KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI

INSTITUTE OF DISTANCE LEARNING

ANALYSIS AND MODELLING OF PREVALENCE OF HEPATITIS B USING DIFFERENTIAL EQUATIONS: A CASE STUDY OF THE TANO NORTH DISTRICT

A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF A MASTER OF SCIENCE DEGREE IN INDUSTRAIL MATHEMATICS

BY:

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Declaration

I hereby declare that this submission is my own work towards the Master of Science (MSc.) 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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ABSTRACT

An SIR model for hepatitis B with vaccination is formulated. The main goal is to use existing clinical hepatitis B data from the Biostatistics Department of the Tano North Health District Directorate to develop a mathematical model to understand the transmission dynamics in the Tano North District and assist decision makers to formulate the best ideas to prevent, control and eradicate the disease. Analyses are made of the existence and stability of the disease free and endemic equilibrium. It is proven that the disease free equilibrium is locally asymptotically stable if the basic reproductive ratio, $R_0 < 1$ and when $R_0 > 1$ we have the endemic equilibrium. MATLAB was used for the programming. Appendix contains the Matlab code used in simulating the model.

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DEDICATION

In loving memory of my late father, Nana Obiri-Apraku. May your gentle soul rest in perfect peace.

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CHAPTER 1

INTRODUCTION

1.1 OVERVIEW

Hepatitis, inflammation of the liver caused by viruses, bacterial infections, or continuous exposure to alcohol, drugs, or toxic chemicals, such as those found in aerosol sprays and paint thinners (Ganem, D., & Prince, A. M. 2004). Inflammation is the painful, red swelling that result when tissues of the body become injured or infected (Williams, 2006). Inflammation can cause organs to not work properly. Hepatitis can also result from an autoimmune disorder, in which the body mistakenly sends disease-fighting cells to attack its own healthy tissue, in this case the liver (Barker *et al.*, 1996). The liver is located in the upper right hand side of the abdomen, mostly behind the rib cage. The liver of an adult normally weighs close to three pounds (Chang, June 2007). No matter what its cause, hepatitis reduces the liver's ability to perform life-preserving functions, including filtering harmful infectious agents from the blood, storing blood sugar and converting it to usable energy forms, and producing many proteins necessary for life (Edmunds *et al*., 1993).

When doctors speak of viral hepatitis, they usually are referring to hepatitis caused by a few specific viruses that primarily attack the liver. There are several hepatitis viruses; they have been named types A, B, C, D, E, F (not confirmed), and G (Anderson *et al*., 1992). As our knowledge of hepatitis viruses grows, it is likely that this alphabetical list will become longer (Hahnea *et al.,* 2004). The most common hepatitis viruses are types A, B, and C (Anderson *et al.,* 1991).

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV) (Edmunds *et al.,* 1993). It is a major global health problem and the most serious type of viral hepatitis (Cui *et al.,* 2006). Originally known as "serum hepatitis", the disease has caused epidemics in parts of Asia and Africa, and it is endemic in China (Williams, 2006). About a third of the world population has been infected at one point in their lives, including 350 million who are chronic carriers which causes 620,000 deaths worldwide each year (WHO, 2004; Shepard *et al*., 2006). If your body is able to fight off the hepatitis B infection, any symptoms that you had should go away over a period of weeks to months, this is termed acute hepatitis B. some people's bodies are not able to completely get rid of the hepatitis B infection. This is called chronic hepatitis B (Shepard *et al*., 2006).

1.1.1 Transmission

Hepatitis B virus is transmitted between people by direct blood-to-blood contact or semen and vaginal fluid of an infected person (Hyams, 1995). Modes of transmission are the same as those for the human immunodeficiency virus (HIV), but the hepatitis B virus is 50 to 100 times more infectious (Thornley *et al*. 2008). Unlike HIV, the hepatitis B virus can survive outside the body for at least seven days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine (Liu, G.-T., *et al.*, 2002).

In developing countries, common modes of transmission are:

- ✓ perinatal (from mother to baby at birth)
- ✓ early childhood infections (in apparent infection through close interpersonal contact with infected household contacts)
- ✓ unsafe injection practices

- ✓ unsafe blood transfusions
- ✓ Unprotected sexual contact.
- ✓ Shared personal items (such as toothbrushes, razors, and nail clippers) with an infected person.

  (Swetz *et al*., 1991).

In many developed countries (e.g. those in Western Europe and North America), patterns of transmission are different from those in developing countries. The majority of infections in developed countries are transmitted during young adulthood by sexual activity, tattoo or acupuncture with unclean needles and instruments, and injecting drug use (Gane, E. 2005). Hepatitis B is a major infectious occupational hazard of health workers (Barker *et al.* 1996).

The hepatitis B virus is not spread by contaminated food or water, and cannot be spread casually in the workplace (McManhon *et al*., 1985).

The incubation period of the hepatitis B virus is 90 days on average, but can vary from 30 to 180 days (D´ebarre, 2010). The virus may be detected 30 to 60 days after infection and persists for variable periods of time (Juszczyk, 2000).

1.1.2 Symptoms

Symptoms may not appear for up to six months after the time of infection. Early symptoms may include:

- ✓ Appetite loss
- ✓ Fatigue
- ✓ Fever, low grade
- ✓ Muscles and joint aches

- ✓ Nausea and vomiting
- ✓ Yellow skin and eyes, and dark urine due to jaundice
- ✓ a longer than usual amount of time for bleeding to stop
- ✓ swollen stomach or ankles
- ✓ easy bruising
- ✓ tiredness
- ✓ upset stomach
- ✓ diarrhea
- ✓ light-colored stools

(Diekmann *et al*., 1990)

People with chronic hepatitis may have no symptoms, even though gradual liver damage may be occurring. Over time, some people may develop symptoms of chronic liver damage and cirrhosis of the liver (Cirrhosis is scarring of the liver and poor liver function. It is the final phase of chronic liver disease) (Wilson *et al*., 1998).

1.1.3 Hepatitis B Vaccine

What Is the Hepatitis B Vaccine, and How Effective Is It?

The hepatitis B vaccine contains a protein (antigen) that stimulates the body to make protective antibodies (Goldstein *et al*., 2005). Examples of hepatitis B vaccines available include hepatitis B vaccine-injection (Engerix-B, Recombivax-HB). Three doses (given at 0, 1, and 6 months of age) are necessary to assure protection (Edmunds *et al*., 1993).

There are also combination vaccines on the market that provide protection against hepatitis B and other diseases (Kretzschma *et al.* 2002).

Other examples of the hepatitis B vaccine include:

- ✓ Hepatitis-b-hepatitis-a vaccine - injection (Twinrix), which provides protection against both hepatitis A and hepatitis B.
- ✓ Haemophilus B/hepatitis B vaccine - injection (Comvax) provides protection against hepatitis B and Haemophilus influenza type b (a cause of meningitis).
- ✓ Pediarix provides protection against hepatitis B, tetanus, pertussis (whooping cough), and polio.

  (Shepard *et al*., 2006; Goldstein *et al*., 2005)

Hepatitis B vaccines are effective and safe. Up to 95% of vaccinated individuals form effective antibodies when they get the vaccine and are protected from hepatitis B (Edmunds et al., 1993; McLean and Blumberg, 1994; Zhao et al., 2000). In healthcare workers, high-risk public safety workers, dialysis patients, and sexual partners of infected persons, a blood test for antibodies is recommended after vaccination to ensure that the person produced antibodies (Shi *et al*., 1994). For the few who do not form antibodies, revaccination may improve response, especially in infants. However, a small proportion of individuals will never respond to hepatitis B vaccination (Liu *et al*., 2002).

1.1.4 Who Is At Risk For Chronic Disease?

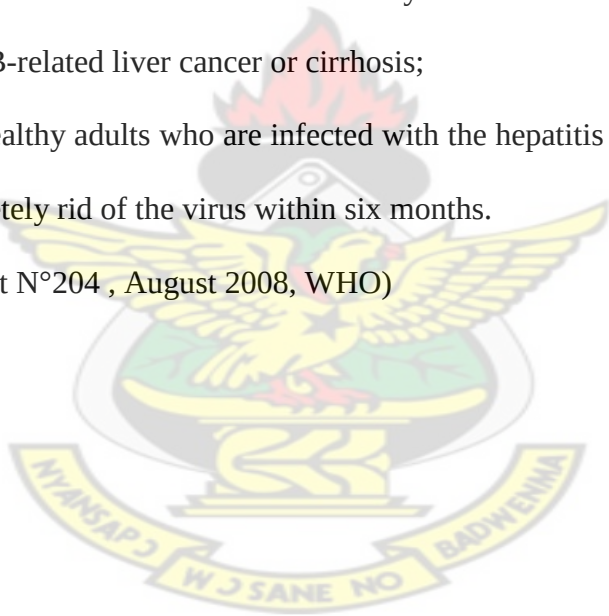
The likelihood that infection with the hepatitis B virus becomes chronic depends upon the age at which a person becomes infected (Hyams, 1995). Young children who become infected with the hepatitis B virus are the most likely to develop chronic infections:

- ✓ 90% of infants infected during the first year of life develop chronic infections;
- ✓ 30–50% of children infected between one to four years of age develop chronic infections.

In adults:

- ✓ 25% of adults who become chronically infected during childhood die from hepatitis B-related liver cancer or cirrhosis;
- ✓ 90% of healthy adults who are infected with the hepatitis B virus will recover and be completely rid of the virus within six months.

(Fact sheet N°204 , August 2008, WHO)



1.1.5 Diagnosis

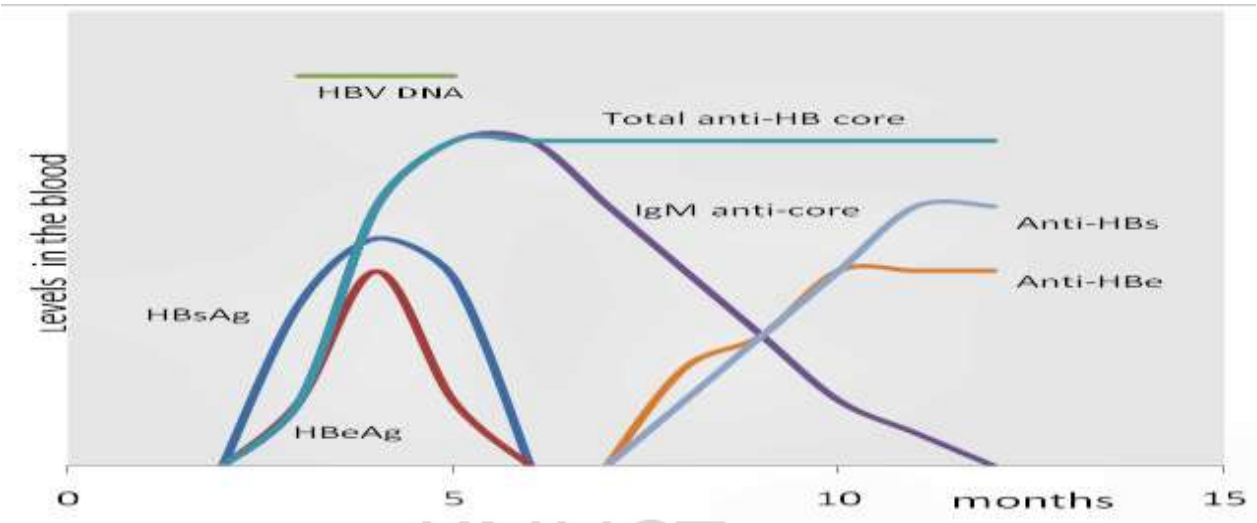


Figure 1.1*: Hepatitis B viral antigens and antibodies detectable in the blood following acute infection.*

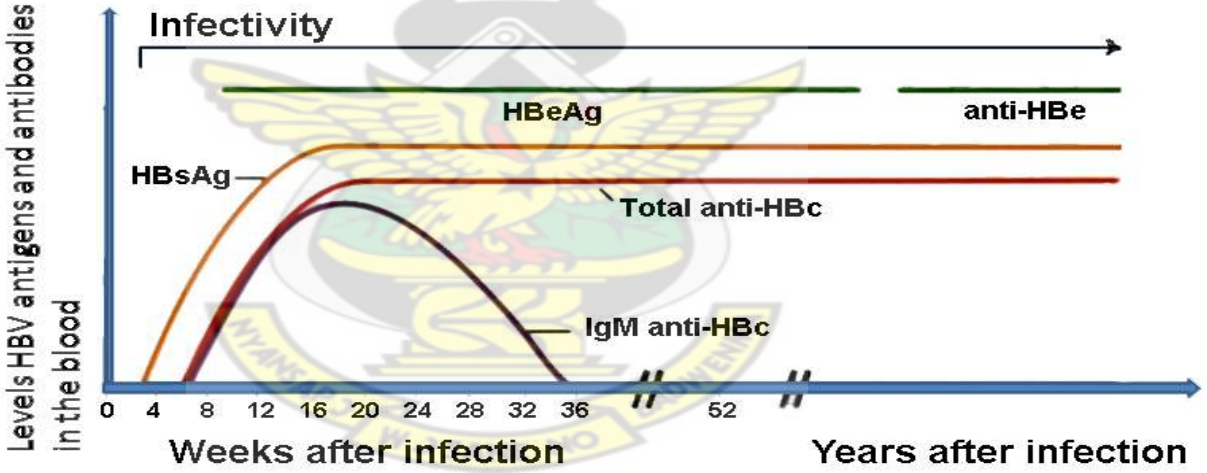


Figure 1.2: *Hepatitis B viral antigens and antibodies detectable in the blood of a chronically infected person.*

A number of blood tests are available to diagnose and monitor people with hepatitis B. They can be used to distinguish acute and chronic infections (Xu *et al*., 1995).

Laboratory diagnosis of hepatitis B infection centers on the detection of the hepatitis B surface antigen HBsAg. A positive test for the hepatitis B surface antigen (HBsAg)

indicates that the person has an active infection (either acute or chronic) (World Health Assembly, 1992). WHO (World Health Organization) recommends that all blood donations are tested for this marker to avoid transmission to recipients (World Health Organization, 2004).

Other commonly used tests include the following:

- ✓ Testing for antibodies to the hepatitis B surface antigen – a positive test indicates that the person has either recovered from an acute infection and cleared the virus, or has received a hepatitis B vaccine. The person is immune to future hepatitis B infection and is no longer contagious.
- ✓ Testing for antibodies to the hepatitis B core antigen – a positive test indicates that the person has had a recent infection or an infection in the past. Combined with a positive test for the hepatitis B surface antigen, a positive test usually indicates a chronic infection.

(World Health Organization, 2004; Centre for Disease Control, 2008)

1.2 STATEMENT OF PROBLEM

We seek to model the transmission of a disease through a population. Such modeling is very important to the study of epidemiology and the practice of medicine, since examining the relative effect of factors that govern the spread of a disease can help communities and health workers better prepare for and combat an outbreak.

A detailed understanding of the transmission of the hepatitis B virus and other emerging pathogens is crucial in its containment (Goldstein *et al.*, 2005). Mathematical models can give

insight into potential impact interventions (Hou *et al.,* 2005). The complex interaction of different infection control strategies and their likely impact on transmission can be predicted using mathematical models (Wang *et al.,* 2004).

The hepatitis B infection is an increasing burden on our health care systems. Hepatitis B is not only one of the leading causes of morbidity and mortality, but it is also a serious health problem in Ghana and the hepatitis B virus is on the rise worldwide (Acheampong, 1991). Mr Stephen Corquaye, a Clinical Pharmacist, Korle Bu Teaching Hospital, who was speaking at the launch of the World Hepatitis Day organized by the Pharmaceutical Society of Ghana, last year on the 28th of July, 2011 said "it is estimated that about four million people in the country are infected with the Hepatitis B virus". This figure is quite alarming looking at the rate of transmission of the hepatitis B virus. Mr Yusuf Inua, a pharmacist at the MOH (ministry of health), who is also the Head of Logistics at the MOH, pledged Government's commitment towards the fight against the disease and urged corporate entities to also come on board. He noted that the Ministry will soon carry out a program for hepatitis B as it has done for malaria and HIV and AIDS to minimize its prevalence. This thesis may assist in that direction.

In the natural history of HBV infection it is estimated that 10% to 33% of those who develop persistent infection end up with chronic hepatitis of which 20% to 50% may develop liver cirrhosis (world health organization, 2004). Hepatitis B is considered an important public health problem necessitating high priority strategies for prevention and control (Maynard *et al.*, 1989). An estimated worldwide carrier of hepatitis B virus is 350 million, with an estimated 50 million chronic carriers of HBV in Africa (Lavanchy., 2004). In sub-Saharan Africa, carrier rates range from 9% to 20% (world health organization, 2004). HBV is endemic in Ghana with sero-

prevalence rates ranging from 6.7% to 10% in blood donors, 6.4% in pregnant women and 15.6% in children among the general population. In jaundiced patients the rate is 54.1% (Sarkodie *et al*., 2001).

The purpose of this study is to investigate the prevalence of HBV infections among patients in the Tano north district. In a report by the district health directorate this year it was noted that there has been a considerable increase in the number of cases since 2009 to date. For instance the incidence has increased by 22% from 2010 to 2011. Therefore measures must be put in place to reduce the incidence of the disease.

The district has put in place policies to eradicate hepatitis B, we seek to know how effective those policies are. There is also a vaccination program initiated by the district, we investigate if the program is helping and the number of people they have to vaccinate to put the disease under control.

1.3 OBJECTIVES OF STUDY

The following are the objectives of the study:

- To determine the impact of the mass vaccination program started by the district health directorate.
- By carrying out sensitivity analysis of the basic reproduction number on various parameters, some optimal strategies shall be suggested to control HBV infection in the Tano North District.
- To do mathematical analysis of the model and to interpret the results of the model.

1.4 METHODOLOGY

The branch of mathematics to be used to develop the model is differential equations. The population is made up of the people of Tano North district in the Brong-Ahafo region. A formal request will be made to obtain data on hepatitis B from the biostatistics department of the district health directorate Tano North district. The data would be made up of the number of hepatitis B cases from 2000 to 2011. Where necessary either the graphical calculator (TI-nspire CAS CX) or MATLAB (Matrix Laboratory) will be used to solve differential equations and other calculations.

1.5 JUSTIFICATION OF STUDY

Epidemiology has provided valuable insights for analysis of different types of diseases in the world. This study seeks to be justified based on the following;

- ✓ The disease has been extensively studied in other countries but not in Ghana, precisely the Tano North district. As of now we are unaware of any mathematical publication specifically looking at hepatitis B epidemics in the Tano North district.
- ✓ Although there are records on hepatitis B, they normally underestimate the number of those who have been infected by the disease. Some people have the disease but have not been diagnosed.
- ✓ People get infected daily but we are generally unaware of the trend of the spread of the disease.
- ✓ The occurrence of death from the disease generally affects the productivity of the district and the country at large but we are not taking into consideration other

measures apart from vaccinations been carried out at some cost born my individuals of controlling the disease.

- ✓ This thesis will assist the Tano North district directorate tremendously, because it will give decision makers and stakeholders a mathematical model to understand the transmission and spread of the hepatitis B in order to make precise policy interventions.
- ✓ The thesis may also assist research scientists, mathematicians, etc to further develop suitable models to help public health professionals make better strategies for controlling the disease. It will help and guide the district chief executive to estimate precise amount of resources needed to control and eradicate hepatitis B in the district.
- ✓ Finally, it will assist to measure the performance of the interventions the government has made in controlling the disease in the Tano North District.

1.6 LIMITATIONS

Epidemiological data on infection outbreaks are challenging to analyze due to the censored nature of infection transmission events (Govindarajan, 2005). Each new transmission in an epidemic, increase the infected pressure on those remaining susceptible, hence infection outbreak data are serially dependent (Lian-jie *et al*., 1990). Statistical methods that assume independence of the infection events are misleading and prone to over-estimate the impact of infection control intervention. Structured mathematical models that include transmission pressure are essential.

1.7 STRUCTURE OF THE THESIS

The thesis is organized as follows: Chapter 1 presents an overview of the thesis, statement of problem, objectives of the thesis, the methodology that will be used for the thesis, thesis justification, limitations and the structure of the thesis. Chapter 2 reviews related literature on the thesis. Chapter 3 is about the methodology. Chapter 4 is the analysis of results, discussion and Modeling. Finally in Chapter 5, findings, conclusions are drawn and recommendations are made.

CHAPTER 2

REVIEW OF RELATED LITERETURE

2.1 INTRODUCTION

Several hepatitis B researchers have attempted to model epidemiology of hepatitis B in various countries. Before universal infant immunization against hepatitis B virus (HBV) in 1986, China was a region endemic for HBV infection (Tsiang *et al*., 1999). The prevalence of HBV infection in the population was about 60% and the proportion of chronic HBV carriers around 10% (Chuang *et al*., 1992). These HBV carriers could progress to chronic hepatitis B, cirrhosis, and primary hepatocellular carcinoma. Since 1976, large-scale sero-surveys of HBV infection have been carried out and a lot of data have been collected.

Zhao *et al*. (2000) developed a mathematical model of the hepatitis B virus transmission and its application for vaccination strategy in china. The paper described a mathematical model developed to predict the dynamics of HBV transmissions and to evaluate the long-term effectiveness of the vaccination program. They used a compartmental model expressed by a set of partial differential equations based on the characteristics of the HBV infection. Based on the characteristics of HBV transmissions, the population was divided into five compartments: (1) susceptible $S(a,t)$; (2) Latent period (the time interval from infection to development of infectiousness), $L(a,t)$; (3) temporary HBV carriers, $T(a,t)$; (4) chronic HBV carriers, $C(a,t)$; (5) the immune, $I(a,t)$. Here "a" represents the age and "t" represents the length of follow up. Of the five stages, compartment 3 and 4 are infectious. According to natural history of HBV, a susceptible subject acquires an acute HBV infection through effective contact with a temporary or a chronic HBV carrier, and shifts to the next compartment—the latent period. A proportion of susceptible move directly into the immune state when they are successfully immunized with hepatitis B vaccine. The immune status was assumed to be life-long and newborns assumed to be

susceptible. They admitted that, clinical manifestations, such as acute and chronic hepatitis B were beyond the scope of their study so they were not considered. In the model birth rate was considered a constant. The immune status was assumed to be lifelong and new born babies were assumed to be susceptible.

The parameter $\lambda(a,t)$ is the force of infection; α is the rate of transition from the latent period to temporary HBV viraemia; $\beta(a)$ is the risk of transient viraemia progressing to chronic HBV carriage; ε is the rate of transition from temporary HBV viraemia to immune per time unit; $V(a)$ is designated as the rate of HBV clearance in chronic HBV carriers. $\tau(a)$ is the mortality rate of HBV related diseases and estimated using the data of age specific mortality rates from date also its value was not given. The age specific mortality rate,$\mu(a)$ is also estimated using the age-stratified death notification data set. Finally the effectiveness of hepatitis B immunization value $V_c(a,t)$ is estimated based on the data set. These estimates fit the dynamics of HBV transmission in the population during the pre-vaccination period. Their model successfully simulated not only the age specific HBV carrier rate observed in 1985 sero-surveys in four provinces, but also those observed in the 1978 sero-surveys among 176068 subjects in all 29 provinces of china.

It was observed that, compared to different vaccination strategies being used in china, their model have 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 high efficacy. Also their results show that the goal of eliminating HBV transmission in some developed region of china will be realized in only one generation.

William *et al*. (1996) considered a model on the transmission dynamics of hepatitis B in the United Kingdom (UK). They found that complex hepatitis B epidemiology makes it difficult to

evaluate and compare effectiveness of different immunization policies. They present a method for doing so by using mathematical model of hepatitis B virus transmission dynamics. It had six infection and immunity related population compartments, namely, those susceptible to infection (x), latently infected (h), acutely infected (y), immune following (z), chronic carriers (c), and immune following vaccination (v). A proportion Pa of acutely infected individuals in age class become carriers, the remainder recovering to the immune class.

In their work, they considered a population which is heterogeneous in age and rates of sexual activity. They therefore assumed that a single infected individual is distributed over all age groups and sexual activity in accordance with the age and activity class distribution of acutely infected individuals at the model equilibrium. Each component of this 'distributed' individual produces secondary infections through sexual partnerships and, in the case of females during births. The number of these infections is summed to give the overall number of secondary infections produced by the individual.

In conclusion, they stated in their work that more relevant data are needed before their model can be used for accurate predictions which is not so in their research.

Another mathematical model on hepatitis B presented by Thornely *et al*. (2008) is aimed to apply an established mathematical model of disease transmission (Medley *et al*., 2001) to develop a strategy for eliminating HBV from high prevalence population groups. They used the model described by Medley *et al*. (2001), combined with data from the hepatitis B screening program (HBSP) on the prevalence of chronic hepatitis B (CHB) in New Zealand Tongan adults, together with estimate of vaccine coverage levels, to estimate population-specific infection transmission

parameters. Vaccination coverage levels were converted to modeled immunization estimates by multiplying vaccination coverage by 90% efficacy.

The host population is divided into five different epidemiological classes expressed as a proportion: susceptible $x - c$, infected but not infectious (latent) $-h$, with acute infection $-y$, with CHB (carriers) $-c$, with protective immunity $y - z$. Of particular interest is the proportion of the population that has been infected with the HBV which is equal to $l - x$.

They used Diekmann and Hesterbeek (2000) mathematical definition for their basic reproductive number, R_0 as the largest eigenvalue of their next generation matrix. The critical proportion required to be vaccinated to eliminate infection from a population was given by $Pc = 1 - (\frac{1}{R_0})$. Their model shows that 50% reduction in infectivity produces a dramatic reduction in CHB prevalence similar to that from 95% vaccination coverage.

Their model shows that high levels of vaccination coverage alone have the potential to hasten elimination of infection from high prevalence population in New Zealand, with a significant effect produced by herd immunity. In addition, their model suggests that, HBSP swiftly arrest the transmission of infection within similar timeframe, without any change in vaccination coverage. They concluded that their model did not completely fit the data supplied for Tongan population from HBSP. For example there was a difference between model predictions and actual serological data. The most important discrepancy was an overestimation of the infected class in the modeled population. In summary, their model over estimates the extent of virus exposure were compared to data from Tongan population.

Sutton *et al*. (2006) published a research article; modeling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales, where less than 1% of the

population is likely to be injecting drug users (IDUs), approximately 38% of laboratory reports of HBV, and 95% of HCV reports are attributed to injecting drug use. A key measure of transmission within a given population is the force of infection (FOI). This is defined as the instantaneous per capita rate at which the susceptible acquire infection and reflects the degree of contact with potential for transmission between the susceptible and infected. The aim of their study was to estimate FOI for HBV and HCV in the IDU population in England and Wales and how this may have evolved, both over time and as IDUs' injecting careers progress.

Their analysis considered those IDUs tested for HBV and HCV (n = 5,682) from 1998–2003. The study derives maximum likelihood estimates of the force of infection (the rate at which susceptible IDUs acquire infection) for HBV and HCV in the IDU population and their trends over time and injecting career length. The presence of individual heterogeneity of risk behavior and background HBV prevalence due to routes of transmission other than injecting were also considered. HBV prevalence is included in the model and reflects the possibility of transmission of HBV from outside the IDU population. As 95% of reports with exposure data to HCV indicate injecting drug use, it was assumed that there was no non-injecting related transmission of HCV. To incorporate HBV background prevalence and the sensitivity of the HBV and HCV tests into the model the equations describing the prevalence of the two viruses was modified to both reflect the possibility that HBV infection can occur for reasons other than injecting and that the tests for HBV and HCV have a sensitivity and specificity that is less than 100%. It was assumed in the model that the risk of background HBV infection is constant through time and injecting career length, and that there is no possibility of background infection from HCV. They concluded that the estimation of the FOI from serial prevalence data provides added epidemiological value. Previous authors have studied the incidence of infection in a cohort of IDUs although to their

knowledge no previous studies have used this method of modeling to estimate the FOI for HBV and HCV in the IDU population. The models highlight the need to increase interventions that target new initiates to injecting to reduce the transmission of blood-borne viruses. Although from the evidence they gathered, identification of those individuals that engage in heightened at-risk behavior should be undertaken. The data and methods described provided a baseline for monitoring the success of public health interventions.

Another model of interest to this study was presented by Goldstein *et al*. (2005). They worked on a mathematical model to estimate global hepatitis B disease burden and vaccination impact. The model was developed to calculate the age-specific risk of acquiring HBV infection, acute hepatitis B (illness and death), and progression to chronic HBV infection. HBV-related deaths among chronically infected persons were determined from HBV-related cirrhosis and hepatocellular carcinoma (HCC) mortality curves, adjusted for background mortality. The effect of hepatitis B vaccination was calculated from vaccine efficacy and vaccination series coverage, with and without administration of the first dose of vaccine within 24 hours of birth (i.e. birth dose) to prevent prenatal HBV infection. For the year 2000, the model estimated 620 000 persons died worldwide from HBV-related causes: 580 000 (94%) from chronic infection-related cirrhosis and HCC and 40 000 (6%) from acute hepatitis B. In the surviving birth cohort for the year 2000, the model estimated that without vaccination, 64.8 million would become HBV-infected and 1.4 million would die from HBV-related disease. Infections acquired during the prenatal period, in early childhood (5 years old), and those over 5 years of age accounted for 21, 48, and 31% of deaths, respectively. Routine infant hepatitis B vaccination, with 90% coverage and the first dose administered at birth would prevent 84% of global HBV-related deaths. It was concluded that globally, most HBV-related deaths result from the chronic sequel of infection

acquired in the prenatal and early childhood periods. Inclusion of hepatitis B vaccine into national infant immunization programs could prevent 80% of HBV related deaths.

Zou *et al*. (2009) used a mathematical model to understand the transmission dynamics and the prevalence of HBV in mainland China. The model they constructed was based on the characteristics of HBV transmission in china and the model of Medely *et al*. (2001). In this model, the host population is divided into six epidemiological groups: the proportion susceptible to infection S; those latently infected L; acute infection I; carriers C; recovered and with protective immunity R; and immune following vaccination V.

They assume that the population of newborn carriers born to carriers is less than the sum of the death of carriers and the population moving from carrier to immune state. In this case they have $\mu\omega V < \mu_0 + \mu_1 + \gamma_2$. Otherwise carriers would keep increasing rapidly as long as this is an infection.

Following van den Driessche and Watmough (2002), they obtained that the basic reproductive number, defined as the expected number of secondary infections produced by an index case.

The sensitivity analysis of this model shows that the parameters ω and $\gamma_3$are important for the prevalence of HBV infection. In particular the equilibrium states, including the states of susceptible, acute infections, and carriers. They obtained the reproductive ratio 2.406. Their model failed to consider Herd immunity threshold which is one of the most effective ways of controlling epidemics; and needs less money to carry it out as will be shown in the model of the researcher.

O'Leary *et al*. considered another intervention option and that would be to focus on the treatment of CHB carriers. They assume that the treatment is administered to 50% of the chronic HBV carriers and the effectiveness of the treatment is 20%, the prevalence of hepatitis **B** will decrease to 1.56 and incidence will decrease to 0.73/100,000 persons in 50 years. If the effectiveness of this treatment is 30%, then the prevalence and incident rates decrease to 1.41% and 0.69/100,000 persons respectively. They concluded that immunization coverage and treatment would produce the greatest decrease in hepatitis B prevalence and incidence.

In Ghana some researchers have found the need to consider analyzing HBV. Jean-Pierre *et al*. (2002) studied the risk of hepatitis B virus infection by transfusion in Kumasi, Ghana. It was noted that the risk of hepatitis B virus (HBV) transmission by transfusion in sub-Saharan Africa is considered to be relatively low, and testing of blood donors is often not done or is done relatively poorly. To re-examine this attitude, they identified HBV chronically infected blood donors from a major hospital in Ghana with a range of hepatitis B surface antigen (HBsAg) assays. Test efficacy was estimated using HBV DNA as a gold standard, and the risk of HBV infection in blood recipients was estimated for different testing strategies. Particle agglutination, dipstick, and enzyme immunoassay (EIA) HBsAg screening detected 54%, 71%, and 97% of HBV infectious donors, respectively. The probability that released donations would infect recipients was calculated for different donor sources, testing strategies, and recipient age groups (older and younger than 10 years) by multiplying the prevalence of HBsAg and/or HBV DNA positivity among donations by 1 minus the sensitivity of the test and then by the proportion of recipients expected to be susceptible to infection. The probable range around these point estimates was calculated using the upper and lower 95% confidence intervals of the proportions of donors with infections and the proportions of recipients who were susceptible (the test

sensitivity was not varied). The risk of HBV transmission to recipients less than 10 years old ranged between 1:11 and 1:326 with blood unscreened and screened by EIA, respectively. For older recipients, the risk decreased a further 4-fold because of the high frequency of natural exposure to HBV. A total of 98% of HBsAg-confirmed positive samples contained HBV DNA. HBV DNA load was less than 1×10^4 IU/mL in 75% of HBsAg-reactive samples, most of them anti-HBe reactive. Approximately 0.5% of HBsAg-negative but anti-HBc-positive samples contained HBV DNA. The use of sensitive HBsAg tests is critical to prevent transfusion transmission of HBV infection to young children in a population with a 15% prevalence of chronic HBV infection in blood donors. However, this will not have much effect on the prevalence of this infection unless other strategies to protect children from infection are also advanced in parallel.

Also in Tamale, Dongdem *et al*. (2009) researched on the topic; Prevalence of hepatitis B virus infection among blood donors at the Tamale Teaching Hospital, Ghana. They note that transfusion of infected blood, unprotected sex and mother to child transmission are 3 key transmission routes of HBV in Ghana. There is high incidence of blood demanding health situations in northern Ghana resulting from anemia, accidents, malnutrition, etc. The higher the demand, the higher the possibility of transmitting HBV through infected blood. The aim of the investigation was to estimate the prevalence of HBV in blood donors which will provide justification for interventions that will help minimize or eliminate HBV infection in Ghana. The study samples included all individuals who donated blood from 01 January to 31 December, 2009. The study recruited 6,462 individuals in two categories; 5,878 blood replacement donors (individuals called upon to donate blood to patients) and 584 voluntary donors (individuals who willingly donated blood to the blood bank). Donor consent was obtained and confidentiality

guaranteed. Clearance was also obtained from the Regional Health Directorate to use the data for the purpose of research only. A 5^{cc} syringe and needle were used to bleed approximately 5 ml of blood from each donor, transferred into a vacutainer and centrifuged at 1500 rpm for 3 min to obtain serum. The Wondfo One Step Cassette Style HBsAg test kit (Guangzhou Wondfo Biotech Co. Ltd, China) was used to determine the concentration of HBsAg as being ≥1 ng/ml. A test strip was immersed in each serum. The strips were removed after 10 sec and placed on a dry clean non-absorbent table surface for 15 min after which they were visualized. Negative test for HBV: Only one colored band appears on the control (C) region. Positive test for HBV: In addition to a pink colored control (C) band, a distinct pink colored band also appears in the test (T) region. Invalid test for HBV: A total absence of color in both regions. Also, results of recruits who could not tell their ages were eliminated. The data obtained was double entered into a spread sheet. Descriptive analysis involved a display of summary statistics and cross tabulation of HBV, age groups and gender. We generated a binary logistic variable (as our primary dependent variable) to represent the status of HBV infection coded 0/1. The prevalence was then estimated as the proportion with infection alongside the exact binomial confidence interval. The statistical differences within age groups and between genders were tested with Pearson's chi square as well as bivariate logistic regression. A logistic regression was further used to identify the independent associations between the categories and the respective probability of HBV infection among individuals at the time of blood donation. The data was analyzed using Stata version 11.2 (Special Edition, College Station, Texas 77845 USA) statistical package set at 95% Confidence Interval (and a p-value < 0.05 as considered statistically significant). They concluded that risk of infection was age, sex and donor type dependent. The 20-29 year category had the highest prevalence of HBsAg + cases, mostly males residing within the metropolis.

The models above are other peoples work most of it done outside Ghana, the once done in Ghana tend to look at specific aspects of HBV transmissions especially in blood transfusions. This research tends to look holistically at all HBV cases at the Tano north district in the Brong-Ahafo region where the disease is endemic according to the district health director's report (2011).

We propose a mathematical model to understand the transmission dynamics and prevalence of HBV in Tano North district. The model is constructed based on the characteristics of HBV transmission in Tano North district and the SIR model of Kermack and Mckendrick (Kermack and Mckendrick, 1927).

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

In this chapter, mathematical models that capture salient aspects of epidemiology of hepatitis B disease in the Tano North District in Ghana are presented. Two variations of the standard susceptible-infected-recovered epidemiology model are utilized to study and analyze the spread of the disease.

The Tano North District is one of the Twenty-two (22) Administrative Districts of Brong-Ahafo Region of Ghana. It shares boundaries with Offinso and Ahafo-Ano Districts both in Ashanti Region in the North-East and South-West respectively. Other Districts that share boundaries with the Tano North include Tano South in the South, Asutifi in the West and Sunyani Municipal in the North. The District lies between longitude 7° 00' 25', latitude 1° 45' W and 2° 15' W with a total land area of 876sq kilometers, constituting about 1.8% of the total land area of the Brong-Ahafo Region.The Tano North District has a total population of 78,415 comprising 39,338 males and 39,077 females as at 2010 (Ghana Statistical Board). The district has population growth rate of 2.4%.

The geology of the District is basically made of the middle Precambrian formation. Most parts of the District are underlain by lower Biriman rocks with few areas such as Bosomkese and Kwannisa underlain by granite. It must be noted that, the lower Birimian rocks formation in the District contain weathered phyllites and schist which account for the substantial deposits of red and white clay in areas such as Tanoso where ceramics, brick and tile and pottery industries are located.

Agriculture is the main occupation in the District; it employs about 64.4% of the total active work force in the District. The major food crops grown are maize, cassava, plantain, cocoyam and yam. Some of the cash crops cultivated include cocoa, coffee, oil palm and citrus. Apart from the food and cash crops cultivated, vegetables such as tomatoes, garden eggs, okro and pepper are grown in large quantities during the dry season. Major livestock produced include poultry, cattle, sheep, goats and pigs. Below is the map of Tano North district of the Brong-Ahafo region of Ghana.

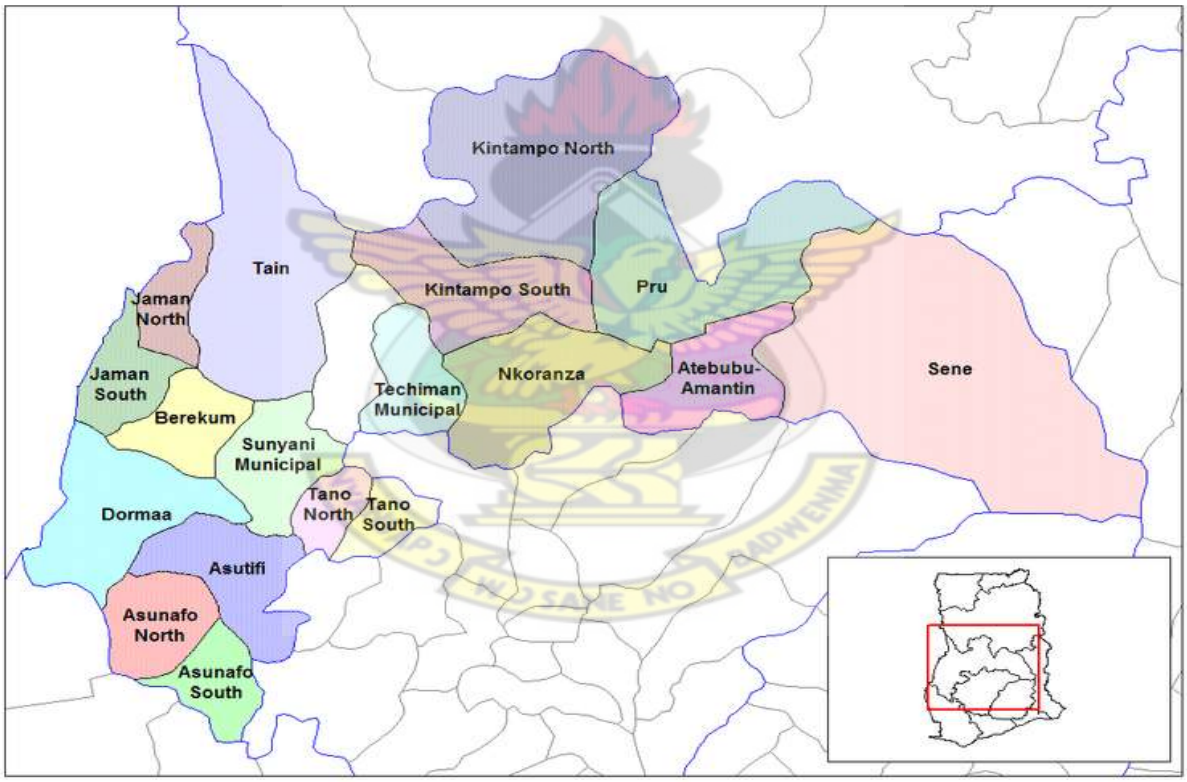


Figure: 3.1 *Map of Tano North District within the map of Brong-Ahafo Region of Ghana.*

3.2 OVERVIEW OF DIFFERENTIAL EQUATIONS

Differential equations have been a very important tool in many fields of study such as the physical sciences (especially in physics and mathematics), engineering and social sciences

(mostly in economics) (Keeling, 2001). In physics, most of their laws are simply and naturally formulated as differential equations.

Let's consider modeling the acceleration of a ball falling through the air (considering only gravity and air resistance). The ball's acceleration towards the ground is the acceleration due to gravity minus the acceleration due to air resistance. Gravity is a constant but air resistance is proportional to the ball's velocity. This means the ball's acceleration is dependent on its velocity. Because acceleration is the derivative of velocity, solving this problem requires a differential equation.

What then is a differential equation? A ***differential equation*** is an equation in which the unknowns are functions of one or several variables and which contain not only the functions themselves but also their derivatives.

3.2.1 Solution of an Ordinary Differential Equation

A solution of the ordinary differential equation

$$y^{(n)} = f\left(x, y, y', \dots, y^{(n-1)}\right) \tag{2.1}$$

on the interval $\alpha < x < \beta$ is a function φ such that $\varphi', \varphi'', \dots, \varphi^{(n)}$ exist and satisfy the equation

$$\varphi^{(n)}(x) = f\left[x, \varphi(x), \varphi'(x), \dots, \varphi^{(n-1)}(x)\right] \tag{2.2}$$

for every x in $\alpha < x < \beta$. Assuming that equation (1.1) is a real-valued function and $y = \varphi(x)$ is a real-valued solution. For example $\frac{dR}{dt} = -kR$ which has the solution

$R = \varphi(t) = ce^{-kt}$, $-\infty < t < \infty$. Where c is an arbitrary constant. If

$\varphi(t) = ce^{-kt}\ then\ \varphi'(t) = -cke^{-kt}\ which\ implies\ that\ \frac{dR}{dt} + kR = 0$ hence proved that is a solution. Also for $y'' + y = 0, \varphi(x) = \cos x$ is a solution since for $\varphi'(x) = -\sin x\ \ and\ \varphi''(x) = -\cos x\ \ then - \cos x + \cos x = 0$ hence proved.

3.2.2 Initial Condition(s):

Initial Conditions are a set of conditions, on the solution that will allow us to determine which solution that we are after. Initial conditions (often abbreviated I.C.'s) are of the form $y(t_0) = y_0$ and/or $y^{(k)} = y_k$

So, in other words, initial conditions are values of the solution and/or its derivative(s) at specific points.

The number of initial conditions that are required for a given differential equation will depend upon the order of the differential equation.

3.2.3 General Solution:

The general solution to a differential equation is the most general form that the solution can take and doesn't take any initial conditions into account.

3.2.4 Actual Solution:

The actual solution to a differential equation is the specific solution that not only satisfies the differential equation, but also satisfies the given initial condition(s).

3.3 MATHEMATICAL MODEL

Of the several kinds of creative activity being promoted in contemporary developments, arguably the most empowering for students is mathematical modelling (Galbraith, 1995, p. 312).

A mathematical model is a simplified or idealized description of a system or process in mathematical terms, devised to facilitate calculation and prediction. Mathematical operations are used to define the quantitative relationships between various items or groups of items in the system (maybe time in minutes, maybe dollars ...) (Galbraith, 1989, p. 82). These items or groups of items are the independent and dependent variables, and the numbers that relate them are parameters.

As a schematic description of a system, process or phenomenon, a mathematical model accounts for the known or inferred properties of the system and may be used to further study its characteristics(Swetz *et al*., 1991). It is important to understand the purpose of models. In particular, in this research, models are not intended to be a complete, accurate representation of the system. ***It was once said that having a complete, accurate model would be like having a map of a city that was as big as the city. It would be accurate, but not very useful*** (Lowe, 1989).

Simplifications have been carefully chosen to de-emphasize parts of the system that are not being examined, and to emphasize parts of the system that we would like to know more about. Models are often used in this way, and so different models of the same system will look different, depending upon their purpose (Li J and Zou X, 2009). Since the purpose of these models is

educational, the simplifications are chosen to produce mathematically intuitive models that may no longer retain a great deal of their detailed predictive nature.

The usefulness of a model lies in the fact that it allows for the understanding and prediction of a phenomena without the work of performing the complex and expensive experiments (White, 1995). Of the several kinds of creative activity being promoted in contemporary developments, arguably the most empowering for students is mathematical modeling (Galbraith, 1995, p. 312).

3.4 THE SIR MODEL

The model is a modification of the Kermack and Mckendrick model (Kermack and Mckendrick, 1927).

Of particular interested to this research is in the spread of an infectious disease where individuals may be susceptible to the disease, may be currently infected with the disease, removed or may be immune from the disease. Thus we have three groups or states in which we can place individuals. In addition we see that our data is a time series where we have a number of infected individuals at each point in time. Similarly we also have a number of susceptible and recovered individuals at each point in time. Let us begin with some notation.

S_t = the number of susceptible individuals in the population at time *t*.

I_t = the number of infected individuals in the population at time *t*.

R_t = the number of recovered individuals in the population at time *t*.

N = the population size.

Correspondingly define the three groups as fractions of the total population N in lower case.

$s_t = S_t/N$ (The susceptible fraction of the population at time *t*.)

$i_t = I_t/N$ (The infected fraction of the population at time *t*.)

$r_t = R_t/N$ (The recovered fraction of the population at time *t*.)

We will work with both of these sets of notation in the modelling process. Note that each individual in the population is in one of the three groups. Thus $S_t + I_t + R_t = N$ and

$s_t + i_t + r_t = 1$

Figure 3.2 *Flowchart of the SIR model*

Where α *is* the transmission rate coefficient and β is the removed rate coefficient.

3.5 THE MODEL ASSUMPTIONS

1. Age, sex, social status and race do not affect the probability of been infected.
2. The rate of change of the susceptible is proportional to the number of contacts (here contact refers to any of the modes of transmission stated in chapter one, 1.1.1) between the susceptible and the infected individuals.
3. The number of susceptible who are infected by an infective individual per unit of time, at time t, is proportional to the total number of susceptible with the proportional coefficient

(transmission rate coefficient) α, so that the total number of new infective, at time t is $\alpha S(t)I(t)$.

4. The Tano North district has a fixed area size and only the population size is varying.
5. All immigrants and newborn are assumed uninfected hence they join the susceptible group.
6. There is no inherited immunity

3.6 MODEL EQUATIONS

If we let $\alpha -$represent the infection rate of HBV and let $\beta -$ represent the rate of recovery. The model equations are as follows;

$$\frac{dS}{dt} = -\alpha SI \quad (3.1)$$

$$\frac{dI}{dt} = \alpha SI - \beta I \quad (3.2)$$

$$\frac{dR}{dt} = \beta I \quad (3.3)$$

With initial conditions $S(0) = S_0 > 0,\ I(0) = I_0 > 0,\ R(0) \geq 0.$

The equation for variable R is decoupled from the first two equations of the system, equations (3.1) and (3.2), so we only need to consider the system;

$$\frac{dS}{dt} = -\alpha SI$$

$$\frac{dI}{dt} = \alpha SI - \beta I$$

The above equations can be simplified as follows

$$\frac{dI}{dS} = \frac{dI}{dt} \times \frac{dt}{dS}$$

$$\frac{dI}{dS} = (\alpha SI - \beta I) \times \left(\frac{1}{-\alpha SI}\right)$$

$$\frac{dI}{dS} = -\frac{\alpha SI}{\alpha SI} + \frac{\beta I}{\alpha SI}$$

$$\frac{dI}{dS} = -1 + \frac{\beta}{\alpha S} \tag{3.4}$$

$$\frac{dI}{dS} = -1 + \frac{\rho}{S} \tag{3.5}$$

Where $\rho = \frac{\beta}{\alpha}$ and ρ is the relative removal rate and its reciprocal $\frac{\alpha}{\beta}$ is the infections contact rate. We say an epidemic occurs $if\ \frac{dI}{dS} > 0$. That infected individuals grow. If $\frac{dI}{dS} < 0$, then the number of infected individuals do not increase hence no wider outbreak of the disease takes place.

If

$$S > \frac{\beta}{\alpha}\ then\ \frac{dI}{dS} > 0$$

$$S = \frac{\beta}{\alpha}\ then\ \frac{dI}{dS} = 0$$

$$S < \frac{\beta}{\alpha}\ then\ \frac{dI}{dS} < 0$$

Since $\frac{\beta}{\alpha} = \rho$ which is the removal rate, we can say;

$$S > \rho\ then\ \frac{dI}{dS} > 0$$

$$S = \rho\ then\ \frac{dI}{dS} = 0$$

$$S < \rho\ then\ \frac{dI}{dS} < 0$$

3.7 THE BASIC REPRODUCTIVE RATIO (R_0) OF HBV TRANSMISSION WITHOUT VACCINATION

The basic reproductive number, R_0, is defined as the expected number of secondary cases produced by a single infection in a completely susceptible population ($S(0) \approx N$) (Anderson and May, 1979). If more than one secondary infection is produced from one primary infection, that is, Ro > 1, then an epidemic occurs. When Ro < 1, then there is no epidemic, meaning the disease dies out. When Ro = 1, then the disease becomes endemic, meaning the disease remains in the population at a constant rate (Feitelson *et al.*, 2001). This infective individual makes αN contacts per unit time producing new infections with a mean infectious period of $1/\beta$ (Edmund *et al*., 1996). Therefore, the basic reproduction number is

$$R_0 = \frac{\alpha N}{\beta}$$

The reproductive ratio can therefore be defined as;

$$R_0 = \frac{\alpha S_o}{\beta} = \frac{S_o}{\rho} \qquad (3.6)$$

That is the infectious contact rate multiplied by the initial number of susceptible. This value quantifies the transmission potential of a disease.

Now solving the differential equation (3.4) by using the method of separating the variables;

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

$$dI = \left(-1 + \frac{\beta}{\alpha S}\right) dS$$

$$\int dI = -1\int dS + \frac{\beta}{\alpha}\int \frac{1}{S}dS$$

$$I = -S + \frac{\beta}{\alpha} lnS + C \qquad (3.7)$$

Where C is an arbitrary constant. Thus the orbits of the solution are given multiplicity by the equation;

$$I + S - \frac{\beta}{\alpha} lnS = C \qquad (3.8)$$

Let's assume the following as initial conditions: $S_o = S(0)\ and\ I_o = I(0)$. We also assume that $\lim_{t\to\infty} I(t) = 0\ where\ \lim_{t\to\infty} S(t) = S_\infty$ gives the final number of susceptible individuals after the epidemic is over. The above holds for both $(S_0, I_o)\ and\ for\ (S_\infty, 0)$.

Thus

$$I_o + S_o - \frac{\beta}{\alpha} lnS_o = C$$

$$I_o + S_o - \frac{\beta}{\alpha} lnS_o = S_\infty - \frac{\beta}{\alpha} lnS_\infty$$

$$I_o + S_o - S_\infty = \frac{\beta}{\alpha}(lnS_0 - lnS_\infty)$$

$$\frac{\beta}{\alpha} = \frac{I_o + S_o - S_\infty}{lnS_o - lnS_\infty} \qquad (3.9)$$

If we let $k = I_o + S_o\ and\ \frac{\beta}{\alpha} = \rho$ then the equation (3.9) becomes;

$$\rho = \frac{k - S_\infty}{lnS_0 - lnS_\infty} \qquad (3.10)$$

Also from equation (3.9)

$$\frac{\alpha}{\beta} = \frac{lnS_o - lnS_\infty}{I_o + S_o - S_\infty} \tag{3.11}$$

$$\frac{\alpha}{\beta} = \frac{\ln\left(\frac{S_o}{S_\infty}\right)}{I_o + S_o - S_\infty} \tag{3.12}$$

We note that since the population is constant $S_\infty < S_o + I_o$.

The implicit solution also allows us to compute the maximum number of infected individuals that is attained. This number occurs when $I_o = 0$ and that is $\rho = S = \frac{\beta}{\alpha}$.

From

$$I + S - \frac{\beta}{\alpha} lnS = I_O + S_O - \frac{\beta}{\alpha} lnS_O \tag{3.13}$$

Substituting the expression for S and moving all the terms but *I* to the right-hand side leads to

$$I_{max} = -\frac{\beta}{\alpha} + \frac{\beta}{\alpha} ln\frac{\beta}{\alpha} + S_O + I_O - \frac{\beta}{\alpha} lnS_O \tag{3.14}$$

Finally if the expression for ρ is substituted into the equation (3.12) we have

$$I_{max} = -\rho + \rho ln\rho + S_o + I_o - \rho lnS_o \tag{3.15}$$

$$I_{max} = -\rho + \rho ln\rho + K - \rho lnS_o$$

For $K = S_O + I_O$

$$I_{max} = K - \rho + \rho(ln\rho - lnS_O) \tag{3.16}$$

$$I_{max} = K - \rho + \rho ln\frac{\rho}{S_O}$$

$$I_{max} = k - \rho(1 - lnR_O) \tag{3.17}$$

Equation (3.17) will be used to calculate for the maximum number of infective during the epidemic.

3.8 EFFECTIVE REPRODUCTIVE NUMBER

The Effective Reproductive number, denoted E_R, is the average number of secondary cases generated by an infectious case during an epidemic (Wang, 1991). To estimate this number we used the formula stipulated in Wang's 1991 article;

$$E_R = R_0 \frac{S_t}{N} \tag{3.18}$$

The Effective Reproductive number is important since it helps to determine how effective policies on controlling diseases have been. When $E_R < 1$, the policies concerning the containing of the disease are effective.

3.9 SIR MODEL OF HBV TRANSMISSION WITH VACINNATION

We assume that the vaccination against HBV leads to permanent immunity. We also assume that a portion of susceptible, pS go to the removed compartment R directly, due to permanent immunity obtained from vaccination.

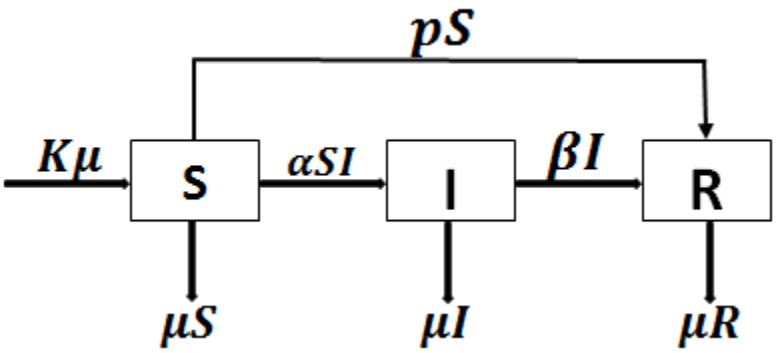


Figure 3.3 *Flow chat for SIR with Vaccination*

Where;

$K\mu$= birth rate of the population

pS= vaccinated susceptible

μ= natural death rate

α= infection rate

β=recovery rate

$$\frac{dS}{dt} = \mu K - \alpha SI - \mu S - pS \tag{3.19}$$

$$\frac{dI}{dt} = \alpha SI - (\beta + \mu)I \tag{3.20}$$

$$\frac{dR}{dt} = \beta I - \mu R + pS \tag{3.21}$$

Where p is the vaccinating rate coefficient for susceptible.

3.10 EQUILIBRIUM POINTS

In other to determine the stability of the model we first evaluate the equilibrium points or steady states of the system of the ordinary differential equations (3.19), (3.20), and (3.21). The points to be found are disease-free (where I=0), and endemic ($I \neq 0$). We set the right-hand side of the equations in the system (3.19), (3.20) and (3.21) to zero and then solve for the values of S, I, and R as follows:

At the steady state,

$$\frac{dS}{dt} = 0, \frac{dI}{dt} = 0 \; and \; \frac{dR}{dt} = 0$$

$$\mu K - \alpha SI - \mu S - pS = 0 \tag{3.22}$$

$$\alpha SI - \beta I - \mu I = 0 \tag{3.23}$$

$$\beta I - \mu R + pS = 0 \tag{3.24}$$

From equation (3.21) above

$$(\alpha S - \beta - \mu)I = 0$$

$$I = 0 \; and \; \alpha S - \beta - \mu = 0$$

$$\therefore \; S = \frac{\beta + \mu}{\alpha} \tag{3.25}$$

From equation (3.22)

$$\mu K = \alpha SI + \mu S + pS$$

$$\mu K = (\alpha I + \mu + p)S$$

$$\frac{\mu K}{S} = \alpha I + \mu + p$$

$$\frac{\mu K}{S} - \mu - p = \alpha I$$

$$\frac{\mu K}{S} - (\mu + p) = \alpha I$$

$$I = \frac{\mu K}{\alpha S} - \frac{(\mu + p)}{\alpha}$$

But from equation (3.25) $S = \frac{\beta+\mu}{\alpha}$

$$I = \frac{\mu K}{\alpha(\frac{\beta + \mu}{\alpha})} - \frac{(\mu + p)}{\alpha}$$

$$I = \frac{\mu K}{\left(\frac{\alpha(\beta + \mu)}{\alpha}\right)} - \frac{(\mu + p)}{\alpha}$$

$$I = \frac{\alpha\mu K}{\alpha(\beta + \mu)} - \frac{(\mu + p)}{\alpha}$$

$$I = \frac{\alpha\mu K - (\beta + \mu)(\mu + p)}{\alpha(\beta + \mu)} \quad (3.26)$$

From equation (3.22)

$$\beta I - \mu R + pS = 0$$

$$\mu R = \beta I + pS$$

$$R = \frac{\beta I + pS}{\mu} \quad (3.27)$$

Substituting equations (3.25) and (3.26) into equation (3.27)

$$R = \frac{\beta\left[\frac{\alpha\mu K-(\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}\right]+p\left(\frac{\beta+\mu}{\alpha}\right)}{\mu}$$

$$R = \frac{\beta[\alpha\mu K-(\beta+\mu)(\mu+p)]+p(\beta+\mu)(\beta+\mu)}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\beta\alpha\mu K-\beta(\beta+\mu)(\mu+p)+p(\beta+\mu)(\beta+\mu)}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\beta\alpha\mu K+(\beta+\mu)[-\beta(\mu+p)+p(\beta+\mu)]}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\beta\alpha\mu K+(\beta+\mu)[-\beta\mu-\beta p+p\beta+P\mu]}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\beta\alpha\mu K+(\beta+\mu)[-\beta\mu+P\mu]}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\beta\alpha\mu K+(\beta+\mu)(\beta-P)(-\mu)}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\mu[\beta\alpha K-(\beta+\mu)(\beta-P)]}{\mu\alpha(\beta+\mu)}$$

$$R = \frac{\beta\alpha K-(\beta+\mu)(\beta-P)}{\alpha(\beta+\mu)} \qquad (3.28)$$

$$(S^*, I^*, R^*) = \left[\frac{\beta+\mu}{\alpha}, \frac{\alpha\mu K-(\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}, \frac{\beta\alpha K-(\beta+\mu)(\beta-P)}{\alpha(\beta+\mu)}\right] \qquad (3.29)$$

Now when $I = 0$, equation (3.22)

$$\mu K-\alpha SI-\mu S-pS = 0$$

$$\mu K-\alpha S(0)-\mu S-pS = 0$$

$$\mu K-\mu S-pS = 0$$

$$\mu K = \mu S+pS$$

$$\mu K = S(\mu + p)$$

$$S = \frac{\mu K}{\mu + p} \tag{3.30}$$

Putting $I = 0$, into equation (3.24)

$$\beta I - \mu R + pS = 0$$

$$\beta(0) - \mu R + pS = 0$$

$$-\mu R + pS = 0$$

$$\mu R = pS$$

$$R = \frac{pS}{\mu} \tag{3.31}$$

Substituting equation (3.30) into equation (3.31)

$$R = \frac{p\left(\frac{\mu K}{\mu + p}\right)}{\mu}$$

$$R = \frac{p\mu K}{\mu(\mu + p)}$$

$$R = \frac{pK}{(\mu + p)} \tag{3.32}$$

At the disease free equilibrium

$$(S^*, I^*, R^*) = \left(\frac{\mu K}{\mu + p}, 0, \frac{pK}{(\mu + p)}\right)$$

The reproductive ratio R_O can be calculated from equations (3.22), (3.23) and (3.24) as follows.

The Jacobian matrix for the equations will be written as;

$$J(S, I, R) = \begin{bmatrix} -\alpha I - \mu - p & -\alpha S & 0 \\ \alpha I & \alpha S - \beta - \mu & 0 \\ p & \beta & -\mu \end{bmatrix}$$

The first two equations (3.22) and (3.23) do not depend on R. Thus, we need to consider the system of equations

$$\mu K - \alpha SI - \mu S - pS = 0$$

$$\alpha SI - \beta I - \mu I = 0$$

Therefore the Jacobian matrix becomes

$$J(S,I) = \begin{bmatrix} -\alpha I - \mu - p & -\alpha S \\ \alpha I & \alpha S - \beta - \mu \end{bmatrix}$$

3.11 THE DISEASE-FREE EQUILIBRIUM

At the disease-free equilibrium, we consider the case where there is no infection. That is when $I = 0$. Putting $\frac{dS}{dt} = 0$, the disease free equilibrium is $(S^*, I^*) = (1,0)$. Thus, in the absence of infective the susceptible have an equilibrium value S^*.

3.11.1 Stability Analysis of Disease-Free Equilibrium Point

To determine the stability of the system of the disease-free equilibrium (S, I) = (1, 0), we will consider the linearized system of the equations (3.19) and (3.20) below about the equilibrium point by taking the Jacobian.

$$\frac{dS}{dt} = \mu K - \alpha SI - \mu S - pS$$

$$\frac{dI}{dt} = \alpha SI - (\beta + \mu)I$$

The Jacobian is therefore given by

$$J(S,I) = \begin{bmatrix} -\alpha I - \mu - p & -\alpha S \\ \alpha I & \alpha S - \beta - \mu \end{bmatrix}$$

The Jacobian matrix becomes

$$J(S,0) = \begin{bmatrix} -\mu - p & -\alpha S \\ 0 & \alpha S - \beta - \mu \end{bmatrix}$$

Since S=1 and I=0 at the disease free equilibrium

$$Det(J - \lambda) = \begin{vmatrix} -\mu - p - \lambda & -\alpha S \\ 0 & \alpha S - \beta - \mu - \lambda \end{vmatrix} = 0$$

$$Det(J - \lambda) = 0$$

$$(-\mu - p - \lambda)(\alpha S - \beta - \mu - \lambda) = 0$$

$$\lambda_1 = -\mu - p \; and \; \lambda_2 = \alpha S - \beta - \mu$$

For $Det(J - \lambda)$ to be asymptotically stable, both eigenvalues must be negative. From

$Det(J - \lambda) = 0$, it is clear that $\lambda_1 = -\mu - p$ is negative and therefore if $\lambda_2 = \alpha S - \beta - \mu < 0$ then both eigenvalues are negative and $R_0 < 1$. Hence the disease free-equilibrium is asymptotically stable if $R_0 < 1$. On the other hand, if $\lambda_2 = \alpha S - \beta - \mu > 0$, then $Det(J - \lambda)$ is unstable. We now investigate the stability of the equilibrium by deriving the reproductive ratio R_0.

3.12 THE BASIC REPRODUCTIVE RATIO (R_0) OF HBV TRANSMISSION WITH VACCINATION

In order to determine the stability of the systems (3.22) and (3.23) at the point $(S^*, 0)$, we substitute $I = 0$ and $S = S^*$ into the linearized Jacobian matrix to find the eigenvalues as follows

$$J(S,0) = \begin{bmatrix} -\mu - p & -\alpha S \\ 0 & \alpha S - \beta - \mu \end{bmatrix}$$

$$Det(J - \lambda) = \begin{vmatrix} -\mu - p - \lambda & -\alpha S \\ 0 & \alpha S - \beta - \mu - \lambda \end{vmatrix}$$

$$Det(J - \lambda) = 0$$

$$(-\mu - p - \lambda)(\alpha S - \beta - \mu - \lambda) = 0$$

$$-\mu - p - \lambda = 0$$

$$\lambda_1 = -\mu - p$$

Also

$$[(\alpha S - \beta - \mu) - \lambda] = 0$$

$$-\lambda = -(\alpha S - \beta - \mu)$$

$$\lambda_2 = \alpha S - \beta - \mu$$

The parameter ranges are as follows $0 < \mu < 1, 0 < p < 1, 0 < \beta < 1 \; and \; 0 < \alpha < 1$. λ_2 depends on $\alpha, \beta, S \; and \; \mu$. Although, the first term αS is positive, the second and third terms are negative. This implies that the sign of λ_2 depends on αS, but $0 < \alpha < 1$. If S becomes large, λ_2 will be positive and if S becomes small, α will make the value of the first term small, thereby making the value of λ_2 negative. Therefore $\alpha S \ll \beta$ and λ_2 is negative. Also $p \gg \beta$ and that makes λ_2 the most negative.

Therefore λ_2 is the dominant eigenvalue, since it is the most negative eigenvalue.

$$R_O = \lambda^* \times (infectious\ period) + 1$$

We now consider the initial condition $S = S_O$

$$R_O = \left(\frac{\alpha S_O - \beta - \mu}{1}\right) \times \frac{1}{(\mu + \beta)} + 1$$

$$R_O = \frac{\alpha S_O - \beta - \mu}{(\mu + \beta)} + 1$$

$$R_O = \frac{\alpha S_O - \beta - \mu + \mu + \beta}{(\mu + \beta)}$$

$$R_O = \frac{\alpha S_O}{(\mu + \beta)} \qquad (3.33)$$

This is the average number of secondary infections caused by one infected individual during the mean course of infection in the case where the number of susceptible is counted from the disease free equilibrium; that is the total susceptible of the population when disease is free. When $R_O > 1$ there is an endemic and the solution is unstable but when $R_O < 1$ a positive equilibrium occurs and the solution is stable (Zhao *et al*., 1995)

3.13 THE ENDEMIC EQUILIBRIUM

Considering the case where $R_O > 1$ when the system has an endemic infection then $(S^*, 0)$ is unstable.

From the equations (3.22), (3.23) and (3.24)

$$S^* = \frac{\beta + \mu}{\alpha}$$

And

$$I^* = \frac{\alpha\mu K - (\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}$$

Thus the endemic equilibrium is

$$(S^*, I^*) = \left[\left(\frac{\beta+\mu}{\alpha}\right), \left(\frac{\alpha\mu K - (\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}\right)\right]$$

The prove that (S^*, I^*) is asymptotically stable, substitute $S=S^*$ and $I=I^*$ into the Jacobian matrix to find the eigenvalues λ.

$$(J-\lambda I) = \begin{bmatrix} \frac{\alpha\left(\alpha\mu K - (\beta+\mu)(\mu+p)\right)}{\alpha(\beta+\mu)} - \mu - p - \lambda & \frac{-\alpha(\beta+\mu)}{\alpha} \\ \alpha\left(\frac{\alpha\mu K - (\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}\right) & \alpha\left(\frac{\beta+\mu}{\alpha}\right) - \beta - \mu - \lambda \end{bmatrix}$$

$$(J-\lambda I) = \begin{bmatrix} \frac{-\alpha\mu K}{(\beta+\mu)} - \lambda & -\beta-\mu \\ \frac{\alpha\mu K}{(\beta+\mu)} - (\mu+p) & -\lambda \end{bmatrix}$$

$$Det(J-\lambda I) = \begin{vmatrix} -\left(\frac{\alpha\mu K}{(\beta+\mu)} + \lambda\right) & -(\beta+\mu) \\ \frac{\alpha\mu K}{(\beta+\mu)} - (\mu+p) & -\lambda \end{vmatrix} = 0$$

$$-\left(\frac{\alpha\mu K}{(\beta+\mu)} + \lambda\right)(-\lambda) - \left[\frac{\alpha\mu K}{(\beta+\mu)} - (\mu+p)\right][-(\beta+\mu)] = 0$$

$$\left(\frac{\alpha\mu\lambda K}{(\beta+\mu)} + \lambda^2\right) + \left[\frac{-\alpha\mu K}{(\beta+\mu)} + (\mu+p)\right][(\beta+\mu)] = 0$$

$$\left(\frac{\alpha\mu\lambda K}{(\beta+\mu)} + \lambda^2\right) + [-\alpha\mu K + (\mu+p)(\beta+\mu)] = 0$$

$$\lambda^2 + \lambda\left(\frac{\alpha\mu K}{\beta+\mu}\right) - \alpha\mu K + (\mu+p)(\beta+\mu) = 0 \qquad (3.34)$$

3.13.1 Stability Analysis of Endemic Equilibrium

The Jacobian matrix $(J - \lambda I)$ at the endemic equilibrium state,

$$(S^*, I^*) = \left[\left(\frac{\beta+\mu}{\alpha}\right), \left(\frac{\alpha\mu K - (\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}\right)\right]$$

Is given by

$$(J - \lambda I) = \begin{bmatrix} \frac{\alpha\left(\alpha\mu K - (\beta+\mu)(\mu+p)\right)}{\alpha(\beta+\mu)} - \mu - p - \lambda & \frac{-\alpha(\beta+\mu)}{\alpha} \\ \alpha\left(\frac{\alpha\mu K - (\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}\right) & \alpha\left(\frac{\beta+\mu}{\alpha}\right) - \beta - \mu - \lambda \end{bmatrix}$$

The characteristic equation of $(J - \lambda I)$ is given by equation (3.34)

$$\lambda^2 + \lambda\left(\frac{\alpha\mu K}{\beta+\mu}\right) - \alpha\mu K + (\mu+p)(\beta+\mu) = 0$$

If the trace $\lambda_1 + \lambda_2 < 0$ and its determinant,

$$\alpha\left(\frac{\alpha\mu K - (\beta+\mu)(\mu+p)}{\alpha(\beta+\mu)}\right)\left(\frac{-\alpha(\beta+\mu)}{\alpha}\right) > 0$$

Is positive, the endemic equilibrium is asymptotically stable. This conclusion is true since $R_O > 1$ in the endemic equilibrium. On the other hand it becomes unstable when $R_O < 1$. Comparing equation (3.34) to the equation $\lambda^2 - p\lambda + q$

$$p = -\frac{\alpha\mu K}{\beta+\mu} \; and \; q = -\alpha\mu K + (\mu+p)(\beta+\mu)$$

If $\lambda_1 \; and \; \lambda_2$ are the eigenvalues of J then we have

$$p(\lambda) = (\lambda - \lambda_1)(\lambda - \lambda_2) = \lambda^2 - (\lambda_1 + \lambda_2)\lambda + \lambda_1\lambda_2$$

Thus we have the identities

$$\lambda_1 + \lambda_2 = tr(J) and \; \lambda_1\lambda_2 = Det(J)$$

Let *p=tr (J)* and $q = \det(J)$ in the following discussion. By quadratic formula, the eigenvalues are given by

$$\lambda_1, \lambda_2 = \frac{p \pm \sqrt{p^2 - 4q}}{2}$$

$$\lambda_1 = \frac{p + \sqrt{p^2 - 4q}}{2} \; and \; \lambda_2 = \frac{p - \sqrt{p^2 - 4q}}{2}$$

The nature of the roots is determined by the discriminant $\Delta = p^2 - 4q$

The parameters p, q and Δ allow us to determine the stability of the fixed points (origin) of the endemic equilibrium and classify them as follows;

3.13.1.1 Case 1

a. For $\Delta > 0$, we have two distinct real eigenvalues. If q < 0, the eigenvalues are real and have opposite signs; hence the fix point is a saddled point. Suppose that $\lambda_1 < 0 > \lambda_2$. The solution $x(t) = x_o e^{\lambda_1 t} \; and \; y(t) = y_0 e^{\lambda_2 t}$. The points on the x-axis approach the

origin asymptotically, while points on the y-axis go away from the origin. If we have the coordinate of the trajectory goes to zero, while the y-coordinate goes to $\pm\infty$. Again, the coordinates must satisfy $y = y_o \left|\frac{x}{x_0}\right|^{\frac{\lambda_2}{\lambda_1}}$ so trajectories lie in the power curves $y = C|x|^{\frac{\lambda_2}{\lambda_1}}$. In this case, the exponent is negative, so the curves have the coordinate axes as an asymptote. The origin is unstable.

b. If $q > 0$, the product of the eigenvalues is positive and so they must have the same sign. The common sign is the same sign p. the eigenvalues are either real with the same sign (nodes), or complex conjugate (spirals and centers). Nodes satisfy $p^2 - 4q > 0$ and spirals satisfy $p^2 - 4q < 0$. The parabola $p^2 - 4q = 0$ is the borderline between nodes and spirals. The stability of the nodes and spirals is determined by p.

   i. When $p < 0$, we have $\lambda_2 < \lambda_1 < 0$ and both eigenvalues have negative real parts, so the fixed point is asymptotically stable. In this case we have $\frac{\lambda_2}{\lambda_1} > 1$. if $x_o = 0$, the integral curve approaches the origin along the y-axis. $if\ x_o \neq 0, \left|\frac{x(t)}{x_o}\right| = e^{\lambda_1 t} S_o y(t) = y_o e^{\lambda_2 t} = y_o (e^{\lambda_1 t})^{\frac{\lambda_2}{\lambda_1}} \left|\frac{x(t)}{x_0}\right|^{\frac{\lambda_2}{\lambda_1}}$. Thus the integral curve must lie in the locus of a power curve of the form $y = C|x|^{\lambda_2/\lambda_1}$. The integral curves lie in one of the parabolas $y = Cx^2$.

   If $q = 0$, one of the eigenvalues is zero and the other is not. The non-zero eigenvalue is equal to p. the origin is not an isolated fixed point. There is either a whole line of fixed points or a plane of fixed points.

   ii. When we have one negative eigenvalue and one zero eigenvalue and we choose $\lambda_2 < \lambda_1 = 0$. The solution of the system is $x(t) \equiv x_o$ and $x(t) = y_o e^{\lambda_2 t}$.

Thus, the points on the x-axis are all fixed. A point on the x-axis approaches the x-axis asymptotically along the vertical line $x = x_o$. In this case, the origin is stable, but not asymptotically stable. If $\lambda_2 = 0$ and $\lambda_1 < 0$, we have a similar picture, with the roles of x and y interchanged.

iii. When we have one zero eigenvalue and one positive eigenvalue, and we let $0 = \lambda_1 < \lambda_2$. The solution $x(t) \equiv x_o$ and $x(t) = y_o e^{\lambda_2 t}$. Thus, points on the x-axis are fixed, and other points escape to infinity along the vertical line $x = x_o$. The origin is unstable. If the eigenvalues are exchanged, we get a similar picture with x and y interchanged.

3.13.1.2 Case 2

a. For non-real eigenvalues, suppose that $\lambda = \alpha + i\beta$, is a complex, non-real, eigenvalue of J. this means there is a complex vector ω such that $J\omega = \lambda\omega$. The conjugate $\bar{\lambda}$ of λ is also an eigenvalue, with eigenvector $\bar{\omega}$. The vectors ω and $\bar{\omega}$ are linearly independent over the complex numbers.

The general solution of the system $z' = Jz$ *is* $z(t) = e_{z0}^{jt}$. Since ω and $\bar{\omega}$ are eigenvectors, we have $e_{\omega}^{jt} = e_{\omega}^{\lambda t}$ and $e_{\bar{\omega}}^{jt} = e_{\bar{\omega}}^{\bar{\lambda}}$. We can write $\omega = u + iv$ for real vectors u and v. these vectors span R^2.

$$e_u^{Jt} = e^{\alpha t}\cos(\beta t)u - e^{\alpha t}\sin(\beta t)\, v$$

$$e_v^{Jt} = e^{\alpha t}\sin(\beta t)u - e^{\alpha t}\cos(\beta t)v$$

Thus, in this conical coordinate system, the solutions are

$$x(t) = e^{\alpha t}x_o\cos(\beta t) + e^{\alpha t}\, y_0\sin(\beta t)$$

$$y(t) = -e^{\alpha t}x_o \sin(\beta t) + e^{\alpha t}\, y_0 \cos(\beta t)$$

b. Imaginary eigenvalues suppose that $\alpha = 0$. Then the solution is

$$\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} = \begin{bmatrix} \cos(\beta t) & \sin(\beta t) \\ -\sin(\beta t) & \cos(\beta t) \end{bmatrix} \begin{bmatrix} x_0 \\ y_0 \end{bmatrix}$$

The matrix in this equation is the clockwise rotation through βt radians. Thus, each point travels around a circle. The fixed point is described as a center.

c. Non real eigenvalues with negative real parts

Suppose that the eigenvalues are $\alpha = i\beta$, where $\alpha < 0$. The solution can be written as

$$\begin{bmatrix} x \\ y \end{bmatrix} = e^{\alpha t} \begin{bmatrix} \cos(\beta t) & \sin(\beta t) \\ -\sin(\beta t) & \cos(\beta t) \end{bmatrix} \begin{bmatrix} x_O \\ y_O \end{bmatrix}$$

Thus, we have $e^{\alpha t}$ times a vector that is rotating at a fixed rate. Every trajectory spirals into the origin, the fixed point is a spiral sink and so the origin is asymptotically stable.

d. Non real eigenvalues with positive real part

In this case, the solution is again given by

$$\begin{bmatrix} x \\ y \end{bmatrix} = e^{\alpha t} \begin{bmatrix} \cos(\beta t) & \sin(\beta t) \\ -\sin(\beta t) & \cos(\beta t) \end{bmatrix} \begin{bmatrix} x_O \\ y_O \end{bmatrix}$$

With $\alpha > 0$ Thus every trajectory spirals away from the origin, and the origin is a spiral source and therefore unstable.

3.13.1.3 Case 3

a) The eigenvalue λ_o must be real, and the characteristic polynomial of J is $(\lambda - \lambda_o)^2$. Thus by the Caley-Hamilton theorem, we must have $(J - \lambda_o)^2 = 0$, we must then consider the major subcases.

i. When $J = \lambda_o I$

In this case, the solution is just $x(t) = x_o e^{\lambda_o t}, y(t) = y_o e^{\lambda_o t}$. The solution stays on the radial lines through the origin. If $\lambda_o = 0$, all solutions approach the origin asymptotically, if $\lambda_o > 0$, all solutions go to infinity along the radial lines. If $\lambda_o = 0$ all points are fixed.

ii. When $J \neq \lambda_o I$

Let $N = J - \lambda_o I$, in this case, we have $N^2 = 0$ but $N \neq 0$. Since $N \neq 0$, we can find some vector v_2 such that $v_1 = N v_2 \neq 0$.

Note that $N v_1 = N^2 v_2 = 0$.

We claim that the vectors $v_1 \; and \; v_2$ are linearly independent. Therefore $c_1 v_1 + c_2 v_2 = 0$. Applying N to both sides of this equation yields $c_2 v_1 = 0$. This implies that $c_2 = 0$ since v_1 is non-zero, and this in turn implies that c_1=0. Using the definition of N

$$J v_1 = \lambda_o v_1$$

$$J v_2 = \lambda_o v_1$$

Thus, in the conical coordinates, the solution of the system is $x(t) = x_o e^{\lambda_o t} + y_0 t e^{\lambda_o t}, y(t) = y_0 e^{\lambda_o t}$

If $\lambda_o < 0$, every solution will approach the origin. If $y_0 = 0$, the solution approaches the origin along the x-axis. If $y_0 \neq 0$, the difference $y(t) - x(t)$

approaches 0 about the same rate as $(x(t), y(t))$approaches the origin as $t \to \infty$, so the trajectory is asymptotic to the line y=x as $t \to \infty$.

3.14 THE HERD IMMUNITY THRESHOLD

The herd Immunity Threshold (H1) is the percentage of the population that needs to be immune to control transmission of the disease. The equation given by Diekmann and Heesterbeek for the Herd Immunity Threshold is

$$H1 = \frac{R_0 - 1}{R_0} = 1 - \frac{1}{R_0}$$

$$H1 = 1 - \frac{1}{\left(\frac{\alpha S_0}{\mu + \beta}\right)}$$

$$H1 = 1 - \frac{\mu + \beta}{\alpha S_0}$$

$$H1 = \frac{\alpha S_0 - (\mu + \beta)}{\alpha S_0} \qquad (3.35)$$

As the amount of vaccinations increase, the Herd Immunity Threshold also increases. By decreasing the amount of susceptible people, the Head Immunity Threshold decreases.

3.15 CONTROL VACCINATION NUMBER

The Control Vaccination Number, denoted C_v, is the average number of secondary cases generated by an infectious case during epidemic with control measure, in this case vaccination.

The formula for estimating the control vaccination number is given by

$$C_v = R_0(1 - hp)$$

Where h is the vaccine efficacy (the effectiveness of the vaccine) and p is the vaccination coverage (the fraction of the population that has been vaccinated).

The goal of researchers is to have $C_v < 1$ (Maynard *et al.*, 1989). To have $C_v < 1$, knowing the efficacy of the vaccine we can estimate the proportion of the population that need to be vaccinated.

This is given by

$$p > \frac{1 - (\frac{1}{R_0})}{h}$$

CHAPTER 4

MODEL ANALYSIS AND RESULTS

4.1 INTRODUCTION

The prevalence of hepatitis B is becoming alarming in the Tano North District of Ghana in recent years. In this paper, the year 2000 will be used as the base year. The initial population of Tano North District according to the 2000 population and housing census was 74,775. A formal request made to obtain data on hepatitis B from the Biostatistics Department of the District Health Directorate Tano North District indicated 25 people were infected with hepatitis B. It was estimated that during the base year, about 1,275 people had received the hepatitis B vaccine and therefore were immune to the disease. Therefore they belong to the removed compartment, leaving the number of susceptible at 73475. So our initial susceptible value is 73475, $S_0 = 73475$, initial infective value, $I_O = 25$, $S_\infty = 71246$, representing the total population (excluding those who have received the hepatitis B vaccine) of the district in 2010. The initial susceptible fraction of the population, initial infective fraction of the population and the final number of susceptible fraction of the population are 0.982615,3.343363×10^{-4}, 0.952805 respectively.

In case of the reply the number and the date of this letter Should be quoted.

My Ref No. DHD/HB/01/2012
Your Ref No.....

GHANA HEALTH SERVICE
DISTRICT HEALTH DIRECTORATE
P. O. BOX 82
TANO NORTH -DUAYAW-NKWANTA

13 September 2012

E-mail: TANO.NORTH_DHD@YAHOO.COM

Telephone: 0208154104

TREND OF HEPATITIS B CASES IN TANO NORTH DISTRICT – 2000 - 2011

Please below are the figures and trend of cases of hepatitis B in the Tano North district for your perusal and research purpose.

YEAR	NUMBER OF CASES
2000	25
2001	32
2002	38
2003	30
2004	32
2005	35
2006	40
2007	49
2008	22
2009	36
2010	54
2011	85
Total	**478**

Thank you.

DR YAKUBU BAYAYINAH
DISTRICT DIRECTOR OF HEALTH SERVICES
TANO NORTH DISTRICT
DUAYAW NKWANTA-B/A

Figure 4.1 *number of cases of hepatitis B in the tano north district from 2000 to 2011.*

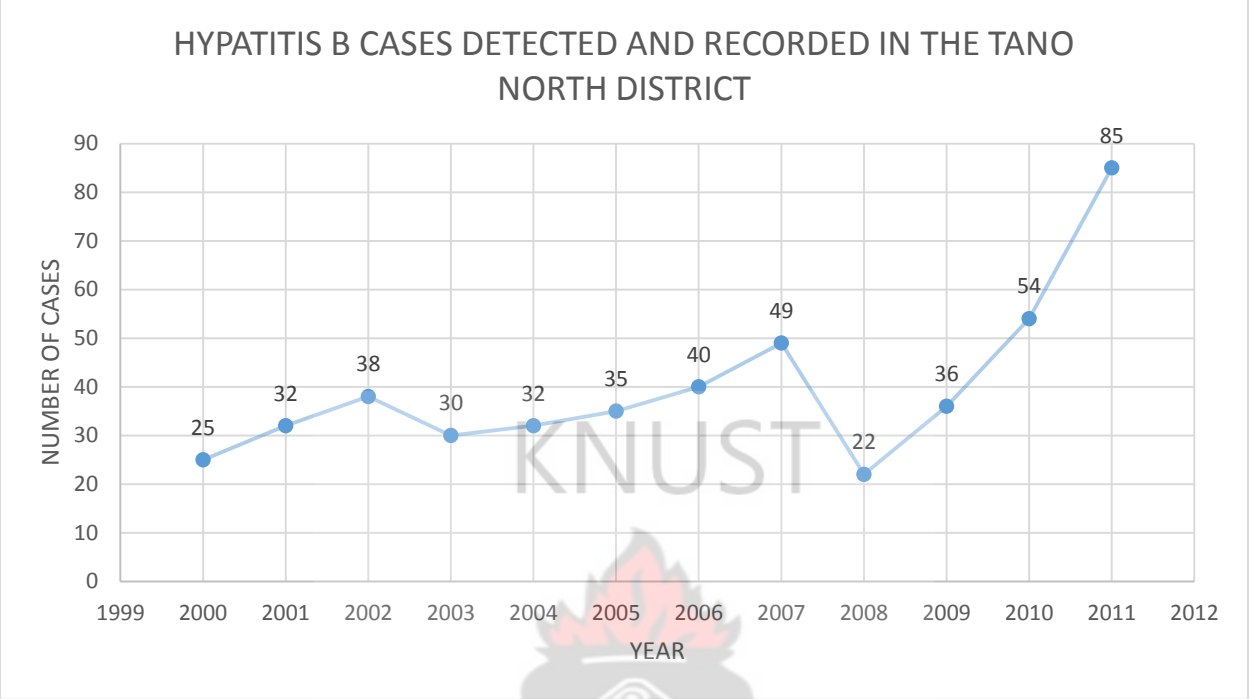


Figure 4.2 *graph of the number of the years against the number of cases of hepatitis B*

4.2 ESTIMATING PARAMETERS FOR SIR MODEL OF HBV VIRUS TRANSMISSION WITHOUT VACCINATION.

From equation 3.12, we can make the following calculations;

$$\frac{\alpha}{\beta} = \frac{\ln\left(\frac{S_o}{S_\infty}\right)}{I_o + S_o - S_\infty}$$

$$\frac{\alpha}{\beta} = \frac{\ln\left(\frac{0.982615}{0.952805}\right)}{3.343363 \times 10^{-4} + 0.982615 - 0.952805}$$

$$\frac{\alpha}{\beta} = \frac{0.030807}{0.030144}$$

$$\frac{\alpha}{\beta} = 1.02199$$

We measure time in years. Let's take $t_0 = 0$ corresponding to January, 2000 and $t_f = 11$ corresponding to December, 2011.

4.3 THE INFECTIOUS PERIOD OF HEPATITIS B

The infectious period of hepatitis B is 3 to 6 weeks (Shoujun et al., 2000). The average infectious period can be estimated as follows;

The average infectious period of hepatitis B in months is $= \frac{21+28+35+42}{31\times4}$

$$= \frac{126}{124}$$

$$= 1.0161\ months$$

From the information above, we can estimate the recovery rate (β) as the reciprocal of the infectious period.

Recovery rate $(\beta) = \frac{1}{infectious\ period} = \frac{1}{1.0161} = 0.984155102$

$$\beta = 0.984155102$$

The value of the infectious rate α can be obtained as;

$$\alpha = \frac{\alpha}{\beta} \times \beta$$

But

$$\frac{\alpha}{\beta} = 1.02199$$

$$\therefore\ \alpha = 1.02199 \times 0.9842 = 1.0058$$

Using the values of $\alpha\ and\ \beta$ we can estimate the maximum number of infectives during the epidemic;

$$\rho = \frac{\beta}{\alpha} = \frac{0.984155}{1.0058} = 0.97848$$

Again,

$$K = S_0 + I_0 = 0.982615 + 3.343363 \times 10^{-4} = 0.982949$$

Also from equation 3.16

$$I_{max} = K - \rho + \rho(ln\rho - lnS_O)$$

$$I_{max} = 0.982949 - 0.97848 + 0.97848(\ln 0.97848 - \ln 0.982615)$$

$$I_{max} = 3.427126 \times 10^{-4}\ persons$$

4.4 ESTIMATION OF REPRODUCTIVE RATIO OF HEPATITIS B WITHOUT VACCINATION

From the SIR model in chapter 3, the reproductive ratio of hepatitis B without vaccination for the model is given by;

$$R_0 = \frac{\alpha S_0}{\beta} = \frac{S_0}{\rho} = \frac{0.982615}{0.97848} = 1.00423 > 1$$

Since $R_0 > 1$, the prevalence of hepatitis B in the Tano North district is considered as endemic.

4.5 ESTIMATING PARAMETERS FOR SIR MODEL OF HBV WITH VACCINATION

The parameters for the SIR model of hepatitis B is estimated as follows:

4.5.1 Death Rate Parameter Estimation (μ)

Death rate from Tano North District from 2000 to 2011=

$$\left(\frac{number\ of\ deaths\ from\ hepatitis\ B\ in\ the\ 2000\ in\ the\ tano\ north\ district}{number\ of\ persons\ in\ the\ population\ per\ 100}(\mu)\right) \times 100$$

$$(\mu) = \frac{7\ deaths}{74775\ persons} \times 100$$

$$\mu = 0.0094\ deaths\ per\ 100\ population$$

4.5.2 Estimation of Vaccinated Susceptible (*P*)

HB vaccinated susceptible (p) in the population is given by

$$(1275 \div 74775) = 0.017051$$

4.5.3 Estimating the Basic Reproduction Ratio, R_0 of Hepatitis B with Vaccination

According to the model, the Basic Reproduction Ratio, R_0 of hepatitis B with vaccination is

$$R_0 = \frac{\alpha S_0}{(\mu + \beta)}$$

Substituting $\alpha = 1.00588, \mu = 0.0294, \beta = 0.984155 \; and \; S_0 = \; 0.983283 \; into \; R_0$ gives

$$R_0 = \frac{1.0058 \times 0.982615}{(0.0094 + 0.984155)} = 0.994725$$

$$R_0 = 0.994725 < 1$$

4.6 STABILITY ANALYSIS OF EQUILIBRIUM POINTS

$$(s^*, I^*) = \left(\frac{\beta + \mu}{\alpha}, 0\right)$$

Substituting $\alpha = 1.00588, \mu = 0.0094, \beta = 0.984155$ into (s^*, I^*) gives

$$(s^*, I^*) = \left(\frac{0.984155 + 0.0094}{1.0058}, 0\right)$$

$$(s^*, I^*) = (0.987826, 0)$$

Substituting this into the Jacobian matrix below gives

$$Det(J - \lambda) = \begin{vmatrix} -\mu - p - \lambda & -\alpha S \\ 0 & \alpha S - \beta - \mu - \lambda \end{vmatrix} = 0$$

$$Det(J - \lambda) = \begin{vmatrix} -0.0094 - 0.017051 - \lambda & -1.0058(0.982615) \\ 0 & 1.0058(0.982615) - 0.984155 - 0.0094 - \lambda \end{vmatrix} = 0$$

$$Det(J - \lambda) = \begin{vmatrix} -0.026451 - \lambda & -0.988314 \\ 0 & 3.908 \times 10^{-7} - \lambda \end{vmatrix} = 0$$

$$(-0.026451 - \lambda)(3.908 \times 10^{-7} - \lambda) = 0$$

$$-1.03371 \times 10^{-8} + 0.026451\lambda - 3.908 \times 10^{-7}\lambda + \lambda^2 = 0$$

$$\lambda^2 + 0.026451\lambda - 1.03371 \times 10^{-8} = 0$$

$$\lambda_1 = -0.026451 \; and \; \lambda_2 = 3.90796 \times 10^{-7}$$

This is a saddled point, since $\lambda_1 \; and \; \lambda_2$ have distinct eigenvalues. The equilibrium point $(s^*, I^*) = (0.987826,0)$ is therefore unstable. This is so because the transmission rate of HBV in the Tano North District is greater than the recovery rate of the disease in the district.

4.7 STABILITY ANALYSIS OF THE ENDEMIC EQUILIBRIUM

$$(S^*, I^*) = \left[\left(\frac{\beta + \mu}{\alpha}\right), \left(\frac{\alpha\mu K - (\beta + \mu)(\mu + p)}{\alpha(\beta + \mu)}\right)\right]$$

(S^*, I^*)

$$= \left[\left(\frac{0.984155 + 0.0094}{1.0058}\right), \left(\frac{1.0058(0.0094)(0.982949) - (0.984155 + 0.0094)(0.0094 + 0.017051)}{1.0058(0.984155 + 0.0094)}\right)\right]$$

$$(S^*, I^*) = \left(\frac{0.993555}{1.0058}, \frac{0.009293 - 0.026281}{0.999318}\right)$$

$$(S^*, I^*) = (0.987826, -0.0169998)$$

Substituting it into the Jacobian matrix below gives;

$$\det(J - \lambda) = \begin{vmatrix} -\alpha I - \mu - p - \lambda & -\alpha S \\ \alpha I & \alpha S - \beta - \mu - \lambda \end{vmatrix} = 0$$

$$\Rightarrow \begin{vmatrix} -1.0058(3.34336 \times 10^{-4}) - 0.0094 - 0.017051 - \lambda & -1.0058(0.987826) \\ 1.0058(3.34336 \times 10^{-4}) & 1.0058(0.987826) - 0.984155 - 0.0094 - \lambda \end{vmatrix}$$

$$= 0$$

$$\Rightarrow \begin{vmatrix} -0.026787 - \lambda & -1.01357 \\ 0.000336 & 0.019998 - \lambda \end{vmatrix} = 0$$

$$\Rightarrow (-0.026809 - \lambda)(0.01998 - \lambda) - (0.000336 \times -1.01357) = 0$$

$$\lambda^2 + 0.006811\lambda - 0.000536 = 0$$

$$\lambda_1 = -0.026806, \lambda_2 = 0.019995$$

This is a saddle point since λ_1 *and* λ_2 have distinct eigenvalues. The equilibrium point (S^*, I^*) is therefore unstable.

4.8 THE HERD IMMUNITY THRESHOLD (H_1) ESTIMATION

When there is an epidemic outbreak in a certain part of a country, a vaccination program is considered; this can be expensive. Because of that, there is the need to decide how many people to be vaccinated in order to control and contain the epidemic. In the same way, the required number of people that needs to be vaccinated in the Tano North District can be estimated as follows;

$$H_1 = \frac{R_0 - 1}{R_0} = \frac{1.00423 - 1}{1.00423} = 0.004212$$

That is about 0.42% of the susceptible population should be immune in order to bring the spread of hepatitis B under total control in the Tano north district.

4.9 CONTROL VACCINATION NUMBER

Research has shown that that the vaccine for HBV has 95% effectiveness (Edmunds *et al.*, 1993; McLean and Blumberg, 1994; Zhao *et al.*, 2000). Knowing the efficacy of the vaccine we estimate the proportion of the population that need to be vaccinated.

This is given by

$$p > \frac{1 - \left(\frac{1}{1.00423}\right)}{0.95} = 0.004434$$

We can observe from calculation above that when the effectiveness is 95%, then about 0.44% of the population needs to be vaccinated in order for $C_v < 1$.

4.10 SENSITIVITY ANALYSIS

This aspect of the thesis deals with the analysis of the models and the discussion of the results obtained. We use MatLab to run our simulations. For our systems of nonlinear differential equations, we use the ode 15s which is a fourth order variable Runge-Kutta method.

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

The estimated parameters of the model which have been used for the analysis are shown in the table below.

Table 4.1 *Parameter values for the model*

PARAMETER	DESCRIBTION	VALUE
α	Transmission rate	1.0058
β	Removal rate	0.984155
μ	Death rate	0.009422

The number of contacts between susceptible and hepatitis B patients during his/her infectious period is

$$\rho = \frac{\alpha}{\beta} = \frac{1.0058}{0.984155} = 1.02199$$

This means that on the average one hepatitis B patient contacts 1.02199 susceptible people in the district during his/her infectious period.

4.10.1 Sensitivity Analysis of R_0 of Hepatitis B without Vaccination

a. If $\boldsymbol{\alpha}$ **and** $\boldsymbol{\beta}$ values are increased and S_0 remains the same, that is 2.0058 and 0.999155 respectively.

$$\boldsymbol{R_0} = \frac{\alpha S_0}{\beta} = \frac{2.0058(0.982615)}{0.999155} = 1.9726 > 1$$

That is to say, keeping the number of susceptible individuals in Tano North district constant any value of α and βgreater than the values used in this thesis (thus $\alpha = 1.0058$ and $\beta = 0.984155$) will make R_0 greater than 1.

b. If α and β values are reduced to $\alpha = 0.0058$ and $\beta = 0.884155$ but S_0 maintained at 0.982615.

$$R_0 = \frac{\alpha S_0}{\beta} = \frac{0.0058(0.982615)}{0.884155} = 0.006446 < 1$$

That is to say, reducing the values of $\alpha \; and \; \beta$ and maintaining the number of susceptible will make $R_0 < 1$.

4.10.2 Sensitivity Analysis of R_0 of Hepatitis B with Vaccination

a. If $\boldsymbol{\alpha \; and \; \beta}$ values are increased and S_0 remains the same, that is 2.0058 and 0.999155 respectively.

$$\boldsymbol{R_0} = \frac{\alpha S_0}{(\mu + \beta)} = \frac{2.0058(0.982615)}{(0.0094 + 0.999155)} = 1.95421 > 1$$

That is to say, when the values of $\boldsymbol{\alpha \; and \; \beta}$ are increased above $\alpha = 1.0058 \; and \; \beta = 0.984155$, R_0 remains greater than 1 as required.

b. If $\alpha \; and \; \beta$ values are reduced to $\alpha = 0.0058 \; and \; \beta = 0.884155$ but S_0 maintained at 0.982615.

$$\boldsymbol{R_0} = \frac{\alpha S_0}{(\mu + \beta)} = \frac{0.0058(0.982615)}{(0.0094 + 0.884155)} = 0.006378 < 1$$

That is to say, when the values of $\boldsymbol{\alpha \; and \; \beta}$ are reduced below $\alpha = 1.0058 \; and$ $\beta = 0.984155$ the value of R_0 will be less than 1.

4.10.3 Sensitivity Analysis of Hepatitis B Transmission without Vaccination by Simulation.

We proceed to simulate our model using Matlab R2012a (7.14.0.739). The values of S, I and R, are altered and the changes that occur in model are observed.

Assuming the number of susceptible in the population is 500 and there is no vaccinated individual meaning no removed individuals, we introduce one infective into our system. The simulation gives us these graphs.

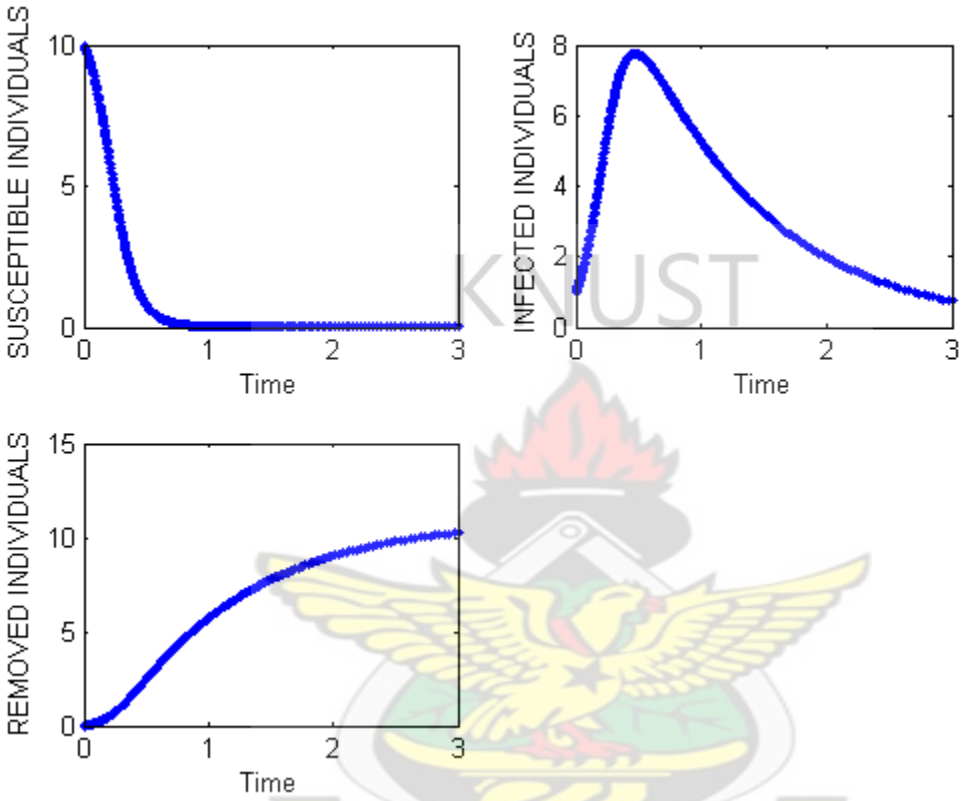


Figure 4.3 S=500, I=1 and R=0.

You will observe that by a short period, the number susceptible would have decreased to zero. This is because of the negative sign in the model. Since we assumed a constant population, the number susceptible decrease to zero.

The number of infected individuals increases gradually till it reaches its peak value.

The removed individuals increase gradually that is due to deaths by infected individuals moving from the infected compartment to the removed compartment.

4.10.4 Sensitivity Analysis of Hepatitis B Transmission with Vaccination by Simulation.

Assuming the number susceptible in our population is 500, no infected individuals and no removed persons. The simulation gives these graphs;

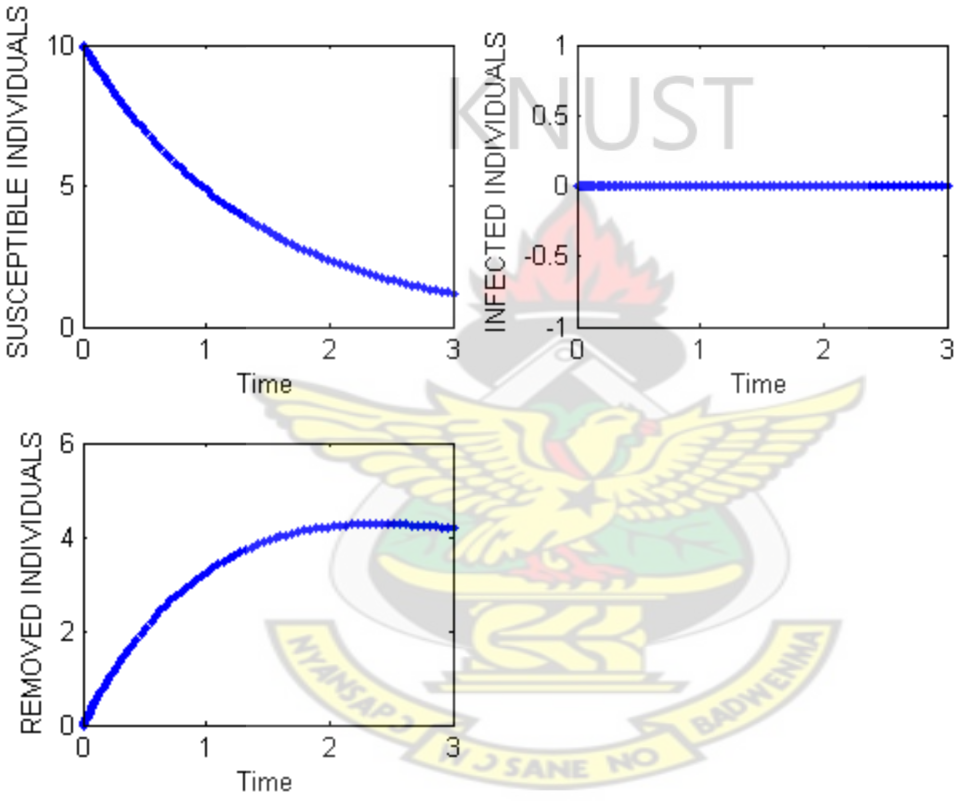


Figure 4.4 S=500, I=0 and R=0

It will observe that the number susceptible decrease in a short time and move to the removed compartment due to vaccination.

Since there is no infected individual in the population, the number remains a constant at zero.

The number of removed individuals also gradually moves up as a result of vaccination of the susceptible. Those vaccinated move to the removed compartment straight. It will be observed that the graph begins to move down with time, which is due to natural death.

Now, we decrease the number of susceptible to 499 and the number of removed individuals still at zero, we introduce one infective into our system. The simulation gives us these graphs.

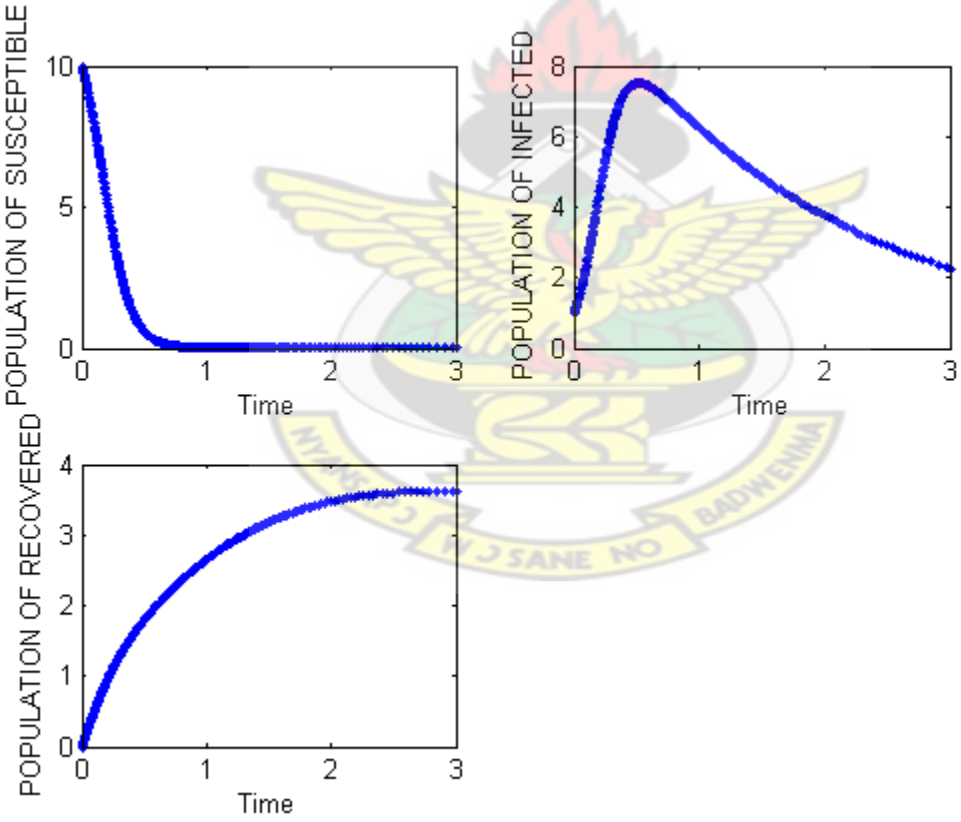


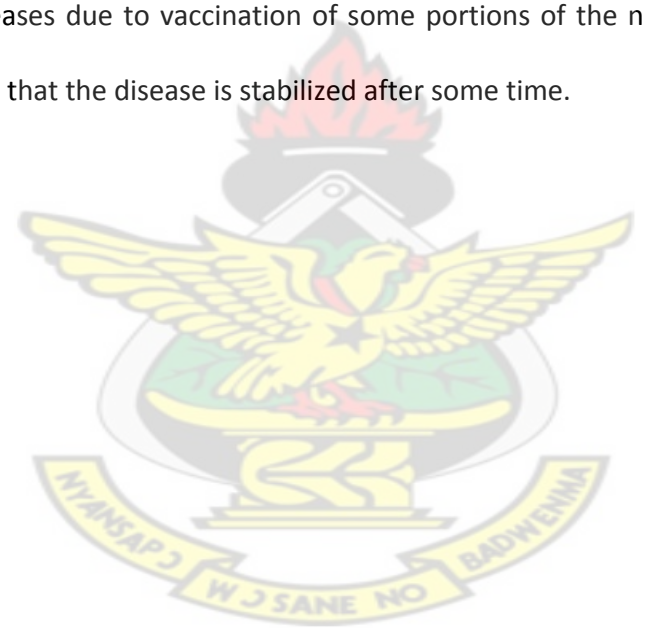
Figure 4.5 S=499, I=1 and R=0

It will be observed that the number susceptible decrease in a short period. This is due to two reasons:

1. People who have not been vaccinated acquiring the disease and moving to the infected compartment.
2. The vaccinated one's moving to the removed compartment.

The infected graph moves up for some time and in a little while decreases, this is due to the proportion of susceptible that were infected moving into the infective compartment. But they die of the disease and hence the decrease in the graph.

The removed also increases due to vaccination of some portions of the number of susceptible. It will be further observed that the disease is stabilized after some time.



CHAPTER 5

CONCLUSION AND RECOMMENDATION

5.1. INTRODUCTION

In this chapter we discuss the results obtained from the analysis, conclude and give necessary recommendation for further study

5.2. FINDINGS

From the preliminary analysis, one hepatitis B patient contacts on the average of 1.02199 approximately 1 susceptible person in the district during his/her infectious period.

The increasing use of the hepatitis B vaccine is having significant impact on the rate of HBV transmission and related deaths in the Tano North District. An increase in the hepatitis B vaccination coverage rate in the district will further decrease the prevalence of hepatitis B in the district. Maintaining it will result in increase in the rate of transmission of hepatitis B in the Tano North District which will affect the development of human resource in the district and country at large.

The sensitivity analysis indicates that there exist a direct (linear) relationship between the transmission rate, and the reproductive ratio, R_0. The higher the transmission rate relative to the recovery rate the higher the reproductive number whilst the lower the transmission rate relative to the recovery rate the lower the reproductive number since the natural death rate is relatively small.

The perturbation analysis of the disease free equilibrium revealed that when the reproductive number R_0 is less than unity the disease free equilibrium is stable, whilst when it is greater than unity the disease free equilibrium is unstable (Diekmann and Heesterbeek, 2000).

The herd immunity threshold shows that about 0.42% of the susceptible population of Tano North District should be immune in order for the disease not result in an epidemic. From further analysis with a control measure such as vaccination, and having a vaccine efficacy of 95% about 0.44% of the susceptible population should be vaccinated in order to have HBV under total control in the Tano North District.

Vaccinating this percentage of the entire population reduces the proportion of the susceptible population who risk infection upon outbreak.

5.3 CONCLUSION

The derivation and analysis of the modified SIR mathematical model (SIR), enabled a better understanding of the dynamics of the spread of HBV within the Tano North District population. Numerical simulations and sensitivity analysis was extensively helpful in the determination of the effect of the various parameters especially the transmission rate and recovery rate on the spread of the disease.

The reproductive ratio estimated indicates that the disease outbreak will be epidemic in the district. About 0.42% of the susceptible population should be immune in order not to have an epidemic. The simulation results and the sensitivity analysis of the study confirmed the transmission rate and recovery rate as the dominant parameters in the spread of the disease in Ghana.

Essentially, the chances of an epidemic are possible as far as the reproductive ratio is greater than one.

5.4. RECOMMENDATIONS

It is recommended that it might be more reasonable and interesting to use age-structured models to study the transmission and control of HBV (Edmunds *et al*., 1993;McLean and Blumberg, 1994;Zhao *et al*., 2000).

Vaccination programs should be introduced by the ministry of health and should target at vaccinating the about 0.42% of the susceptible population in order to fully bring the disease under control.

More importantly, education on the disease in the district should be intensified.

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Appendix

M-File for Hepatitis B Model without Vaccination

```
function dy=model(t,y,beta,alpha)

dy=zeros(3,1); % a column vector

dy(1)= -alpha*y(1)*y(2);

dy(2)= alpha*y(1)*y(2)-beta*y(2);

dy(3)= beta*y(2);
```


M-File for Hepatitis B Model with Vaccination

```
function dy=model(t,y,beta,alpha,k,p,mu)

dy=zeros(3,1); % a column vector

dy(1)= mu*k-alpha*y(1)*y(2)-mu*y(1)-p*y(1);

dy(2)= alpha*y(1)*y(2)-(beta+mu)*y(2);

dy(3)= beta*y(2)-mu*y(3)+p*y(1);
```

Scripts Used in Calling the M-File for Hepatitis B Model without Vaccination

```
alpha=1.0058;

beta= 0.984155;


options = odeset('RelTol',1e-9,'AbsTol',1e-9);

[T,Y] = ode15s(@sir,[0 3],[500 0 0],options, beta,alpha);

subplot(2,2,1)

plot(T,Y(:,1),'.')

xlabel('Time');ylabel('SUSCEPTIBLE INDIVIDUALS');

subplot(2,2,2)
```

```
plot(T,Y(:,2),'.')
xlabel('Time');ylabel('INFECTED INDIVIDUALS');
subplot(2,2,3)
plot(T,Y(:,3),'.')
xlabel('Time');ylabel('REMOVED INDIVIDUALS');
```

Scripts Used in Calling the M-File for Hepatitis B Model with Vaccination

```
beta= 0.30417;
gamma= 0.2293;
mu= 0.21429;
k=0.5149;
p=0.1994;

options = odeset('RelTol',1e-9,'AbsTol',1e-9);
[T,Y] = ode15s(@sirV,[0 3],[500 0 0],options, beta,alpha,p,k,mu);
subplot(2,2,1), plot(T,Y(:,1),'.')
xlabel('Time');ylabel('POPULATION OF SUSCEPTIBLE');
subplot(2,2,2), plot(T,Y(:,2),'.')
xlabel('Time');ylabel('POPULATION OF INFECTED');
subplot(2,2,3), plot(T,Y(:,3),'.')
xlabel('Time');ylabel('POPULATION OF RECOVERED');
```