma < 1$	μ_v	μ_v	μ_v
	β_{hv}	β_{hv}	γ_s
	β_{vh}	β_{vh}	β_{hv}
	σ	γ_s	β_{vh}
	γ_a		
$\sigma = 1$	μ_v	μ_v	μ_v
	σ	β_{hv}	γ_s
	γ_a	β_{vh}	β_{hv}
	β_{hv}	σ	β_{vh}
	β_{vh}	γ_a	
$\sigma > 1$	μ_v	μ_v	μ_v
	σ	β_{hv}	q
	γ_a	β_{vh}	ρ
	β_{hv}	σ	β_{hv}
	β_{vh}	γ_a	β_{vh}
			γ_s

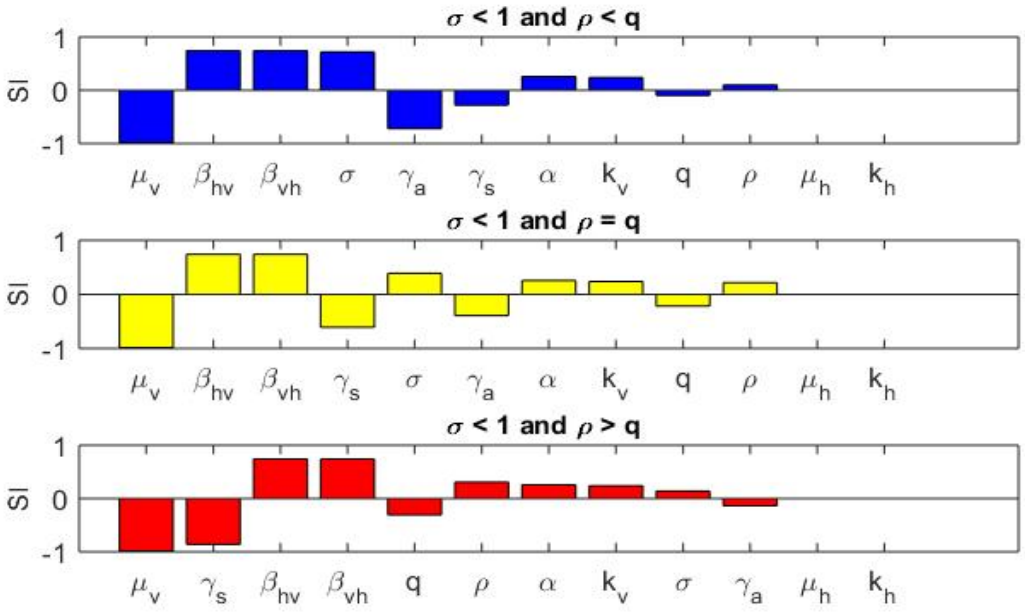

Figure 6–3: Graphical representation of SI associated to each parameter for $\sigma < 1$ and all possible cases σ, ρ and q.

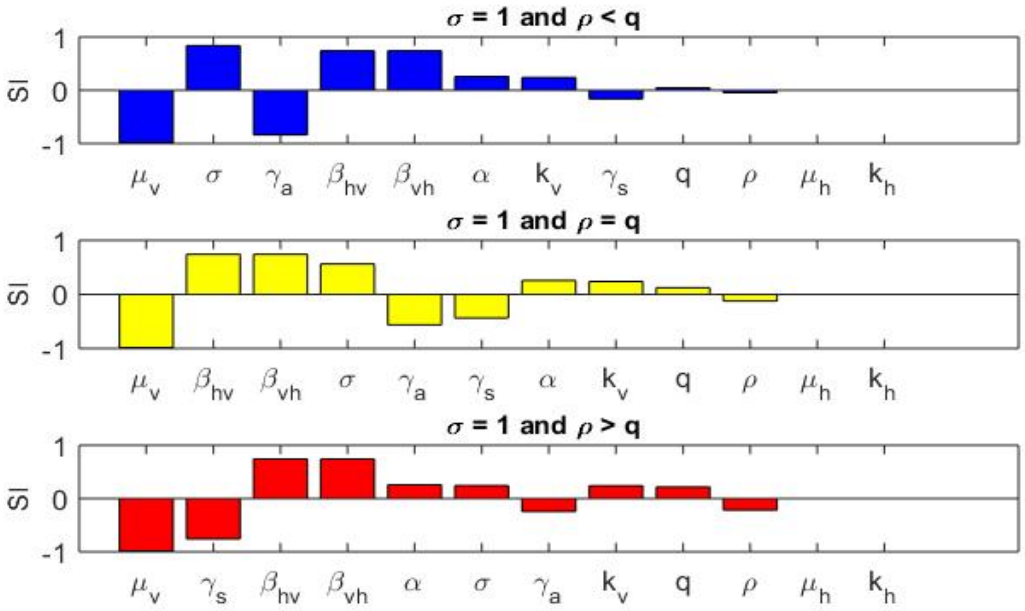

Figure 6–4: Graphical representation of SI associated to each parameter for $\sigma = 1$ and all possible cases σ, ρ and q.

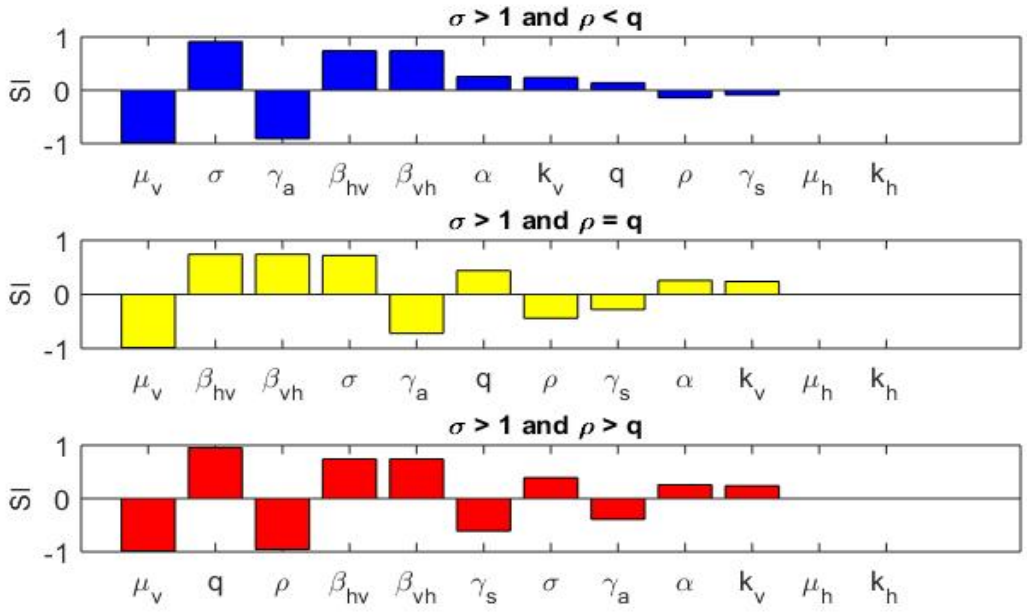

Figure 6–5: Graphical representation of SI associated to each parameter for $\sigma > 1$ and all possible cases σ, ρ and q.

Note the similarity of the results obtained in the sensitivity analysis for some cases, for example, the cases $\sigma < 1$, $\rho < q$, $\sigma = 1$, $\rho = q$ and the case $\sigma > 1$, $\rho = q$ or when $\sigma = 1$, $\rho < q$ and $\sigma > 1$, $\rho < q$ or when $\sigma < 1$, $\rho > q$ and $\sigma = 1$, $\rho > q$ has equal results.

In the case in which the number of asymptomatic and symptomatic infected are equals ($\rho = q$) we have that parameter for which R_0 is most sensitive are β_{hv}, β_{vh} and σ with positive SI's and μ_v with negative SI's, for any infectious value but when the asymptomatic individuals are less infectious that symptomatic ($\sigma < 1$), R_0 is sensitivity to γ_s with negative SI's therefore if γ_s grows the decrease R_0, while when $\sigma \geq 1$, R_0 is sensitivity to γ_a with negative SI's. Therefore if γ_s grows then decreases R_0. This is correct, since, if $\rho = q$ and $\sigma < 1$, then the symptomatic recovery rate has more influence on R_0 than γ_a, because the asymptomatic individuals are less infectious than the symptomatic ones.

Note that, when $\sigma > 1$ and $\rho > q$, R_0 is very sensitive to ρ and q, that is to say that R_0 grows if ρ decreases and q increases, since, if the number of infected asymptomatic grows and as these are more infectious than the symptomatic, consequently R_0 also increases. This case is interesting because it appears only once, in the sensitivity analysis, which indicates that only in it case the amount of infectious population has a decisive influence on a possible outbreak of the disease.

When $\sigma \geq 1$ and $\rho < q$, μ_v and the parameter of infectiousness alteration σ is very influential in an outbreak of the ZIKV.

Finally, the sensitivity analysis determines that for any infectious situation of the infected population ($\sigma < 1, \sigma = 1, \sigma > 1$) and the probability of reaching some type of infection in the population, ($\rho < q, \rho = q, \rho > q$), the basic reproductive number R_0 is more sensitive to the mosquito mortality rate μ_v and the mosquito bite rate β_{hv} and β_{vh}. Consequently, the decrease in the number of mosquitoes is the best way to prevent and control an outbreak. Which agrees the words of the current state epidemiologist Carmen Deseda, MD. of Puerto Rico, who reports that one of the influential factors for controlling the spread of ZIKV was the population's own action to control mosquito breeding sites [12].

Chapter 7
CONCLUSIONS

In this work, a comprehensive bibliographic review and a summary on the epidemiology of Zika virus disease was carried out, as well as the review of some publications of previous mathematical epidemiological models on the dynamics of ZIKV spread.

The found notions that motivated our investigation were that the Zika Virus (ZIKV) develops Zika fever or Zika disease which has turned emergency alarms in the last few years in tropical and subtropical regions. The ZIKV is today known as the first example of an infection that can be transmitted both sexually and through mosquitoes. The Zika disease has no vaccine and no treatments or medicines that heal the burden of the patient for this is of great scientific interest. Zika is an asymptomatic and symptomatic disease. According to some reports, most cases are asymptomatic (8 : 2). There is scientific consensus that ZIKV can cause microcephaly and Guillain Barre syndrome. Moreno, V. (December 2016), et. al., assess that there is no complete knowledge of the dynamics of Zika Virus transmission. Hence, they assume that symptomatic and asymptomatic humans are equally infectious. Other authors such as P. Padmanabhan, (May 2017) conducted their research on the disease under similar assumptions.

With these notions, we constructed the first model that considers variable infectiousness in the human populations as well as populations of to be susceptible, exposed, *symptomatic infected*, *asymptomatic infected* and recovered and the

mosquitoes population to be, susceptible, exposed and infected we also considered parameters that promote the development of the disease under sexual and vector transmission. We found the basic reproductive number associated to the model which is interpreted as the number of secondary infections produced by a typical infected human in a completely susceptible population of humans and mosquitoes. In terms of this condition, we performed a qualitative, numerical and sensitivity analysis of the model.

In the qualitative analysis, we made a rescale version of the model and found two basic reproductive number R_0 and R_0^*, both valid in the study of the modeling of infectious diseases. The value of R_0 provides a threshold condition when new infections are considered only for humans and the process of infection human-vector-human is considered as one generation. Meanwhile, R_0^* provided a threshold condition for Zika virus spread when we also incorporated mosquitoes contributing to new infections where the process of infection human-vector-human is considered as two generations. We chose to use R_0 for the basic reproductive number as it is a simpler expression of the process. This can be expressed as the sum of two reproductive ratios, one associated to the vector transmission and one to sexual transmission ($R_0 = R_v + R_d$) (See Brauer et. al. [4], Valega, W. and Ríos-Soto, K. [33]). In terms of R_0 , we found two equilibrium points of the system. One of them, the Zika-free equilibrium, was determined explicitly and for the second, which is the endemic equilibrium, we demonstrate its existence and uniqueness since it cannot be found explicitly. In summary, if $R_0 \leq 1$, then there exists an unique equilibrium point $E_1 = (1, 0, 0, 0, 0)$ the Zika-free equilibrium, which indicates a healthy state where there is no infection and if $R_0 > 1$, then in addition to E_1, there exist an infected equilibrium, the Zika equilibrium $E_2 = (S^*, L^*, I_s^*, I_a^*, E_v^*, I_v^*)$, where all populations co-exist.

We analyzed the stability of the Zika free equilibrium using the basic reproductive number. In Theorem 5, we concluded that if $R_0 < 1$, then the Zika-free equilibrium E_1 is locally asymptotically stable indicating that, in this case, the disease does not develop [14]. While, if $R_0 > 1$ then E_1 is unstable, but in this region the endemic equilibrium emerges as a second equilibrium point E_2 which we showed numerically that is locally asymptotically stable using our fixed parameter values. Therefore, in this case it is always possible that ZIKV never dies out. Due to the complexity of our model, deduced by its 8 equations and its non-linearity, the global equilibrium stability will be considered for future work.

In Chapter 5, Figures 5–3 and 5–4 with parameters taken from the bibliographic review verify the existence of the two equilibria based on the basic reproductive number, the Zika-free equilibrium and Endemic equilibrium. As well as it is performed a regions diagram which illustrates the different behaviors of R_0 as a function of R_d and R_v Figure 5–2 shows simulations of the epidemics that develop when $R_0 > 1$ and six possible variations of the contributions of the direct and vectorial transmission R_d and R_v are considered. We learned that that when the vector transmission ratio is larger than the sexual transmission ratio there is a time delay for ZIKV to invade the population. Under this scenario there is a window of opportunities to prevent an epidemic of ZIKV with preventive measures, such as insecticide, repellents, condoms, etc.

Figures 5–5, 5–7 and 5–13 present the behavior of the asymptomatic and symptomatic infected populations, when the vector to human transmission rate (β_{hv}), the sexual transmission rate (α) and the infectious alteration (σ) rates are varied. Here, the impact that the three parameter has in the ZIKV diseases spread on an epidemic is notable since the maximum number of infected grows, by the direct relationship increasing R_0.

Figure 5–11 verified the role of the infectivity that is the development or extinction in the disease of the infected population. If σ decreases, then the area of the region where the basic reproductive number is less than one increases, consequently, increasing the possibility of Zika's disease extinction.

In summary, the numerical analysis predicts an epidemic, where the number of infected can grow or decrease depending on the value of the parameters σ, β_{hv}, ρ or q. It is observed that mainly the population of asymptomatic infected individuals ($q > \rho$) influence the growth of the infected population spreading the ZIKV and therefore generating a greater number of infected, by its silent transmission of the disease. In addition,campaigns for the detection of the ZIKV by means of tests, as well as by invitation to the community, even if individual do not show symptoms or have suspicions can help to decrease the number of cases. Efforts should also focus on the appropiate manage to detect the asymptomatic infected individuals and isolate them.

The sensitivity analysis showed the impact of the parameters μ_v, β_{hv} and β_{vh} in the dynamics of the development of the disease. An important conclusion from the sensitivity analysis is that, the basic reproductive number R_0 is more sensitive to the mosquito mortality rate μ_v and the mosquito transmission rates β_{hv} and β_{vh}. Therefore, mosquito eradication is the best way to prevent and control an epidemic. This agrees with words of the current state epidemiologist MD Carmen Deseda of Puerto Rico [12], who reports that one of the influential factors for controlling the spread of ZIKV is the population's own action to control mosquito breeding sites.

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