MATHEMATICAL MODEL OF HEPATITIS B IN THE NORTH TONGU DISTRICT OF THE VOLTA REGION OF GHANA

BY

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Declaration

I hereby declare that this submission is my own work towards the Master of Philosophy (M.Phil.) and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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Dedication

To my loving wife Mrs. Salome Letsa-Agbozo and my sweet daughters Francisca Seyram Letsa-Agbozo, Josephine Mawunyo Letsa-Agbozo and Bubune Michelle Letsa-Agbozo.

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Abstract

Hepatitis B spreads in a host population through direct transmission from the parent to the offspring (vertical transmission) and also through contact with infective individuals (horizontal transmission). In this thesis, we consideedr a mathematical model for the infectious disease (Hepatitis B) and developed a model based on the Susceptible-Infected-Recovered (SIR). The North Tongu District of the Volta Region of Ghana was considered as the host population. The district was assumed to have a constant population size. A system of non-linear differential equations was used to model the spread of the disease in the district. We solveed the system numerically using the forth-order Runge-Kutta method. Simulation and sensitivity analyses were also performed on the model equations to determine the effect of different parameter values on the spread of the disease. It was shown that the global dynamics were completely determined by the basic reproductive number R_0. If $R_0 < 1$, the disease-free equilibrium is globally stable and the disease always die out. On the other hand, if $R_0 > 1$, an endemic equilibrium exists and was globally stable in the interior of the feasible region, and the disease persists at an endemic equilibrium state if it initially exists.

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CHAPTER 1

INTRODUCTION

1.1 Background Information

Hepatitis B is one of the major health problems in the world. The World Health Organization (WHO) (2007) reported that over one-third of the world's population (more than 2 billion people) has been or is actively infected with Hepatitis B Virus (HBV); more than 350 million have chronic (lifelong) infections and 25-40 percent of these chronic infection carriers die from liver cirrhosis or primary hepatocellular carcinoma. HBV is the 10th leading cause of death worldwide (World Health Organization, 1997). The hepatocellular cancer (HCC) alone accounted for more than 500,000 deaths per year, making it the 3rd most common cause of cancer death worldwide (Parkin, et al. 2005).

National and regional prevalence ranges from over 10% in Asia to under 0.5% in the United States and Northern Europe (WHO, 2007). Routes of infection include vertical transmission (such as through childbirth), early life horizontal transmission (bites, lesions, and sanitary habits), and adult horizontal transmission (sexual contact, intravenous drug use).

The primary method of transmission reflects the prevalence of chronic HBV infection in a given area. In low prevalence areas such as the continental United States and Western Europe, injection drug abuse and unprotected sex are the primary methods, although other factors may also be important. In moderate prevalence areas, which include Eastern Europe, Russia, and Japan, where 2–7% of the population is chronically infected, the disease is predominantly spread among children. In high prevalence areas such as China and South East Asia, transmission during childbirth is most common, although in other areas of high endemicity such as Africa, transmission during childhood is a significant factor. The prevalence of chronic HBV infection in areas of high endemicity is at least 8%.

The HBV disease prevelence are generally classified as percentage of Hepatitis B surface antigen (HBsAg) carriers in the population and categorized as; low ($< 2\%$), intermediate ($2 - 7\%$) or high ($> 8\%$), as shown in Figure 1.1

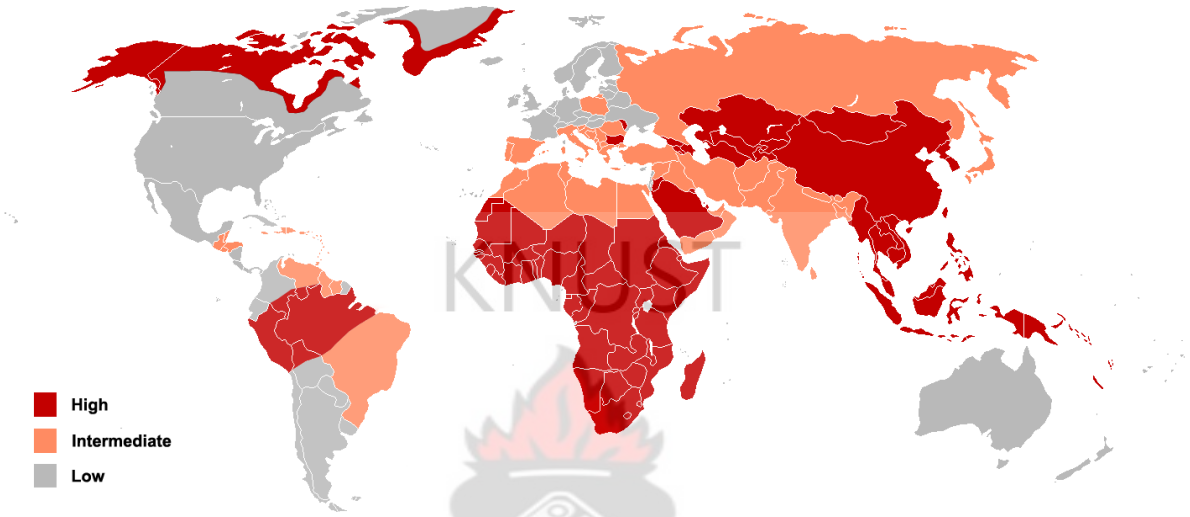

Figure 1.1: Global Hepatitis B virus prevalence

Source: http://en.wikipedia.org/wiki/File:HBV_prevalence_2005.png (22/07/12)

Hepatitis B virus is a Deoxyribonucleic acid (DNA) virus with a remarkably compact genomic structure; it has a relaxed circular (but not covalently closed), partially double stranded DNA genome. The complete genome is approximately 3200 nucleotides (3.2 kilobases or kb) long. There are four sets of HBV DNA codes for viral products with a complex, multiparticle structure. HBV achieves its genomic economy by relying on an efficient strategy of encoding proteins from four overlapping genes: the envelope (S); core (C); polymerase (P); and X regions (Scanglioni, et al. 1996). See Figure 1.2.

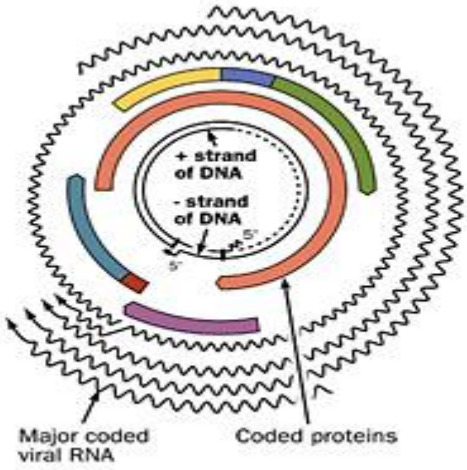

Figure 1.2: Genomic organization of Hepatitis B virus

The virus belongs to the Hepadnaviridae family. Its members are divided into two genera; Orthohepadnaviruses infecting mammals, and Avihepadnaviruses affecting birds. The two genera of HBV, all have the same distinctive three morphologic forms, and counterparts to the envelope and nucleocapsid virus antigens of HBV. They replicate in the liver but exist in extrahepatic sites, contain their own endogenous DNA polymerase and have partially double-strand and partially single-strand genomes.

The hepatitis B virus consists of an outer 42nm diameter spherical lipoprotein envelope and an inner 27nm diameter icosahedral necleocapsid core enclosing the DNA genome, polymerase and a protein Kinase (Dane et al, 1970). The outer envelope contains embedded proteins which are involved in viral binding of, and entry into, susceptible cells. The virus is one of the smallest enveloped animal viruses with a virion diameter of 42 nm, but pleomorphic forms exist, including filamentous and spherical bodies lacking a core. These particles are not infectious and are composed of the lipid and protein that forms part of the surface of the virion, which is called the surface antigen (HBsAg), and is produced in excess during the life cycle of the virus.

1.1.1 Epidemiology of Hepatitis B

In order to reproduce, the hepatitis B virus (HBV), must first attach onto a cell which is capable of supporting its replication. Though the liver is the most effective cell type for replicating HBV, other extrahepatic sites have been found to be able to support replication to a lesser degree. HBV replicative intermediates and/or viral transcripts have been found in mononuclear cells, bile duct epithelial, endothelial, pancreatic acinar cells, and smooth muscle tissue, as well as in adrenal glands, gonads, cultured bone marrow, kidneys, lymph nodes, spleen and thyroid glands of acute hepatitis B infected patients. (Dienstag, 2008). Although the virus does not appear to be associated with tissue injury in any of these extrahepatic sites, its presence in these "remote" reservoirs has been invoked to explain the recurrence of HBV infection after orthotopic liver transplantation.

Hepadnaviruses rely on a replicative strategy unique among DNA viruses but typical of retroviruses. Instead of DNA replication directly from a DNA template, hepadnaviruses rely on reverse transcription (effected by the DNA polymerase) of minus-strand DNA from a "pregenomic" Ribonucleic acid (RNA) intermediate. The plus-strand DNA is transcribed from the minus-strand DNA template by the DNA dependent DNA polymerase and converted in the hepatocyte nucleus to a covalently closed circular DNA (cccDNA) by host proteins called chaperones, which serves as a template for messenger RNA and pregenomic RNA. Viral proteins are translated by the messenger RNA, and the proteins and genome are packaged into virions and secreted from the hepatocyte. Although HBV is difficult to cultivate in vitro in the conventional sense from clinical material, several cell lines have been transfected with HBV DNA. Such transfected cells support in vitro replication of the intact virus and its component proteins.

1.2 Problem Statement

Continuous acquisition of HBV infection throughout children with horizontal transmission within the household is the main mode of HBV spread in Ghana. Specific risky behaviours like sharing of bath towels, chewing gum and partially eaten candies, dental cleaning materials, and biting of findernails in conjunction with scratching a carrier's back, were shown to be highly prevalent in households and is significantly associated with horizontal transmission, (Martinson et al., 1998).

It is also shown that HBV infection is strongly associated with the development of cirrhosis of the liver (Guan et al., 2011). In a study, sero-positivity for infection with HBV in patients with cirrhosis of the liver was 42.9%, suggesting that most cases of cirrhosis of the liver were virus-related chronic liver diseases. Furthermore, in both sexes, the age distribution of HBsAg positive patients with cirrhosis of the liver showed that 70% were in the age 20-49 years indicating that HBV infection was acquired in childhood through to early adulthood, (Blankson et al., 2005).

Universal childhood immunization with three doses of hepatitis B vaccine in the first year of life has been proven to be the most effective strategy for prevention and control of hepatitis B (World Health Organization, 2007). They went on to say that in striving to build upon the gains achieved in immunization systems during the poliomyelitis eradication initiative, the Region has adopted hepatitis B control through universal childhood immunization as one of the pillars for strengthening immunization service delivery systems.

The above statements brings us to the fact that Ghana as a Country is very far from eradicating HBV since we still live in households where most personal items are shared and universal childhood immunization programmes for Hepatitis B virus is never mentioned in the government of Ghana's current, intermediate or long term plans.

1.3 Objectives

The objectives of this research are

1. to use the SIR model to predict the spread of Hepatitis B disease in the North Tongu district of the Volta Region of Ghana.
2. determine the nature of the outbreak.
3. show how the proportion of susceptibles, infectives, and recovered change with time.
4. determine the effect of the initial number of infectives on the population.
5. estimate the proportion of the population that should be vaccinated.

1.4 Methodology

We employ the Susceptible-Infective-Recovered (SIR) compartmental model which was developed by Karnack and McKendrick in 1927. This model would be used to describe the epidemiology and to compute the amount of susceptibles, infectives and recovered people in a population. This model works on the following principles: upon recovery from the disease, the person receives lifelong immunity and an infected person becomes infectious soon after infection.

The model equations are solved numerically using the forth-order Runge-Kutta method. All algorithms employed were implemented using MatLab. Simulation and sensitivity analysis are then performed on the model equations to determine the effect of the parameter values on the spread of the disease.

1.5 Justification

Epidemiology has provided valuable insights for analysis of different types of diseases in the world. This study is justified based on the following:

1. The thesis seeks to predict whether or not the measures put in place could check the spread of Hepatitis B disease in the North Tongu district is enough or more still needs to be done in order to prevent it from becoming endemic so that lives will be saved.
2. The outcome of the thesis will help improve upon the welfare of the people, as people recover from the sickness and are able to earn their livelihood and improve their lot.
3. This thesis will contribute to the research information of Hepatitis B in the country, so that it could help in further research.

1.6 Organization of the Thesis

This thesis is organized into five main chapters. Chapter 1 gives the introduction of the thesis. This consists of a biological background of HBV, statement of the problem, objectives, methodology, justification and organization of the thesis.

In the second chapter, we review previous research works. The formation of the mathematical model was presented in chapter 3. Chapter 4 presents the analysis and results of the model. In chapter 5, conclusions were drawn from the model and recommendations stated with suggestions for further studies.

CHAPTER 2

REVIEW OF RELATED LITERATURE

2.1 Introduction

The hepatitis B infection is endemic in many parts of the world including Ghana. It has become a matter of emergency to curb its' spread in Ghana as a country and the world as a whole. To do that effectively, there is the need to take a look at the models other researchers used and how we can shape it to be Ghanaian in eradicating the spread of Hepatitis B in the country.

Six Compartmental Models

Zou et al. 2010, proposed a mathematical model to understand the transmission dynamics and prevalence of HBV in mainland China. The model is constructed based on the characteristics of HBV transmission in China and the model of Medley et al. 2001. But instead of considering only five epidemiological groups, they considered six by distinguishing the recovered and vaccinated subgroups. They were of the view that, the immunity after recovery is lifetime, whilst that following vaccination might wane after some time. Therefore, the epidemiological groups considered under the population were: the proportion susceptible to infection, those latently infected, acute infections, carriers, recovered and with protective immunity, and immune following vaccination.

There was a small discrepancy between the data reported by Ministry of health of China and their simulation solution due to the overestimation of some parameters and the initial proportion of latency. Based on the model and used parameter values, they estimated the

basic reproduction number $R_0 = 2.406$. This indicates that hepatitis B is endemic in mainland China and a lot has to be done in reducing $R_0 < 1$. Based on their simulations as to ways to reduce $R_0 < 1$, the optimal control strategy will be a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of contacts.

Zou et al. 2010, again proposed an age-structured model to study the transmission dynamics of HBV. As the model includes age-dependent processes such as the force of infection and the probability of developing the carrier state, the host population is stratified by age. They divided the population into six subclases: the susceptible, latently infected, acutely infectious, carrier, recovered, and vaccinated, with age distribution of time. In their discussion, they say that the transmission of HBV is characterized by two age-dependent processes: the per-capita rate of infection and the risk of becoming a carrier.

Taking age-dependent heterogeneity into consideration, several groups proposed age-structured models to study the transmission dynamics of HBV. Zhao et al. 2010, used an age-structured model to predict the transmission dynamics of HBV and to evaluate the long-term effectiveness of the vaccination program in China. Their results suggests HBV infection in China can be controlled in just one generation and eventually eliminated if all infants are immunized throughout the country, especially in poor rural areas.

However, achieving such a high vaccination rate for infants in a country such as China is almost impossible. In fact, despite an effective national vaccination programme for newborn babies since 1992, which had reduced chronic HBV infection in children, the incidence of hepatitis B in China is still increasing.

Mass vaccination in infants increases the average age of infection to older age groups (Edmunds, et al 1993). This indicates that mass vaccination in infants might not be enough

to control the infection and eradication of the virus. The analytical results and numerical simulations of the model suggested that the optimal control strategy is a combination of immunization of newborns and retroactive immunization of susceptible adults.

Five compartmental models

Zhao et al. 2000, developed a compartmental mathematical model expressed by a set of first-order partial differential equations. Based on the characteristics of HBV transmission, the population was divided into five compartments: Susceptibles, Latent period (the time interval from infection to development of infectiousness), Temporary HBV carries, Chronic HBV carries and the Immune. Of the five stages, compartments 3 and 4 are infectious.

In this model, birth rate was considered as a constant; age-specific death rates were collected from death notification systems. The immune status was assumed to be lifelong and newborns were assumed to be susceptible. A few infants born to both hepatitis B surface antigen (HBsAg) positive mothers can be infected by HBV in untero. The rate was reported to be about $3-5\%$, and the proportion of their mothers in all pregnant women was only $2-3\%$. Therefore, the probability of intra-uterine fetal infection was very low (about $0.0006-0.0015$). For simplicity of modeling, intrauterine HBV infection, the short period of newborn maternal antibody protections and sex differences were ignored.

Upon the model simulation, not only HBV transmission dynamics but also the proportion of age-specific HBV carriers was obtained from two large-scaled, cross-sectional sero-surveys undertaken 7 years apart. It was also a powerful tool to study the impact of parameters on long-term vaccine effectiveness. It demonstrated that the HBV carrier rate, the most important indicator of the vaccine's effectiveness, will fall from 10% to less than 0.2% 70 years after the start of the universal infant vaccination programme. Thus, long-term

vaccination effectiveness is foreseeable and disease is eradicable. The model also suggests that vaccination coverage is the most important parameter for vaccine effectiveness. Compared to different vaccination strategies being applied in China, their model had shown that a low dose strategy with higher vaccination coverage and lower vaccine efficacy provided higher long-term effectiveness than a high dose strategy with lower coverage and higher efficacy.

Min et al. 2008, were of the view that the basic virus infection model (BVIM) is widely used in the studies of hepatitis B virus HBV infection dynamics. This model assumes that the infection process follows a mass action law. The basic infection reproductive number of the model is proportional to the number of cells of the host's organa prior to the infection. This suggests that the BVIM may not be a reasonable model for describing the HBV virus infection since it implies that an individual with a smaller liver may be more resistant to virus infections than an individual with a larger one. In their work, they formulated a standard incidence based model that amends the BVIM (also called ABVIM) which will correct this mass action induced model artifact. If the basic infection reproductive number is less than 1, then every positive solution will converge to the infection-free steady state. They also presented an application of ABVIM to some clinic HBV infection data.

The basic virus infection model (BVIM) introduced by Zeuzem et al. 1997, and Nowak et al. 1996, is widely used in the studies of virus infection dynamics. The BVIM with three variables were numbers of uninfected (Susceptible) cells, infected cells and free virus. Clearly, if the reproductive number $R_0 > 1$, then the BVIM also has two steady states, that is, the infection free steady-state E_f and the endemic steady state. It is known that if the basic reproductive number R_0^* is less than 1, then E_f is locally asymptotically stable and E^* does not exist.

Observe that the basic infection reproductive number R_0^* is proportional to the number of total cells of the liver. This suggests that the BVIM may not be a reasonable model for describing HBV virus infection since it implies that an individual with a smaller liver may be more resistant to the liver infection than an individual with a larger one. Therefore, the practical meaning of R_0^* is biologically questionable at the best. A typical chronically infected HBV patient has a total serum daily production rate of about 2×10^{11} to 3×10^{12} virions. An average human liver consists of billions of liver cells. These large numbers suggests that a more plausible HBV model should employ a standard incidence function, instead of the mass action incidence used in BVIM. They therefore proposed the following amended basic HBV virus model (to be referred to as ABVIM).

Notice that for ABVIM, if the reproductive number $R_0 > 1$, then the ABVIM also has two steady states, that is, the disease free steady-state and the endemic steady state. Observe that the biological meaningful steady-state (meaning its component must be nonnegative) does not exist if $R_0 < 1$, and it becomes E_f when $R_0 = 1$.

It was seen that simulation results of the BVIM and the ABVIM equations are similar. However, the ABVIM can interpret the clinical data better in biological terms since it does not imply the absurd statement that an individual with a smaller liver may be more resistant to virus infections than an individual with a larger one. Prolonging the drug treatment to three years and then followed up in seven years, the corresponding simulation results the calculations shows that, even though the HBV DNA load of the patient is reduced to about 1 copies/ml at the end point of the three years' treatment, the HBV DNA load can still relapse to about 5×10^3 log copies/ml soon after stopping treatment for 10 days, and then gradually increase to 1.8×10^8 copies/ml after the treatment is withdrawn in about seven years. Only after delaying the therapy to about 4.8 years, all infected cells can be replaced by uninfected ones (HBV DNA load less than 1/3000 copies/ml), so that the treatment benefit can be kept.

A similar case appears in the simulation of BVIM equations. However, treatment only needs to be prolonged to 3.56 years to delete all HBV in vivo. Clinical trials demonstrated that it is too short to cure HBV infection with the drug lamivudine for most patients.

The widely used BVIM has been examined. It has been found that its basic infection reproductive number R_0^* is questionable. The basic infection reproductive number of ABVIM denoted by R_0 seemed to be reasonable. The simulation results of the ABVIM appeared more close to the clinical trial. The predictions of the treatment endpoint with the drug lamivudine are given, which are longer than 3.5 years for patients with mean plasma HBV DNA levels.

Long and Qi 2008, made a number of inputs on the pathogenesis of Hepatitis B using mathematical models. According to the pathogenesis of Hepatitis B, a mathematical description of the relationship between hepatitis B virus (HBV) and the cellular immune response to the infection is built based on Nowak's population dynamics model of immune responses to persistent viruses. The model has two possible equilibrium states: complete recovery (HBV will be eliminated from the body entirely), uninfected and infected hepatocytes coexisting state.

The model contains five variables. i.e. uninfected hepatocytes, infected hepatocytes, total host hepatocytes, free virus and a CTL response. The changes of population over time can be described by a system of differential equations. According to this model, if the virus has a weak infectious capability and replicates slowly, the CTL response to HBV is vigorous and enough to eliminate the virus from the liver entirely and the patient will completely recover after the infection, therwise serious problem will be caused. If the virus with strong infectious capability replicates rapidly, most hepatocyte cells in the liver will get infected, resulting in massive liver necrosis due to the strong CTL response. The outcome will be fulminant hepatitis. If the immune system depends against the HBV with a weak ability and

weak CTL level, the infected cells cannot be cleared out entirely. The outcome will be chronic hepatitis.

Though the dynamic behaviors of HBV infection are very complex, this simple model may provide a possible interpretation for the different outcomes of HBV infection. This model can also be applied to fit clinical and immunoinfectomics data for evaluating the interplay between the immune system and virus, thus providing holistic information about the potency of antiviral therapies and guiding development of optimal drug dosages and regimens.

Momoh et al. 2011, made a great contribution with their paper. They proposed an MSEIR model to understand the transmission dynamics and control of HBV taking into consideration passive immunization, treatment of exposed individual at latent period and infectious Hepatitis B treatment.

The MSEIR model is partitioned into compartments of passively immune infants, susceptible individuals, exposed individuals in the latent period, infectious individuals and removed individuals. The immunized compartment changes due to the coming in of the immunized children into the population where they assume that a proportion of B of the incoming individuals are immunized against hepatitis B infection. This compartment reduces due to expiration of duration of vaccine efficacy and also by natural death. The susceptible population increases due to the coming of individuals from the immunized compartment as a result of the expiration of the duration of vaccines efficacy. The susceptible population also reduces due to natural death and infections.

Analysis of the equations brought up the point that there is stability around the disease free equilibrium state. This implies that the susceptible individuals produced must be less than the natural death rate. It is possible to reduce the risk of perinatal transmission in several ways. The first step is identification of persons at risk. Testing for HBsAg should be

performed in all women at the first prenatal visit and repeated later in pregnancy if appropriate. New borns to HBV-positive mothers can be effectively protected by passive immunization. Hepatitis B immunoglobulin (HBIB) for passive immunization should be given as early as possible (within 12 hours), but can be given up to seven days after birth.

World Health Organization in 2007, reported that children have a 90% chance of developing chronic HBV infection if infected initially at birth, a 30% chance if infected between the ages of one and five years and only a 5% to 10% chance if infected after five years of age. In setting hyperendemic for hepatitis B, as is the case in most countries of the Western Pacific Region, most chronic infections were acquired by age five. Goldstein et al. 2005, estimated that in 75% of all HBV-related deaths, infection is acquired by age five, measuring the goal among children aged five years or older will take into account the complete exposure period when the risk of horizontal transmission and likelihood of becoming chronically infected are highest. Setting the goal among children under five years of age may overestimate the impact of vaccination programmes if some of the children who were uninfected and unprotected at the time of evaluation later become infected by age five and become chronically infected with HBV.

The WHO observed in some of the countries in the South Pacific that, even those with the same schedule for the combination vaccine: Diphtheria, Tetanus and Pertussis (DTP) and hepatitis B vaccination, that fewer vaccination sessions were organized for HepB than for DPT (e.g. DTP sessions may be organized four days a week and a HepB session only once a week, forcing mothers to bring children twice). This is ostensible to reduce the wastage rate for the more expensive hepatitis B vaccine. However, this practice may reduce the vaccine coverage rates for HepB. Procuring smaller vaccine vials (one- or two-dose vials) may be a better alternative to reduce vaccine wastage. In addition, smaller vaccine vials will discourage service providers to schedule fewer vaccination sessions for hepatitis B.

Four compartmental models

Georgescu and Hsieh 2006, considered a compartmental model for the propagation of a virus in vivo. The compartments are concentration of the cells in the susceptible (i.e. uninfected) class, concentration of cells in the exposed (i.e. latent) class, concentration of cells in the infected class and concentration of the virus itself.

They assumed that the major infection pathway is virus-to-cell, since the cell-to-cell pathway is sometimes less documented and less considered, particularly in diseases such as AIDS. As the concentration of viral cells becomes higher, the simple mass action law may not necessarily suffice. Moreover, the rate at which an infected cell or virus will die as a function of their concentrations is generally not known, hence we make the further generalization by assuming that the removal rates is also nonlinear.

Three compartmental models

Salathé and Jones 2010, were of the view that the dynamics of infectious diseases spread via direct person-to-person transmission depending on the underlying host contact network. Human contact networks exhibit strong community structure. Understanding how such community structure affects epidemics may provide insights for preventing the spread of diseases between communities by changing the structure of the contact network through pharmaceutical or non-pharmaceutical interventions. They used empirical and simulated networks to investigate the spread of diseases in networks with community structure. They found that community structure had a major impact on disease dynamics, and showed that in networks with strong community structure, immunization interventions targeted at individuals bridging communities are more effective than those simply targeting highly connected individuals. Because the structure of relevant contact networks was generally not

known, and vaccine supply was often limited, and there was great need for efficient vaccination algorithms that do not require full knowledge of the network. They developed an algorithm that acts only on locally available network information and was able to quickly identify targets for successful immunization interventions. The algorithm generally outperformed existing algorithms when vaccine supply was limited, particularly in networks with strong community structure. Understanding the spread of infectious diseases and designing optimal control strategies was a major goal of public health. Social networks showed marked patterns of community structure, and their results, based on empirical and simulated data, demonstrated that community structure strongly affects disease dynamics.

Individuals in a population were represented as nodes in a network, and the edges between the nodes represented the contacts along which an infection can spread. Contact networks were abstracted by undirected, unweighted graphs (i.e. all contacts were reciprocal, and transmit an infection with the same probability). Edges always link between two distinct nodes (i.e. no self-loops), and there must be maximally one edge between any single pair of nodes (i.e. no parallel edges). Each node can be in one of three possible states: Susceptible, Infected, or Resistant/Immune (as in standard SIR models). Initially, all nodes were susceptible.

Simulations with immunization strategies implement those strategies before the first infection occurs. Targeted nodes were chosen according to a given immunization algorithm until a desired immunization coverage of the population was achieved, and then their state was set to resistant. After this initial set-up, a random susceptible node was chosen as patient zero, and its state set to infected. Then, during a number of time steps, the initial infection could spread through the network, and the simulation is halted once there are no further infected nodes. After a simulation, they recorded the total number of cases infected (the epidemic size), the maximum frequency of infection at any point during the simulation (the

peak prevalence), and the number of days that have passed between the first infected case and the simulation stop (the duration of the epidemic).

Bonhoeffer et al. 1997, presented a resent development of potential antiviral drugs which has raised hopes for effective treatment of infections with HCV or the hepatitis B virus, and also led to important quantitative insights into viral dynamics in vivo. Interpretation of the experimental data depended upon mathematical models that describe the nonlinear interaction between virus and host cell populations. Here we discuss the emerging understanding of virus abundance, the dynamics of viral drug resistance, and the question of whether virus infection can be eliminated from individual patients by drug treatment.

They begin with a very simple model, which captures some of the essentials. This model of viral dynamics has three variables: uninfected cells, infected cells, and free virus particles. Before information, uninfected cells are at the equilibrium. An intuitive understanding of the properties of these equations can be obtained, along lines familiar to ecologists and epidemiologists. A small initial amount of virus, can grow if its basic reproductive ratio, R_0, defined as the average number of newly infected cells that arise from any one infected cell when almost all cells are uninfected, is larger than one. Subsequently, the system converges in damped oscillations to the equilibrium. At equilibrium, any one infected cell would on average, give rise to one newly infected cell. The fraction of free virus particles that manage to infect new cells was given by the reciprocal of the burst size. The probability that a cell (born uninfected) remains uninfected during its lifetime is $\frac{1}{R_0}$. Hence the equilibrium ration of uninfected cells before and after infection is R_0.

In the life cycle of HBV, the virus-encoded (reverse transcriptase) is responsible for transcribing the unspliced viral mRNA into the DNA genome of new virus particles. Therefore the reverse-transcriptase inhibitor, lamivudine, stops already-infected cells from

producing new virus particles. Thus plasma virus, simply falls as an exponential function of time. Hence the slope of the virus decay reflects the half-life of free virus particles, which turns out to be about 24 hours. The half-life of infected cells in HBV infection has been estimated from the decay of virus production (comparing the rate of virus production before and after therapy) or from the decline of hepatitis E antigen levels during therapy. In contrast to HIV, virus producing cells in HBV are long-lived. There is also great variation in turnover rates in different patients, ranging from about 10 days to more than 100 days. HBV is considered to be noncytopathic, and the difference in infected cell half-lives can be attributed to different Cytotoxic T Lymphocytes (CTL) activities. In HBV infection it is also possible that infected cells lose their HBV DNA and can thus become uninfected. CTL may accelerate the process. Thus our estimated turnover rates of infected cells may not simply describe cell death, but rather the time span a cell remains infected or in the state of virus production.

Emergence of resistance to lamivudine in HBV infection is slower and rarer than in HIV infection. There was no indication of resistance in 50 chronic HBV carries treated for 20 weeks, whereas the same drug usually induces HIV resistance in a few weeks. HBV resistance, however, is possible and was observed after about 30 weeks in three patients receiving liver transplantation. The 10- to100-day half-life of HBV-producing cells suggests that the generation time is 5 to 50 times longer in HBV than in HIV, which could explain the slower adaptive response.

Hattif et al. 2009, presented a mathematical model on Hepatitis B viral. The model contains three variables; uninfected target cells, infected cells and free virions. Upon analysis, it was concluded that an efficient numerical method based on optimal control to identify the best treatment strategy of hepatitis B viral in order to block new infection and prevent viral production is by using drug therapy with minimum side effects. Their numerical results

showed that viral load decreases after 10 days of treatment and the population of uninfected cells increases after 52 days of therapy.

According to Korobeimibov 2004, if there is no exposed class E, the movement of cells from the susceptible class directly into the infection class, the (reduced three-dimensional) system(s) is equivalent to a SEIR model with a constant population assumption. It is therefore expected that the dynamics of our model will share some features with the dynamics of a SEIR model.

Most of the models presented by various researchers may not apply to Ghana. It is therefore my objective to use the SIR model to address the problems arising in the North Tongu District, in the Volta Region of Ghana and could be applied to all districts of the Country.

CHAPTER 3

MATHEMATICAL MODEL

3.1 Introduction

In this chapter, we model the spread of Hepatitis B using the classic epidemic theory of Kermack and Mckendrick (1927), to help study the epidemiology of this disease. The research results would be helpful in predicting the epidemic patterns of Hepatitis B, and to seek the optimum strategies of preventing and controlling the spread of Hepatitis B in the North Tongu District, of the Volta Region of Ghana.

3.2 Description of SIR Model of Hepatitis B

In using the SIR model, we can divide the population into three classes of individuals: the susceptible class (S), the infective class (I), the removed class (R). The susceptible class consists of individuals who are not infective, but are capable of catching the disease and becoming infective. The infective class consists of individuals who are capable of transmitting the Hepatitis B disease to others. The removed class consists of individuals who have had the disease and are dead, or have recovered and are permanently immune, or are isolated until recovery.

Below are the assumptions of the SIR model:

1. Hepatitis B confers permanent immunity upon any individual who has completely recovered from it.
2. The members of the population mix homogeneously
3. It has a negligible short incubation period.

4. The population remains at a fixed level N in the time interval under consideration. This means that we neglect births, and deaths from causes unrelated to the disease under consideration, as well as immigration and emigration.

Figure 3.1 represents an SIR model of Hepatitis B without vital dynamics.

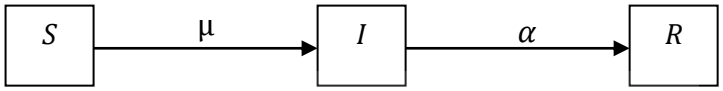

Figure 3.1: Flowchart of the SIR model of Hepatitis B without vital dynamics

Where the proportionality constants μ and α are the infection and removal rates respectively, based on the assumptions, the following model equations are obtained:

$$\frac{dS}{dt} = -\mu SI \tag{3.1}$$

$$\frac{dI}{dt} = \mu SI - \alpha I \tag{3.2}$$

$$\frac{dR}{dt} = \alpha I \tag{3.3}$$

With initial conditions $S(0) = S_0$, $I(0) = I_0 > 0$, $R(0) = 0$. Since $S(t) + I(t) + R(t) = 1$, we can calculate R from $R(t) = 1 - S(t) - I(t)$, once we know $S(t)$ and $I(t)$ from the reduced system

$$\frac{dS}{dt} = -\mu SI \tag{3.4}$$

$$\frac{dI}{dt} = \mu SI - \alpha I \tag{3.5}$$

The term $-\mu SI$ in equation (3.4) describes a transition of infection due to the interaction between susceptibles and infectives. The term $-\alpha I$ in equation (3.5) describes the recovery from the infection.

We observe from equation (3.5) that $\frac{dI}{dt} = 0$ when $I = 0$ or $S = \frac{\alpha}{\mu}$. When $S < \frac{\alpha}{\mu}$, and $\frac{dI}{dt} < 0$ then $I(t)$ decreases, and the disease dies out. On the other hand, when $S > \frac{\alpha}{\mu}$ and $\frac{dI}{dt} > 0$, then $I(t)$ increases and an epidemic occurs i.e. an increase in infective individuals. Figure 3.2 illustrates the above statement.

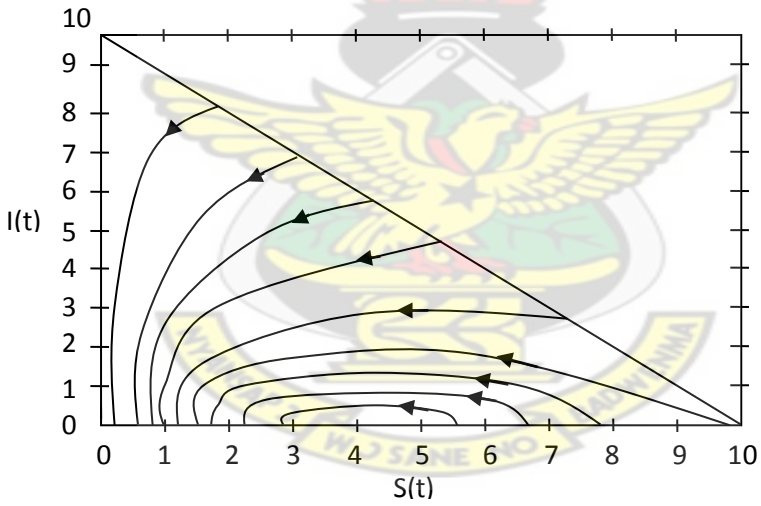

Figure 3.2: The phase portrait for the SI phase plane.

Also, equation (3.4) implies that if the term $-\mu SI = 0$, then we get either $S = 0$ or $I = 0$. If $I = 0$, then $\frac{dI}{dt} = 0$, which means an infection-free population will remain infection-free forever. On the contrary, if $I \neq 0$, and $S > \frac{\alpha}{\mu}$ then $\frac{dI}{dt} > 0$, which is a threshold condition.

3.2.1 Basic Reproductive Number (R_0) of Hepatitis B without Vital Dynamics

The basic reproduction number is one of the most important threshold quantities used in epidemiology. It is denoted by R_0, and it is defined as the average number of secondary infections produced when one infective is introduced into a host population where everyone is susceptible, (Heffernan et al., 2005). This implies that, $S(0) \approx N$, or equivalently $\frac{S(0)}{N} \approx 1$. When $S(0) < \frac{\alpha}{\mu}$, it implies $\frac{\mu S(0)}{\alpha} < 1$ and this statement gives us $\frac{\mu}{\alpha} < 1$. Again when $S(0) > \frac{\alpha}{\mu}$, it implies $\frac{\mu S(0)}{\alpha} > 1$ and this statement gives us $\frac{\mu}{\alpha} > 1$. We refer to

$$R_0 = \frac{\mu}{\alpha} \tag{3.6}$$

.

When $R_0 = \frac{\mu}{\alpha} < 1$, then $\mu < \alpha$, implying that the disease will die out. On the other hand, $R_0 = \frac{\mu}{\alpha} > 1$ implies that $\mu > \alpha$, so an epidemic occurs.

Also, $R_0 = \frac{\mu}{\alpha} = \mu \times \frac{1}{\alpha}$, is the product of the contact rate μ per unit time and the average infection period $\frac{1}{\alpha}$. It can therefore be interpreted as the average number of adequate contacts a typical infective makes with both susceptible and infected persons, during his/her infectious period.

To obtain an expression for the final size of an epidemic, we divide equation (3.5) by (3.4) which gives

$$\frac{dI}{dS} = \frac{\mu SI - \alpha I}{-\mu SI} = -1 + \frac{\alpha}{\mu S}$$

$$dI = \left(-1 + \frac{\alpha}{\mu S}\right) dS = \left(-1 + \frac{1}{R_0 S}\right) dS \tag{3.7}$$

Integrating equation (3.7) using the initial conditions gives

$$dI = -dS + \frac{1}{R_0 S} dS$$

$$\int_{I_0}^{I} dx = -\int_{S_0}^{S} dy + \frac{1}{R_0}\int_{S_0}^{S} \frac{1}{y} dy$$

$$I - I_0 = -(S - S_0) + \frac{1}{R_0} \ln \left|\frac{S}{S_0}\right|$$

Taking limits as $t \to \infty$ of $S(t)$ and $I(t) = 0$, then

$$S_0 + I_0 = S_\infty - \frac{1}{R_0} \ln \left|\frac{S_\infty}{S_0}\right|$$

Let$K = S_0 + I_0$, then

$$K = S_\infty - \frac{1}{R_0} \ln \left|\frac{S_\infty}{S_0}\right|$$

Making the reciprocal of R_0 the subject, we have

$$\frac{1}{R_0} = \frac{K - S_\infty}{lnS_0 - lnS_\infty} \tag{3.8}$$

Equation (3.8) is known as the final size equation.

3.3. The SIR Model of Hepatitis B with Vital Dynamics

When a disease persists in a population for a long period of time, birth and death must be taken into consideration. Let $S(t), I(t)$ and $R(t)$ be proportions of susceptibles, infectives and recovered individuals respectively, each with natural death rate of σ and birth rate of ε. Fig 3.3 represents the flowchart of the SIR model of Hepatitis B with vital dynamics.

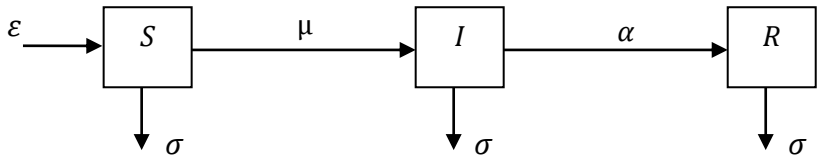

Fig 3.3: Flowchart of the SIR model of Hepatitis B with vital dynamics

With the notations given above, the SIR model with vital dynamics for Hepatitis B is obtained as

$$\frac{dS}{dt} = \varepsilon - \mu SI - \sigma S, \tag{3.9}$$

$$\frac{dI}{dt} = \mu SI - \sigma I - \alpha I, \tag{3.10}$$

$$\frac{dR}{dt} = \alpha I - \sigma R, \tag{3.11}$$

With initial conditions $S(0) = S_{0,}\ I(0) = I_0 > 0, R(0) = 0$, where we assume $\varepsilon = \sigma$. Since $S(t) + I(t) + R(t) = 1$, we can calculate R from $R(t) = 1 - S(t) - I(t)$, once we know $S(t)$, and $I(t)$ from the reduced system

$$\frac{dS}{dt} = \varepsilon - \mu SI - \sigma S, \tag{3.12}$$

$$\frac{dI}{dt} = (\mu S - \sigma - \alpha)I \tag{3.13}$$

Linearization approximation is a standard phase plane technique used to analyze system dynamics. For an SIR system with a constant host population size, we have equations (3.12) and (3.13) to solve for the equilibrium points, thus $\frac{dS}{dt} = \frac{dI}{dt} = 0$. .

$$\varepsilon - \mu SI - \sigma S = 0 \tag{3.14}$$

$$(\mu S - \sigma - \alpha)I = 0 \tag{3.15}$$

Solving simultaneously, let $I = 0$ from equation (3.14), then

$$\varepsilon - \sigma S = 0$$

$$S = \frac{\varepsilon}{\sigma}$$

Since $\varepsilon = \sigma$, then it implies $S = 1$. Hence the equilibrium point is $E_0(S^*, I^*) = (1,0)$.

This gives us a disease-free equilibrium of Hepatitis B.

From equation (3.15)

$$S = \frac{(\sigma + \alpha)}{\mu}$$

Substituting the value of S into equation (3.14), we have

$$\varepsilon - \mu\left(\frac{\sigma + \alpha}{\mu}\right) I - \sigma\left(\frac{\sigma + \alpha}{\mu}\right) = 0 \tag{3.16}$$

Making I the subject from equation (3.16)

$$I = \frac{\mu\varepsilon - \sigma(\sigma + \alpha)}{\mu} \times \frac{1}{(\sigma + \alpha)} = \frac{\mu\varepsilon - \sigma(\sigma + \alpha)}{\mu(\sigma + \alpha)}$$

Thus the equilibrium point is

$$\left(\frac{\sigma + \alpha}{\mu}, \frac{\mu\varepsilon - \sigma(\sigma + \alpha)}{\mu(\sigma + \alpha)}\right) \tag{3.17}$$

This equilibrium point is called the endemic equilibrium point.

Hartman-Grobman Theorem states that in a continuous model, a steady state will be stable provided the eigenvalues of the characteristic equation are both negative (if real) or have a negative real part (complex).

We can determine the stability by finding the Jacobian matrix from equations (3.14) and (3.15). This gives

$$J = \begin{pmatrix} -\mu I - \sigma & -\mu S \\ \mu I & \mu S - (\sigma + \alpha) \end{pmatrix} \tag{3.18}$$

Before the hepatitis B virus was introduced into the population, we have only the susceptible present. From earlier calculations, the disease free equilibrium is $E_0(S^*, I^*) = (1,0)$. In order to determine the stability of the model at this point, we evaluate the Jacobian matrix at this

equilibrium point and find the eigenvalues corresponding to this point. Evaluating the Jacobian at the disease free equilibrium point, we have

$$J(1,0) = \begin{pmatrix} -\mu(0) - \sigma & -\mu(1) \\ \mu(0) & \mu(1) - (\sigma + \alpha) \end{pmatrix} = \begin{pmatrix} -\sigma & -\mu \\ 0 & \mu - \sigma - \alpha \end{pmatrix} \qquad (3.19)$$

We then find the characteristic equation which is given by $det(A - \lambda I) = 0$ where λ is the eigenvalues of A and A is an $n \times n$ matrix. Thus

$$\det(A - \lambda I) = det\left[\begin{pmatrix} -\sigma & -\mu \\ 0 & \mu - \sigma - \alpha \end{pmatrix} - \lambda \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}\right]$$

$$= det\begin{pmatrix} -\sigma - \lambda & -\mu \\ 0 & \mu - \sigma - \alpha - \lambda \end{pmatrix}$$

$$= (-\sigma - \lambda)(\mu - \sigma - \alpha - \lambda) - (-\mu)(0)$$

Because $\det(A - \lambda I) = 0$, implies $(-\sigma - \lambda)(\mu - \sigma - \alpha - \lambda) - (-\mu)(0) = 0$

Therefore, $\lambda_1 = -\sigma < 0$ and $\lambda_2 = \mu - \sigma - \alpha$. (3.20)

The stability of the disease free equilibrium depends on the values of σ, α and μ.

3.3.1. The Basic Reproductive Ratio (R_0) of Hepatitis B with Vital Dynamics

From equations (3.12) and (3.13), we conclude that the average time of an infection is $\frac{1}{\alpha+\sigma}$, and as infectious individuals infect others at rate μ, the basic reproductive number

$$R_0 = \frac{\mu}{\alpha + \sigma} \qquad (3.21)$$

For $\det(A - \lambda I)$ to be asymptotically stable, both eigenvalues must be negative. From $\det(A - \lambda I) = 0$, it is clear that $\lambda_1 = -\sigma$ and therefore if $\lambda_2 = \mu - \sigma - \alpha < 0$ then both eigenvalues are negative and $R_0 < 1$. Hence the disease-free equilibrium is asymptotically stable. On the other hand, if $\lambda_2 = \mu - \sigma - \alpha > 0$, then $\det(A - \lambda I)$ is unstable.

The endemic equilibrium at the point in time where all the compartments of the population coexist, is called the endemic period. We consider the situation whereby there is coexistence of the two main categories (i.e. the susceptible and the infectives). This is seen in the endemic equilibrium point in the equation below

$$\left(\frac{\sigma+\alpha}{\mu}\ ,\frac{\mu\varepsilon-\sigma(\sigma+\alpha)}{\mu(\sigma+\alpha)}\right) \tag{3.22}$$

In order to determine the stability of this point, we resort to the same approach used in determining the stability of the disease free equilibrium. We evaluate the Jacobian matrix at the endemic point by putting equation (3.22) into equation (3.18)

$$J(S^*,I^*)=\begin{pmatrix} -\mu\left(\frac{\mu\varepsilon-\sigma(\sigma+\alpha)}{\mu(\sigma+\alpha)}\right)-\sigma & -\mu\left(\frac{\sigma+\alpha}{\mu}\right) \\ \mu\left(\frac{\mu\varepsilon-\sigma(\sigma+\alpha)}{\mu(\sigma+\alpha)}\right) & \mu\left(\frac{\sigma+\alpha}{\mu}\right)-(\sigma+\alpha) \end{pmatrix}$$

$$=\begin{pmatrix} \left(\frac{-\mu\varepsilon+\sigma(\sigma+\alpha)-\sigma(\sigma+\alpha)}{(\sigma+\alpha)}\right) & -(\sigma+\alpha) \\ \left(\frac{\mu\varepsilon-\sigma(\sigma+\alpha)}{(\sigma+\alpha)}\right) & 0 \end{pmatrix}$$

$$=\begin{pmatrix} \frac{-\mu\varepsilon}{(\sigma+\alpha)} & -(\sigma+\alpha) \\ \frac{\mu\varepsilon-\sigma(\sigma+\alpha)}{(\sigma+\alpha)} & 0 \end{pmatrix}$$

We then find the characteristic equation which is given by

$$\det(A-\lambda I)=0$$

Where λ is the eigenvalues and A is an $n\times n$ matrix. Thus,

$$\det(A-\lambda I)=det\left[\begin{pmatrix} \left(\frac{-\mu\varepsilon}{(\sigma+\alpha)}\right) & -(\sigma+\alpha) \\ \frac{\mu\varepsilon-\sigma(\sigma+\alpha)}{(\sigma+\alpha)} & 0 \end{pmatrix}-\lambda\begin{pmatrix}1 & 0\\ 0 & 1\end{pmatrix}\right]$$

$$= det\begin{pmatrix} \left(\frac{-\mu\varepsilon}{(\sigma+\alpha)} - \lambda\right) & -(\sigma+\alpha) \\ \frac{\mu\varepsilon - \sigma(\sigma+\alpha)}{(\sigma+\alpha)} & -\lambda \end{pmatrix}$$

$$= \left(\frac{-\mu\varepsilon}{(\sigma+\alpha)} - \lambda\right)(-\lambda) + \left(\frac{\mu\varepsilon - \sigma(\sigma+\alpha)}{(\sigma+\alpha)}\right)(\sigma+\alpha)$$

Because $\det(A - \lambda I) = 0$, implies

$$\left(\frac{-\mu\varepsilon}{(\sigma+\alpha)} - \lambda\right)(-\lambda) + \mu\varepsilon - \sigma(\sigma+\alpha) = 0$$

$$\frac{\mu\varepsilon}{(\sigma+\alpha)}\lambda + \lambda^2 + \mu\varepsilon - \sigma^2 - \sigma\alpha = 0$$

$$(\sigma+\alpha)\lambda^2 + \mu\varepsilon\lambda + (\sigma+\alpha)(\mu\varepsilon - \sigma^2 - \sigma\alpha) = 0$$

$$\lambda_{1,2} = \frac{-\mu\varepsilon \pm \sqrt{(\mu\varepsilon)^2 - 4(\sigma+\alpha)(\sigma+\alpha)(\mu\varepsilon - \sigma^2 - \sigma\alpha)}}{2(\sigma+\alpha)}$$

$$= \frac{\frac{-\mu\varepsilon}{\sigma+\alpha} \pm \sqrt{\left(\frac{\mu\varepsilon}{\sigma+\alpha}\right)^2 - 4(\mu\varepsilon - \sigma(\sigma+\alpha))}}{2} \tag{3.23}$$

The stability of the endemic equilibrium depends on the values of σ, α, μ and ε.

3.4 The SIR Model with Vaccination

In general, we can use SIR model to describe the transmission dynamics of the disease if the vaccination leads to permanent immunity. E.g. We assume that a portion of susceptible, bS, go to the removal compartment R directly, due to permanent immunity obtained from vaccination. Figure 3.4 show the flowchart of an SIR model with vaccination.

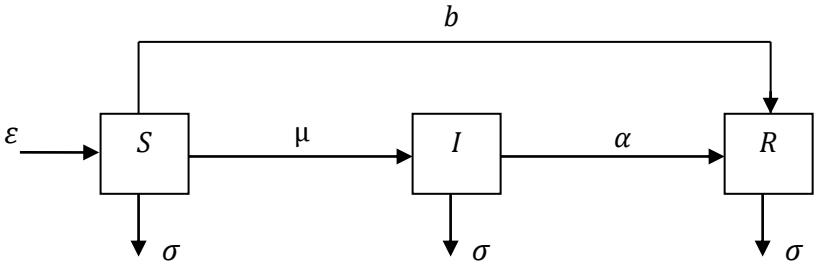

Figure 3.4: Flowchart of an SIR model with vaccination.

Where b is the vaccinating rate for the susceptibles. From the diagram

$$\frac{dS}{dt} = \varepsilon - \mu SI - \sigma S - bS, \tag{3.24}$$

$$\frac{dI}{dt} = \mu SI - (\sigma - \alpha)I, \tag{3.25}$$

$$\frac{dR}{dt} = \alpha I - \sigma R + bS, \tag{3.26}$$

where we assume $\varepsilon = \sigma + b$. Here, the reduced system is

$$\frac{dS}{dt} = \varepsilon - \mu SI - \sigma S - bS, \tag{3.27}$$

$$\frac{dI}{dt} = \mu SI - (\sigma - \alpha)I, \tag{3.28}$$

3.4.1 Equilibrium Points

To solve for the equilibrium points we have:

$$\varepsilon - \mu SI - \sigma S - bS = 0 \tag{3.29}$$

$$(\mu S - \sigma - \alpha)I = 0 \tag{3.30}$$

Solving simultaneously and from equation (3.30)

$$\mu S - \sigma - \alpha = 0$$

$$S = \frac{\sigma + \alpha}{\mu} \tag{3.31}$$

Since $\varepsilon = \sigma + b$, then it implies $S = 1$. Hence the equilibrium point is $E_0(S^*, I^*) = (1,0)$. This gives us a disease-free equilibrium of Hepatitis B. Substituting the value of S into equation (3.29), we have

$$\varepsilon - \mu SI - \sigma S - bS = 0$$

$$\mu SI = \varepsilon - \sigma S - bS$$

$$I = \frac{\varepsilon}{\mu S} - \frac{\sigma S}{\mu S} - \frac{bS}{\mu S}$$

$$I = \frac{\varepsilon}{\mu S} - \frac{\sigma}{\mu} - \frac{b}{\mu}$$

$$I = \frac{\varepsilon}{\mu}\left(\frac{\mu}{\sigma + \alpha}\right) - \frac{\sigma}{\mu} - \frac{b}{\mu}$$

$$= \frac{\varepsilon\mu - \sigma(\sigma + \alpha) - b(\sigma + \alpha)}{\mu(\sigma + \alpha)}$$

$$= \frac{\varepsilon\mu - (\sigma + b)(\sigma + \alpha)}{\mu(\sigma + \alpha)} \tag{3.32}$$

Thus, the equilibrium point is

$$\left(\frac{\sigma + \alpha}{\mu}, \frac{\varepsilon\mu - (\sigma + b)(\sigma + \alpha)}{\mu(\sigma + \alpha)}\right) \tag{3.33}$$

This equilibrium point is called the endemic equilibrium point.

We determine the stability by finding the Jacobian matrix using equation (3.29) and (3.30). This gives

$$J = \begin{pmatrix} -\mu I - \sigma - b & -\mu S \\ \mu I & \mu S - (\sigma + \alpha) \end{pmatrix} \tag{3.34}$$

3.4.2 Disease Free Equilibrium

Evaluating the Jacobian at the disease free equilibrium point, we have

$$J(1,0) = \begin{pmatrix} -\mu(0) - \sigma - b & -\mu(1) \\ \mu(0) & \mu(1) - (\sigma + \alpha) \end{pmatrix}$$

$$J(1,0) = \begin{pmatrix} -\sigma - b & -\mu \\ 0 & \mu - \sigma - \alpha \end{pmatrix} \tag{3.35}$$

Thus

$$\det(A - \lambda I) = det\left[\begin{pmatrix} -\sigma - b & -\mu \\ 0 & \mu - \sigma - \alpha \end{pmatrix} - \lambda \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}\right]$$

$$= det\begin{pmatrix} -\sigma - b - \lambda & -\mu \\ 0 & \mu - \sigma - \alpha - \lambda \end{pmatrix}$$

$$= (-\sigma - b - \lambda)(\mu - \sigma - \alpha - \lambda) - (-\mu)(0)$$

Because $\det(A - \lambda I) = 0$, implies $(-\sigma - b - \lambda)(\mu - \sigma - \alpha - \lambda) - (-\mu)(0) = 0$

Therefore, $\lambda_1 = -\sigma - b$ or $\lambda_2 = \mu - \sigma - \alpha$. The eigenvalues corresponding to the disease free equilibrium

$E_0(S^*, I^*) = (1,0)$ are $-\sigma - b$ or $\mu - \sigma - \alpha$. (3.36)

The stability of the disease free equilibrium with vaccination depends on the values of $\sigma, \alpha, b \; and \; \mu$.

3.4.3. The Basic Reproductive Ratio (R_0) Of Hepatitis B with Vaccination

For $\det(A - \lambda I)$ to be asymptotically stable, both eigenvalues must be negative. From $\det(A - \lambda I) = 0$, it is clear that $\lambda_1 = -\sigma - b$ is negative and therefore if $\lambda_2 = \mu - \sigma - \alpha < 0$ then both eigenvalues are negative and $R_0 < 1$. Hence the disease-free equilibrium is asymptotically stable. On the other hand, if $\lambda_2 = \mu - \sigma - \alpha > 0$, then $\det(A - \lambda I)$ is unstable.

The stability of the disease free equilibrium with vaccination depends on the values of σ, α, b and μ.

3.4.4. The Endemic Equilibrium

The endemic equilibrium point is given by equation (3.37) where there is coexistence between the two main categories.

$$\left(\frac{\sigma+\alpha}{\mu}, \frac{\varepsilon\mu-(\sigma+b)(\sigma+\alpha)}{\mu(\sigma+\alpha)}\right) \tag{3.37}$$

In order to determine the stability of this point, we resort to the same approach used in determining the stability of the disease free equilibrium. The Jacobian matrix at the endemic point is given by:

$$J(S^*, I^*) = \begin{pmatrix} -\mu\left(\frac{\mu\varepsilon-(\sigma+b)(\sigma+\alpha)}{\mu(\sigma+\alpha)}\right)-\sigma & -\mu\left(\frac{\sigma+\alpha}{\mu}\right) \\ \mu\left(\frac{\mu\varepsilon-(\sigma+b)(\sigma+\alpha)}{\mu(\sigma+\alpha)}\right) & \mu\left(\frac{\sigma+\alpha}{\mu}\right)-(\sigma+\alpha) \end{pmatrix}$$

$$J(S^*, I^*) = \begin{pmatrix} -\left(\frac{\mu\varepsilon-(\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)}\right)-\sigma & -(\sigma+\alpha) \\ \left(\frac{\mu\varepsilon-(\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)}\right) & 0 \end{pmatrix}$$

$$J(S^*, I^*) = \begin{pmatrix} \frac{-\mu\varepsilon+(\sigma+b)(\sigma+\alpha)-\sigma(\sigma+\alpha)}{(\sigma+\alpha)} & -(\sigma+\alpha) \\ \frac{\mu\varepsilon-(\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)} & 0 \end{pmatrix}$$

$$J(S^*, I^*) = \begin{pmatrix} \frac{-\mu\varepsilon+(\sigma+\alpha)(\sigma+b-\sigma)}{(\sigma+\alpha)} & -(\sigma+\alpha) \\ \frac{\mu\varepsilon-(\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)} & 0 \end{pmatrix}$$

$$J(S^*, I^*) = \begin{pmatrix} \dfrac{-\mu\varepsilon + b(\sigma+\alpha)}{(\sigma+\alpha)} & -(\sigma+\alpha) \\ \dfrac{\mu\varepsilon - (\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)} & 0 \end{pmatrix}$$

We then find the characteristic equation which is given by $\det(A - \lambda I) = 0$. Where λ is the eigenvalue and A is an $n \times n$ matrix. Thus,

$$\det(A - \lambda I) = det\left[\begin{pmatrix} \dfrac{-\mu\varepsilon + b(\sigma+\alpha)}{(\sigma+\alpha)} & -(\sigma+\alpha) \\ \dfrac{\mu\varepsilon - (\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)} & 0 \end{pmatrix} - \lambda\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}\right]$$

$$= det\begin{pmatrix} \dfrac{-\mu\varepsilon + b(\sigma+\alpha)}{(\sigma+\alpha)} - \lambda & -(\sigma+\alpha) \\ \dfrac{\mu\varepsilon - (\sigma+b)(\sigma+\alpha)}{(\sigma+\alpha)} & -\lambda \end{pmatrix}$$

$$= \left(\frac{-\mu\varepsilon + b(\sigma+\alpha)}{(\sigma+\alpha)} - \lambda\right)(-\lambda) + \left(\frac{\mu\varepsilon - \sigma(\sigma+\alpha)}{(\sigma+\alpha)}\right)(\sigma+\alpha)$$

Because $\det(A - \lambda I) = 0$, implies

$$\left(\frac{-\mu\varepsilon + b(\sigma+\alpha)}{(\sigma+\alpha)} - \lambda\right)(-\lambda) + \left(\frac{\mu\varepsilon - \sigma(\sigma+\alpha)}{(\sigma+\alpha)}\right)(\sigma+\alpha) = 0$$

$$\lambda^2 + \frac{\mu\varepsilon - b(\sigma+\alpha)}{(\sigma+\alpha)}\lambda + \mu\varepsilon - \sigma(\sigma+\alpha) = 0$$

$$(\sigma+\alpha)\lambda^2 + (\mu\varepsilon - b(\sigma+\alpha))\lambda + (\sigma+\alpha)(\mu\varepsilon - \sigma^2 - \sigma\alpha) = 0$$

$$\lambda_{1,2} = \frac{-(\mu\varepsilon - b(\sigma+\alpha)) \pm \sqrt{\left(\mu\varepsilon - b(\sigma+\alpha)\right)^2 - 4(\sigma+\alpha)(\sigma+\alpha)(\mu\varepsilon - \sigma^2 - \sigma\alpha)}}{2(\sigma+\alpha)}$$

$$= \frac{\frac{-(\mu\varepsilon - b(\sigma+\alpha))}{\sigma+\alpha} \pm \sqrt{\left(\frac{\mu\varepsilon - b(\sigma+\alpha)}{\sigma+\alpha}\right)^2 - 4(\mu\varepsilon - \sigma(\sigma+\alpha))}}{2} \qquad (3.38)$$

The stability of the endemic equilibrium with vaccination depends on the values of $\sigma, \alpha, \mu, \varepsilon$ and b.

3.5. Herd Immunity Threshold

In a large group of individuals where there exists a contagious disease, if a large enough of individuals is immune to the disease, the chances that a chain of disease transmission will be interrupted are very high, resulting in self-contained, small outbreaks that will die out quickly, (Diekman and Heesterbeek, 2000). Thus, individuals that are not immune will be protected by the wall that is set up by the vaccinated ones. The Herd Immunity Threshold (H_1) is percentage of the population that needs to be immune to control transmission of a disease. Diekman and Heesterbeek (2000) provided an equation for estimating the Herd Immunity Threshold. The equation is given as

$$H_1 = 1 - \frac{1}{R_0}$$

Substituting $R_o = \frac{\mu}{\sigma+\alpha}$, into the equation above, we have

$$H_1 = 1 - 1 \div \left(\frac{\mu}{\sigma + \alpha}\right)$$

$$H_1 = 1 - \left(\frac{\sigma + \alpha}{\mu}\right)$$

$$H_1 = \frac{\mu - \sigma - \alpha}{\mu} \tag{3.39}$$

Therefore, the level of vaccination is directly proportional to the herd immunity threshold. As the amount of vaccination increases, the herd immunity threshold also increases.

CHAPTER FOUR

RESULTS AND DISCUSSIONS

4.1. Introduction

In this chapter, we analyze the model using clinical values and discuss the results obtained. In solving the systems of differential equations, we employed the forth order Runge-Kutta method. The algorithms for the analysis were implemented using Matlab.

Sensitivity analysis was performed on the parameter values to determine the effect of these values on the rate of spread of Hepatitis B virus.

4.2. Simulations and Results of SIR model with vital dynamics

Considering the SIR model with vital dynamics we use the estimated parameters in table 4.1

Table 4.1: Parameter values for the SIR model with vital dynamics

Description	Parameter	Value
Birth rate	ε	0.03
Infectious rate	μ	0.13
Recovered rate	α	0.085
Natural death rate	σ	0.03

Source: Battor Catholic Hospital, Battor.

From equation (3.21), we obtained the reproductive number to be

$$R_0 = \frac{0.13}{0.085 + 0.03} = 1.1304$$

This means that on the average, one hepatitis B patient contacts 1.1304 susceptible people in the population during his/her infectious period. Since the reproductive number $R_0 = 1.1304 > 1$, an outbreak of hepatitis B will result in an epidemic in the North Tongu District.

Figure 4.1 depicts the dynamics of the various compartments (susceptible, infectives and recovered) during the outbreak, where $S(t) = 0.95, I(t) = 0.05$ and $R(t) = 0.00$. When the initial infectives is 0.05, the proportion of the susceptibles declines from an initial value of 0.95 to an approximate minimum value of 0.83 from week one to week 60 and begins to increase gradually afterwards, reaching a value of 0.89.

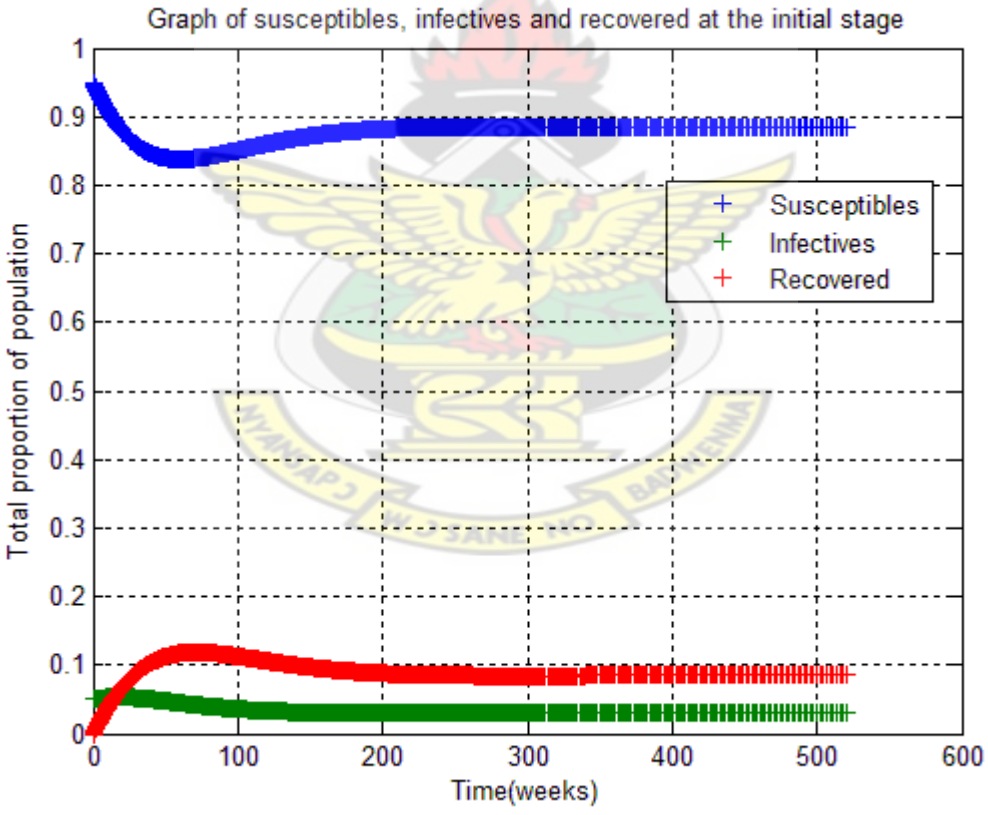

Figure 4.1: The dynamics of the various compartments during the outbreak.

The population of the infectives declines asymptotically from the first week reaching a minimum value of 0.03 on the 160th week and maintaining that value onwards. Also, the proportion of the recovered population increased after the initial week and reaches a maximum value of 0.12 on the 70th week and then declining steadily with time until it reaches a value of 0.08 on the 180th week and maintaining that value afterwards.

4.2.1. Effects of initial infectives on the various compartments.

Experiments were performed to verify the effect of varying initial infectives on the dynamics of the susceptible, infective, and recovered populations. Table 4.2 contains the various instances considered for the initial number of infectives. The number of susceptibles vary appropriately with change in the number of infectives.

Table 4.2: Varying the initial number of infectives

Infectives	Susceptibles	Recovered
0.05	0.95	0.00
0.10	0.90	0.00
0.20	0.80	0.00
0.30	0.70	0.00

From Figure 4.2 below, when the initial proportion of the infectives is 0.05, the proportion of the susceptibles declined from an initial value of 0.95 to an approximate minimum value of 0.84 from week one to week 60 and then began to increase until attaining a constant value of 0.89 at week 200.

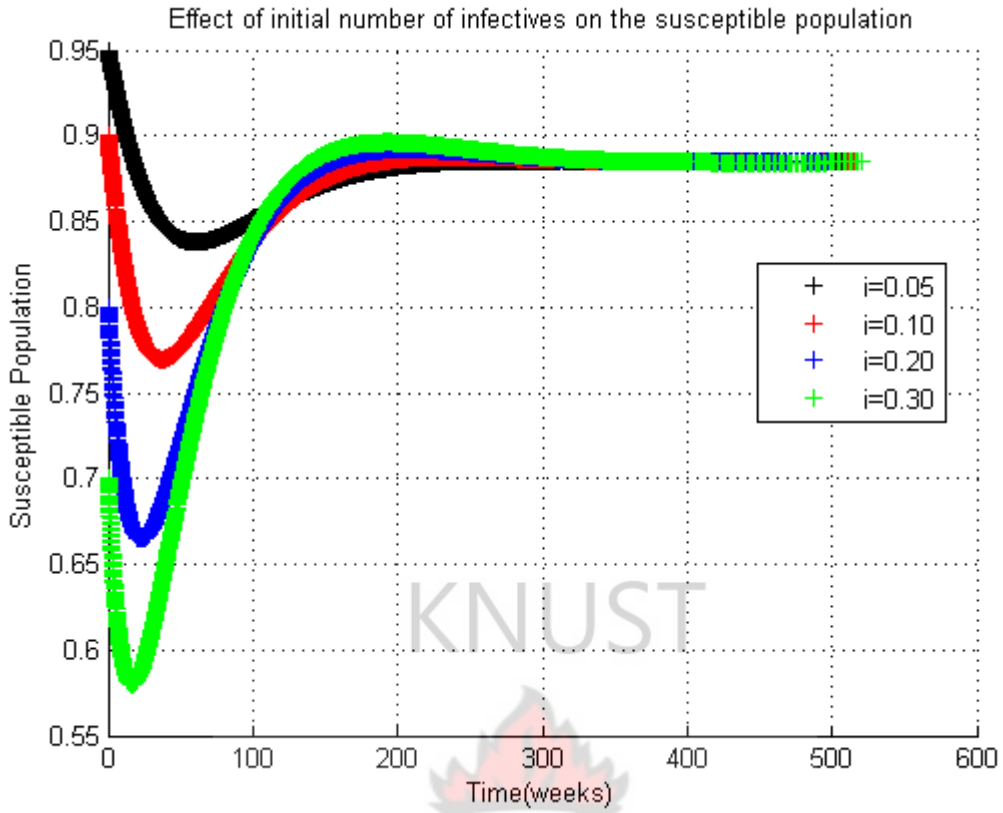

Figure 4.2: Effects of initial infectives on the susceptible population with vital dynamics.

When the initial proportion of infectives is increased to 0.10, 0.20 and 0.30, the proportion of the susceptibles declined from an initial value of 0.90, 0.80 and 0.70 to a minimum value of 0.77 in 40 weeks, 0.67 within 30 weeks, and 0.58 within 20 weeks respectively. After week 340, they all attained a steady state of 0.89.

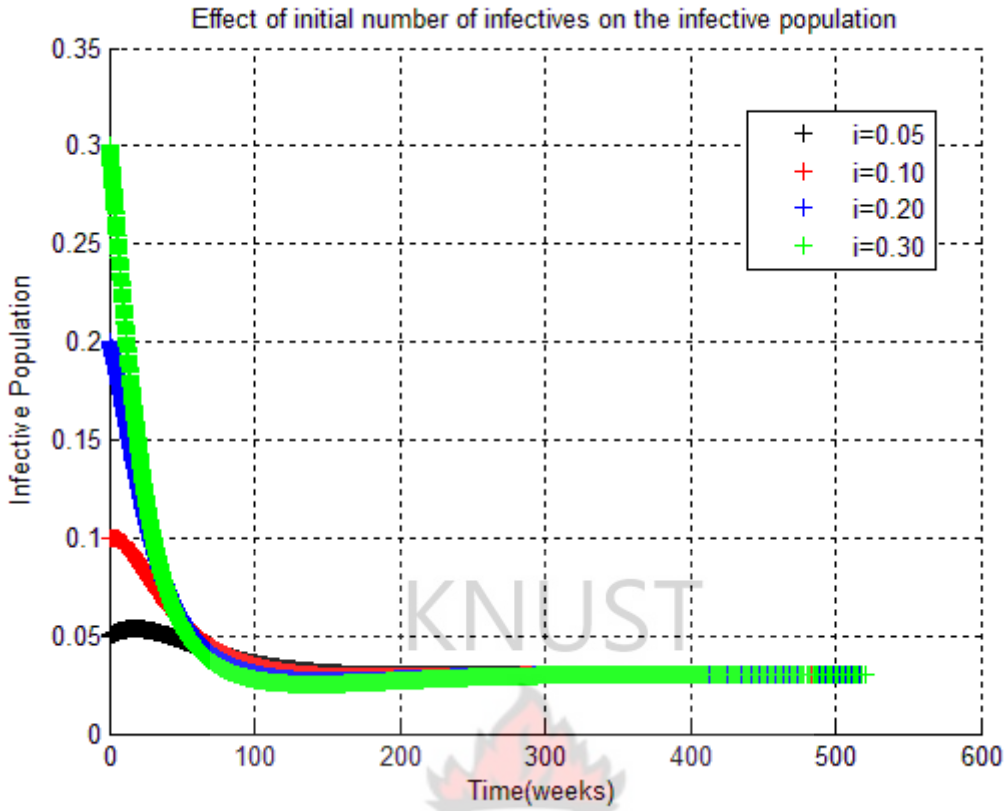

Fig 4.3: Effects of initial infectives on the infective population with vital dynamics

In Figure 4.3 above, as the initial proportion of infectives is 0.05, the proportion of the infectives declines from its initial value of 0.05 to its minimum value of 0.03 within 160 weeks. With the initial proportion being 0.10, 0.20 and 0.30, the infective populations exhibited similar behavior by declining exponentially to 0.03 by week 150. It is observed that the higher the initial proportion of the infectives, the faster the declination.

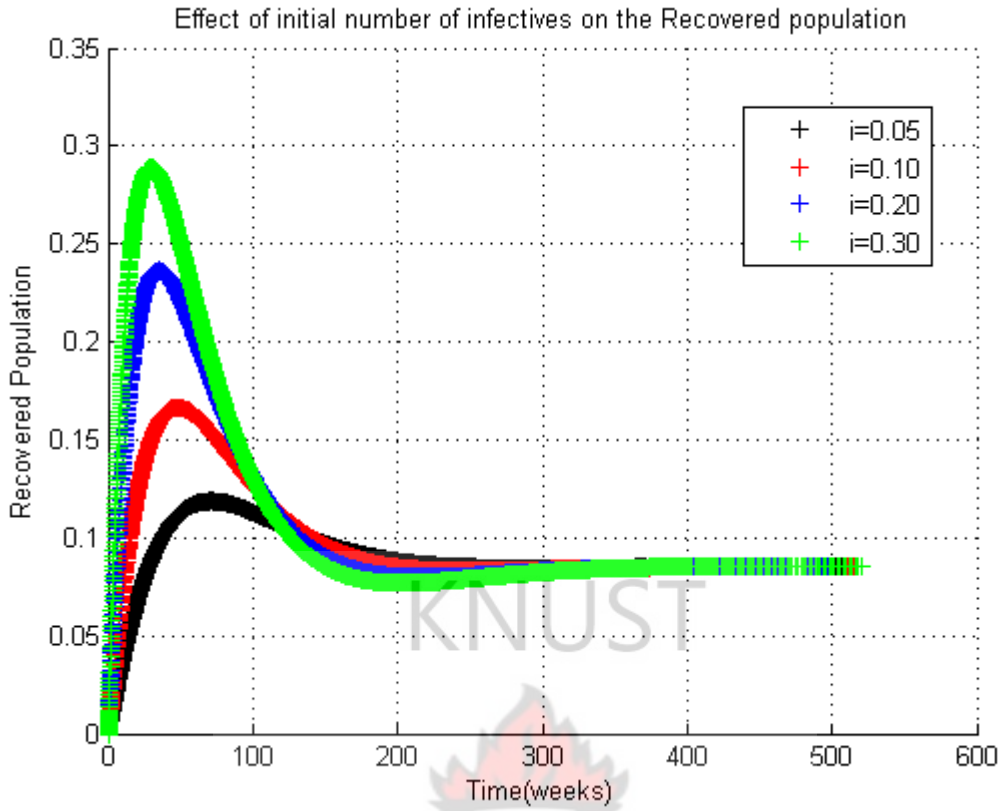

Figure 4.4: Effects of initial infectives on the recovered population with vital dynamics

From Figure 4.4, as the initial proportion of infectives is 0.05, the proportion of the recovered population rises exponentially from zero at week one to a peak value of 0.12 on week 70 before reducing gradually to 0.08 on week 210 and remained stable at that value as the weeks go by. As the initial proportion of the infectives is increased to 0.10, the maximum value of 0.17 was reached on week 50.

Similar observations are made for increasing number of initial proportion of infectives. However, each proportion of the recovered population attains different peak values but at different times with all declining to a minimum of 0.08.

4.2.2. Stability Analysis of the model with vital dynamics

We now look at the linear stability of the infectious free equilibrium point $E_0(S^*, I^*) = (1,0)$. By substituting the parameter values in table 4.1 into equation (3.20), the eigenvalues corresponding to the infectious free equilibrium are $\lambda_1 = -0.03$ and $\lambda_2 = 0.015$. Because the two eigenvalues are both real, one is positive and the other negative, it implies the disease free equilibrium is a saddle point, therefore unstable. The unstable equilibrium implies that the presence of a Hepatitis B positive patient in North Tongu will eventually result in an outbreak of the disease.

The endemic equilibrium point occurs at a time where all the compartments of the population coexists in the population. The introduction of an infected person will infect others, therefore changing the health condition of a lot of people. Substituting the parameter values in Table 4.1 into equation (3.23), we obtain the eigenvalues corresponding to the endemic equilibrium. This is given by

$$\lambda_{1,2} = \frac{\left(\frac{\mu\varepsilon}{\sigma+\alpha}\right) \pm \sqrt{\left(\frac{\mu\varepsilon}{\sigma+\alpha}\right)^2 - 4\left(\mu\varepsilon - \sigma(\sigma+\alpha)\right)}}{2}$$

$$\lambda_{1,2} = \frac{-\left(\frac{0.13\times0.03}{0.03+0.085}\right) \pm \sqrt{\left(\frac{0.13\times0.03}{0.03+0.085}\right)^2 - 4\left(0.13\times0.03 - 0.03(0.03+0.085)\right)}}{2}$$

$$\lambda_{1,2} = \frac{-0.0339 \pm \sqrt{(0.0339)^2 - 0.0018}}{2}$$

$\lambda_1 = -0.01695 + 0.01276i$ and $\lambda_2 = -0.01695 - 0.01276i$

Since the eigenvalues have real negative parts with complex conjugates, it implies the endemic equilibrium is asymptotically stable.

4.2.3. Sensitivity Analysis of the model with Vital Dynamics

Vital dynamics is introducing birth and death into a population when a disease persists for a long period of time.

Table 4.3: Parameter values, Eigenvalues and classification of the disease free equilibrium with Vital Dynamics.

ε	μ	α	λ_1	λ_2	σ	R_0	Nature of the equilibrium
0.03	0.095	0.085	-0.03	-0.02	0.03	0.8261	Stable sink
0.03	0.130	0.085	-0.03	0.015	0.03	1.1304	Unstable saddle
0.03	0.085	0.085	-0.03	-0.03	0.03	0.7390	Stable improper sink
0.03	0.115	0.085	-0.03	0	0.03	1.000	Neutrally stable

Source: Battor Catholic Hospital, Battor.

From equation (3.20), we could observe that the eigenvalues, $\lambda_1 = -\sigma$ and since $\sigma > 0$, it implies that $\lambda_1 < 0$. Considering the second eigenvalue, $\lambda_2 = \mu - \sigma - \alpha$, stability can only be obtained if $\lambda_2 < 0$. Thus $\mu < \sigma + \alpha$, and $\frac{\mu}{\sigma+\alpha} < 1$ implying $R_0 < 1$.

The disease free equilibrium will be stable if the reproductive number is less than unity, i.e. $R_0 < 1$, whilst the disease free equilibrium is unstable if the reproductive number is greater than unity.

Table 4.4: Parameter values, Eigenvalues and classification of equilibrium points of the endemic equilibrium with Vital Dynamics

ε	μ	α	λ_1	λ_2	σ	R_0	Nature of the equilibrium
0.03	0.095	0.085	0.01506	-0.03984	0.03	0.8261	Unstable saddle
0.03	0.130	0.085	0.02090	-0.04307	0.03	0.7391	Unstable saddle
0.03	0.085	0.085	-0.01696 + 0.01275i	-0.01696 -0.01275i	0.03	1.1304	Stable spiral sink
0.03	0.115	0.085	0	-0.03	0.03	1.000	Neutrally stable

Source: Battor Catholic Hospital, Battor.

From the above table, it is observed that the endemic equilibrium is stable when the reproductive number is greater than unity, i.e. $R_0 > 1$, and unstable when the reproductive number is less than unity, i.e. $R_0 < 1$.

4.3. Simulations and Results of SIR model with Vaccination

Considering the SIR model with vaccination, we use the estimated parameters in Table 4.5

Table 4.5: Parameter values for the SIR model with vaccination

Description	Parameter	Value
Birth rate	ε	0.03
Infectious rate	μ	0.13
Recovered rate	α	0.085
Natural death rate	σ	0.03
Vaccination rate	b	0.01

Source: Battor Catholic Hospital, Battor.

From Figure 4.5, when the initial infectives is 0.05, the proportion of the susceptibles declines from an initial value of 0.95 to an approximate minimum value of 0.69 from the first week to week 50 and then begins to increase gradually as the weeks go by until week 180 when it assumes a constant value of 0.75.

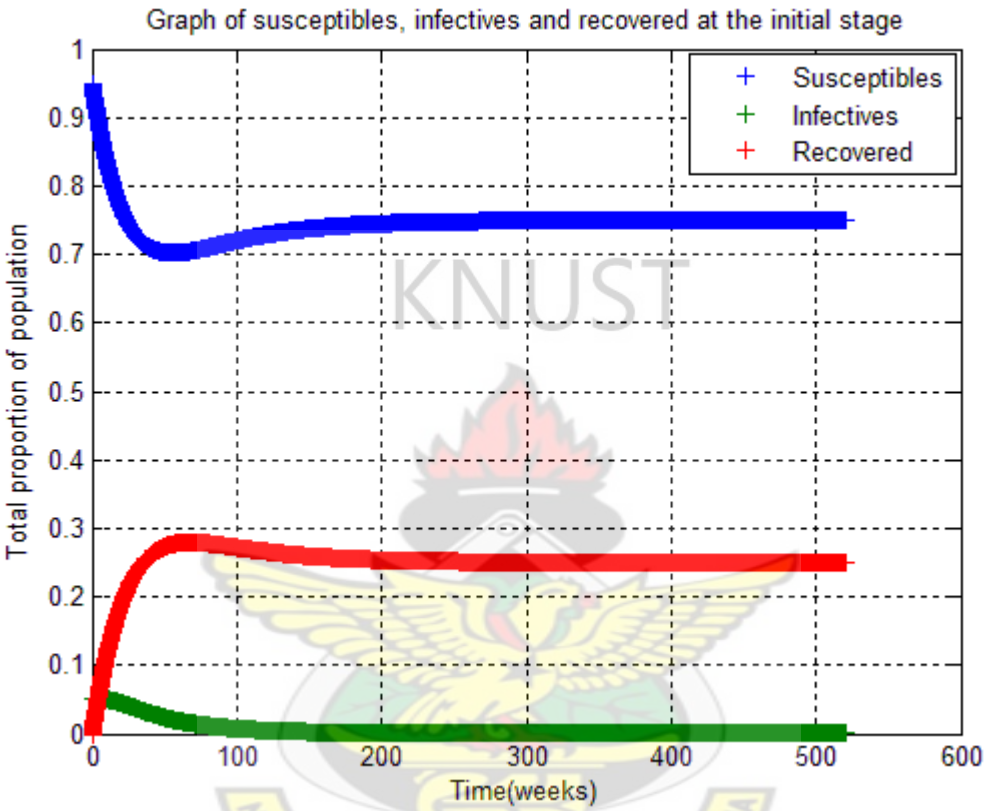

Figure 4.5: The effect of vaccination on the dynamics of the various compartments during the outbreak.

The population of infectives declines from a value of 0.05 to zero within the first 90 weeks and remained constant at zero. Also, the proportion of the recovered population increases sharply from zero to reach a maximum value of 0.29 in the range of week one to week 60 before reducing gently afterwards to a value of 0.25 by week 180 where it remained stable from then forward.

Hence, the susceptibles decreased due to the introduction of the infectives and also by the introduction of vaccines which moved a lot more people from the susceptible state to the recovered state. This accounted for the decline in the infectives to approximately zero as the weeks go by.

4.3.1: Effects of initial infectives on the various compartments with vaccination.

We consider the experimental setup as in the case of the effects of initial infectives on the various compartments with vital dynamics. The various number of initial infectives considered are contained in Table 4.2.

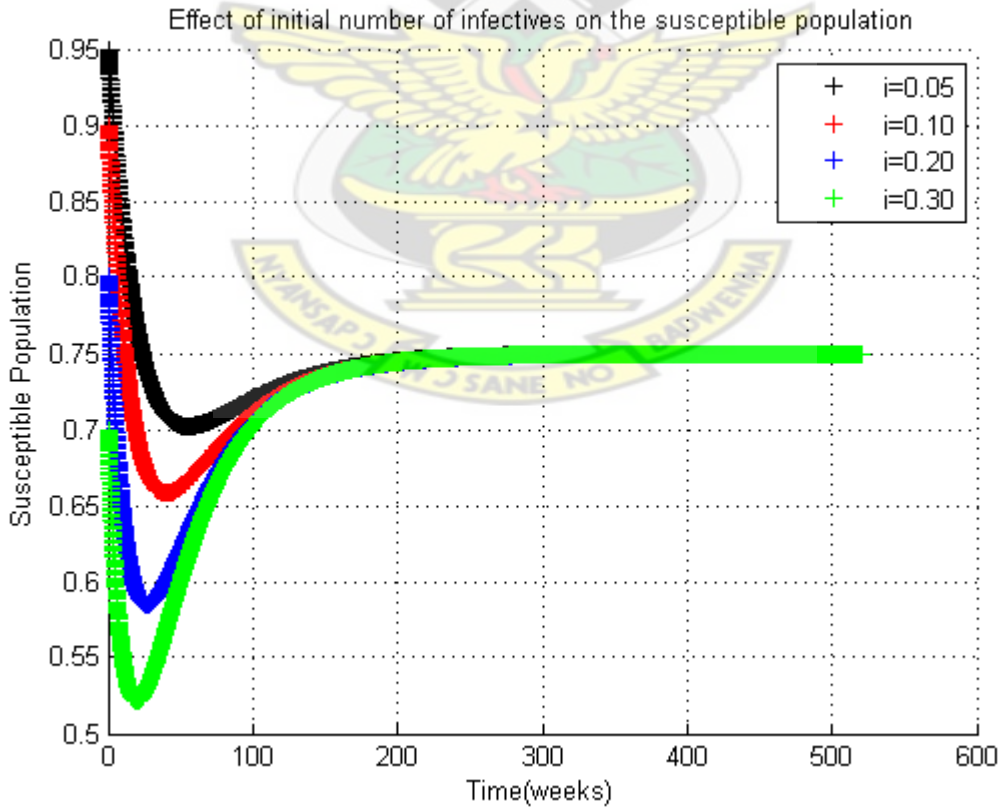

Figure 4.6: Effects of initial infectives on susceptible population with vaccination

From Figure 4.6 above, when the initial proportion of the infectives is 0.05, the proportion of the susceptibles declines from an initial value of 0.95 to an approximate minimum value of 0.7 from week one to week 55 and begans to rise until week 200 where it attains a value of 0.75 and remains constant as the weeks go by.

When the initial proportion of infectives is increased to 0.10, 0.20 and 0.30, the proportion of the susceptibles, declines to a value of 0.66 at week 45, value of 0.58 at week 35 and value of 0.52 at week 25 respectively, and they all rise at varying slopes but all reach a constant value of 0.75 at week 200 and remains constant.

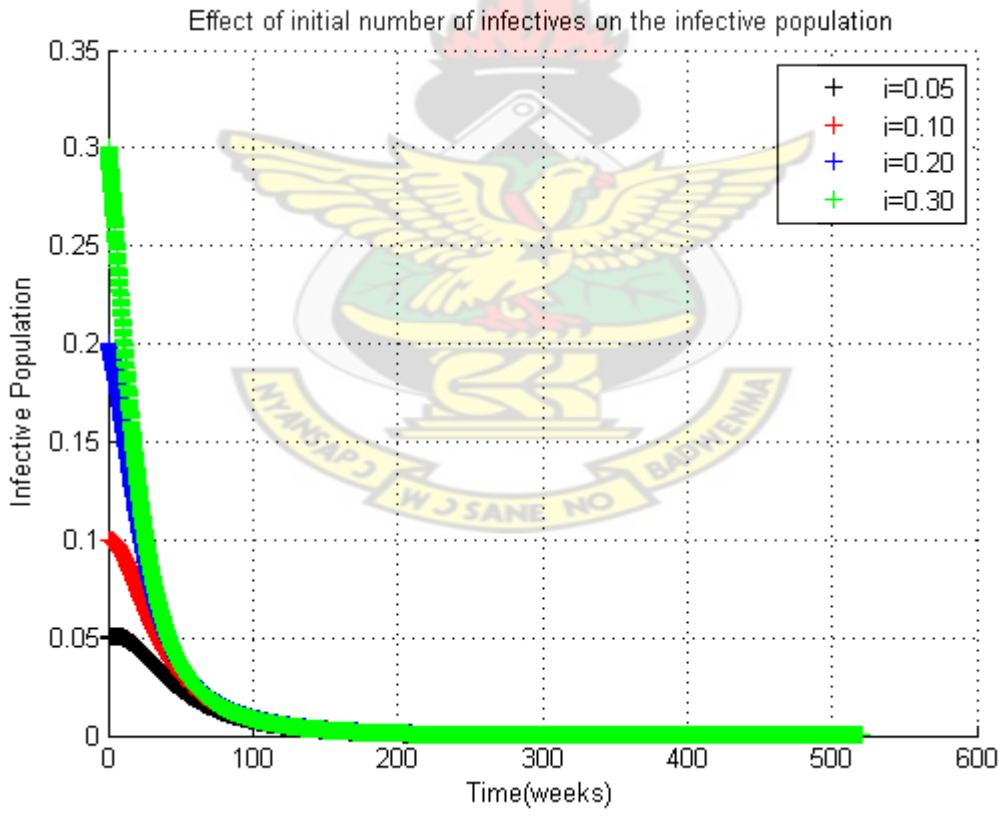

Fig 4.7: Effects of initial infectives on the infective population with vaccination.

In Figure 4.7 above, as the initial proportion of infectives is 0.05, the proportion of the infectives declines from its initial value of 0.05. Due to the vaccination, the proportion of the infectives declines from its initial value of 0.05 to zero within 130 weeks. With the initial proportion being 0.10, 0.20 and 0.30, the infective population exhibits similar behavior as before by declining exponentially to zero by week 130. It is observed that the presence of vaccination has forced the infective population to zero all by week 130.

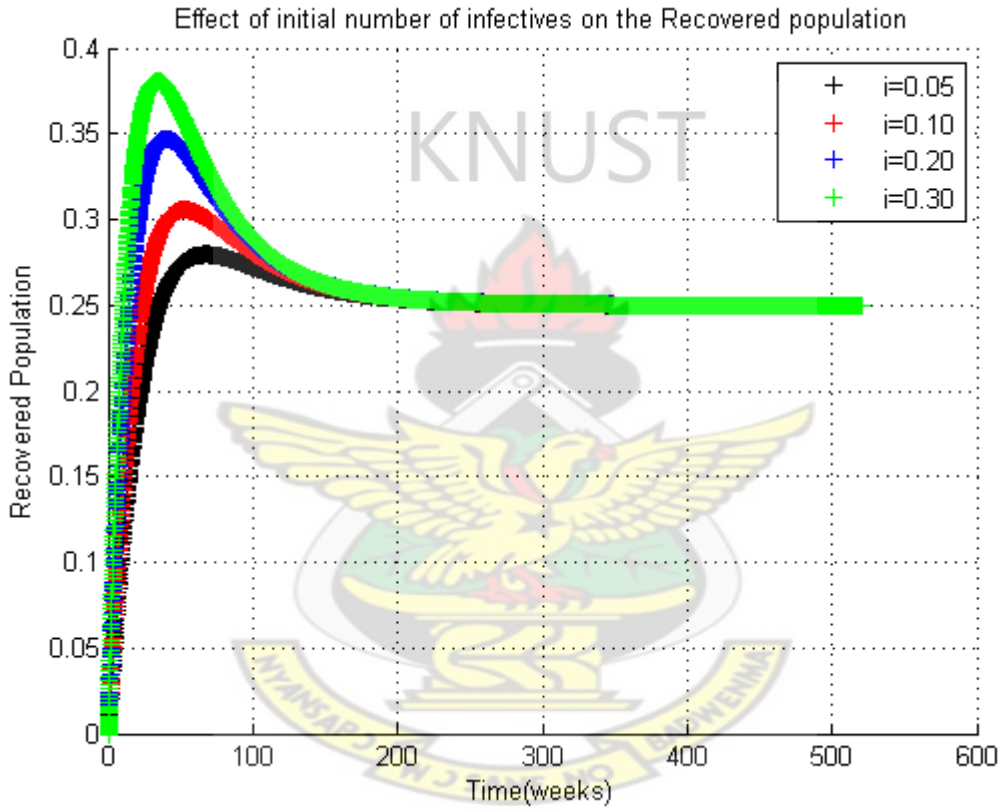

Figure 4.8: Effects of initial infectives on the recovered population with vaccination.

From Figure 4.8, as the initial proportion of infectives is 0.05, the proportion of the recovered population rises to a peak value of 0.28 on week 65 before reducing gradually to a value of 0.25 on week 190 and remains stable at that value as the weeks go by. As the initial value of infectives is increased, the recovered population values increased accordingly before reaching their varying turning points. By week 190, all the values decrease to a

constant value of 0.25. It is observed that the presence of vaccination has contributed to the very high recovery population.

4.3.2. Effect of varying initial Vaccination Parameter on the model

In this section, our simulations will focus on the effects of varying levels of vaccination on the susceptibles, infectives and recovered population.

Table 4.6: Varying vaccination parameters

Birth rate (ε)	Infection rate (μ)	Vaccination rate (b)	Recovery rate (α)	Natural death rate (σ)
0.03	0.13	0.01	0.085	0.03
0.03	0.13	0.02	0.085	0.03
0.03	0.13	0.03	0.085	0.03

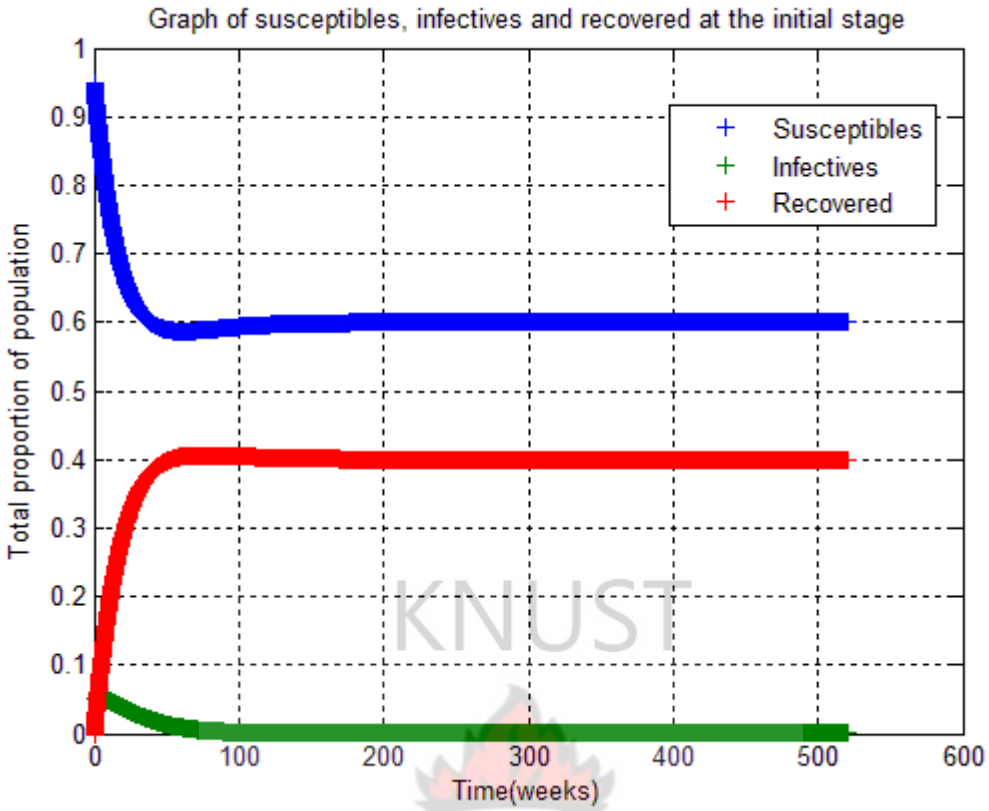

Figure 4.9: Dynamics of various compartments during the outbreak with vaccination rate $b = 0.02$

From Figure 4.9, when the initial infectives is 0.05, the proportion of the susceptibles declines from an initial value of 0.95 to an approximate minimum value of 0.58 from week one to week 50 and increased slightly to a value of 0.60 after 50 weeks and remained constant as the weeks go by. The proportion of infectives declined from a value of 0.05 to zero within the first 50 weeks and remained at zero.

The proportion of the recovered population increased sharply from zero to a value of 0.4 within 50 weeks. It can be observed that the sharp decrease in the susceptibles is caused by the increase in vaccination as it moves the susceptible population to the recovery class.

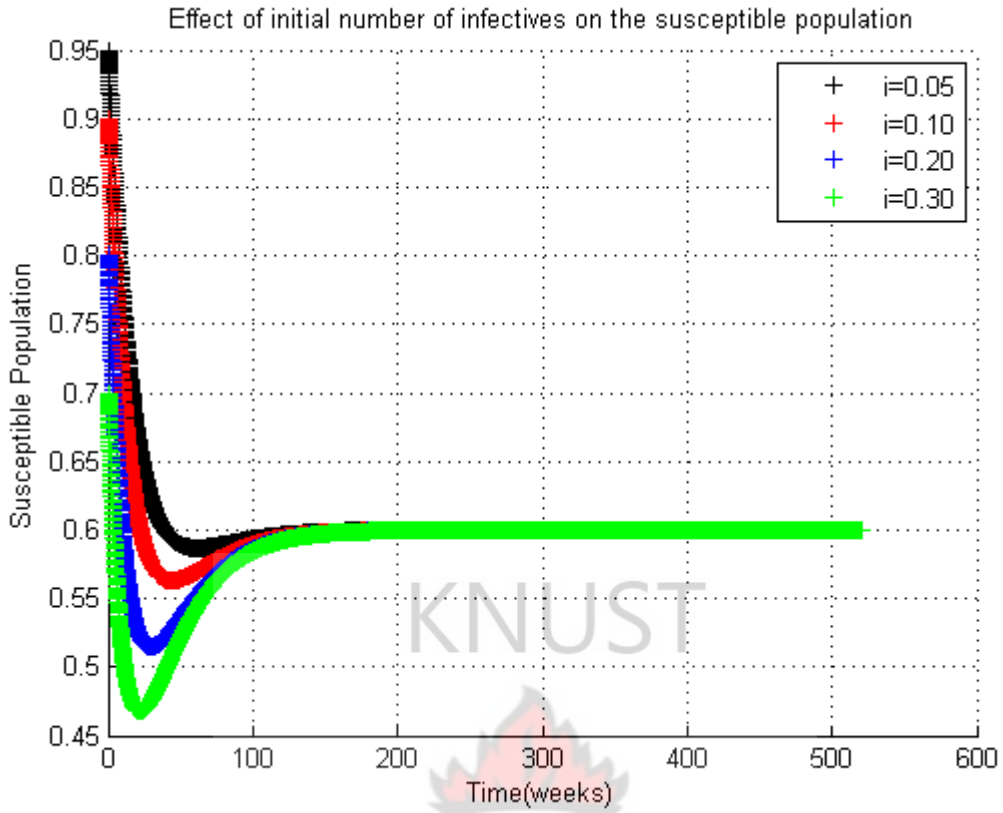

Figure 4.10: Effects of initial infectives on the susceptible population with vaccination rate $b = 0.02$

In the Figure 4.10 above, when the initial proportion of the infectives is 0.05, the proportion of the susceptibles declines from an initial value of 0.95 to an approximate minimum value of 0.58 from week one to week 65 before rising to a value of 0.60 by week 100 and remained constant.

As the initial proportion of infectives is increased, there was a corresponding decrease in the susceptible turning point values as well as the number of weeks it takes to get to the turning point. It can be observed that no matter the initial infectives introduced into the susceptible population, by week 120, they will all reach a value 0.6 and remain there as the weeks progresses.

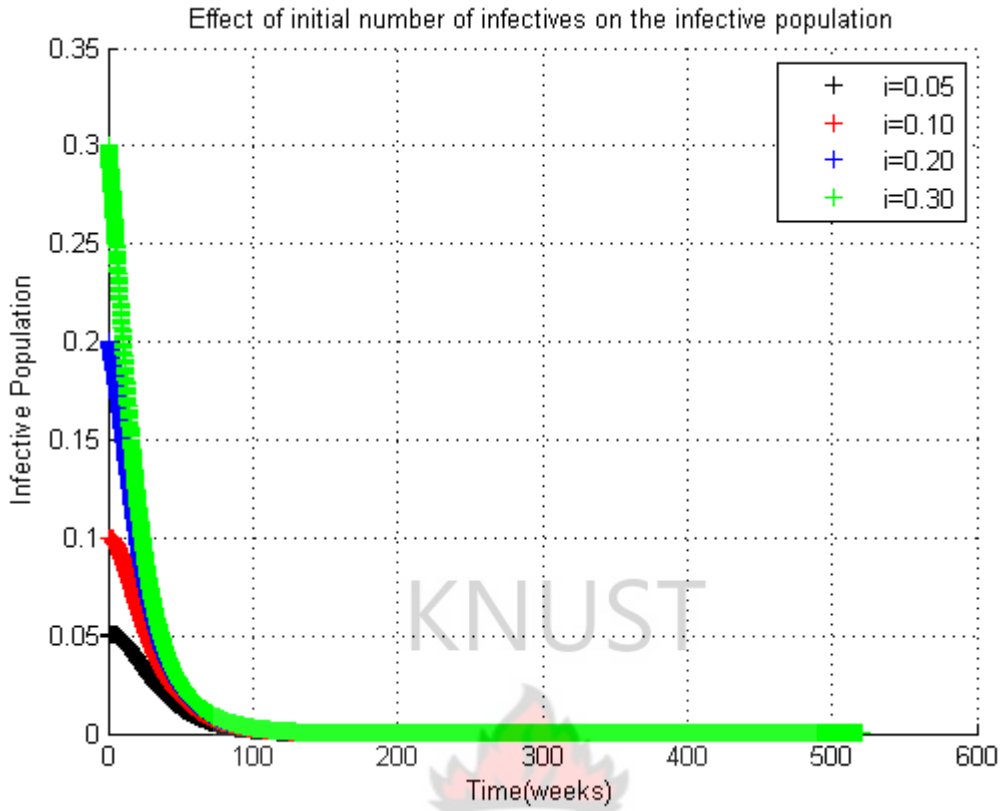

Figure 4.11: Effects of initial infectives on the infective population with vaccination rate $b = 0.02$

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From Figure 4.11, for a proportion of 0.05 of the initial infectives, the proportion of the infectives declines from its initial value of 0.05 to zero within 90 weeks. With the initial proportion being 0.10, 0.20 and 0.30, the infective population exhibited similar behavior by declining exponentially to zero all by week 90. It was observed that the higher the initial proportion of the infectives, the faster the declination.

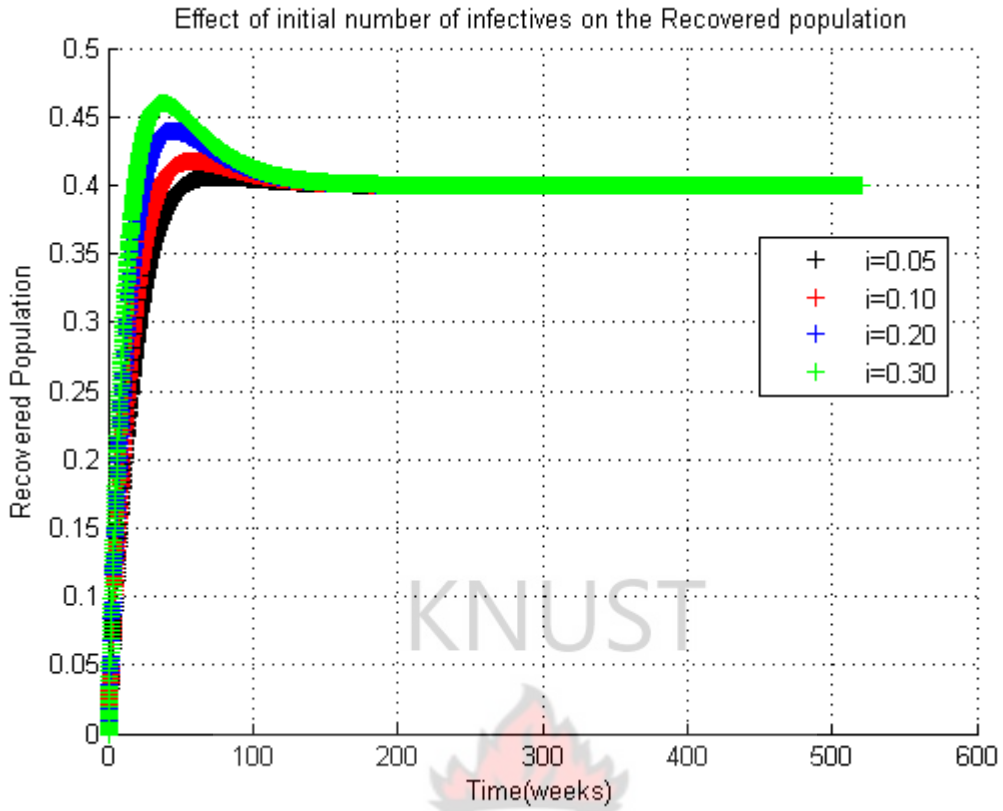

Figure 4.12: Effect of initial infectives on the recovered population with vaccination rate $b = 0.02$

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From Figure 4.12, as the initial proportion of infectives is 0.05, the proportion of the recovered population rises exponentially from week one to a value of 0.41 at week 60 and declined slightly to 0.40 within 40 weeks and remained constant as the weeks go by. As the initial proportion of the infectives is increased, there is a corresponding increase in their turning point but reductions in the number of weeks they take to arrive at the turning points. However, each proportion of the recovered population declined and stabilizes at a value of 0.40 by week 110.

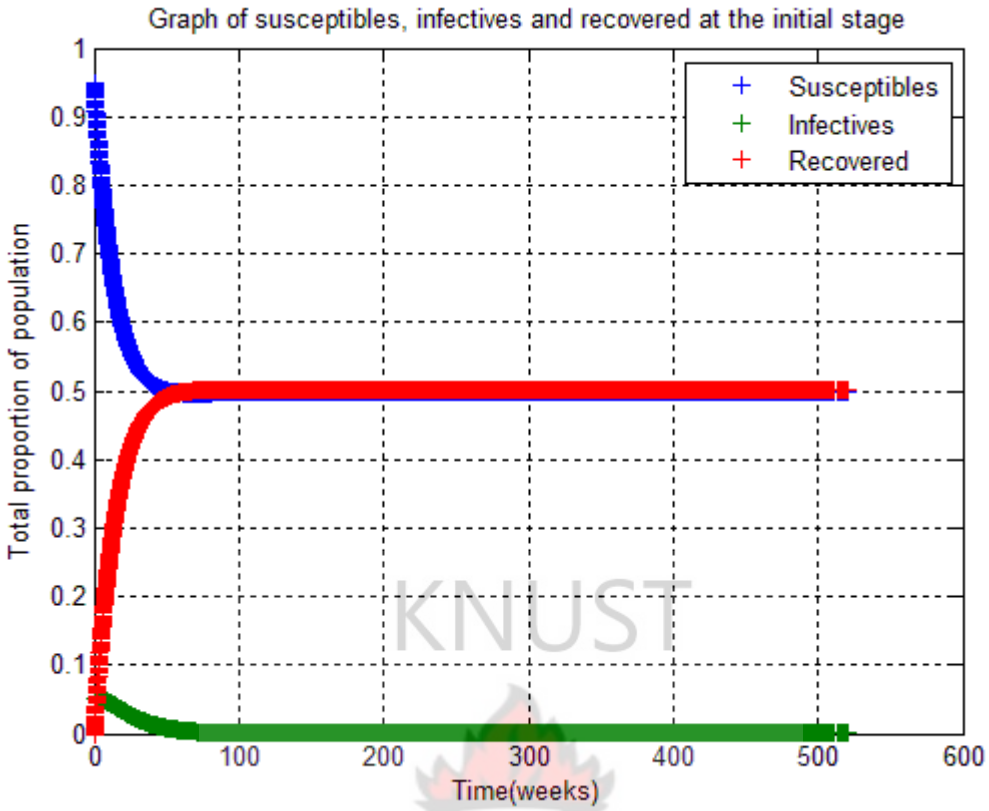

Figure 4.13: Dynamics of various compartments during the outbreak with vaccination rate $b = 0.03$

From Figure 4.13, when the initial infectives is 0.05, the proportion of the susceptible fell sharply from an initial value of 0.95 to 0.50 within 50 weeks whiles the recovered as well rose sharply from zero to meet the susceptible populase at 0.05 within the same time frame and then moved at the same constant as the weeks pass by. The infective population moved from 0.05 to zero also within the first 50 weeks and stayed at zero in subsequent weeks.

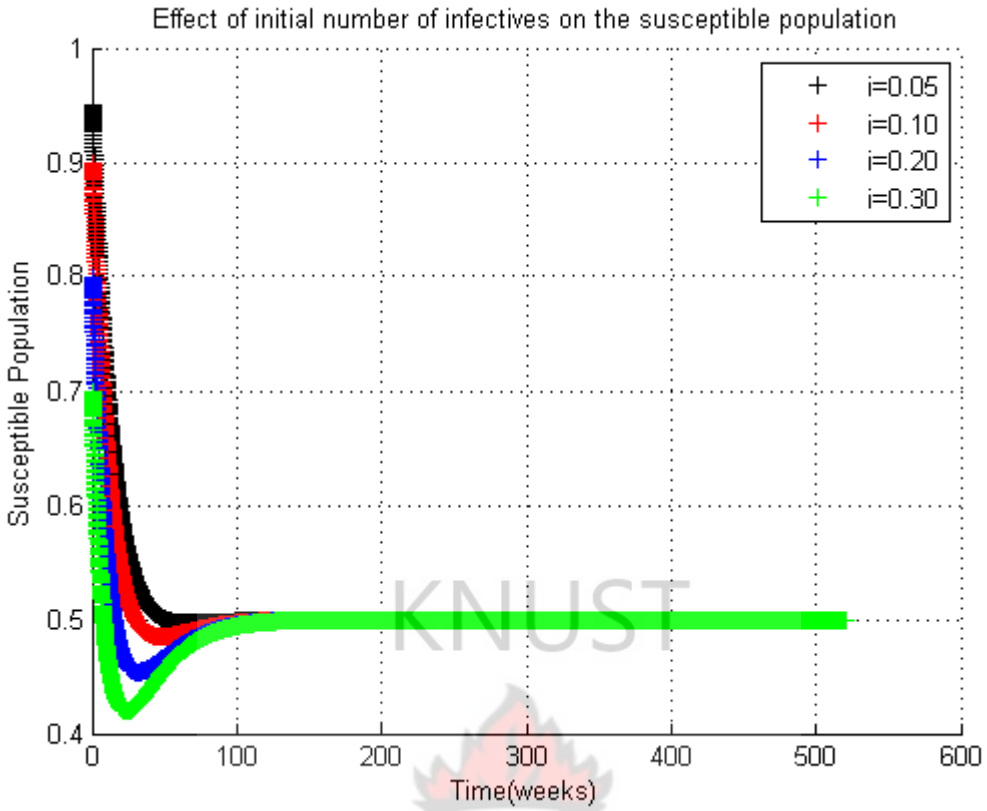

Figure 4.14: Effects of initial infectives on the susceptible population with vaccination rate $b = 0.03$

In the Figure 4.14 above, when the initial proportion of the infectives is 0.05, the proportion of the susceptibles declines from an initial value of 0.95 to the value of 0.50 at week 50 and it remained stable then onwards. As the initial proportion of infectives is increased, there was a corresponding decrease in the susceptible turning point values as well as the number of weeks it takes to get to the turning points. All the susceptibles with varying initial infection rates all rose to reach 0.05 at week 100 where they forever stayed.

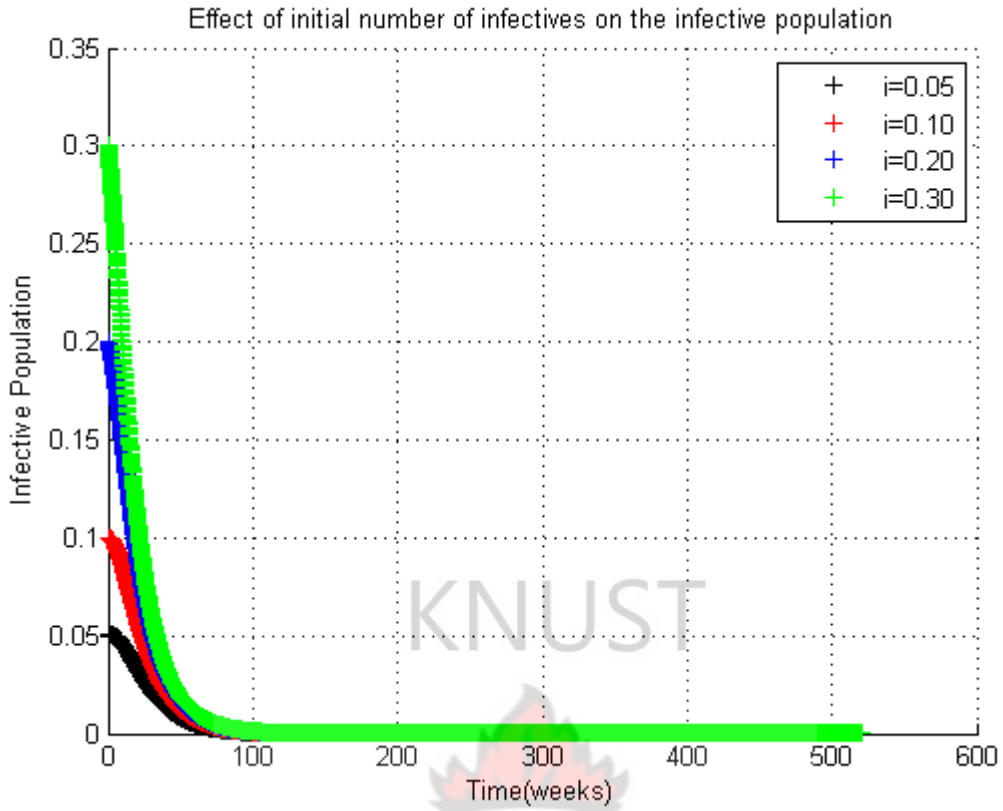

Figure 4.15: Effects of initial infectives on the infective population with vaccination rate $b = 0.03$

From Figure 4.15 above, as the initial proportion of infectives is 0.05, the proportion of the infectives declines from its initial value of 0.05 to zero within 70 weeks. With the initial proportion being 0.10, 0.20 and 0.30, the infective population all reduced to zero by the 80th week after the introduction of the infectives.

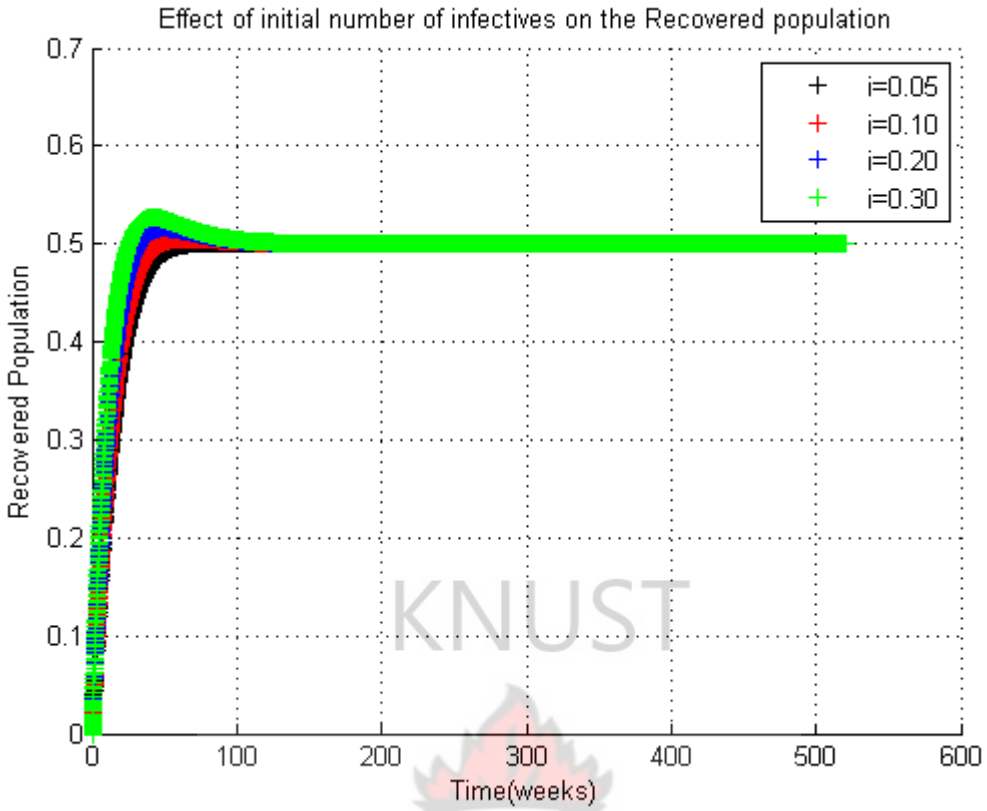

Figure 4.16: Effect of initial infectives on the recovered population with vaccination rate $b = 0.03$

From figure 4.16 above, as the initial proportion of infectives is 0.05, the proportion of the recovered population rose exponentially from zero at week one to a value of 0.50 at week 55 and stayed at that level whilst the simulation of the initial infectives of 0.10, 0.20 and 0.30 all have their recovered populations rising sharply from zero to corresponding peak heights of 0.51 at week 50, height of 0.52 at week 45 and height of 0.53 at week 40. By week 90, the recovered population decreased to a value of 0.5 as in the case of the first infective level of 0.05 and they all remained at that value as the weeks go by.

4.3.3. Stability Analysis of the model with Vaccination

We substituted the parameter values in Table 4.5 into equation (3.36). The eigenvalues corresponding to the infectious free equilibrium are $\lambda_1 = -0.04$ and $\lambda_2 = 0.015$. The eigenvalues are both real, one being positive and the other negative, implies the disease free equilibrium is a saddle point, therefore unstable.

The endemic equilibrium point occurs when an infective is introduced into the population. We substituted the parameter values in Table 4.5 into equation (3.38) to obtain the eivenvalues corresponding to the endemic equilibrium. This is given by

$$\lambda_{1,2} = \frac{\frac{-(\mu\varepsilon - b(\sigma+\alpha))}{\sigma+\alpha} \pm \sqrt{\left(\frac{\mu\varepsilon - b(\sigma+\alpha)}{\sigma+\alpha}\right)^2 - 4(\mu\varepsilon - \sigma(\sigma+\alpha))}}{2}$$

$$= \frac{\frac{-(0.13\times0.03 - 0.01(0.03+0.085))}{0.03+0.085} \pm \sqrt{\left(\frac{0.13\times0.03 - 0.01(0.03+0.085)}{0.03+0.085}\right)^2 - 4(0.13\times0.03 - 0.03(0.03+0.085))}}{2}$$

$$\lambda_{1,2} = \frac{-0.023913 \pm \sqrt{(0.023913)^2 - 0.0018}}{2}$$

$$\lambda_1 = -0.01196 + 0.01752i \text{ and } \lambda_1 = -0.01196 - 0.01752i$$

Since the eigenvalues have a complex conjugate with negative real parts, it implies the endemic equilibrium is asymptotically stable.

4.3.4. Sensitivity Analysis of the model with Vaccination

Table 4.7: Parameter values, Eigenvalues and classification of the disease free equilibrium with Vaccination.

ε	μ	α	λ_1	λ_2	σ	R_0	Nature of the equilibrium
0.03	0.095	0.085	-0.04	-0.02	0.03	0.8261	Stable sink
0.03	0.130	0.085	-0.04	0.015	0.03	1.1304	Unstable saddle
0.03	0.085	0.085	-0.04	-0.04	0.03	0.7390	Stable improper sink
0.03	0.115	0.085	-0.04	0	0.03	1.000	Neutrally stable

From equation (3.36), the eigenvalues $\lambda_1 = -\sigma - b$ and since σ and $b > 0$, it implies that $\lambda_1 < 0$.

The second eigenvalue is given as $\lambda_2 = \mu - \sigma - \alpha$. Stability can only be obtained if $\lambda_2 < 0$. Thus $\mu < \sigma + \alpha$, and $\frac{\mu}{\sigma+\alpha} < 1$.

The disease free equilibrium will be stable if the reproductive number is less than unity, i.e. $R_0 < 1$, whilst the disease free equilibrium is unstable if the reproductive number is greater than unity.

Table 4.8: Parameter values, Eigenvalues and classification of equilibrium points of the disease endemic equilibrium with Vaccination.

ε	μ	α	λ_1	λ_2	σ	R_0	Nature of the equilibrium
0.03	0.095	0.085	0.018194	-0.03298	0.03	0.8261	Unstable saddle
0.03	0.130	0.085	-0.01196+ 0.01752i	-0.01196- 0.01752i	0.03	1.1304	Stable spiral sink
0.03	0.085	0.085	0.024524	-0.03670	0.03	0.7391	Unstable saddle

From the above table, it is observed that the endemic equilibrium is stable when the reproductive number is greater than unity, i.e. $R_0 > 1$, and unstable when the reproductive number is less than unity, i.e. $R_0 < 1$.

4.4. Herd Immunity Threshold

The Herd Immunity Threshold (H_1) is percentage of the population that needs to be immune to control transmission of a disease, (Diekman and Heesterbeek 2000). From equation (3.39), the herd immunity ratio is given as

$$H_1 = \frac{0.13 - 0.03 - 0.085}{0.13}$$

$$= 0.1154$$

This implies that approximately 11.54% of the susceptible population should be immune in order to bring the spread of Hepatitis B under total control in the North Tongu District of Ghana.

CHAPTER 5

CONCLUSION

5.1 Conclusion

The numerical simulations and sensitivity analysis gave us a clear picture of how sensitive and important each parameter is in the simulation. The infectious rate and the recovery rate play the dominant role in determining the outcome of Hepatitis B virus in the North Tongu District of Ghana when there happens to be an outbreak.

In the absence of vaccination, the susceptible population will reduce sharply when an infective is introduced into the population. The rate of decrease is directly proportional to the number of infectives introduced into the population. With time, the infective population will reduce as more and more infectives recover from the disease and become immune.

The calculated reproductive ratio was 1.1304 and this suggests that the North Tongu District is in danger should there be an outbreak. There is therefore the need to reduce the reproductive ration to less than one. To do this vaccination of more susceptible populace needs to be done, since it will give immunity to the individual. Also, awareness campaigns needs to preached about the silent killer and by the campaign, horizontal transmission will be reduced since more and more people would be aware of the seriousness and consequence of sharing household items like tooth brush, towels and partially eaten candies with a brother or a sister whose HBV status is not known.

The effect of vaccination was paramount in the simulations and sensitivity analysis. The pictorial representations shows that with increase in vaccination up to 3% of the population, in addition to those who had already recovered from the disease will keep the District safe from an outbreak.

The herd immunity from our calculations is 0.1154 that implies that when 11.54% of the populace is immune to the disease, the chances that the chain of the disease transmission will be interrupted is assured. Thus, the susceptible populace will be protected by the walls that are set up by the immune ones.

5.2 Further Work

Further work is needed particularly on the case that Hepatitis B confers permanent immunity upon any individual who has recovered from the disease but a partial immunity when vaccinated against the disease.

Further research work is needed for non-constant population since population cannot remain constant in reality and non-homogeneous population since the members of the population cannot always mix homogeneously.

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APPENDICES

MATLAB CODES

Parameters

```
%{
input parameter:
-epsilon : birth rate
- mu : infectious rate
- sigma : natural death rate
- alpha : recovery rate
- S : susceptible
- I : infectives
- R : recovered
- t : time
%}


epsilon = 0.03;
mu =  0.130;
sigma = 0.03;
alpha = 0.085;
b =  0.02 ;


%Default values of S, I & R
S = 0.95;
I = 0.05;
R = 0.00;
per = 520;


%Varying the values of initial Infectives
Ivar = [0.05; 0.10; 0.20; 0.30];
```

SIR model with Vital Dynamics

```
%{
input parameter:
- epsilon : birth rate
- mu : infectious rate
- sigma : natural death rate
- alpha : recovery rate
- S : susceptible
- I : infectives
- R : recovered
- t : time

SIR_vd - SIR with vital dynamics
y = [ S; I; R]
%}
function dy = SIR_vd(t,y,epsilon,mu,sigma,alpha)
%zero vector storing the output
dy = zeros(3,1);

dy(1) = epsilon - mu*y(1)*y(2) - sigma*y(1);
dy(2) = mu*y(1)*y(2) - sigma*y(2) - alpha*y(2);
dy(3) = alpha*y(2) - sigma*y(3);
```

Analysis of SIR model with Vital Dynamics

```
clear all; close all; clc;

%% Call for parameter values
para;
options=odeset('RelTol',2e-12,'AbsTol',1e-19);
```

```
%% Effect of initial infectives on susceptible population
%% soving the ode with the default paramters
[t,y]=ode15s(@SIR_vd,[0 520],[S I
R],options,epsilon,mu,sigma,alpha);

%plot of results
figure;
plot(t,y(:,1),'+',t,y(:,2),'+',t,y(:,3),'+'); grid;
legend('Susceptibles','Infectives','Recovered'), ylabel('Total
proportion of population'),
xlabel('Time(weeks)'), title('Graph of susceptibles,
infectives and recovered at the initial stage')

%% Performing some stability analysis by varying some of the
parameters

%% Effect of initial infectives on susceptible population
%% Experiment 1
I = Ivar(1);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
figure;  hold on
plot(t,y(:,1),'k+')

%% Experiment 2
I = Ivar(2);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,1),'r+')

%% Experiment 3
I = Ivar(3);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,1),'b+')
```

```
%% Experiment 4
I = Ivar(4);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,1),'g+'); grid;
hold off

legend('i=0.05','i=0.10','i=0.20','i=0.30');
xlabel('Time(weeks)');
ylabel('Susceptible Population');
title('Effect of initial number of infectives on the
susceptible population');
%}


%% Effect of initial infectives on infective population
%{-
%% Experiment 1
I = Ivar(1);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
figure;  hold on
plot(t,y(:,2),'k+')

%% Experiment 2
I = Ivar(2);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,2),'r+')

%% Experiment 3
I = Ivar(3);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,2),'b+')
```

```
%% Experiment 4
I = Ivar(4);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,2),'g+'); grid;
hold off

legend('i=0.05','i=0.10','i=0.20','i=0.30');
xlabel('Time(weeks)');
ylabel('Infective Population');
title('Effect of initial number of infectives on the infective
population');
%}


%% Effect of initial infectives on recovered population
%% Experiment 1
I = Ivar(1);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
figure;  hold on
plot(t,y(:,3),'k+')

%% Experiment 2
I = Ivar(2);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,3),'r+')

%% Experiment 3
I = Ivar(3);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,3),'b+')
```

```
%% Experiment 4
I = Ivar(4);  S = 1-I;
[t,y]=ode15s(@SIR_vd,[0 per],[S I
R],options,epsilon,mu,sigma,alpha);
plot(t,y(:,3),'g+'); grid;
hold off

legend('i=0.05','i=0.10','i=0.20','i=0.30');
xlabel('Time(weeks)');
ylabel('Recovered Population');
title('Effect of initial number of infectives on the Recovered
population');
%}
```


SIR model with Vaccination

```
%{
input parameter:
- epsilon : birth rate
- mu : infectious rate
- sigma : natural death rate
- alpha : recovery rate
- S : susceptible
- I : infectives
- R : recovered
- t : time
- b : vaccination rate

SIR_vaci - SIR with vaccination
y = [ S; I; R]
%}
function dy = SIR_vaci(t,y,epsilon,mu,sigma,alpha,b)
%zero vector storing the output
dy = zeros(3,1);
```

```
dy(1) = epsilon - mu*y(1)*y(2) - sigma*y(1) - b*y(1);
dy(2) = mu*y(1)*y(2) - sigma*y(2) - alpha*y(2);
dy(3) = alpha*y(2) - sigma*y(3) + b*y(1);
```

Analysis of SIR model with Vaccination

```
clear all; close all; clc;
%% Call for parameter values
para;
options=odeset('RelTol',2e-12,'AbsTol',1e-19);

%% Effect of initial infectives on susceptible population
%% soving the ode with the default paramters
[t,y]=ode15s(@SIR_vaci,[0 520],[S I
R],options,epsilon,mu,sigma,alpha,b);

%plot of results
figure;
plot(t,y(:,1),'+',t,y(:,2),'+',t,y(:,3),'+'); grid;
legend('Susceptibles','Infectives','Recovered'), ylabel('Total
proportion of population'),
xlabel('Time(weeks)'), title('Graph of susceptibles,
infectives and recovered at the initial stage')

%% Performing some stability analysis by varying some of the
parameters

%% Effect of initial infectives on susceptible population
%% Experiment 1
I = Ivar(1);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
figure;  hold on
plot(t,y(:,1),'k+')
```

```
%% Experiment 2
I = Ivar(2);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,1),'r+')

%% Experiment 3
I = Ivar(3);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,1),'b+')

%% Experiment 4
I = Ivar(4);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,1),'g+'); grid;
hold off

legend('i=0.05','i=0.10','i=0.20','i=0.30');
xlabel('Time(weeks)');
ylabel('Susceptible Population');
title('Effect of initial number of infectives on the
susceptible population');
%}

%% Effect of initial infectives on infective population
%{-
%% Experiment 1
I = Ivar(1);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
figure;  hold on
plot(t,y(:,2),'k+')
```

```
%% Experiment 2
I = Ivar(2);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,2),'r+')

%% Experiment 3
I = Ivar(3);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,2),'b+')

%% Experiment 4
I = Ivar(4);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,2),'g+'); grid;
hold off

legend('i=0.05','i=0.10','i=0.20','i=0.30');
xlabel('Time(weeks)');
ylabel('Infective Population');
title('Effect of initial number of infectives on the infective
population');
%}

%% Effect of initial infectives on recovered population
%{-
%% Experiment 1
I = Ivar(1);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
figure;  hold on
plot(t,y(:,3),'k+')
```

```
%% Experiment 2
I = Ivar(2);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,3),'r+')

%% Experiment 3
I = Ivar(3);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,3),'b+')

%% Experiment 4
I = Ivar(4);  S = 1-I;
[t,y]=ode15s(@SIR_vaci,[0 per],[S I
R],options,epsilon,mu,sigma,alpha,b);
plot(t,y(:,3),'g+'); grid;
hold off

legend('i=0.05','i=0.10','i=0.20','i=0.30');
xlabel('Time(weeks)');
ylabel('Recovered Population');
title('Effect of initial number of infectives on the Recovered
population');
%}
```