

**Mathematical Modeling and Analysis for the
Dynamics of a Two Stage Hepatitis B Virus with
Vaccination and Vertical Transmission**



MSc Thesis

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Hawassa, Ethiopia

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**Mathematical Modeling and Analysis for the Dynamics of a
Two Stage Hepatitis B Virus with Vaccination and Vertical
Transmission**

MSc. Thesis

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Master of Science in Computational Mathematics**

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Declaration

I declare that this thesis entitled “**Mathematical Modeling and Analysis for the Dynamics of a two stage hepatitis B Virus with Vaccination and Vertical transmission** ”is my own work and has not been submitted to any university for similar purpose. The references used in this thesis are duly recognized by proper citations.

Name of the student

Signature

Date

Approval sheet-1

This is to officially state that the study entitled “**Mathematical Modeling and Analysis for the Dynamics of a two stage hepatitis B Virus with Vaccination and Vertical transmission**” is an original work carried out by **Fikeradis Nega** under my guidance and supervision. This is a genuine work that has been done by **Fikeradis Nega** for the partial fulfillment of the award of the Degree of Master of Science in Computational Mathematics from Hawassa University.

Advisor’s Name

Signature

Date

Approval Sheet-2

We, the undersigned, members of the Board of Examiners of the final open defense by **Fikeradis Nega** have read and evaluated his thesis entitled “**Mathematical Modeling and Analysis for the Dynamics of a two stage hepatitis B Virus with Vaccination and Vertical transmission** ” and examined the candidate. This is therefore, to certify that the thesis has been accepted in partial fulfillment of the requirement of the Degree of Master of Science in Computational Mathematics.

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Name of Internal Examiner-I	signature	Date
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Name of External Examiner	signature	Date
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Final approval and acceptance of the thesis is contingent upon the submission of the final copy of the thesis to the school of Graduate Studies (SGS) through the Department/School Graduate Committee (DGC/SGC) of the candidate’s department.

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List of Abbreviations

Abbreviation	Meaning
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
HBV	Hepatitis B virus
MATLAB	Matrix laboratory
ODE	Ordinary differential equation
WHO	World Health Organization

Abstract

In this thesis, we proposed a deterministic mathematical model for acute and chronic hepatitis B virus with vaccination and vertical transmission. We examined the well-posedness of the model by proved its positivity, uniqueness, and boundedness of the solutions to the system equation. We computed both the disease-free (DFE) and endemic equilibrium (EEP) points of the model and analyzed their local and global stability by computing its basic reproduction number. We have shown that when the reproduction number $R_0 < 1$, the illness will die out or go extinct, as the disease-free (DFE) equilibrium point is stable for $R_0 < 1$. The global stability of the disease-free equilibrium point is also proved by applying the castillo-Chavez theorem. The local stability of the endemic equilibrium point was determined using center manifold theory and its bifurcation analysis, and it was found that the model exhibits a forward bifurcation at $R_0 = 1$. The global stability of the endemic equilibrium point is also determined by using the Lyapounov function. We have also performed a sensitivity analysis of the model with respect to the model parameters. We observed that, the recruitment rate, and the transmission rate of hepatitis B virus have positive correlation with R_0 , while the vaccination rate of newborns(pediatric vaccination) and vaccination rate have negative correlation with R_0 . Numerical simulation of the model is also performed using some assumed and literaturized values of the parameters.

Key words: acute, chronic, HBV, Vertical transmission, Vaccination.

1 Introduction

1.1 Background of study

Many diseases are caused by liver infections. One of the infectious disorders that inflames the liver is hepatitis B. The virus does not directly harm liver cells; instead, the immune system's reaction causes the liver to become inflamed. Hepatocytes are the cells in the liver that become infected when the hepatitis B virus (HBV) enters the body. Consequently, the immune system attacks the hepatocyte, causing inflammation in the liver [3].

The primary causes of hepatitis are bacterial infections, drinking alcohol and drug use[27]. Hepatitis B is spread when blood, semen, or other body fluids from a person infected with the virus enters the body of someone who is not infected. The transmission can happen through sexual contact sharing needles, syringes, or other drug-injection equipment, or during pregnancy or child delivery. There are two basic stages of HBV infection: acute (short-lived) and chronic (long-lived). The first six months following infection are when the hepatitis B virus enters the acute stage of the illness. Some individuals with the infection may fight off and eradicate it at this point, but for others, the infection progresses to a chronic or lifelong illness and becomes a major health issue. Hepatitis B infection acquired in adulthood leads to chronic hepatitis in less than 5% of cases, whereas infection in infancy and early childhood leads to chronic hepatitis in about 95% of cases. This is the basis for strengthening and prioritizing infant and childhood vaccination. [19].

Acute Hepatitis B infection is first infected with the hepatitis B virus, it is called an acute infection or a new infection. Most healthy adults who are infected do not experience any symptoms and are able to clear the virus without complications. Acute hepatitis B can cause symptoms such as fatigue, nausea, jaundice (yellowing of the skin and eyes), and abdominal pain. It is crucial to monitor acute infections closely, especially in cases where symptoms are severe. Chronic HBV infection is a global healthcare burden and can lead to chronic liver disease, cirrhosis, liver failure, and liver cancer. Unfortunately, there is no definitive cure for the virus. Although extensive vaccination programs have reduced the burden of liver disease in future populations, eradicating the virus from the host remains a challenge. Current treatments for chronic HBV infection have seen important updates, including considerations for treating patients in the immune tolerant phase and clarity on end points for treatment with nucleos(t)ide inhibitors [21].

Vertical transmission of Hepatitis B Virus (HBV) refers to the passing of the virus from an infected mother to her newborn during the time of birth. This mode of transmission is particularly significant because it can lead to both acute and chronic HBV infections in the infant. For HBV, vertical transmission is defined as positivity for HBsAg (Hepatitis B surface antigen) or HBV-DNA in infants at 6–12 months of life[9]. The risk of developing chronic HBV infection is

inversely proportional to the age at the time of exposure, with the highest risk in newborns[14]. In highly endemic areas, vertical transmission is a common route of transmission. There are several strategies for the prevention of HBV vertical transmission, such as antiviral treatment during the third trimester of pregnancy and immunoprophylaxis to newborns that includes the administration of hepatitis B immune globulin (HBIG) and an HBV vaccine [9]. A positive test for the hepatitis B e-antigen (HBeAG) means that there is an active infection with the hepatitis B virus, likely in someone with chronic hepatitis B. For Hepatitis B e Antigen-positive mothers, the risk of vertical transmission ranges from 70% to 90% and Hepatitis B e Antigen-negative mothers, the risk ranges from 10% to 40%[18].

The hepatitis B virus can survive outside the body for at least 7 days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine. The latency period, also known as the incubation period, for hepatitis B virus (HBV) typically ranges from 30 to 180 days. The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B, especially when transmitted in infancy or childhood [19].

Hepatitis B can be prevented with a safe and effective vaccine. The vaccine is usually given soon after birth with boosters a few weeks later. It offers nearly 100% protection against the virus. Hepatitis B can be passed from mother to child. This can be prevented by taking antiviral medicines to prevent transmission, in addition to the vaccine. WHO recommends the following: to reduce the risk of getting or spreading hepatitis B: practice safe sex by using condoms and reducing the number of sexual partners, avoid sharing needles or any equipment used for injecting drugs, piercing, or tattooing, wash your hands thoroughly with soap and water after coming into contact with blood, body fluids, or contaminated surfaces and get a hepatitis B vaccine if working in a healthcare setting [19].

In this study, we are going to formulate a modified mathematical model for the disease transmission of the hepatitis B virus with additional assumptions of vaccination and latent period. When a pregnant woman has hepatitis B, it can be easily spread to her baby at birth. Babies and young children can also get hepatitis B from close contact with family members or others who might be infected. When babies become infected with hepatitis B, they have about 90% chance of developing a lifelong, chronic infection. Fortunately, there is a vaccine to prevent babies from getting hepatitis B. The incubation period of the hepatitis B virus ranges from 30 to 180 days.

We extend a recent study on the dynamics of HBV given in [12] by adding the vaccination class, and by taking the fact that HBV has a latent period, we also added an exposed class of the infection. The authors [12] studied the dynamics of acute and chronic HBV, while this work will be generalized by adding vaccination and exposed class. With this new assumptions of vaccination together with controls, are more useful and bring some new interested information about the possible elimination of the disease.

1.2 Statement of the problem

Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is most commonly transmitted from mother to child during birth and delivery, in early childhood, as well as through contact with blood or other body fluids during sex with an infected partner, unsafe injections or exposures to sharp instruments. The World Health Organization (WHO) estimates that 254 million people were living with chronic hepatitis B infection in 2022, with 1.2 million new infections each year. In 2022, hepatitis B resulted in an estimated 1.1 million deaths, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer) [19]. The WHO has set a goal to eliminate viral hepatitis by 2030, which is defined as a 90% reduction in incidence and a 65% reduction in liver-related deaths from the 2015 baseline [9].

Hepatitis B is a major global health problem. The burden of infection is highest in the WHO Western Pacific Region and the WHO African Region, where 97 million and 65 million people, respectively, are chronically infected. Sixty-one million people are infected in the WHO South-East Asia Region, 15 million in the WHO Eastern Mediterranean Region, 11 million in the WHO in the WHO European Region and 5 million in the WHO Region of the Americas [19]. All the existing papers, and all we reviewed here have used adult vaccination and treatment as the control measures. Most of the literatures didn't included adult vaccination, newborns vaccinated (pediatric vaccination) and the latency period in their models simultaneously. Based on the above literature's, we will develop a mathematical model by adding pediatric vaccination, adult vaccination, and vertical transmission. We want to include the latency period of the virus by including an exposed individuals in the population as a compartment. As HBV is a public health concern, in this study we are going to address the following research question.

- How to formulate a mathematical model for the dynamics of acute and chronic hepatitis B, by incorporating vaccination and vertical transmission?
- How to analyze the formulated model qualitatively?
- How to investigate the bifurcation analysis of the model ?
- How to perform the sensitivity analysis and the numerical simulation of the model?

1.3 Objective of the study

There are two objectives of the study, this are general objective and specific objectives.

1.3.1 General objective

The general objective of this study is to formulate and analyze a mathematical model for the dynamics of both acute and chronic hepatitis B with vaccination and vertical transmission.

1.3.2 Specific objective

The specific objectives of this study are to:

- formulate a model by incorporating vaccination and vertical transmission for the dynamics of acute and chronic HBV.
- establish the positivity and boundedness and compute the equilibria and basic reproduction number of the modified model.
- analyze the stability analysis of the equilibrium points.
- investigate the bifurcation analyses of the model.
- examine the sensitivity analysis and numerical simulation of the model.

1.4 Significance of the study

The significance of the study will be:

- to identify and eliminate the transmission of acute and chronic HBV through vaccination and treatment.
- used as a source for further studies in this area.

1.5 Organization of the thesis

The thesis is organized as follows:

Chapter 2 presents a review of related literature. Chapter 3 presents the methodology of the study. Chapter 4 presents mathematical model formulation. Chapter 5 presents a qualitative analysis of the modified model, which includes the equilibrium points and its stability analysis. Bifurcation analysis and sensitivity analysis are also studied in this chapter. In chapter 6 presents a numerical simulation and the value of the parameters are described in this chapter. In the last Chapter 7, describe the conclusion of the study.

2 Review of Related Literature

Hepatitis B virus (HBV) infection is a worldwide public health problem. The infection is one of the global health problems and potentially life-threatening liver infection. It has distinct infection phases and multiple transmissions. As mathematical modeling is instrumental in enhancing our understanding of the viral dynamics of hepatitis B virus (HBV) infection, there are some studies which are conducted for the dynamics of HBV, and here, we are going to review some of them.

Kamyad et al. (2014) studied mathematical modeling of transmission dynamics and optimal control of vaccination and treatment for hepatitis B virus. In this paper, the authors studied the dynamics of hepatitis B virus (HBV) infection which can be controlled by vaccination as well as treatment. Initially the author consider constant controls for both vaccination and treatment. In the constant controls case, by determining the basic reproduction number, the author study the existence and stability of the disease-free and endemic steady-state solutions of the model. Next, they take the time dependent controls and formulate the appropriate optimal control problem and obtain the optimal control strategy to minimize both the number of infectious humans and the associated costs. Finally at the end numerical simulation results, they showed that optimal combination of vaccination and treatment is the most effective way to control hepatitis B virus infection [11].

Akbari et al.(2016) studied the dynamics of hepatitis B virus (HBV) infection which can be controlled by vaccination as well as treatment. Initially they consider constant controls for both vaccination and treatment. In the constant controls case, by determining the basic reproduction number, They studied the existence and stability of the disease-free and endemic steady-state solutions of the model. Next, The author taken the controls as time and formulated the appropriate optimal control problem and obtain the optimal control strategy to minimize both the number of infectious humans and the associated costs. Finally at the end numerical simulation results showed that optimal combination of vaccination and treatment is the most effective way to control hepatitis B virus infection[1].

Khan et al (2017) studied the dynamics of acute and chronic hepatitis B with optimal control. They formulated an epidemic problem depending on the disease's characteristics. After calculating the reproduction number to determine the equilibria, the epidemic model's stability analysis is carried out. The proposed pandemic problem also includes an investigation of a backward bifurcation. They created control plans to reduce the infected population (acute and chronic) with the use of two control measures: vaccination and therapy. They applied the Pontryagin's Maximum Principle to the suggested control problem. To demonstrate the examination of the analytical work and the impact of control analysis, they run few numerical simulations [12].

Desta et al.(2019) studied the transmission dynamic of the acute and chronic hepatitis B epi-

demographic problem and developed an optimal control strategy to control the spread of hepatitis B in a community. In order to do this, first they presented the model formulation and find the basic reproduction number R_0 . We show that if $R_0 \leq 1$, then the disease-free equilibrium is both locally as well as globally asymptotically stable. Then, they proved that the model is locally and globally asymptotically stable, if $R_0 > 1$. To control the spread of this infection, they developed a control strategy by applying three control variables such as isolation of infected and non-infected individuals, treatment and vaccination to minimize the number of acute infected, chronically infected with hepatitis B individuals and maximize the number of susceptible and recovered individuals. Finally, the author presented numerical simulation to illustrate the feasibility of the control strategy[8].

Alrabaiah et al. (2020) studied optimal control analysis of hepatitis B virus with treatment and vaccination. This infection is preventable and can be controlled using vaccination and proper treatment. The mathematical modeling approach could be used effectively to study the dynamics and to present the appropriate control interventions of infectious diseases including hepatitis B infection. This paper presents the analysis of the Hepatitis B virus through a new mathematical model in the presence of treatment and vaccinations. They showed that the model is stable asymptotically (locally and globally) at the disease-free case. Using the persistence analysis, the author prove that the model is uniformly persistent if the threshold quantity is greater than unity. The global sensitivity of the threshold quantity is carried out in order to set appropriate control measures for infection minimization. In view of the sensitivity results, the author formulated the control model using optimal control theory by considering three control variables. Considering of different controls combination, we introduce four different control strategies to minimize the spread of the hepatitis B infection in the population. Finally, to illustrate the effectiveness of each strategy for the eradication of infection, the author performed and discuss the numerical simulations in detail [2].

Wodajo et al.(2022) studied the effect of intervention of vaccination and treatment on the transmission dynamics of HBV disease. They present the characteristics of HBV virus transmission in the form of a mathematical model. The author proved that the solution of the considered dynamical system is positive and bounded. The model is studied qualitatively using the stability theory of differential equations and the effective reproductive number which represents the epidemic indicator. Both local and global asymptotic stability conditions for disease-free and endemic equilibria are determined. The sensitivity index showed that the transfer rate from exposed class to acute infective class and transfer rate from exposed class to chronic infective class are the most dominant parameters contributing to the transmission of HBV. The combined efforts of vaccination, effective treatment, and interruption of transmission make elimination of the infection plausible and may eventually lead to the eradication of the virus[25].

Belay et al.(2023) studied a mathematical model of hepatitis B disease with a two-dose vaccine series has been formulated and analyzed. They demonstrated that the model's disease-free equilibrium is globally asymptotically stable when the basic reproduction number (R_0) is less than one, whereas the model's endemic equilibrium is locally asymptotically stable when R_0 is greater than one. Sensitivity analysis is performed, and based on its results, the model is extended to an optimal control problem by incorporating two control interventions, namely, prevention and enhanced newborn vaccination. Finally, simulation analyses of the model are conducted to illustrate the theoretical findings and effectiveness of each strategy, which indicates that the use of prevention efforts is the most cost-saving strategy[4].

Garcia et al.(2023) studied the dynamics of HBV via a mathematical modeling approach to measure its dynamics of antibody responses after natural infection or vaccination. Their study gives a primer on HBV infection in humans and a brief overview of the development of within-host mathematical models of HBV infection. In the last decade, models have advanced from considering chronic HBV infections under therapy to the pathogenesis of infection. The author also summarized estimates of key viral dynamic parameters that have varied greatly among studies, and showed that they impact model predictions. Future directions for mathematical modeling of HBV infection are proposed to better understand emerging therapies, the HBV life cycle, predicting cure, and the mechanisms involved in the immune response to HBV infection [10].

In (2017), Khan et al [12]proposed a mathematical model dynamics for acute and chronic hepatitis B with optimal control, according to Khan et al. we will develop a mathematical model dynamics of hepatitis B virus transmission and vaccination by adding vaccination of newborns(pediatric vaccination) by including the vaccinated individuals in the population as a compartment, adult vaccination, and vertical transmission. We want to include the latency period of the virus by including an exposed individuals in the population as a compartment.

3 Methodology of the study

Research methodology is the method that we will use to accomplish our proposed study. Hence, in order to accomplish our study, we will follow the following basic methodologies.

Firstly, we will modify the existing mathematical model by adding vaccination and exposed compartments to a mathematical model for the dynamics of acute and chronic hepatitis B. After formulating the model, we will study its wellposedness of the model by showing its uniqueness, positivity and continuous dependence on the initial points.

Secondly, we will analyze the model qualitatively by finding the equilibrium points and by showing the local and global stabilities of the points. Two of the basic equilibrium points are DFE and EEP, in which the points are obtained as follows. The DFE is obtained by assuming that there is no disease in the community, i.e., by assuming the diseased compartments are zero. The EEP can also be obtained by assuming that there is disease in the community.

One of the essential elements in studying mathematical models in epidemiology is the basic reproduction number (R_0). Using the next-generation matrix, we calculate the basic reproductive number R_0 . Then, we will analyze the stability of the disease equilibrium point by using the linearization technique for the system of non-linear differential equations to give the Jacobian matrix. Lastly, simulations of our model will be conducted using parameters. We will carry out numerical simulations using MATLAB's ode45.

In order to facilitate the upcoming debate, we provide the following some preliminaries.

3.1 Differential equations

Differential equation is an equation containing the derivatives of one or more dependent variable, with respect to one or more independent variables. When the function involved in the equation depends on only a single variable, its derivatives are ordinary derivatives and the differential equation is classed as an ordinary differential equation. On the other hand, if the function depends on several independent variables, so that its derivatives are partial derivatives, the differential equation is classed as a partial differential equation.

Let us consider an n- dimensional autonomous system of the form:

$$\begin{aligned}x'(t) &= f(x(t)), x \in \mathbb{R}^n \\x(t_0) &= x_0,\end{aligned}\tag{3.1}$$

Definition 3.1. ([26]). [Well-posedness]

Well-posedness is a concept in mathematics that refers to the properties of a mathematical problem or model. A problem is said to be well-posed if it satisfies three criteria:

- The problem has a solution
- The solution is unique
- The solution's behavior changes continuously with the initial conditions

In the context of differential equations, a well-posed problem has a unique solution that exists for a given set of initial conditions, and small changes in the initial conditions lead to small changes in the solution.

Definition 3.2. ([7]). A vector-valued function $f(t, x)$ is said to satisfy a Lipschitz condition in a region \mathbb{R}^n in (t, x) space if, for some constant k (called the Lipschitz constant), we have $\|f(t, x) - f(t, y)\| \leq K\|x - y\|$, whenever $(t, x) \in \mathbb{R}^n$ and $(t, y) \in \mathbb{R}^n$.

Theorem 3.1. ([17]). [Picard's theorem]

Consider the initial value problem given in (3.1), if the function f is continuous and that all its partial derivatives $\frac{\partial f_i}{\partial x_j}$ for $i, j = 1, 2, 3, \dots, n$ are continuous for x in some open connected set $D \subset \mathbb{R}^n$, then for $x_0 \in D$ the problem (3.1) has a solution $x(t)$ on some time interval (τ, τ) , $\tau > 0$ about $t = 0$, and the solution is unique.

Definition 3.3. ([23]). (Positivity of solution) The solution of a given autonomous system, of (3.1) is said to be positive, if all trajectories $x(t)$ is positive for any $t \geq 0$.

Definition 3.4. ([22]) (Boundedness of solution) The positive solution given in (3.1) of an autonomous system, of (3.1) is said to be bounded, if any solution, $x(t, t_0, x_0)$ (3.1) satisfies

$$\|x(t, t_0, x_0)\| \leq C(\|x_0\|, t_0)$$

for all $t \geq t_0$ where, $C : \mathbb{R}^+ \times \mathbb{R}^+ \rightarrow \mathbb{R}^+$ is a constant that depends on t_0 and x_0 .

Theorem 3.2 (Uniqueness of the model). If the vector field $f(t, x)$ satisfies a Lipschitz condition in a domain \mathbb{R}^n , then there is at most one solution $x(t)$ of the differential system $x' = f(t, x)$, that satisfies a given initial condition $x(t_0) = x_0$ in \mathbb{R}^n .

Theorem 3.3. ([13]) Let a linear ordinary differential equation is given by

$$y'(x) + p(x)y = q(x). \tag{3.2}$$

Then using integrating factor method the integrating factor and its general solution, respectively, are given by

$$I_f(x) = e^{\int p(x)dx} \quad (3.3a)$$

$$y(x) = e^{-\int p(x)dx} \left(C + \int q(x)e^{\int p(\tau)d\tau} dx \right), \quad (3.3b)$$

where C is an arbitrary constant of integration.

3.2 Stability analysis of equilibrium points

Definition 3.5. ([20]). Given the autonomous system (3.1), a state x^* is said to be an equilibrium point of the system if $f(x^*) = 0$.

Definition 3.6. ([16]). An equilibrium point x^* is asymptotically stable if it is stable and attracting. In other words, the solution x^* is said to be asymptotically-stable if:

i it is stable, and

ii there exists a constant $\delta > 0$ such that for any solution $x(t)$ of (3.1) satisfying

$$|x^* - x(0)| < \delta, \text{ then } \lim_{t \rightarrow \infty} |x(t) - x^*| = 0$$

Definition 3.7. ([16]). An equilibrium point x^* is said to be globally asymptotically stable if it is asymptotically stable for all initial condition $x_0 \in \mathbb{R}^n$.

Definition 3.8. ([16]). An equilibrium point x^* of the model (3.1) is said to be locally asymptotically stable if it is locally stable and every trajectory that starts sufficiently close to x^* tend towards x^* as $t \rightarrow \infty$. A steady state x^* which is not stable is said to be unstable.

Definition 3.9. An equilibrium point of a given dynamical system is stable means all solution curves of the equation attracts towards the equilibrium point, while an equilibrium point is unstable means all solution curves of the dynamic system go away from the equilibrium point.

Definition 3.10. ([20]). An equilibrium point x^* is globally stable if all trajectories converge to x^*

$$\text{i.e } \lim_{t \rightarrow \infty} x(t) = x^*.$$

3.2.1 Local stability (linearization technique)

Theorem 3.4 (Hartman-Grobman Theorem). *The Hartman-Grobman theorem says that the solutions of an $n \times n$ autonomous system of ordinary differential equations in a neighborhood of a hyperbolic steady state (none of the eigenvalues of J have zero real part) look “qualitatively” just like the solutions of the linearized system near the point $(0, 0)$.*

3.2.2 Principle of linearized stability:

The principle of linearized stability is analyzed by expanding solutions of the system around the equilibrium: $x(t) = x^* + y(t)$. So, we obtain

$$y' = D_x f(x^*)y + \psi(y)y$$

with $\psi(y)$ being a matrix such that $\psi(y) \rightarrow 0$ for $y \rightarrow 0$, and $D_x f$ denotes the derivative of f called the Jacobian matrix. The variational matrix or Jacobian matrix J of $f(x_1, x_2, \dots, x_n)$ is:

$$J(x) = \begin{pmatrix} \frac{\partial f_1(x^*)}{\partial x_1} & \frac{\partial f_1(x^*)}{\partial x_2} & \cdots & \frac{\partial f_1(x^*)}{\partial x_n} \\ \frac{\partial f_2(x^*)}{\partial x_1} & \frac{\partial f_2(x^*)}{\partial x_2} & \cdots & \frac{\partial f_2(x^*)}{\partial x_n} \\ \cdots & \cdots & \cdots & \cdots \\ \frac{\partial f_n(x^*)}{\partial x_1} & \frac{\partial f_n(x^*)}{\partial x_2} & \cdots & \frac{\partial f_n(x^*)}{\partial x_n} \end{pmatrix}$$

- (a) The equilibrium x^* is locally asymptotically stable if all eigenvalues of $J(x^*)$ have strictly negative real parts.
- (b) x^* is unstable if at least one eigenvalue of $J(x^*)$ has a strictly positive real part.

3.2.3 Global stability

Lyapunov function: Lyapunov theory is used to make conclusions about trajectories of a system $x' = f(x)$ (globally asymptotically stable) without finding the trajectories (i.e., solving the differential equation).

Theorem 3.5. ([24]).[Lyapunov theorem] *Let x^* be an equilibrium solution of (3.1) and suppose that we can find a Lyapunov function i.e a continuously differentiable, real valued function V such that*

- i $V(x) > 0$ for all $x \neq x^*$, and $V(x^*) = 0$ (V is positive definite)*

ii $V'(x) < 0$ for all $x \neq 0$, $V'(0) = 0$,

then, every trajectory of $x' = f(x)$ converges to zero as $t \rightarrow \infty$ (i.e., the system is globally asymptotically stable).

Theorem 3.6. ([6]) (Castillo Chavez theorem) Assume that the system (3.1) can be rewritten in the form

$$\frac{dX}{dt} = F(X, I) \quad (3.4a)$$

$$\frac{dI}{dt} = G(X, I) \quad (3.4b)$$

where the $X \in \mathbb{R}^m$ (represents the classes of non-infected individuals) and $I \in \mathbb{R}^{n-m}$ (represents the classes of infected individuals). Assume that $G(X, 0) = 0$ and let $E_0 = (X^*, 0)$ be a steady state of (3.1) (the disease free equilibrium point). If the following conditions are satisfied:

i . For the system $\frac{dX}{dt} = F(X, 0)$, the steady state X^* is globally asymptotically stable.

ii . $G(X, I) = AI - \hat{G}(X, I)$, $\hat{G}(X, I) \geq 0$ for $(X, I) \in \Omega$, where A is a Metzler matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense.

Then the steady state $E_0 = (X^*, 0)$ is a globally asymptotically stable for the system (3.4) provided that the basic reproduction number of the model is less than one.

3.2.4 Routh- Hurwitz stability criterion

Routh Hurwitz Stability Criterion is based on ordering the coefficients of the characteristic equation into an array, also known as Routh Array. Suppose the characteristic equation of a control system is given as:

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \dots + a_n = 0$$

where all the polynomial coefficients a^i , for $i = 1, 2, \dots, n$ are real constant. Define the $n \times n$ Hurwitz matrix using the coefficients a_i of the characteristic polynomial

$$H_1 = (a_1), H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, \dots, H_n = \begin{bmatrix} a_1 & 1 & 0 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & 1 & \dots & 0 \\ a_5 & a_4 & a_3 & a_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \dots & a_n \end{bmatrix}$$

where $a_j = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negative or have negative real part if and only if the determinant of all Hurwitz matrix are positive.

$$\det(H_j) > 0, \text{ for } j = 1, 2, \dots, n.$$

For polynomials of degree $n = 2, 3, 4$ and 5 the Routh-Hurwitz criteria are summarized as:

$$n = 2 : a_1 > 0 \text{ and } a_2 > 0$$

$$n = 3 : a_1 > 0; a_3 > 0 \text{ and } a_1 a_2 > a_3$$

$$n = 4 : a_1 > 0; a_3 > 0; a_4 > 0 \text{ and } a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$$

$$n = 5 : a_i > 0; \text{ for } i = 1, 2, 3, 4, 5; a_1 a_2 a_3 > a_3^2 + a_1^2 a_4 \text{ and } (a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2.$$

3.3 Center manifold theory

Center manifold theory has been used to decide the local stability of a non-hyperbolic equilibrium (linearization matrix has at least one eigenvalue with zero real part)[5]. We shall describe a theory that not only can determine the local stability of the non-hyperbolic equilibrium but also the existence of another equilibrium (bifurcated from the non-hyperbolic equilibrium). This theory is based on the general center manifold theory. To describe it, consider a general system of ODEs with a parameter ϕ :

$$\frac{dx}{dt} = f(x, \phi), \quad f : R^n \times R \rightarrow R^n, f \in C^2(R^n \times R). \quad (3.5)$$

It is assumed that 0 is an equilibrium for system 3.5 for all values of the parameter ϕ , that is $f(0, \phi) = 0$ for all ϕ .

Assume

- A_1 : $A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_j}(0, 0) \right)$ is the linearization matrix of system (3.5) around the equilibrium 0 with ϕ evaluated at 0 . Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts:

- A_2 : Matrix A has a non-negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0) \quad \text{and} \quad b = \sum_{i,k=1}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0)$$

The local dynamics of system (3.5) around 0 is totally determined by the signs of a and b :

i $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.

- ii $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium.
- iii $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears.
- iv $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Particularly, if $a < 0, b > 0$ then a forward bifurcation occurs at $\phi = 0$; if $a > 0, b > 0$ then a backward bifurcation occurs at $\phi = 0$.

3.4 Sensitivity analysis

In order to see how a change in the values of the predictor parameter impacts the dynamic behavior of the system, sensitivity analysis is typically carried out as a series of tests using several sets of input parameters. Determining the degree of relationship between input parameters and a predictor parameter is a helpful technique. It assists in figuring out how much of a change an input parameter must undergo in order for a predictor parameter to take on the intended value. Changing the values of the most sensitive parameters will be the most efficient way for changing the model's output.

Definition 3.11. *The relative sensitivity coefficient (or normalized forward sensitivity index) of a quantity Q with respect to a parameter p is defined as:*

$$Q_p = \frac{\partial Q}{\partial p} \times \frac{p}{Q}$$

3.5 Numerical simulation

Numerical simulation is a technique used to solve complex mathematical models that are difficult or impossible to solve analytically. This involves using numerical methods to approximate the solutions to the equations that describe the system being studied.

By using numerical simulation on mathematical models, researchers and engineers can gain insights into the behavior of the system under study, make predictions about future outcomes, and test different scenarios without the need for expensive and time-consuming physical experiments.

4 Model Formulation

4.1 The Existing Mathematical Model

Based on disease transmission characteristics, an epidemic model is proposed by Khan et al [12] to investigate hepatitis B virus transmission. There are four classes of host populations, symbolized by the susceptible class $S(t)$, the acutely infected compartment $A(t)$, the chronically ill class $B(t)$, and the immunized/recovered class $R(t)$. The total population is $N(t)$, and they used the following assumptions to formulate their in model.

- The portion of newborns with maternal infection leads to $B(t)$.
- The vaccine for hepatitis B is very effective because it provides indefinite protection; therefore, the susceptible individuals, after being vaccinated successfully, lead to the recovered population.
- Both the acutely infected and chronically infected individuals will cause the infection to be susceptible, and by successful interaction, the susceptible will lead to the acute class.

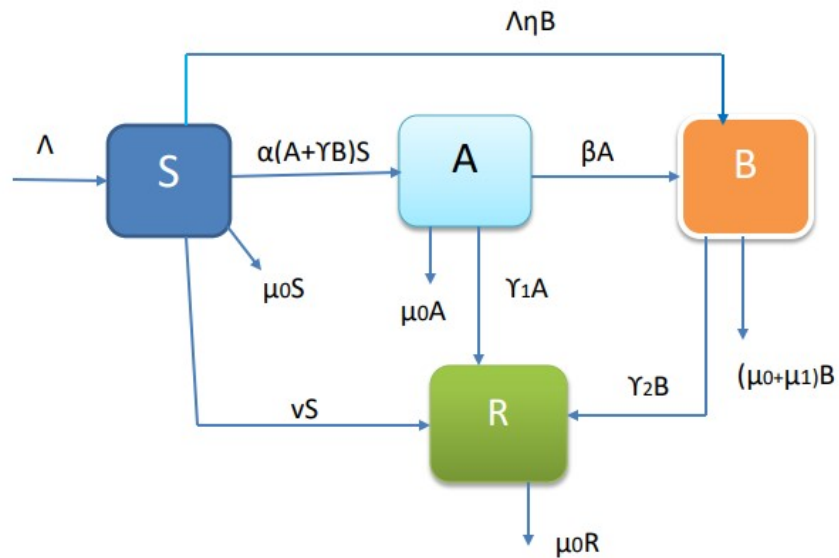


Figure 1: The schematic diagram for the transmission of the disease.

The schematic disease transmission process is demonstrated by fig.1. By grouping all of the above assumptions, a system of autonomous differential equations can be derived that describes the com-

plete model.

$$\begin{aligned}
\frac{dS(t)}{dt} &= (1 - \eta B(t)) \Lambda - (v + \mu_0) S(t) - (A(t) + \gamma B(t)) \alpha S(t), \\
\frac{dA(t)}{dt} &= \alpha S(t) A(t) + \gamma \alpha S(t) B(t) - (\gamma_1 + \beta + \mu_0) A(t), \\
\frac{dB(t)}{dt} &= \beta A(t) - (\mu_1 + \gamma_2 + \mu_0) B(t) + \eta \Lambda B(t), \\
\frac{dR(t)}{dt} &= \gamma_2 B(t) - \mu_0 R(t) + \gamma_1 A(t) + v S(t),
\end{aligned} \tag{4.1}$$

with

$$S(0) > 0, A(0) \geq 0, B(0) \geq 0, R(0) > 0. \tag{4.2}$$

4.2 The Modified Mathematical Model

Based on the above existing model, we will modify the dynamics of hepatitis B virus transmission by adding essential assumptions to the model. We assumed that there are six classes of host populations: susceptible class $S(t)$, vaccinated population $V(t)$, the exposed population $E(t)$, the acutely infected compartment $A(t)$, infected HBV chronically $C(t)$, and immunized/recovered class $R(t)$.

4.3 Model Assumptions

The following assumptions are made to modify and formulate our model:

- There is a latent period of hepatitis B; hence, we incorporate an exposed compartment in the model.
- Chronic hepatitis B can be treated with medicines.
- The disease can be transmitted from both acute and chronically infected individuals.
- Hepatitis B can be prevented by vaccines, and we assumed that the vaccine is effective.
- Natural death occurs in each model group, while death due to the disease occurs only in the chronic class.
- We have also assumed that individuals can be recovered from the disease permanently.
- Vertical transmission occurs when an HBV-infected mother passes the virus to her child during pregnancy, childbirth, or breastfeeding.
- Horizontal transmission(exposure to infected blood), especially from an infected child to uninfected child during the first 5 years of life.

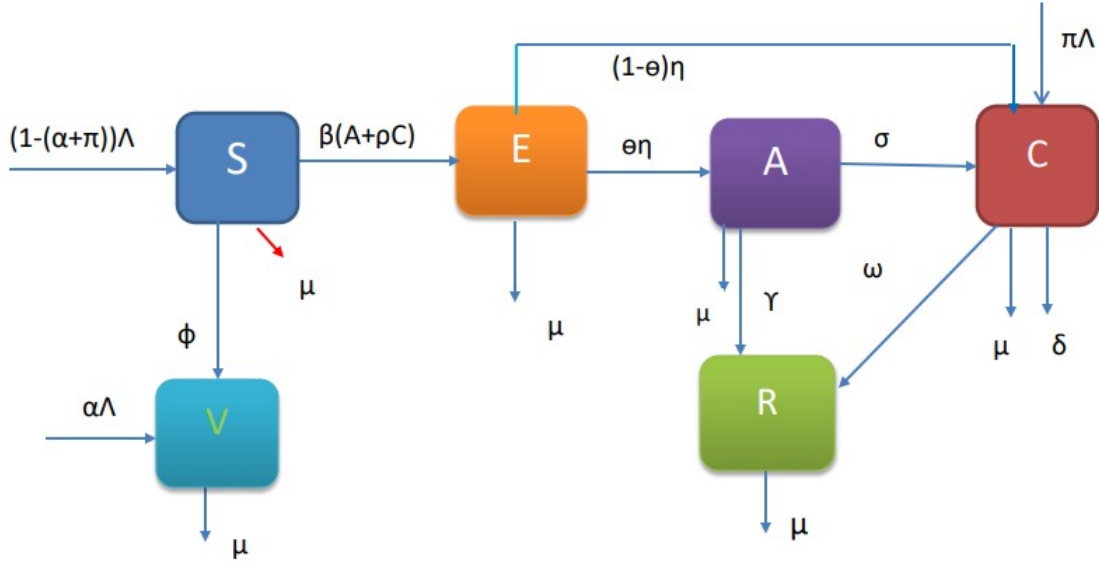


Figure 2: Schematic diagram of modified mathematical model for the dynamics of Hepatitis B by considering vaccination and disease latency

The modified model of transmission disease process is demonstrated by fig.2. A system of non-linear differential equations can be derived that describes the complete modified model has the form

$$\begin{aligned}
 \frac{dS}{dt} &= (1 - (\alpha + \pi)) \Lambda - \beta (A + \rho C) S - (\phi + \mu) S, \\
 \frac{dV}{dt} &= \alpha \Lambda + \phi S - \mu V, \\
 \frac{dE}{dt} &= \beta (A + \rho C) S - (\eta + \mu) E, \\
 \frac{dA}{dt} &= \theta \eta E - (\sigma + \gamma + \mu) A, \\
 \frac{dC}{dt} &= \pi \Lambda + (1 - \theta) \eta E + \sigma A - (\mu + \omega + \delta) C, \\
 \frac{dR}{dt} &= \gamma A + \omega C - \mu R,
 \end{aligned} \tag{4.3}$$

with

$$S(0) > 0, V(0) \geq 0, E(0) \geq 0, A(0) \geq 0, C(0) \geq 0, R(0) \geq 0. \tag{4.4}$$

4.4 Description of Variables and Parameters

Table 1: State variables of HBV model

Symbol	Description
$S(t)$	The numbers of susceptible population at time t
$V(t)$	The numbers of individual who have vaccinated
$E(t)$	The number of exposed individual in HBV at time t
$A(t)$	The number of acutely infected HBV
$C(t)$	The number of chronically infected HBV
$R(t)$	The numbers of individual recovered from HBV

Table 2: Parameters of HBV model

Symbol	description
Λ	Recruitment rate
β	Transmission rate of HBV
α	Vaccination rate of newborns (pediatric vaccination)
π	Proportion of vertical transmission rate
$\frac{1}{\eta}$	Latent period
σ	Rate of acute moves to chronic class by developing symptoms
ω	Recovery rate of chronically infected individuals
γ	Recovery rate of acutely infected individuals
μ	Natural death rate
δ	Death rate due to the diseases
ρ	Modification parameter
θ	Proportionality constant
ϕ	Vaccination rate

5 Qualitative Analysis of the Modified Model

In this section, we present some basic qualitative properties of the modified model. These analyses seek to show that the modified model is epidemiologically appropriate in the sense that the model and its predictions make sense. These analyses include finding the set inside which the model can be sufficiently studied (i.e., the invariant region); local and global stability of equilibrium points of the model(4.3).

5.1 Well-posedness

Since all the functions on the right hand side of the system (4.3) are continuously differentiable. Thus, the existence and uniqueness of the solutions is established by the Picard's theorem (3.1). Now, we show the positivity and boundedness of solutions.

Proposition 5.1 (Positivity). *If $S(0) > 0$, $V(0) \geq 0$, $E(0) \geq 0$, $A(0) \geq 0$, $C(0) \geq 0$ and $R(0) \geq 0$, then the solution $\{S(t), V(t), E(t), A(t), C(t), R(t)\}$ of the dynamical system (4.3) is non-negative for all time $t \geq 0$.*

Proof. To show the positivity of the solution of the dynamical system (4.3), we will perform the proof by using contradiction. We assume that $S(t) \leq 0$ for some $t \geq 0$, that is there exists small $t_0 > 0$ such that $S(t_0) = 0$, $S'(t_0) \leq 0$ and $S(t) > 0$ for $t \in [0, t_0]$. Then $V(t) \geq 0$, $A(t) \geq 0$, $C(t) \geq 0$ and $E(t) \geq 0$ for $t \in [0, t_0]$.

If this is not the case, then there exists:

- I $t_1 \in [0, t_0]$ such that $V(t_1) = 0$, $V'(t_1) < 0$ and $V(t) > 0$ for $t \in [0, t_1]$. Then $E(t_1) \geq 0$, $A(t_1) \geq 0$ & $C(t_1) \geq 0$ for $t \in [0, t_1]$.
- II $t_2 \in [0, t_1]$ such that $E(t_2) = 0$, $E'(t_2) < 0$ and $E(t) > 0$ for $t \in [0, t_2]$. Then $V(t_2) \geq 0$, $A(t_2) \geq 0$ & $C(t_2) \geq 0$ for $t \in [0, t_2]$.
- III $t_3 \in [0, t_2]$ such that $A(t_3) = 0$, $A'(t_3) < 0$ and $A(t) > 0$ for $t \in [0, t_3]$. Then $V(t_3) \geq 0$, $E(t_3) \geq 0$ & $C(t_3) \geq 0$ for $t \in [0, t_3]$.
- IV $t_4 \in [0, t_3]$ such that $C(t_4) = 0$, $C'(t_4) < 0$ and $C(t) > 0$ for $t \in [0, t_4]$. Then $V(t_4) \geq 0$, $E(t_4) \geq 0$ & $A(t_4) \geq 0$ for $t \in [0, t_4]$.

Now from the first equation of system (4.3) , we have:

$$\begin{aligned}\frac{dS}{dt} &= (1 - (\alpha + \pi)) \Lambda - \beta (A + \rho C) S - (\phi + \mu) S, \\ S'(t_0) &= (1 - (\alpha + \pi)) \Lambda - \beta (A(t_0) + \rho C(t_0)) S(t_0) - (\phi + \mu) S(t_0), \\ S'(t_0) &\geq (1 - (\alpha + \pi)) \Lambda, \quad \text{since } S(t_0) = 0, \\ S'(t_0) &\geq (1 - (\alpha + \pi)) \Lambda\end{aligned}$$

$S'(t_0) > 0$, which contradicts the assumption that $S'(t_0) \leq 0$. Thus, $S(t) > 0$ for all $t \geq 0$. It follows from the second equation of system (4.3) that, we get:

$$\begin{aligned}\frac{dV}{dt} &= \alpha \Lambda + \phi S - \mu V, \\ V' + \mu V &\geq \alpha \Lambda, \quad \text{since } S(t) > 0,\end{aligned}$$

Using integrating factor, solving the differential inequality, we obtain

$$\begin{aligned}V(t) &\geq \frac{\alpha \Lambda}{\mu} + \left(V(0) - \frac{\alpha \Lambda}{\mu} \right) e^{-\mu t}, \\ V(t) &\geq \frac{\alpha \Lambda}{\mu} + \left(V(0) - \frac{\alpha \Lambda}{\mu} \right) e^{-\mu t} \geq 0 \quad \text{for } t \in [0, t_1].\end{aligned}$$

It follows from the fourth equation of system (4.3) that, we have:

$$\begin{aligned}A'(t_3) &= \theta \eta E(t_3) - (\sigma + \gamma + \mu) A(t_3), \\ A'(t_3) &= \theta \eta E(t_3) >, \quad \text{since } A(t_3) = 0 \quad \text{from(III)}, \\ A'(t_3) &> 0,\end{aligned}$$

which contradicts the assumption that $A(t_3) > 0$. Thus $A(t_3) < 0$ for all $t \geq 0$.

It follows from the fifth equation of system (4.3) that, we have:

$$\begin{aligned}C'(t_4) &= \pi \Lambda + (1 - \theta) \eta E(t_4) + \sigma A(t_4) - (\mu + \omega + \delta) C(t_4) \\ C'(t_4) &= \pi \Lambda + (1 - \theta) \eta E(t_4) + \sigma A(t_4), \quad \text{since } E(t_4) > 0, A(t_4) > 0 \quad \text{and } C(t_4) = 0 \quad \text{from(IV)}.\end{aligned}$$

$C'(t_4) > 0$, which contradicts the assumption that $C(t_4) < 0$. Thus $C(t_4) < 0$ for all $t \geq 0$.

From the third equation of the system (4.3) that, we obtain:

$$\frac{dE}{dt} = \beta (A + \rho C) S - (\eta + \mu) E$$

$$\begin{aligned}\frac{dE}{dt} &= \beta (A(t) + \rho C(t)) S(t) - (\eta + \mu) E, \\ \frac{dE}{dt} &\geq -(\eta + \mu) E(t), \quad \text{since } S(t) > 0, C(t) > 0 \quad \text{and } A(t) > 0\end{aligned}$$

By rearranging and integrating both sides of the inequality, we get:

$$\begin{aligned}\frac{dE}{E} &\geq -(\eta + \mu)dt \\ \int \frac{dE}{E} &\geq - \int (\eta + \mu)dt \\ E(t) &\geq e^{-(\eta+\mu)t+c}, \quad E(0) = e^c > 0\end{aligned}$$

$E(t) \geq E(0)e^{-(\eta+\mu)t} > 0$. Thus $E(t) > 0$ for all $t \geq 0$.

It follows from the last equation of system (4.3) that, we get:

$$\begin{aligned}\frac{dR}{dt} &= \gamma A + \omega C - \mu R \\ \frac{dR}{dt} &= \gamma A(t) + \omega C(t) - \mu R(t) \\ \frac{dR}{dt} &\geq -\mu R(t)\end{aligned}$$

By rearranging and integrating both sides of the inequality, we get:

$$\begin{aligned}\int \frac{dR}{R} &\geq - \int \mu dt \\ R(t) &\geq e^{-\mu t+c}, \quad R(0) = e^c > 0\end{aligned}$$

$R(t) \geq R(0)e^{-\mu t}$. Thus $R(t) > 0$ for all $t \geq 0$. □

Theorem 5.1 (Boundedness). *There exists a positively invariant region Ω in which the solution $S(t), V(t), E(t), A(t), C(t), R(t)$ of the dynamical system (4.3) is bounded.*

Proof. In order to show that the population sizes of each compartment is bounded, we prefer to show that the total population size, of the whole system is bounded.

The total population size N , is given by:

$$N(t) = S(t) + V(t) + E(t) + A(t) + C(t) + R(t)$$

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dE}{dt} + \frac{dA}{dt} + \frac{dC}{dt} + \frac{dR}{dt}$$

Then, we obtain:

$$\frac{dN}{dt} = \Lambda - \mu N - \delta C$$

$$\frac{dN}{dt} \leq \Lambda - \mu N, \text{ since } C(t) \text{ is positive.}$$

Solving the differential inequality by applying integrating factor method, we get

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t},$$

If $N(0) \leq \frac{\Lambda}{\mu}$, then we obtain $0 \leq N(t) \leq \frac{\Lambda}{\mu}$, for all $t \geq 0$.

Thus, the total population $N(t)$ and each population classes are remain bounded for all time $t \geq 0$. Therefore, the model (4.3) is well posed epidemiologically and mathematically in a positively invariant set

$$\Omega = \left\{ (S(t), V(t), E(t), A(t), C(t), R(t)) \in \mathbb{R}_+^6 : 0 \leq N(t) \leq \max \left(N(0), \frac{\Lambda}{\mu} \right) \right\}.$$

□

5.2 Disease free equilibrium point and its stability

5.2.1 HBV free equilibrium point

Disease-free equilibrium points are the steady-state solution, when there is no acute and chronic HBV infection $E = 0$, $A = 0$ and $C = 0$. That is,

$$\begin{aligned} ((1 - (\alpha + \pi)) \Lambda - \beta (A + \rho C) S - (\phi + \mu) S &= 0, \\ \alpha \Lambda + \phi S - \mu V &= 0, \\ \beta (A + \rho C) S - (\eta + \mu) E &= 0, \\ \theta \eta E - (\sigma + \gamma + \mu) A &= 0, \\ \pi \Lambda + (1 - \theta) \eta E + \sigma A - (\mu + \omega + \delta) C &= 0, \\ \gamma A + \omega C - \mu R &= 0. \end{aligned}$$

Thus, the disease-free equilibrium point for the system of equations implies that $E = 0$, $A = 0$, $C = 0$, $R = 0$, $S = \frac{((1 - (\alpha + \pi)) \Lambda)}{\phi + \mu}$ and $V = \frac{\alpha \Lambda + \phi S}{\mu}$
 $V = \frac{\alpha \Lambda (\phi + \mu) + \phi \Lambda (1 - (\alpha + \pi))}{\mu (\phi + \mu)}$

Thus, we obtain the disease-free equilibrium point: $E_0 = (S^0, V^0, E^0, A^0, C^0, R^0)$

$$E_0 = \left(\frac{(1 - (\alpha + \pi)) \Lambda}{\phi + \mu}, \frac{\alpha \Lambda (\phi + \mu) + \phi \Lambda (1 - (\alpha + \pi))}{\mu (\phi + \mu)}, 0, 0, 0, 0 \right).$$

5.2.2 Basic Reproductive Number

The basic reproductive number R_0 measures the average number of new acute and chronic HBV infections generated by a single infected individual in a completely susceptible population.

We have specified that E , A and C are the infected compartments. So,

$$\begin{aligned}\frac{dE}{dt} &= \beta(A + \rho C)S - (\eta + \mu)E, \\ \frac{dA}{dt} &= \theta\eta E - (\sigma + \gamma + \mu)A, \\ \frac{dC}{dt} &= \pi\Lambda + (1 - \theta)\eta E + \sigma A - (\mu + \omega + \delta)C,\end{aligned}\tag{5.1}$$

- \mathcal{F}_i is the rate of appearance of new infection in compartment i .
- \mathcal{V}_i is transfer of individuals in and out of compartment i by an other means.

$$\mathcal{F}_i = \begin{pmatrix} f_1 \\ f_2 \\ f_3 \end{pmatrix} = \begin{pmatrix} \beta(A + \rho C)S \\ 0 \\ 0 \end{pmatrix}$$

$$\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+ = \begin{pmatrix} (\eta + \mu)E \\ (\sigma + \gamma + \mu)A - \theta\eta E \\ (\mu + \omega + \delta)C - \pi\Lambda - (1 - \theta)\eta E - \sigma A \end{pmatrix} = g_i$$

\mathcal{F} and \mathcal{V} respectively are the Jacobian matrices of $F(x)$ and $V(x)$ at E_0 :

$$\begin{aligned}F &= \left[\frac{\partial \mathcal{F}_i}{\partial E, A, C}(E_0) \right] \text{ and } V = \left[\frac{\partial g_i}{\partial E, A, C}(E_0) \right] \\ F &= \begin{pmatrix} \frac{\partial f_1}{\partial E} & \frac{\partial f_1}{\partial A} & \frac{\partial f_1}{\partial C} \\ \frac{\partial f_2}{\partial E} & \frac{\partial f_2}{\partial A} & \frac{\partial f_2}{\partial C} \\ \frac{\partial f_3}{\partial E} & \frac{\partial f_3}{\partial A} & \frac{\partial f_3}{\partial C} \end{pmatrix} = \begin{pmatrix} 0 & \beta S & \beta \rho S \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, F(E_0) = \begin{pmatrix} 0 & \frac{\beta(1 - (\alpha + \pi))\Lambda}{\phi + \mu} & \frac{\beta\rho(1 - (\alpha + \pi))\Lambda}{\phi + \mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \\ V &= \begin{pmatrix} \frac{\partial g_1}{\partial E} & \frac{\partial g_1}{\partial A} & \frac{\partial g_1}{\partial C} \\ \frac{\partial g_2}{\partial E} & \frac{\partial g_2}{\partial A} & \frac{\partial g_2}{\partial C} \\ \frac{\partial g_3}{\partial E} & \frac{\partial g_3}{\partial A} & \frac{\partial g_3}{\partial C} \end{pmatrix} = \begin{pmatrix} \mu + \eta & 0 & 0 \\ -\theta\eta & (\sigma + \gamma + \mu) & 0 \\ -(1 - \theta)\eta & -\sigma & (\mu + \omega + \delta) \end{pmatrix} \\ \text{and } V^{-1} &= \frac{Adj(V)}{det(V)}\end{aligned}$$

$$= \frac{1}{(\mu+\eta)(\sigma+\gamma+\mu)(\mu+\omega+\delta)} \begin{pmatrix} (\sigma+\gamma+\mu)(\mu+\omega+\delta) & 0 & 0 \\ \theta\eta(\mu+\omega+\delta) & (\mu+\eta)(\mu+\omega+\delta) & 0 \\ \theta\eta\sigma+(1-\theta)\eta(\sigma+\gamma+\mu) & (\mu+\eta)\sigma & (\mu+\eta)(\sigma+\gamma+\mu) \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\eta+\mu} & 0 & 0 \\ \frac{1}{\theta\eta} & \frac{1}{\sigma+\gamma+\mu} & 0 \\ \frac{(\mu+\eta)(\sigma+\gamma+\mu)}{\theta\eta+(1-\theta)\eta(\sigma+\gamma+\mu)} & \frac{1}{\sigma} & \frac{1}{\mu+\omega+\delta} \end{pmatrix}$$

The matrix FV^{-1} is known as the next-generation matrix and its spectral radius (largest eigenvalue) is the basic reproduction number of the model.

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

$$FV^{-1} =$$

$$\begin{pmatrix} \frac{\theta\eta\beta\Lambda(1-(\alpha+\pi))}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)} + \frac{\beta\rho\Lambda(1-(\alpha+\pi))(\theta\eta\sigma+(1-\theta)\eta(\sigma+\gamma+\mu))}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)(\mu+\omega+\delta)} & \frac{\beta\Lambda(1-(\alpha+\pi))}{(\phi+\mu)(\sigma+\gamma+\mu)} + \frac{\beta\rho\Lambda(1-(\alpha+\pi))}{(\phi+\mu)(\sigma+\gamma+\mu)} & \frac{\beta\Lambda\rho(1-(\alpha+\pi))}{(\pi+\mu)(\mu+\omega+\delta)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

The eigenvalues are

$$\lambda_1 = \frac{\theta\eta\beta\Lambda(1-(\alpha+\pi))}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)} + \frac{\beta\rho\Lambda(1-(\alpha+\pi))(\theta\eta\sigma+(1-\theta)\eta(\sigma+\gamma+\mu))}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)(\mu+\omega+\delta)},$$

$$\lambda_2 = 0 \quad \text{and}$$

$$\lambda_3 = 0.$$

Hence, the reproduction number is $R_0 = \max\{\lambda_1, \lambda_2, \lambda_3\}$. As a result, we have:

$$R_0 = \frac{\eta\beta\Lambda(1-(\alpha+\pi))[\theta(\mu+\omega+\delta) + \rho(\theta\sigma+(1-\theta)(\sigma+\gamma+\mu))]}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)(\mu+\omega+\delta)}.$$

We can split R_0 as $R_0 = R_1 + R_2 + R_3$, where,

$$R_1 = \frac{\theta\eta\beta\Lambda(1-(\alpha+\pi))}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)},$$

$$R_2 = \frac{\beta\rho\Lambda(1-(\alpha+\pi))\theta\eta\sigma}{(\phi+\mu)(\mu+\eta)(\sigma+\gamma+\mu)(\mu+\omega+\delta)},$$

$$R_3 = \frac{\beta\rho\Lambda(1-(\alpha+\pi))(1-\theta)\eta}{(\phi+\mu)(\mu+\eta)(\mu+\omega+\delta)}.$$

5.2.3 Local stability of disease free equilibrium point

Theorem 5.2. *The disease free equilibrium point (DFE) E_0 of the system (4.3) is locally asymptotically stable if $R_0 < 1$.*

Proof. The Jacobian matrix (4.3) at the disease-free equilibrium E_0 is:

The Jacobian matrix of the dynamical system (4.3) is

$$J = \begin{bmatrix} -\beta(A + \rho C) - (\phi + \mu) & 0 & 0 & -\beta S & -\beta \rho S & 0 \\ \phi & -\mu & 0 & 0 & 0 & 0 \\ \beta(A + \rho C) & 0 & -(\mu + \eta) & \beta S & \beta \rho S & 0 \\ 0 & 0 & \theta \eta & -(\sigma + \gamma + \mu) & 0 & 0 \\ 0 & 0 & (1 - \theta) \eta & \sigma & -(\mu + \omega + \delta) & 0 \\ 0 & 0 & 0 & \gamma & \omega & -\mu \end{bmatrix}$$

- At E_0 , the Jacobian matrix becomes:

$$J(E_0) = \begin{bmatrix} -(\phi + \mu) & 0 & 0 & \frac{-\beta \Lambda (1 - (\alpha + \pi))}{\phi + \mu} & \frac{-\beta \Lambda \rho (1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ \phi & -\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\mu + \eta) & \frac{\beta \Lambda (1 - (\alpha + \pi))}{\phi + \mu} & \frac{\beta \Lambda \rho (1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ 0 & 0 & \theta \eta & -(\sigma + \gamma + \mu) & 0 & 0 \\ 0 & 0 & (1 - \theta) \eta & \sigma & -(\mu + \omega + \delta) & 0 \\ 0 & 0 & 0 & \gamma & \omega & -\mu \end{bmatrix}$$

- The characteristic equation of the Jacobian is given by

$$((\phi + \mu) + \lambda)(\mu + \lambda)(\mu + \lambda)(\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3) = 0. \quad (5.2)$$

To find the eigenvalues from the characteristics polynomial equation (5.2),

$$\lambda_1 = -(\phi + \mu) < 0, \lambda_2 = -\mu < 0, \lambda_3 = -\mu < 0 \text{ and,} \\ \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0 \quad (5.3)$$

$$a_1 = (\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta),$$

$$a_2 = (\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\mu + \eta)(\mu + \omega + \delta) - k_2(1 - \theta)\eta + (\mu + \eta)(\sigma + \gamma + \mu) - k_1\theta\eta, \\ = (\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\mu + \eta)(\mu + \omega + \delta)(1 - R_3) + (\mu + \eta)(\sigma + \gamma + \mu)(1 - R_1)$$

$$a_3 = (\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta) - k_1\theta\eta(\mu + \omega + \delta) - k_2(\theta\eta\sigma + (\sigma + \gamma + \mu)(1 - \theta)\eta). \\ = (\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta)(1 - R_0)$$

where,

$$k_1 = \frac{\beta\Lambda(1 - (\alpha + \pi))}{\phi + \mu}, k_2 = \frac{\beta\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu}.$$

From the Routh–Hurwitz criterion (5.3), we can guarantee that the cubic equation (5.3) has roots with negative real part if, and only if, its coefficients are positive $a_1 > 0$, $a_2 > 0$ and

$$a_3 = (\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta)(1 - R_0) > 0$$

if $R_0 < 1$, it follows that $a_3 > 0$

Moreover, we will show that $a_1 a_2 > a_3$, that is,

$$\begin{aligned} &(\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\mu + \eta)(\mu + \omega + \delta)(1 - R_3) + (\mu + \eta)(\sigma + \gamma + \mu)(1 - R_1) > (1 - R_0). \\ &(\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\mu + \eta)(\mu + \omega + \delta)(1 - R_3) + (\mu + \eta)(\sigma + \gamma + \mu)(1 - R_1) - (1 - R_0) > 0 \end{aligned}$$

holds.

If $R_0 < 1$, then R_1 and R_3 are strictly less than one. Since $R_0 = R_1 + R_2 + R_3$. The coefficients a_1, a_2 and a_3 are positive and $a_1 a_2 > a_3$. Thus, all the eigenvalues of $J(E_0)$ are negative for $R_0 < 1$. It follows by Routh-Hurwitz criteria that the disease free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$. If $R_0 > 1$, then a_3 is negative and the Routh-Hurwitz criterion tells that the disease free equilibrium E_0 is unstable. \square

5.2.4 Global stability of disease free equilibrium

Theorem 5.3. *The disease free equilibrium (DFE) E_0 of the system (4.3) is globally asymptotically stable if $S_0 \geq S$, otherwise unstable.*

Proof. Let us rewrite our model system (4.3) as:

$$\begin{aligned} \frac{dX}{dt} &= F(X, I), \\ \frac{dI}{dt} &= G(X, I), \quad G(X, 0) = 0 \end{aligned}$$

Where, $X = (S, V, R) \in \mathbb{R}_+^3$ represents the class of uninfected HBV individuals and $I = (E, A, C) \in \mathbb{R}_+^3$ represents the class of infected HBV individuals. The disease free equilibrium point of the model is denoted by $E_0 = (X^*, 0)$, where

$$X^* = \left(\frac{(1 - (\alpha + \pi))\Lambda}{\phi + \mu}, \frac{\alpha\Lambda(\phi + \mu) + \phi\Lambda(1 - (\alpha + \pi))}{\mu(\phi + \mu)}, 0 \right).$$

Since the disease free equilibrium

point is locally asymptotically stable (from theorem (5.2)), then to prove global stability, we will apply the Castillo-Chavez theorem. From system (4.3), we have

$$\frac{dX}{dt} = F(X, I) = \begin{bmatrix} (1 - (\alpha + \pi)) \Lambda - \beta (A + \rho C) S - (\phi + \mu) S \\ \alpha \Lambda + \phi S - \mu V \\ \gamma A + \omega C - \mu R \end{bmatrix}$$

$$\frac{dI}{dt} = G(X, I) = \begin{bmatrix} \beta (A + \rho C) S - (\eta + \mu) E \\ \theta \eta E - (\sigma + \gamma + \mu) A \\ \pi \Lambda + (1 - \theta) \eta E + \sigma A - (\mu + \omega + \delta) C \end{bmatrix}$$

I . To show that X^* is globally asymptotically stable for the system $\frac{dX}{dt} = F(X, 0)$, let us consider the reduced system;

$$\frac{dX}{dt} = F(X, 0) = \begin{bmatrix} (1 - (\alpha + \pi)) \Lambda - (\phi + \mu) S, \\ \alpha \Lambda + \phi S - \mu V, \\ -\mu R \end{bmatrix} \quad (5.4)$$

$$\frac{dS}{dt} = (1 - (\alpha + \pi)) \Lambda - (\phi + \mu) S, \quad (5.5a)$$

$$\frac{dV}{dt} = \alpha \Lambda + \phi S - \mu V, \quad (5.5b)$$

$$\frac{dR}{dt} = -\mu R. \quad (5.5c)$$

The system (5.5) is non-homogeneous linear system of ordinary differential equations. Then, we can find its solution as follows:

For system of equation (5.5c), we have: $\frac{dR}{dt} = -\mu R$

$R(t) = R(0)e^{-\mu t}$, (integrating by separation of variables).

As $t \rightarrow \infty$, $R(t) \rightarrow 0$.

For system of equation (5.5a), we have:

$$\frac{dS}{dt} = (1 - (\alpha + \pi)) \Lambda - (\phi + \mu) S$$

Using integrating factor method , solving the differential equality, we get

$$S(t) = \frac{(1 - (\alpha + \pi)) \Lambda}{\phi + \mu} + \left(S(0) - \frac{(1 - (\alpha + \pi)) \Lambda}{\phi + \mu} \right) e^{-(\phi + \mu)t}$$

$$\text{As } t \rightarrow \infty, S(t) = \frac{(1 - (\alpha + \pi))\Lambda}{\phi + \mu}.$$

For system of equation (5.5b), we have:

$$\begin{aligned} \frac{dV}{dt} &= \alpha\Lambda + \phi S - \mu V, \\ \frac{dV}{dt} &= \alpha\Lambda + \frac{(1 - (\alpha + \pi))\Lambda\phi}{\phi + \mu} - \mu V, S(t) = \frac{(1 - (\alpha + \pi))\Lambda}{\phi + \mu}, \\ \frac{dV}{dt} &= \frac{\alpha\Lambda(\phi + \mu) + (1 - (\alpha + \pi))\Lambda\phi}{\phi + \mu} - \mu V, \end{aligned}$$

By applying integrating factor method, solving the differential equality, we get

$$V(t) = \frac{\alpha\Lambda(\phi + \mu) + (1 - (\alpha + \pi))\Lambda\phi}{\phi + \mu} + \left(V(0) - \frac{\alpha\Lambda(\phi + \mu) + (1 - (\alpha + \pi))\Lambda\phi}{\phi + \mu} \right) e^{-\mu t}.$$

$$\text{As } t \rightarrow \infty, V(t) = \frac{\alpha\Lambda(\phi + \mu) + (1 - (\alpha + \pi))\Lambda\phi}{\phi + \mu} \text{ and we obtain}$$

$$\text{Therefore as } t \rightarrow \infty, S(t), V(t), R(t) \rightarrow \left(\frac{(1 - (\alpha + \pi))\Lambda}{\phi + \mu}, \frac{\alpha\Lambda(\phi + \mu) + (1 - (\alpha + \pi))\Lambda\phi}{\phi + \mu}, 0 \right) = X^*.$$

Hence, X^* is globally asymptotically stable for $\frac{dX}{dt} = F(X, 0)$.

II . We will show that $G(X, I) = AI - \hat{G}(X, I)$, $\hat{G}(X, I) \geq 0$ for $(X, I) \in \Omega$ where is a Metzler matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense. Consider a matrix

$$A = \frac{\partial G}{\partial I}(X^*, 0) = \begin{bmatrix} -(\eta + \mu) & \beta S^0 & \beta \rho S^0 \\ \theta \eta & -(\sigma + \gamma + \mu) & 0 \\ (1 - \theta)\eta & \sigma & -(\mu + \omega + \delta) \end{bmatrix}$$

Hence, A is a Metzler matrix (off diagonal elements are non-negatives).

And $\hat{G}(X, I) = AI - G(X, I)$

$$\begin{aligned} &= \begin{pmatrix} -(\eta + \mu) & \beta S^0 & \beta \rho S^0 \\ \theta \eta & -(\sigma + \gamma + \mu) & 0 \\ (1 - \theta)\eta & \sigma & -(\mu + \omega + \delta) \end{pmatrix} \begin{pmatrix} E \\ A \\ C \end{pmatrix} - \begin{pmatrix} \beta(A + \rho C)S - (\eta + \mu)E, \\ \theta \eta E - (\sigma + \gamma + \mu)A, \\ \pi \Lambda + (1 - \theta)\eta E + \sigma A - (\mu + \omega + \delta)C \end{pmatrix} \\ &= \begin{pmatrix} \beta(A + \rho C)(S^0 - S) \\ 0 \\ -\pi \Lambda \end{pmatrix}. \end{aligned} \text{ Hence the proportion of vertical transmission rate is negative.}$$

Therefore by Castillo-Chavez theorem (3.6) since the term by $-\pi \Lambda < 0$, the disease free equilibrium point E_0 of the system (4.3) is globally asymptotically unstable.

□

5.3 Endemic equilibrium point and its stability

5.3.1 HBV endemic equilibrium point

Endemic equilibrium point is a steady state solution where the disease persists in the population. In the presence of disease in the population, there exist an equilibrium point called endemic equilibrium point denoted by $E_1 = (S^*, V^*, E^*, A^*, C^*, R^*)$. It can be obtained by setting each equation of the system (4.3) equation

$$((1 - (\alpha + \pi)) \Lambda - \beta(A + \rho C) S - (\phi + \mu) S = 0, \quad (5.6a)$$

$$\alpha \Lambda + \phi S - \mu V = 0, \quad (5.6b)$$

$$\beta(A + \rho C) S - (\eta + \mu) E = 0, \quad (5.6c)$$

$$\theta \eta E - (\sigma + \gamma + \mu) A = 0, \quad (5.6d)$$

$$\pi \Lambda + (1 - \theta) \eta E + \sigma A - (\mu + \omega + \delta) C = 0, \quad (5.6e)$$

$$\gamma A + \omega C - \mu R = 0. \quad (5.6f)$$

From equation (5.6d), we have

$$E^* = \frac{(\sigma + \gamma + \mu) A^*}{\theta \eta} \quad (5.7)$$

By substituting equations ((5.7)) into equation (5.6e), we have

$$C^* = \frac{\pi \Lambda \theta + ((1 - \theta)(\sigma + \gamma + \mu) + \sigma \theta) A^*}{\theta(\mu + \omega + \delta)} \quad (5.8)$$

By substituting equations (5.7) and (5.8) into equation (5.6c), we have

$$S^* = \frac{(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta) A^*}{\beta \theta \eta (\mu + \omega + \delta) A^* + \beta \rho \eta [\pi \theta \Lambda + (\sigma \theta + (1 - \theta)(\sigma + \gamma + \mu)) A^*]} \quad (5.9)$$

We substituting equations (5.9) into equation (5.6b), we have

$$V^* = \frac{\beta \alpha \theta \eta \Lambda (\mu + \omega + \delta) A^* + \beta \alpha \rho \eta \Lambda [\pi \theta \Lambda + (\sigma \theta + (1 - \theta)(\sigma + \gamma + \mu)) A^*] + (\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta) A^*}{\beta \theta \eta \mu (\mu + \omega + \delta) A^* + \beta \rho \eta \mu [\pi \theta \Lambda + (\sigma \theta + (1 - \theta)(\sigma + \gamma + \mu)) A^*]}$$

We substituting equations (5.8) into equation (5.6f), we have

$$R^* = \frac{\theta \gamma (\mu + \omega + \delta) A^* + \omega (\pi \Lambda \theta + (1 - \theta)(\sigma + \gamma + \mu) A^* + \sigma \theta A^*)}{\mu \theta (\sigma + \gamma + \mu)}$$

$$\begin{aligned}
S^* &= \frac{(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)A^*}{\beta\theta\eta(\mu + \omega + \delta)A^* + \beta\rho\eta[\pi\theta\Lambda + (\sigma\theta + (1 - \theta)(\sigma + \gamma + \mu))A^*]} \\
V^* &= \frac{\beta\alpha\theta\eta\Lambda(\mu + \omega + \delta)A^* + \beta\alpha\rho\eta\Lambda[\pi\theta\Lambda + (\sigma\theta + (1 - \theta)(\sigma + \gamma + \mu))A^*] + (\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)A^*}{\beta\theta\eta\mu(\mu + \omega + \delta)A^* + \beta\rho\eta\mu[\pi\theta\Lambda + (\sigma\theta + (1 - \theta)(\sigma + \gamma + \mu))A^*]} \\
E^* &= \frac{(\sigma + \gamma + \mu)A^*}{\theta\eta} \\
C^* &= \frac{\pi\Lambda\theta + ((1 - \theta)(\sigma + \gamma + \mu) + \sigma\theta)A^*}{\theta(\mu + \omega + \delta)} \\
R^* &= \frac{(\theta\gamma(\mu + \omega + \delta) + \omega(\pi\Lambda\theta + (1 - \theta)(\sigma + \gamma + \mu) + \sigma\theta))A^*}{\mu\theta(\sigma + \gamma + \mu)}
\end{aligned}$$

Substituting the value of S^* and C^* in equation (5.6a) and A^* is obtained by solving the equation,

$$\begin{aligned}
& -\beta\rho[\theta(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2 + (1 - \theta)(\eta + \mu)(\sigma + \gamma + \mu)^2(\mu + \omega + \delta) + \sigma\theta(\eta + \mu)(\sigma + \gamma + \mu)^2(\mu + \omega + \delta)]A^{*2} \\
& + [(1 - (\alpha + \pi))\Lambda\beta\eta\theta(\mu + \omega + \delta)[\theta(\mu + \omega + \delta) + \rho\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)\rho] - \beta\theta\rho\pi\Lambda(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta) - (\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2\theta]A^* \\
& + (1 - (\alpha + \pi))(\mu + \omega + \delta)\Lambda^2\theta^2\beta\rho\eta\pi.
\end{aligned}$$

$$aA^{*2} + bA^* + c = 0 \quad (5.10)$$

$$\begin{aligned}
a &= -\beta\rho[\theta(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2 + (1 - \theta)(\eta + \mu)(\sigma + \gamma + \mu)^2(\mu + \omega + \delta) + \sigma\theta(\eta + \mu)(\sigma + \gamma + \mu)^2(\mu + \omega + \delta)] \\
b &= -[(1 - (\alpha + \pi))\Lambda\beta\eta\theta(\mu + \omega + \delta)[\theta(\mu + \omega + \delta) + \rho\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)\rho]] + \beta\theta\rho\pi\Lambda(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2\theta \\
c &= (1 - (\alpha + \pi))(\mu + \omega + \delta)\Lambda^2\theta^2\beta\rho\eta\pi \\
b &= [(1 - (\alpha + \pi))\Lambda\beta\eta\theta(\mu + \omega + \delta)[\theta(\mu + \omega + \delta) + \rho\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)\rho]] - \beta\theta\rho\pi\Lambda(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta) - (\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2\theta
\end{aligned}$$

$$\begin{aligned}
b &= (\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2\theta [\\
& \frac{[(1 - (\alpha + \pi))\Lambda\beta\eta\theta(\mu + \omega + \delta)[\theta(\mu + \omega + \delta) + \rho\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)\rho]]}{(\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2\theta} \\
& - \frac{\beta\theta\rho\pi\Lambda(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)}{(\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2\theta} - 1]
\end{aligned}$$

$$b = \theta(\phi + \mu)(\eta + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta)^2 (R_0 - R^* - 1) \quad (5.11)$$

where, $R^* = \frac{\beta\rho\pi\Lambda}{(\phi + \mu)(\mu + \omega + \delta)}$

A^* is obtained by solving the quadratic equation (5.10). Substituting the value of A^* in the endemic equation S^*, V^*, E^*, C^*, R^* the endemic equilibrium is obtained.

The existence and number of positive solutions to the HBV model equation (4.3) are determined by the sign of the coefficients a , b , and c . We use the Descartes rule of signs to obtain the number of endemic equilibria [15]. From equation (5.10), the coefficient of a is always negative and a is positive, the number of endemic equilibria depends on the sign of b , which is established by the value of R_0 in b .

For the case when $R_0 = R^* + 1$, $b = 0$, there is one change of sign from negative to positive. The quadratic equation has one positive root. For the case when $R_0 > R^* + 1$, b is positive, the signs for a , b and c are $(- + +)$, which according to Descartes' rule means there is only one change of sign, and so there is only one unique positive endemic equilibrium point. Finally for the case when $R_0 < R^* + 1$, b is negative. The sign for a , b and c includes $(- - +)$ and this again indicates one change of sign. This means there is existence of one positive root which is in this case corresponds to an endemic equilibrium point shown in the theorem. Therefore, the endemic equilibrium of the system of equation for hepatitis B exists and has real positive roots.

5.3.2 Bifurcation Analysis

Theorem 5.4. *The endemic equilibrium E_1 of the system (4.3) is locally asymptotically stable if $R_0 > 1$.*

Proof. To determine the local stability of endemic equilibrium, we used the center manifold theory, we have seen the solution behavior of above sensitivity index by taking β as the bifurcation parameter. We make the following change of variables on the system (4.3).

Let $S = x_1$, $V = x_2$, $E = x_3$, $A = x_4$, $C = x_5$, $R = x_6$.

Moreover, by using vector notation $x = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the system (4.3) can be written in the form $\frac{dx}{dt} = F(x)$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$ as shown below:

$$\begin{aligned}\frac{dx_1}{dt} &= (1 - (\alpha + \pi)) \Lambda - \beta (x_4 + \rho x_5) x_1 - (\phi + \mu) x_1, \\ \frac{dx_2}{dt} &= \alpha \Lambda + \phi x_1 - \mu x_2, \\ \frac{dx_3}{dt} &= \beta (x_4 + \rho x_5) x_1 - (\eta + \mu) x_3, \\ \frac{dx_4}{dt} &= \theta \eta x_3 - (\sigma + \gamma + \mu) x_4, \\ \frac{dx_5}{dt} &= \pi \Lambda + (1 - \theta) \eta x_3 + \sigma x_4 - (\mu + \omega + \delta) x_5, \\ \frac{dx_6}{dt} &= \gamma x_4 + \omega x_5 - \mu x_6.\end{aligned}\tag{5.12}$$

We choose $\beta = \beta^*$ as a bifurcation parameter. Calculating the value of β from $R_0 = 1$, we get

$$\beta^* = \frac{(\phi + \mu)(\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta)}{(1 - (\alpha + \pi))\Lambda[\theta\eta(\mu + \omega + \delta) + \rho(\theta\eta\sigma + (1 - \theta)\eta(\sigma + \gamma + \mu))]}$$

The Jacobian matrix of the system (4.3) evaluated at the diseases free equilibrium E_0 with $\beta = \beta^*$ is given by

$$J(E_0) = \begin{bmatrix} -(\phi + \mu) & 0 & 0 & \frac{-\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu} & \frac{-\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ \phi & -\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\mu + \eta) & \frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu} & \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ 0 & 0 & \theta\eta & -p_1 & 0 & 0 \\ 0 & 0 & (1 - \theta)\eta & \sigma & -p_2 & 0 \\ 0 & 0 & 0 & \gamma & \omega & -\mu \end{bmatrix}$$

where, $p_1 = \sigma + \gamma + \mu$, $p_2 = \mu + \omega + \delta$

The Jacobian matrix $J(E_0)$ at $\beta = \beta^*$ has a left eigenvector (associated with the zero eigenvalue) which is calculated from $VJ(E_0) = 0$. Thus, $V = (v_1, v_2, v_3, v_4, v_5, v_6)$.

$$VJ(E_0) = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{bmatrix}^T \begin{bmatrix} -(\phi + \mu) & 0 & 0 & \frac{-\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu} & \frac{-\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ \phi & -\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\mu + \eta) & \frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu} & \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ 0 & 0 & \theta\eta & -p_1 & 0 & 0 \\ 0 & 0 & (1 - \theta)\eta & \sigma & -p_2 & 0 \\ 0 & 0 & 0 & \gamma & \omega & -\mu \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

This implies:

$$\begin{aligned} -(\phi + \mu)v_1 + \phi v_2 &= 0, \\ -\mu v_2 &= 0, \\ -(\mu + \eta)v_3 + \theta\eta v_4 + (1 - \theta)\eta v_5 &= 0, \\ -\frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu}v_1 + \frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu}v_3 - p_1 v_4 + \sigma v_5 + \gamma v_6 &= 0, \\ -\frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu}v_1 + \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu}v_3 - p_2 v_5 + \omega v_6 &= 0, \\ -\mu v_6 &= 0. \end{aligned} \tag{5.13}$$

Solving system of equation (5.13), we get:

$$v_1 = 0, v_2 = 0,$$

$$\begin{aligned}
v_3 &= v_3 > 0, \\
v_4 &= \frac{p_2(\phi + \mu)(\mu + \eta) - (1 - \theta)\eta\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\theta\eta p_2(\phi + \mu)}v_3, \\
v_5 &= \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{p_2(\phi + \mu)}v_3 \text{ and } v_6 = 0.
\end{aligned}$$

The Jacobean matrix $J(E_0)$ at $\beta = \beta^*$ has a right eigenvector (associated with the zero eigenvalue) which is calculated from $J(E_0)W = 0$. Thus, $W = (w_1, w_2, w_3, w_4, w_5, w_6)^T$.

$$J(E_0)W = \begin{bmatrix} -(\phi + \mu) & 0 & 0 & \frac{-\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu} & \frac{-\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ \phi & -\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\mu + \eta) & \frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu} & \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu} & 0 \\ 0 & 0 & \theta\eta & -p_1 & 0 & 0 \\ 0 & 0 & (1 - \theta)\eta & \sigma & -p_2 & 0 \\ 0 & 0 & 0 & \gamma & \omega & -\mu \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \\ w_6 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

This implies:

$$\begin{aligned}
-(\phi + \mu)w_1 - \frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu}w_4 - \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu}w_5 &= 0, \\
\phi w_1 - \mu w_2 &= 0, \\
-(\mu + \eta)w_3 + \frac{\beta^*\Lambda(1 - (\alpha + \pi))}{\phi + \mu}w_4 + \frac{\beta^*\Lambda\rho(1 - (\alpha + \pi))}{\phi + \mu}w_5 &= 0, \\
\theta\eta w_3 - p_1 w_4 &= 0, \\
(1 - \theta)\eta w_3 + \sigma w_4 - p_2 w_5 &= 0, \\
\gamma w_4 + \omega w_5 - \mu w_6 &= 0.
\end{aligned} \tag{5.14}$$

Solving system of equation (5.14), we get:

$$\begin{aligned}
w_1 &= \frac{-\beta^* \Lambda(1 - (\alpha + \pi))[p_1 p_2 + \rho((1 - \theta)\eta^2 \theta + \sigma p_1)]}{(\phi + \mu)^2 p_1 p_2} w_4, \\
w_2 &= \frac{-\beta^* \Lambda(1 - (\alpha + \pi)\phi)[p_1 p_2 + \rho((1 - \theta)\eta^2 \theta + \sigma p_1)]}{(\phi + \mu)^2 p_1 p_2 \mu} w_4, \\
w_3 &= \frac{\theta \eta}{p_1} w_4, \\
w_4 &= w_4 > 0, \\
w_5 &= \frac{((1 - \theta)\eta^2 \theta + \sigma p_1)}{p_1 p_2} w_4, \\
w_6 &= \frac{(\gamma p_1 p_2 + (1 - \theta)\eta^2 \theta \omega + \sigma \omega p_1)}{\mu p_1 p_2} w_4.
\end{aligned}$$

let $w_4 = 1$, the right eigenvectors become

$$\begin{aligned}
w_1 &= \frac{-\beta^* \Lambda(1 - (\alpha + \pi))[p_1 p_2 + \rho((1 - \theta)\eta^2 \theta + \sigma p_1)]}{(\phi + \mu)^2 p_1 p_2}, \\
w_2 &= \frac{-\beta^* \Lambda(1 - (\alpha + \pi)\phi)[p_1 p_2 + \rho((1 - \theta)\eta^2 \theta + \sigma p_1)]}{(\phi + \mu)^2 p_1 p_2 \mu}, \\
w_3 &= \frac{\theta \eta}{p_1}, \\
w_4 &= 1, \\
w_5 &= \frac{(1 - \theta)\eta^2 \theta + \sigma p_1}{p_1 p_2}, \\
w_6 &= \frac{\gamma p_1 p_2 + (1 - \theta)\eta^2 \theta \omega + \sigma \omega p_1}{\mu p_1 p_2}.
\end{aligned}$$

Since the first, second and six component of v is zero, we don't need the partial derivatives of f_1 , f_2 and f_6 . From the partial derivatives of f_3 , f_4 and f_5 at the disease free equilibrium point, the only ones that are the following:

$$\begin{aligned}
\frac{\partial^2 f_3}{\partial x_1 \partial x_4} &= \frac{\partial^2 f_3}{\partial x_4 \partial x_1} = \beta, \quad \frac{\partial^2 f_3}{\partial x_1 \partial x_5} = \frac{\partial^2 f_3}{\partial x_5 \partial x_1} = \rho \beta \\
\frac{\partial^2 f_3}{\partial x_4 \partial \beta} &= x_1 = S^0, \quad \frac{\partial^2 f_3}{\partial x_5 \partial \beta} = \rho x_1 = \rho S^0
\end{aligned}$$

$$a = \sum_{k,i,j=1}^6 v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} (S^0, V^0, 0, 0, 0, 0) \quad b = \sum_{i,k=1}^6 v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi} (S^0, V^0, 0, 0, 0, 0)$$

$$a = v_3 \left[\sum_{i,j=1}^6 w_i w_j \frac{\partial^2 f_3}{\partial x_1 \partial x_4} (S^0, V^0, 0, 0, 0, 0) \right] + v_3 \left[\sum_{i,j=1}^6 w_i w_j \frac{\partial^2 f_3}{\partial x_1 \partial x_5} (S^0, V^0, 0, 0, 0, 0) \right]$$

$$a = 2v_3 w_1 w_4 \beta + 2v_3 w_1 w_5 \rho \beta$$

$$a = -2v_3 \frac{\beta^* \Lambda (1 - (\alpha + \pi)) [p_1 p_2 + \rho((1 - \theta)\eta^2 \theta + \sigma p_1)]}{(\phi + \mu)^2 p_2 p_2} \beta$$

$$a = -2v_3 \frac{\beta^* \Lambda (1 - (\alpha + \pi)) [p_1 p_2 + \rho((1 - \theta)\eta^2 \theta + \sigma p_1)]}{(\phi + \mu)^2 p_2 p_2} \times \frac{((1 - \theta)\eta^2 \theta + \sigma p_1)}{p_1 p_2} \rho \beta < 0$$

$$b = \sum_{i,k=1}^6 v_3 w_i \frac{\partial^2 f_3}{\partial x_i \partial \beta} (S^0, V^0, 0, 0, 0, 0)$$

$$b = \sum_{i,k=1}^6 v_3 w_4 \frac{\partial^2 f_3}{\partial x \partial \beta} (0, 0) + \sum_{i,k=1}^6 v_3 w_5 \frac{\partial^2 f_3}{\partial x_5 \partial \beta} (S^0, V^0, 0, 0, 0, 0)$$

$$b = v_3 [w_4 S^0 + w_5 \rho S^0]$$

$$b = v_3 \left[\frac{(1 - (\alpha + \pi)) \Lambda}{\phi + \mu} + \frac{(1 - \theta)\eta^2 \theta + \sigma p_1 \rho (1 - (\alpha + \pi)) \Lambda}{p_1 p_2 (\phi + \mu)} \right] > 0$$

$$b = v_3 \left[\frac{(1 - (\alpha + \pi)) \Lambda [p_1 p_2 + (1 - \theta)\eta^2 \theta + \sigma p_1 \rho]}{(\phi + \mu) p_1 p_2} \right] > 0$$

Since $a < 0$ and $b > 0$ at $\beta = \beta^*$. The system (4.3) undergoes a forward bifurcation at $R_0 = 1$ and the unique endemic equilibrium E_1 is locally asymptotically stable for $R_0 > 1$. \square

5.3.3 Global stability of endemic equilibrium point

Theorem 5.5. *The endemic equilibrium state $E_1 = (S^*, V^*, E^*, A^*, C^*, R^*)$ of the system (4.3) is globally asymptotically stable, if $R_0 > 1$, otherwise unstable.*

Proof. To prove the global stability of the system (4.3) at endemic equilibrium point $E_1 = (S^*, V^*, E^*, A^*, C^*, R^*)$, we define the Lyapunov function which is given by

$$\Phi(S, V, E, A, C, R) = \frac{1}{2} ((S - S^*) + (V - V^*) + (E - E^*) + (A - A^*) + (C - C^*) + (R - R^*))^2. \quad (5.15)$$

Calculating the derivative of the above function with respect to time and then using the system (4.3), we obtain

$$\begin{aligned}\frac{d\Phi}{dt} &= ((S - S^*) + (V - V^*) + (E - E^*) + (A - A^*) + (C - C^*) + (R - R^*)) \\ &\quad \left(\frac{dS}{dt} + \frac{dV}{dt} + \frac{dE}{dt} + \frac{dA}{dt} + \frac{dC}{dt} + \frac{dR}{dt} \right) \\ \frac{d\Phi}{dt} &= ((S - S^*) + (V - V^*) + (E - E^*) + (A - A^*) + (C - C^*) + (R - R^*))(\Lambda - \mu S - \mu V - \mu E \\ &\quad - \mu A - (\mu + \delta)C - \mu R) \\ \frac{d\Phi}{dt} &= ((S - S^*) + (V - V^*) + (E - E^*) + (A - A^*) + (C - C^*) + (R - R^*))(\Lambda - \mu N - \delta C) \\ &= [(S + V + E + A + C + R) - (S^* + V^* + E^* + A^* + C^* + R^*)](\Lambda - \mu N - \delta C) \\ &= (N - \frac{\Lambda - \delta C^*}{\mu})(\Lambda - \mu N - \delta C) \\ &\leq (N - \frac{\Lambda}{\mu})(\Lambda - \mu N) \\ &\leq -(N - \frac{\Lambda}{\mu})(N - \frac{\Lambda}{\mu}) \\ &\leq -\left(\frac{\mu N - \Lambda}{\mu}\right)^2 \leq 0\end{aligned}$$

Hence, $\frac{d\Phi}{dt} \leq 0$ for all $(S^*, V^*, E^*, A^*, C^*, R^*)$. The equality $\frac{d\Phi}{dt} = 0$, holds, only for $S = S^*, V = V^*, E = E^*, A = A^*, C = C^*, R = R^*$. Then the endemic equilibrium E_1 is the only positively invariant set containing in $[(S, V, E, A, C, R), S = S^*, V = V^*, E = E^*, A = A^*, C = C^*, R = R^*]$. Therefore, the endemic equilibrium point E_1 is globally asymptotically stable. \square

5.4 Sensitivity analysis

Sensitivity analysis is used to determine parameters with the most influence on the basic reproduction number (R_0). The elasticity of quantity Q , in our case R_0 , with respect to the parameter p is given by :

$$\Delta_P^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}$$

for R_0 which differentially depends on parameter p is used. We recall that the basic reproduction number R_0 is given by :

$$R_0 = \frac{\eta\beta\Lambda(1 - (\alpha + \pi))[\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))]}{(\phi + \mu)(\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta)}$$

$$\begin{aligned}
\Delta_{\beta}^{R_0} &= \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = 1 \\
\Delta_{\Lambda}^{R_0} &= \frac{\partial R_0}{\partial \Lambda} \times \frac{\Lambda}{R_0} = 1 \\
\Delta_{\alpha}^{R_0} &= \frac{\partial R_0}{\partial \alpha} \times \frac{\alpha}{R_0} = -\frac{\alpha}{1 - (\alpha + \pi)} \\
\Delta_{\eta}^{R_0} &= \frac{\partial R_0}{\partial \eta} \times \frac{\eta}{R_0} = \frac{\mu}{\mu + \eta} \\
\Delta_{\pi}^{R_0} &= \frac{\partial R_0}{\partial \pi} \times \frac{\pi}{R_0} = \frac{-\pi}{1 - (\alpha + \pi)} \\
\Delta_{\sigma}^{R_0} &= \frac{\partial R_0}{\partial \sigma} \times \frac{\sigma}{R_0} = \frac{\sigma[(\rho\theta + (1 - \theta))(\sigma + \gamma + \mu) - \theta(\mu + \omega + \delta) + \rho\theta\sigma + \rho(1 - \theta)(\sigma + \gamma + \mu)]}{(\sigma + \gamma + \mu)(\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)))} \\
\Delta_{\theta}^{R_0} &= \frac{\partial R_0}{\partial \theta} \times \frac{\theta}{R_0} = \frac{\theta((\mu + \omega + \delta) + \rho\sigma - \rho(\sigma + \gamma + \mu))}{\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))} \\
\Delta_{\rho}^{R_0} &= \frac{\partial R_0}{\partial \rho} \times \frac{\rho}{R_0} = \frac{\rho[\theta(\mu + \omega + \delta) + \theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)]}{\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))} \\
\Delta_{\delta}^{R_0} &= \frac{\partial R_0}{\partial \delta} \times \frac{\delta}{R_0} = \frac{\delta[\theta(\mu + \omega + \delta) - \theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))]}{(\mu + \omega + \delta)(\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)))} \\
\Delta_{\phi}^{R_0} &= \frac{\partial R_0}{\partial \phi} \times \frac{\phi}{R_0} = \frac{-\phi}{\phi + \mu} \\
\Delta_{\gamma}^{R_0} &= \frac{\partial R_0}{\partial \gamma} \times \frac{\gamma}{R_0} = \frac{\gamma[\rho(1 - \theta)(\sigma + \gamma + \mu) - \theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))]}{\sigma + \gamma + \mu(\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)))} \\
\Delta_{\omega}^{R_0} &= \frac{\partial R_0}{\partial \omega} \times \frac{\omega}{R_0} = \frac{\omega[\theta(\mu + \omega + \delta) - \theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))]}{(\mu + \omega + \delta)(\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu)))} \\
\Delta_{\mu}^{R_0} &= \frac{\partial R_0}{\partial \mu} \times \frac{\mu}{R_0} = \frac{\mu}{(\phi + \mu)(\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \gamma)[\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))]} \\
&\quad - [\theta(\mu + \omega + \delta) + \rho(\theta\sigma + (1 - \theta)(\sigma + \gamma + \mu))] \times [(\mu + \eta)(\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\phi + \mu)(\sigma + \gamma + \mu)(\mu + \omega + \delta) + (\phi + \mu)(\mu + \eta)(\mu + \omega + \delta) + (\phi + \mu)(\mu + \eta)(\sigma + \gamma + \mu)] + \mu(\theta + \rho(1 - \theta))
\end{aligned}$$

Figure (3) shows that the recruitment rate Λ , the vaccination rate of newborns vaccinated rate (pediatric vaccination) α , the Proportionality constant θ , the transmission rate of HBV β and the vaccination rate of susceptible individual ϕ are the most sensitive parameters.

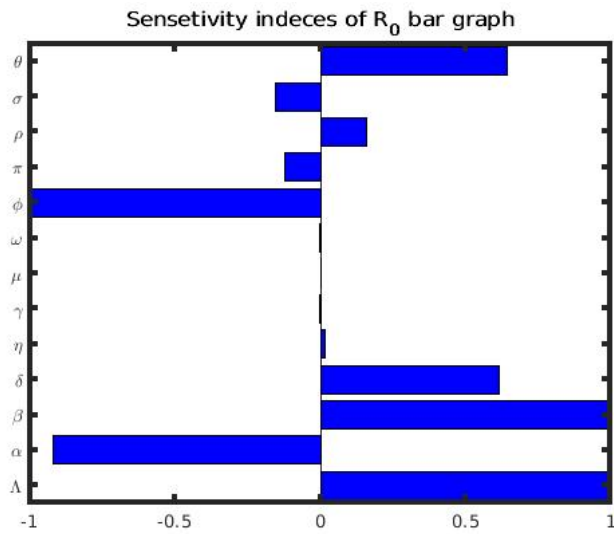


Figure 3: Sensitivity indices of R_0 bar plot

Table 3: Table of sensitivity indices

No	parameter	sensitivity indices	value
1	Λ	+ve	1
2	α	-ve	-0.9184
3	β	+ve	1
4	η	+ve	0.0149
5	π	-ve	-0.1224
6	ϕ	-ve	-0.9925
7	μ	+ve	0.00000132
8	ω	-ve	-0.000589
9	γ	-ve	-0.0015
10	θ	+ve	0.6444
11	δ	+ve	0.6155
12	ρ	+ve	0.16
13	σ	-ve	-0.1546

Thus, we can observe that the parameters $\Lambda, \beta, \eta, \mu, \theta, \delta,$ and ρ have positive correlation with R_0 . This indicates that the spread of HBV decreases as this parametric value decreases. The parameters $\alpha, \pi, \phi, \omega, \gamma,$ and σ have a negative impact, which means increasing the value of these parameters decreases the infection.

6 Numerical Simulation

We use the values of the parameter from another review of the literature and some assumed values. We have simulated the model using the Ode45 routine in Matlab using the parameter values given in the table and the initial conditions. $S(0) = 10000$, $V(0) = 1000$, $E(0) = 300$, $A(0) = 200$, $C(0) = 100$ and $R(0) = 700$.

Table 4: Parameter values

Parameter	Value	Source
Λ	50	Assume
α	0.45	Assume
β	0.0015	Assume
ρ	0.16	[12]
π	0.06	Assume
γ	0.004	[12]
ω	0.002	[12]
ϕ	0.16	Assume
θ	0.8	Assume
μ	0.00121	Assume
δ	0.8	[12]
η	0.08	Assume

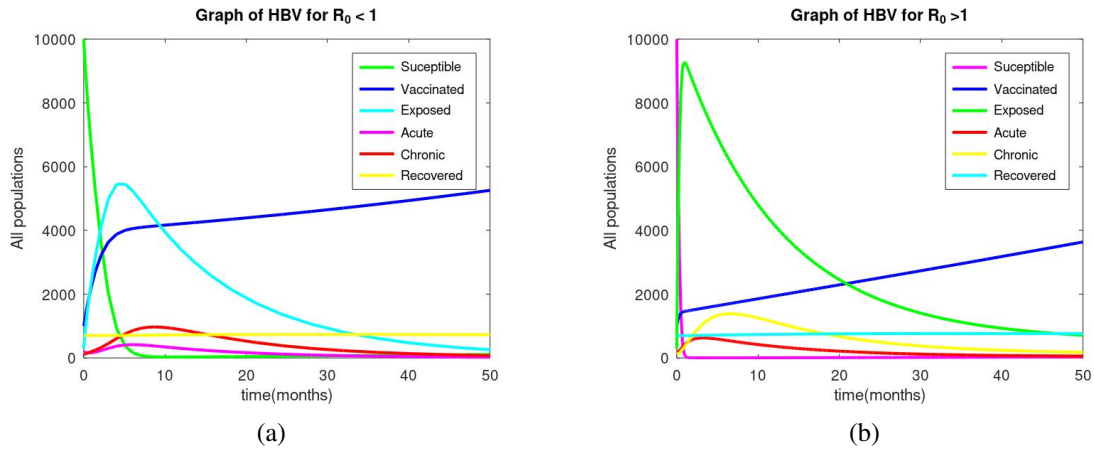


Figure 4: (a) Trajectories of the state variable for $R_0 = 0.2531$, (b) Trajectories of the state variable for $R_0 = 5.0623$.

In figure (4a), with $R_0 = 0.2531 < 1$, we observe that every solution curve approaches the disease-free equilibrium point whenever $R_0 < 1$. As a result, the illness either dies out or becomes extinct. In figure (4b), with $R_0 = 5.0623$, we note that any solution curve moves away from the disease-free equilibrium point for every $R_0 > 1$. These suggest that for values of $R_0 > 1$, the disease-free equilibrium point is unstable and that the solutions will approach the endemic equilibrium point. As a result, the disease spreads throughout a community.

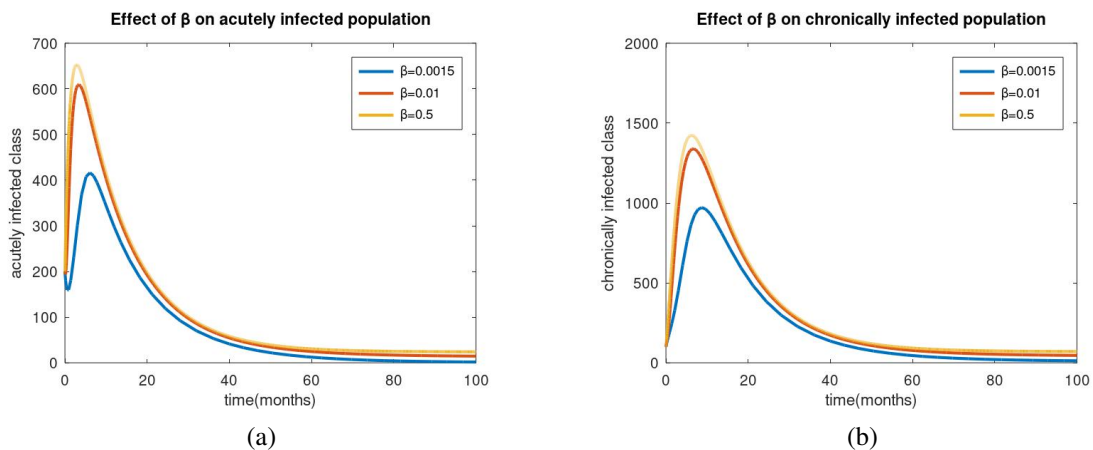


Figure 5: (a) Effect of contact rate (β) on acutely infected population, (b) Effect of contact rate (β) on chronically infected population.

Figure (5) shows the effect of contact rate (β) on acutely and chronically infected populations.

Figure (5a) shows that as the value of contact rate (β) increases, the acutely infected population also increases, which means that as the value of contact rate (β) increases, the number of acutely infected people will increase. Figure (5b) shows that as the value of the contact rate (β) increases, the chronically infected population also increases. This implies that increasing the value of contact rate (β) increases the number of chronically infected people.

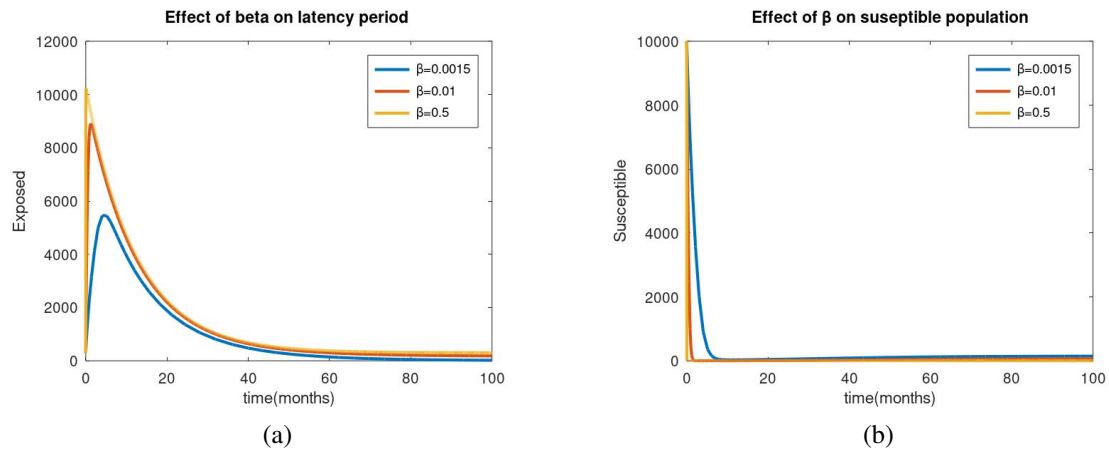


Figure 6: (a) Effect of contact rate (β) on exposed individuals, (b) Effect of contact rate (β) on susceptible population.

Figure (6a) shows the effect of contact rate (β) on exposed individuals. As the value of the contact rate (β) increases, the exposed population also increases. This means the spread of HBV decreases with a decrease in the value of the contact rate (β). Figure (6b) shows the effect of contact rate (β) on susceptible populations. As the value of the contact rate (β) increases, the susceptible population also decreases. This indicates that the spread of HBV decreases with a decrease in the value of contact rate (β).

Figure (7a) shows the effect of the vaccination rate of newborns (pediatric vaccination) (α). As the value of the vaccination rate of newborns (pediatric vaccination) (α) increases, the vaccinated population increases. This means increasing the value of the vaccination rate of newborns (pediatric vaccination) (α) decreases the number of people infected with the disease. Figure (7b) shows the effect of the rate of vaccination (ϕ). As the value of the rate of vaccination (ϕ) increases, the susceptible population decreases and the vaccinated population also increases. This means increasing the rate of vaccination (ϕ) decreases the number of people infected with the disease.

Figure (8) shows the effect of vaccination rate (ϕ) on acutely and chronically infected popu-

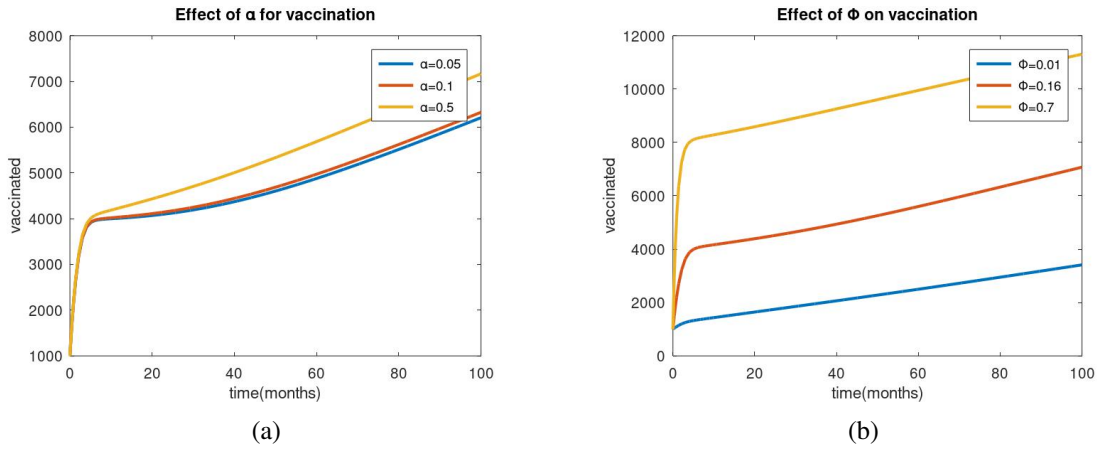


Figure 7: (a) Effect of vaccination rate of newborns (pediatric vaccination) (α) on vaccinated population, (b) Effect of the vaccination rate of (ϕ) on vaccinated population.

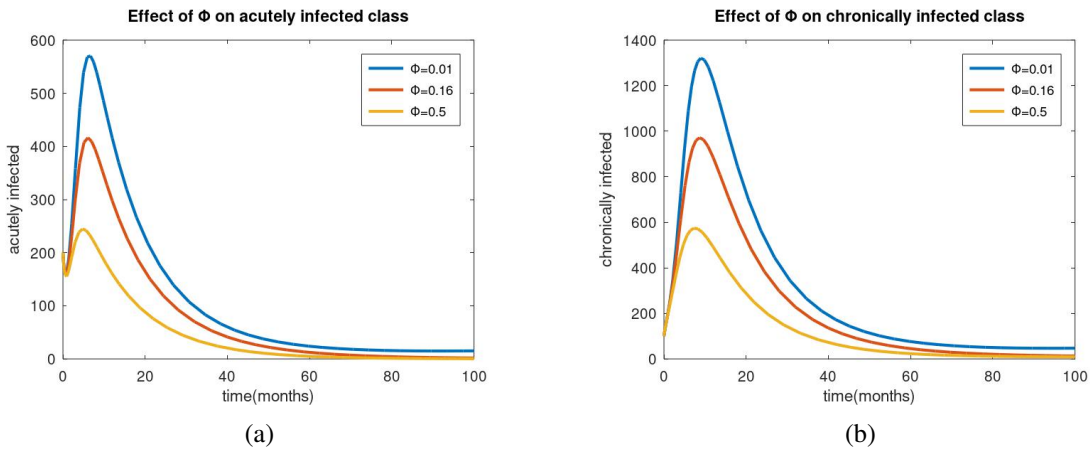


Figure 8: (a) Effect of vaccination rate (ϕ) on acutely infected population, (b) Effect of vaccination rate (ϕ) on chronically infected population.

lations. In figure (8a), we observe that as the vaccination rate (ϕ) increases, the acutely infected population also decreases. This implies that increasing the value of the vaccination rate (ϕ) decreases the number of acutely infected people. In figure (8b), we observe that as the vaccination rate (ϕ) increases, the chronically infected population decreases. This implies that as the vaccination rate (ϕ) increases, the number of chronically infected people also decreases.

Figure (9) shows the effect of vaccination rate of newborns (pediatric vaccination) (α) on acutely and chronically infected populations. In figure (9a), we observe that as the vaccination rate of

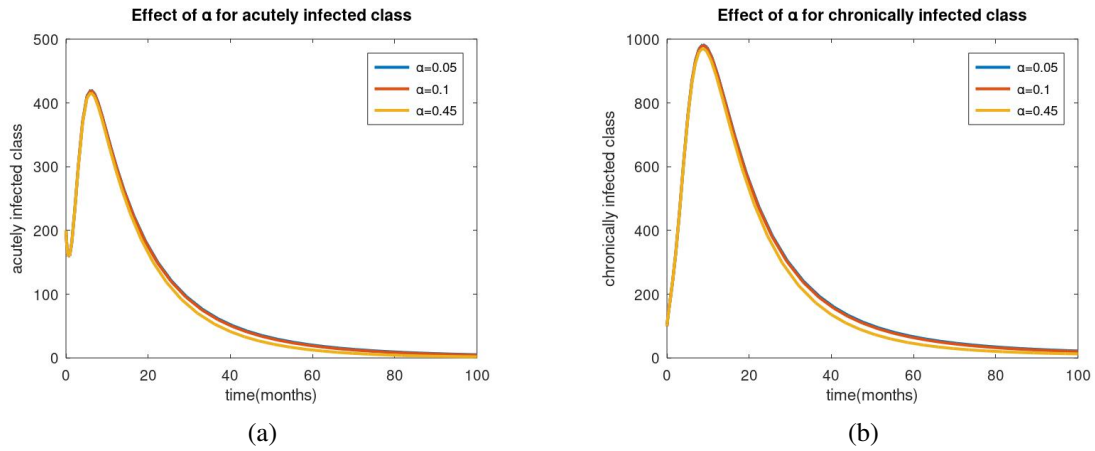


Figure 9: (a) Effect of vaccination rate of newborns (pediatric vaccination) (α) on acutely infected population, (b) Effect of vaccination rate of newborns (pediatric vaccination) (α) on chronically infected population.

newborns (pediatric vaccination) (α) increases, the acutely infected population decreases. This implies that increasing the value of the vaccination rate of newborns (pediatric vaccination) (α) decreases the number of acutely infected people. In figure (9b), we observe that as the value of the vaccination rate of newborns (pediatric vaccination) (α) increases, the chronically infected population decreases. This implies that as the value of the vaccination rate of newborns (pediatric vaccination) increases, the number of chronically infected people also decreases.

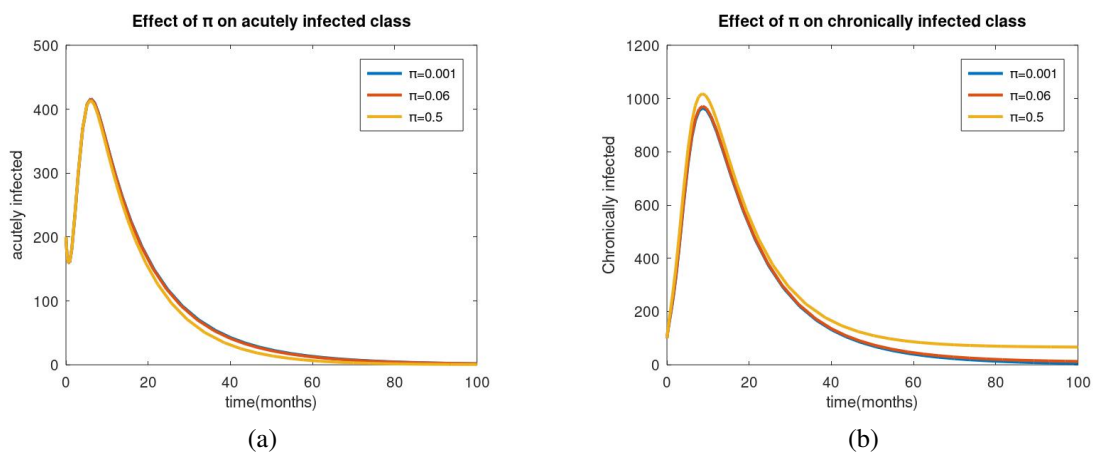


Figure 10: (a) Effect of the proportion of vertical transmission rate (π) on acutely infected HBV, (b) Effect of the proportion of vertical transmission rate (π) on chronically infected HBV.

Figure (10) shows the proportion of vertical transmission rate (π) in acutely and chronically

infected populations. In 10a shows the proportion of vertical transmission rate (π) on an acutely infected population. As the value of the proportion of vertical transmission rate (π) increases, the acutely infected population decreases, which means that increasing the value of the proportion of vertical transmission rate (π) decreases the number of people infected with acute HBV. In 10b shows the proportion of vertical transmission rate (π) in chronically infected population. As the value of the proportion of vertical transmission rate (π) increases, the chronically infected population also increases, which means that increasing the value of the proportion of vertical transmission rate (π) increases the number of people infected with chronic HBV.

Figure (11) shows the effect of the Proportionality constant (θ) on acutely and chronically infected

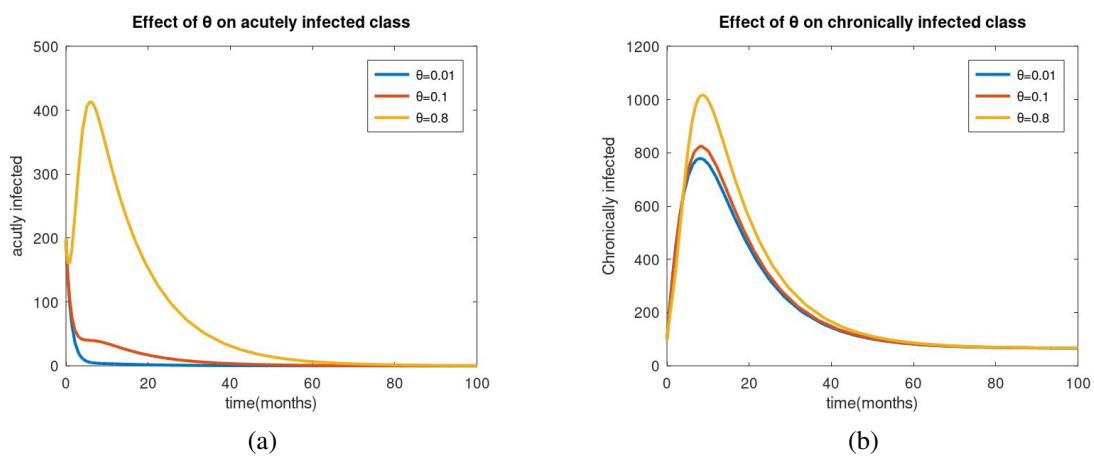


Figure 11: (a) Effect of the Proportionality constant (θ) on acutely infected population ,(b) Effect of the Proportionality constant (θ) on chronically infected population.

populations. Figure (11a) shows the effect of the Proportionality constant on acutely infected populations. As the value of the Proportionality constant (θ) increases, the number of acutely infected people decreases, which means that the spread of acutely infected people decreases with a decrease in the value of the Proportionality constant (θ). Figure (11b) shows the effect of Proportionality constant to chronically infected population (θ). As the value of the Proportionality constant (θ) increases, the chronically infected population decreases, which means that the spread of chronically infected people decreases as the value of the Proportionality constant (θ) increases.

7 Conclusions

In this thesis, a deterministic mathematical model for acute and chronic HBV transmission has been suggested. The modified model was an extension of a recent study on the dynamics of HBV, by adding the vaccination class and by taking the fact that HBV has a latent period, which is the exposed class of the infection. We have also included the vertical transmission of HBV to modify the existing model, and to formulate our model.

We proved the wellposedness of the formulated model. The next generation matrix was used to derive the basic reproduction number R_0 , which is the average number of new cases that one infected case will generate. The disease-free equilibrium point of the model was proved to be locally asymptotically stable and globally asymptotically unstable whenever the reproduction is less than unity. Using center manifold theory for the bifurcation analysis of the model, it was proven that there is a forward bifurcation at $R_0 = 1$, and the endemic equilibrium point E_1 is locally asymptotically stable. We have also proved that the endemic equilibrium point of the model is globally asymptotically stable, upon its existence.

Moreover, we initialized the state variables, and set the values of the parameters from some literature and assumed values. The sensitivity analysis and the numerical simulation of the model are then performed. From the sensitivity analysis of R_0 , we have observed that the recruitment rate (Λ), the vaccination rate of newborns (pediatric vaccination) (α), the transmission rate of HBV (β), and the vaccination rate of susceptible individual (ϕ) are the most sensitive parameters. As the proportion of negatively correlated parameters increases, the number of new infections will decrease, while as the proportion of positively correlated parameters increases, the number of infections will increase. As a result, the vaccination rate of newborns (pediatric vaccination) (α), increases, as well as the vaccination rate (ϕ), increases and the proportion of vertical transmission rate (π) decreases, the number of acute and chronic HBV infected people also decreases from the society. Hence, we recommend that increasing the negatively sensitive parameters, and decreasing the positively sensitive parameters will eradicate the virus from the community.

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Appendices

MATLAB codes for sensitivity analysis :

```
% Matlab codes for sensitivity analysis bar graph
%clear
%clc
mu=0.00121; omega=0.002; beta=0.0015;%alpha=0.5; lambda=1000;
gamma=0.004;delta=0.38; phi=0.16;pi=0.06; sigma=0.8;
theta= 0.8;eta=0.08;rho=0.16;alpha=0.45; Lambda=50;
R0=eta*beta*theta*Lambda*(1-(alpha+pi))*(theta*(mu+omega+delta)+...
rho*(theta*sigma+(1-theta)*(sigma+gamma+mu)))/...
((phi+mu)*(eta+mu)*(sigma+gamma+mu)*(mu+omega+delta));
sLambda= 1;
salpha=(alpha)/((alpha+pi)-1);
sbeta=1;
seta= mu/(mu+eta);
spi= (-pi)/(1-(alpha+pi));
sphi= (-phi)/(phi+mu);
smu=mu*((theta+rho*(1-theta))-mu*theta*(mu+omega+delta)+rho*(theta+sigma+...
(1-theta)*(sigma+gamma+mu))*(mu+eta)*(sigma+gamma+mu)*(mu+omega+delta)+...
(phi+mu)*(sigma+gamma+mu)*(mu+omega+delta)+...
(phi+mu)*(mu+eta)*(mu+omega+delta)+(phi+mu)*(mu+eta)*(sigma+gamma+mu)))/...
(phi+mu)*(mu+eta)*(sigma+gamma+mu)*(mu+omega+gamma)*(theta*(mu+omega+delta)+...
rho*(theta*sigma+(1-theta)*(sigma+gamma+mu)));
somega=(omega*(theta*(mu+omega+delta)-(theta*(mu+omega+delta)+rho*...
(theta*sigma+(1-theta)*(sigma+gamma+mu))))/...
(theta*(mu+omega+delta)+rho*(theta*sigma+(1-theta)*(sigma+gamma+mu)));
sgamma=gamma*(rho*(sigma+gamma+mu)*(1-theta)-(theta*(mu+omega+delta)+...
rho*(theta*sigma+(1-theta)*(sigma+gamma+mu)))/...
(mu+omega+delta)*((sigma+gamma+mu)*(theta*(mu+omega+delta)+...
rho*(theta*sigma+(1-theta)*(sigma+gamma+mu))));
stheta=(theta*(mu+omega+delta)+theta*sigma*rho-rho*(sigma+gamma+mu))/...
(theta*(mu+omega+delta)+rho*(theta*sigma+(1-theta)*(sigma+gamma+mu)));
sdelta=sigma*(theta*(mu+omega+delta)-theta*(mu+omega+delta)+rho*...
(theta*sigma+(1-theta)*(sigma+gamma+mu)))/((mu+omega+delta)*...
(theta*(mu+omega+delta)+rho*(theta*sigma+(1-theta)*(sigma+gamma+mu))));
srho=rho*(theta*(mu+omega+delta)+rho*(theta*sigma+(1-theta)*...
(sigma+gamma+mu)))/(theta*(mu+omega+delta)+rho*(theta*sigma+...
```

```

(1-theta)*(sigma+gamma+mu));
%seta=mu/(mu+eta);
ssigma=sigma*(rho*(theta*sigma+(1-theta))*(sigma+gamma+mu)-rho*...
(theta*sigma+(1-theta)*(sigma+gamma+mu)))/...
((sigma+gamma+mu)*rho*(theta*sigma+(1-theta)*(sigma+gamma+mu)));
senv=[sLambda salpha sbeta seta spi sphi smu somega sgamma stheta...
sdelta srho ssigma];
names=categorical({'\Lambda','\alpha','\beta', '\eta','\pi', '\phi','\mu',...
'\omega', '\gamma','\theta','\delta','\rho','\sigma'},'ordinal',true);
barh(names,senv,'b')
set(gca, 'linewidth', 3)
title('Sensetivity indeces of R_0 bar graph')

```

MATLAB codes for stability analysis of disease free equilibrium point:

```

function dx = hepatitisbv(t,x)
global alpha lambda mu omega beta gamma delta phi pi sigma theta eta rho
dx=zeros(6,1);
dx(1)=(1-(alpha+pi))*lambda-(x(4)+rho*x(5))*beta*x(1)-(phi+mu)*x(1);
dx(2)=alpha*lambda+phi*x(1)-mu*x(2);
dx(3)= beta*x(1)*(x(4)+rho*x(5))-(eta+mu)*x(3);
dx(4)=theta*eta*x(3)-(sigma+gamma+mu)*x(4);
dx(5)= pi*lambda+(1-theta)*eta*x(3)+sigma*x(4)-(mu+omega+delta)*x(5);
dx(6)=gamma*x(4)+omega*x(5)-mu*x(6);
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
global alpha lambda mu omega beta gamma delta phi pi sigma theta eta rho
mu=0.00121; omega=0.002; beta=0.0015;%alpha=0.5; lambda=1000;
gamma=0.004;delta=0.38; phi=0.16;pi=0.06; sigma=0.8;
theta= 0.8;eta=0.08;rho=0.16;alpha=0.45; lambda=50;
%alpha=0.12; lambda=50; mu=0.0012; omega=0.002; beta=0.0015;
%gamma=0.004;delta=0.8; phi=0.06;pi=0.006; sigma=0.8;
%theta= 0.63;eta=0.38;rho=0.16;
ts=[0, 50];
N0=[10000 1000 300 200 100 700];
%N0=[1000 600 90 70 100 200];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,1),'g','linewidth',2,t,y(:,2),'b','linewidth',2,...

```

```

t,y(:,3),'c','linewidth',2,t,y(:,4),'m','linewidth',2,...
t,y(:,5),'r','linewidth',2,t,y(:,6),'y','linewidth',2)
xlabel('time (months)')
ylabel('All populations')
legend('Suceptible','Vaccinated','Exposed ','Acute','Chronic','Recovered')
R0=(eta*beta*theta*lambda*(1-(alpha+pi))*(theta*(mu+omega+delta)+...
rho*(theta*sigma +(1-theta)*(sigma+gamma+mu)))/...
((phi+mu)*(eta+mu)*(sigma+gamma+mu)*(mu+omega+delta))
title('Graph of HBV for R_0 < 1')
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% Graphs of HBV in R0>1 with \beta=0.015
global alpha lambda mu omega beta gamma delta phi pi sigma theta eta rho
mu=0.00121; omega=0.002; beta=0.015;alpha=0.45; lambda=100;
gamma=0.004;delta=0.38; phi=0.16;pi=0.06; sigma=0.8;
theta= 0.8;eta=0.08;rho=0.16;%alpha=0.45; lambda=50;
%alpha=0.12; lambda=50; mu=0.0012; omega=0.002; beta=0.0015;
%gamma=0.004;delta=0.8; phi=0.06;pi=0.006; sigma=0.8;
%theta= 0.63;eta=0.38;rho=0.16;
ts=[0, 50];
N0=[10000 1000 300 200 100 700];
%N0=[10000 4000 900 700 900 1000];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,1),'m','linewidth',2,t,y(:,2),'b','linewidth',2,...
t,y(:,3),'g','linewidth',2,t,y(:,4),'r','linewidth',2,...
t,y(:,5),'y','linewidth',2,t,y(:,6),'c','linewidth',2)
xlabel('time (months)')
ylabel('All populations')
legend('Suceptible','Vaccinated','Exposed ','Acute','Chronic','Recovered')
title('Graph of HBV for R_0 >1' )
R0=(eta*beta*theta*lambda*(1-(alpha+pi))*(theta*(mu+omega+delta)+...
rho*(theta*sigma +(1-theta)*(sigma+gamma+mu)))/...
((phi+mu)*(eta+mu)*(sigma+gamma+mu)*(mu+omega+delta))

```

MATLAB codes for the impact of β and infected classes:

```

global alpha lambda mu omega beta gamma delta phi pi sigma theta eta rho
mu=0.00121; omega=0.002; %alpha=0.5; lambda=1000;
gamma=0.004;delta=0.38; phi=0.16;pi=0.06; sigma=0.8;
theta= 0.8;eta=0.08;rho=0.16;alpha=0.45; lambda=50;

```

```

%alpha=0.12; lambda=50; mu=0.0012; omega=0.002; beta=0.0015;
%gamma=0.004;delta=0.8; phi=0.06;pi=0.006; sigma=0.8;
%theta= 0.63;eta=0.38;rho=0.16;
ts=[0, 100];
for beta =[0.0015 0.01 0.5];
%N0=[1000 400 90 70 100 200];
N0=[10000 1000 300 200 100 700];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,3),'Linewidth',2)
xlabel('time (months)')
ylabel('Exposed')
title('Effect of beta on latency period ')
legend ('\beta=0.0015', '\beta=0.01', '\beta=0.5')
hold on
end
figure(2)
for beta =[0.0015 0.01 0.5];
N0=[10000 1000 300 200 100 700];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,4),'Linewidth',2)
xlabel('time (months)')
%ylabel('Susceptible')
ylabel('acutely infected class')
%title('Effect of \beta on suseptible population')
title('Effect of \beta on acutely infected population')
legend ('\beta=0.0015', '\beta=0.01', '\beta=0.5')
hold on
end
figure(3)
for beta =[0.0015 0.01 0.5];
N0=[10000 1000 300 200 100 700];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,5),'Linewidth',2)
xlabel('time (months)')
%ylabel('Susceptible')
ylabel('chronically infected class')
%title('Effect of \beta on suseptible population')
title('Effect of \beta on chronically infected population')

```

```

legend ('\beta=0.0015', '\beta=0.01', '\beta=0.5')
hold on
end

```

MATLAB codes for the impact of new born vaccination rate α on infected classes:

```

global alpha lambda mu omega beta gamma delta phi pi sigma theta eta rho
mu=0.00121; omega=0.002; beta=0.0015;%alpha=0.5; lambda=1000;
gamma=0.004;delta=0.38; phi=0.16; pi= 0.5; sigma=0.8;
%theta= 0.8;
eta=0.08;rho=0.16; alpha=0.45; lambda=50;
%alpha=0.12; lambda=50; mu=0.0012; omega=0.002; beta=0.0015;
%gamma=0.004;delta=0.8; phi=0.06;pi=0.006; sigma=0.8;
%theta= 0.63;eta=0.38;rho=0.16;
ts=[0, 100];
%for pi =[0.001 0.06 0.5];
for theta=[0.01 0.1 0.8]
N0=[10000 1000 300 200 100 700];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,4),'Linewidth',2)
xlabel('time(months)')
ylabel('acutely infected')
legend('\theta=0.01', '\theta=0.1', '\theta=0.8')
title('Effect of \theta on acutely infected class')
hold on
end
figure(2)
for theta=[0.01 0.1 0.8]
N0=[10000 1000 300 200 100 700];
[t,y]=ode45('hepatitisbv',ts,N0);
plot(t,y(:,5),'Linewidth',2)
xlabel('time(months)')
ylabel('Chronically infected')
legend('\theta=0.01', '\theta=0.1', '\theta=0.8')
title('Effect of \theta on chronically infected class')
hold on
end

```