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By

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MODELING THE TRANSMISSION DYNAMICS OF HEPATITIS B

A project report Submitted in partial fulfillment of the requirements for the degree of Master of Science in Mathematics

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The project entitled “Modeling the transmission dynamics of Hepatitis B” by Ms. Mistir Getu is approved for the degree of Masters of Science in mathematics.

Board of Examiners

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Examiner 2: …….	……

Date: ……

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Abstract

In this project we model the transmission dynamics of Hepatitis B using SLICRV model. Hepatitis B is a potentially life threatening liver infection caused by the Hepatitis B Virus (HBV) and is a major global health problem. HBV is the most common and serious viral infection. We present characteristics of HBV transmission in the form of a mathematical model. The model has two equilibrium points: the disease free equilibrium and the endemic equilibrium points. The stability condition of each equilibrium point is discussed and has been found to be stable and unstable. Based on the basic reproduction number we can predict the future course of the epidemics and determine the stability of equilibrium points. The disease free equilibrium is asymptotically stable if $R_0 < 0$, in this case the disease dies out (the transmission rate was reduced or recovery rate increased), and endemic equilibrium is asymptotically stable if $R_0 > 0$, in this case the disease will spread (the transmission rate was increased or the recovery rate reduced). A combination of increased vaccination of newborns and immunization of susceptible adults appears to reduce HB prevalence. Numerical techniques have been carried out to solve the system of ordinary differential equations which are obtained in the process of modeling. These solutions show the behavior of the populations in time and the stability of disease free and endemic equilibrium points.

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Symbols and Acronyms

HB	Hepatitis B
HBV	Hepatitis B Virus
R_0	Basic reproduction number
S	Susceptible
L	Latently infected
I	Acute infected
C	Carrier
R	Recovered
V	Vaccinated

CHAPTER ONE

Introduction and Background of the Project

1.1. Introduction

Mathematical models which are used for studying the spread of infectious disease are called Dynamic epidemiological models because they describe change over time [1]. Mathematical modeling of infectious disease is an important area of mathematical Biology. The relationship between mathematics and epidemiology has been increasing. For the mathematician, epidemiology provides new and exciting branches, while for the epidemiologist, mathematical modeling offers an important research tool in the study of the evolution of diseases.

Mathematical models have become important tools in analyzing the spread and control of infectious disease. The model formulation process clarifies assumptions, variables, and parameters. Understanding the transmission characteristics of infectious disease in communities, regions and countries can lead to better approaches to decreasing the transmission of this disease [2]. Based on some mathematical assumptions, known epidemics can be modeled mathematically in order to study the prevention mechanisms. A SLICRV model is one of the models used to describe the epidemiology of infectious diseases. This model (SLICRV) is used in epidemiology to compute the number of susceptible, latently infected (exposed), acute infection, carrier, recovered and, vaccinated, people in the population at any time. It can be used to explain the change in the number of people needing medical attention during an epidemic. It is important to note that this model does not work with all diseases.

Epidemic modeling has three main aims. The first is to understand the spreading mechanisms of the disease. For this, the essential part is a mathematical structure. The second aim is to predict the future course of the epidemic. The third is to understand how we may control the spread of the epidemic [3]. Mathematical modeling is to help; we have a great motivation to understand the spread and control of infectious diseases and their transmission characteristics. Mathematical epidemiology contributed to the understanding of the behavior of infectious diseases, its impacts and future predictions about its spreading. Epidemiology is the branch of a science dealing with

the spread and control of disease. It is the study of the distribution and determinant of health related events in specified populations, and the application of this study to control health problem. There are two classic epidemiology models; such as epidemic and endemic. Epidemic models are used to describe rapid out breaks that occur in less than one year, while endemic models are used for studying disease over longer period [2].

Many types of infectious diseases exist, all of which have their own unique set of behaviors. One of those infectious diseases is hepatitis; hepatitis means inflammation of the liver. There are five types of hepatitis; such as hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E. Hepatitis A and E viruses cause infectious hepatitis transmitted by eating food contaminated with fecal material from infected individuals. Viruses B, C and D are called serum hepatitis and are transmitted by contact with blood or body fluids of an infected person. But in this project we will discuss only hepatitis B and its mathematical model. Hepatitis B (HB) is an infectious disease caused by Hepatitis B Virus (HBV) that affects the liver. It is the most common and serious viral disease. The virus is found in the blood and certain body fluids [4].

1.2. Literature Review

This section reviews the work of other researcher related to this project. Some of the related works are as follow.

Grob and Esteban (1995) stated that HBV may be transmitted horizontally and vertically.

Horizontal transmission occurs during contact with infected person, sexual contact with infected person, exposure to blood or other infected fluids and contact with HBV contaminated instrument. A vertical transmission occurs when an infected mother transmits the virus directly to the infant during child birth. Such transmission are usually possible when the expectant mothers suffers an acute infection of hepatitis B during pregnancy or if she is a chronic carrier during that period. Majority of countries in south East Asia, the western pacific and Africa have high endemicity of HBV [5].

In 1996, Nowak et al. proposed a basic model to study the spread of hepatitis B Virus infection which described the interaction between uninfected cells, infected cells and free virus [6]. In 2010, Wang et al. modified the model of Nowak et al. by replacing the rate of infection term by a

mass action incidence term and by assuming that the infected cells could be cured. They showed that the model had two equilibrium points and that these two points were globally asymptotically stable [7]. In 2011, Hattaf et al. generalized the Nowak et al. model by including the effect of drug therapy and they also replaced the assumption of constant infusion of healthy hepatocytes with a logistic growth term. They showed that their model had two globally asymptotically stable equilibrium points [8].

Momoh, Ibrahim and Tahir from Nigeria in July-August 2012, they proposed a SVEIR model to understand the effect of detection and treatment of Hepatitis B at latent stage on the transmission dynamics of Hepatitis B disease. Mathematical analysis was carried out that completely determines the global dynamics of the model. The impact of detection and treatment of Hepatitis B at latent stage on the transmission dynamics are discussed through the stability analysis of the disease free equilibrium [9].

Tahir Khan, Gul Zaman and Ikhlak Chohan from United Kingdom in 2016 they presented the model for the transmission dynamic of acute and chronic HBV. They incorporated in the model acute-infected class and chronic-infected class and then developed the model with these new features. After formulating the model, they find the basic Reproduction number R_0. As in epidemiological models, the model has two steady states: infected and uninfected steady state. Thus, they investigated both the states, disease free and endemic state and proved that the disease free and endemic equilibra are both locally as well as globally stable under certain conditions. For the global stability, they developed the Lyapnove function and showed that both the local and global dynamic are completely determined by the basic Reproduction number R_0 [10]. Many scholars have done research on how to eliminate Hepatitis B. But in this project we will present what is the spreading mechanism of Hepatitis B and how we may control this disease.

1.3. Background of the project

1.3.1. Biological background

The first record of an epidemic caused by Hepatitis B Virus (HBV) was in 1885. The virus was first identified in 1966 by Baruch Blumberg at the national institutes of Health in USA and it has now become a major public health problem. In recent years, many researchers have used mathematical modeling to study HBV infection [11].

The most important organ in the human body is the liver. Liver infection caused different diseases. The most common disease affecting the liver is hepatitis. Hepatitis is a term referring to a serious inflammation of the liver. Several viruses can cause hepatitis; such as Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis D Virus (HDV) and Hepatitis E Virus (HEV). But Hepatitis B virus (HBV) is the most common and serious type of viral Hepatitis. Hepatitis B is an infectious disease caused by hepatitis B virus (HBV) that affects the liver. It is a major global health problem. The virus is found in the blood and certain body fluids and is spread when blood or body fluid from an infected person inters the body of a person who is not infected [2].

This can occur in variety of ways including:

- Unprotected sexual contact
- From mother to baby during birth
- Sharing drugs and sharp materials
- Contact with wounds or skin sores
- Blood transfusion
- When the infected person bits another person…

Hepatitis B virus particle can be found on objects, even in the absence of visible blood. The virus can remain infectious and capable of spreading infection for at least seven days outside the human body. Hepatitis B is not spread through food, water, sharing eating utensils, hugging, kissing, coughing, sneezing, insects and other vectors.

An infection of Hepatitis B has two possible phases, such as acute and chronic. *Acute* hepatitis B infection lasts less than six months. In this stage the immune system is usually able to clear the virus from the body, and the individual may recover completely within a few months. Most people who acquire hepatitis B as adults have an acute infection. *Chronic* hepatitis B infection lasts six months or longer. Most infants infected with HBV at birth and many children infected between 1 and 6 years of age become chronically infected. About two _third of people with chronic HBV infection are chronic carriers. These people do not develop symptoms, even though they harbor the virus and transmit it to other people. Over time it can cause liver scarring that causes liver failure and may also develop liver cancer.

Many people infected with hepatitis B have no symptoms during the initial infections, when people have symptoms they usually appear between 60 and 150 days after onset of infection. People who have symptoms generally feel quite ill and might need to be hospitalized. Symptoms of hepatitis B might include the following:

- Dark colored urine
- Loss of appetite
- Extreme tiredness
- Fever
- Pain in joints
- Abdominal pain
- Vomiting
- Jaundice

Jaundice, which presents with yellow of the skin or a yellow color in the whites of eyes. Prevention of Hepatitis B diseases is by vaccination which is 95 % effective. A combination of increased vaccination of newborns and immunization of susceptible adults appears to reduce HB prevalence. Generally, HBV control measures include vaccination, education, screening of blood and blood products; and treatment.

1.3.2. Mathematical back ground

Mathematical models have been used in life sciences to interpret experimental data, to understand the process that produced the data, and even to test hypothesis and make predictions. In 1760 Daniel Bernoulli introduced the first mathematical method into the field of epidemiology which showed that vaccination against smallpox was advantageous for protection. Bernoulli's results motivated the incorporation of mathematical models into biological studies. In the field of epidemiology, mathematical modeling gave valuable insight into the spread of a disease among humans [12]. In 1906 Hamer formulated and analyzed a discrete time model in his attempt to understand the recurrence of measles epidemics [13]. Ross was interested in the incidence and control of malaria, so he developed differential equation models for malaria as a host vector disease in 1911 [14]. Other deterministic epidemiology models were developed in papers by Ross, Ross and Hudson, Martin, and Lottka. Starting in 1926 Kermack and Mckenderic

published papers on epidemic models and obtained the epidemic threshold result that the densities of susceptible must exceed a critical value in order for an epidemic out break occur [15].

1.4. The General Epidemic model (Kermack and McKendrick 1927) SIR model

In 1927, Kermack and McKendrick created a model in which they considered a fixed population with only three compartments:

Susceptible(S): is the class of individuals who are not immune or who can easily infected by the disease.

Infected (I): individuals who are infected and can transmit on to the susceptible individual.

Recovered (R): individuals who have been infected and have recovered from the disease or are removed from HBV infection.

The proportion of individuals in the compartments S, I and R at time t, is denoted as S(t), I(t)and R(t) respectively.

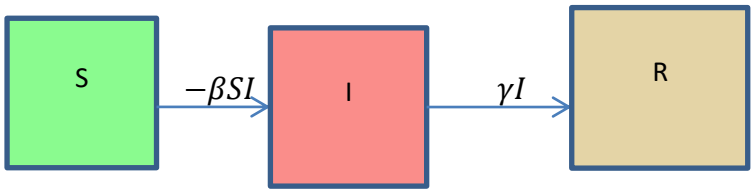


Figure 1: Flow chart of SIR model

Assume the population is constant for all t.

- ✓ The rate at which susceptible become infective (βSI), and the rate at which infective are recovered (γI).

  The model equations as follows:

$$\begin{cases} \frac{dS}{dt} = -\beta SI \\ \frac{dI}{dt} = \beta SI - \gamma I \\ \frac{dR}{dt} = \gamma I \end{cases}$$

where β is the transmission rate and γ is the recovering rate.

This model is the first one of epidemic model proposed by Kermack and Meckenderic, but different researchers extended this basic model in many directions by relaxing some assumptions.

CHAPTER TWO

Model of HBV Infection

Mathematical modeling is a useful tool in the study of virus dynamics because it helps to understand the spread of diseases in host populations, both in time and space. In the last two decades, mathematical models have been used frequently to study the transmission dynamics of HBV in various regions. Anderson and May (1991) used a simple deterministic, compartmental mathematical model to illustrate effects of carriers on the transmission of HBV. There are different types of models in analysis of epidemic diseases. Some of the models used to model different diseases are, SIR, SIS, SIRS, SIR with birth and death, SEIS, SEIR, SVLICR...etc., but the model that I use in this project is SLICRV model. The SLICRV model is made up of a host population which is grouped in to six classes: such as susceptible, latently infected (exposed), acute infection, carrier, recovered and vaccinated with sizes denoted by S, L, I, C, R and V respectively..

Susceptible: is the class of individual who are not immuned or who can be easily infected by the disease.

Vaccinated: individuals who have been successfully immunized by vaccine.

Latently infected (exposed): individuals who are infected but not infectious. In this stage an infection is hidden and inactive.

Acute infection: individuals who are in the initial highly infectious stage of HBV.

Carrier: a person who carries the infection for a long period of time and can transmit the infectious agent to others, but without showing any symptoms of the disease themselves.

Recovered: is a class of individuals who have been infected and have recovered from the disease.

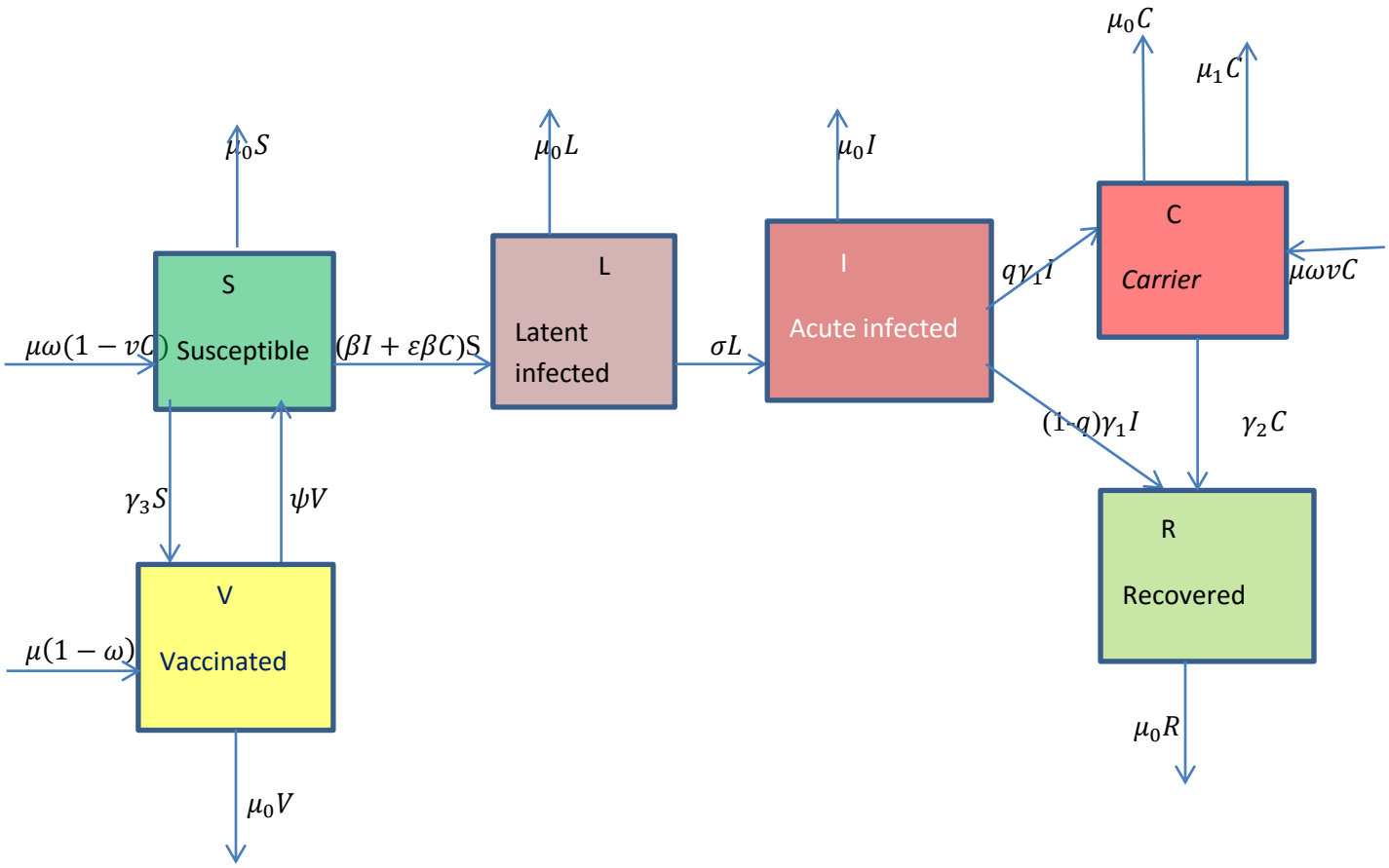


Figure 2: Flow chart of HBV transmission in a population

2.1. Model assumptions

The epidemiological features of the hepatitis B virus (HBV) lead to the following assumptions about the transmission of the disease.

- An individual can be infected only by contacting infectious individuals.
- The population is constant.
- Age, sex, social status and race do not affect the probability of being infected.
- We assume that latently infected individuals (exposed) are not infectious, that is they are not capable of transmitting virus.
- The diseases cannot be transmitted during the exposer period.
- Patients with either acute or chronic infections are capable of transmitting the disease.
- β be the transmission rate of virus attack when susceptible individual contact with infected ones.

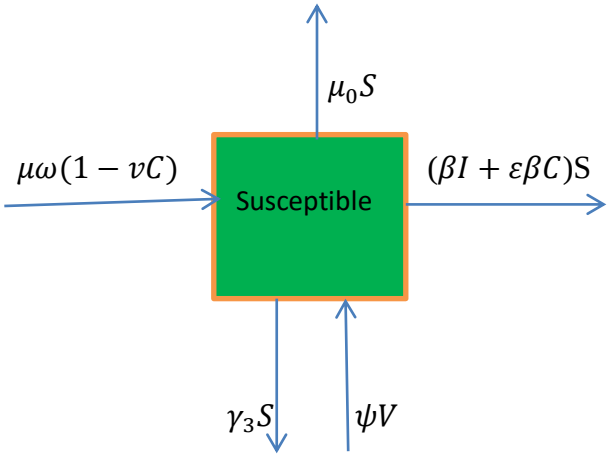
- σ is the rate at which exposed become infectious.
- γ_2 is the recovered rate of carriers.

2.2. Model equations

The population is divided in to six classes based on epidemiological status. Individuals are classified as susceptible, vaccinated, latently infected, acute infection, chronic infection (carrier) and recovered.

Susceptible

Susceptible class decreases when susceptible individuals successfully immunized by vaccine and move to the latent class. It increases when infants born without successful vaccination. Some susceptible individual die naturally.

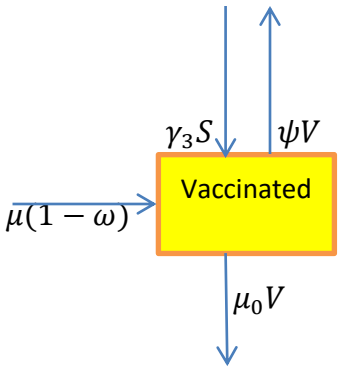


$$\frac{dS}{dt} = \mu\omega(1-vC) + \psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_3)S$$

Figure 3 Flow chart of susceptible compartment

Vaccinated

From the model rate of change of vaccinated members that moved from the susceptible in to latent class and some of vaccinated individuals die naturally.

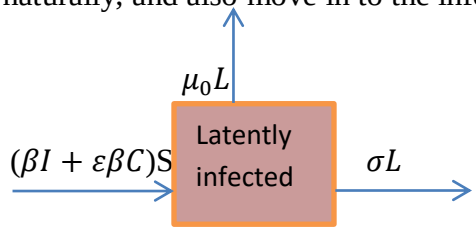


$$\frac{dV}{dt} = \mu(1-\omega) + \gamma_3 S - (\mu_0 + \psi)V$$

Figure 4 Flow chart of vaccinated compartment

Latently infected compartment

The rate of change of the latent class is equal to the difference between latently infected members that moved from the susceptible in to latent class and the rate at which latently infected individuals die naturally, and also move in to the infectious class.

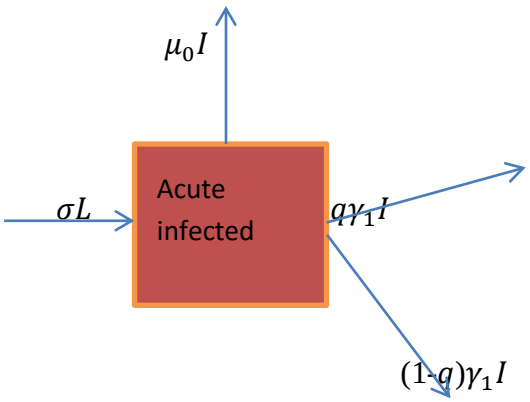


$$\frac{dL}{dt} = (\beta I + \varepsilon\beta C)S - (\mu_0 + \sigma)L$$

Figure 5: Flow chart of latently infected compartment

Acute infection compartment

From the model the number of acute infection increases when people leaving the latent class for the infectious class, decrease when the infectious class moves in to carrier class and recovered class. Some of infectious individual die naturally, while some also die due to the disease.

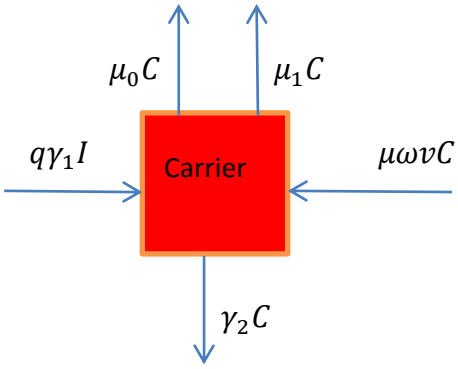


$$\frac{dI}{dt} = \sigma L - (\mu_0 + \gamma_1)I$$

Figure 6: Flow chart of acute infected compartment

Carrier compartment

From the model the number of carriers increase when the infectious class move in to carrier class and when the baby born without successful vaccination and also it decreases when the carrier class move in to recovered class. Some of carrier individual die naturally, while some also die due to the disease.



$$\frac{dC}{dt} = \mu\omega vC + q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C$$

Figure 7: Flow chart of carrier class

Recovered compartment

The rate of change of the recovered class is equal to the number of people leaving the infected class for the recovered class and the carrier class for the recovered class. Some of the recovered individuals die naturally.

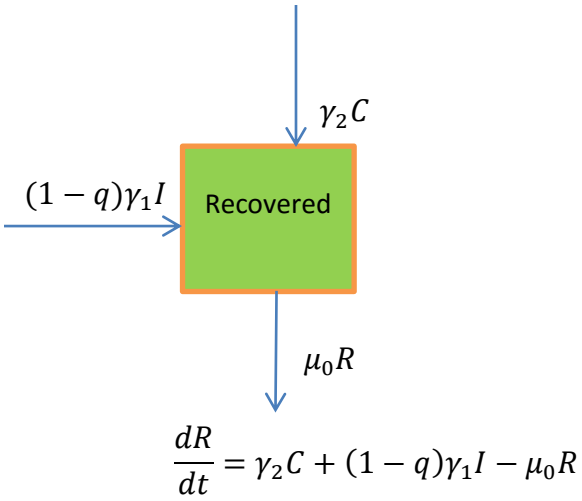


Figure 8: Flow chart of recovered class

Keeping in view of the assumptions, our population dynamic, i.e., "susceptible, vaccinated, latently infected, acute infection, carrier, recovered" is governed by the following set of differential equations:

$$\begin{cases} \frac{\mathrm{dS}}{\mathrm{dt}} = \mu\omega(1-vC) + \psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_3)S \\ \frac{dL}{dt} = (\beta I + \varepsilon\beta C)S - (\mu_0 + \sigma)L \\ \frac{dI}{dt} = \sigma L - (\mu_0 + \gamma_1)I \\ \frac{dC}{dt} = \mu\omega vC + q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \\ \frac{dR}{dt} = \gamma_2 C + (1-q)\gamma_1 I - \mu_0 R \\ \frac{dV}{dt} = \mu(1-\omega) + \gamma_3 S - (\mu_0 + \psi)V \end{cases}$$

where S, L, I, C, R, and V denotes the proportion of individuals at the stage of susceptible, latent, acute, carrier, recovery, and vaccinated to HBV in the total population, respectively. t is time,

Note that, in these equations all populations must be nonnegative and all parameters are assumed to be positive.

Table 1: Description of parameters

Parameter	Interpretation
μ	Birth rate
μ_0	Natural mortality rate
μ_1	HBV related mortality rate
β	Transmission coefficient
ε	Reduced transmission rate
σ	Rate moving from latent to acute
γ_1	Rate moving from acute to carrier
γ_2	Rate moving from carrier to immune
γ_3	vaccination rate
ω	Proportion of birth without successful vaccination
q	Average probability an individual fails to clear an acute infection and develops to carrier state
ψ	Rate of waning vaccine induced immunity
ν	Carrier mothers

2.3. Reproduction Number

Basic reproduction number R_0 is one of the fundamental concepts in mathematical Biology. It defined as, the average number of secondary infections caused by a single infectious individual during their entire infectious life time. The Basic Reproduction number is important since it tells

us if a population is at risk from a disease (that is, Basic reproduction number R_0 predicts whether the disease will become endemic or die out). To determine the basic reproduction number we use Jacobian method. And take the basic reproduction number is the largest Eigenvalue of the Jacobian matrix.

- ✓ If $R_0 < 1$, each individual produces, on average, less than one new infected, and hence the disease dies out.
- ✓ If $R_0 > 1$, each individual produces more than one new infected individuals, and hence the disease is able to invade the susceptible population**.**
- ✓ If $R_0 = 1$, each infection will on average produce exactly one secondary infection, meaning the disease remains in the population at a consistent rate, as one infected individual transmits the disease to one susceptible [16].

How to find Reproduction number

According to Diekmann and Heesterbeek, we can evaluate the basic reproduction number by the formula $R_0 = \rho(FV^{-1})$ where $F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right]$ and $V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right]$ for $i > 1$ for the number of compartments, and $1 \leq j \leq m$ for the infected compartment only, where m is the number of infected classes. The Fi are the new infections, while the Vi are transfers of infections from one compartment to another, x_0 is the disease-free equilibrium state. ρ denotes the spectral radius of a matrix FV^{-1} or the dominant (largest) Eigenvalue of a matrix FV^{-1}[17].

Let us look at the following system of differential equations.

$$\begin{cases} \frac{\mathrm{dS}}{\mathrm{dt}} = \mu\omega(1 - vC) + \psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_3)S \\ \frac{dL}{dt} = (\beta I + \varepsilon\beta C)S - (\mu_0 + \sigma)L \\ \frac{dI}{dt} = \sigma L - (\mu_0 + \gamma_1)I \\ \frac{dC}{dt} = \mu\omega vC + q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \end{cases}$$

The above equations can be represented in matrix form as shown below, where F is the Jacobian of matrix of infection rates and V is the Jacobian of the matrix of transition rate.

$$F = \begin{bmatrix} \beta SI + \varepsilon\beta SC \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad V = \begin{bmatrix} (\mu_0 + \sigma)L \\ -\sigma L + (\mu_0 + \gamma_1)I \\ -q\gamma_1 I + (\mu_0 + \mu_1 + \gamma_2 - \mu\omega v)C \\ \mu\omega(1 - vC) + \psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_3)S \end{bmatrix}$$

Then differentiate matrix F and V with respect to L, I, and C.

$$\Rightarrow F = \begin{bmatrix} 0 & \beta S_0 & \varepsilon\beta S_0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \mu_0 + \sigma & 0 & 0 & 0 \\ -\sigma & \mu_0 + \gamma_1 & 0 & 0 \\ 0 & -q\gamma_1 & \mu_0 + \mu_1 + \gamma_2 - \mu\omega v & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & (\mu_0 + \gamma_3) \end{bmatrix}$$

let a=$\mu_0 + \sigma$, b=$\mu_0 + \gamma_1$, c=$\mu_0 + \mu_1 + \gamma_2 - \mu\omega v$, d=$(\mu_0 + \gamma_3)$

Now find the inverse of matrix V by using row operation.

Note: $(A_n|I_n)$ by using row operation to reduce $(I_n|A^{-1}{}_n)$

where A_n is $n \times n$ square matrix and I_n is $n \times n$ identity matrix.

$$\left(\begin{array}{cccc|cccc} a & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ -\sigma & b & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & -q\gamma_1 & c & 0 & 0 & 0 & 1 & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & d & 0 & 0 & 0 & 1 \end{array}\right) \xrightarrow{\frac{1}{a}R_1}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ -\sigma & b & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & -q\gamma_1 & c & 0 & 0 & 0 & 1 & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & d & 0 & 0 & 0 & 1 \end{array}\right) \xrightarrow{R_2 \to \sigma R_1 + R_2}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & b & 0 & 0 & \frac{\sigma}{a} & 1 & 0 & 0 \\ 0 & -q\gamma_1 & c & 0 & 0 & 0 & 1 & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & d & 0 & 0 & 0 & 1 \end{array}\right) \xrightarrow{\frac{1}{b}R_2}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ 0 & -q\gamma_1 & c & 0 & 0 & 0 & 1 & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & d & 0 & 0 & 0 & 1 \end{array}\right) \xrightarrow{R_3 \to q\gamma_1 R_2 + R_3}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ 0 & 0 & c & 0 & \frac{\sigma q\gamma_1}{ab} & \frac{q\gamma_1}{b} & 1 & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & d & 0 & 0 & 0 & 1 \end{array}\right) \xrightarrow{\frac{1}{c}R_3}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ 0 & 0 & 1 & 0 & \frac{\sigma q\gamma_1}{abc} & \frac{q\gamma_1}{bc} & \frac{1}{c} & 0 \\ 0 & \beta S_0 & \varepsilon\beta S_0 - \mu\omega v & d & 0 & 0 & 0 & 1 \end{array}\right) \xrightarrow{R_4 \to \beta S_0 R_2 - R_4}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ 0 & 0 & 1 & 0 & \frac{\sigma q\gamma_1}{abc} & \frac{q\gamma_1}{bc} & \frac{1}{c} & 0 \\ 0 & 0 & \varepsilon\beta S_0 - \mu\omega v & d & \frac{\sigma\beta S_0}{ab} & \frac{\beta S_0}{b} & 0 & 1 \end{array}\right) \xrightarrow{R_4 \to (\varepsilon\beta S_0 - \mu\omega v)R_3 - R_4}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ 0 & 0 & 1 & 0 & \frac{\sigma q\gamma_1}{abc} & \frac{q\gamma_1}{bc} & \frac{1}{c} & 0 \\ 0 & 0 & 0 & d & \frac{(\varepsilon\beta S_0 - \mu\omega v)\sigma q\gamma_1}{abc} - \frac{\sigma\beta S_0}{ab} & \frac{(\varepsilon\beta S_0 - \mu\omega v)q\gamma_1}{bc} - \frac{\beta S_0}{b} & \frac{(\varepsilon\beta S_0 - \mu\omega v)}{c} & 1 \end{array}\right) \xrightarrow{\frac{1}{d}R_4}$$

$$\left(\begin{array}{cccc|cccc} 1 & 0 & 0 & 0 & \frac{1}{a} & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ 0 & 0 & 1 & 0 & \frac{\sigma q\gamma_1}{abc} & \frac{q\gamma_1}{bc} & \frac{1}{c} & 0 \\ 0 & 0 & 0 & 1 & \frac{(\varepsilon\beta S_0-\mu\omega v)\sigma q\gamma_1}{abcd}-\frac{\sigma\beta S_0}{abd} & \frac{(\varepsilon\beta S_0-\mu\omega v)q\gamma_1}{bcd}-\frac{\beta S_0}{bd} & \frac{(\varepsilon\beta S_0-\mu\omega v)}{cd} & \frac{1}{d} \end{array}\right)$$

Therefore, $V^{-1}=\begin{pmatrix} \frac{1}{a} & 0 & 0 & 0 \\ \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ \frac{\sigma q\gamma_1}{abc} & \frac{q\gamma_1}{bc} & \frac{1}{c} & 0 \\ \frac{(\varepsilon\beta S_0-\mu\omega v)\sigma q\gamma_1}{abcd}-\frac{\sigma\beta S_0}{abd} & \frac{(\varepsilon\beta S_0-\mu\omega v)q\gamma_1}{bcd}-\frac{\beta S_0}{bd} & \frac{(\varepsilon\beta S_0-\mu\omega v)}{cd} & \frac{1}{d} \end{pmatrix}$

FV^{-1}

$$=\begin{pmatrix} 0 & \beta S_0 & \varepsilon\beta S_0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} \frac{1}{a} & 0 & 0 & 0 \\ \frac{\sigma}{ab} & \frac{1}{b} & 0 & 0 \\ \frac{\sigma q\gamma_1}{abc} & \frac{q\gamma_1}{bc} & \frac{1}{c} & 0 \\ \frac{(\varepsilon\beta S_0-\mu\omega v)\sigma q\gamma_1}{abcd}-\frac{\sigma\beta S_0}{abd} & \frac{(\varepsilon\beta S_0-\mu\omega v)q\gamma_1}{bcd}-\frac{\beta S_0}{bd} & \frac{(\varepsilon\beta S_0-\mu\omega v)}{cd} & \frac{1}{d} \end{pmatrix}$$

$$\Rightarrow FV^{-1}=\begin{pmatrix} \frac{\beta S_0\sigma}{ab}+\frac{\varepsilon\beta S_0\sigma q\gamma_1}{abc} & \frac{\beta S_0}{b}+\frac{q\gamma_1}{bc} & \frac{\varepsilon\beta S_0}{c} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

Now find R_0,

$R_0=\rho(FV^{-1})$

First find the Eigenvalue of FV^{-1}.

$$|FV^{-1} - \lambda I| = \begin{vmatrix} \left(\frac{\beta\sigma S_0}{ab} + \frac{\varepsilon\beta S_0\sigma q\gamma_1}{abc}\right) - \lambda & \frac{\beta S_0}{b} + \frac{q\gamma_1}{bc} & \frac{\varepsilon\beta S_0}{c} & 0 \\ 0 & -\lambda & 0 & 0 \\ 0 & 0 & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{vmatrix}$$

$$\Rightarrow \quad \left(\left(\frac{\beta\sigma S_0}{ab} + \frac{\varepsilon\beta S_0\sigma q\gamma_1}{abc}\right) - \lambda\right)\begin{vmatrix} -\lambda & 0 & 0 \\ 0 & -\lambda & 0 \\ 0 & 0 & -\lambda \end{vmatrix} - \left(\frac{\beta S_0}{b} + \frac{q\gamma_1}{bc}\right)\begin{vmatrix} 0 & 0 & 0 \\ 0 & -\lambda & 0 \\ 0 & 0 & -\lambda \end{vmatrix} +$$

$$\frac{\varepsilon\beta S_0}{c}\begin{vmatrix} 0 & -\lambda & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -\lambda \end{vmatrix} = 0$$

$$\left(\left(\frac{\beta\sigma S_0}{ab} + \frac{\varepsilon\beta S_0\sigma q\gamma_1}{abc}\right) - \lambda\right)(-\lambda^3) = 0$$

$$\Rightarrow \lambda = 0, \lambda = \frac{\beta\sigma S_0}{ab} + \frac{\varepsilon\beta\sigma S_0 q\gamma_1}{abc},$$

The basic reproduction number R_0 is the largest Eigenvalue of FV^{-1} .

Therefore, $\rho(FV^{-1}) = \frac{\beta\sigma S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)} + \frac{\varepsilon\beta S_0\sigma q\gamma_1}{(\mu_0+\sigma)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu\omega v)}$

$$= \frac{\beta\sigma S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)}\left(1 + \frac{\varepsilon q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right)$$

Hence, the basic Reproduction number, R_0 of our model is

$$R_0 = \frac{\beta\sigma S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)}\left(1 + \frac{\varepsilon q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right)$$

If $R_0 = \frac{\beta\sigma S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)}\left(1 + \frac{\varepsilon q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right) < 1$, then the disease free equilibrium is stable and the HBV infection dies out. On the other hand, if $R_0 = \frac{\beta\sigma S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)}\left(1 + \frac{\varepsilon q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right) > 1$, then the disease free equilibrium is unstable and the HBV infection increases.

2.4. Equilibrium state

Equilibrium is a state of a system which does not change with time .The equilibrium can be determined by setting a derivative (all derivatives) to zero.

Equilibrium may be stable or unstable. Equilibrium is considered stable if the system always returns to it after small disturbances. If the system moves away from the equilibrium after small disturbances, the equilibrium is unstable. There are two types of equilibrium, such as

2.4.1. Disease free equilibrium

At disease free equilibrium, it is assumed that there is no disease in the system (that is, L=0, I=0, C=0). To obtain the equilibrium points for the system of differential equations by equating each of the equations to zero.

Since R appears only in the sixth equation of the model, we can discuss the following system.

$$\begin{cases} \frac{\mathrm{dS}}{\mathrm{dt}} = \mu\omega(1 - vC) + \psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_3)S \\ \frac{dL}{dt} = (\beta I + \varepsilon\beta C)S - (\mu_0 + \sigma)L \\ \frac{dI}{dt} = \sigma L - (\mu_0 + \gamma_1)I \\ \frac{dC}{dt} = \mu\omega vC + q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \\ \frac{dV}{dt} = \mu(1 - \omega) + \gamma_3 S - (\mu_0 + \psi)V \end{cases}$$

The above equation becomes:

$$\mu\omega + \psi V - (\mu_0 + \gamma_3)S = 0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$\mu(1 - \omega) + \gamma_3 S - (\mu_0 + \psi)V = 0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

From equation (1), we have

$$\mu\omega + \psi V = (\mu_0 + \gamma_3)S$$

$$S = \frac{(\mu\omega + \psi V)}{(\mu_0 + \gamma_3)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

From equation (2), we have

$$\mu(1 - \omega) + \gamma_3 S = (\mu_0 + \psi)V$$

$$V = \frac{\mu(1-\omega) + \gamma_3 S}{(\mu_0 + \psi)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Now substitute equation (1) in equation (2)

$$\Rightarrow V = \frac{\mu(1-\omega) + \gamma_3(\frac{(\mu\omega + \psi V)}{(\mu_0 + \gamma_3)})}{(\mu_0 + \psi)}$$

$$= \frac{\mu(1-\omega)(\mu_0+\gamma_3)+\gamma_3(\mu\omega+\psi V)}{(\mu_0+\psi)(\mu_0+\gamma_3)}$$

$$= \frac{\mu(1-\omega)(\mu_0+\gamma_3)+\gamma_3\mu\omega}{(\mu_0+\psi)(\mu_0+\gamma_3)} - \frac{\gamma_3\psi V}{(\mu_0+\psi)(\mu_0+\gamma_3)}$$

$$\Rightarrow \quad V - \frac{\gamma_3\psi V}{(\mu_0+\psi)(\mu_0+\gamma_3)} = \frac{\mu(1-\omega)(\mu_0+\gamma_3)+\gamma_3\mu\omega}{(\mu_0+\psi)(\mu_0+\gamma_3)}$$

$$\Rightarrow \frac{V(\mu_0 + \psi)(\mu_0 + \gamma_3) - \gamma_3\psi V}{(\mu_0 + \psi)(\mu_0 + \gamma_3)} = \frac{\mu\mu_0 + \mu\gamma_3 - \mu\mu_0\omega - \mu\omega\gamma_3 + \mu\omega\gamma_3}{(\mu_0 + \psi)(\mu_0 + \gamma_3)}$$

$$\Rightarrow \frac{V((\mu_0 + \psi)(\mu_0 + \gamma_3) - \gamma_3\psi)}{(\mu_0 + \psi)(\mu_0 + \gamma_3)} = \frac{\mu\mu_0 + \mu\gamma_3 - \mu\mu_0\omega - \mu\omega\gamma_3 + \mu\omega\gamma_3}{(\mu_0 + \psi)(\mu_0 + \gamma_3)}$$

Then multiply both sides by $\frac{(\mu_0+\psi)(\mu_0+\gamma_3)}{((\mu_0+\psi)(\mu_0+\gamma_3)-\gamma_3\psi)}$

$$\Rightarrow \quad V = \frac{\mu\mu_0+\mu\gamma_3-\mu\mu_0\omega-\mu\omega\gamma_3+\mu\omega\gamma_3}{((\mu_0+\psi)(\mu_0+\gamma_3)-\gamma_3\psi)}$$

$$V = \frac{\mu(\mu_0+\gamma_3-\mu_0\omega)}{\mu_0((\mu_0+\gamma_3+\psi)}$$

From equation (3), we have

$$S = \frac{(\mu\omega+\psi V)}{(\mu_0+\gamma_3)}$$

Now substitute the value of V in S

$$\Rightarrow S = \frac{\mu\omega+\psi(\frac{\mu(\mu_0+\gamma_3-\mu_0\omega)}{\mu_0(\mu_0+\gamma_3+\psi)})}{(\mu_0+\gamma_3)}$$

$$= \frac{\mu\omega\mu_0(\mu_0+\gamma_3+\psi)+\psi\mu(\mu_0+\gamma_3-\mu_0\omega)}{(\mu_0+\gamma_3)\mu_0(\mu_0+\gamma_3+\psi)}$$

$$= \frac{\mu\omega{\mu_0}^2+\mu\omega\mu_0\gamma_3+\psi\mu\mu_0\omega+\psi\mu\mu_0+\psi\mu\gamma_3-\psi\mu\mu_0\omega}{(\mu_0+\gamma_3)\mu_0(\mu_0+\gamma_3+\psi)}$$

$$= \frac{\mu\omega\mu_0(\mu_0+\gamma_3)+\psi\mu(\mu_0+\gamma_3)}{(\mu_0+\gamma_3)\mu_0(\mu_0+\gamma_3+\psi)}$$

$$= \frac{(\mu\omega\mu_0+\psi\mu)(\mu_0+\gamma_3)}{(\mu_0+\gamma_3)\mu_0(\mu_0+\gamma_3+\psi)}$$

$$\Rightarrow \quad S = \frac{(\mu\omega\mu_0+\psi\mu)}{\mu_0(\mu_0+\gamma_3+\psi)}$$

Hence, the disease free equilibrium is $E_0 = (S_0, 0, 0, 0, V_0)$, where

$S_0 = \frac{(\mu\omega\mu_0+\psi\mu)}{\mu_0(\mu_0+\gamma_3+\psi)}, V_0 = \frac{\mu(\mu_0+\gamma_3-\mu_0\omega)}{\mu_0((\mu_0+\gamma_3+\psi)}$

2.4.2. Endemic equilibrium point

Endemic equilibrium point indicates the disease persist in the system. To obtain the equilibrium points for the system of differential equations by equating each of the equations to zero.

To determine the equilibrium points, we must solve

$$\mu\omega(1-\nu C)+\psi V-(\mu_0+\beta I+\varepsilon\beta C+\gamma_3)S=0$$

$$\mu(1-\omega)+\gamma_3 S-(\mu_0+\psi)V=0$$

$$(\beta I+\varepsilon\beta C)S-(\mu_0+\sigma)L=0$$

$$\sigma L-(\mu_0+\gamma_1)I=0$$

$$\mu\omega\nu C+q\gamma_1 I-(\mu_0+\mu_1+\gamma_2)C=0$$

From the above system of differential equation, we have

$\mu\omega(1-\nu C)+\psi V-(\mu_0+\beta I+\varepsilon\beta C+\gamma_3)S=0 \ldots\ldots\ldots\ldots\ldots 1$

$(\beta I+\varepsilon\beta C)S-(\mu_0+\sigma)L=0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$

$I=\frac{\sigma L}{\mu_0+\gamma_1} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 3$

$$C = \frac{q\gamma_1 I}{\mu_0 + \mu_1 + \gamma_2 - \mu\omega v} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 4$$

$$V = \frac{\mu(1-\omega) + \gamma_3 S}{(\mu_0 + \psi)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 5$$

From equation 2, 3 and 4, we have

$$\left(\frac{\beta\sigma L}{\mu_0 + \gamma_1} + \frac{\varepsilon\beta q\gamma_1 \delta L}{(\mu_0 + \gamma_1)(\mu_0 + \mu_1 + \gamma_2 - \mu\omega v)}\right) S - (\mu_0 + \sigma)L = 0$$

$$\Rightarrow \left(\frac{(\mu_0+\mu_1+\gamma_2-\mu\omega v)+\varepsilon q\gamma_1}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right)\beta\sigma LS = (\mu_0 + \sigma)L$$

$$\Rightarrow S = \frac{(\mu_0 + \mu_1 + \gamma_2 - \mu\omega v)(\mu_0 + \gamma_1)(\mu_0 + \sigma)}{((\mu_0 + \mu_1 + \gamma_2 - \mu\omega v) + \varepsilon q\gamma_1)\beta\sigma}$$

From equation (5), we have

$V = \frac{\mu(1-\omega)+\gamma_3 S^*}{(\mu_0+\psi)}$, where $S^* = S = \frac{(\mu_0+\mu_1+\gamma_2-\mu\omega v)(\mu_0+\gamma_1)(\mu_0+\sigma)}{((\mu_0+\mu_1+\gamma_2-\mu\omega v)+\varepsilon q\gamma_1)\beta\sigma}$

And also, from equation (1) we have

$$\mu\omega\left(1 - v\frac{q\gamma_1 I}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right) + \psi\left(\frac{\mu(1-\omega)+\gamma_3 S^*}{(\mu_0+\psi)}\right) - \left(\mu_0 + \beta I + \varepsilon\beta\frac{q\gamma_1 I}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)} + \gamma_3\right)S^* = 0$$

$$\Rightarrow -\frac{\mu\omega v q\gamma_1 I}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)} - \beta I S^* - \frac{\varepsilon\beta S^* q\gamma_1 I}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)} + \mu\omega + \psi\left(\frac{\mu(1-\omega)+\gamma_3 S^*}{(\mu_0+\psi)}\right) - (\mu_0 + \gamma_3)S^* = 0$$

$$\Rightarrow -\left(\frac{\mu\omega v q\gamma_1 + \beta I S^*(\mu_0+\mu_1+\gamma_2-\mu\omega v)+\varepsilon\beta S^* q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right) I + \frac{\mu\omega(\mu_0+\psi)+\psi(\mu(1-\omega)+\gamma_3 S^*)-(\mu_0+\gamma_3)(\mu_0+\psi)S^*}{(\mu_0+\psi)} = 0$$

$$\Rightarrow \left(\frac{\mu\omega v q\gamma_1 + \beta I S^*(\mu_0+\mu_1+\gamma_2-\mu\omega v)+\varepsilon\beta S^* q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right) I = \frac{\mu\omega(\mu_0+\psi)+\psi(\mu(1-\omega)+\gamma_3 S^*)-(\mu_0+\gamma_3)(\mu_0+\psi)S^*}{(\mu_0+\psi)}$$

$$\Rightarrow \mathrm{I} = \frac{(\mu\omega(\mu_0 + \psi) + \psi(\mu(1-\omega) + \gamma_3 S^*) - (\mu_0 + \gamma_3)(\mu_0 + \psi)S^*)(\mu_0 + \mu_1 + \gamma_2 - \mu\omega v)}{(\mu_0 + \psi)(\mu\omega v q\gamma_1 + \beta I S^*(\mu_0 + \mu_1 + \gamma_2 - \mu\omega v) + \varepsilon\beta S^* q\gamma_1)}$$

$$\Rightarrow I = \frac{(\mu\omega\mu_0+\mu\omega\psi+\mu\psi-\mu\omega\psi+\psi\gamma_3 S^*-\mu_0^2 S^*-\mu_0\psi S^*-\gamma_3\mu_0 S^*-\gamma_3\psi S^*)(\mu_0+\mu_1+\gamma_2-\mu\omega v)}{(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

$$I = \frac{\mu_0 S^*(\mu_0+\psi+\gamma_3)(R_0-1)(\mu_0+\mu_1+\gamma_2-\mu\omega v)}{(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

Where $R_0 = \left(1+\frac{\varepsilon q\gamma_1}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}\right)\frac{\sigma\beta\mu(\psi+\mu_0\omega)}{(\mu_0+\gamma_1)(\mu_0+\sigma)\mu_0(\mu_0+\gamma_3+\psi)}$

and from equation (3), we have

$$\frac{\mu_0 S^*(\mu_0+\psi+\gamma_3)(R_0-1)(\mu_0+\mu_1+\gamma_2-\mu\omega v)}{(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]} = \frac{\sigma L}{\mu_0+\gamma_1}$$

$$\Rightarrow \quad \mathrm{L} = \frac{\mu_0 S^*(\mu_0+\psi+\gamma_3)(\mu_0+\mu_1+\gamma_2-\mu\omega v)(R_0-1)(\mu_0+\gamma_1)}{\sigma(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

Eventually, from equation (4), we have

$$C = \frac{q\gamma_1\mu_0 S^*(\mu_0+\psi+\gamma_3)(R_0-1)}{(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

Hence, the endemic equilibrium is $E^* = (S^*, L^*, I^*, C^*, V^*)$, where

$$S^* = \frac{(\mu_0+\mu_1+\gamma_2-\mu\omega v)(\mu_0+\gamma_1)(\mu_0+\sigma)}{((\mu_0+\mu_1+\gamma_2-\mu\omega v)+\varepsilon q\gamma_1)\beta\sigma}$$

$$L^* = \frac{\mu_0 S^*(\mu_0+\psi+\gamma_3)(\mu_0+\mu_1+\gamma_2-\mu\omega v)(R_0-1)(\mu_0+\gamma_1)}{\sigma(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

$$I^* = \frac{\mu_0 S^*(\mu_0+\psi+\gamma_3)(R_0-1)(\mu_0+\mu_1+\gamma_2-\mu\omega v)}{(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

$$C^* = \frac{q\gamma_1\mu_0 S^*(\mu_0+\psi+\gamma_3)(R_0-1)}{(\mu_0+\psi)[\beta I S^*(\mu_0+\mu_1+\gamma_2+\varepsilon q\gamma_1-\mu\omega v)+\mu\omega v q\gamma_1]}$$

$$V^* = \frac{\mu(1-\omega)+\gamma_3 S^*}{(\mu_0+\psi)}$$

2.5. Stability Analysis of equilibrium points

Linearization is the process of changing nonlinear model to linear model. One of the linearization method is Jacobian methods. For the stability analysis of the disease free and endemic equilibrium points, we will find the Jacobian matrix of SLICRV model equations.

A method for determining stability

I. Calculate the disease free equilibrium point and endemic equilibrium point.

II. Create the jacobian matrix

III. Evaluate the jacobian matrix at the equilibrium point

IV. Find the Eigen values

V. If the Eigen values <0 ⇒ stable

If even one Eigen values > 0 ⇒ unstable

VI. Largest Eigen values ⇒ R_0

2.5.1. Routh _Hurwitz stability criterion

Routh_Hurwitz stability criterion is a method that can be used to establish the stability of the system without solving its characteristic equation.

Consider the characteristic equation

$$a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n = 0$$

If the order of the resulting polynomial is at least two and any coefficient a_i is zero or negative, the polynomial has at least one root with non-negative real part. In this case the equilibrium is unstable. But if any coefficient a_i is positive, the polynomial has at least one root with negative real part. In this case the equilibrium is asymptotically stable.

Finding the Jacobian matrix of the above equations becomes

$$\mathbf{J}=\begin{bmatrix} \frac{dS'}{dS} & \frac{dS'}{dV} & \frac{dS'}{dL} & \frac{dS'}{dI} & \frac{dS'}{dC} \\ \frac{dL'}{dS} & \frac{dL'}{dL} & \frac{dL'}{dI} & \frac{dL'}{dC} & \frac{dL'}{dV} \\ \frac{dI'}{dS} & \frac{dI'}{dL} & \frac{dI'}{dI} & \frac{dI'}{dC} & \frac{dI'}{dV} \\ \frac{dC'}{dS} & \frac{dC'}{dL} & \frac{dC'}{dI} & \frac{dC'}{dC} & \frac{dC'}{dV} \\ \frac{dV'}{dS} & \frac{dV'}{dL} & \frac{dV'}{dI} & \frac{dV'}{dC} & \frac{dV'}{dV} \end{bmatrix}, \quad \text{where} \begin{bmatrix} S' \\ L' \\ I' \\ C' \\ V' \end{bmatrix} = \begin{bmatrix} \frac{dS}{dt} \\ \frac{dL}{dt} \\ \frac{dI}{dt} \\ \frac{dC}{dt} \\ \frac{dV}{dt} \end{bmatrix}$$

$$=\begin{bmatrix} -(\mu_0+\beta I+\varepsilon\beta C+\gamma_3) & 0 & -\beta S & -\mu\omega v-\varepsilon\beta S & \psi \\ (\beta I+\varepsilon\beta C) & -(\mu_0+\sigma) & \beta S & \varepsilon\beta S & 0 \\ 0 & \sigma & -(\mu_0+\gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & \mu\omega v-(\mu_0+\mu_1+\gamma_2) & 0 \\ \gamma_3 & 0 & 0 & 0 & -(\mu_0+\psi) \end{bmatrix}$$

Then evaluate at each equilibrium point to decide the stability, which is directly determined from the eigenvalues λ of: $|J(x)-\lambda I|=0$. Based on the eigenvalues λ of the linearized system will be either stable (all the eigenvalues of the Jacobian evaluated at the equilibrium point contain negative real parts) or unstable (at least one of the eigenvalues of the Jacobian evaluated at the equilibrium point has positive real part).

2.5.2. Stability analysis of the disease free –equilibrium

We have a disease free equilibrium E_0 = (s_0, 0, 0, 0, v_0)

where $S_0=\frac{(\mu\omega\mu_0+\psi\mu)}{\mu_0(\mu_0+\gamma_3+\psi)}, V_0=\frac{\mu(\mu_0+\gamma_3-\mu_0\omega)}{\mu_0((\mu_0+\gamma_3+\psi)}$, L_0=0, I_0=0, $C_0=0$. Then substitute in the jacobian matrix

$$J(E_0)=\begin{bmatrix} -(\mu_0+\gamma_3) & 0 & -\beta S_0 & -\mu\omega v-\varepsilon\beta S_0 & \psi \\ 0 & -(\boldsymbol{\mu_0}+\boldsymbol{\sigma}) & \beta S_0 & \varepsilon\beta S_0 & 0 \\ 0 & \sigma & -(\mu_0+\gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & \mu\omega v-(\mu_0+\mu_1+\gamma_2) & 0 \\ \gamma_3 & 0 & 0 & 0 & -(\mu_0+\psi) \end{bmatrix}$$

To determine the characteristic equation solve

$|J(E_0)-\lambda I|=0$

The characteristic equation is

$\phi(\lambda)=-(\mu_0+\lambda)(\psi+\mu_0+\gamma_3+\lambda)[\lambda^3+a_2\lambda^2+a_1\lambda+a_0]=0$

where a_0 =($\mu\omega v-(\mu_0+\mu_1+\gamma_2)$)[($\mu_0+\gamma_1$) ($\mu_0+\sigma$) - $\sigma\beta S_0$]- $\sigma\beta q\gamma_1\varepsilon S_0$,

a_1= ($\mu_0+\gamma_1$) ($\mu_0+\sigma$) + (2 $\mu_0+\gamma_1+\sigma$)($\mu_0+\mu_1+\gamma_2-\mu\omega v$) − $\sigma\beta S_0$,

a_2 =3 $\mu_0+\sigma+\gamma_1-\mu\omega v+\mu_1+\gamma_2$,

when $R_0<1$, we have $0<R_1<1$ and $0<R_2<1$, where $R_1=\frac{\beta\sigma S_0}{(\mu_0+\sigma)(\mu_0+\gamma_1)}$ and

$R_2 = \frac{\varepsilon q \gamma_1 \beta \sigma S_0}{(\mu_0+\mu_1+\gamma_2-\mu\omega v)(\mu_0+\sigma)(\mu_0+\gamma_1)}$. Thus

$a_0 = (\mu\omega v - (\mu_0 + \mu_1 + \gamma_2))(\mu_0 + \gamma_1)(\mu_0 + \sigma)(1 - R_1 - R_1) > 0,$

$a_2 > 0,$

$a_1 a_2 - a_0 = (2\mu_0 + \gamma_1 + \sigma)[(\mu_0 + \gamma_1)(\mu_0 + \sigma) - \sigma\beta S_0 + (\mu_0 + \mu_1 + \gamma_2 - \mu\omega v)(3\mu_0 + \sigma + \gamma_1 - \mu\omega v + \mu_1 + \gamma_2) + \sigma\beta q \gamma_1 \varepsilon S_0 = (2\mu_0 + \gamma_1 + \sigma)(\mu_0 + \gamma_1)(\mu_0 + \sigma)[1 - R_1 + \frac{(\mu_0+\mu_1+\gamma_2-\mu\omega v)}{(\mu_0+\gamma_1)(\mu_0+\sigma)}(3\mu_0 + \sigma + \gamma_1 - \mu\omega v + \mu_1 + \gamma_2)] - \sigma\beta q \gamma_1 \varepsilon S_0 > 0$

Therefore, by Routh Herwitz stability criteria, all roots of $\phi(\lambda)$ have negative real parts, and E_0 is stable. Furthermore, if $R_0 > 1$, we have $a_0 < 0$ and E_0 is unstable.

2.5.3. Stability analysis of endemic equilibrium

To discuss the properties of the endemic equilibrium $E^* = (S^*, L^*, I^*, C^*, V^*)$, we make an elementary row-operation for the Jacobian matrix at E^* and obtain the following matrix:

$$J(E^*) = \begin{bmatrix} -(\mu_0 + \beta I^* + \varepsilon\beta C^* + \gamma_3) & 0 & -\beta S^* & -\mu\omega v - \varepsilon\beta S^* & \psi \\ (\beta I^* + \varepsilon\beta C^*) & -(\mu_0 + \sigma) & \beta S^* & \varepsilon\beta S^* & 0 \\ 0 & \sigma & -(\mu_0 + \gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & \mu\omega v - (\mu_0 + \mu_1 + \gamma_2) & 0 \\ \gamma_3 & 0 & 0 & 0 & -(\mu_0 + \psi) \end{bmatrix}$$

Then, by using elementary row operations we have

$$J(E^*) = \begin{bmatrix} -(\mu_0 + \beta I^* + \varepsilon\beta C^* + \gamma_3) & 0 & -\beta S^* & -\mu\omega v - \varepsilon\beta S^* & \psi \\ 0 & -(\mu_0 + \sigma) & M_1 & \varepsilon M_1 - \mu\omega v M_2 & \psi M_2 \\ 0 & 0 & -(\mu_0 + \gamma_1) + \frac{\sigma M_1}{\mu_0+\sigma} & \frac{\sigma(\varepsilon M_1 - \mu\omega v M_2)}{\mu_0+\sigma} & \frac{\sigma\psi M_2}{\mu_0+\sigma} \\ 0 & 0 & 0 & M_3 - \mu\omega v M_4 & \psi M_4 \\ 0 & 0 & 0 & 0 & M_5 \end{bmatrix}$$

where $M_1 = \frac{\beta S^*(\mu_0+\gamma_3)}{\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3}$,

$M_2 = \frac{(\beta I^*+\varepsilon\beta C^*)}{\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3}$,

$$M_3=(\mu\omega v-\mu_0-\mu_1-\gamma_2)-\frac{q\gamma_1\sigma\varepsilon\boldsymbol{\beta S^*}(\boldsymbol{\mu_0}+\boldsymbol{\gamma_3})}{\sigma\,\beta S^*(\boldsymbol{\mu_0}+\boldsymbol{\gamma_3})-(\mu_0+\gamma_1)(\boldsymbol{\mu_0}+\sigma)\,(\boldsymbol{\mu_0}+\boldsymbol{\beta I^*}+\boldsymbol{\varepsilon\beta C^*}+\boldsymbol{\gamma_3})}$$

$$M_4=\frac{\boldsymbol{q}\gamma_1\,\sigma(\beta I^*+\varepsilon\beta C^*)}{\sigma\,\beta S^*(\boldsymbol{\mu_0}+\boldsymbol{\gamma_3})-(\mu_0+\gamma_1)(\boldsymbol{\mu_0}+\sigma)\,(\boldsymbol{\mu_0}+\boldsymbol{\beta I^*}+\boldsymbol{\varepsilon\beta C^*}+\boldsymbol{\gamma_3})},$$

$$M_5=\frac{\boldsymbol{\gamma_3}\psi M_4[q\gamma_1(\mu\omega v+\varepsilon\beta S^*)-\beta S^*(\mu\omega v-\mu_0-\mu_1-\gamma_2)]}{q\gamma_1(\mu_1+\beta I^*+\varepsilon\beta C^*+\gamma_3)(M_3-\mu\omega v M_4)}+\frac{(\mu_0+\psi)((\mu_1+\beta I^*+\varepsilon\beta C^*)+\mu_0\gamma_3}{(\mu_1+\beta I^*+\varepsilon\beta C^*+\gamma_3)}$$

Since this matrix is a triangular matrix, so the Eigen values will be the diagonal entries.

That is, $\lambda_1=-(\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3)<0$, $\lambda_2=-(\mu_0+\sigma)<0$, $\lambda_3=-(\mu_0+\gamma_1)+\frac{\sigma M_1}{\mu_0+\sigma}$

$\lambda_4=M_3-\mu\omega v M_4$, $\lambda_5=M_5$

Since I^*, C^* and L^* are coordinates of the endemic equilibrium E^*, we have

$$\mu_0+\sigma=(\beta I^*+\varepsilon\beta C^*)\frac{S^*}{L^*},\ \mu_0+\gamma_1=\sigma\frac{L^*}{I^*}$$

Thus $\lambda_3<0$ if and only if

$$\frac{(\mu_0+\gamma_3)I^*}{(\mu_0+\beta I^*+\varepsilon\beta C^*+\gamma_3)(I^*+\varepsilon C^*)}<1$$

$$\Rightarrow(\mu_0+\gamma_3)\varepsilon C^*+\beta(I^*+\varepsilon C^*)^2+(\mu_0+\gamma_3)I^*<(\mu_0+\gamma_3)I^*$$

which is equivalent to,

$$(\mu_0+\gamma_3)\varepsilon C^*+\beta(I^*+\varepsilon C^*)^2>0$$

It holds as long as the endemic equilibrium E^* exists. In addition C^* and I^*satisfy

$$q\gamma_1=(\mu_0+\mu_1+\gamma_2-\mu\omega v)\frac{C^*}{I^*}$$

Similar to the proof of λ_3, we obtain that $\lambda_4<0$ if and only if

$S^*\beta\,(I^*+\varepsilon C^*)+\mu\omega v C^*>0$

which holds as long as E^* exists. Furthermore, $\lambda_3<0$ implies that $M_4<0$. since $\mu\omega v<(\mu_0+\mu_1+\gamma_2)$ and $\lambda_4<0$. We get $\lambda_5<0$.

Therefore, all eigenvalues are negative, and we can conclude E^* is stable node if it exists.

2.6 Numerical solution of the model

The simulations are performed using MATLAB's built-in ode45 function. The ode45 function evaluates the differential equations using an explicit 4^{th} order Runge-Kutta method for solving ODE.

Table 2: Description of estimated parameter value

Parameter	Estimated value
μ	0.0121
μ_0	0.0004
μ_1	0.002
β	0.0001
ε	0.16
σ	0.038
γ_1	0.052
γ_2	0.43
γ_3	0.001
ω	0.2
q	0.885
ψ	0.1
ν	0.11

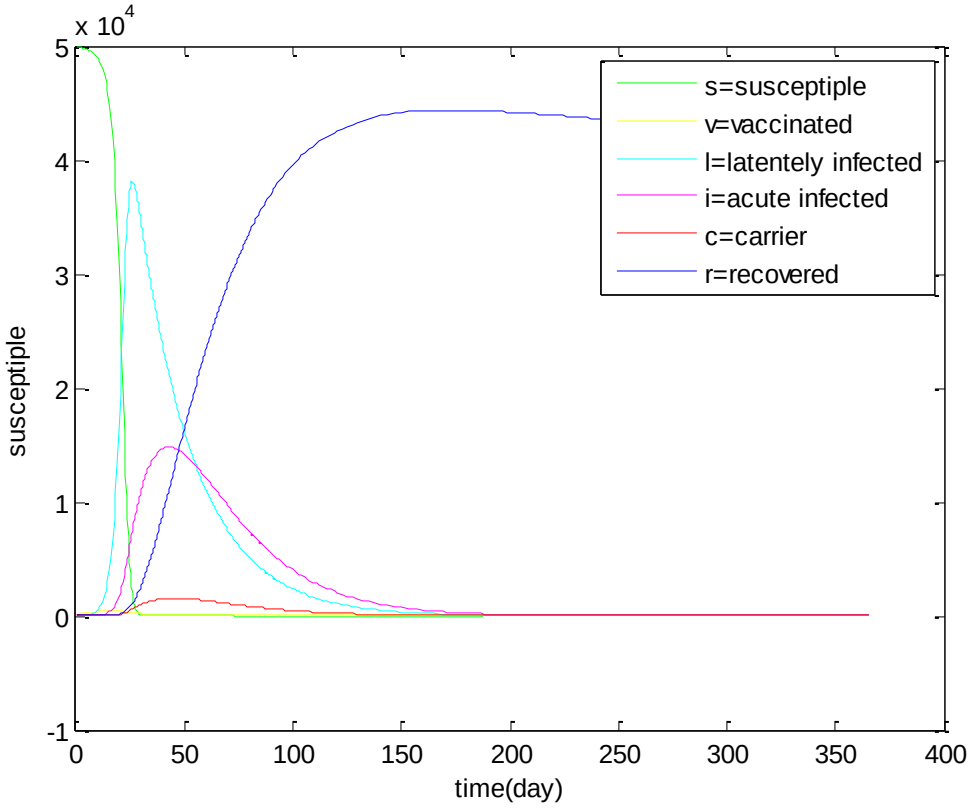


Figure 9: The behavior of S, V, L, I, C and R using ode45

From figure 9, we see that the susceptible population will decrease because it is invaded by the disease and may be, some of the susceptible population removed by death while the latently infected population will increases, after around 60 days the latently infected population disappear because of death and some of latently infected population tend to the acute infected class. Again form figure 9, we see that a few number of acute infected population tends to the carrier class. This indicates more of this population are recovered by hospitalization or removed by death. Again from figure 9, we see that the number of carrier population is very small and the size of recovered population does not change the recovered class, so the recovered class moves constantly and also the carrier population disappear with increase of t.

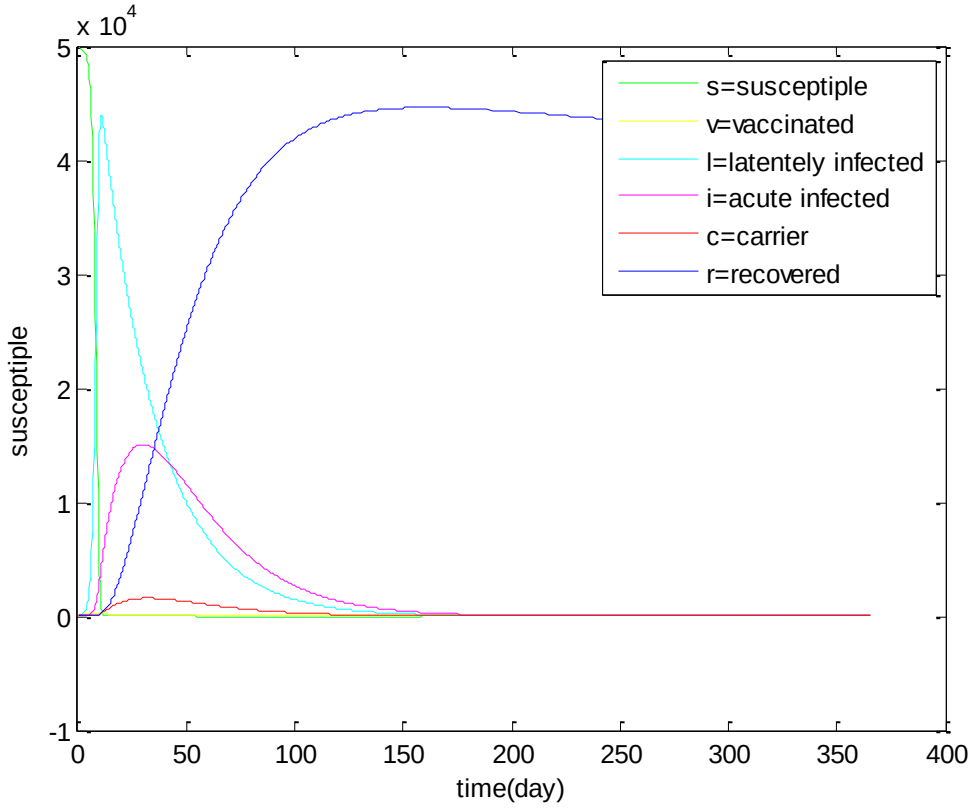


Figure 10: The behavior of S,V,L,I,C and R using ode45, when $\beta = 0.0005$

From this figure, we see that when the transmission rate β is increase, then the susceptible population will be invaded by this epidemic disease (HBV) with in a short period of time.

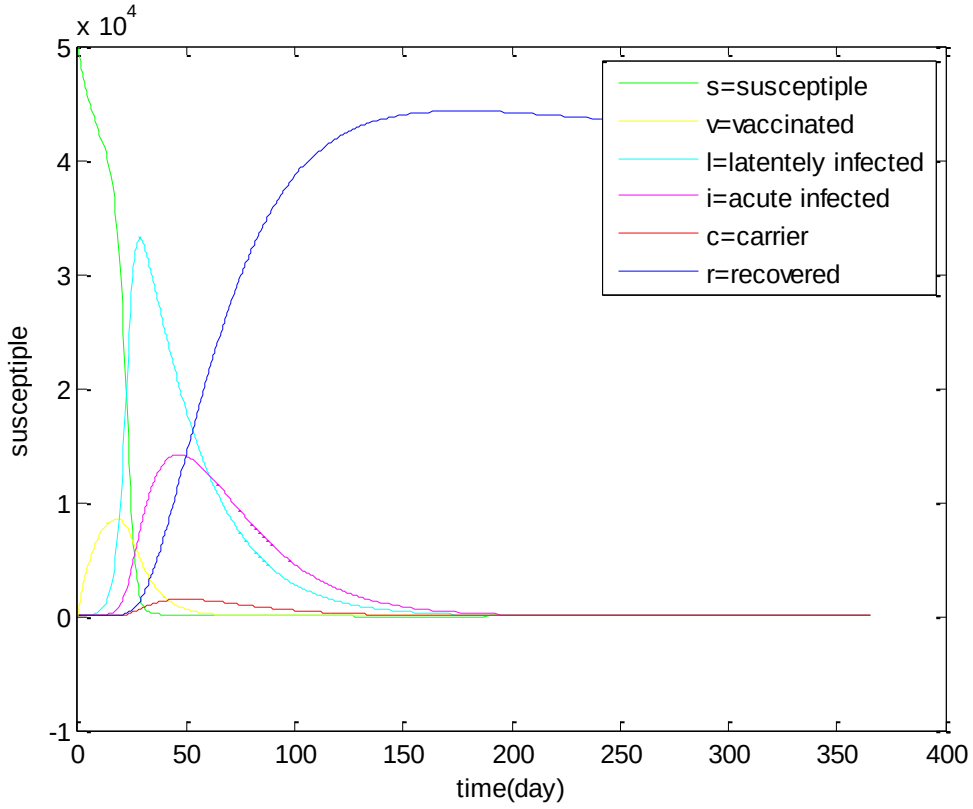


Figure 11: The behavior of S, V, L, I, C and R using ode45, when $\gamma_3 = 0.025$

From this figure, we see that the number of infected population decrease when the vaccination rate(γ_3) is high. Therefore, this numerical simulation results show that vaccination is the most effective way to control hepatitis B virus infection.

2.7. Conclusion

In this project, we discussed the transmission of HBV in the form of mathematical model. One of the fundamental questions of mathematical epidemiology is to find the basic reproduction numbers that determine whether the disease will spread or die out. The basic reproduction number plays an important role in understanding transmission dynamics of epidemics and predicting epidemics spread. By calculating the basic reproduction number we can predict the future course of the epidemics and determine the stability of equilibrium points. There are two equilibrium points of the system, namely, the disease free and endemic. The disease free equilibrium is asymptotically stable if $R_0 < 0$, and endemic equilibrium is asymptotically stable if $R_0 > 0$. Based on the estimated parameter value, we estimated the basic reproduction number

of the HB to be $R_0 = 0.057345$, which implies that on average, each infectious individual transmits less than one new infected. This indicates that Hepatitis B dies out. The value of R_0 indicated the disease free equilibrium point is stable.

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