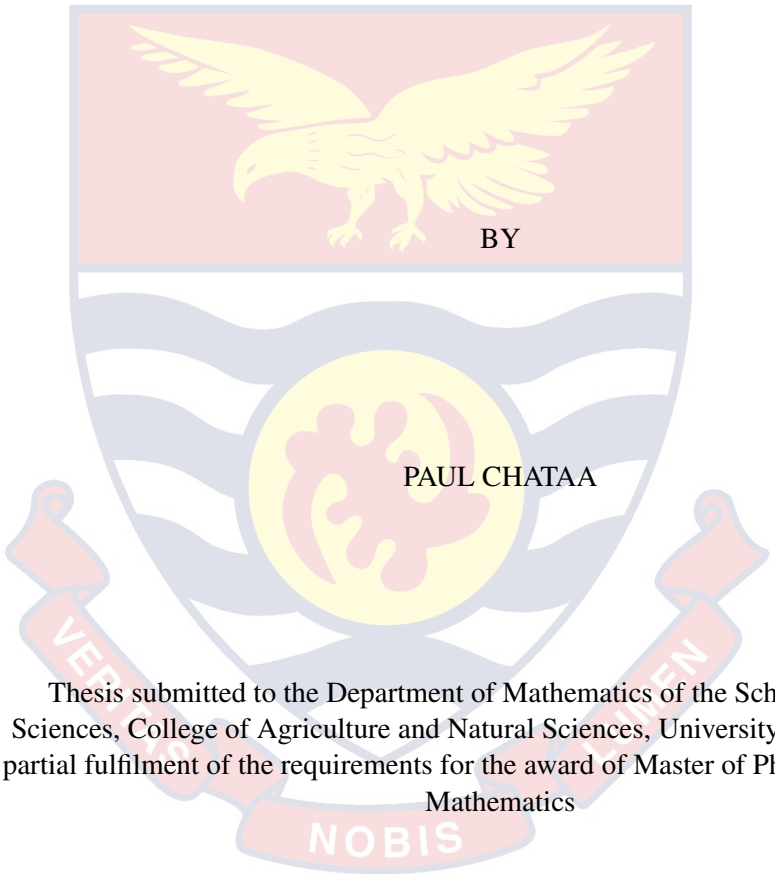
UNIVERSITY OF CAPE COAST

MODELLING HEPATITIS B VIRUS IN THE PRESENCE OF REGULAR INTERVENTIONS.



BY

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Thesis submitted to the Department of Mathematics of the School of Physical Sciences, College of Agriculture and Natural Sciences, University of Cape Coast, in partial fulfilment of the requirements for the award of Master of Philosophy degree in Mathematics

JULY 2020

DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own original research and that no part of it has been presented for another degree in this university or elsewhere.

Candidate's Signature ..... Date .....

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Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

Principal Supervisor's Signature ..... Date .....

Name: Prof. Farai Nyabaza

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ABSTRACT

Hepatitis B infection remains a global problem since the 1990s in Asia and Africa and the reasons for which the hepatitis B virus disease is still in existence remains poorly understood. Mathematical models of HBV transmission dynamics have focused on the influence of prevention and control measures including vaccination, antiviral treatment and linkage to care in certain regions and countries. However, understanding the important role played by imperfect vaccination in describing the hepatitis B virus transmission dynamics is beneficial as a control strategy. In this study, an $SVICTR$ epidemiological model is proposed to model the spread of the hepatitis B virus disease. The basic reproduction number, $\mathbb{R}_0$ and the equilibria of the proposed model are discussed. It is shown that the disease-free equilibrium point is both locally and globally asymptotically stable when $\mathbb{R}_0 < 1$ while the endemic equilibrium point is proved to be locally asymptotically stable when $\mathbb{R}_0 > 1$. However, when $\mathbb{R}_0 = 1$, the model system shows a backward bifurcation phenomenon. Results of the numerical simulations reveal that increasing both the vaccination and treatment rates reduces the populations of both the acutely infected and chronic carriers which eventually fall to zero over a given period. Hence, combining both vaccination and treatment with the use of a vaccine with high vaccine efficacy are essential in controlling the hepatitis B virus disease.

KEY WORDS

Basic Reproduction Number

Hepatitis B Virus (HBV)

Imperfect vaccination

Mathematical Model

Treatment

Vaccination

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DEDICATION

To my family

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LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic Acid
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoa
LHBs	Large Hepatitis B surface Protein
RNA	Ribonucleic Acid
SI	Sensitivity Index
WHO	World Health Organisation

CHAPTER ONE

INTRODUCTION

The revelations of the hepatitis B virus (HBV) infections started in the early 1966 when Dr Baruch Blumberg discovered it. So, over the years, vaccination of susceptible individuals with the hepatitis B vaccine and treating of infected patients with anti-viral therapies have proved to be partially efficient (Rodriguez, 2016). It is of higher interest to understand the connections between the HBV, the human immune responses of the body, both the long-term and short-term effectiveness of the vaccine and drug efficacy and the overall well-being of the human liver.

Hence, in this thesis, we use analytical techniques which will be confirmed by the numerical techniques to provide the connections between the HBV and the human-host characteristics, drug efficacy and the overall well-being of the liver while taking into account the important role played by perfect vaccination that will incorporate imperfect vaccination and treatment of infected persons as control and prevention strategies.

Background to the Study

Hepatitis B virus disease was first recorded as an epidemic in 1885 in Germany (Bremen) (Koonprasert et al., 2016). The virus was first identified in 1966 by Baruch Blumberg at the National Institutes of Health in the USA (Alter & Blumberg, 1966). Hepatitis B is a liver inflammation disease caused by the hepatitis B virus (HBV). The virus is a global problem and the dangerous type among all the hepatitis viruses (World Health Organization, 2008). Hepatitis B virus (HBV) is a DNA virus with a circular genome formed by a partially double-stranded DNA, which reproduces through an RNA intermediate form by transcription which is very difficult to clear ones infected (Locarnini, 2004). It infects the human hepatocytes to cause pathogen in the liver as an acute or chronic infection and puts people at a high risk of death from cirrhosis of the

liver and liver cancer (Farman et al., 2018). According to the World health organization the hepatitis B virus can survive outside the human body for at least seven (7) days and within this period the virus can still cause infection if it enters into any unprotected body (World Health Organization, 2017). The hepatitis B virus causes up to 80% of all cases of hepatocellular carcinoma worldwide and is second to tobacco among the known human carcinogens (Hollinger & Liang, 2001; World Health Organization, 2001). The hepatitis B virus does not cross the placenta due to its huge size and, hence it cannot infect an unborn baby unless there is a break in the maternal-fetal barrier through amniocentesis. However, pregnant women who are infected with HBV can still transmit the disease to their babies at birth. If not vaccinated at birth, many of these babies develop lifelong HBV infections which will later develop into liver failure or liver cancer in their lifetime (Mahoney & Kane, 1999). Hepatitis B is the only sexually transmitted infection for which there is a protective vaccine called the hepatitis B vaccine (Mahoney & Kane, 1999).

Individuals with congenital or acquired immunodeficiency including HIV infection and those with immunosuppression including those with lymphoproliferative disease and patients treated with immunosuppressive drugs including steroids and maintenance using haemodialysis are more likely to develop a persistent infection with HBV (World Health Organization, 2002). Also, only people who have been vaccinated successfully or those who have developed anti-HBs antibodies after HBV infection are either partially or fully immune to HBV infection.

More than 240 million people have long term liver infections and $780,000$ people die every year due to the acute or chronic consequences of the hepatitis B virus infection (World Health Organisation, 2014). Most of the world population are carriers of the hepatitis B virus (HBV) and hence causes endemics in parts of Asia and Africa (Williams, 2006).

In Ghana, the hepatitis B virus is a disease for children and young adults between the ages of 10 years to 50 years. Hence, about 1.6 million people out of Ghana's total population are chronic hepatitis B virus carriers (Wiah et al., 2015).

According to Mahoney & Kane (1999), the world can be categorised into three geographical areas based on HBV infection rate. These include; areas where the prevalence of chronic HBV infection is high ($> 8\%$), intermediate ($2 - 8\%$) and low ($< 2\%$). Hence, areas such as southeast Asia and the Pacific Basin except for Japan, Australia, and New Zealand, sub-Saharan Africa, the Amazon Basin, parts of the Middle East, the Central Asian Republics and some countries in Eastern Europe are considered to be higher endemicity areas of HBV infection. In these areas, about 70% to 90% of the population had the HBV infection before the age of 40 years. Out of this percentage, 8% to 20% of people who are infected are chronic HBV carriers.

Meanwhile, in countries such as China, Senegal and Thailand, infection rates are very high in infants than adults and may continue throughout their childhood life. At that stage, the prevalence of HBsAg in serum may exceed 25%. However, in other countries such as Panama, Papua New Guinea, Solomon Islands, Greenland and Alaskan Indians, infection rates in infants are relatively low and increase rapidly during early childhood life (World Health Organization, 2002).

Low endemicity areas of HBV infection include North America, Western and Northern Europe, Australia, and parts of South America. The carrier rate in these areas is less than 2% and less than 20% of their entire populations are infected with HBV (World Health Organization, 2002). The rest of the world falls into the intermediate range of HBV prevalence, with 2 to 8% of a given population being HBV carriers (Hollinger & Liang, 2001).

The situation of hepatitis B virus (HBV) transmission is very complicated

and grim to understand. Mathematical models have been used extensively to study both dynamical systems in spatial effects and the epidemiology of hepatitis B virus disease to improve our understanding of the major contributing factors to the pandemic (Gui-Quan et al., 2015; Zou et al., 2010; Anderson & May, 1992).

Vaccination of susceptible individuals such as newborn babies with a strong vaccine efficacy rate is the best and most economical way to reduce the number of recorded cases of hepatitis B in terms of both cost-effectiveness and cost-benefit ratios. Some other approved ways of preventing hepatitis B virus infection include testing of blood donors and an educational campaign to make people aware of the dangers of the disease (World Health Organization, 2015).

After the acute HBV infection phase, the risk of developing chronic infection varies inversely to the age of the individual. So, most of the individuals with chronic HBV are infected during or after birth (Guo et al., 2000). According to the World Health Organisation, more than 90% of the infected individuals that are adults will gain natural immunity to the disease within the first six months to one year of infection and some of them will not even show symptoms of infection (World Health Organization, 2015). This makes hepatitis B a deadly disease since two out of every three persons with chronic HBV infection are not even aware that, they are infected with the disease which contributes to the ongoing transmission (Cohen et al., 2011; Lin et al., 2007).

Life Cycle of Hepatitis B Virus

Hepatitis B virus is one of the smallest enveloped animal viruses with a virion diameter of $42nm$. The life cycle of HBV is complex and difficult to understand. This is because HBV is one of a few known non-retroviral viruses which use reverse transcription as part of its replication process. The HBV virion attaches itself to hepatocytes of the human liver through a weak interaction between the preS1 domain of the large HBV surface protein (LHBs) on

the HBV envelope and heparin sulfate proteoglycans (HSPGS) on the surface of hepatocytes (Schulze et al., 2007).

Although the detailed molecular biological mechanisms behind the entry process of HBV into the host cell is still not clearly understood, the sodium taurocholate co-transporting polypeptide (NTCP) on the host cell surface, which serve as a receptor for the HBV entry (Yan et al., 2012) allows the HBV virion to pass through the plasma membrane through clathrin-mediated endocytosis (Huang et al., 2012).

After the endocytosis process, the virus membrane fuses with the host cell's membrane, releasing the nucleocapsid into the cytoplasm (Watashi & Wakita, 2015). Again, the whole mechanisms that are involved in this process are not fully understood. However, one of the mechanisms behind this process is the arginine-rich C-terminal domain of core protein that provides a transport signal to a nuclear pore. The core protein then dissociates from the partially double-stranded viral DNA which made a full double-stranded (by the host DNA polymerases) and transformed into covalently closed circular DNA (cccDNA) that serves as a template for transcription of four viral mRNAs. In other words, the cccDNA is maintained in the nucleus of the host hepatocytes as a stable episome which forms a minichromosome by associating with histones and non-histone proteins (Bock et al., 2001).

Furthermore, the largest mRNA (which is longer than the viral genome) is used to make the new copies of the genome for it to make the capsid core protein and the viral RNA-dependent and DNA-polymerase to produce the four viral transcriptions. These four viral transcriptions undergo additional processing and even form progeny virions which are released from the cells or returned to the nucleus and re-cycled to produce more copies (Beck & Nassal, 2007). The long mRNA is then transported back to the cytoplasm where the virion p-protein synthesizes DNA through its reverse transcriptase activity. The diagram

below shows the life cycle process of hepatitis B virus

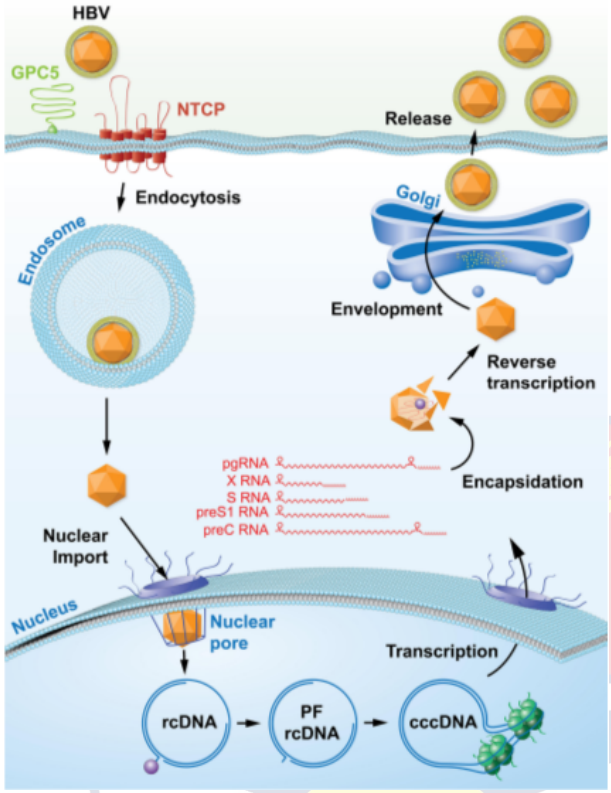

Figure 1: Life cycle of HBV, Source: (Ortega-Prieto et al., 2018).

Stages and Spectrum of Liver Disease after HBV Infection

The two main stages of hepatitis B virus infections include acute hepatitis B virus infection and chronic hepatitis B virus infection. Acute hepatitis B infection is characterized by the presence of IgM antibody to hepatitis B core antigen (IgM anti-HBc) serum antibodies converting to IgG with convalescence and recovery and the transient (which is less than six months) presence of hepatitis B surface antigen (HBsAg), hepatitis B envelope antigen (HBeAg) and viral DNA with the clearance of these markers followed by seroconversion to anti-HBsAg and anti-HBeAg.

In other words, when an individual is infected with the hepatitis B virus for the first six (6) months of the entire infectious period, it called the acute stage of the hepatitis B infection. This acute hepatitis B infection may go away on its

own in the first six months of infection or not. Most people do not show any symptoms of infection and do not need any therapy at this stage of the disease. According to Shepard et al. (2006), if the infected individual is an adult, there is about 90% chance that the person's body immune system will fight the disease off in the first six months (i.e. the acute stage) and no treatment will be needed.

Acute hepatitis B infection can also lead to the fulminant condition of the liver. Fulminant hepatitis B is a rare condition whose development is about 1% of all acute hepatitis B infection cases. This fulminant hepatitis B is caused by massive necrosis of liver substance which is usually very fatal (Hollinger & Liang, 2001; Mahoney & Kane, 1999). The survival rate in adults is very low which means that the prognosis for children is rather better. However, the few individuals who manage to survive usually recover completely without permanent liver damage and no chronic infection (Hollinger & Liang, 2001; Robinson, 2000). Also, individuals who have been tested positive for the hepatitis B virus for more than six months are diagnosed to be suffering from chronic hepatitis B infection. They may not able to clear the virus at this stage of the infection. Hence, people with chronic hepatitis B will need long therapy to be able to live longer and healthy life (Wilson et al., 1998).

According to Mahoney & Kane (1999), chronic hepatitis has caused serious destructive diseases of the liver and it contributes greatly to the worldwide burden of hepatitis disease. Unlike the acute stage of the hepatitis B infection where the individual may not show any sign of the infection, some of the patients with chronic hepatitis B infection persistently may also have no clinical or biochemical evidence of liver disease, while others may show signs of easy fatigue, anxiety, anorexia, and malaise. Chronic hepatitis B virus infection can be mild or severe depending on the body immune system of the Patient. The severity of this chronic hepatitis B infection is associated with inflammatory liver diseases such as cirrhosis and hepatocellular carcinoma (Hollinger & Liang, 2001).

Cirrhosis refers to the case where the liver cells of an infected person die and are progressively replaced with fibrotic tissue leading to nodule formation. The internal structure of the liver is deranged leading to the obstruction of blood flow and a decrease in liver function. This damage is caused by recurrent immune responses stimulated by the presence of the virus and because liver inflammation can be symptomless, the progression of inflammation to cirrhosis can occur without the knowledge of the patient.

Hepatocellular carcinoma (HCC) on the other hand is a liver disease developed by patients with chronic hepatitis B infection. According to Mahoney & Kane (1999), individuals who are at higher risk of developing HCC include adult male who had hepatitis B infection and chronic hepatitis B patients with cirrhosis who contracted hepatitis B in early childhood. The issue of developing HCC varies directly with geographical location, race, age and sex of the infected individual. Hence, HCC is responsible for 90% of the primary malignant tumours of the liver observed in adults (World Health Organization, 2002). The general process of the stages and spectrum of liver disease after HBV infection are summarised in the tree diagram below.

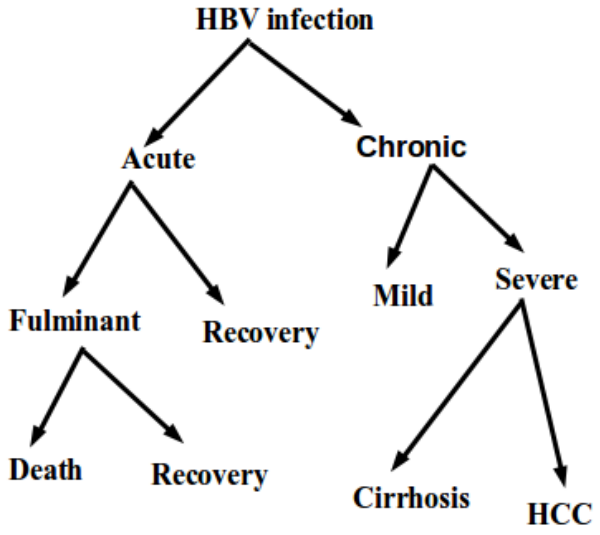

Figure 2: Stages and spectrum of liver disease after HBV infection, Source:(World Health Organization, 2002).

Testing for Hepatitis B Infection

Hepatitis B serologic testing involves the measurement of hepatitis B virus (HBV) specific antigens and antibodies. So, different serologic results or a combination of results will indicate which phases of HBV infection a patient falls. This will determine whether the patient is in an acute or chronic HBV infection stage or immune to HBV infection as a result of prior infection or vaccination or still susceptible to the HBV infection.

Hepatitis B surface antigen (HBsAg) is a protein on the surface of the hepatitis B virus. The presence of HBsAg indicates that the infected individual is infectious. Hence, the body system of any infected person normally produces antibodies to HBsAg as part of the normal immune response to infection. This HBsAg is the antigen used to make the hepatitis B vaccine.

The presence of hepatitis B surface antibody (anti-HBs) is usually an indication of recovery and gaining of immunity from hepatitis B virus infection. Anti-HBs are also developed in persons who have been successfully vaccinated against hepatitis B.

Total hepatitis B core antibody (anti-HBc) appears at the acute stage of hepatitis B infection and persists for life. A test of anti-HBc positive indicates previous or ongoing hepatitis B infection in an undefined time frame, hence the need for a follow-up test called hepatitis B-profile test.

IgM antibody to hepatitis B core antigen (IgM anti-HBc) positive test indicates recent infection with HBV for at most six (6) months. Hence, the patient is acutely infected (Centers for Disease Control and Prevention, 2005). Table 1 below gives a summary of an HBV serologic Lab test results and their interpretations.

Table 1: **Hepatitis B test status and their interpretation**

Test	Status	Interpretation
HBsAg	Negative	
anti-HBc	Negative	Susceptible
anti-HBs	Negative	
HBsAg	Negative	
anti-HBc	Positive	Immune due to natural infection
anti-HBs	Positive	
HBsAg	Negative	
anti-HBc	Positive	Immune due to hepatitis B vaccination
anti-HBs	Positive	
HBsAg	Positive	
anti-HBc	Positive	Acutely infected
IgM anti-HBc	Positive	
anti-HBs	Negative	
HBsAg	Positive	
anti-HBc	Positive	Chronically infected
IgM anti-HBc	Negative	
anti-HBs	Negative	
		Interpretation unclear; four possibilities
HBsAg	Negative	1. Resolved infection
anti-HBc	Positive	2. False-positive anti-HBc test
anti-HBs	Negative	3. Low level of chronic infection
		4. Resolving acute infection

Source:(Centers for Disease Control and Prevention, 2005)

Hepatitis B Vaccine

The human hosts which are susceptible to hepatitis B infection are protected against hepatitis B virus infection by producing an immune system that responds to the protein which is on the surface of the virus. Hence, when the hepatitis B virus grows in the human liver, an excess amount of this surface protein called hepatitis B surface antigen (HBsAg) is produced. Therefore, the hepatitis B vaccine is produced by taking the part of the virus that makes this surface protein called the surface protein gene and put it into yeast cells. The yeast cells then produce many copies of the protein that are subsequently used to make the vaccine. When the surface protein in the vaccine is given to children through vaccination, their immune systems make an immune response that protects against infection with the hepatitis B virus (Nurhasen, 2017).

Four years after discovering the hepatitis B virus, Drs. Blumberg and Millman developed the first hepatitis B vaccine which was initially a heat-treated form of the virus. This first hepatitis B vaccine was made in the 1980s by taking samples of blood from people that were infected with hepatitis B virus and separate the surface protein from the infectious virus. Because human blood was used, there was a high probability of contaminating the vaccine with other viruses that might be found in the human blood system, such as HIV. Although contamination with HIV was a risk of the early blood-derived hepatitis B vaccine, research has shown that no one was infected with HIV as a result of the use of the hepatitis B vaccine. This is because the blood used to make the vaccine was subjected to several chemical treatments that will inactivate any possible contaminating virus (Nurhasen, 2017).

Today, there is no risk of contaminating the vaccine with other viruses because the surface protein is manufactured in the laboratory (Dickens, 2011).

Hepatitis B Vaccine Exception

Susceptible individuals who are capable of getting hepatitis B infection should not receive the dose of the hepatitis B vaccine if they have the following health problems:

(i) Anyone who is an allergy to baker's yeast or any other component of the vaccine should not be vaccinated with the hepatitis B vaccine.

(ii) Anyone who has a life-threatening allergic reaction to a previous dose of hepatitis B vaccine should not get another dose.

(iii) Anyone who is sick when a dose of the vaccine is scheduled should wait until fully recovered before receiving the vaccine. However, pregnant women who are susceptible to hepatitis B infection should get vaccinated (Dickens, 2011).

Statement of the Problem

Hepatitis is a general term meaning inflammation of the liver and can be caused by a variety of different viral agents or drugs. The viral agents which cause this deadly disease include the hepatitis A, B, C, D, E, F, G and H viruses. Continuous exposure to alcohol, drugs, or toxic chemicals, such as aerosol sprays and paint thinners can also cause hepatitis B disease. This virus is very difficult to clear after infection because of the formation of cccDNA.

According to the World Health Organisation, about 350 million people are infected with hepatitis B virus and 170 million people that are chronically infected live with hepatitis C virus (HCV). Hepatitis B infection can be transmitted from carrier mothers to children during birth (vertical transmission; that is almost 90% of infants born to HBsAg-positive/ HBeAg-positive women and 10% of infants born to HBsAg-positive/HBeAg-negative women become infected), contact with an infected person (horizontal transmission), sexual intercourse

(that is through semen and vaginal fluid contact with an infected person), exposure to blood or fluid of an infected person (blood transfusion and blood-related products) and contact with HBV contaminated materials such as needle, razor blades, toothbrush, etc. Hepatitis B virus (HBV) can be controlled through vaccination (that is vaccination during birth and after birth), antiviral treatment of both acute and chronic infections, an educational campaign, screening of blood and blood products and linkage to care method.

Several mathematical models of HBV transmission dynamics have focused on the influence of prevention and control measures including perfect vaccination, antiviral treatment and linkage to care in certain regions and countries. These mathematical models have provided us with useful information, facts and ideas about the impact of perfect vaccination and treatment as control strategies of HBV. J. Zhang & Zhang (2018) formulated a mathematical model that incorporates perfect vaccination and treatment as control strategies to study the transmission dynamics of hepatitis B virus in China. However, understanding the important role play by imperfect vaccination in describing the hepatitis B virus transmission dynamics proved beneficial.

Against this background, we seek to develop a mathematical model where the total population is divided into Susceptible, Vaccinated, Acutely infected, Chronic carriers, Treated and Recovered (SVICTR) individuals to model the process of transmission mechanisms of hepatitis B in the presence of regular interventions. More precisely, following the work done by J. Zhang & Zhang (2018), an SVICTR model was proposed that will take into account imperfect vaccination in describing hepatitis B virus transmission dynamics in the presence of regular interventions.

Significance of the Study

Mathematical models can help us to gain a clear understanding of disease transmission dynamics, assess the effectiveness of various preventive measures

and strategies and the ways to control it eventually. However, there has not been any mathematical modelling of the hepatitis B virus using the SVICTR model that takes into account imperfect vaccination. Hence, incorporating imperfect vaccination as a control strategy of hepatitis B transmission dynamics will pave the way for its total eradication. Hepatitis B has always contributed negatively towards a nation's total productivity due to the loss of human labour and other resources as a result of death related to hepatitis B virus infections. Hence, this thesis will be of importance in the understanding of the disease, its transmission dynamics and its total eradication. This work will also help decision-makers and health practitioners to evaluate the effectiveness of intervention strategies put in place to fight the hepatitis B virus disease.

Research Objectives

General Objective

The general objective of this thesis is to assess the knowledge of hepatitis B transmission dynamics using SVICTR model that will explore the important role played by imperfect vaccination and treatment as control strategies.

Specific Objectives

This research has the following specific objectives:

- to develop a mathematical model by extending the model of J. Zhang & Zhang (2018) to incorporate imperfect vaccination
- to determine the equilibrium points of the model and the basic reproduction number, $\mathbb{R}_0$
- to perform the stability analysis and numerical simulations of the model
- to determine which parameters influence the model dynamics most

Delimitation

The thesis is limited to finding out the important role played by imperfect vaccination in controlling the hepatitis B virus transmission dynamics.

Limitation

This thesis has a limitation of accurate estimation of parameter values since we largely rely on literature values and some estimated values for the numerical simulations.

Organisation of the Study

This thesis is organised into five (5) chapters. Chapter ONE is the background of the study. In Chapter TWO, we provide related literature on both mathematical and statistical models on hepatitis B transmission dynamics. Chapter THREE was devoted to the model formulation and analysis. The numerical simulations and sensitivity analysis of the proposed model were carried out and discussed in Chapter FOUR and Chapter FIVE was devoted for the recommendation.

Chapter Summary

This chapter introduced the thesis, by first looking at the biological background of hepatitis B disease, the life cycle of the hepatitis B virus, the various stages and spectrum of liver diseases after HBV infection, hepatitis B testing results and their meaning, how the hepatitis B vaccine was made and the vaccine exemptions. We also give the motivation for studying the problem stated in the thesis together with the research objectives of our study. We concluded the chapter by given an outline for the structure of the thesis.

CHAPTER TWO

LITERATURE REVIEW

Introduction

Hepatitis B virus infection is endemic in many parts of the world. It has become a matter of fact to check its spreading dynamics globally. To do this effectively, there is the need to take a look at the model's other researchers used and how we can modify them to help eradicate the hepatitis B virus disease. Based on the literature review, we have also notice that many researchers and policy-makers have used mathematical models to investigate the behaviour, consequences and effects of the hepatitis B virus infection in the human population over a given period. The aim was to come out with interventions and control strategies for this deadly disease. Hence, in this chapter, the focus was on the review of empirically related literature on hepatitis B virus infection, the history of mathematical modelling as a tool for studying infectious diseases and the incorporation of perfect vaccination, imperfect vaccination and treatment as control strategies.

Infectious Diseases

In this section, we will give the history behind using a mathematical model as a tool for studying and controlling infectious diseases. A disease is said to be infectious if its causal agent such as virus, bacterium, protozoa, or toxin, can be transferred from one host to another through various modes of transmission. These modes of transmission include physical contact, airborne, water, food, disease vectors and carrier mothers to newborn babies (Zhien & Jia, 2009).

The spread of infectious diseases has always been of concern in the communities in which the outbreak occurs and serves to endanger public health and decision making bodies. This is because, infectious diseases have caused serious health problems, economic and social hardship to human societies in several areas of the world. For example, the Antonine plague in the early 165 to 180

AD was an ancient pandemic which was by either through smallpox or measles, brought back to the Roman Empire by troops returning from campaigns in the near-East (Zhien & Jia, 2009). These infectious diseases invade the entire Roman Empire, kill two of the Romans and caused economic hardships to the whole Roman empire (Zhien & Jia, 2009). Also, in areas such as the Caribbean, Mexico, Peru and Brazil, smallpox was transmitted by the Spanish armies led by Cortez. This has a reduction on the Mexican population from up to 30 million to less than 2 million for a period of 50 years (Brauer & Castillo-Chávez, 2001; Geddes, 2006). Again, the outbreak of coronavirus disease in Wuhan, China in 2019 has caused a global pandemic and claim millions of lives worldwide.

The control of these infectious diseases had a long history and great progress has been made so far. Through the worldwide vaccination programme (Zhien & Jia, 2009), the smallpox outbreak is now eradicated. Furthermore, the passing of the World Health Assembly resolution in 1991 has successfully eradicated leprosy as a public health problem (Zhien & Jia, 2009). Although there is a massive achievement in the prevention and controlling of infectious diseases, a lot of effort is still needed to completely eradicate these infectious diseases worldwide. To prevent and control infectious diseases effectively, it is crucial to, first of all, understood the transmission mechanisms and dynamics of its spreading and then provide pragmatic measures using mathematical models.

Mathematical Model

The word "modelling" comes from a Latin word called modellus which means a human way of coping with reality. As explain by Andrews & McLone (1976), mathematical modelling is the representation of real-world problems in mathematical terms and ways so that a more precise understanding, significance and properties of these problems will be obtained. Hence, mathematical models are base on population dynamics, the behaviour of disease transmissions, features of the infectious agents, and the connections with other societal and phys-

iological factors. Through the use of analysis such as quantitative, qualitative, sensitivity and numerical simulations, mathematical models provide us with a clear understanding of how infectious diseases spread from one host to another, discover the factors governing the transmission dynamics of the diseases, and identify the most significant and sensitive parameters, to make reliable predictions, provide useful prevention and control strategies.

The background of mathematical modelling of infectious diseases can be traced back to the early 1760s when Bernoulli used mathematical models to study the smallpox disease (Bernoulli, 1760). However, researchers use deterministic mathematical models to study infectious diseases in the 20th century. A good example is a discrete-time model Hamer formulated to study the spread of measles in 1906 (Hamer, 1906). Later on, Dr Ross also proposed a differential equation model to study the transmissions dynamics of malaria between the human population and the mosquitoes population in 1910. Dr Ross was able to establish a threshold for the mosquitoes population size in his model below which the spread of malaria can be controlled. This earned him his second Nobel Prize award in medicine (Ross, 1911).

Moreover, Kermack and McKendrick formulated the SIR (susceptible, infective, recovered) deterministic model, in 1926, to study the Black Death disease in London between the period of 1665 to 1666, and the outbreak of plague in Mumbai in 1906. They later, in 1932, formulated an SIS (susceptible, infective, susceptible) compartmental model. The analysis and investigation of these two models, formally introduced the concept of thresholds quantity in mathematical modelling which determines whether a disease spreads in a given population or die out (Kermack & McKendrick, 1932). The ideal of thresholds gives the foundations of the theory of epidemic dynamics. More intensive studies on epidemic dynamics took place after the middle of the 20th century and hence several developments and progress have been particularly made during

the past 20 years in mathematical models to study various infectious diseases such as hepatitis B virus disease, malaria, the human cancer disease, tuberculosis, cholera etc.

Empirical Review of Related Literature on Hepatitis B Virus Infection

In this section, we will review related literature on the use of mathematical models as a tool for controlling and prevention of hepatitis B infectious disease in some countries and regions in the world. For hepatitis B virus infection, in particular, Khan et al. (2013) proposed a mathematical model to study the effect of immigrants on the host population in describing the hepatitis B virus transmission. Their model was obtained by modifying the model of Pang et al. (2010) to include some new transmission dynamics. These new transmission dynamics include; the migrated compartment, HBV transmission rate between the migrated compartment and the exposed compartment, the transmission rate between the migrated compartment and the acutely infected compartment and the natural death rate of individuals in the migrated compartment. The model was solved numerically and it was shown that when the transfer rate of the migrated compartment to the exposed compartment (μ_1) and the transfer rate of the migrated compartment to the acute infection compartment (μ_2) varies, there is a corresponding change in the population for both exposed, acutely infected and chronic carriers compartments. Hence, Khan et al. (2013) observed that there is a direct relationship between the number of immigrants and the number of infective individuals in the population. That is the proportion of infective individuals decreases when the proportion of migrated individuals decreases. Hence, policies of the government should be geared towards these immigrants and subject them to tests about the disease status before allowing them to enter any country.

To further get a clear understanding of hepatitis B virus transmission dynamics and its control measures through mathematical modelling, Zou et al.

(2010) used the characteristics of HBV infection such as vertical transmission from carrier mothers to newborn babies to formulate a mathematical model that will help in the studying of the transmission dynamics and control of hepatitis B virus (HBV) infection in mainland China. The total population was categorized into six (6) epidemiological groups. These include the proportion of individuals susceptible to infection (S), individuals that were latently infected (L), acutely infected individuals (I), chronic carriers of the hepatitis B virus (C), recovered individuals with protective immunity (R) and individuals who recovered through vaccination (V). Vaccination was included as the only control strategy and obtained a system of six (6) differential equations. They assume that newborns by carrier mothers infected during birth move only to the carrier compartment. The existence and stability analysis of the disease-free and endemic equilibria were discussed in their model. Sensitivity analysis was also performed on the model parameters to determine the most sensitive parameter. The basic reproduction number $\mathbb{R}_0$ of their model was estimated to be 2.406 in China with suitable model parameter values the model system follows the reported HBV data from the Ministry of Health of China. This data describes China as a hepatitis B endemic region in the Asia continent and approaching its equilibrium with the current immunization programme as a control measure. Based on the sensitivity analysis carried out on the model parameter values of the basic reproduction number $\mathbb{R}_0$, Zou et al. (2010) observed that the optimal control strategy for the hepatitis B virus disease in China is by combining both immunizations of newborns, retroactive immunization of susceptible adults and reduction of contact rate with infective individuals.

There were some potholes on the work done by Zou et al. (2010) that needed to be filled in to make the model more accurate. Hence, Kimbir et al. (2014) extend the work done by Zou et al. (2010) to incorporate treatment as a control parameter. The main aim was to study the impact of treating infected

persons as a control strategy for hepatitis B virus disease. They were of the view that newborns by carrier mothers that are infected during birth, first move to the latently infected compartment instead of the chronic carriers compartment. The basic reproduction number $\mathbb{R}_0$ was numerically assessed for its sensitivity to vaccination and treatment parameters. Based on the sensitivity analysis of the parameter values of the basic reproduction number, Kimbir et al. (2014) realized that increasing the vaccination and treatment rate will reduce the $\mathbb{R}_0$. Hence, the combination of both vaccination and treatment is the best strategy in controlling HBV infection.

Similarly, Dontwi et al. (2014) used the standard of Susceptible S, Infected I, Recovered R (SIR) model by Kermack and McKendrick to study the hepatitis B transmission dynamics with vaccination as a control parameter. The idea was to use hepatitis B virus infection data recorded from the Tano North District Health Directorate to study and understood the hepatitis B dynamics in the Tano North District through mathematical modelling. It will also assist decision-makers to come out with the best preventive and control strategies that will eradicate the hepatitis B disease in Ghana. Base on the numerical and sensitivity analysis carried out on the model parameters, Dontwi et al. (2014) concluded that an increase in the hepatitis B vaccination coverage in the district will lead to a decrease in the prevalence rate of hepatitis B virus disease in the Tano North district.

Later on, J. Zhang & Zhang (2018) proposed a model for hepatitis B virus with control strategies of newborn vaccination and treatment. An optimal control constraint was used to simulate the yearly reported data of newly infected cases of hepatitis B in China from 2004 to 2016. Hence, they divided the total population into susceptible individuals S, acutely infected individuals I, chronic carrier individuals C, treated patients T and immunized individuals R. In their work, vertical transmission, that is the transmission of the hepatitis B virus from

carrier mother to child was incorporate since it has a great impact on HBV prevalence most especially in highly endemic areas like China. They also assume that the infected individuals who experience treatment failure enter into the chronic population only due to the short period of acute infection. Results from the numerical simulation of their model indicate that, if the transmission rate increases, then both chronic and acute infective populations also increase. Therefore, the studies of Desta & Koya (2019) confirm that the prevention of hepatitis B virus disease requires both vaccinations of newly born babies and medical treatment of chronic infective populations to be increased.

Emerenini & Inyama (2018) observed that, studying the transmission of HBV with considerations of different population level of individuals with vaccination of newborn babies and the treatment of infected individuals as control strategies prove beneficial. Hence, they propose a model by incorporating vaccination of newborn babies and treatment as control strategies to study HBV. Based on the stability analysis of the model system, they conclude that since the disease-free equilibrium state is locally asymptotically stable, vaccination and treatment played an important role in controlling hepatitis B transmission dynamics in a population.

Furthermore, Farman et al. (2018) extended the model proposed by Williams (2006) to study the transmission dynamics of acute and chronic hepatitis B epidemic problem in a community. This was done by dividing the infectious compartment into two stages; acutely infected stage and chronically infected stage respectively. In their work unconditionally convergent nonstandard finite difference scheme was developed by applying Michens approach $\phi(h) = h + O(h^2)$ instead of the usual h to control the spread of hepatitis B virus. Treatment and vaccination were also incorporated to minimize the number of acutely infected individuals, chronic carriers with hepatitis B virus while maximizing the number of recovered individuals. Since there is a reduction in the acutely in-

fected as well as the chronically infected rates for both disease-free and endemic equilibria using the unconditionally convergent nonstandard finite difference scheme, controlling the spreading of hepatitis B virus disease in the community is achieved.

Although China has included hepatitis B vaccination in their national vaccination programme, the infection rate of hepatitis B virus disease is still at an alarming rate. Hence a lot of models were formulated by researchers to help control the spreading of HBV in major cities of China. Therefore, T. Zhang et al. (2015) observed that incorporating both the exponential birth rate and vertical transmission in a mathematical model to study the transmission dynamics of the hepatitis B virus in Xinjiang, China prove beneficial. Hence, they concluded that enhancing the vaccination rate for newborns in Xinjiang is a very effective way of controlling the transmission of HBV. That is all infants in Xinjiang should receive the hepatitis B vaccine as soon as possible after birth.

Koonprasert et al. (2016) used a mathematical model consisting of uninfected liver cells, infected liver cells and free virus as the total population to study the hepatitis B virus disease. Their model includes a logistic growth term for uninfected cells, a mass action term for infection of uninfected cells, a free virus term, a loss of free viruses on infection of a cell and a non-cytolytic cure process. Base on sensitivity and numerical analysis of the model parameter values, Koonprasert et al. (2016) concluded that the parameters that affect reducing the number of infected cells are the rate of infection of uninfected cells (β), the rate infected cells can be cured (ρ) and should be reduced to control the hepatitis B virus transmission dynamics.

Finally, S. Zhang & Zhou (2012) claimed that intrauterine infection in pregnant carrier mothers is relatively low, hence vertical transmission from HBV carriers mothers occurs either during delivery or after birth. They further claim that the acutely infected stage of HBV infection is relatively short compare to

the pregnancy period of a carrier mother and the prolonged chronic phase of the hepatitis B virus infection. Thus perinatal infection from carrier mothers who are acutely infected is not possible. These two characteristics of hepatitis B virus transmission dynamics were used to formulate a mathematical model to describe the spread of hepatitis B virus disease in China. Numerical results from the model system show that the increasing use of the hepatitis B vaccine and treatment of infected individuals with interferon or lamovudine may be of great importance for the control of HBV. However, S. Zhang & Zhou (2012) noticed that a mathematical model with an age-dependent probability of developing the carrier stage will probably make the simulations fit the hepatitis B virus disease data reported from China better.

Vaccination as a Control Strategy of HBV Infection

In this section, we will elaborate and review the literature on the important role play by vaccination in the control and prevention of hepatitis B virus infections. Vaccination with the hepatitis B vaccine is the most effective measure to prevent HBV infection and its complications such as cirrhosis of the liver, liver cancer, liver failure and death (Centers for Disease Control and Prevention, 2006; Shepard et al., 2006). The vaccine confers protection in more than 90% of healthy adults younger than 40 years who receive the complete vaccine series (Venters et al., 2004; Assad & Francis, 1999) and immunity lasts at least for three decades (Simons et al., 2016; McMahon et al., 2011). When a vaccine confers between $80\% - 90\%$ protection to a susceptible individual in a population against hepatitis B virus infection, then the vaccine is said to be a perfect vaccine. Since 1982 a vaccine against HBV infection has been produced and made available (Lewin et al., 2001). Most of the vaccines developed for the prevention of HBV infection depend on the viral envelope protein called the hepatitis B surface antigen (HBsAg). The vaccine against HBV can be received by infants to adults and protects 85-90% of susceptible individuals (Shepard et

al., 2006; Maynard et al., 1989). The two main types of vaccinations against HBV infection include the 3-dose hepatitis B vaccination and the timely hepatitis B birth dose which is within 24 hours of birth.

Nowadays, the group that vaccination focuses on is the one with the highest risk of developing chronic infection, more especially children less than six years (World Health Organization, 2015). According to Trépo et al. (2014), 40% of men and 15% of women with HBV infection acquired at birth die of liver cirrhosis or hepatocellular carcinoma. The optimal vaccination strategy is for newborns to receive the first dose within 24 hours after birth and two boasters during their childhood. In 95% of the cases, children will be protected from infection for at least 20 years and may even acquire immunity for life (World Health Organization, 2015). Hence, in 1991 the world health organisation recommended that hepatitis B vaccination should be included in national immunization programmes in all countries with chronic carriers prevalence of 8% by 1995 and all countries by 1997 (Anderson & May, 1992).

So, around 2002, 154 countries had routine infant immunization with hepatitis B as a national immunization programme (Hou et al., 2005; Lok & McMahon, 2004). As a result, the number of liver cancer cases has diminished (Lok & McMahon, 2004). Furthermore, to reduce HBV infection to a larger extent, it is recommended to vaccinate other high-risk groups such as individuals who require transplantations or dialysis, health care workers, travellers before visiting endemic areas, people in prisons or people with multiple sexual partners (World Health Organization, 2015). In 1983, the world health organisation designed and initiated a demonstration project on a large scale controlled clinical trial to vaccinate 80,000 newborns in high incidence areas such as Qidong in Jiangsu province in China (Sun et al., 2002; Tsung-Tang et al., 1986; Zuckerman et al., 1983). This is because, since about 20 million children are born in China every year, national hepatitis B immunization would offer protection to about 1.5

million children from becoming HBV chronic carriers in China every year. The vaccine gives positive predictions about the eradication of the disease. However, it will take a longer time before vaccination will be available to everybody. Hence, we need good therapy to treat individuals that are already infected and have progress into the chronic carriers stage of the hepatitis B virus infection.

Treatment of Chronic HBV Infection as a Control Strategy

In this section, we will elaborate and review the literature on the important role play by the treatment of infected patients in the control and prevention of hepatitis B infections. Treatment of hepatitis B virus infection is the process of improving liver histology and reducing the risk of progression in a desirable control in addition to newborns vaccination designated as a high priority to prevent the disease. Chronic hepatitis B infection has been proven to be a difficult disease to overcome. Hence, there is a need for long therapies in many cases (Rodriguez, 2016). In any viral infection, a therapy could lose its effectiveness with time since the virus may develop resistance to the drugs. When an infected person is diagnosed with chronic HBV infection (this means the individual is capable of transferring the disease to a susceptible person in the population), if the infected person is in the early stages of the chronic infection and the level of antigens is low, it is always advisable for the patient to wait until the virus replication is complete and the damage of the liver is high before going in for any therapy. However, the decision depends on each patient's situation and predisposition to other diseases such as cirrhosis or HCC (Lok, 2015).

There are currently seven approved drugs for the treatment of chronic hepatitis B virus disease. They include two formulations of interferon (IFN), conventional and pegylated IFN (PEG-IFN), five nucleoside or nucleotide analogues, lamivudine (LMV), telbivudine, adefovir, entecavir and tenofovir (Lok, 2015). Among these seven approved drugs, treatment with nucleoside or nucleotide analogues is the most efficient and effective because it inhibits virus

replication in most patients for at least five (5) years long (Lampertico et al., 2009). Also, all nucleoside or nucleotide analogues are known to reduce drug resistance, so in most cases treatment is delayed or stopped which is frequently in a virus relapse (Lampertico et al., 2009).

Mathematical models have proved beneficial for the understanding of the virus and drugs dynamics under drug therapy infections such as human immunodeficiency virus (HIV), Hepatitis C virus (HCV) and hepatitis B virus (HBV) (Perelson, 2002; Tsiang et al., 1999; Zeuzem et al., 1997; Perelson et al., 1997). To get a clear understanding of these virus-host dynamics, various studies conducted by some researchers focused on the combination of clinical data and mathematical models. Hence, (Guidotti et al., 1996) have shown that a strong immune response is a success to overcome an infectious disease. For hepatitis B disease, in particular, various studies have been made to understand the efficacy of drugs in curing the disease. Lewin et al. (2001) estimated 95% lamivudine efficacy in preventing new hepatitis B virus production which can be increased to 99% when combined with famciclovir. Furthermore, clinical data have shown that, in the case of HBV, for patients that are undergoing therapy, most of the virus decay profiles are biphasic (Tsiang et al., 1999; Zeuzem et al., 1997; Nowak et al., 1996). However, mathematical models applied to the same data have shown that for some patients, drug therapy yields faster clearance of the virus whereas, for other patients, the clearance is much slower (Lewin et al., 2001). Hence, the incorporation of treatment parameter as a control strategy to study the hepatitis B virus disease will pave a way for its total eradication.

Role of Imperfect Vaccination in Controlling HBV Infection

In this section, how imperfect vaccination contributes to the ongoing transmission of hepatitis B virus infections was elaborated. Despite an effective vaccination program for newborn babies since the 1990s and treatment of infected patients, which has reduced chronic HBV infection in children (Centers for Dis-

ease Control and Prevention, 2007; Cui et al., 2006), the incidence of hepatitis B virus infection is still on an increasing rate from 21.9% in $100,000$ people in 1990 to 53.3% in $100,000$ in 2003 (Wang et al., 2004). Imperfect vaccination is one of the defining issues in connection to the hepatitis B virus (HBV) transmission of our time. So, it is important to forecast the long-term trends in hepatitis B virus (HBV) prevalence and provide useful information for public health decision making. One of the feasible methods to predict the prevalence of any infectious disease is to use a mathematical model (Liang et al., 2017).

The control of hepatitis B virus disease using mathematical models has proved to be difficult even in countries that maintain high vaccination coverage. Again, this may be due to the use of imperfect vaccine and there has been a lot of work done on the different modes by which vaccines might fail (Magpantay et al., 2014). Different types of vaccines can have different impacts on population-level dynamics. The three main types of the imperfect vaccine include; the vaccine that reduces the probability of infection upon exposure by the factor ε, the vaccine that does not protect a fraction ε of the vaccinees and perfect lifetime immunity to the remaining population and the vaccine that provides perfect protection to each vaccinee for an exponentially distributed time after which the vaccinee becomes as susceptible as unvaccinated individuals (Magpantay et al., 2014). The probability of immunity waning within a vaccinated individual's lifetime is given by ε. These imperfect vaccines may not completely prevent the infections but could reduce the probability of been infected or reduce the consequences of being infected thereby reducing the disease burden.

According to McLean & Blower (1993), when a vaccine only reduces the probability of infection upon exposure but does not eliminate the disease it is called failure in degree; when a vaccine does not protects some individuals but provide complete protection in others, it is called failure in taking. However, when the protection conferred wanes over time, this is called failure in duration.

Halloran et al. (1992) also used the term leaky vaccine to describe a vaccine that only exhibits failure in degree, the all-or-nothing vaccine for the vaccine that demonstrates a failure in taking and a vaccine that displays failure in duration as a waning vaccine.

According to Farrington (2003), the vaccine for pertussis is described as a possibly leaky vaccine, those for measles and rubella as an all-or-nothing vaccine and the vaccine for cholera as a waning vaccine. The direct effects of these vaccines at the individual level are given in their descriptions, but the indirect protection that they confer as a result of a reduction in the disease transmission is not easily surmised from the individual effects. Since the hepatitis B vaccine does not provide the vaccinee with permanent immunity (World Health Organization, 2015; Zou et al., 2010), it follows that the vaccine for HBV is imperfect which contributes to the ongoing transmission.

Chapter Summary

The review in this chapter was about the use of different mathematical models to study the transmission dynamics and mechanisms of hepatitis B virus infections and the important role, vaccination, treatment and imperfect vaccination play in controlling the hepatitis B virus disease. The history behind using mathematical models as a tool for studying and controlling infectious diseases was also discussed. The models were base on the characteristics of hepatitis B virus transmission dynamics. While some of the studies based the hepatitis B virus transmission dynamics on the standard SIR model, others equally based their hepatitis B virus transmission dynamics on variations of the standard SIR model. The basic reproductive number, $\mathbb{R}_0$ was determined in both models and used for the analyses of whether the hepatitis B virus disease will be endemic in the entire population or not. So, this study looked at the hepatitis B virus transmission dynamics by using a deterministic model based on variations and modifying the standard SIR model developed by (Kermack & McKendrick, 1927).

Despite the numerous studies done in fighting this hepatitis B virus disease, to the best of our knowledge, there has not been any mathematical modelling of hepatitis B virus transmission dynamics using the SVICTR model that will incorporate imperfect vaccination, perfect vaccination and treatment as control strategies. Hence, a combination of this work and the review mathematical models of hepatitis B virus transmission dynamics above will prove beneficial and helps in the eradication of this global disease.

CHAPTER THREE

RESEARCH METHODS

Introduction

Mathematical models for hepatitis B virus disease can either be a deterministic model or a stochastic model. Deterministic models are models which have a finite number of compartments where the mechanisms by which individuals move from one compartment to another are specified through a series of ordinary differential equations. Stochastic models on the other hand are models that deal with estimating probability distributions of potential outcomes by allowing for random variation in one or more inputs over some time. Hence, Stochastic models depend on the chance variations in the risk of exposure, disease and other illness dynamics. In this chapter, we model the spread of hepatitis B virus disease using the characteristics of the hepatitis B virus transmission dynamics. Hence, a Susceptible, Vaccination, Acutely infected, Chronic carriers, Treatment and Recovered $(SVICTR)$ model will be formulated based on the deterministic approach and develop a system of differential equations and expressions for which the equilibrium points, basic reproduction number and stabilities of these equilibrium points will be determined.

The Existing Model

We begin the model formulation by introducing the model by J. Zhang & Zhang (2018). We first present the assumptions, flowchart, parameters and equations of the existing model followed by the assumptions, flowchart, equations and parameters of the modified and extended model.

Basic Model Assumptions of Existing Model

(A1) Vertical transmission from mother to child was incorporated. That is newborns to carrier mothers infected at birth proceed to the chronic carrier state immediately.

(A2) Recruitment into the susceptible population is simplified as a new birth and the birth rate and death rate are assumed identical (ie $\lambda = \mu_0$).

(A3) Infected individuals who experience treatment failure move back only to the chronic compartment due to the short period of acute infection.

(A5) Exit out of the population is by natural death only and no HBV-related death.

(A6) Immunity acquired by treatment and vaccination is for lifelong.

(A7) Chronic carriers can clear the virus and become immune at the rate γ_2.

The general process of this model is shown in Figure 3 below.

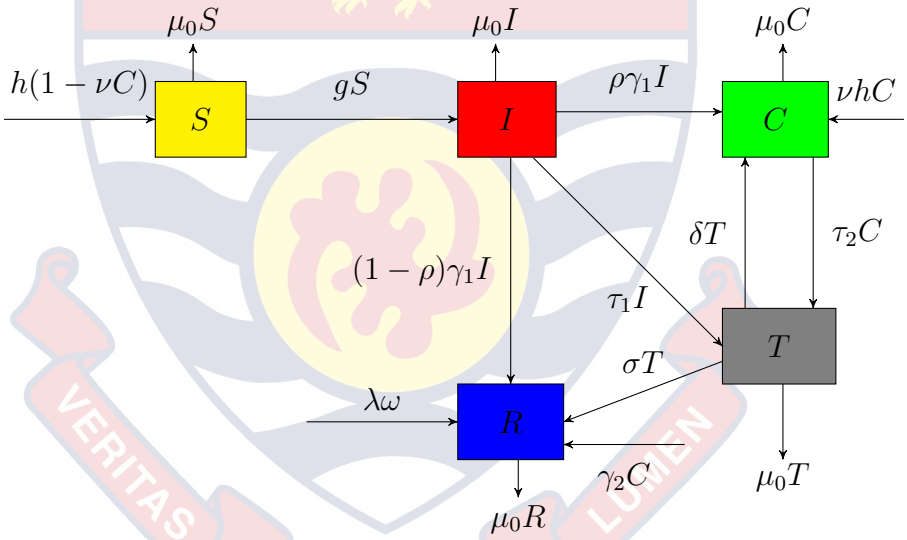

Figure 3: The schematic diagram of HBV Transmission dynamics, where $g = (\beta_1 I + \eta_1 C + \eta_2 T)$ and $h = \lambda(1-\omega)$.

The remaining parameters are defined in detailed in Table 2 and Table 3 below.

Table 2: **State variables of exiting model and their description**

Variables	Description
S	Susceptible individuals
I	Acutely infected individuals
C	Chronic carriers
T	Treated individuals
R	Immunized individuals

Table 3: **Parameters of exiting model and their description**

Parameter	Description
λ	birth rate
μ_0	natural human mortality rate
ν	probability of children been vertically infected
σ	successful treatment rate
γ_1	acute infection progressive rate
τ_1	treatment rate for acute infection
τ_2	treatment rate for chronic carriers
ω	successfully immunized proportion
δ	unsuccessfully treatment rate
β_1	reduced transmission rate relative to acute infection
η_1	reduced transmission rate relative to chronic carriers
η_2	reduced transmission rate relative to treatment
ρ	average probability of failing to clear acute infection
γ_2	rate of clearing chronic infection

Equations of the Existing Model

From the model digram in Figure 3 above, we obtain a system of five (5) differential equations.

$$\begin{cases} S'(t) = \lambda(1-\omega)(1-\nu C) - (\beta_1 I + \eta_1 C + \eta_2 T) S - \mu_0 S, \\ I'(t) = (\beta_1 I + \eta_1 C + \eta_2 T) S - (\mu_0 + \gamma_1 + \tau_1) I, \\ C'(t) = \rho\gamma_1 + \lambda(1-\omega)\nu C + \delta T - (\mu_0 + \gamma_1 + \tau_2) C, \\ T'(t) = \tau_1 I + \tau_2 C - (\mu_0 + \sigma + \delta) T, \\ R'(t) = \lambda\omega + (1-\rho)\gamma_1 I + \gamma_2 C + \sigma T - \mu_0 R. \end{cases}$$

The Extended Model

Based on the fact that hepatitis B vaccination is not completely effective due to imperfect vaccination, we present a mathematical formulation of a compartmental model of hepatitis B virus transmission dynamics using $SVICTR$ model with vaccination and treatment as intervention strategies that will also incorporate imperfect vaccination. We divide the total population $N(t)$ into six compartments. They include; Susceptible individuals $S(t)$, Vaccinated individuals $V(t)$, Acutely infected individuals $A(t)$, Chronic carriers $C(t)$, Treated individuals $T(t)$, Immunized individuals $R(t)$ and obtain a system of six (6) ordinary differential equations.

Basic Model Assumptions of the Extended Model

In addition to the assumptions made by J. Zhang & Zhang (2018) except (A1), (A5), (A6) and (A7), we make the following assumptions:

(A1) We assume that vaccination with hepatitis B vaccine can reduce but not eliminate the susceptibility of infection. We model this by including a factor $\varepsilon \in [0, 1]$ in the infection rate to vaccinated individuals when contact with infected individuals and $(1 - \varepsilon)$ describes the vaccine efficacy.

(A2) We assume that immunity acquired by vaccination is not life long, hence making the vaccine imperfect.

(A3) We take no consideration of vertical transmission from carrier mothers to unborn babies since it is not a hundred per cent (100%).

(A4) We also consider HBV-induced death (μ_1) due to treatment failure, and infected individuals may die as a result of the disease.

The general process of the extended model is shown in Figure 4 below.

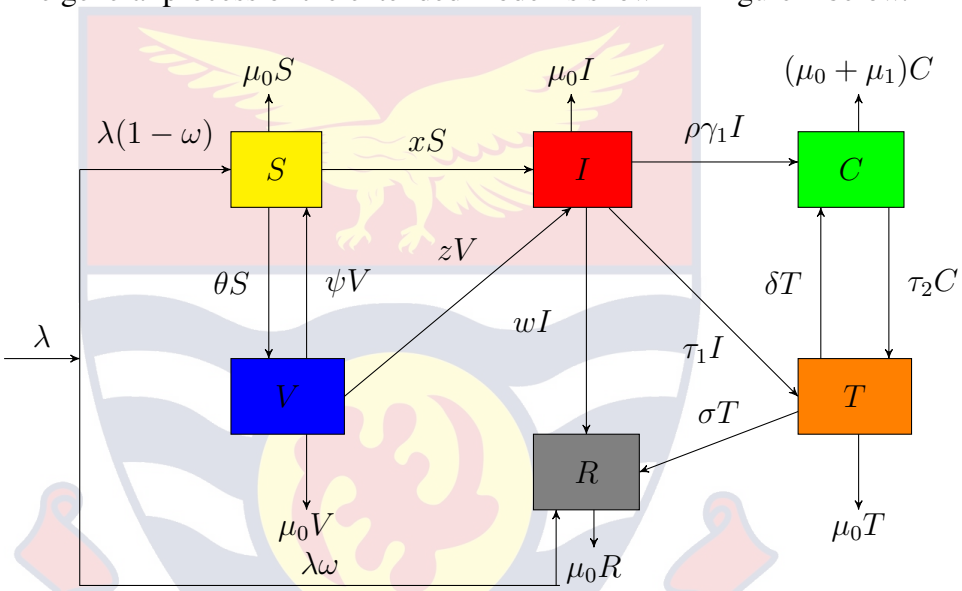

Figure 4: The schematic diagram of HBV transmission dynamics in the presence of regular interventions, where $w = (1-\rho)\gamma_1$, $x = \beta(I+\eta_1 C+\eta_2 T)$ and $z = \beta\,(1-\varepsilon)\,(I+\eta_1 C+\eta_2 T)$.

The remaining parameters and variables are defined in detailed in Table 4 and Table 5 respectively.

Table 4: **State variables of extended model and their description**

Variables	Description
S	Susceptible individuals
V	Vaccinated individuals
I	Acutely infected individuals
C	Chronic carriers
T	Treated individuals
R	Immunized individuals

Table 5: **Parameters of extended model and their description**

Parameter	Description
λ	birth rate
μ_0	natural human mortality rate
μ_1	HBV-related mortality rate
β	transmission rate
σ	successful treatment rate
γ_1	acute infection progressive rate
τ_1	treatment rate of acute infection
τ_2	treatment rate of chronic carriers
ω	successfully immunized proportion
ρ	average probability of failing to clear acute infection
δ	unsuccessfully treatment rate
ψ	rate of waning vaccine- induced immunity
η_1	reduced transmission rate relative to chronic infections
η_2	reduced transmission rate relative to treatment
θ	vaccination rate of susceptible individuals
ε	vaccine efficacy rate

Equations of the Extended Model

From the model diagram in Figure 4, we obtain a system of six (6) ordinary differential equations that describe hepatitis B virus transmission dynamics with the vaccination and treatment as control strategies that will incorporate imperfect vaccination. We derived the following system of non-linear ordinary differential equations:

$$\left.\begin{aligned}
\frac{dS}{dt} &= \lambda(1-\omega) + \psi V - [\beta(I+\eta_1 C+\eta_2 T) + (\theta+\mu_0)]\,S,\\
\frac{dV}{dt} &= \theta S - [(\mu_0+\psi) + \beta(1-\varepsilon)(I+\eta_1 C+\eta_2 T)]\,V,\\
\frac{dI}{dt} &= \beta(I+\eta_1 C+\eta_2 T)\,S + \beta(1-\varepsilon)(I+\eta_1 C+\eta_2 T)\,V\\
&\quad -(\gamma_1+\tau_1+\mu_0)\,I,\\
\frac{dC}{dt} &= \rho\gamma_1 I + \delta T - (\mu_0+\mu_1+\tau_2)\,C,\\
\frac{dT}{dt} &= \tau_1 I + \tau_2 C - (\delta+\sigma+\mu_0)\,T,\\
\frac{dR}{dt} &= \lambda\omega + (1-\rho)\,\gamma_1 I + \sigma T - \mu_0 R.
\end{aligned}\right\} \tag{3.1}$$

Reduced System

Since the variable R does not appear in the other equations in system Eq. (3.1), the equation of R can be discarded, and the reduced system which is studied has the same dynamical behaviour as the original system in Eq. (3.1). Hence the reduced form of the model system without the ordinary differential

equation for R is given as

$$\left.\begin{aligned}
\frac{dS}{dt} &= \lambda(1-\omega) + \psi V - [\beta(I+\eta_1 C+\eta_2 T) + (\theta+\mu_0)]\,S,\\
\frac{dV}{dt} &= \theta S - [(\mu_0+\psi) + \beta(1-\varepsilon)(I+\eta_1 C+\eta_2 T)]\,V,\\
\frac{dI}{dt} &= \beta(I+\eta_1 C+\eta_2 T)S + \beta(1-\varepsilon)(I+\eta_1 C+\eta_2 T)V\\
&\quad -(\gamma_1+\tau_1+\mu_0)I,\\
\frac{dC}{dt} &= \rho\gamma_1 I + \delta T - (\mu_0+\mu_1+\tau_2)C,\\
\frac{dT}{dt} &= \tau_1 I + \tau_2 C - (\delta+\sigma+\mu_0)T.
\end{aligned}\right\} \tag{3.2}$$

Basic Model Properties

In this section, we present the positivity and boundedness of solutions of the extended model.

Positivity of Solutions

For the system in Eq. (3.2) to be biologically meaningful, we need to prove that all the state variables in the model system are non-negative. Thus, given any positive initial condition, the solutions of the model equation will remain positive.

Lemma 1

Given that the initial solutions and parameters of the system in Eq. (3.2) are positive, the solutions $S(t)$, $V(t)$, $I(t)$, $C(t)$ and $T(t)$ are non-negative for all $t \geq 0$.

Proof. Let us consider

$$\kappa = \sup\{t > 0 : S(t) > 0, V(t) \geq 0, I(t) \geq 0, C(t) \geq 0, \quad \text{and} \quad T(t) \geq 0\},$$

this implies that

$$S(t) > 0, \quad V(t) \geq 0, \quad I(t) \geq 0, \quad C(t) \geq 0$$
$$\text{and} \quad T(t) \geq 0 \quad \forall \quad t \in [0, \kappa).$$

Considering the first equation of the model system in Eq. (3.2), we have

$$\frac{dS}{dt} = \lambda(1-\omega) + \psi V - [\beta(I + \eta_1 C + \eta_2 T) + (\theta + \mu_0)]\, S,$$

it follows that

$$\frac{dS}{dt} \geq -[\beta(I + \eta_1 C + \eta_2 T) + (\theta + \mu_0)]\, S \quad \forall \quad t \in [0, \kappa).$$

Separating of variables and integrating, we obtain

$$S(\kappa) \geq S(0) \exp\left\{ -(\theta + \mu_0)\,\kappa \right.$$
$$\left. -\beta\left(\int_0^\kappa I(t)dt + \eta_1 \int_0^\kappa C(t)dt + \eta_2 \int_0^\kappa T(t)dt\right)\right\} > 0.$$

For the second equation of the model system in Eq. (3.2), we have

$$\frac{dV}{dt} = \theta S - [(\mu_0 + \psi) + \beta(1-\varepsilon)(I + \eta_1 C + \eta_2 T)]\, V,$$

it follows that

$$\frac{dV}{dt} \geq -[(\mu_0 + \psi) + \beta(1-\varepsilon)(I + \eta_1 C + \eta_2 T)]\, V.$$

Upon separating variables and integration, we obtain

$$V(\kappa) \geq V(0)\exp\left\{-(\mu_0+\psi)\kappa \right.$$
$$\left. -\beta(1-\varepsilon)\left(\int_0^\kappa I(t)dt+\eta_1\int_0^\kappa C(t)dt+\eta_2\int_0^\kappa T(t)dt\right)\right\}\geq 0.$$

For the third equation of the model system in Eq. (3.2), we have

$$\frac{dI}{dt} = \beta(I+\eta_1 C+\eta_2 T)S+\beta(1-\varepsilon)(I+\eta_1 C+\eta_2 T)V$$
$$-(\gamma_1+\tau_1+\mu_0)I,$$

it follows that

$$\frac{dI}{dt} \geq -(\gamma_1+\tau_1+\mu_0)I, \quad \forall \quad t\in[0,\kappa).$$

Separating variables and integrating gives

$$I(\kappa) \geq I(0)\exp\left[-(\gamma_1+\tau_1+\mu_0)\kappa\right]\geq 0.$$

Similarly, the remaining equations give the following

$$C(\kappa) \geq C(0)\exp\left[-(\mu_0+\mu_1+\tau_2)\kappa\right]\geq 0,$$

and

$$T(\kappa) \geq T(0)\exp\left[-(\delta+\sigma+\mu_0)\kappa\right]\geq 0.$$

In conclusion, we have prove that the solutions $S(t)>0$, $V(t)\geq 0$, $I(t)\geq 0$, $C(t)\geq 0$ and $T(t)\geq 0$ for all $t>0$. □

Boundedness of Solutions

Given the initial conditions of the model system in Eq. (3.2) to be $S(0) > 0$, $V(0) \geq 0$, $I(0) \geq 0$, $C(0) \geq 0$ and $T(0) \geq 0$ and the fact that the model system we have monitors human population, it follows that the total population is given by

$$N(t) = S(t) + V(t) + I(t) + C(t) + T(t).$$

Hence, the rate at which the total population is changing over some time is given

$$\frac{dN}{dt} = \lambda - \mu_0 N - \mu_1 C. \tag{3.3}$$

We have the following results on the boundedness of the model system in Eq. (3.2).

Lemma 2

The feasible region Ω is defined by the set:

$$\Omega = \left\{ (S(t), V(t), I(t), C(t), T(t)) \in {\mathbb{R}_+}^5 | \right.$$
$$\left. S(t) + V(t) + I(t) + C(t) + T(t) \leq \frac{\lambda}{\mu_0} \right\}.$$

From Eq. (3.3), we have

$$\frac{dN}{dt} + \mu_0 N \leq \lambda. \tag{3.4}$$

Since Eq. (3.4) is a standard form first-order differential equation, we use the integrating factor approach to solve it. Hence, the solution for Eq. (3.4) is given by

$$N(t) \leq \frac{\lambda}{\mu_0} + \left(N_0 - \frac{\lambda}{\mu_0} \right) e^{-\mu_0 t},$$

where $N_0 = N(0)$. Hence, as $t \to \infty$, $N(t) \to \frac{\lambda}{\mu_0}$. So, if $N_0 \leq \frac{\lambda}{\mu_0}$, the total population at time t is bounded above by $\dfrac{\lambda}{\mu_0}$. Therefore, for any solution $\{S(0) > 0, \quad V(0) \geq 0, \quad I(0) \geq 0, \quad C(0) \geq 0, \quad \text{and} \quad T(0) \geq 0\}$ at $t > 0$ of the system in Eq. (3.2) of the total population that begins in $\mathbb{R}_+{}^5$ either remains in or approaches Ω asymptotically. Similarly, if $N_0 > 0$ then the total population will decrease and later approaches Ω asymptotically. Hence, the region Ω is positively invariant and attracting with respect to the model system in Eq. (3.2).

Model Steady State

In this section, we investigate the equilibrium points of the model. Equilibrium points are points where the state variables do not change with time. Hence, at equilibrium, the system in Eq. (3.2) becomes,

$$\begin{aligned}
\lambda(1-\omega) + \psi V - [\beta(I + \eta_1 C + \eta_2 T) + (\theta + \mu_0)]S &= 0, \\
\theta S - [(\mu_0 + \psi) + \beta(1-\varepsilon)(I + \eta_1 C + \eta_2 T)]V &= 0, \\
\beta(I + \eta_1 C + \eta_2 T)S + \beta(1-\varepsilon)(I + \eta_1 C + \eta_2 T)V - (\gamma_1 + \tau_1 + \mu_0)I &= 0, \\
\rho\gamma_1 I + \delta T - (\mu_o + \mu_1 + \tau_2)C &= 0, \\
\tau_1 I + \tau_2 C - (\delta + \sigma + \mu_0)T &= 0.
\end{aligned}$$

Disease-free Equilibrium (DFE)

At the disease-free equilibrium, we assume that there is no hepatitis B virus in the population and as a result, there is no transmission of the virus that will either lead to acute or chronic infection and hence no treatment of individuals in the population. Therefore, at the disease-free equilibrium, we

have $I^\star = C^\star = T^\star = 0$ so that

$$\lambda(1-\omega) + \psi V^\star - \theta S^\star - \mu_0 S^\star = 0, \tag{3.5}$$

$$\theta S^\star - \mu_0 V^\star - \psi V^\star = 0. \tag{3.6}$$

Solving Eq. (3.5) and Eq. (3.6) simultaneously, we obtain

$$\begin{aligned} S^\star &= \frac{\lambda(1-\omega)(\mu_0+\psi)}{\mu_0(\theta+\mu_0+\psi)}, \\ V^\star &= \frac{\theta\lambda(1-\omega)}{\mu_0(\theta+\mu_0+\psi)}. \end{aligned}$$

Therefore, the disease-free equilibrium is given as

$$E_0(S^\star, V^\star, I^\star, C^\star, T^\star) = \left(\frac{\lambda(1-\omega)(\mu_0+\psi)}{\mu_0(\theta+\mu_0+\psi)}, \frac{\theta\lambda(1-\omega)}{\mu_0(\theta+\mu_0+\psi)}, 0, 0, 0\right).$$

Basic Reproduction Number; $\mathbb{R}_0$

In this section, we compute the basic reproduction number, $\mathbb{R}_0$. The basic reproduction number denoted by $\mathbb{R}_0$ is the average number of secondary HBV infections caused by an individual infected patient during his/her entire period of infectiousness (Diekmann & Heesterbeek, 2000). We use the next generation matrix operator to compute the basic reproduction number. By the next generation matrix operator, the basic reproduction number is the spectral radius of the next-generation matrix denoted by $\pi(FV^{-1})$; where F is the rate at which secondary infection increases the infected compartment and V the rate at which infection progression and recovery decrease the infected compartment.

The basic reproduction number is significant non-dimensional quantity in hepatitis B virus transmission dynamics as it serves as the threshold in the study

of the infection both for predicting its outbreak and for evaluating its control strategies. Thus, whether an infection becomes persistent or dies out in the entire population depends on the value of the basic reproduction number $\mathbb{R}_0$. Moreover, the stability of both the disease-free and endemic equilibria can be analysed using $\mathbb{R}_0$. If $\mathbb{R}_0 < 1$, it means that every infected person will cause less than one secondary infection and hence the hepatitis B virus will die out and when $\mathbb{R}_0 > 1$, every infected person will cause more than one secondary infection and hence the hepatitis B virus will invades the entire population. From the model system in Eq. (3.2), we denote F_i to be the rate at which secondary infection increases the $\mathbf{i}^{th}$ infected compartment and by V_i the rate at which infection progression and recovery decrease the $\mathbf{i}^{th}$ compartment. It follows that the epidemic hepatitis B virus model is given as

$$\frac{dx}{dt} = F_i(x) - V_i(x).$$

Hence,

$$F_i = \begin{pmatrix} \beta\left(I + \eta_1 C + \eta_2 T\right) S + \beta\left(1-\varepsilon\right)\left(I + \eta_1 C + \eta_2 T\right) V \\ 0 \\ 0 \end{pmatrix} \quad \text{and}$$

$$V_i = \begin{pmatrix} \left(\gamma_1 + \tau_1 + \mu_0\right) I \\ -\rho\gamma_1 I - \delta T + \left(\mu_0 + \mu_1 + \tau_2\right) C \\ -\tau_1 I - \tau_2 C + \left(\delta + \sigma + \mu_0\right) T \end{pmatrix}.$$

Taking the Jacobian of F_i at the DFE, we have

$$\mathbb{F}_i = \begin{pmatrix} \frac{\beta\lambda(1-\omega)\chi}{\mu_0(\theta+\mu_0+\psi)} & \frac{\beta\lambda\eta_1(1-\omega)\chi}{\mu_0(\theta+\mu_0+\psi)} & \frac{\beta\lambda\eta_2(1-\omega)\chi}{\mu_0(\theta+\mu_0+\psi)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

where

$$\chi = (\mu_0 + \psi) + \theta\,(1-\varepsilon)\,.$$

Also, taking the Jacobian of V_i at the DFE, we have

$$\mathbb{V}_i = \begin{pmatrix} \gamma_1 + \tau_1 + \mu_0 & 0 & 0 \\ -\rho\gamma_1 & \mu_0 + \mu_1 + \tau_2 & -\delta \\ -\tau_1 & -\tau_2 & \delta + \sigma + \mu_0 \end{pmatrix}.$$

It follows that

$$\mathbb{R}_0 = \pi(\mathbb{F} \cdot \mathbb{V}^{-1}),$$

which gives

$$\mathbb{R}_0 = \mathbb{R}_1 + \mathbb{R}_2 + \mathbb{R}_3,$$

where

$$\mathbb{R}_1 = \frac{\beta\lambda\,(1-\omega)\,[(\mu_0+\psi)+\theta\,(1-\varepsilon)]}{\mu_0\,(\theta+\mu_0+\psi)\,(\gamma_1+\tau_1+\mu_0)},$$

$$\mathbb{R}_2 = \frac{\beta\lambda\eta_1\,(1-\omega)\,[(\mu_0+\psi)+\theta\,(1-\varepsilon)]\,(\rho\gamma_1\,(\delta+\sigma+\mu_0)+\delta\tau_1)}{\mu_0\,(\theta+\mu_0+\psi)\,(\gamma_1+\tau_1+\mu_0)\,[(\mu_0+\mu_1+\tau_2)\,(\delta+\sigma+\mu_0)-\delta\tau_2]},$$

$$\mathbb{R}_3 = \frac{\beta\lambda\eta_2\left(1-\omega\right)\left[\left(\mu_0+\psi\right)+\theta\left(1-\varepsilon\right)\right]\left(\rho\gamma_1\tau_2+\tau_1\left(\mu_0+\mu_1+\tau_2\right)\right)}{\mu_0\left(\theta+\mu_0+\psi\right)\left(\gamma_1+\tau_1+\mu_0\right)\left[\left(\mu_0+\mu_1+\tau_2\right)\left(\delta+\sigma+\mu_0\right)-\delta\tau_2\right]}.$$

The basic reproduction number, $\mathbb{R}_0$ is observed to be the sum of the reproduction number for the three infectious compartments. Thus $\mathbb{R}_1$ is the average number of secondary infection from the acutely infected compartment. Similarly, $\mathbb{R}_2$ is the average number of secondary infection from the chronically infected compartment whiles $\mathbb{R}_3$ represent that of the treatment compartment. This shows the effect each compartment had on the HBV transmission dynamics. When the transmission rate is zero ($\beta = 0$), then $\mathbb{R}_0 = 0$ and no acutely or chronically or treatment is reproducing any new cases of HBV infection. However, when no one show any symptoms of chronic HBV infection and no one is undergoing treatment of HBV disease ($\eta_1 = 0, \eta_2 = 0$); we have the reproduction of new infection from the acutely infected individuals only. Thus we cannot have chronic HBV infections without acute infection. Therefore, the reproduction number for both chronic infection and treatment cannot stand alone.

Endemic Equilibrium (EE)

In this section, we determine the endemic equilibrium point by solving the system in Eq. (3.2) simultaneously for the state variables. The endemic equilibrium points are the steady-state solutions where the hepatitis B virus cannot be eradicated but remains in the total population. At the endemic equilibrium, the following equations are satisfied:

$$\left.\begin{aligned}
\lambda\left(1-\omega\right)+\psi V^\star-\left[\beta\left(I^\star+\eta_1C^\star+\eta_2T^\star\right)+\left(\theta+\mu_0\right)\right]S^\star&=0,\\
\theta S^\star-\left[\left(\mu_0+\psi\right)+\beta\left(1-\varepsilon\right)\left(I^\star+\eta_1C^\star+\eta_2T^\star\right)\right]V^\star&=0,\\
\beta\left(I^\star+\eta_1C^\star+\eta_2T^\star\right)S^\star+\beta\left(1-\varepsilon\right)\left(I^\star+\eta_1C^\star+\eta_2T^\star\right)V^\star&\\
-\left(\gamma_1+\tau_1+\mu_0\right)I^\star&=0,\\
\rho\gamma_1I^\star+\delta T^\star-\left(\mu_0+\mu_1+\tau_2\right)C^\star&=0,\\
\tau_1I^\star+\tau_2C^\star-\left(\delta+\sigma+\mu_0\right)T^\star&=0.
\end{aligned}\right\} \quad (3.7)$$

Let assume with positive constant

$$\begin{aligned}
\varepsilon_0 &= \lambda(1-\omega), \\
\varepsilon_1 &= \theta + \mu_0, \\
\varepsilon_2 &= \mu_0 + \psi, \\
\varepsilon_3 &= \gamma_1 + \tau_1 + \mu_0, \\
\varepsilon_4 &= \mu_0 + \mu_1 + \tau_2, \\
\varepsilon_5 &= \delta + \sigma + \mu_0.
\end{aligned}$$

It follows that

$$\left.\begin{aligned}
\varepsilon_0 + \psi V^\star - \beta\left(I^\star + \eta_1 C^\star + \eta_2 T^\star\right) S^\star - \varepsilon_1 S^\star = 0, \\
\theta S^\star - \varepsilon_2 V^\star - \beta(1-\varepsilon)\left(I^\star + \eta_1 C^\star + \eta_2 T^\star\right) V^\star = 0, \\
\beta\left(I^\star + \eta_1 C^\star + \eta_2 T^\star\right) S^\star + \beta(1-\varepsilon)\left(I^\star + \eta_1 C^\star + \eta_2 T^\star\right) V^\star \\
-\varepsilon_3 I^\star = 0, \\
\rho\gamma_1 I^\star + \delta T^\star - \varepsilon_4 C^\star = 0, \\
\tau_1 I^\star + \tau_2 C^\star - \varepsilon_5 T^\star = 0.
\end{aligned}\right\} \tag{3.8}$$

So, making $T^\star$ the subject from the last equation of the system in Eq. (3.8), we obtain

$$T^\star = \frac{\tau_1 I^\star + \tau_2 C^\star}{\varepsilon_5}. \tag{3.9}$$

Substituting Eq. (3.9) into the fourth equation of the system in Eq. (3.8) and make $I^\star$ the subject, we obtain

$$I^\star = \phi_1 C^\star. \tag{3.10}$$

From Eq. (3.9), we thus have

$$T^\star = \phi_2 C^\star. \tag{3.11}$$

Substituting Eq. (3.10) and Eq. (3.11) into the third equation of the system in Eq. (3.8) gives

$$\left[\beta\left(\phi_1+\eta_1+\eta_2\phi_2\right)S^\star+\beta\left(1-\varepsilon\right)\left(\phi_1+\eta_1+\eta_2\phi_2\right)V^\star-\varepsilon_3\phi_1\right]C^\star = 0.$$

Here, $C^\star = 0$, which corresponds to the DFE determined in the previous section. The remaining part of the expression gives

$$\beta\phi_3 S^\star+\beta\phi_3\left(1-\varepsilon\right)V^\star-\varepsilon_3\phi_1 = 0,$$

where

$$\phi_3 = \phi_1+\eta_1+\eta_2\phi_2.$$

We thus has

$$S^\star = \phi_4-\left(1-\varepsilon\right)V^\star, \tag{3.12}$$

where $\phi_4 = \frac{\varepsilon_3\phi_1}{\beta\phi_3}$.

Substituting Eq. (3.12), Eq. (3.11) and Eq. (3.10) into the second equation of the system in Eq. (3.8) gives

$$V^\star = \frac{\phi_7}{\phi_5+\phi_6 C^\star}, \tag{3.13}$$

Theorem 1

The model system in Eq. (3.2)*:*

- *has a unique positive solution if* $\mathbb{R}_0 > 1$*;*
- *has two positive equilibria if and only if* $a_1 < 0$ *for* $\mathbb{R}_0 < 1$*;*
- *has backward bifurcation phenomenon at* $\mathbb{R}_0 = 1$*;*
- *otherwise has no positive endemic equilibrium.*

We also use numerical simulations to show the stability and existence of the endemic equilibrium.

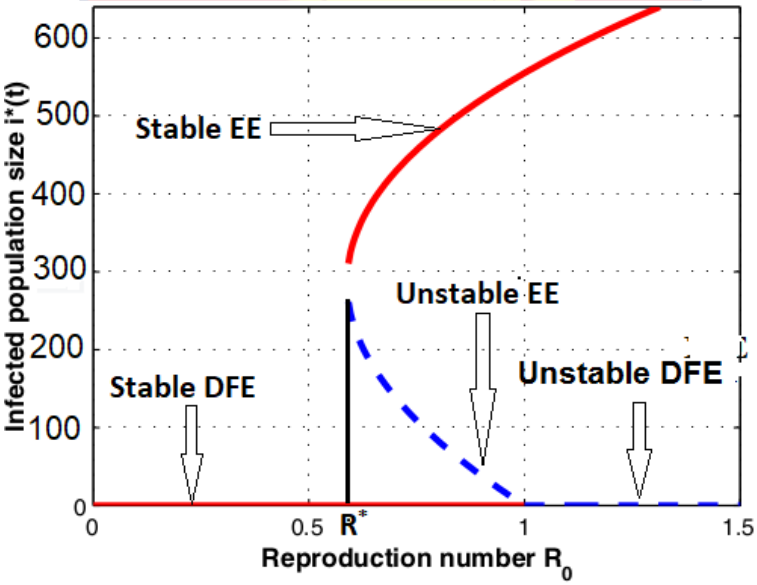

Figure 5: Backward bifurcation analysis of the model system in Eq. (3.2) with the transmission rate β chosen as the bifurcation parameter. The saddle-node bifurcation occurs at $\mathbb{R}_0 = \mathbb{R}^\star$, where the stable endemic equilibrium node intersects the other unstable endemic equilibrium.

Figure 5 show the bifurcation diagram of the model system in Eq. (3.2). The infectious population at equilibria against the basic reproduction number $\mathbb{R}_0$ shows a backward bifurcation when $\mathbb{R}_0 = 1$, leading to the existence of multiple endemic equilibria. The lower dashed curve with a negative slope indicates unstable endemic equilibria and the upper bold curve with a positive slope indicates locally stable endemic equilibria. The diagram shows that when the basic

reproduction number, $\mathbb{R}_0$ is less than one then eradication of the disease depends on the size of the population under consideration. However, reducing the saddle node bifurcation value $\mathbb{R}^\star$ called the $\mathbb{R}_0$ critical which is obtained by setting the discriminant of the quadratic polynomial in Eq. (3.15) to zero to gives

$$\mathbb{R}^\star = 1 - \left(\frac{a_1^2 + \phi_{10}}{4 a_2 \phi_9} \right),$$

where

$$\begin{aligned} \Psi_0 &= (\delta + \sigma + \mu_0)(\mu_0 + \mu_1 + \tau_2)[1 - \Upsilon], \\ \phi_9 &= \frac{1}{\mu_0 (\theta + \mu_0 + \psi)(\gamma_1 + \tau_1 + \mu_0) \Psi_0}, \\ \phi_{10} &= \frac{\theta \psi}{\mu_0 (\theta + \mu_0 + \psi)}, \end{aligned}$$

may result in controlling the HBV disease. This condition is guaranteed when the disease-free equilibrium state is globally asymptotically stable. Thus, an increase in the vaccine efficacy rate used to vaccinate individuals to a value of one $(\varepsilon = 1)$ will lead to the disappearance of the backward bifurcation curve. The biological meaning is that with an increase in the efficacy rate which corresponds with the extinction of the backward bifurcation curve, lowering $\mathbb{R}_0 < 1$ will be sufficient to eliminate the HBV disease from the population. Hence, $\mathbb{R}_0 < 1$ would be enough to make the disease-free equilibrium globally stable.

Local Stability of the Disease-free Equilibrium

In this section, we determine the local stability of the disease-free equilibrium by computing the eigenvalues of the linearized Jacobian matrix at the disease-free equilibrium.

Theorem 2

The disease-free equilibrium of the system in Eq. (3.2) *is locally asymptotically stable if* $\mathbb{R}_0 < 1$ *and unstable if* $\mathbb{R}_0 > 1$.

Proof. We use the Jacobian matrix associated with system Eq. (3.2) at the disease-free equilibrium and obtain

$$J_0 = \begin{pmatrix} w_1 & \psi & -\beta S^\star & -\beta\eta_1 S^\star & -\beta\eta_2 S^\star \\ \theta & w_2 & w_3 & w_4 & w_5 \\ 0 & 0 & w_6 & w_7 & w_8 \\ 0 & 0 & \rho\gamma_1 & w_9 & \delta \\ 0 & 0 & \tau_1 & \tau_2 & w_{10} \end{pmatrix}.$$

Where

$$\begin{aligned} w_1 &= -(\theta + \mu_0), \\ w_2 &= -(\mu_0 + \psi), \\ w_3 &= -\beta(1-\varepsilon)V^\star, \\ w_4 &= -\beta\eta_1(1-\varepsilon)V^\star, \\ w_5 &= -\beta\eta_2(1-\varepsilon)V^\star, \\ w_6 &= \beta S^\star + \beta(1-\varepsilon)V^\star - (\gamma_1 + \tau_1 + \mu_0), \\ w_7 &= \beta\eta_1(S^\star + V^\star(1-\varepsilon)), \\ w_8 &= \beta\eta_2(S^\star + V^\star(1-\varepsilon)), \\ w_9 &= -(\mu_0 + \mu_1 + \tau_2), \\ w_{10} &= -(\delta + \sigma + \mu_0). \end{aligned}$$

Upon determining the eigen values from the Jacobian matrix J_0, we have

$$(J_0 - \alpha I) = \begin{pmatrix} w_1 - \alpha & \psi & -\beta S^\circ & -\beta\eta_1 S^\circ & -\beta\eta_2 S^\circ \\ \theta & w_2 - \alpha & w_3 & w_4 & w_5 \\ 0 & 0 & w_6 - \alpha & w_7 & w_8 \\ 0 & 0 & \rho\gamma_1 & w_9 - \alpha & \delta \\ 0 & 0 & \tau_1 & \tau_2 & w_{10} - \alpha \end{pmatrix}.$$

The characteristic equation $|J_0 - \alpha I| = 0$ obtained from the Jacobian determinant with the eigen values $\alpha_i \, (i = 1, 2, 3, 4, 5)$ is given by

$$[(w_1 - \alpha)(w_2 - \alpha) - \theta\psi][X] = 0, \tag{3.17}$$

where

$$X = \begin{vmatrix} w_6 - \alpha & w_7 & w_8 \\ \rho\gamma_1 & w_9 - \alpha & \delta \\ \tau_1 & \tau_2 & w_{10} - \alpha \end{vmatrix}.$$

From equation Eq. (3.17), either

$$(w_1 - \alpha)(w_2 - \alpha) - \theta\psi = 0 \tag{3.18}$$

or

$$\begin{vmatrix} w_6 - \alpha & w_7 & w_8 \\ \rho\gamma_1 & w_9 - \alpha & \delta \\ \tau_1 & \tau_2 & w_{10} - \alpha \end{vmatrix} = 0.$$

From equation Eq. (3.18), we deduce

$$\alpha_1 = -\mu_0 < 0,$$
$$\alpha_2 = -(\theta + \mu_0 + \psi) < 0.$$

Let

$$A = \begin{pmatrix} w_6 - \alpha & w_7 & w_8 \\ \rho\gamma_1 & w_9 - \alpha & \delta \\ \tau_1 & \tau_2 & w_{10} - \alpha \end{pmatrix}$$

be a sub matrix of det(J_0). The characteristic equation $|A - \alpha I| = 0$ obtained from the Jacobian determinant with the eigen values $\alpha_i \, (i = 3, 4, 5)$ is given by

$$\alpha^3 + a_1\alpha^2 + a_2\alpha + a_0 \;=\; 0. \tag{3.19}$$

From Eq. (3.19), we have

$$\begin{aligned} a_1 &= \varrho_1 + 1 - \mathbb{R}_1, \\ a_2 &= \varrho_2 - \frac{\varrho_3}{\varrho_4}, \\ a_0 &= 1 - \mathbb{R}_0, \end{aligned}$$

where

$$\begin{aligned} \varrho_1 &= \mu_0\left(\theta + \mu_0 + \psi\right)\left[\left(\delta + \sigma + \mu_0\right) + \left(\mu_0 + \mu_1 + \tau_2\right)\right], \\ \varrho_2 &= \left(\gamma_1 + \tau_1 + \mu_0\right)\left[\left(\delta + \sigma + \mu_0\right) + \left(\mu_0 + \mu_1 + \tau_2\right)\right] \\ &\quad + \left(\delta + \sigma + \mu_0\right)\left(\mu_0 + \mu_1 + \tau_2\right), \\ \varrho_3 &= -\beta\lambda\left(1 - \omega\right)\left[\left(\mu_0 + \psi\right) + \theta\left(1 - \varepsilon\right)\right] \\ &\quad \times \left[\left(\delta + \sigma + \mu_0\right) + \left(\mu_0 + \mu_1 + \tau_2\right) + \rho\gamma_1\eta_1 + \tau_1\eta_2\right] - \delta\tau_2, \\ \varrho_4 &= \mu_0\left(\theta + \mu_0 + \psi\right). \end{aligned}$$

The coefficients $a_1 > 0$, $a_2 > 0$ and $a_0 > 0$ when $\mathbb{R}_1 < 1$, $\varrho_2 > \varrho_3$ and $\mathbb{R}_0 < 1$ respectively. Also,

$$a_1a_2 - a_0 \;=\; \varrho_2\left(\varrho_1 + 1\right) + \frac{\varrho_3\mathbb{R}_1}{\varrho_4} + \mathbb{R}_0 - \left(\frac{\varrho_1\varrho_3}{\varrho_4} + \varrho_2\mathbb{R}_1 + \frac{\varrho_3}{\varrho_4} + 1\right).$$

Hence $a_1a_2 - a_0 > 0$ is accomplished when $\varrho_2\left(\varrho_1 + 1\right) + \varrho_3\mathbb{R}_1 + \mathbb{R}_0 > \varrho_1\varrho_3 + \varrho_2\mathbb{R}_1 + \varrho_3 + 1$.

The Routh-Hurwitz theorem states that the equilibrium state of a system

will be asymptotically stable if and only if all the eigenvalues of the characteristic equation $|J_0 - I\alpha| = 0$ have a negative real part. From equation Eq. (3.18), α_1 and α_2 of the Jacobian matrix (J_0) all have negative real parts. Since $a_1 > 0$, $a_2 > 0$, $a_0 > 0$ and $a_1 a_2 - a_0 > 0$ when $\mathbb{R}_1 < 1$, $\varrho_2 > \varrho_3$, $\mathbb{R}_0 < 1$ and $\varrho_2(\varrho_1 + 1) + \varrho_3\mathbb{R}_1 + \mathbb{R}_0 > \varrho_1\varrho_3 + \varrho_2\mathbb{R}_1 + \varrho_3 + 1$ respectively, it follows that, the DFE state $E_0 = (S^\star, V^\star, 0, 0, 0)$ of the model system is locally asymptotically stable and this complete the proof.

□

Global Stability of Disease-free Equilibrium

We also apply the approach of (Castillo-Chavez et al., 2002) to prove the global stability of the disease-free equilibrium. This approach is stated in the Theorem below.

Theorem 3

If a model system can be written in the form:

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

where $X \in \mathbb{R}^m$ denotes the number of uninfected individuals and $I \in \mathbb{R}^n$ denotes the number of infected individuals including latent, acute, infectious e.t.c. $U_0 = (X^\star, 0)$ denotes the disease-free equilibrium of the system. Then, the conditions (H_1) and (H_2) below must satisfied to guarantee local asymptotic stability.

(H_1) for $\frac{dX}{dt} = F(X^\star, 0)$, $X^\star$ is globally asymptotically stable.

(H_2) $G(X, I) = AI - \hat{G}(X, 0) \geq 0$ for $(X, I) \in \Omega$, where $A = D_1 G(X^\star, 0)$ is a Metzler matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense and well-posed.

Then the fixed point $U_0 = (X^\star, 0)$ *is globally asymptotically stable equilibrium of the hepatitis B virus model system in Eq.* (3.2) *provided* $\mathbb{R}_0 < 1$.

Theorem 4

The disease-free equilibrium of the model system $E_0 = (S^\star, V^\star, 0, 0, 0)$ *is globally asymptotically stable if* $\mathbb{R}_0 < 1$ *and the conditions* (H_1) *and* (H_2) *are satisfied.*

Proof. From the model system in Eq. (3.2), $X \in \mathbb{R}^2 = (S, V)$ and $I \in \mathbb{R}^3 = (I, C, T)$. Hence for condition (H_1), we have

$$F(X, 0) = \begin{pmatrix} \lambda(1-\omega) + \psi V - (\theta + \mu_0) S \\ \theta S - (\mu_0 + \psi) V \end{pmatrix}.$$

So, for the equilibrium $U_0 = (X^\star, 0)$, the system reduces to

$$\begin{aligned} \frac{dS(t)}{dt} &= \lambda(1-\omega) + \psi V - (\theta + \mu_0) S, \\ \frac{dV(t)}{dt} &= \theta S - (\mu_0 + \psi) V. \end{aligned}$$

It follows that

$$F(X, 0) = \begin{pmatrix} -(\theta + \mu_0) & \psi \\ \theta & -(\mu_0 + \psi) \end{pmatrix}.$$

The characteristics polynomial of the system is given by

$$\alpha^2 + \alpha(2\mu_0 + \theta + \psi) + (\mu_0 + \theta)(\mu_0 + \psi)[1 - L] = 0, \qquad (3.20)$$

where

$$L = \frac{\theta\psi}{(\mu_0 + \theta)(\mu_0 + \psi)} < 1.$$

Since all the coefficients of the characteristics polynomial in Eq. (3.20) are positive, by the Routh-Hurwitz criterion the solutions to the characteristic polynomial have negative real parts. This means that the eigenvalues have negative real parts. Hence, $X^\star$ is always globally asymptotically stable. Also, applying Theorem 3 to the hepatitis B virus model system in Eq. (3.2) gives

$$\begin{aligned} G(X,I) &= AI - \hat{G}(X,I) \\ &= \begin{pmatrix} \Theta - (\gamma_1 + \tau_1 + \mu_0) & \Theta\eta_1 & \Theta\eta_2 \\ \rho\gamma_1 & -(\mu_0 + \mu_1 + \tau_2) & \delta \\ \tau_1 & \tau_2 & -(\delta + \sigma + \mu_0) \end{pmatrix} \begin{pmatrix} I \\ C \\ T \end{pmatrix} \\ &\quad - \begin{pmatrix} \beta\left(I + \eta_1 C + \eta_2 T\right)\left(S^\star - S\right) \\ \beta\left(1-\omega\right)\left(I + \eta_1 C + \eta_2 T\right)\left(V^\star - V\right) \\ 0 \end{pmatrix}, \end{aligned}$$

where $\Theta = \beta S^\star + \beta\left(1-\omega\right)V^\star$. So, A is a Metzler matrix with non-negative off diagonal elements. Also, it follows from Eq. (3.3) that, as $t \to \infty$, $(I, C, T) \to (0, 0, 0)$. Therefore, $\hat{G}(X, I) \geq 0$ and the disease-free equilibrium is globally asymptotically stable. □

Stability of the Endemic Equilibrium

In this section, we present a stability analysis of the endemic equilibrium point. However, the system in Eq. (3.2) gave rise to multiple endemic equilibrium points which shows a bifurcation phenomenon at $\mathbb{R}_0 = 1$. When the disease-free equilibrium is locally asymptotically stable for $\mathbb{R}_0 < 1$, then the endemic equilibrium co-exist with the disease-free equilibrium due to a backward bifurcation phenomenon of the system in Eq. (3.2). Also, when $\mathbb{R}_0 < 1$, the global stability of the disease-free equilibrium ensures that any endemic equilibrium that exists will be unstable. Therefore, the two endemic equilibria that exist for the case when $\mathbb{R}_0 < 1$ and $a_0 > 0$ are unstable. The occurrence of

a backward bifurcation plays an important role in the epidemiological control measures of hepatitis B virus, since an epidemic may persist at a steady-state even when $\mathbb{R}_0 < 1$. So, we are interested to know the properties of an endemic equilibrium for $\mathbb{R}_0 > 1$ by the use of Centre Manifold Theory. We shall establish the conditions necessary and sufficient on the parameter values that cause the bifurcation phenomenon to the system in Eq. (3.2) based on the used of Centre Manifold Theory proposed by Castillo-Chavez & Song (2004).

Theorem 5

Consider the following general system of ordinary differential equations with a parameter ϵ *such that*

$$\frac{dx}{dt} = f(x,\epsilon), \quad f:\mathbb{R}^n \times \mathbb{R} \mapsto \mathbb{R}, \quad \text{and} \quad f \in C^2(\mathbb{R}^n \times \mathbb{R}). \tag{3.21}$$

Without loss of generality, it is assumed that $x = 0$ *is an equilibrium for the system in Eq.* (3.21) *for all values of the parameter* ϵ, $(i.e \quad f(0,\epsilon) = 0)$. *We assume that*

(A_1) $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_i}, 0, 0\right)$ *is the linearized matrix of the system in Eq.* (3.21) *around the equilibrium point* $x = 0$ *with* ϵ *evaluated at zero which is the simple eigenvalue of* A *and all other eigenvalues of* A *have negative real parts.*

(A_2) *Matrix* A *has a non-negative right eigenvector* q *and a left eigenvector* v *corresponding to the zero eigenvalue. Let* f_k *be the* k^{th} *component of* f *and*

$$\left.\begin{aligned} a &= \sum_{i,j,k=1}^{5} v_k q_i q_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}, \\ b &= \sum_{i,k=1}^{5} v_k q_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \beta}. \end{aligned}\right\} \tag{3.22}$$

The local dynamics of the system in Eq. (3.21) *around* 0 *are totally determined by* a *and* b*.*

(i) In the case where $a > 0$, $b > 0$, *when* $\epsilon < 0$ *with* ϵ *close to zero,* $x = 0$ *is unstable; when* $0 \leq \epsilon \leq 1$, $x = 0$ *is unstable and there exists a negative and locally asymptotically stable equilibrium;*

(ii) In the case where $a < 0$, $b < 0$, *when* $\epsilon < 0$ *with* $|\epsilon|$ *close to zero,* $x = 0$ *is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 \leq \epsilon \leq 1$, $x = 0$ *is locally asymptotically stable and there exists a positive unstable equilibrium;*

(iii) In the case where $a > 0$, $b < 0$, *when* $\epsilon < 0$ *with* $|\epsilon|$ *close to zero,* $x = 0$ *is unstable and there exists a locally asymptotically stable negative equilibrium; when* $0 \leq \epsilon \leq 1$, $x = 0$ *is locally unstable and a positive unstable equilibrium occurs;*

(iv) In the case where $a < 0$, $b > 0$, *when* $\epsilon < 0$ *changes from negative to positive,* $x = 0$ *changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if* $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\epsilon = 0$*.*

Application of Centre Manifold Theory to Local Stability of Endemic Equilibrium

To apply the stable Centre Manifold Theory to the model system in Eq. (3.2), we change the state variables by letting $x_1 = S(t)$, $x_2 = V(t)$, $x_3 = I(t)$, $x_4 = C(t)$ and $x_5 = T(t)$ so that the total host population $N(t) = S(t) + V(t) + I(t) + C(t) + T(t)$ becomes $N(t) = x_1 + x_2 + x_3 + x_4 + x_5$. Furthermore, by using vector notation, $x = [S(t), V(t), I(t), C(t), T(t)]$, the system

can be written in the form

$$\frac{dx}{dt} = (f_1, f_2, f_3, f_4, f_5) \quad \text{as follows;}$$

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \lambda(1-\omega) + \psi x_2 - [\beta(x_3 + \eta_1 x_4 + \eta_2 x_5) + (\theta + \mu_0)]\, x_1, \\
\frac{dx_2}{dt} &= f_2 = \theta x_1 - [(\mu_0 + \psi) + \beta(1-\varepsilon)(x_3 + \eta_1 x_4 + \eta_2 x_5)]\, x_2, \\
\frac{dx_3}{dt} &= f_3 = \beta(x_3 + \eta_1 x_4 + \eta_2 x_5)\, x_1 + \beta(1-\varepsilon)(x_3 + \eta_1 x_4 + \eta_2 x_5)\, x_2 \\
&\quad - (\gamma_1 + \tau_1 + \mu_0)\, x_3, \\
\frac{dx_4}{dt} &= f_4 = \rho\gamma_1 x_3 - (\mu_0 + \mu_1 + \tau_2)\, x_4 + \delta x_5, \\
\frac{dx_5}{dt} &= f_5 = \tau_1 x_3 + \tau_2 x_4 - (\delta + \sigma + \mu_0)\, x_5.
\end{aligned}$$

The Jacobian matrix evaluated at the disease-free equilibrium

$$E_0 = (S^\star, V^\star, 0, 0, 0) \quad \text{with} \quad \beta = \beta^\star \quad \text{is given as}$$

$$J_1 = \begin{pmatrix}
-\varepsilon_1 & \psi & -\beta S^\star & -\beta\eta_1 S^\star & -\beta\eta_2 S^\star \\
\theta & -\varepsilon_2 & -w_3 & -w_4 & -w_5 \\
0 & 0 & w_6 & w_7 & w_8 \\
0 & 0 & \rho\gamma_1 & -\varepsilon_4 & \delta \\
0 & 0 & \tau_1 & \tau_2 & -\varepsilon_5
\end{pmatrix},$$

where

$$\begin{aligned} w_3 &= \beta\left(1-\varepsilon\right)V^{\star}, \\ w_4 &= \beta\eta_1\left(1-\varepsilon\right)V^{\star}, \\ w_5 &= \beta\eta_2\left(1-\varepsilon\right)V^{\star}, \\ w_6 &= \beta S^{\star}+\beta\left(1-\varepsilon\right)V^{\star}-\varepsilon_3, \\ w_7 &= \beta\eta_1\left(S^{\star}+V^{\star}\left(1-\varepsilon\right)\right), \\ w_8 &= \beta\eta_2\left(S^{\star}+V^{\star}\left(1-\varepsilon\right)\right). \end{aligned}$$

Choosing β as the bifurcation parameter and solving for $\beta=\beta^{\star}$ when $\mathbb{R}_0=1$, we obtain

$$\beta^{\star} = \frac{\mu_0\left(\theta+\mu_0+\psi\right)\left(\gamma_1+\tau_1+\mu_0\right)\Psi_0}{\Psi_5\left[\Psi_0+\eta_1\left(\rho\gamma_1\left(\delta+\sigma+\mu_0\right)+\delta\tau_1\right)+\eta_2\left(\rho\gamma_1\tau_2+\tau_1\left(\mu_0+\mu_1+\tau_2\right)\right)\right]},$$

with

$$\begin{aligned} \Psi_0 &= \left(\delta+\sigma+\mu_0\right)\left(\mu_0+\mu_1+\tau_2\right)\left(1-\Upsilon\right), \\ \Upsilon &= \frac{\delta\tau_2}{\left(\delta+\sigma+\mu_0\right)\left(\mu_0+\mu_1+\tau_2\right)}<1, \\ \Psi_5 &= \lambda\left(1-\omega\right)\left[\left(\mu_0+\psi\right)+\theta\left(1-\varepsilon\right)\right]. \end{aligned}$$

The Jacobian matrix J_1 of the linearized system has a simple zero eigenvalue and all other eigenvalues have negative real parts. Hence, the Centre Manifold Theory can be used to analyse the stability dynamics of the model system in Eq. (3.2). For the case when $\mathbb{R}_0=1$, it can be shown that the Jacobian matrix J_1 has a right eigenvector $q=\left(q_1,q_2,q_3,q_4,q_5\right)^T$ corresponding to the zero

eigenvalue obtain by solving

$$\begin{pmatrix} -\varepsilon_1 & \psi & -\beta S^\star & -\beta\eta_1 S^\star & -\beta\eta_2 S^\star \\ \theta & -\varepsilon_2 & -w_3 & -w_4 & -w_5 \\ 0 & 0 & w_6 & w_7 & w_8 \\ 0 & 0 & \rho\gamma_1 & -\varepsilon_4 & \delta \\ 0 & 0 & \tau_1 & \tau_2 & -\varepsilon_5 \end{pmatrix} \begin{pmatrix} q_1 \\ q_2 \\ q_2 \\ q_4 \\ q_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{3.23}$$

Solving Eq. (3.23) simultaneously for q_1, q_2, q_3, q_4 and q_5 in terms of q_4, we have

$$q_1 = \left[\frac{\beta\lambda(1-\omega)[\Psi_0+\Psi_1+\Psi_2+\Psi_3]}{\mu_0(\theta+\mu_0+\psi)[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1]}\right] q_4,$$

$$q_2 = \left[\frac{\beta\lambda(1-\omega)[\Psi_0+\Psi_1+\Psi_2+\Psi_4]}{\mu_0(\theta+\mu_0+\psi)[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1]}\right] q_4,$$

$$q_3 = \left[\frac{\Psi_0}{\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1}\right] q_4,$$

$$q_5 = \left[\frac{\rho\gamma_1\tau_2+\tau_1(\mu_0+\mu_1+\tau_2)}{\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1}\right] q_4,$$

we let $q_4 = 1,$

and

$$\begin{aligned}
\Psi_0 &= (\delta+\sigma+\mu_0)(\mu_0+\mu_1+\tau_2)(1-\Upsilon), \\
\Psi_1 &= \eta_1(\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1), \\
\Psi_2 &= \eta_2(\rho\gamma_1\tau_2+\tau_1(\mu_0+\mu_1+\tau_2)), \\
\Psi_3 &= \left[(\mu_0+\psi)^2+\left[(\theta+\mu_0)(1-\varepsilon)+(\theta+\mu_0)^2(\mu_0+\psi)(1-\varepsilon)\right]\right], \\
\Psi_4 &= \left[(\mu_0+\psi)+(\theta+\mu_0)(1-\varepsilon)\right].
\end{aligned}$$

Similarly, the components of the left eigenvectors of the Jacobian matrix J_1 corresponding to the zero eigenvalue is given by $v = (v_1, v_2, v_3, v_4, v_5)^T$ and can be obtain from

$$\begin{pmatrix} v_1 & v_2 & v_3 & v_4 & v_5 \end{pmatrix} \begin{pmatrix} -\varepsilon_1 & \psi & -\beta S^\star & -\beta\eta_1 S^\star & -\beta\eta_2 S^\star \\ \theta & -\varepsilon_2 & -w_3 & -w_4 & -w_5 \\ 0 & 0 & w_6 & w_7 & w_8 \\ 0 & 0 & \rho\gamma_1 & -\varepsilon_4 & \delta \\ 0 & 0 & \tau_1 & \tau_2 & -\varepsilon_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Solving the system above simultaneously for v_1, v_2, v_3, v_4 and v_5 in terms of v_3, we obtain

$$v_1 = v_2 = 0,$$

if and only if

$$\theta\psi\left[1-\nu^\star\right] = 0,$$

where

$$\nu^\star = \frac{(\theta+\mu_0)(\mu_0+\psi)}{\theta\psi},$$

and

$$v_4 = \left[\frac{\beta\Psi_5\left[\eta_1\left(\delta+\sigma+\mu_0\right)+\eta_2\tau_2\right]}{\mu_0\left(\theta+\mu_0+\psi\right)\Psi_0}\right]v_3,$$

$$v_5 = \left[\frac{\beta\Psi_5\left[\delta\eta_1+\eta_2\left(\mu_0+\mu_1+\tau_2\right)\right]}{\mu_0\left(\theta+\mu_0+\psi\right)\Psi_0}\right]v_3,$$

we let

$$v_3 = 1 \quad .$$

Computation of a and b

From the transformed system, the associated non-zero partial derivatives of f evaluated at DFE which we need in the computation of a are given as

$$\frac{\partial^2 f_3(0,0)}{\partial x_1\partial x_3} = \frac{\partial^2 f_3(0,0)}{\partial x_3\partial x_1} = \beta, \quad \frac{\partial^2 f_1(0,0)}{\partial x_1\partial x_3} = \frac{\partial^2 f_1(0,0)}{\partial x_3\partial x_1} = -\beta,$$

$$\frac{\partial^2 f_3(0,0)}{\partial x_1\partial x_4} = \frac{\partial^2 f_3(0,0)}{\partial x_4\partial x_1} = \beta\eta_1, \quad \frac{\partial^2 f_1(0,0)}{\partial x_1\partial x_4} = \frac{\partial^2 f_1(0,0)}{\partial x_4\partial x_1} = -\beta\eta_1,$$

$$\frac{\partial^2 f_3(0,0)}{\partial x_1\partial x_5} = \frac{\partial^2 f_3(0,0)}{\partial x_5\partial x_1} = \beta\eta_2, \quad \frac{\partial^2 f_1(0,0)}{\partial x_1\partial x_5} = \frac{\partial^2 f_1(0,0)}{\partial x_5\partial x_1} = -\beta\eta_2,$$

$$\frac{\partial^2 f_3(0,0)}{\partial x_2\partial x_3} = \frac{\partial^2 f_3(0,0)}{\partial x_3\partial x_2} = \beta\left(1-\varepsilon\right),$$

$$\frac{\partial^2 f_3(0,0)}{\partial x_2\partial x_4} = \frac{\partial^2 f_3(0,0)}{\partial x_4\partial x_2} = \beta\eta_1\left(1-\varepsilon\right),$$

$$\frac{\partial^2 f_3(0,0)}{\partial x_2\partial x_5} = \frac{\partial^2 f_3(0,0)}{\partial x_5\partial x_2} = \beta\eta_2\left(1-\varepsilon\right),$$

$$\frac{\partial^2 f_2(0,0)}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2(0,0)}{\partial x_3 \partial x_2} = -\beta(1-\varepsilon),$$

$$\frac{\partial^2 f_2(0,0)}{\partial x_2 \partial x_4} = \frac{\partial^2 f_2(0,0)}{\partial x_4 \partial x_2} = -\beta\eta_1(1-\varepsilon),$$

$$\frac{\partial^2 f_2(0,0)}{\partial x_2 \partial x_5} = \frac{\partial^2 f_2(0,0)}{\partial x_5 \partial x_2} = -\beta\eta_2(1-\varepsilon),$$

and all the other second-order partial derivatives are equal to zero.

From

$$a = \sum_{i,j,k=1}^{5} v_k q_i q_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}, \quad \text{it follows that}$$

$$a = v_3 \sum_{i,j=1}^{5} q_i q_j \frac{\partial^2 f_3(0,0)}{\partial x_i \partial x_j}.$$

Hence,

$$a = 2v_3 \Big\{ \beta q_1 q_3 + \beta\eta_1 q_1 q_4 + \beta\eta_2 q_1 q_5 + \beta(1-\varepsilon) q_2 q_3 + \beta\eta_1(1-\varepsilon) q_2 q_4 + \beta\eta_2(1-\varepsilon) q_2 q_5 \Big\}.$$

By substitution, we obtain

$$\beta q_1 q_3 = \frac{2\beta^2\lambda(1-\omega)\left[\Psi_0+\Psi_1+\Psi_2+\Psi_3\right]\Psi_0}{\mu_0(\theta+\mu_0+\psi)\left[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1\right]^2},$$

$$\beta\eta_1 q_1 q_4 = \frac{2\beta^2\eta_1\lambda(1-\omega)\left[\Psi_0+\Psi_1+\Psi_2+\Psi_3\right]}{\mu_0(\theta+\mu_0+\psi)\left[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1\right]},$$

$$\beta\eta_2 q_1 q_5 = \frac{2\beta^2\eta_2\lambda(1-\omega)\left[\Psi_0+\Psi_1+\Psi_2+\Psi_3\right]\left[\rho\gamma_1\tau_2+\tau_1(\mu_0+\mu_1+\tau_2)\right]}{\mu_0(\theta+\mu_0+\psi)\left[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1\right]^2},$$

$$\beta(1-\varepsilon)q_2 q_3 = \frac{2\beta^2(1-\varepsilon)\lambda(1-\omega)\left[\Psi_0+\Psi_1+\Psi_2+\Psi_4\right]\Psi_0}{\mu_0(\theta+\mu_0+\psi)\left[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1\right]^2},$$

$$\beta(1-\varepsilon)\eta_1 q_2 q_4 = \frac{2\beta^2\eta_1(1-\varepsilon)\lambda(1-\omega)\left[\Psi_0+\Psi_1+\Psi_2+\Psi_4\right]}{\mu_0(\theta+\mu_0+\psi)\left[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1\right]},$$

$$\beta\eta_2(1-\varepsilon)q_2 q_3 = 2\beta^2\eta_2(1-\varepsilon)\lambda(1-\omega)\frac{\left[\Psi_0+\Psi_1+\Psi_2+\Psi_4\right]\left[\rho\gamma_1\tau_2+\tau_1(\mu_0+\mu_1+\tau_2)\right]}{\mu_0(\theta+\mu_0+\psi)\left[\rho\gamma_1(\delta+\sigma+\mu_0)+\delta\tau_1\right]^2}.$$

Therefore, $a > 0$.

From the transformed system, the associated non-zero partial derivatives of f evaluated at DFE which we need in the computation of b are given as

$$\frac{\partial^2 f_3}{\partial x_3\partial\beta} = \frac{\Psi_5}{\mu_0(\theta+\mu_0+\psi)},$$

$$\frac{\partial^2 f_3}{\partial x_4\partial\beta} = \frac{\Psi_5\eta_1}{\mu_0(\theta+\mu_0+\psi)},$$

$$\frac{\partial^2 f_3}{\partial x_5\partial\beta} = \frac{\Psi_5\eta_2}{\mu_0(\theta+\mu_0+\psi)}.$$

From

$$b = \sum_{i,k=1}^{5} v_k q_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \beta}, \quad \text{it follows that}$$

$$b = v_3 \sum_{i=1}^{5} q_i \frac{\partial^2 f_3(0,0)}{\partial x_i \partial \beta}.$$

Hence,

$$b = v_3 \left[q_3 \frac{\partial^2 f_3(0,0)}{\partial x_3 \partial \beta} + q_4 \frac{\partial^2 f_3(0,0)}{\partial x_4 \partial \beta} + q_5 \frac{\partial^2 f_3(0,0)}{\partial x_5 \partial \beta} \right].$$

By substitution, we obtain

$$\begin{aligned} b = & \frac{\Psi_5 \eta_1}{\mu_0 (\theta + \mu_0 + \psi)} \\ & + \frac{\Psi_5 \Psi_0}{\mu_0 [\rho \gamma_1 (\delta + \sigma + \mu_0) + \delta \tau_1] (\theta + \mu_0 + \psi)} \\ & + \frac{\Psi_5 \eta_2 [\rho \gamma_1 \tau_2 + \tau_1 (\mu_0 + \mu_1 + \tau_2)]}{\mu_0 [\rho \gamma_1 (\delta + \sigma + \mu_0) + \delta \tau_1] (\theta + \mu_0 + \psi)}. \end{aligned}$$

Hence, $b > 0$.

Since $a > 0$ and $b > 0$ holds when $\mathbb{R}_0 = 1$ as stated in Theorem 5 above, then the model system in Eq. (3.2) undergoes a backward bifurcation at $\mathbb{R}_0 = 1$ and has a negative unstable endemic equilibrium point ($E^\star$) which becomes positive and locally asymptotically stable when $\mathbb{R}_0 = 1$. Thus, multiple equilibria exist. This means that $\mathbb{R}_0 < 1$ does not guarantee the disease will die out but much effort should be done to keep the $\mathbb{R}_0 < 1$ more below unity. Otherwise, the system will exhibit a forward bifurcation. That is the disease-free equilibrium becomes unstable and the endemic equilibrium becomes locally asymptotically stable as $\mathbb{R}_0$ changes values from less than one to values slightly greater than one. The cause of backward bifurcation in the model is as a result of the imperfect vaccination. Imperfect vaccination, just like reinfection of any infectious

disease produces three categories of protection with different susceptibilities to the hepatitis B virus disease which may, in turn, lead to the backward bifurcation phenomenon.

Chapter Summary

In this chapter, we looked at the model formulation of hepatitis B virus transmission dynamics by extending the model proposed by J. Zhang & Zhang (2018) to incorporate imperfect vaccination, perfect vaccination and treatment as control strategies. The basic model assumptions together with the model flowchart and the various state variables, parameters and their description were given in detailed. Since the model system monitors human population, we proved that all the state variables and their solutions are non-negative at all-time t and bounded above by a certain limit $\frac{\lambda}{\mu_0}$ above which the human population cannot exceed. The system in Eq. (3.2) has two non-negative equilibrium points which include; the disease-free equilibrium (DFE) denoted by $E^{\star}$ and the endemic equilibrium (EE). The two steady states influence the behaviour of the disease transmission dynamics in a community. Even though there could be infinitely many different initial distributions of hepatitis B virus disease in a community, these equilibrium points are the final reachable states. We also determine the stabilities of these equilibrium points using the basic reproduction number, $\mathbb{R}_0$. Stability analysis from the model system shows that the disease-free equilibrium is both locally asymptotically stable by the Routh-Hurwitz criterion and globally asymptotically stable using the Castillo-Chavez, Feng and Huang approach. We conclude the chapter by using the Centre Manifold Theory to proved that the model system has a backward bifurcation phenomenon as a result of the imperfect vaccination.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

In this chapter, numerical simulations of the hepatitis B virus model dynamics in the presence of regular interventions were considered and discuss the results obtained. Parameter values from literature and some estimated parameter values were used for the spread of the hepatitis B virus disease. Numerical simulations were conducted using Matlab. The objective is to verify the analytical results and also to demonstrate the model solutions that were obtained in Chapter THREE. This will help in determining future trends of hepatitis B virus disease transmission dynamics and its preventive measures.

Sensitivity analysis of the model system in Eq. (3.2) was also performed for the following parameters: transmission rate β, successful immunized proportion rate ω, rate of waning vaccine-induced immunity ψ, the vaccination rate of susceptible individuals θ, vaccine efficacy rate ε, reduced transmission rate relative to chronic infections η_1, reduced transmission rate relative to treatment η_2, acute infection progressive rate γ_1, unsuccessfully treatment rate δ, successful treatment rate σ, treatment rate of acute infection τ_1, treatment rate of chronic carriers τ_2, natural death rate μ_0, HBV-induced death rate μ_1 and the average probability of individuals failing to clear an acute infection rate ρ to know which parameter contributed most towards the hepatitis B virus transmission.

Numerical Analysis

The mathematical analysis of the hepatitis B virus epidemic model with nonlinear ordinary differential equations is presented. To observe the effects of the parameters used in this hepatitis B virus model dynamics in Figure 3.2 leads to several numerical simulations by varying the values of the parameters given in

Table 6 which also result in the variability of the values $\mathbb{R}_0 < 1$ and $\mathbb{R}_0 > 1$ respectively. The initial conditions of the state variables are given to be $S(0) = 500$, $V(0) = 450$, $I(0) = 350$, $C(0) = 250$, $T(0) = 200$ and the rest of the parameters and their values are presented in Table 6 below.

Table 6: **Parameters and their values**

Parameter	Standard value/year	Source
λ	0.0096	(J. Zhang & Zhang, 2018)
μ_0	0.0096	(J. Zhang & Zhang, 2018)
μ_1	0.025	(Desta & Koya, 2019)
β	0.017	(Desta & Koya, 2019)
σ	$0.06 \leq \sigma \leq 0.6$	(J. Zhang & Zhang, 2018)
γ_1	4	(Zhao et al., 2000)
τ_1	0.0576	(J. Zhang & Zhang, 2018)
τ_2	0.0936	(J. Zhang & Zhang, 2018)
ω	0.65	(J. Zhang & Zhang, 2018)
ρ	0.885	(Hahné et al., 2004)
δ	0.2323	(J. Zhang & Zhang, 2018)
ψ	0.1	(Edmunds et al., 1996b)
η_1	0.4002	(J. Zhang & Zhang, 2018)
η_2	1.7352	(J. Zhang & Zhang, 2018)
θ	0.4	(Desta & Koya, 2019)
ε	$0 \leq \varepsilon \leq 1$	(Magpantay et al., 2014)

Numerical Results in the Presence of Perfect Vaccination

Figure 6 demonstrate how the reproduction number, $\mathbb{R}_0$ is evolve with a vaccination rate $\theta = 0.4$, treatment rate $\sigma = 0.6$ and a strong vaccine efficacy rate $\varepsilon = 1$. With other parameter values stated in Table 6 above, we observe that the model system settles at the disease-free state with $\mathbb{R}_0 = 0.3122$. At the disease-free state, all the infective (acutely infected, chronic carriers and treatment) compartments tend to zero, but because of the constant recruitment

of new individuals into the susceptible population, the susceptible compartment shows a downward sloping curve that decreases, attain minimum and continues to approach the x-axis asymptotically because of individuals moving to the vaccination compartment while the vaccination compartment approaches the x-axis asymptotically due to the presence of individuals being vaccinated. Figure 6 has also confirmed the local and global stability of the hepatitis B virus model at the disease-free equilibrium state. The biological meaning is that the hepatitis B virus disease will die out of the total population in the short-run period, say three years.

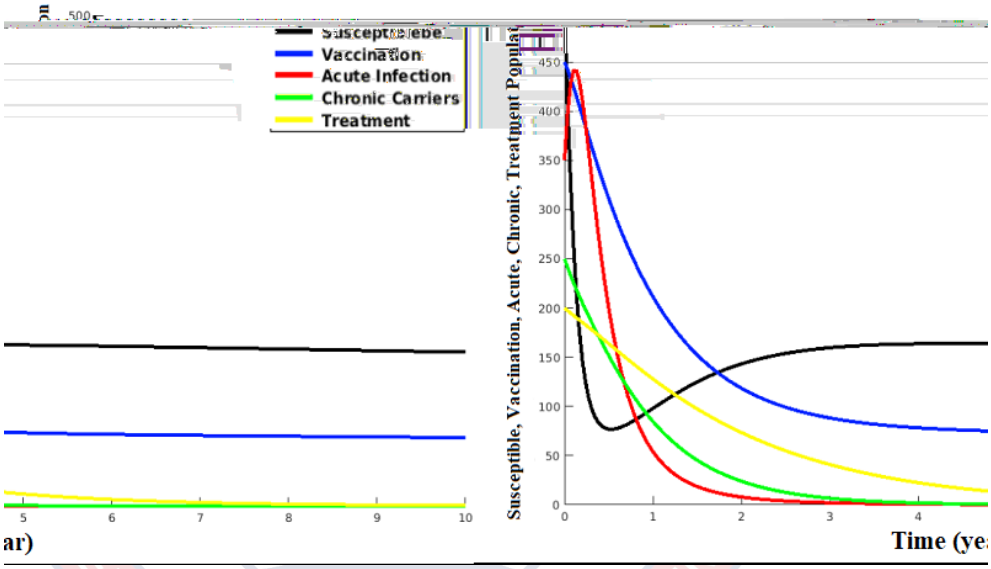

Figure 6: Numerical Simulation of SVICTR Model for $\mathbb{R}_0 > 1$.

To further investigate the evolution of the reproduction number with the vaccination rate θ, treatment rate σ and vaccine efficacy rate, ε, we vary the values of these three parameters (θ, σ and ε). The results are shown in Figure 7. The graph in Figure 7 above also shows the model system 3.2 attained the endemic equilibrium state with the reproduction number, $\mathbb{R}_0 = 8.7022$ base on the parameter values in Table 6. The susceptible compartment started to decrease at the initial stage, attain minimum and tend to increase at a constant rate which depicts the presence of hepatitis B virus disease on the susceptible

individuals' population as shown in Figure 7 below. Similarly, the presence of the hepatitis B virus has increased the number of individuals in the infective compartments as depict in Figure 7 below.

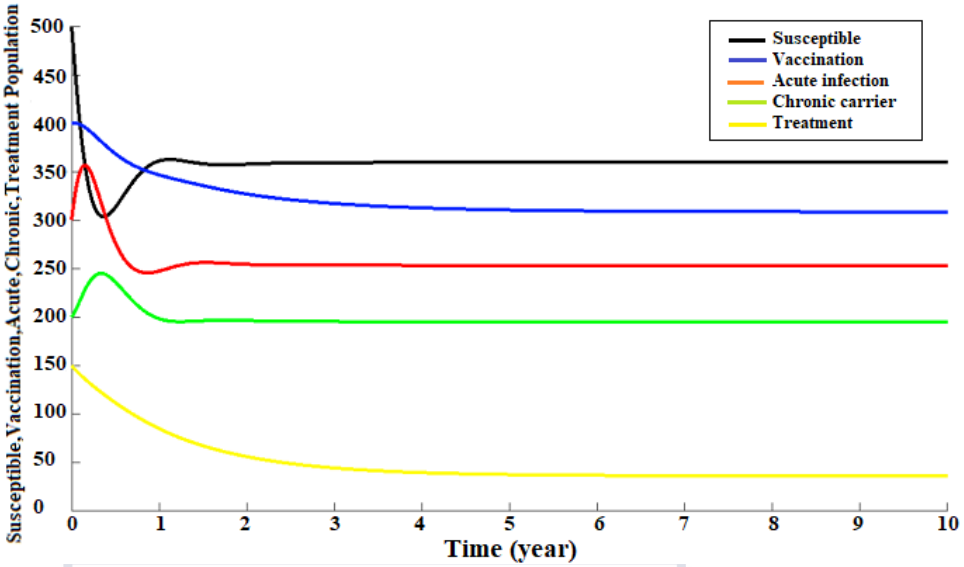

Figure 7: Numerical Simulation of SVICTR Model for $\mathbb{R}_0 > 1$.

Effect of Perfect Vaccination on Acutely Infected and Chronic Carriers Population

In Figures 8 and 9 below, we have noticed that as we increase the vaccination rate from 0.6 to 0.9 with a vaccine efficacy rate, say $\varepsilon = 1$, there is a corresponding decrease in both the acutely infected and chronic carriers populations. This implies that the majority of the individuals in the susceptible compartment have been vaccinated causing a reduction in the number of individuals who get infected with the hepatitis B virus disease. The simulation results in Figures 8 and 9 below demonstrate the important role perfect vaccination play in controlling the spread of hepatitis B virus disease in the population.

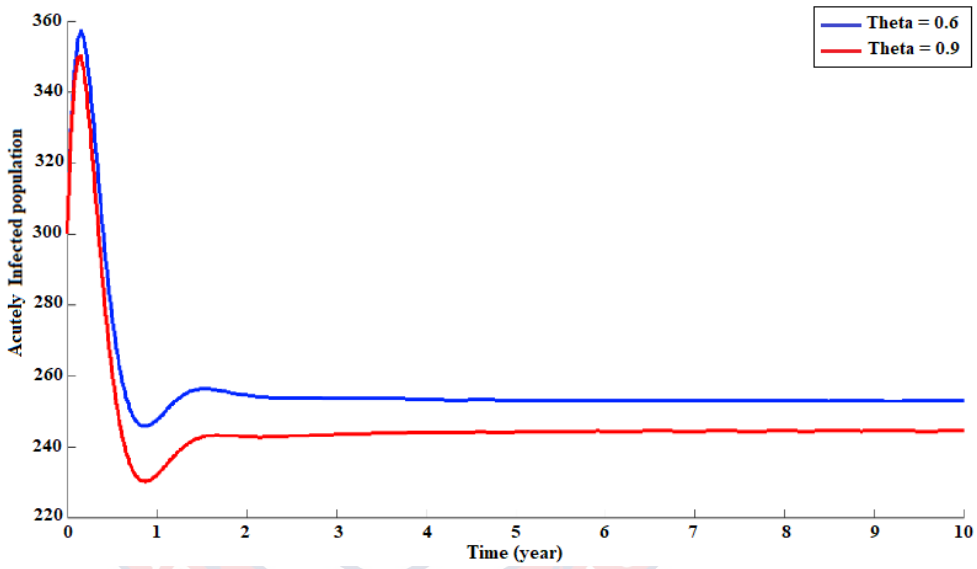

Figure 8: Simulation Results showing the Effect of varying the Vaccination rate ($\theta = 0.6$, $\theta = 0.9$) with Vaccine Efficacy rate, $\varepsilon = 1$ on the Acutely Infected population. The rest of the parameter values, as stated in Table 6.

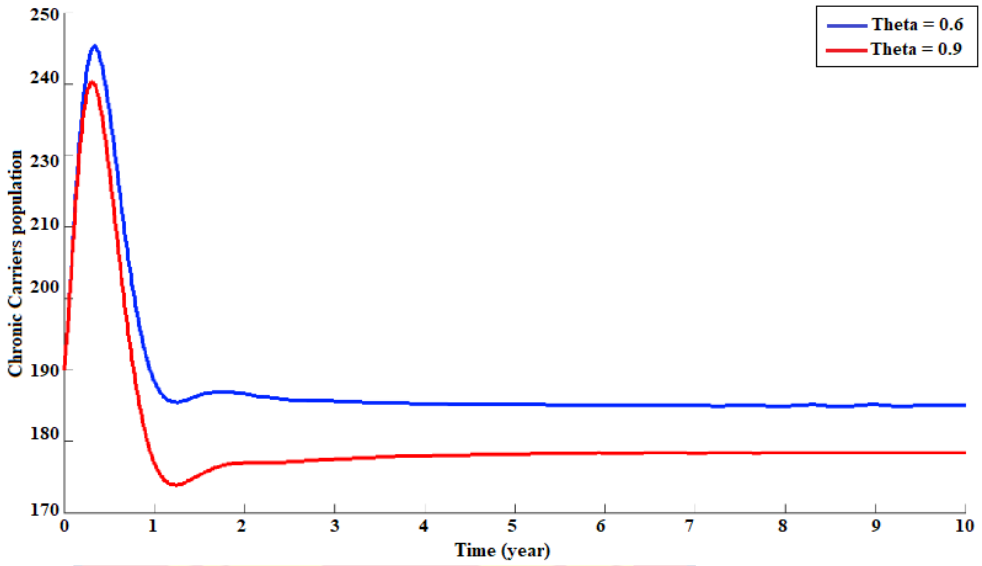

Figure 9: Simulation Results showing the Effect of varying the Vaccination rate, ($\theta = 0.6$, $\theta = 0.9$) with Vaccine Efficacy rate, $\varepsilon = 1$ on the chronic carriers population. The rest of the parameter values, as stated in Table 6.

Effect of Imperfect Vaccination on Acutely Infected and Chronic Carriers Population

In Figures 10 and 11 below, we noticed that as we increased the vaccination rate from 0.6 to 0.9 with a weak vaccine efficacy rate, say $\varepsilon = 0.1$, there is a small corresponding decreased in both the acutely infected and chronic carriers populations. This implies that, though the majority of the individuals in the susceptible compartment have been vaccinated with the hepatitis B vaccine, only a small percentage of these individuals vaccinated are protected against the hepatitis B virus. Hence, a small reduction in the number of individuals who get infected with hepatitis B virus disease. The simulation results in Figures 10 and 11 below demonstrate the important role imperfect vaccination play in preventing the spread of hepatitis B virus disease in the population.

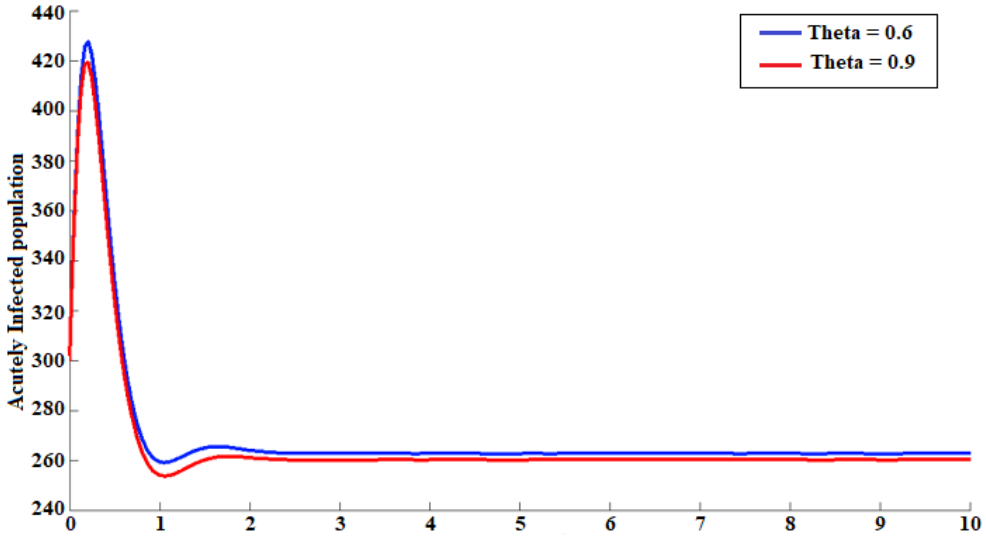

Figure 10: Simulation Results showing the Effect of varying the Vaccination rate ($\theta = 0.6$, $\theta = 0.9$) with Vaccine Efficacy rate, $\varepsilon = 0.1$ on the Acutely Infected population. The rest of the parameter values, as stated in Table 6.

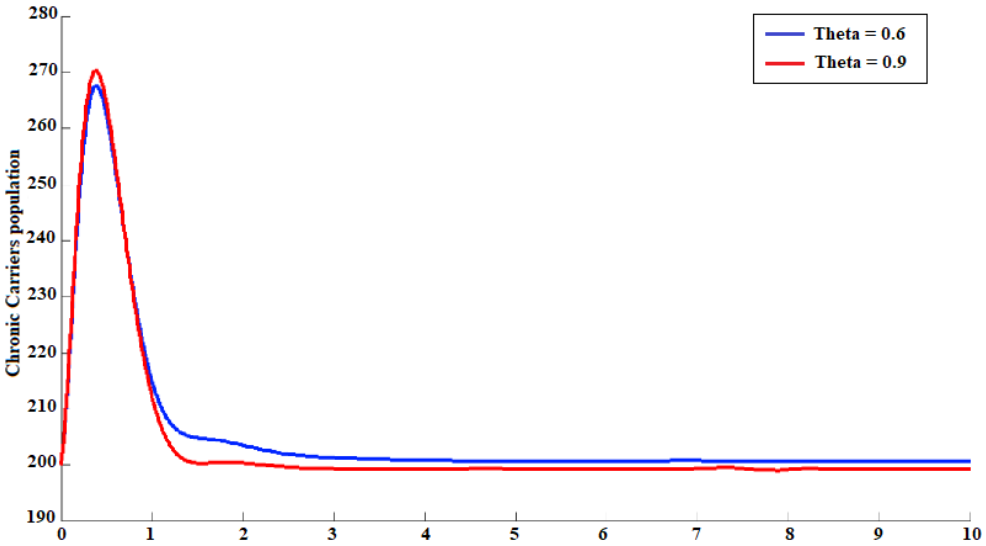

Figure 11: Simulation Results showing the Effect of varying the Vaccination rate (ie $\theta = 0.6$, $\theta = 0.9$) with Vaccine Efficacy rate, $\varepsilon = 0.1$ on the Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

Effect of Treatment on Acutely Infected and Chronic Carriers Population

It was observed in Figures 12 and 13 below that as the treatment rate, σ increases from $\sigma = 0.6$ to $\sigma = 0.9$, there is a corresponding decreased in both acutely in-

fected and chronic carriers population sizes respectively. This demonstrates that the treatment of acutely infected and chronic carriers individuals has an impact on eradicating the hepatitis B virus disease. Hence, the general public should be educated on the importance of seeking medical treatment when infected with the hepatitis B virus to help eliminate the disease.

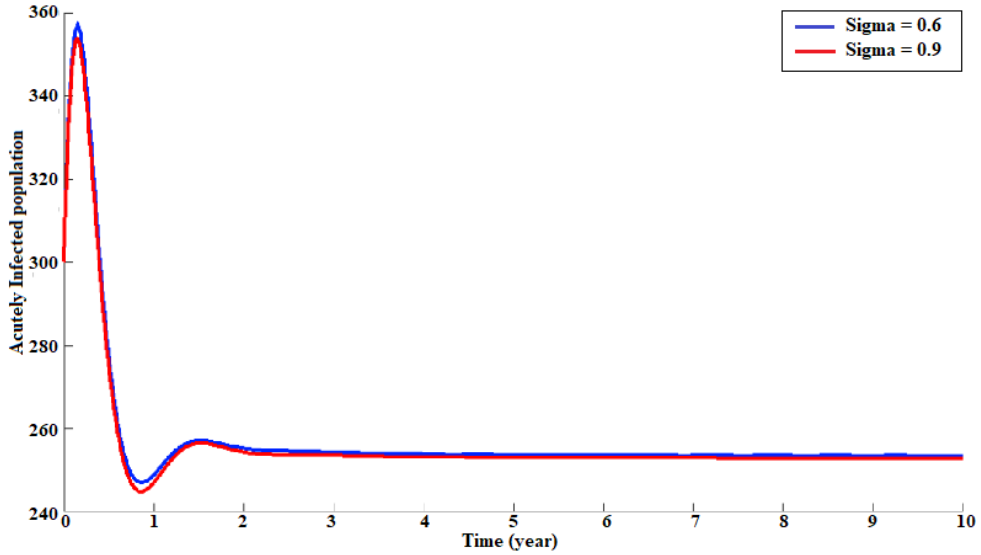

Figure 12: Simulation Results showing the Effect of varying the Treatment rate (ie $\sigma = 0.6$, $\sigma = 0.9$) on the Acutely Infected population. The rest of the parameter values, as stated in Table 6.

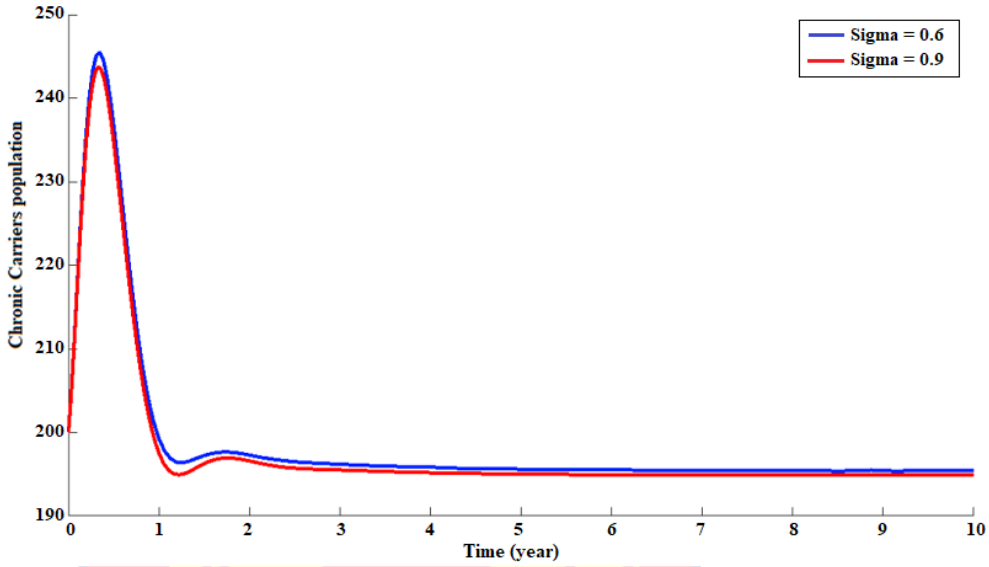

Figure 13: Simulation Results showing the Effect of varying the Treatment rate (ie $\sigma = 0.6$, $\sigma = 0.9$) on the Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

Effect of Waning Vaccination on Susceptible, Acutely Infected and Chronic Carriers Population

Figures 14, 15 and 16 below depicts the effect of individuals waning off their vaccine. This further justifies the important role vaccination plays in reducing the incidence of hepatitis B virus infection in the population. It was noticed that when the waning rate increases from 0.1 to 0.9, the chance of an individual been infected with the disease also increases as depicted in Figure 14 below. Similarly, an increase in the rate at which individuals wane their vaccine leads to a higher probability of being acutely infected as depicted in Figure 15 below. Furthermore, an increase in the rate at which individuals wane their vaccine leads to a higher probability of progressing to chronic carrier stage as depicted in Figure 16 below. More precisely, as the waning rate increases the number of susceptible individuals who become infected as well as individuals who were acutely infected progressing to chronic carrier stage increases.

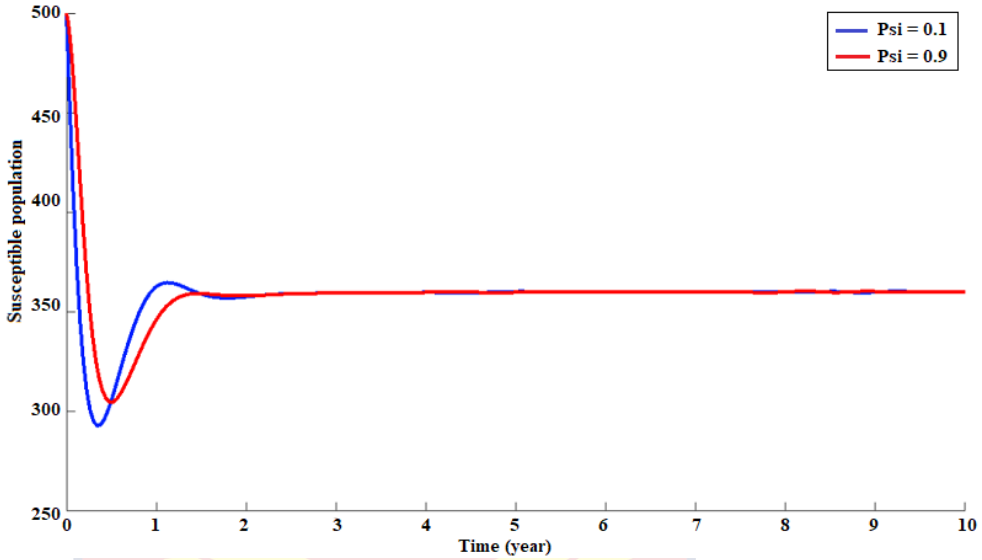

Figure 14: Simulation Results showing the Effect of varying the Waning Immunity rate (ie $\psi = 0.1$, $\psi = 0.9$) on the Susceptible population. The rest of the parameter values, as stated in Table 6.

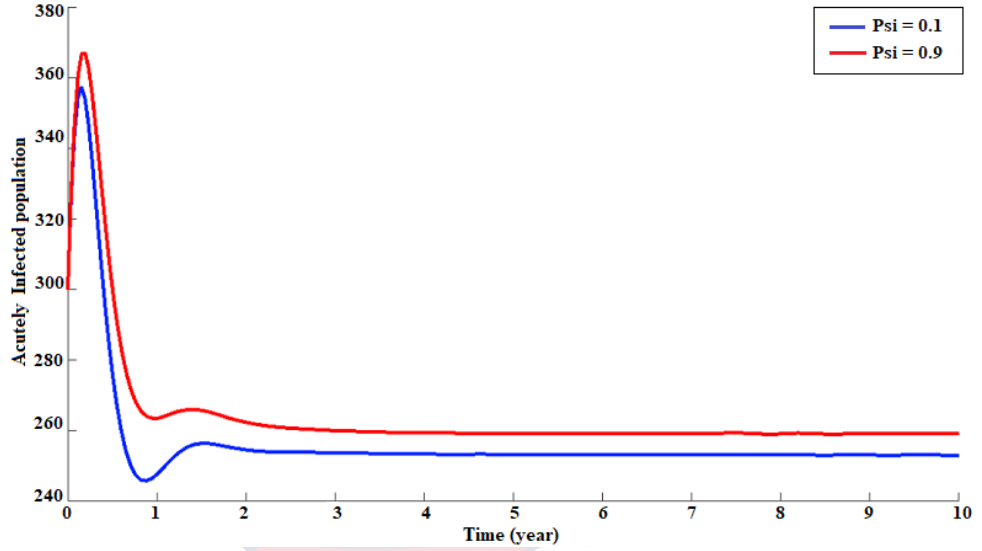

Figure 15: Simulation Results showing the Effect of varying the Waning Immunity rate (ie $\psi = 0.1$, $\psi = 0.9$) on the on Acutely Infected population. The rest of the parameter values, as stated in table 6.

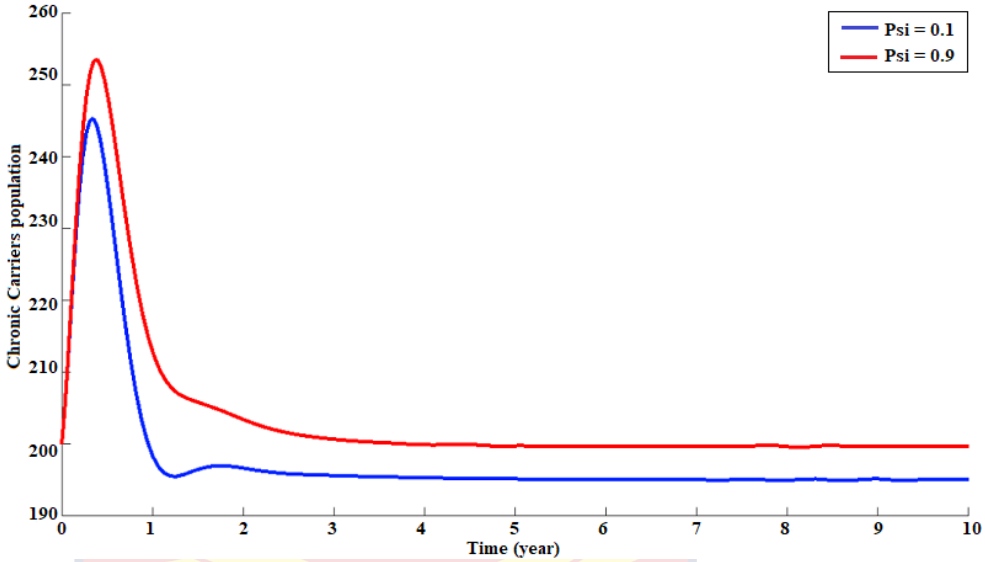

Figure 16: Simulation Results showing the Effect of varying the Waning Immunity rate (ie $\psi = 0.1$, $\psi = 0.9$) on the on Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

Effect of both Vaccination and Treatment on Acutely Infected and Chronic Carriers Population

Figures 17, 18, 19 and 20 below shows the effect of combining both treatment and vaccination with a high vaccine efficacy rate as control strategies of HBV infection. The main aim was to determine the best control strategy. Figure 17 demonstrates the prevalence of HBV infection with no control parameter. That is no vaccination; $(\theta = 0)$, treatment; $(\sigma = 0)$ and vaccine efficacy; $\varepsilon = 0$. We notice that the HBV infection decreases at a constant rate. This means that without any control strategy, HBV disease cannot be eradicated. However, with a high vaccination rate of 0.6 and vaccine efficacy rate of 1 without treatment parameter $(\sigma = 0)$, it will take a longer time, say 7 years to eradicate the HBV disease as depicted in Figure 18. It was observed that a high treatment rate of 0.6 with no vaccination parameter $(\theta = 0)$ will only reduce the number of infections but cannot eradicate the HBV infection as depicted in Figure 19. This is because most infected individuals are not aware of their infection and do not seek any medical treatment. Figure 20 also demonstrates a decreasing preva-

lence of hepatitis B virus infection with a high vaccination rate ($\theta = 0.9$), high vaccine efficacy rate ($\varepsilon = 1$) and a high treatment rate ($\sigma = 0.8$) combined as control strategies. We notice that all the infective compartments (both acutely infected and chronic carriers) population turn to zero in a short time. This means that the disease can be eradicated within the shortest possible time. Thus, this study reveals that a combination of treatment and vaccination with a high vaccine efficacy rate as a control strategy is the most effective way of controlling and eradication of hepatitis B virus disease.

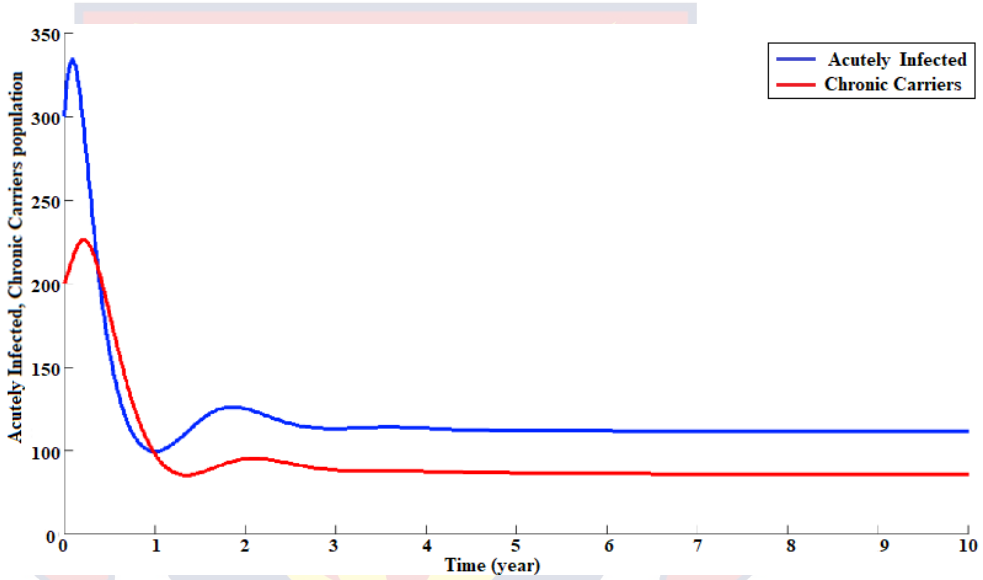

Figure 17: Simulation Results showing the Effect of no control measures such as Vaccination rate ($\theta = 0$), Vaccine Efficacy rate ($\varepsilon = 0$) and Treatment rate ($\sigma = 0$) on acutely infected and Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

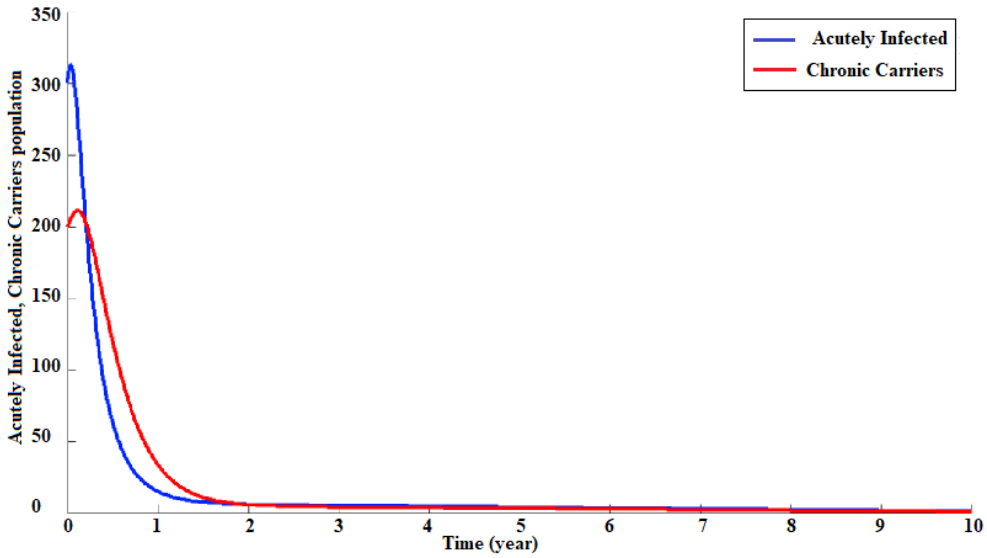

Figure 18: Simulation Results showing the effect of high Vaccination rate ($\theta = 0.6$), strong Vaccine Efficacy rate ($\varepsilon = 1$) and no Treatment rate ($\sigma = 0$) on Acutely Infected and Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

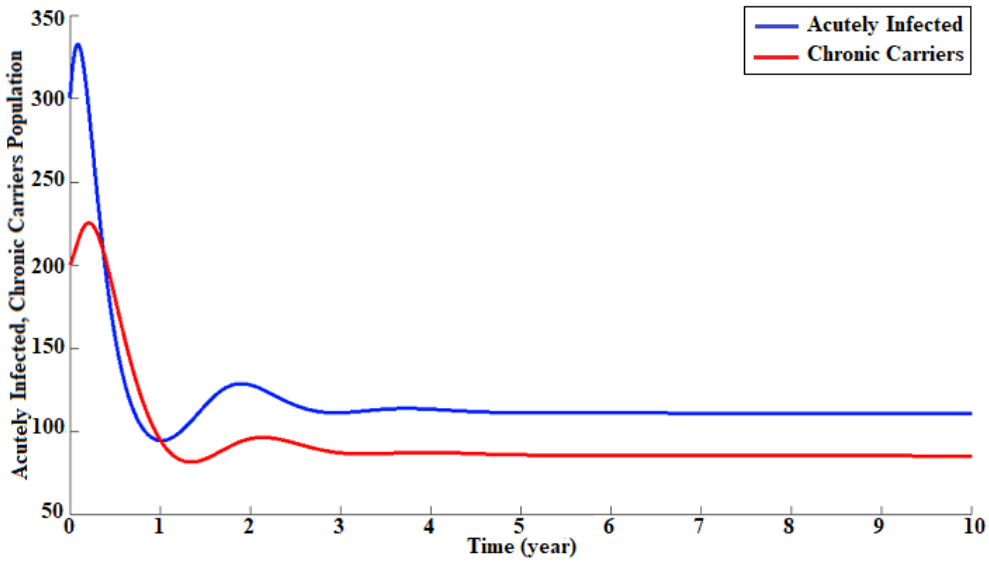

Figure 19: Simulation Results showing the Effect of no Vaccination rate ($\theta = 0$), strong Vaccine Efficacy rate ($\varepsilon = 0$) and a high Treatment rate ($\sigma = 0.6$) on Acutely Infected and Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

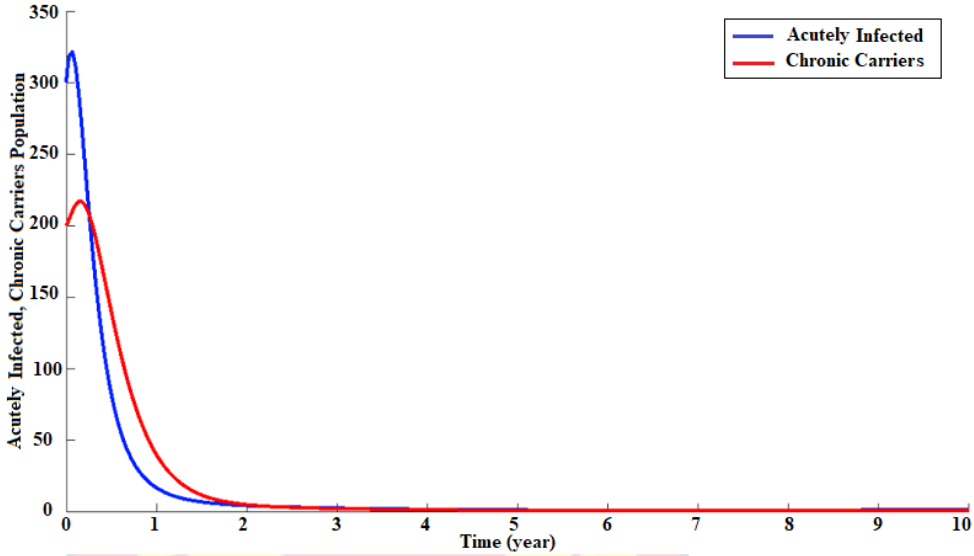

Figure 20: Simulation Results showing the Effect of a very high Vaccination rate ($\theta = 0.9$), strong Vaccine Efficacy rate ($\varepsilon = 1$) and a very high Treatment rate ($\sigma = 0.8$) on Acutely Infected and Chronic Carriers population. The rest of the parameter values, as stated in Table 6.

Sensitivity Analysis on the Basic Reproduction Number

The basic reproduction number $\mathbb{R}_0$ is a function of the parameters β, λ, ω, μ_0, μ_1, ψ, ε, θ, ρ, γ_1, δ, σ, τ_1, τ_2, η_1 and η_2. To control the outbreak of a disease, it is important to control the parameter values that will make $\mathbb{R}_0 < 1$. This is because these parameters contribute most toward the spread of the disease. Hence, we are interested in determining the rate of change of $\mathbb{R}_0$ as the parameter values changes. The rate of change of $\mathbb{R}_0$ for a change in the value of a parameter, say k can be estimated from a normalized sensitivity index defined as follows:

$$SI(k) = \frac{\partial \mathbb{R}_0}{\partial k}, \tag{4.1}$$

where k represents the parameter. Also, when there are changes in the parameter, the relative change in the state variables can be measured using the sensitivity indices. Hence, using the normalized sensitivity index in Eq. (4.1) to determine the effects of each parameter on $\mathbb{R}_0$, we obtain the following partial

derivatives:

$$\frac{\partial \mathbb{R}_0}{\partial \beta} = \frac{\lambda(1-\omega)\left[(\mu_0+\psi)+\theta(1-\varepsilon)\right]\left[\Psi_0+\Psi_1+\Psi_2\right]}{\mu_0(\theta+\mu_0+\psi)(\gamma_1+\tau_1+\mu_0)\Psi_0} \geq 0,$$

$$\frac{\partial \mathbb{R}_0}{\partial \lambda} = \frac{\beta(1-\omega)\left[(\mu_0+\psi)+\theta(1-\varepsilon)\right]\left[\Psi_0+\Psi_1+\Psi_2\right]}{\mu_0(\theta+\mu_0+\psi)(\gamma_1+\tau_1+\mu_0)\Psi_0} \geq 0.$$

The rest of the parameters can be shown in a similar way to determine their sensitivity status with the basic reproduction number, $\mathbb{R}_0$. The results are summarized in Table 7 below.

Table 7: **Parameters and their relationship with** $\mathbb{R}_0$

Parameter	Relationship
λ	+
β	+
σ	-
η_1	+
η_2	+
θ	-
ρ	+
ω	-
ε	-
μ_0	-
μ_1	-
τ_1	+
τ_2	-
δ	+
ψ	-
γ_1	+

Discussions

Hepatitis B virus disease is a dangerous health problem in the world. Therefore, HBV control is always a globally public health concern. J. Zhang & Zhang (2018) provide a model that explains the complex transmission dynamics of HBV with vaccination of newborn babies and treatment of infected patients as control strategies. That is susceptible newborn babies are vaccinated while those who progress either to both acutely and chronically infected compartments are treated.

In this thesis, we extended their analytical analysis to incorporate imperfect vaccination and investigated the parameter space that gave rise to the observed patterns of hepatitis B virus transmission dynamics. The increasing use of the hepatitis B vaccine and treating of infected persons has shown a significant impact on the rates of HBV infection and future HBV-related deaths. For the model with the control strategies of vaccination and treatment that incorporate imperfect vaccination presented in this work, a detailed stability and persistence analysis are investigated. Numerical simulations are also performed using parameter values obtained from standard published articles. Analysis from the model system shows that the qualitative behaviours of the model are completely determined by the magnitude of the basic reproductive number $\mathbb{R}_0$. More precisely, when $\mathbb{R}_0 < 1$, the endemic status of the hepatitis B virus disease will naturally settle to the disease-free equilibrium and for that matter, the disease will die out from the entire population. Otherwise, the disease will be uniform persistence and remain to invade the entire population.

Numerical results from the model show that when we increase the proportion of individuals who are vaccinated and the proportion of individuals seeking treatment, the basic reproduction number can be reduced below unity. Hence, $\mathbb{R}_0$ is a decreasing function concerning the vaccination rate and treatment rate indicating that vaccination and treatment are very useful in controlling and total

eradication of the hepatitis B virus infections. The model system studied in this thesis, however, indicated that the basic reproduction number $\mathbb{R}_0$ which forms the threshold is not enough to completely eradicate the spread of hepatitis B virus infection. This is because the result of the stability analysis investigated show that the model exhibit local asymptotic stability under certain conditions at the disease-free equilibrium provided $\mathbb{R}_0 < 1$ while the stability of the endemic equilibrium examined using the centre manifold theory proved the existence of a backward bifurcation phenomenon under certain conditions.

Sensitivity analysis performed on the parameters in the basic reproduction number show that parameters; $\lambda, \beta, \rho, \eta_1, \eta_2, \delta, \tau_1$ and γ_1 has a positive relationship with $\mathbb{R}_0$ while parameters; $\theta, \sigma, \omega, \varepsilon, \mu_0, \mu_1, \psi$ and τ_2 has a negative relationship with $\mathbb{R}_0$. It was also noticed that the model system settles at the disease-free equilibrium state with a very strong vaccine efficacy rate, $\varepsilon = 1$ and both the vaccination rate, θ and treatment rate, σ having values 0.4 and 0.6 respectively. Thus, vaccination of susceptible individuals and treatment of infected individuals play an important role in controlling the hepatitis B virus disease. Although total eradication of the hepatitis B virus disease remains a global problem, base on the finding of these studies, we suggested that a combination of massive vaccination and treatment of infected individuals to the highest level should be included in government hepatitis B virus control programmes. However, vaccines with a very strong vaccine efficacy rate should be used to help eradicate this deadly disease.

Chapter Summary

In this chapter, numerical simulations of the model were performed using literature values and some estimated parameter values for the spread of the hepatitis B virus disease and discuss the results obtained. The numerical simulations were performed using Matlab. It was shown that vaccination of susceptible individuals using a vaccine with a strong vaccine efficacy rate and treatment of

infected individuals play a key role in controlling hepatitis B virus transmission dynamics with the combination of the two strategies being the best.

Also, sensitivity analysis of the model system was perform for the model parameters to determine the relationship with the basic reproduction number; $\mathbb{R}_0$. It was shown that, the parameters; $\lambda, \beta, \rho, \eta_1, \eta_2, \delta, \tau_1$ and γ_1 has a positive relationship with $\mathbb{R}_0$ while parameters; $\theta, \sigma, \omega, \varepsilon, \mu_0, \mu_1, \psi$ and τ_2 has a negative relationship with $\mathbb{R}_0$.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Overview

A mathematical model for the transmission dynamics of hepatitis B virus disease has been presented in this study. Imperfect vaccination was incorporate to examine its impact on hepatitis B virus transmission dynamics. The analytical and numerical results of this model were discussed. It was suggested that the combination of a high vaccination rate and a high treatment rate with a strong vaccine efficacy rate is the best control strategy to reduce the spread of the disease. The results obtained from the model presented in THREE and FOUR are summarised below.

Summary

A mathematical model of hepatitis B virus transmission dynamics with vaccination and treatment that will incorporate imperfect vaccination as control strategies were studied. Hence, using analytical techniques we were able to determine when the disease will die out of the population or persist to invade the entire population. These will depend on the value of the basic reproduction number, $\mathbb{R}_0$. That is when $\mathbb{R}_0 < 1$ an infected person cannot transfer the disease to any susceptible individual in the population and the disease will die out. But, if $\mathbb{R}_0 > 1$ then an infected person can transfer the disease to more than one susceptible individuals in the population and for that matter, the disease will invade the entire population. However, when $\mathbb{R}_0$ is less than unity ($\mathbb{R}_0 < 1$), the eradicating of the hepatitis B virus disease will depend on the size of the population under consideration due to the backward bifurcation phenomenon when $\mathbb{R}_0 = 1$.

Using numerical techniques, we predicted the types of control strategies that should be adopted in other to control the hepatitis B virus disease. That is

the combination of vaccination with a high vaccine efficacy rate and treatment of infected individuals to the highest level is the best control strategy. The results of this study, therefore, provide a framework that should be taken into consideration by the government, health practitioners and decision-making bodies when formulating policies to control the hepatitis B virus disease.

Conclusions

A mathematical model for the transmission dynamics of the hepatitis B virus by J. Zhang & Zhang (2018) was modified to incorporate imperfect vaccination. The model was derived with the aid of a schematic diagram in Figure 4 while the model parameters are given in Table 5. The proposed model is mathematically well-posed and biologically meaningful since all the model solutions were proved to be both positive and bounded. The disease-free and the multiple endemic equilibria state of the model were also determined. Vaccination of susceptible individuals and treatment of infected individuals were incorporated to know their impact on the hepatitis B virus transmission dynamics using the sensitivity index of the model parameters.

The model was also solved numerically using $ode45$ in MATLAB and the result from the numerical simulations indicates that increasing the vaccination rate, treatment rate and using a vaccine with a high vaccine efficacy rate will reduce both the acute infection and chronic carriers populations. Therefore, most of the limited resources that will be used to control hepatitis B virus disease should be geared toward the reduction of these two (acutely infected and chronic carriers) populations through vaccination and treatment.

Furthermore, sensitivity analysis was performed on the basic reproduction with all the model parameters, from which we notice that the most sensitive parameters are the $\theta, \sigma, \omega, \varepsilon, \mu_0, \mu_1, \psi$ and τ_2. These parameters need high attention when considering measures to control hepatitis B virus disease. Hence, the incorporation of the imperfect vaccination helps in determining an optimal

control strategy to reduce the transmission dynamics of the hepatitis B virus disease.

Recommendations

Based on the findings in this study, we give the following recommendations:

(a) The Governments, stakeholders and policymakers should consider using both effective vaccinations with strong vaccine efficacy rate and treatment of infected individuals as control strategies on hepatitis B virus control programmes.

(b) Although Vaccination of all susceptible individuals against the hepatitis B virus disease and treatment of every individual chronically infected with the hepatitis B virus disease may be impossible due to limited resources, this study has given threshold values for a vaccination rate of 0.9 and treatment rate of 0.8 with a high vaccine efficacy rate of 1 to be used to obtain optimal results.

(c) Individuals should minimize the amount of alcohol intake to prevent HBV disease.

(d) Individuals should take drug recommended by medical doctors.

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