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Epidemiological model of the transmission and spread of Hepatitis B pandemic in Ghana

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EPIDEMIOLOGICAL MODEL OF THE TRANSMISSION AND SPREAD OF HEPATITIS B PANDEMIC IN GHANA

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Abstract

The world's attention to the burden and spread of hepatitis B has increased significantly in the recent past. A number of interventions by way of treatment and immunisation have been initiated to fight the pandemic, especially in high prevalence regions such as Africa and Asia. Lack of good quality information about hepatitis B is a major hindrance to policy direction and comprehensive implementation of interventions in Sub-Saharan Africa designated as an endemic region. Limited studies on hepatitis B, coupled with lack of adequate health care systems and infrastructure, have led to ignorance or misconceptions and stigmatisation about the disease and worsened the disease prevalence in Ghana a Sub-Saharan African country. As a contribution, this study employed a $SEIR$ deterministic compartmental model, which incorporates latent period and vertical transmission, to examine the transmission and spread of hepatitis B in the context of the Sub-Saharan Africa with incidence data obtained from Ghana.

The $SEIR$ deterministic compartmental modelling divided the human population into separate classes namely susceptible (S), exposed (E), infectious (I) and removed (R) or recovered, and disease progression among population members in the various classes was described using a system of nonlinear ordinary differential equations (ODEs). The model has two equilibrium states namely, the disease-free equilibrium Q_0 and the endemic equilibrium Q^*. Stability analysis indicated that the model has an epidemiological threshold parameter R_0 which is defined as the expected proportion of secondary infections generated as a result of introducing a single infected individual into the population. When $R_0 \leq 1$ the disease-free equilibrium state is globally asymptotically stable whilst the endemic equilibrium state is unstable and so the disease is brought under control. When $R_0 > 1$, the disease-free equilibrium is unstable whilst the endemic equilibrium state is stable and so the disease persists in the population. Stability of the model was analysed in terms of proportions instead of the absolute number of cases and so disease eradication or persistence referred to the infected proportions vanishing or persisting respectively. A

hybrid nonlinear least squares method, that combines a Genetic Algorithm (GA) and a modified Levenberg-Marquadt (LM) algorithm, was applied to the hepatitis B incidence data to estimate the parameters of the model for Ghana (global) and also for each of the ten regions of Ghana. By numerical simulations, sensitivity analysis was performed to examine the effects of the model parameters on the threshold parameter R_0 using MATLAB. Furthermore, the model was modified to include a vaccination component to examine the impact of an intervention on the transmission and spread of the disease. The vaccination model also has an epidemiological threshold parameter R_{v0} such that when the vaccination rate k is greater than a threshold value k^*, then $R_{v0} < 1$ and the disease decreases; and when k is less than k^*, $R_{v0} > 1$ and the disease increases. This indicated that when the rate of vaccination k was increased beyond the threshold value k^*, the disease would be kept under control.

The threshold parameter was calculated as $R_0 = 1.6854$ for Ghana. This indicated that the endemic proportion equilibrium is asymptotically stable and so hepatitis B persists in the population of Ghana. The contact rate β, latency rate γ and vertical transmission rate α were identified as driving the disease spread in the population. A critical proportion of $H = 0.4067$ was calculated as the herd immunity threshold value of the population. This means that about 41% of the population are needed to be immune in order to adequately reduce the rates of transmission to keep the disease under control. Variability in the regional threshold parameters R_0 indicated significant disparities in the spread and burden of hepatitis B across the ten regions of Ghana. The highest and the least values of $(R_0 = 3.7212, H = 0.7312)$ and $(R_0 = 1.3669, H = 0.2684)$ were calculated for Upper West and Volta regions respectively. The regional threshold parameters R_0 also indicated that the trend of transmission and spread of the disease increase from south to north across the regions of Ghana. A simple regression analysis performed indicated that the increasing trend from south to north is highly associated with poverty and health sector differentials. Another factor that was considered in this study to have potentially impacted the distribution and pattern of spread and burden of hepatitis B in Ghana is prevalence differentials among regions and between Ghana and its neighbouring countries.

Declaration

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Chapter 1

Background and introduction

1.1 Introduction

Hepatitis B is known to be a global health concern. It is caused by the Hepatitis B virus (HBV). Hepatitis B is characterised by a broad spectrum of clinical outcomes; ranging from asymptomatic hepatitis to fulminant liver failure [1, 2]. Failure to clear the disease at the acute stage leads to chronic carriage, with asymptomatic course, progressing to cirrhosis of the liver or hepatocelular carcinoma. In fact, chronic hepatitis B has increasingly gained recognition as the major cause of cirrhosis and liver cancer in recent times [3]. Rated second to tobacco globally as a major cause of human malignancy, the disease is also known to be a major cause of death of HIV/AIDS co-infected individuals [4, 5]. Hepatitis B is also associated with extrahepatic diseases such as polyarteritis nodosa and glomerulonephritis [6, 7, 8].

This global health burden has seen some efforts from health bodies, worldwide on all fronts, to stem the ravaging effects of the disease. The World Health Organisation (WHO) through its agency, the World Health Assembly (WHA) has rolled out a number of programmes aimed at prevention and control of the disease. An outright cure has not been found. However, antiviral drugs are available for treatment of chronic hepatitis B that are meant to suppress viral replication and consequent liver damage. These drugs come at a cost and most invariably pose some financial difficulty especially to developing countries. Apart from these antiviral treatments, effective vaccines are also available for prevention through immunisation programmes [9, 10, 11]. In fact, vaccination has been identified as the single major measure of intervention for controlling hepatitis B [12].

The disease is transmitted mainly through contaminated blood and body fluids, which puts people in developing countries at the greatest risk [11, 13]. Ghana in Sub-Saharan Africa is noted to have high hepatitis B prevalence, which places an enormous burden on the economy and health management system of the country. Poverty, unavailability of standard health care systems, lack of relevant information and ignorance or misconceptions about the disease have together contributed to the worsening disease prevalence among the people in this part of the world. Surveys in Ghana report a lack of adequate information on hepatitis B to support necessary political decisions [14, 15]. The Ghana Health Service (GHS) admits to using inefficient data collection tools for the surveillance and management of hepatitis B in the country [16]. Like many other weak economies, lack of resources has also contributed to little or no response to some of the interventions suggested by WHO which include general education about the disease, vaccination and antiviral treatments [11, 13, 14, 15, 16, 17].

A number of studies have sought to provide a theoretical framework for understanding the dynamics of the hepatitis B pandemic worldwide. Compartmental modelling as a key tool has been used to explain the dynamics of hepatitis B pandemic in Africa and elsewhere [9, 17, 18, 19]. Many of these studies placed emphasis on the horizontal route of transmission of the disease [20, 21]. Some studies have also tried to review the impact of the latent period in the dynamics of hepatitis B on the key parameters defining the epidemiological threshold parameter usually referred to as the basic reproduction number [1, 22, 23, 24].

There have been few instances in which compartmental models were used to study hepatitis B in Ghana and with limited geographical scope [9, 17, 19]. These studies neglected the latent period which some literature indicate as important in the study of hepatitis B [25]. The studies also placed emphasis on the horizontal mode of transmission but other studies have shown that vertical transmission is a major route through which hepatitis B is acquired [7, 18]. Lack of knowledge and awareness about the disease and committed action towards treatment, prevention and control of the disease is a complete setback to policy development and implementation in fighting hepatitis B in Ghana. This study seeks to use the SEIR compartmental model to address the enumerated gaps which have led to the state of misinformation and misconceptions about hepatitis B in Ghana, and to inform policy directives in the attempt to control the disease in the country [26, 27]. Particularly, the modelling could provide information on the major parameters that determine the dynamics of the disease, which include the mode of transmission and the rates of disease

progression in the population. This information could determine the current state and trend of the disease and whether or not it can be controlled with time.

1.2 Background to hepatitis B

Hepatitis B, originally known as Serum Hepatitis, is an infectious viral disease which causes inflammation of the liver. Caused by the HBV, the disease is known to affect all hominoidea including humans. It transmits through contact with infectious blood and body fluids, such as semen and vaginal discharges. Studies have shown that Viral DNA has been present in saliva, tears and urine of individuals with the chronic disease [11, 13, 28, 29, 30].

The HBV will survive for a minimum of 7 days outside the body and can still cause infection on entering the body of another person who is not protected by immunisation. The virus incubates for a period of 75 days on average, ranging from 30 to 180 days or even much longer depending on the age and the viral load of the infected individual. The disease is an important occupational hazard to health practitioners. Other risk factors include transfusion and dialysis, acupuncture, tattooing and all practices involving use of contaminated needles [11, 29, 30, 31].

Hepatitis B is characterised by the presence of the Hepatitis B surface antigen (HBsAg) and the immunoglobulin M (IgM), which is an antibody to the Hepatitis B core antigen (HBcAg). The presence of Hepatitis B envelope antigen (HBeAg) is an indication that the blood and body fluids of the infected individual are highly contagious [10, 11]. At the acute stage, some individuals exhibit symptoms such as yellowing of skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pains lasting for several weeks. The disease may be entirely asymptomatic and may go unrecognised. The disease may be first detected between 30 to 60 days after an individual has been infected [13, 30, 32, 33, 34].

The disease may be cleared at the acute stage [35, 36], or may continue to develop into the chronic stage where the individual will begin to experience cirrhosis of the liver or liver cancer [5, 17, 37]. Hepatitis B is however preventable with the current availability of safe and effective vaccines [35, 38, 39]. There is no found cure but there are available antiviral treatments for chronic hepatitis that can help stop or minimise virus replication and thus reduce the risk of liver damage [13, 30].

1.3 The global hepatitis B burden

Hepatitis B threatens life and as a result constitutes a global health burden. Viral hepatitis substantially contributes to the burden of chronic diseases, which is associated with morbidity and premature mortality worldwide. The epidemiology of hepatitis B is said to be geographically diverse, essentially regarding population prevalence, age and mode of contraction and the likelihood of progression to the chronic infection [3, 12]. The disease has caused epidemics in Asia and Africa and it is endemic in China. WHO Global report indicated that one out of every three of the world's population has been infected with the disease [10, 12]. Over 240 million people are estimated to have chronic hepatitis B with more than $780,000$ dying each year as a result of the disease [10, 40].

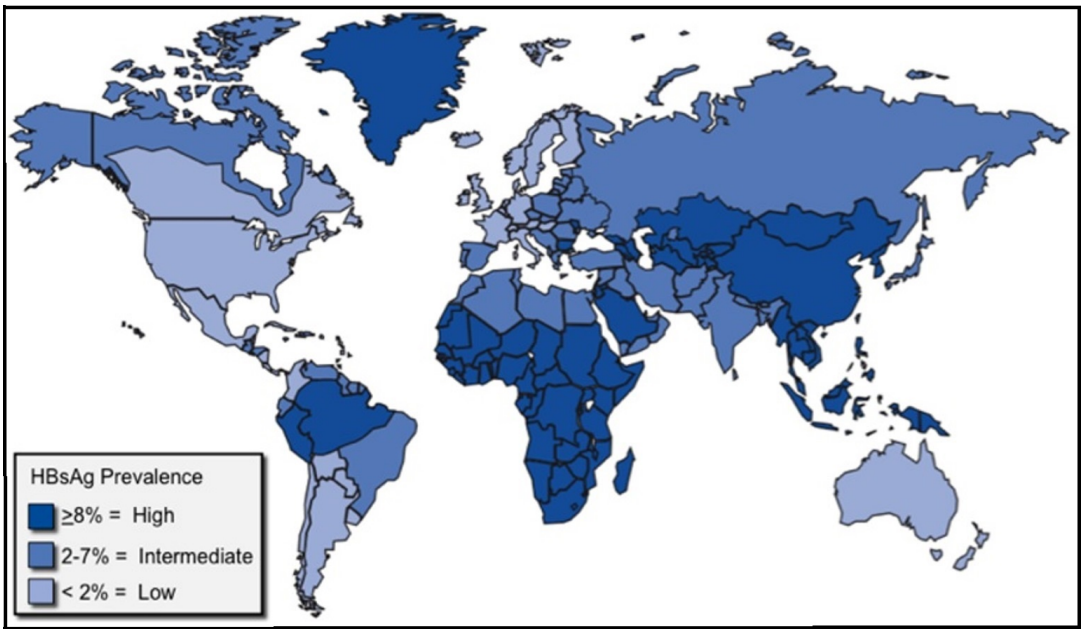


Figure 1.1: Global prevalence of hepatitis B (CDC - 2012)

The prevalence of hepatitis B is highest in Sub-Saharan Africa and East Asia where most people become infected with the disease during childhood and $5 - 10\%$ of adults are chronically infected. High rates of infection are also found in the Amazon and parts of Eastern and Central Europe. Approximately $2 - 5\%$ of the general population in the Middle East and India and less than 1% of the population in Western Europe and North America are chronically infected. The most common routes for the spread of hepatitis B

in highly endemic regions are vertical (from mother-to-child) and horizontal (from person-to-person), with the majority of infections acquired at early childhood [10, 35]. Figure 1.1 displays the global distribution of HBsAg prevalence of hepatitis B.

Africa with 12% of the world's population carries 18% of the global burden of hepatitis B [41]. Although hepatitis B is endemic in Africa and hyperendemic (disease is constantly present at a high incidence and/or prevalence rate and affects all groups equally) in some regions of Africa, not much attention has been given to its management and control. In Africa, studies have indicated that hepatitis B has shown severe virologic expressions in HIV-infected patients [42, 43, 44, 45, 46]. Hepatitis B is estimated at 15% among HIV infected individuals in Africa as a whole, 8% in West Africa and $5 - 7\%$ in Central Africa [41]. Poor management of hepatitis B/hepatitis C virus (HBV/HCV) coinfection has resulted in high risk levels of mortality of patients especially in Sub-Saharan Africa [42, 43, 44, 45, 46, 47, 48, 49].

In spite of Hepatitis B being a significant global concern, there is a lack of quality data on the burden of disease [50]. Obtaining hepatitis related incidence, prevalence, morbidity and mortality is challenging. Thus the utility of case reporting data is limited by the fact that it is primarily a reflection of testing availability and practises and of the willingness of healthcare providers to report cases to the relevant health authorities [50]. Limitations in surveillance programmes and the asymptomatic nature of the disease also result in underestimation of the true number of cases of incidence [50, 51]. Data on the precise burden of the disease is lacking in most countries even though available information indicates that the disease related burden is considerable [50].

1.4 The state of hepatitis B in Ghana

Ghana, like many other Sub-Saharan African countries, is threatened by the hepatitis B pandemic. Ghana is located in the West African sub-region, bounded on the south by the gulf of Guinea, to the north by Burkina Faso, to the east by Togo and to the west by Ivory Coast. The population of the country is currently estimated at 28.9 million with a growth rate of about 2.4% per year [52]. The birth and death rates stand at 31.4 births and 7.37 deaths per $1,000$ population per year respectively. Occupying a land area of $239,460$ square kilometres ($92,456$ square miles) with an estimated population density of 107.6 persons/km^2, the country is divided into 10 administrative regions and 216 districts, metropolitans and municipals [52, 53, 54]. Figure 1.2 shows the administrative boundaries

of the country [55].

Figure 1.2: Ghana administrative map [Library of Congress - Washington, D.C. : Central Intelligence Agency, 2007]

Only limited epidemiological data pertaining to prevalence of common persistent viruses has been reported in Ghana [56]. There is limited screening, unavailability and inaccessibility of vaccination due to large scale absence of standard health facilities especially

in the rural areas [15]. There is a general lack of knowledge and many misconceptions about hepatitis B among the people of Ghana. Many people resort to herbal medicine which is relatively cheap instead of officially reporting to the available health facilities to be treated and so to be captured into the national database [26, 27]. About one third of Ghanaians living with viral hepatitis are unaware of their status and are not receiving care and treatment for the condition [26, 27].

In 2011, the annual report of the Ghana Health Service (GHS) indicated that their current data collection tools did not capture confirmed cases of the disease in the syndromic diagnosis state [16]. A total of $22,851$ cases of hepatitis B diagnosis, of which 100 resulted in fatalities, were reported for all the regions in Ghana; constituting an estimated national incidence rate of 89.1 per $100,000$ population. The highest incidence of $1,059.4$ per $100,000$ population was recorded for the Upper East region. Other regional incidence clearly above the average national rate recorded were 212.9 and 123.5 per $100,000$ population for the Brong Ahafo and the Upper West regions respectively [16].

In 2013, WHO reported that Ghana was conspicuously absent from a survey they conducted to determine the capacity of its member states pursuant to the WHA's resolution 2010 [10]. This seeks, among other policy interventions, to develop a comprehensive approach to prevention and control of hepatitis B through awareness creation and urgent action with respect to vaccination and antiviral treatments. Nonetheless, the implementation of these policies pose complexities and challenges for most economies and health communities in developing countries including Ghana [57]. This has generated concern and apprehension from the general public. As a result, civil society and nongovernmental organisations (NGO) through the various media are making the effort to create awareness in the populace regarding the hazards of the disease and the need for action to fight it [26, 27, 58].

The GHS in its 2014 annual report indicated that there were 108 deaths out of $51,052$ suspected acute viral hepatitis cases, representing a Case Fatality Ratio (CFR) of 0.2%, reported from 9 out 10 regions (Northern region did not report), with $7,581$ cases confirmed positive representing an incidence rate of about 14.8% (approximately 1 in 7 people reporting) [59]. Studies have indicated that prevalence of hepatitis B in Ghana is estimated between $10 - 15\%$ and out of every 100 Ghanaians, 13 may test positive for hepatitis B [58, 60, 61, 62, 63]. In line with WHO's health assembly Resolution 2010, for all member states to generate reliable information as a foundation for building prevention and con-

trol measures that match the local epidemiological profile and health systems capacities, Ghana has produced and launched a policy document on viral hepatitis in 2015 [60, 64]. The Ministry of Health Ghana (MOHG) admitted in the policy document that there are effective tools available to prevent and manage viral hepatitis, including hepatitis B vaccination, surveillance, screening and treatment, but there are challenges to build the capacity to extend these interventions country-wide [60, 64].

The document reports of scanty national data on specific types of viral hepatitis in Ghana. There is also lack of policy and guidelines for service delivery and research agenda to guide a response to viral hepatitis. Screening and vaccination programmes for hepatitis B are left to private unauthorised persons who manage it in an uncontrolled and uncoordinated manner. However surveillance data available at the Disease Surveillance Department, captured by the Infectious Disease Surveillance Response (IDSR) standard case definition for viral hepatitis, shows an annual increasing trend of reported clinical viral hepatitis cases across the ten regions of Ghana [64]. It is estimated that there are about 2.5 million Ghanaians living with hepatitis B with a high fatality rate due to misinformation and late reporting [64]. It is also estimated that there is an eight-fold increase in risk of patients infected with hepatitis B to develop cirrhosis than any other disease.

Studies available, although limited in geographic range, create a general basis for concern with the threat of hepatitis B in Ghana [28, 65]. The disease is described as a hidden epidemic and concerns have been raised for the needed national policy attention [15, 26, 65, 66, 67]. Recent surveys on prevalence of hepatitis B in Ghana however indicated a limited availability of data and information. There is also a low level of awareness which has given rise to many misconceptions about the disease in Ghana [15, 68]. Lack of adequate data on prevalence of hepatitis B in Ghana has resulted in less financial and political attention and commitment towards its inclusion in the National Health Insurance Scheme (NHIS). There is also a lack of provision of universal access to vaccination against hepatitis B in the national childhood immunisation programmes [27, 69, 70].

The health sector in Ghana is both public and private. Health care administration and delivery in Ghana is the responsibility of the Ministry of Health (MOH) which formulates and oversees the implementation of policies on behalf of government. The Ghana Health Service (GHS) through its regional, district and sub-district/community branches implements the health policies in the public health sector which constitute the main health delivery engine of Ghana. Private health care run mainly by religious bodies and private

individuals also plays a significant role in health delivery in Ghana. The public health sector is categorised into three: the primary level is in charge of the district, sub-district and community health care delivery; the secondary level consists of the ten regional hospitals, situated in the regional capitals, which receive referrals from the districts and provide outreach support to the primary level; and the tertiary level which consists of the four teaching hospitals namely Korle-Bu and Komfo Anokye, situated in Accra the capital and Kumasi the second largest city of Ghana respectively, and Cape Coast and Tamale which are responsible for tertiary health care and training of doctors [71].

1.5 Justification of study

The most recent works that used mathematical modelling to study hepatitis B in Ghana, though extensive in content, are limited in scope [9, 19]. Each of the studies covered a part (one district) of the country and did not include vertical transmission and the latent period of the disease which are important in the study of hepatitis B. Although deterministic compartmental modelling was applied to hepatitis B incidence data obtained from the districts in which the studies were conducted, the parameter estimation methodology was not transparent in any of the case studies. The pseudo-mass action incidence term βSI used in these studies to model hepatitis B in Ghana was not appropriate for a population whose size varies with time.

Studies have indicated that not accounting for the latent period in modelling hepatitis B has an adverse impact on the results and the predictions of any such study [21, 24, 72, 73]. Vertical transmission of hepatitis B in high prevalence and endemic regions has also been indicated in many studies as notable [1, 20, 21, 22, 23, 24]. Limitations of the use of the pseudo mass-action incidence term βSI in studies also suggest that the standard (true) proportionate incidence term $\frac{\beta SI}{N}$ gives a better result in modelling an infectious disease in population with varying size [74, 75, 76]. Studies on hepatitis B related to Ghana have failed to address these important concepts.

This study is motivated by these limitations and gaps, and seeks to address them in a deterministic compartmental model that incorporates the proportionate incidence term, latent period, vertical transmission and a vaccination component to study the incidence and spread of hepatitis B in Ghana. A transparent hybrid optimization method was used to estimate the parameters of the model using data gathered from health authorities of Ghana. The findings would be useful in making relevant and informed policy recommen-

dations to guide public health management decisions towards controlling the incidence and spread of hepatitis B in Ghana, which by extension would apply to Africa and other high prevalence regions of the world.

1.6 Research objectives

The objectives of the study are listed below.

1. To formulate an appropriate compartmental model, which incorporates the limitations identified in models previously applied to hepatitis B in Ghana, to estimate model parameters using hepatitis B incidence data from Ghana, and to use the model to examine the transmission and spread of the pandemic of the disease in Ghana.

2. To subject the formulated model to sensitivity and stability analysis to assess its veracity and to examine how robust the model would be in the face of perturbation.

3. To predict the future of the national hepatitis B pandemic on the basis of the model developed and further examine the regional burden.

4. To investigate the impact of vaccination on the transmission and spread of hepatitis B and interpret the results in relation to a management framework which can be used by policy makers to take informed decisions.

The objectives outlined therefore focus on formulating an appropriate model to examine the transmission and spread of hepatitis B in Ghana and do not need to include stages of chronic infection and treatment interventions. These objectives were addressed in the following manner in the thesis: Items 1 and 2 were addressed in Chapters 3 and 4, where the model was presented and stability and sensitivity analysis were discussed respectively, and parts of Chapters 5 and 6 where the model and parameter estimation method were applied to the hepatitis B incidence data to estimate the national and regional parameters respectively; Item 3 was addressed in Chapters 5 and 6 and item 4 was addressed in Chapter 7.

1.7 Data collection

The main data for the study consisted of reported monthly incidence cases of hepatitis B, aggregated and deidentified (not identified with any group of persons or individuals),

for the ten regions of Ghana. These were categorised into cases of individuals aged less than five years old (age$<$ 5) and those aged five years or older (age$\geq$ 5), covering the period 2008 to 2014. Categorising the data into these age brackets was meant to divide the population into two, accounting for the number of incidence cases assumed to be vertically transmitted (age$<$ 5) and those from the other routes (age$\geq$ 5). These data were collected from the Regional Informant Units (RIU) and the Center for Health Information Management (CHIM) of Ghana Health Service (GHS) and neither involved face-to-face interaction nor identified with the addresses of any respondents.

In addition, annual regional demographic data consisting of projected population figures covering the period 2008 to 2014 and birth and death rates from the 2010 population and housing census and Ghana Living Standards Survey (GLSS6) were sourced from the Population Statistics Division (PSD) of the Ghana Statistical Service (GSS). This dataset formed the parameter constants that were identified in the model for the parameter estimation process, which in turn was used to determine the epidemiological threshold parameter, R_0 and the herd immunity threshold value H of the study.

1.8 Thesis outline

In Chapter 2, a theoretical framework that gives the basic structure underlying the concept of modelling infectious disease generally, and hepatitis B in particular, as in a $SEIR$ deterministic compartmental model is reviewed. The classical SIR model and relevant literature on some of its modifications including the $SEIR$ adopted to use in this study is reviewed. Also reviewed in this chapter is literature on vertical transmission, latent and incubation periods of hepatitis B, which are important features in the epidemiology of hepatitis B, as well as the epidemiological threshold parameter R_0 and herd immunity threshold value H.

The methodology of the research is outlined in Chapter 3. In this chapter the outline of the $SEIR$ model used in the study is presented and the system of ordinary differential equation that defines the model is formulated. The epidemiological threshold parameter R_0, otherwise referred to as the basic reproduction number, is derived based on the concept of spectral radius of the second generation matrix of the Jacobian of the model and the corresponding herd immunity threshold value H is defined. Stability of the model in terms of its disease-free and endemic equilibrium states is discussed analytically indicating a threshold value of the disease contact rate that defines a crossover between stability

and instability of either equilibrium state. The parameter estimation method, which describes a hybrid method that combines a random search Genetic Algorithm and a modified gradient search Levenberg Marquardt Algorithm is presented in Chapter 4.

The $SEIR$ model is applied to the hepatitis B incidence data of Ghana in Chapter 5. The methods discussed in Chapter 4 are used in this chapter to estimate the national parameters for the model. The parameters of the model are used to calculate the epidemiological threshold parameter R_0 and the herd immunity threshold value H for Ghana, and also to examine the model predictions of the state variables s, e and i representing the proportions of the susceptible S, exposed E and infectious I populations respectively. The impact of the model parameters on the epidemiological threshold parameter R_0, and also on the stability of the equilibrium states of the model are presented in a sensitivity analyses of both R_0 and the model to the key parameters of the model. Discussion of results and a summary of findings from the national data analysis conclude the chapter.

In Chapter 6 the $SEIR$ model is applied to the regional hepatitis B data to examine the burden of the disease on each region. Methods discussed in Chapter 3 are used to estimate the regional parameters for the model, which are then used to calculate the epidemiological threshold parameter R_0 and the corresponding herd immunity threshold values H for each region. The parameters are also used to predict the state variables s, e and i of the model for each region. A simple regression analysis is applied to discuss some potential factors that influence the trend of incidence and spread and the associated burden of hepatitis B across the ten regions of Ghana. A summary of findings from the regional data analysis closes the chapter.

A modification of the $SEIR$ model to include vaccination, a crucial intervention for controlling hepatitis B pandemic, to examine its impact on the incidence and spread of the disease in Ghana is presented in Chapter 7. Stability of the modified model is discussed analytically with respect to the disease-free and endemic equilibrium states. The epidemiological threshold parameter R_{v0} of the vaccination model is derived analytically and subjected to sensitivity analysis, through simulation of the model over a range of possible values of the vaccination rate k, based on the parameters estimated for the original $SEIR$ model presented in Chapter 5. Discussion of results and a summary of findings from the application of vaccine to the $SEIR$ model conclude the chapter.

Finally in Chapter 8 is presented the concluding remarks of the research. A summary

and conclusion of the analysis of results is presented in a way that reflects the research objectives of the study. The chapter also outlines some recommendations for policy consideration, based on the main findings of the research. The chapter is concluded with some constraints that were identified as potential limitations of the study, some research contributions and recommended areas for possible future research.

Chapter 2

Literature review

2.1 Modelling hepatitis B

Mathematical modelling has been widely used as a tool to provide a theoretical framework for understanding the dynamics of the spread and control of infectious disease in a population [23, 77, 78]. Knowledge of the transmission characteristics of an infectious disease in a population is essential in finding steps to eradicate it. Apart from its use in planning, implementing, evaluating, and optimising measures of detection, prevention and control programmes, mathematical modelling also contributes to the design and analysis of epidemiological surveys. As experimental tools, the usefulness of mathematical models combined with computer simulations in testing theories, assessing quantitative conjectures, providing answers to specific scientific and epidemiological questions, examining sensitivities to parameter changes, and parameter estimations from observed data cannot be overemphasised [23].

In broad terms, parasites that cause infectious diseases are categorised into micro and macro-parasites on biological grounds [1]. Most viral and bacterial diseases are classified as caused by micro-parasites and compartmental modelling is prescribed as the most preferred modelling approach, due to the typically short duration of such infections relative to the expected life span of the host [1]. It is conceded, however, that there are important exceptions where the duration of some micro-parasitic infections may be relatively long and compartmental modelling is still preferred [1].

Many studies have used compartmental modelling to gain insight into the spread and control of such infectious diseases [9, 17, 19, 21, 38, 79]. Stochastic and deterministic com-

partmental models have been useful tools to study infectious diseases on a population scale. Stochastic models are prescribed as more useful in studies conducted in small or isolated populations in which individuals in the population are considered to be independent units of observation and chance fluctuations or known heterogeneities are important [80, 81]. Deterministic or compartmental models, on the other hand, are deemed to be more useful for studies of more complex systems involving nonlinear dynamics where individuals are observed to be more interdependent [80, 81].

2.2 The classical deterministic compartmental model

The best known deterministic compartmental model that is used to describe the spread of contagious epidemic diseases was developed by Kermack and Mckendrick and has since been adopted and modified in most epidemiological studies [82]. The model divides the population into three epidemiological compartments, namely the Susceptible (S) class, individuals who are not yet infected at a time but are at risk of being infected; the Infectious (I) class, individuals who are infected and can infect anyone in contact who is not immune to the disease; and the Recovered or Removed (R) class, individuals who have recovered or have been removed either by acquiring immunity to the infection or death after being infected. The progression of infection through the epidemiological compartments is illustrated by the flow diagram in Figure 2.1,where $S(t)$, $I(t)$ and $R(t)$ are the number of individuals in the population who are susceptible, infectious and removed at a given time t respectively.

This model is thus called the SIR model after the designated compartments. Transmission occurs when there is an adequate contact of a susceptible individual with an infectious individual so that after infection the susceptible individual then moves into the infectious compartment. An infectious individual enters into the removed or recovered compartment after acquiring immunity to the infection or upon death, ending progression of infection. The rate of transmission β is defined as the average number of individuals infected per unit time, assuming all the contacts between susceptible individuals and infectious individuals result in infection, and γ is the rate of recovery per unit time.

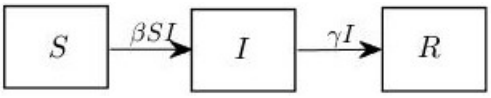


Figure 2.1: The Classical SIR Model.

The system of differential equations that describes the model is given by:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I \end{aligned} \tag{2.1}$$

subject to $S(t_0) = S_0$, $I(t_0) = I_0$ and $R(t_0) = R_0$, where S_0, I_0 and R_0 are the susceptible, infectious and recovered populations at time $t = t_0$. The following are the assumptions underlying this classical deterministic compartmental model:

i. The total population size is considered as remaining constant, $S(t)+I(t)+R(t) = N$, since the course of an epidemic is relatively short compared to the life-span of an individual, births and deaths including disease-induced are ignored.

ii. All the members of the community are initially susceptible to the disease.

iii. Complete immunity is conferred by a single infection and so there is no progression from the recovered class into the susceptible class.

It is noted that for each particular set of infectivity, recovery and death rates, there exists a critical epidemiological threshold value, often referred to as the basic reproduction number, R_0 that determines whether the disease dies out or persists in an epidemic. A slight perturbation in these rates may cause a marked epidemic or vice versa [82]. The epidemiological threshold value for the classical SIR model in Figure 2.1 is given by $R_0 = \frac{\beta}{\gamma}$. Whenever $R_0 > 1$, a typical infectious individual gives rise, on average, to more than one secondary infection leading to an epidemic. When $R_0 < 1$, an infectious individual gives rise to less than one secondary infection and the disease decreases or dies out [1, 83, 84]. The epidemiology of the infectious disease is determined by

i. The rate of transmission β which measures the risk of transmission per contact per unit time.

ii. The number of potentially infectious contacts an average individual in a population makes per unit time defined by the bilinear (pseudo) mass action term βSI.

iii. The duration of the infectivity period $\frac{1}{\gamma}$.

The bilinear incidence term βSI represents horizontal transmission in the model and is suitable for modelling infectious diseases in a population with constant size.

Other studies indicated that a time-dependent threshold value called the effective reproduction number, $R(t) = \frac{S(t)}{N} R_0$, is more appropriate and better quantifies the transmissibility in a non-naive host population [83]. This value $R(t)$, is defined as the mean number of secondary infections caused by introducing a single infectious individual into a host population at a given susceptible fraction. The determination of $R(t)$ by definition depends on the accurate estimation of the susceptible fraction $\frac{S(t)}{N}$ which is often a challenge to come by [83]. The upper bound of $R(t) \leq R_0$ can only be achieved when the entire population is susceptible. The prevalence of an infection will increase or decrease depending on whether $R(t)$ is greater than or less than one respectively [1, 83]. At a critical susceptible fraction $s_c = \frac{S_c}{N}$ when the dynamical system of an infectious disease model is in equilibrium, the effective reproduction number $R(t) = 1$ and so $R_0 s_c = 1$, assuming the host population is homogeneously mixed [1]. The rate of transmission is a function of many biological, social and environmental factors and is therefore often best inferred indirectly from data at the population level. However, host death and birth rates, disease-induced death rates, recovery rates and rates of immunity can be measured directly by appropriate studies [1, 83, 85].

2.3 Modifications of the classical model and other relevant studies

Since the formulation of this simple but powerful standard model displayed in Figure 2.1, modifications have emerged in various studies. One notable modification is the $SEIR$ model which introduces a latent period and the exposed class E into the SIR model. The SIR model is a special case of the $SEIR$ model in which the latent period is non-existent and so fits well for short-term epidemics in a closed population [1, 72]. Some common modifications include, but are not limited to SIS, $SIRS$, $SEIR$, $SEIRS$ and $SEIS$ (see Table 2.1).

A $SEIR$ model was modified into $SEI_A I_C R$ to study the transmission dynamics and

control of hepatitis B in Gambia [86]. In this model, the infectious class I was split into two classes, namely acute I_A and chronic I_C. The model was defined by a system of partial differential equations and incorporated horizontal, perinatal and sexual transmission (see Model 1 of Table 2.2). Age-specific rates of infection were estimated from cross-sectional serological survey data on hepatitis B from Gambia using a maximum likelihood method called the Grenfell and Anderson technique, which was not outlined in the paper [86, 87]. Other parameters such as proportions of infants infected from chronic carrier mothers, latent period and duration of the carrier state were values obtained from an existing case studies.

Table 2.1: Some common modifications of the SIR compartmental model

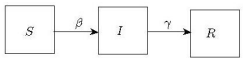
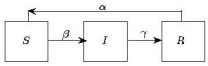
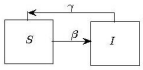
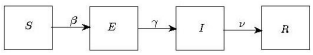
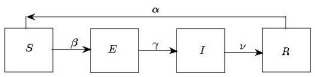
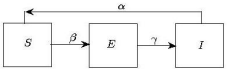
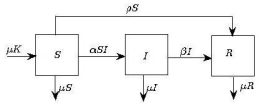
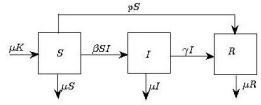
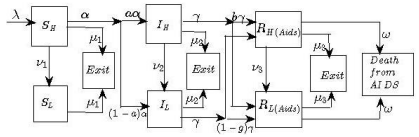
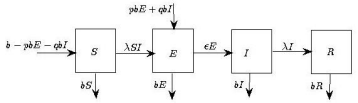
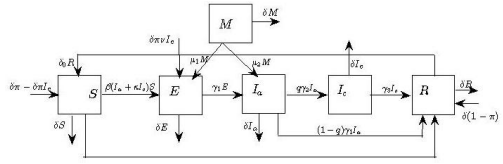
Model	**Systems**	**Key Parameters**
1. SIR 	$\frac{dS}{dt} = -\beta SI$ $\frac{dI}{dt} = \beta SI - \gamma I$ $\frac{dR}{dt} = \gamma I$	β=rate of susceptible becoming infectious, γ=rate of recovery.
2. $SIRS$ 	$\frac{dS}{dt} = \alpha R - \beta SI$ $\frac{dI}{dt} = \beta SI - \gamma I$ $\frac{dR}{dt} = \gamma I - \alpha R$	β=rate of susceptible becoming infectious, γ=rate of recovery, α=rate of recovered becoming susceptible.
3. SIS 	$\frac{dS}{dt} = \gamma I - \beta SI$ $\frac{dI}{dt} = \beta SI - \gamma I$	β=rate of susceptible becoming infectious, γ=rate of infectious becoming susceptible.
4. $SEIR$ 	$\frac{dS}{dt} = -\beta SI$ $\frac{dE}{dt} = \beta SI - \gamma E$ $\frac{dI}{dt} = \gamma E - \nu I$ $\frac{dR}{dt} = \nu I$	β=rate of susceptible becoming exposed, γ=rate of exposed becoming infectious, ν=rate of recovery.
5. $SEIRS$ 	$\frac{dS}{dt} = \alpha R - \beta SI$ $\frac{dE}{dt} = \beta SI - \gamma E$ $\frac{dI}{dt} = \gamma E - \nu I$ $\frac{dR}{dt} = \nu I - \alpha R$	β=rate of susceptible becoming exposed, γ=rate of exposed becoming infectious, ν=rate of recovery, α=rate of recovered becoming susceptible,
6. $SEIS$ 	$\frac{dS}{dt} = \alpha I - \beta SI$ $\frac{dE}{dt} = \beta SI - \gamma E$ $\frac{dI}{dt} = \gamma E - \alpha I$	β=rate of susceptible becoming exposed, γ=rate of exposed becoming infectious, α=rate of infectious becoming susceptible,

Table 2.2: Summary of some compartmental models from the literature

Model	Systems	Key Parameters	Key Points
1. SEI_AI_CR (Gambia - No diagram)	$\frac{\partial S_g}{\partial a} + \frac{\partial S_g}{\partial t} = -\lambda_g(a,t)S_g(a,t) - q(a,t)S_g(a,t) - \mu_g(a)S_g(a,t)$ $\frac{\partial E_g}{\partial a} + \frac{\partial E_g}{\partial t} = \lambda_g(a,t)S_g(a,t) - [\mu_g(a)+\sigma]E_g(a,t)$ $\frac{\partial I_{Ag}}{\partial a} + \frac{\partial I_{Ag}}{\partial t} = \sigma E_g(a,t) - [\mu_g(a)+\gamma_1]I_{Ag}(a,t)$ $\frac{\partial I_{Cg}}{\partial a} + \frac{\partial I_{Cg}}{\partial t} = p(a)\gamma_1 I_{Ag}(a,t) - [\mu_g(a)+\omega_g(a)+\gamma_2]I_{Cg}(a,t)$ $\frac{\partial R_g}{\partial a} + \frac{\partial R_g}{\partial t} = [1-p(a)]\gamma_1 I_{Ag}(a,t) + \gamma_2 I_{Cg}(a,t) + q(a,t)S_g(a,t) - \mu_g(a)R_g(a,t)$	Force of infection (λ_i); $\lambda_1 = 0.159, \lambda_2 = 0.144$, $\lambda_3 = 0.116, \lambda_4 = 0.089, \lambda_5 = 0.030$, Rates of recovery($\gamma_i$);$\gamma_1 = 4, \gamma_2 = 0.025$, Proportion perinatal(acute,carrier)$\nu_c = 0.109$, $\nu_y = 0.711$	Force of infection is highest in the younger ages declining through childhood, and rising suggest transmission is entirely horizontal or sexual. Vertical, (infected mothers),horizontal and sexual modes were included in the model.
2. SIR (Tano-North,Ghana) 	$\frac{ds}{dt} = \mu K - \alpha SI - \mu S - \rho S$ $\frac{dI}{dt} = \alpha SI - (\beta+\mu)I$ $\frac{dR}{dt} = \beta I - \mu R + \rho S$	Recovery rate; $\beta = 0.98415$, Infectious rate; $\alpha = 1.0058$, Death/Birth rate; $\mu = 0.0094$, Vaccinated fraction; $\rho = 0.017051$, $N = 74775, S_0 = 73475$, $I_0 = 25$.	Vaccination impact on the model was significant; increasing vaccination could reduce rate of transmission.
3. SIR (Tano-North,Ghana) 	$\frac{dS}{dt} = \mu K - \beta SI - \mu S - pS$ $\frac{dI}{dt} = \beta SI - (\gamma+\mu)I$ $\frac{dR}{dt} = \gamma I - \mu R + pS$	Death/Birth rates; $\mu = 0.0219$, Infectious rate; $\beta = 0.9842$, Recovery rate; $\gamma = 2.5447$, Vaccinated fraction; $pS = 1.0 \times 10^{-}4$.	Vaccination class was included. Increasing vaccination could reduce rate of transmission.
4. $S_HI_HI_{H_A}R_H/S_LI_LI_{A_L}R_L$ (General case) 	$\frac{dS_H}{dt} = \lambda - \alpha S_H(t) - (\nu_1+\mu_1)S_H(t)$ $\frac{dS_L}{dt} = \nu_1 S_H(t) - \mu_1 S_L(t)$ $\frac{dI_H}{dt} = a\alpha S_H(t) - (\gamma+\mu_2+\nu_2)I_H$ $\frac{dI_L}{dt} = (1-a)\alpha S_H(t) + \nu_2 I_H(t) - (\gamma+\mu_2)I_L(t)$ $\frac{dR_{H(Aids)}}{dt} = b\gamma I_H(t) + g\gamma I_L(t) - (\omega+\mu_3+\nu_3)R_{H(Aids)}$ $\frac{dR_{L(Aids)}}{dt} = (1-b)\gamma I_H(t) + (1-g)\gamma I_L(t) + \nu_3 R_{H(t)} - (\omega+\mu_3)R_L(t)$	Death rates (non-AIDS); $\mu_1 = \mu_2 = \mu_3 = 1/3$, Susceptible fraction; $a = 0.9$, High risk Infective; $b = 0.5$, Low risk infective; $g = 0.1$, Transfer rates from High to Low risk; $\nu_1 = \nu_2 = 0.1, \nu_3 = 0.5$, AIDS development rate; $\gamma = 0.1$, Death rate(AIDS); $\omega = 1$, Transmission rate; $\beta c = 1$, $N = 100,000; S_H(0) = 99,999$; $I_H(0) = 1$,$S_L(0) = I_L(0) = R_L(0) = R_H(0) = 0$.	Approximate analytic solutions to the model showed close agreement with numerical solutions
5. $SEIR$ (General case) 	$\frac{dS}{dt} = b - \lambda SI - pbE - qbI - bS$ $\frac{dE}{dt} = \lambda SI + pbE + qbI - (\epsilon+b)E$ $\frac{dI}{dt} = \epsilon E - (\gamma+b)I$ $\frac{dR}{dt} = \gamma I - bR$	Infectious rate; λ, Removal from Exposed; ϵ, Recovery rate; γ, Birth/Death rates; b, Newborns(fractions);p, q	The latent period is non-negligible.Vertical transmission has significant effect on model.
6. SEI_aI_cRM (General case) 	$\frac{dS}{dt} = \delta\pi(1-\eta I_c) - \delta S - \beta(I_a+\kappa I_c)S + \delta_0 R - pS$ $\frac{dE}{dt} = \beta(I_a+\kappa I_c)S - \delta E + \delta\pi\eta I_c - \gamma_1 E + \mu_1 M$ $\frac{dI_a}{dt} = \gamma_1 E - \delta I_a - q\gamma_2 I_a - (1-q)\gamma_1 I_a + \mu_2 M$ $\frac{dI_c}{dt} = q\gamma_2 I_a - \delta I_c - \gamma_3 I_c$ $\frac{dR}{dt} = \gamma_3 I_c + (1-q)\gamma_1 I_a - \delta_0 R - \delta R + \delta(1-\pi) + pS$ $\frac{dR}{dt} = \gamma_3 I_c + (1-q)\gamma_1 I_a - \delta_0 R - \delta R + \delta(1-\pi) + pS$ $\frac{dM}{dt} = -(\mu_1+\mu_2)M - \delta M$	Death/Birth rates;$\delta = 0.0143$,Transfer rates (from latent to Infectious); $\gamma_1 = 6, \gamma_2 = 4, \gamma_3 = 0.34$, Transmission rate; $\beta = 0.8$, Loss of Immunity; $\delta_0 = 0.03$, Transfer to carrier; $q = 0.005$, Vaccinated fraction; $p = 0.3$, Rates (from Migrated class to Exposed/Acute classes); $\mu_1 = 0.23, \mu_2 = 0.56$, Non-immunized children; ($\eta = 0.7$, Rate of infection (carriers) $\kappa = 0-1$ (all parameters sourced from literature).	Migration class was included. The number of infected persons is directly proportional to the number of migrated persons.

The study indicated that horizontal transmission was a major route of incidence and spread of hepatitis B, complicated by the high age-dependent risk of developing into the chronic carrier state. The high prevalence of chronic carrier state increases the rate of infection, leading to hyperendemicity of hepatitis B in the population. The disease therefore persists due to the long-lasting chronic carrier state, many years after immunisation, which calls for proper design of immunisation programmes. The inclusion of age in modelling hepatitis B would be very important when the purpose of study is to assess the risk of progression from the acute stage to the chronic stage with its attendant age-dependent complications. Obviously, the challenge would be the availability of adequate data to estimate parameters of the model or the existence of reliable parameters to achieve the needed result.

A SIR model was applied to existing clinical incidence data to study the prevalence and incidence of hepatitis B in the Tano North and Bosomtwe districts of the Brong Ahafo and Ashanti regions of Ghana respectively [9, 19]. The model was defined by a system of ordinary differential equations and parameters of the model were estimated based on the incidence data, although the method of estimation was not provided (see Models 2 and 3 of Table 2.2). The epidemiological threshold parameters calculated were greater than unity, which indicated that hepatitis B persists in the districts. With an introduction of a vaccination component into the model, the studies indicated that an increase in vaccination reduced the rate of transmission and that the rate of transmission of hepatitis B in childhood appeared to be a major determinant of endemicity of the disease in that part of Ghana [19]. Both studies by the choice of the model did not incorporate the latent period and vertical transmission, which other studies deemed important in modelling hepatitis B [20, 21]. The pseudo mass action incidence rate βSI, which describes horizontal transmission of the disease in a closed population with constant size was used. The population size was assumed to be constant over the period of study. Although this incidence term is widely used in modelling infectious diseases, the standard incidence term $\frac{\beta SI}{N}$ is considered more suitable, in reality, for a population with changing size [75].

A SIR model was modified into $SS_LII_LRR_L$ to include a low risk component $S_LI_LR_L$ to study a general case of HIV and AIDS epidemic over a period of fifty years [79]. The model was defined by a system of ordinary differential equation (see model 4 of Table 2.2). Parameter values were sourced from existing literature to solve the system of equations in terms of the incidence cases of HIV and AIDS over the fifty year period. In the study, numerical methods namely Euler, Taylor series, Predictor-Corrector and Runge-Kutta (4^{th} order) were compared against a linearised piece-wise analytical method which divided

the time-scale into three stages, i.e. initial, mid and end. The objective of the study was to develop approximate analytic solutions to compartmental models where previously numerical methods were used. The study indicated that analytic approaches give more insight into the dynamics of an epidemic and a clearer picture of sensitivity of results to variation of parameter values than the numerical methods [79]. The study, for example, indicated that analytic solutions allow explicit forms of the maximum likelihood function to estimate parameter values whereas the numerical approaches do not. In a large parameter space, the study indicated that analytic solutions are very good approximations to the numerically derived results [79].

A $SEIR$ model that incorporates vertical transmission was used in a theoretical study for an infectious disease that spreads in the host population through both horizontal and vertical transmission [20]. The incidence term was of the pseudo-mass action form λSI, where λ, S and I were the transmission rate and the number of susceptible and infectious hosts respectively. Vertical transmission was introduced into the model, via the E class, as a fraction of offsprings of the infected hosts E and I who are infected at birth and so stay latent before becoming infectious. The model was defined by a system of ordinary differential equations displayed in Model 5 of Table 2.2. In the study, the natural birth and death rates were assumed to be equal and disease-related death assumed negligible so that the total population was constant. Compared to some SIR models that incorporate vertical transmission, the model was considered suitable, by the authors, for studying, infectious diseases such as hepatitis B, Chagas and AIDS that have nonnegligible latent periods and can spread through both direct horizontal transmission and vertical transmission [20].

Migration is also known to have a significant impact on the spread and control of hepatitis B. A study modified the SIR into MSI_AI_cR by introducing a migration class M that presents with hepatitis B and splitting the infectious class I into two, namely acute I_A and chronic I_C classes, to examine the effect of immigrants with respect to transmission and spread of hepatitis B on the host population [88]. Model 6 in Table 2.2 displays the model for the study, which consists of a system of ordinary differential equations. In the study, parameter estimates were either sourced from works by different authors in existing literature or assumed and did not involve any dataset. Numerical simulation, which applied the Runge-Kutta method of order 4 to vary the recruitment rate of infected migrants into the model keeping all other parameters constant, indicated that the number of infected population members increased with increased number of infected immigrants introduced

into the population [88]. It was concluded that the number of infected individuals is directly proportional to the number of individuals migrated with hepatitis B.

2.4 Results from other relevant studies

Time series and correlation analysis were used to assess the strength of impact of medical intervention on some risk factors of hepatitis B in Kharkiv, Ukraine [89]. The result indicated that, with increased medical intervention, the risk of vertical transmission was reduced whilst other common risks such as drug usage, sexuality and injection of medicine outside of health facilities increased. People aged between 20-29 years were found to have the highest risk of infection. There was positive dependence between morbidity and infection through dental procedures and injection. This result suggests that with medical intervention which guarantees safety health practices, the risk of contracting HB through vertical transmission and its associated morbidity can be minimised compared to the risk involved in acquiring the disease through drug usage, sexuality and injections of drugs outside health facilities. People aged between 20-29 years were found to have the highest risk of infection compared to those outside this age bracket perhaps due to the higher risk of indulging in drug use, sexuality and injections of drugs outside health facilities. The study, however, suggested the need for deeper analysis of dependencies between risk factors and symptoms for early identification of high risk individuals for preventive action against morbidity due to hepatitis B [89].

An effective immunisation programmes simultaneously backed by a treatment regimen would have the best result in controlling hepatitis B prevalence in a population [90]. The study used a generalised compartmental model to examine the effects of HBV drug treatment and immunisation on the Inuit population of Canada. The model was applied to simulate clinical trial data to determine an optimal strategy for hepatitis B control among the Canadian Inuit population. Comparing the two interventions, the study revealed that increasing immunisation decreases both prevalence and incidence whilst increasing treatment decreases prevalence but barely decrease incidence. This result suggests that with medical intervention which guarantees safety health practices, the risk of contracting HB through vertical transmission and its associated morbidity can be minimised compared to the risk involved in acquiring the disease through drug usage, sexuality and injections of drugs outside health facilities. People aged between $20 - 29$ years were found to have the highest risk of infection compared to those outside this age bracket perhaps due to the higher risk of indulging in drug use, sexuality and injections of drugs outside health

facilities. The study thus indicated that a combination of immunisation and treatment is optimal because it reduces both prevalence and incidence substantially [90].

In another situation, a theoretical study on chronic hepatitis B patients using clinical trial data indicated that as soon as treatment was stopped, viral levels shot up [75]. In this study, two virus infection models, one using the pseudo mass-action term and the other using the standard proportionate incidence term, were applied to simulate the use of an antiviral drug in a treatment of a group of HBeAg-positive chronic hepatitis B patients for 48 weeks followed by a 24 week treatment-free follow-up. The study indicated that although the simulation results achieved with both models were similar, the model with the proportionate incidence term interpreted the clinical data better. Furthermore, if the drug treatment was prolonged for three years followed by a seven year follow-up, the viral load of patients reduced to significantly lower levels at the end point of the three years but relapsed soon after stopping treatment for 10 days and then gradually increase thereafter [75]. The study, however, suggested that further research into the quantitative analysis of the dynamics of hepatitis B using more detailed assay data may give more insight into finding optimal treatment strategies for affected patients [75].

The essence of disease transmission models is to be able to provide valid and reliable predictions of the disease with time. Although all models are at best partial descriptions of the mechanisms operating in reality, a good model must have assumptions that correspond to reality as a basis for good prediction [57]. The underlying assumptions of a model reflect the reality of the disease phenomenon and contribute immensely to the validity of the predictions made [57]. Even though the basic virus infection model which hinges on the pseudo mass-action βSI assumption is widely used, some studies indicated that it may not be ultimately all-embracing to describe hepatitis B infection especially in the case of a population that changes size with time [75]. Employing standard or proportionate incidence functions like $\frac{\beta SI}{N}$ and $\frac{\beta SI}{S+I}$ in place of the pseudo mass-action in a study showed results closer to that of a clinical trial [75]. Similarly, not accounting for certain unidentified sub-populations which may be naturally immune or isolated may lead to underestimating key parameters and thereby influence the prediction of an epidemic negatively [91].

2.5 Vertical transmission of hepatitis B

A vertically transmitted disease is caused by bacteria, viruses, or in minor cases parasites transmitted directly from mother to embryo, foetus or baby during pregnancy or childbirth

[7, 92]. Vertical transmission is also referred to as mother-to-child or perinatal infection which pertains to transmission of infection immediately before or after birth [7]. It is termed congenital if the vertically transmitted infection persists after childbirth. Vertical transmission occurs through two main routes; transplacental where transmission is across the placenta and during birth where transmission is across the female reproductive tract [7].

Hepatitis B is classified as a vertically transmitted disease which occurs via three modalities; intrauterine, at-birth and postpartum transmissions [7, 93]. Interuterine transmission occurs only in rare cases, with very high maternal viral load, when the hepatitis B virus crosses the placental barrier or there is a transplacental leakage of the maternal blood into the foetal circulation [7, 93]. Transplacental leakage is not common since the hepatitis B virus is a large virus and rarely crosses the placenta [94]. Transmission during delivery is the most common case when the newborn is exposed to the mother's infected body fluids [7, 95]. Postpartum which is also in a minority refers to transmission of infection to the baby after birth due to close contact with mother but not through breastfeeding [7, 96]. Prophylaxis can prevent at-birth and postpartum transmissions but not interuterine especially in cases where the maternal viral load is high [7, 93].

Neonatal and childhood exposure to hepatitis B have impacted significantly on the public health burden globally. Vertical transmission as a route of spreading infectious diseases has a significant impact on the determination of the epidemiological threshold parameter, the basic reproduction number R_0 [20]. The occurrence of vertical transmission of hepatitis B is highly influenced by carrier mothers and the risk of transmission of the virus from a carrier mother to her child [40, 97]. Some studies have indicated that there is a high probability of transmission and risk for chronic hepatitis B carriage associated with childbearing women [40, 95]. Results from similar studies have also indicated that chronic hepatitis B carriers mostly arise as a result of vertical transmission [90, 98, 99, 100]. Newborns exposed to HBeAg, have the highest risk of becoming chronically infected with hepatitis B [40]. In a disease epidemiological modelling, vertical incidence is sometimes assumed to be a fixed fraction of the newborns who are infected vertically [23].

Sub-Saharan Africa and East Asia are noted to have higher prevalence of carrier mothers and greater risk of vertical transmission than any other developing country [40]. A survey of hepatitis B in Ghana indicated that 15% of the disease carrier rate was acquired through vertical transmission [14]. A study of hepatitis B in Tano-North district of Ghana (see

Model 2 in Table 2.2), indicated that transmission of hepatitis B in childhood appeared to be a major determinant of endemicity of the disease in that part of the country [19]. Some studies have indicated that mother to child transmission of hepatitis B is a major public health concern to regions of high endemicity [101]. Some other studies however indicated that the exact mode of transmission of hepatitis B in Sub-Saharan Africa is uncertain, although a covert perinatal transmission manifesting later during childhood cannot be discounted [102]. It is noted that African infants may contract hepatitis B at birth, but due to some genetically determined reasons they persistently test negative until the virus is reactivated later during early childhood [102]. Furthermore, Africa with much of its population living in vast rural areas with limited resources, inaccurate determination of hepatitis B incidence rates results from under-reporting and poor quality data [102].

2.6 Latent and incubation periods of hepatitis B

A $SEIR$ model used in a theoretical study of infectious diseases indicated that offspring may already be infected at birth by their mothers, and these newborns stay in a latent period before becoming infectious [20]. The study also indicated that using a model to predict the disease prevalence for such infectious diseases that have this latent period, but not accounted for, may therefore lead to inaccuracies [21]. In other related studies a $SEIR$ model was used to show that the latent period has a significant impact on the epidemiological threshold parameter (basic reproduction number), R_0, that is used to determine whether an infectious disease epidemic persists or die out with time. Other studies noted that ignoring the latent period often leads to underestimating the basic reproduction number, R_0, making predictions of the model less accurate [1, 20, 21, 22, 23, 24]. Some of the studies indicated that hepatitis B, like HIV/AIDS and Chagas diseases, has a non-negligible latent period [20, 21].

The epidemiology of hepatitis B like all infectious diseases is characterised by different stages in the course of infection [2]. The course of infection begins when the pathogen, in this case, the HBV enters the host, a stage called exposure. The pathogen then moves to the preferred tissue or organ which is the liver in the case of hepatitis B where it can effectively multiply. Virus replication triggers the host's immune response in defence. This process, called infection, may not be clinically visible but laboratory diagnostics may show signs such as increased sedimentation rate and change in orientation of white blood cells [2]. The blood and body fluids of an infected individual become infectious when the HBeAg marker is detected in a laboratory investigation. The time elapsed

between infection (exposure) and the onset of the state of infectiousness is known as the latent period [1, 2]. The latent period is therefore a period within the incubation period stretching from the point when an individual becomes infected to the point when an individual becomes infectious [1, 2].

An infected host may transmit infection without necessarily showing any symptoms of the disease [2]. In many infectious diseases, the duration of symptoms and the period when an infected host is infectious may not happen together [1]. The period between when an individual becomes exposed (infection) and the time clinical symptoms begin to show is known as the incubation period [1, 2]. With hepatitis B, the onset of infectiousness occurs during the incubation period and may continue indefinitely especially in the case of chronic infection [103]. Figure 2.2 shows the relationship between incubation, latent and infectious periods of a typical infectious disease.

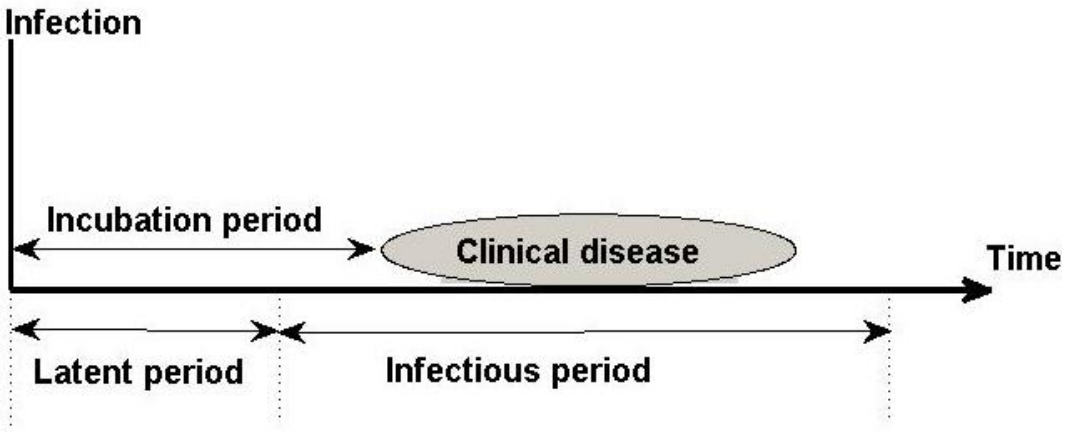


Figure 2.2: Diagrammatic illustration of the relationship between incubation, latent and infectious periods (Modified from [1, 2]).

The incubation period of hepatitis B is 75 days on average, but varies from 30 to 180 days or even more depending on the size of the viral load of the infected host [10, 11, 30]. It is also noted that the natural course of hepatitis B is different from person to person [10, 11, 30]. Many infected hosts during the early stage of infection with hepatitis B, the acute infection phase which spans the first 6 months, show no symptoms at all [104]. About 90% of adults who contract hepatitis B are able to clear the virus at the acute stage of the infection and about 90% of newborns who contract the disease at birth develop the chronic infection [29, 92]. Studies on the characteristics of the dynamics of hepatitis B indicate that the

disease can be cleared at the acute stage without the need for intervention or antiviral treatment depending on the age and immune competence of the infected individual at the time of infection [29, 92].

2.7 The epidemiological threshold parameter R_0 of a compartmental epidemic model

The most important concern in the study of an infectious disease epidemiology is to determine the ability of the disease to increase or decrease in a population. In most epidemiological models this concern is addressed by an epidemiological threshold parameter, also known as the basic reproduction number, denoted by R_0. An infectious disease epidemic increases or decreases when $R_0 > 1$ or $R_0 < 1$ respectively. In a simple compartmental model with a single infected compartment ($m = 1$), the epidemiological threshold parameter R_0 is simply the product of the rate of infection and the mean infection period and so its determination is also simple [1, 105, 106]. However, when the number of infected compartments in a model is greater than one ($m > 1$), the determination of the threshold parameter becomes more complicated.

In essence, a clear distinction must be made between the infected and uninfected compartments based on both the epidemiological interpretation of the model and the structure of the model equations. A more general epidemiological threshold parameter is defined as the number of new infections caused by introducing a typical infective into a population at the disease-free equilibrium [105]. For the purpose of this work, the next generation method which defines the threshold parameter R_0 as the spectral radius of the next generation matrix is discussed in this section.

Let $\boldsymbol{w} = (w_1, w_2, w_3, \ldots, w_n)^T$, where $w_i \geq 0$ denotes the number of members in the i^{th} compartment of an epidemiological model, which has a total of n compartments. Classification of the infected and uninfected compartments is determined based on the structure of the model equations given by the epidemiological interpretation of the model. The compartments have to be arranged in such a way that the first m compartments correspond to infected members and the remaining $n - m$ are uninfected members. Denote by

$$W_0 = \{w \geq 0 | w_i = 0, \quad i = 1, 2, ..., m\},$$

the set of all disease-free states of the model. Let $\mathscr{A}_i(w)$ be the rate of appearance of

new infection in the i^{th} compartment, $\mathscr{B}_i^+(w)$ be the rate of transfer of members of the population into compartment i by all other means, and $\mathscr{B}_i^-(w)$ be the rate of transfer of members out of compartment i. Note that the transfer rates $\mathscr{B}_i^+(w)$ and $\mathscr{B}_i^-(w)$ describe the progression of infection through the n compartments of the model whilst $\mathscr{A}_i(w)$ involves a recruitment of new infection into the model. Each of the functions $\mathscr{A}_i(w)$, $\mathscr{B}_i^+(w)$ and $\mathscr{B}_i^-(w)$ is assumed to be at least twice continuously differentiable in each variable w_i. Then the disease transmission model is given by [105]

$$\dot{w}_i = g_i(w) = \mathscr{A}_i(w) - \mathscr{B}_i(w), \quad i = 1, 2, ..., n \tag{2.2}$$

where $\mathscr{B}_i = \mathscr{B}_i^- - \mathscr{B}_i^+$ and the underlying assumptions for all functions are [105]:

i. All functions are nonnegative since each of them moves members of the population through the compartments in a particular direction; that is if $w \geq 0$, then $\mathscr{A}_i, \mathscr{B}_i^+, \mathscr{B}_i^- \geq 0$ for $i = 1, 2, ..., n$.

ii. If a compartment is empty, then no outbound transfer can take place; that is if $w_i = 0$, then $\mathscr{B}_i^- = 0$ for $i = 1, 2, ..., m$ and for $w \in W_0$, $\mathscr{B}_i^- = 0$ for $i = 1, 2, ..., m$.

   By this assumption, $g_i \geq 0$ and hence the nonnegative cone $w_i \geq 0, \quad i = 1, 2, ..., n$ is forward invariant and so for each nonnegative initial condition, there is a unique nonnegative solution [105, 107]

iii. No new infection is introduced into the uninfected compartments; that is $\mathscr{A}_i = 0$ for all $i > m$.

iv. If the population is free of disease, then the population will remain free of disease. This ensures that the set of all disease-free states W_0 is invariant and there is no immigration of infectives; that is if $w \in W_0$ then $\mathscr{A}_i(w) = 0$ and $\mathscr{B}_i^+(w) = 0$ for $i = 1, 2, \ldots, m$.

v. In the absence of new infection, the disease-free state of a system is stable and it follows that all the eigenvalues of the Jacobian of the system have negative real parts; that is if $\mathscr{A}(w)$ is set to zero, then all eigenvalues of the Jacobian matrix $Dg(w_0)$ evaluated at the disease-free equilibrium w_0, have negative real parts.

By conditions (i) - (v), the Jacobian matrix $Dg(w_0)$ can be partitioned using the following lemma [105].

Lemma 1 *If w_0 is a disease-free equilibrium of Equation (2.2) and $g_i(w)$ satisfies conditions i - v, then the derivatives $D\mathscr{A}(w_0)$ and $D\mathscr{B}(w_0)$ are partitioned as*

$$D\mathscr{F}(w_0) = \begin{pmatrix} A & 0 \\ 0 & 0 \end{pmatrix} \qquad D\mathscr{B}(w_0) = \begin{pmatrix} B & 0 \\ J_3 & J_4 \end{pmatrix} \tag{2.3}$$

where A and B are the $m \times m$ matrices defined by

$$A = \left[\frac{\partial \mathscr{A}_i}{\partial w_j}(w_0)\right], \quad \textit{and} \quad B = \left[\frac{\partial \mathscr{B}_i}{\partial w_j}(w_0)\right], \quad \textit{with} \quad 1 \leq i, j \leq m. \tag{2.4}$$

Further, A is nonnegative and B is a nonsingular M-matrix.

Since A is nonnegative and B is a nonsingular M-matrix, B^{-1} and AB^{-1} are also nonnegative. The components of the matrix B^{-1} determine the mean length of time an infected individual introduced into a disease population spends in a compartment in their life time whilst that of A determine the rate of new infections produced by this individual in the compartment. Hence the product AB^{-1} known as the next generation matrix of the model is the expected number of new infections generated as a result of a single infective introduced into a population. The spectral radius of the next generation matrix is defined as the epidemiological threshold parameter (basic reproduction number) for the system in Equation 2.2 [105].

$$R_0 = \rho(AB^{-1}) \tag{2.5}$$

This is the biggest nonnegative or the dominant eigenvalue of the next generation matrix. The following theorem states that R_0 is the threshold parameter for the stability of the disease-free equilibrium [105].

Theorem 1 *Consider the disease transmission model given by Equation 2.2 with $g(w)$ satisfying conditions i - v. If w_0 is a disease-free equilibrium of the model, then w_0 is locally asymptotically stable if $R_0 < 1$, but unstable if $R_0 > 1$ where R_0 is defined by Equation 2.5.*

2.8 Herd immunity threshold

The spread of an infectious disease is driven by how quickly effective contacts are made between the infectious and susceptible individuals in a population. High effective contact rates most likely result in high infection rates and greater spread of the disease [108]. To

stop or slow down the transmission and spread of an infectious disease requires that a critical proportion of the population is immune to the disease [108]. The greater the proportion of immunity achieved in a population, the smaller the likelihood for an infectious individual to come into contact with an individual who is not immune since many chains of infection are likely to have been broken [109, 110]. The implication is that the risk of infection among susceptible individuals in a population is reduced by the presence and proximity of immune individuals who serve as a barrier to transmission of the disease. This process of creating transmission barriers is referred to as indirect protection or herd effect and the threshold parameter that defines the critical proportion of the population is called the herd immunity threshold value [109].

The herd immunity threshold value is the threshold proportion of immune individuals necessary for the incidence of the disease to decline and protect the population from invasion of new infection [108, 109, 110]. Given that the epidemiological threshold parameter (basic reproduction number) is R_0, then at the critical proportion of the susceptible population s_c [1], for $R_0 > 1$, one has

$$R_0 \times s_c = 1.$$

Let H denote the proportion of the population that is immune, then $s_c + H = 1$ and so

$$\begin{aligned} & R_0(1 - H) = 1 \\ \implies \qquad & H = 1 - \frac{1}{R_0} \end{aligned} \tag{2.6}$$

Equation 2.6 defines the herd immunity threshold for an infectious disease model whose epidemiological threshold parameter is R_0 [108, 111]. Since R_0 is a measure of the incidence and spread of the disease in a population, lower values of R_0 require lower herd immunity threshold values and vice versa. [108, 111].

Chapter 3

The research model

3.1 The $SEIR$ deterministic model

The $SEIR$ model is a modification of the SIR model in which the exposed class E is introduced. This study adopts the $SEIR$ model and incorporates the true mass-action incidence term $\frac{\beta SI}{N}$ and the latent period which are found to be critical in modelling hepatitis B. It is also assumed that a fraction of newborns of exposed and infectious hosts α, accounting for vertical transmission, are infected at birth and like the host will stay latent before becoming infectious.

The population is divided into four mutually exclusive compartments namely the Susceptible S, Exposed E, Infectious I, and Removed or Recovered R. After infection an individual moves from the susceptible class into the exposed class, then into the infectious class and then finally into the recovered or removed class by protective immunity, or may die naturally in the course of progression through the model. Figure 3.1 illustrates the progression of infection through the compartments of the model.

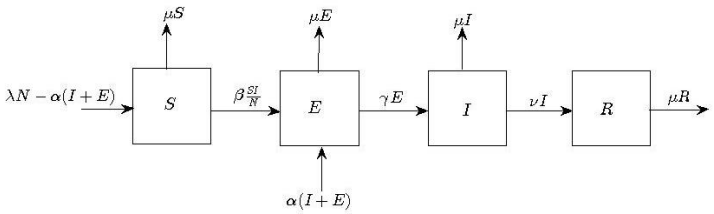


Figure 3.1: A model for the transmission of hepatitis B

The model displayed in Figure 3.1 is defined by the system of non-linear differential equations

$$\begin{aligned} \frac{dS}{dt} &= \lambda N - \alpha(I+E) - \beta\frac{SI}{N} - \mu S \\ \frac{dE}{dt} &= \beta\frac{SI}{N} + \alpha(I+E) - \mu E - \gamma E \\ \frac{dI}{dt} &= \gamma E - \mu I - \nu I \\ \frac{dR}{dt} &= \nu I - \mu R \end{aligned} \tag{3.1}$$

subject to $S(t), E(t), I(t), R(t) \geq 0$ and $S(t) + E(t) + I(t) + R(t) = N(t)$, where λ is the natural birth rate, μ is the natural death rate, γ the rate of removal from the exposed class and ν the rate of recovery per unit time. The force of infection is $\beta\frac{I}{N}$, where β is the effective contact rate of an infectious individuals with a susceptible individual, and the incident rate is $\beta\frac{SI}{N}$. Furthermore, $\frac{1}{\lambda+\nu}$ is the mean time-duration an infected individual remains infectious and $\frac{1}{\lambda+\gamma}$ is the mean latent period [23].

The underlying assumptions of the model are:

- The population has a homogeneous distribution which guarantees mass-action in terms of mixing of hosts. Thus the local density of the total population is considered constant though the total population size $S(t)+E(t)+I(t)+R(t) = N(t)$ may vary with time.
- Horizontal transmission of disease is taken to be the effective direct contact between an infectious and a susceptible host, measured by the term $\beta\frac{SI}{N}$, and referred to as proportionate (bilinear true) mass-action or freely mixed [76].
- Vertical transmission is taken to come from a fraction α of the exposed and infectious classes. Thus $\alpha(I+E)$ and $\lambda N - \alpha(I+E)$ are the birth flux introduced into the system via the exposed and susceptible compartments respectively.
- The recovered hosts have permanent immunity and cannot re-enter the susceptible hosts.

From the model in Equation 3.1, let $s(t) = S(t)/N(t)$, $e(t) = E(t)/N(t)$, $i(t) = I(t)/N(t)$ and $r(t) = R(t)/N(t)$ be the proportions of S - susceptible, E - exposed, I - infectious

and R - recovered populations respectively in the total population of size $N(t)$ in time t such that $s(t) + e(t) + i(t) + r(t) = 1$. By the product rule

$$\frac{ds}{dt} = \frac{1}{N}\frac{dS}{dt} - \frac{S}{N^2}\frac{dN}{dt} \tag{3.2}$$

From Equation (3.1)

$$\frac{dS}{dt} = \lambda N - \alpha(I + E) - \beta\frac{SI}{N} - \mu S$$

and the population varying with birth and death by

$$\frac{dN(t)}{dt} = (\lambda - \mu)N(t) \tag{3.3}$$

It follows that

$$\begin{aligned}\frac{ds}{dt} &= \lambda - \alpha(i + e) - \beta si - \mu s - s(\lambda - \mu) \\ &= \lambda - \alpha(i + e) - \beta si - s\lambda \end{aligned} \tag{3.4}$$

Following the same procedure for e, i and r, the system in Equation 3.1 becomes

$$\begin{aligned}\frac{ds}{dt} &= \lambda - \alpha(i + e) - \beta si - s\lambda \\ \frac{de}{dt} &= \beta si + \alpha(i + e) - \gamma e - e\lambda \\ \frac{di}{dt} &= \gamma e - \nu i - i\lambda \\ \frac{dr}{dt} &= \nu i - r\lambda.\end{aligned} \tag{3.5}$$

Eliminating r by $1 - s(t) - e(t) - i(t) = r(t)$, the system in Equation 3.5 can be reduced to

$$\begin{aligned}\frac{ds}{dt} &= \lambda - \alpha(i + e) - \beta si - s\lambda \\ \frac{de}{dt} &= \beta si + \alpha(i + e) - \gamma e - e\lambda \\ \frac{di}{dt} &= \gamma e - \nu i - i\lambda.\end{aligned} \tag{3.6}$$

on the closed positively invariant set $\Sigma = \{(s, e, i) \in \mathbb{R}^3_+ : 0 \leq s + e + i \leq 1\}$ [112]. The set Σ is positively invariant with respect to the system in Equation 3.6 in the sense that for all

$t \geq 0$, $(s(t), e(t), i(t)) \in \Sigma$ whenever $(s(0), e(0), i(0)) \in \Sigma$ [113]. The system in Equation 3.6 is therefore well-posed since given an initial state $(s_0, e_0, i_0) \in \Sigma$, all solutions to Equation 3.6 remain in Σ. The dynamics of the system are therefore discussed in Σ whose boundary and interior are denoted by $\partial\Sigma$ and $\mathring{\Sigma}$ respectively. Disease eradication in this regard is considered to be achieved when the sum of the proportions of $e(t) + i(t) \to 0$ as $t \to \infty$. The system in Equation 3.6 has two equilibrium solutions: the disease-free proportion equilibrium $Q_0 = (1, 0, 0)$ and the endemic proportion equilibrium $Q^* = (s^*, e^*, i^*)$ where

$$\begin{aligned} s^* &= \frac{(\lambda+\gamma)(\lambda+\nu) - \alpha(\lambda+\gamma+\nu)}{\beta\gamma} \\ e^* &= \frac{\lambda\beta\gamma + \alpha\lambda(\lambda+\gamma+\nu) - \lambda(\lambda+\gamma)(\lambda+\nu)}{\beta\gamma(\lambda+\gamma)} \\ i^* &= \frac{\lambda\beta\gamma + \alpha\lambda(\lambda+\gamma+\nu) - \lambda(\lambda+\gamma)(\lambda+\nu)}{\beta(\lambda+\gamma)(\lambda+\nu)}. \end{aligned} \tag{3.7}$$

The stability discussions of the model in this thesis will refer to disease eradication and persistence that involve the proportions e and i of the exposed and infectious cases and not the absolute cases E and I respectively of the population. Although the same outcome cannot be guaranteed for the proportionate and absolute cases, studies indicate that the former can be used to predict the infectious disease spread in a population in the same manner as the absolute case [114]

3.2 The epidemiological threshold parameter and herd immunity threshold value

In this section, the epidemiological threshold parameter R_0 and hence the herd immunity threshold value H of the model in Equation 3.6 are derived, using the methods involving the spectral radius of the second generation matrix of the model discussed in Section 2.7. The model in Equation 3.6 has two infected compartments, the exposed e and the infectious i, represented by the second and third equations respectively and one uninfected compartment S represented by the first equation of the system. The proportions of S, E and I in the total population of N are given by $s, e, i \geq 0$ respectively. Thus the number of infected compartments is $m = 2$ (E, and I from Fig 3.1) corresponding to the second and third equations of Equation 3.6. From Equation 3.6, the rate at which new infection (new appearance) is introduced into the model and the rate of progression of already existing infection through the model are given by

$$\mathscr{A} = \begin{bmatrix} \beta si + \alpha(i+e) \\ 0 \end{bmatrix} \quad \text{and} \quad \mathscr{B} = \begin{bmatrix} \gamma e + e\lambda \\ -\gamma e + \nu i + \lambda i \end{bmatrix} \tag{3.8}$$

respectively. The corresponding partial derivatives of $\mathscr{A}$ and $\mathscr{V}$ with respect to the infected compartments e and i taken at the disease-free equilibrium $Q_0 = (1, 0, 0)$ are

$$A = \begin{bmatrix} \alpha & \alpha+\beta \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} \gamma+\lambda & 0 \\ -\gamma & \nu+\lambda \end{bmatrix} \tag{3.9}$$

respectively where A and B are 2×2 matrices corresponding to the submatrices A and B in Equation 2.3. The inverse of B is given by

$$B^{-1} = \frac{1}{(\lambda+\gamma)(\lambda+\nu)} \begin{bmatrix} \lambda+\nu & 0 \\ \gamma & \lambda+\gamma \end{bmatrix}. \tag{3.10}$$

Hence the second generation matrix of the model in Equation 3.6 is

$$\begin{aligned} AB^{-1} &= \frac{1}{(\lambda+\gamma)(\lambda+\nu)} \begin{bmatrix} \alpha & \alpha+\beta \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \lambda+\nu & 0 \\ \gamma & \lambda+\gamma \end{bmatrix} \\ &= \begin{bmatrix} \frac{\alpha(\lambda+\nu)+\gamma(\alpha+\beta)}{(\lambda+\gamma)(\lambda+\nu)} & \frac{\alpha+\beta}{\lambda+\nu} \\ 0 & 0 \end{bmatrix}. \end{aligned} \tag{3.11}$$

Since the second generation matrix AB^{-1} is upper triangular, the eigenvalues of AB^{-1} are

$$\xi_1 = 0, \qquad \xi_2 = \frac{\beta\gamma + \alpha(\lambda+\gamma+\nu)}{(\lambda+\gamma)(\lambda+\nu)} \tag{3.12}$$

Therefore the spectral radius is given by

$$\rho(AB^{-1}) = \frac{\beta\gamma + \alpha(\lambda+\gamma+\nu)}{(\lambda+\gamma)(\lambda+\nu)}$$

so that

$$R_0 = \frac{\beta\gamma + \alpha(\lambda+\gamma+\nu)}{(\lambda+\gamma)(\lambda+\nu)}. \tag{3.13}$$

Hence, the herd immunity threshold value of the model in Equation 3.6 is given as [108, 111]

$$H = 1 - \frac{1}{R_0} = 1 - \frac{(\gamma + \lambda)(\lambda + \nu)}{\beta\gamma + \alpha(\gamma + \lambda + \nu)} \tag{3.14}$$

The result in Equation 3.14 is important in the epidemiology of hepatitis B as it defines a threshold proportion of the population needed to be immune in order for the transmission and spread of the disease to decline and to protect the population from invasion of new infection. The value of the herd immunity threshold H, however, is a function of the epidemiological threshold parameter R_0 that determines the intensity of the transmission and spread of the disease, which in turn depends on the parameters of the model in Equation 3.6.

3.3 Stability analysis

To analyse the stability of the model in the neighbourhood of the equilibrium points, the linearised form of the system in Equation 3.6 is determined first. The key to linearising such a system of nonlinear differential equations is to construct the Jacobian matrix

$$J(s, e, i) = \begin{bmatrix} -(\beta i + \lambda) & -\alpha & -(\alpha + \beta s) \\ \beta i & \alpha - \lambda - \gamma & \alpha + \beta s \\ 0 & \gamma & -(\lambda + \nu) \end{bmatrix} \tag{3.15}$$

whose eigenvalues at the equilibrium solutions can be used to determine the stability of those solutions.

3.3.1 The disease-free equilibrium state

At the disease-free equilibrium $Q_0 = (1, 0, 0)$, the Jacobian is

$$J(1, 0, 0) = \begin{vmatrix} -\lambda & -\alpha & -(\alpha + \beta) \\ 0 & (\alpha - \lambda - \gamma) & \beta + \alpha \\ 0 & \gamma & -(\lambda + \nu) \end{vmatrix} \tag{3.16}$$

and its characteristic equation is

$$(\lambda + \xi)[((\alpha - \lambda - \gamma) - \xi)((\lambda + \nu) + \xi) + \gamma(\beta + \alpha)] = 0 \tag{3.17}$$

and so the eigenvalues are

$$\xi_1 \quad = \quad -\lambda \tag{3.18}$$

and

$$\xi_{2\&3} = \frac{-((\lambda+\nu)-(\alpha-\gamma-\lambda))}{2} \pm \frac{\sqrt{\triangle}}{2}$$

where

$$\begin{aligned}
\triangle &= ((\lambda+\nu)-(\alpha-\gamma-\lambda))^2 + 4((\lambda+\nu)(\alpha-\gamma-\lambda)+\gamma(\alpha+\beta)) \\
&= (\lambda+\nu)^2 - 2(\lambda+\nu)(\alpha-\gamma-\lambda) + (\alpha-\gamma-\lambda)^2 + 4(\lambda+\nu)(\alpha-\gamma-\lambda) + 4\gamma(\alpha+\beta)) \\
&= (\lambda+\nu)^2 + (\alpha-\gamma-\lambda)^2 + 2(\lambda+\nu)(\alpha-\gamma-\lambda) + 4\gamma(\alpha+\beta) \\
&= ((\lambda+\nu)+(\alpha-\gamma-\lambda))^2 + 4\gamma(\alpha+\beta) \\
&= (\alpha+\nu-\gamma)^2 + 4\gamma(\alpha+\beta),
\end{aligned}$$

and so

$$\begin{aligned}
\xi_2 \quad &= \quad \frac{(\alpha-\gamma-\nu-2\lambda)+\sqrt{(\alpha+\nu-\gamma)^2+4\gamma(\alpha+\beta)}}{2} \\
\xi_3 \quad &= \quad \frac{(\alpha-\gamma-\nu-2\lambda)-\sqrt{(\alpha+\nu-\gamma)^2+4\gamma(\alpha+\beta)}}{2}.
\end{aligned} \tag{3.19}$$

In Equation 3.19, $\alpha-\gamma-\nu-2\lambda$ is always negative and real since the birth rate of babies with hepatitis B is less than the overall birth rate of the population, $\alpha < \lambda$. Furthermore, $(\alpha+\nu-\gamma)^2+4\gamma(\alpha+\beta)$ is positive since $\alpha, \gamma, \lambda \geq 0$, and so the eigenvalues ξ_2 and ξ_3 are real. The eigenvalues ξ_2 and ξ_3 are both negative if $(\alpha+\nu-\gamma)^2+4\gamma(\alpha+\beta) < (\alpha-\gamma-\nu-2\lambda)^2$. In this case the three eigenvalues ξ_1, ξ_2 and ξ_3 are negative, the disease-free equilibrium state is asymptotically stable and the equilibrium point is a sink node. Otherwise if $(\alpha+\nu-\gamma)^2+4\gamma(\alpha+\beta) > (\alpha-\gamma-\nu-2\lambda)^2$, the eigenvalue ξ_2 is positive whilst ξ_1 and ξ_3 are both negative and so the disease-free equilibrium state is unstable and the point is a saddle point. Crossover from stability to instability occurs when

$$\begin{aligned}
(\alpha+\nu-\gamma)^2+4\gamma(\alpha+\beta) &= (\alpha-\gamma-\nu-2\lambda)^2 \\
\implies 2\alpha\nu-2\alpha\gamma-2\gamma\nu+4\alpha\gamma+4\beta\gamma &= -2\alpha\gamma-2\alpha\nu-4\alpha\lambda+2\gamma\nu+4\gamma\lambda+4\lambda\nu+4\lambda^2 \\
\implies \quad 4\alpha\nu-4\gamma\nu+4\alpha\gamma+4\gamma\beta &= -4\alpha\lambda+4\gamma\lambda+4\lambda\nu+4\lambda^2 \\
\implies \quad \gamma\beta &= -\alpha\lambda+\gamma\lambda+\nu\lambda+\lambda^2-\alpha\nu-\alpha\gamma+\gamma\nu \\
\implies \quad \beta &= \frac{\gamma(\lambda-\alpha+\nu)+\lambda(\lambda+\nu-\alpha)-\alpha\nu}{\gamma} \\
\implies \quad \beta &= \frac{(\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu}{\gamma} \qquad (3.20)
\end{aligned}$$

Equation 3.20 defines a threshold value $\beta^* = ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$ of β for the crossover of the disease-free equilibrium state from stability to instability. At this threshold value, the eigenvalue ξ_2 is zero whilst the other two eigenvalues ξ_1 and ξ_3 remain negative. For $\beta < ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$, all eigenvalues are negative and for $\beta > ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$, one eigenvalue is positive.

In summary

i. If $\beta < ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$, then $\xi_2 < 0$.

ii. If $\beta = ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$, then $\xi_2 = 0$.

iii. If $\beta > ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$, then $\xi_2 > 0$.

Hence there is a threshold value

$$\beta^* = \frac{(\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu}{\gamma} \qquad (3.21)$$

of β such that if $\beta < \beta^*$, $\xi_1, \xi_2, \xi_3 < 0$ and Q_0 is asymptotically stable and if $\beta > \beta^*$, $\xi_1, \xi_3 < 0$ and $\xi_2 > 0$ so that Q_0 is unstable (saddle). The corresponding thresholds for γ, ν, α and λ are

$$\begin{aligned}
\gamma &= \frac{(\lambda+\nu)(\lambda-\alpha)}{\alpha+\beta-\lambda-\nu}, \\
\nu &= \frac{\gamma(\alpha+\beta)}{\gamma-\alpha+\lambda} - \lambda, \\
\alpha &= \lambda - \frac{\gamma(\beta-\nu)}{\gamma+\lambda+\nu} \\
\lambda &= \frac{(\alpha-\gamma-\nu) \pm \sqrt{(\alpha+\gamma+\nu)^2 + 4\gamma(\beta-\nu)}}{2},
\end{aligned} \tag{3.22}$$

respectively, ignoring the negative sign in the expression for λ, since $\lambda \not< 0$. Furthermore, if $\beta < \beta^*$, then from Equations 3.13 and 3.21

$$\begin{aligned}
& & \beta &< \beta^* \\
& \iff & \beta &< \frac{(\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu}{\gamma} \\
& \iff & \gamma\beta &< (\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu \\
& \iff & \gamma\beta &< (\lambda+\nu)(\gamma+\lambda)-\alpha(\gamma+\lambda+\nu) \\
\iff & & \gamma\beta+\alpha(\gamma+\lambda+\nu) &< (\lambda+\nu)(\gamma+\lambda) \\
\iff & & \frac{\gamma\beta+\alpha(\gamma+\lambda+\nu)}{(\lambda+\nu)(\gamma+\lambda)} &< 1 \\
& \iff & R_0 &< 1
\end{aligned} \tag{3.23}$$

In conclusion, the statement $\beta < \beta^*$ is equivalent to the restriction $R_0 < 1$. By the same analogy, the condition $\beta > \beta^*$ is also equivalent to the restriction $R_0 > 1$. Hence if $\beta < \beta^*$, $R_0 < 1$ and the disease-free equilibrium is locally asymptotically stable; and if $\beta > \beta^*$, $R_0 > 1$ and the disease-free equilibrium is unstable.

3.3.2 Global stability of disease-free equilibrium

Local stability of the disease-free proportion equilibrium Q_0 has been established to be equivalent to all real parts of the eigenvalues of the characteristic equation of the Jacobian matrix in Equation 7.12 being negative, which is guaranteed by the threshold parameter $R_0 < 1$. In this section, the parameter restriction $R_0 < 1$ is used to show the global stability of the disease-free equilibrium Q_0 in Σ in the sense of Lyapunov and LaSalle as given by the following theorems [115, 116].

Theorem 2 (LaSalle's Theorem) *Let $\Omega \subset D \subset \mathbb{R}^n$ be a compact positively invariant set with respect to an autonomous system of equations $\dot{x} = f(x), \quad f(0) = x_0$. Let V :*

$D \to \mathbb{R}$ be a continuously differentiable function such that $\dot{V}(x(t)) \leq 0$ in Ω. Let $E \subset \Omega$ be the set of all points in Ω where $\dot{V}(x) = 0$. Let $\mathrm{M} \subset \mathrm{E}$ be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \to \infty$, that is

$$\lim_{t\to\infty} \left(\underbrace{\inf_{z\in \mathrm{M}} ||x(t) - z||}_{dist(x(t),\mathrm{M})} \right) = 0.$$

The inclusion of the sets in this theorem is $\mathrm{M} \subset \mathrm{E} \subset \Omega \subset \mathrm{D} \subset \mathbb{R}^{\mathrm{n}}$ and a formal proof of this theorem can be found in [115].

Theorem 3 *The disease-free equilibrium $Q_0 = (1, 0, 0)$ of Equation 3.6 is globally asymptotically stable in Σ if $R_0 \leq 1$.*

Proof. Let $R_0 \leq 1$ and $V(s(t), e(t), i(t)) = \gamma e + (\lambda + \gamma - \alpha)i$, where $V : \mathbb{R}^3_+ \longrightarrow \mathbb{R}$ is a scalar function that is continuous and has continuous derivatives in $\mathbb{R}$. Differentiating V with respect to time t and using Equation 3.6 where $\frac{de}{dt} = e'$ and $\frac{di}{dt} = i'$ gives

$$\begin{aligned}
\dot{V}(s, e, i) &= \gamma e' + (\lambda + \gamma - \alpha)i' \\
&= \gamma[\beta si + \alpha(i + e) - \gamma e - e\lambda] + (\lambda + \gamma - \alpha)[\gamma e - \nu i - i\lambda] \\
&= \gamma[(\beta s + \alpha)i - (\lambda + \gamma - \alpha)e] + (\lambda + \gamma - \alpha)[\gamma e - (\lambda + \nu)i] \\
&= i[\gamma(\beta s + \alpha) - (\lambda + \gamma - \alpha)(\lambda + \nu)] \\
&= i[\gamma\beta s + \gamma\alpha - (\lambda + \gamma - \alpha)(\lambda + \nu)] \\
&= i[\gamma\beta s + \alpha(\lambda + \gamma + \nu) - (\lambda + \gamma)(\lambda + \nu)]. \qquad (3.24)
\end{aligned}$$

Equation 3.24 can be written in the form

$$\begin{aligned}
\dot{V}(s, e, i) &= i\left[\frac{\gamma\beta s - \gamma\beta + \gamma\beta + \alpha(\lambda + \gamma + \nu) - (\lambda + \gamma)(\lambda + \nu)}{(\lambda + \gamma)(\lambda + \nu)}\right](\lambda + \gamma)(\lambda + \nu) \\
&= i\left[\frac{\gamma\beta s - \gamma\beta}{(\lambda + \gamma)(\lambda + \nu)} + \frac{\gamma\beta + \alpha(\lambda + \gamma + \nu)}{(\lambda + \gamma)(\lambda + \nu)} - 1\right](\lambda + \gamma)(\lambda + \nu) \\
&= i\left[\frac{\gamma\beta(s - 1)}{(\lambda + \gamma)(\lambda + \nu)} + R_0 - 1\right](\lambda + \gamma)(\lambda + \nu) \\
&= i[\gamma\beta(s - 1) + (R_0 - 1)(\lambda + \gamma)(\lambda + \nu)]. \qquad (3.25)
\end{aligned}$$

Since $R_0 \leq 1$ and $s \leq 1$ in Σ, it follows that

$$\gamma\beta(s-1) + (R_0 - 1)(\lambda+\gamma)(\lambda+\nu) \leq 0 \tag{3.26}$$

Hence for $i \geq 0$ in Σ,

$$\dot{V}(s,e,i) \leq 0 \qquad \forall (s,e,i) \in \Sigma. \tag{3.27}$$

Furthermore, $\dot{V} = 0$ if $i = 0$ or

$$\gamma\beta(s-1) + (R_0 - 1)(\lambda+\gamma)(\lambda+\nu) = 0$$

and so $s = 1$ and $R_0 = 1$.

But if $s = 1$, it follows that $i = 0$ which then implies that $i = 0$ is the necessary and sufficient condition for $\dot{V} = 0$ regardless of the value of R_0. The set $E = \{(s,e,i)|0 \leq s + e \leq 1, i = 0\}$ is the set of all points in Σ where $\dot{V}(x) = 0$ and $\{Q_0\}$ is invariant, since $(s(0), e(0), i(0)) = Q_0$ implies $(s(t), e(t), i(t)) = Q_0$, $\forall t \in \mathbb{R}$. For any trajectory (s,e,i) starting in E to remain in E requires that $i' = 0$. But if $i = 0$, it follows from the third equation of the system in Equation 3.6 that

$$i' = \gamma e$$

so that

$$L = \{(s,e,i)|0 \leq s \leq 1, i = e = 0\}$$

is the only positively invariant subset of E because the system in Equation 3.6 reduces to

$$\begin{aligned} s' &= (1-s)\lambda \\ e' &= 0 \\ i' &= 0 \end{aligned} \tag{3.28}$$

and so all trajectories (s,e,i) starting on the s-axis remain on the s-axis for $t \geq 0$ and in fact approach the singleton $\{Q_0\} \subset L \subset E$ as $t \longrightarrow \infty$. But for $t < 0$, all trajectories (s,e,i) starting in L move in the negative s-direction and so ultimately fall outside of the closed positive set Σ as $t \longrightarrow -\infty$ thereby making the set L only positively invariant, not invariant. Thus, the maximum invariant set in E is the singleton $\{Q_0\} \subset L \subset E \subset \Sigma$. Hence by Theorem 2, setting $\Omega = \Sigma$, $M = Q_0$ and $D = \mathbb{R}^3_+$

$$\lim_{t\to\infty} ||(s(t), e(t), i(t)) - Q_0|| = 0.$$

Hence Q_0 is globally asymptotically stable when $R_0 \leq 1$.

3.3.3 The endemic equilibrium state

At the endemic state $Q^* = (s^*, e^*, i^*)$, the characteristic equation is

$$\det(J(s^*, e^*, i^*) - \xi I) = \begin{vmatrix} -(\beta i^* + \lambda) - \xi & -\alpha & -(\alpha + \beta s^*) \\ \beta i^* & (\alpha - \lambda - \gamma) - \xi & \alpha + \beta s^* \\ 0 & \gamma & -(\lambda + \nu) - \xi \end{vmatrix} = 0 \quad (3.29)$$

Thus

$$((\beta i^*+\lambda)+\xi)[((\alpha-\lambda-\gamma)-\xi)((\lambda+\nu)+\xi)+\gamma(\alpha+\beta s^*)]-\alpha\beta i^*((\lambda+\nu)+\xi)-\gamma\beta i^*(\alpha+\beta s^*) = 0 \quad (3.30)$$

which when expanded and simplified can be written in the form

$$\xi^3 + a_2\xi^2 + a_1\xi + a_0 = 0 \quad (3.31)$$

where the constant coefficients a_2, a_1 and a_0 are respectively

$$\begin{aligned} a_2 &= \beta i^* + \gamma + \nu + 3\lambda - \alpha, \\ a_1 &= 3\lambda^2 + 2\gamma\lambda + 2\lambda\nu + 2\lambda\beta i^* + \gamma\beta i^* + \nu\beta i^* + \gamma\nu - \alpha\gamma - \alpha\nu \\ &\quad - 2\alpha\lambda - \gamma\beta s^*, \\ a_0 &= (\lambda + \beta i^*)(\lambda + \gamma - \alpha) + \alpha\beta i^*)(\lambda + \nu) - \alpha\gamma\lambda - \gamma\lambda\beta s^* \end{aligned} \quad (3.32)$$

Substituting s^* and i^* from Equation 3.7, the coefficients a_2, a_1 and a_0 become

$$\begin{aligned} a_2 &= \frac{(\lambda+\nu)(\gamma\nu + \lambda\nu + \gamma^2 + 2\lambda^2) + \gamma\lambda(3\lambda + \beta) + 2\gamma\lambda\nu + \gamma\nu(\lambda - \alpha)}{(\gamma + \lambda)(\lambda + \nu)}, \\ a_1 &= \frac{\lambda(\alpha\gamma^2 + \alpha\lambda^2 + \beta\gamma^2 + \alpha\nu^2 + \beta\gamma\nu + \alpha\gamma\nu + 2\alpha\gamma\lambda + 2\beta\gamma\lambda + 2\alpha\nu\lambda)}{(\lambda + \nu)(\gamma + \lambda)}, \\ a_0 &= \lambda(\beta\gamma + \alpha\nu) - \lambda(\lambda + \nu - \alpha)(\lambda + \gamma). \end{aligned} \quad (3.33)$$

By making the substitution $\xi = x - a_2/3$, Equation 3.31 is reduced to

$$x^3 + px + q = 0 \tag{3.34}$$

where

$$\begin{aligned} p &= a_1 - \frac{a_2^2}{3} \\ q &= \frac{2a_2^3 - 9a_1a_2 + 27a_0}{27} \end{aligned} \tag{3.35}$$

Making the further substitution $x = v - p/3v$ into Equation 3.34 gives

$$\begin{aligned} v^3 - \frac{p^3}{27v^3} + q &= 0 \\ \implies (v^3)^2 + qv^3 - \frac{p^3}{27} &= 0 \end{aligned} \tag{3.36}$$

and so

$$v^3 = \frac{1}{2}\left(-q \pm \sqrt{q^2 + \frac{4p^3}{27}}\right) \tag{3.37}$$

which gives three conjugate pairs of solutions of v in the form of cube roots. Each conjugate pair of solutions gives a single solution when substituted into $x = v - p/3v$ and subsequently into $\xi = x - a_2/3$ to obtain the eigenvalues of the endemic equilibrium [117].

The roots of Equation 3.34 can be written as [118]

$$\begin{aligned} x_1 &= A + B \\ x_2 &= -\frac{1}{2}(A+B) + \frac{i\sqrt{3}}{2}(A-B) \\ x_3 &= -\frac{1}{2}(A+B) - \frac{i\sqrt{3}}{2}(A-B) \end{aligned} \tag{3.38}$$

where

$$A = \sqrt[3]{-\frac{q}{2} + \sqrt{\frac{q^2}{4} + \frac{p^3}{27}}}$$
$$B = \sqrt[3]{-\frac{q}{2} - \sqrt{\frac{q^2}{4} + \frac{p^3}{27}}}.$$

When a_2, a_1 and a_0 are real (and hence p and q are real), three cases exist [118]:

i. $\frac{q^2}{4} + \frac{p^3}{27} > 0$. There is one real and two conjugate complex roots.

ii. $\frac{q^2}{4} + \frac{p^3}{27} = 0$. There are three real roots with two or more being equal.

iii. $\frac{q^2}{4} + \frac{p^3}{27} < 0$. There are three real and distinct roots.

Using Equations (3.33) and (3.35), it can be numerically verified for the parameters $\beta, \gamma, \nu \geq 0$ that

$$\frac{q^2}{4} + \frac{p^3}{27} < 0, \tag{3.39}$$

from which it follows that Equations 3.31 and 3.34 have three distinct real roots. The condition in Inequality 3.39, however, could not be analytically verified due to difficulty in simplifying p and q in Equation 3.35 with respect to the coefficients a_0, a_1 and a_2 in Equation 3.33.

3.3.4 Characterisation of the eigenvalues of the endemic equilibrium state

There are several approaches to characterising the eigenvalues of the Jacobian of the endemic equilibrium state for the purpose of stability analysis. These approaches include, but are not limited to, the Routh-Hurwitz criterion and the spectral properties of the second additive compound matrix of the Jacobian, which are routinely used in stability discussions of the endemic state [74, 119]. However, due to challenges associated with determining the coefficients of the characteristic equation of the Jacobian of the endemic state, approaches like the Routh-Hurwitz and other similar methods are technically difficult to use [74]. In view of this difficulty, stability of the endemic equilibrium state of the model in Equation 3.6 of this study is analysed using Descartes' rule of signs for a polynomial function to characterise the eigenvalues of the Jacobian of the endemic state.

Descartes' rule of signs is a technique for determining an upper bound on the number of positive or negative real roots of a polynomial. The rule is applied by counting the number of sign changes in the sequence formed by the polynomial's coefficients. If a coefficient is zero, that term is simply omitted from the sequence [120, 121, 122, 123]. Descartes' rule is stated in the following theorem.

Theorem 4 (Descartes' rule: positive roots) *If the terms of a single variable polynomial with real coefficients are ordered by descending variable exponent, then the number of positive roots of the polynomial is either equal to the number of sign differences between consecutive nonzero coefficients, or is less than it by an even number. Multiple roots of the same value are counted separately.*

The proof of Theorem 4 can be found in [120, 121, 122]. Since $a_2 > 0$ and $a_1 > 0$, three cases arise when the Descartes' rule of signs is applied to Equation 3.31.

i. If $a_0 < 0$, the equation
$$\xi^3 + a_2\xi^2 + a_1\xi + a_0 = 0$$
has a single sign difference between the coefficient of ξ and the constant a_0, and so there is only one positive root, say $\xi_1 > 0$ since there cannot be negative number of positive roots. The remaining two roots ξ_2 and ξ_3 must be negative since $a_0 \neq 0$.

ii. If $a_0 = 0$, there is no sign change in the coefficients of the equation
$$\xi^3 + a_2\xi^2 + a_1\xi = 0,$$
which means there is no positive root. Since $a_0 = 0$ one of the roots is zero, say $\xi_1 = 0$, and so the remaining two roots ξ_2 and ξ_2 must be negative.

iii. If $a_0 > 0$, the equation
$$\xi^3 + a_2\xi^2 + a_1\xi + a_0 = 0$$
has no sign difference in the coefficients. All the signs of the constant coefficients are the same (positive), which means there is no positive root. Since $a_0 \neq 0$, all three roots ξ_1, ξ_2 and ξ_3 must be negative.

From Equation 3.33 $\lambda - \alpha > 0$, $a_2 > 0$ and $a_1 > 0$. The constant a_0 can attain either sign and
$$a_0 = \lambda(\beta\gamma + \alpha\nu) - \lambda(\lambda + \nu - \alpha)(\lambda + \gamma) = 0,$$

if

$$\beta = \frac{(\lambda + \nu - \alpha)(\lambda + \gamma) - \alpha\nu}{\gamma}.$$

which is equal to the threshold value β^* in Equation 3.21 that defines the crossover of the disease-free equilibrium state from stability to instability.

The preceding analysis, subject to Inequality 7.33, shows that the characteristic polynomial, Equation 3.31, of the Jacobian of the model at the endemic state has three distinct real eigenvalues with one positive and two negative ($\xi_1 > 0$, $\xi_2 < 0$, $\xi_3 < 0$) if $a_0 < 0$; one zero and two negative ($\xi_1 = 0$, $\xi_2 < 0$, $\xi_3 < 0$) if $a_0 = 0$; or all three negative ($\xi_1 < 0$, $\xi_2 < 0$, $\xi_3 < 0$) if $a_0 > 0$. As the value of a_0 goes from negative to positive, there is a transition of the endemic state from instability to stability where $a_0 = 0$ and $\beta = ((\lambda + \nu - \alpha)(\lambda + \gamma) - \alpha\nu)/\gamma$ define the threshold for the crossover. This is consistent with the Routh-Hurwitz criterion, which is routinely used to discuss the stability of dynamical systems.

3.3.5 Validating the threshold value β^* for stability crossover between equilibrium states

In the stability analysis of the equilibrium states Q_0 and Q^* of the model in Sections 3.3.1 and 3.3.3 respectively, $\beta^* = ((\lambda + \nu - \alpha)(\gamma + \lambda) - \alpha\nu)/\gamma$ was determined as a threshold value in each case for the crossover from stability to instability and vice versa. In order to verify whether the threshold values of β^* as obtained in Sections 3.3.1 and 3.3.3 are in fact the same crossover value for the two equilibrium states Q_0 and Q^* of the model to switch stability, the value of $\beta^* = ((\lambda + \nu - \alpha)(\gamma + \lambda) - \alpha\nu)/\gamma$ was substituted into s^*, e^* and i^* in Equations 3.7 and also in Equations 3.33.

By substituting $\beta^* = ((\lambda + \nu - \alpha)(\gamma + \lambda) - \alpha\nu)/\gamma$ into Equation 3.7 gives

$$
\begin{aligned}
s^* &= \frac{(\gamma+\lambda)(\lambda+\nu)-\alpha(\gamma+\lambda+\nu)}{(\gamma+\lambda)(\lambda+\nu-\alpha)-\alpha\nu} \\
&= \frac{(\gamma+\lambda)(\lambda+\nu)-\alpha(\gamma+\lambda+\nu)}{(\gamma+\lambda)(\lambda+\nu)-\alpha(\gamma+\lambda+\nu)} \\
&= 1 \\
e^* &= \frac{\lambda((\gamma+\lambda)(\lambda+\nu-\alpha)-\alpha\nu)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu)}{(\lambda+\nu-\alpha)(\gamma+\lambda)^2-\alpha\nu(\gamma+\lambda)} \\
&= 0 \\
i^* &= \frac{\gamma(\lambda((\gamma+\lambda)(\lambda+\nu-\alpha)-\alpha\nu)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu))}{(\gamma+\lambda)^2(\lambda+\nu)((\lambda+\nu-\alpha)-\alpha\nu)} \\
&= \frac{\gamma(\lambda(\gamma+\lambda)(\lambda+\nu)-\alpha\lambda(\gamma+\lambda+\nu)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu))}{(\gamma+\lambda)^2(\lambda+\nu)((\lambda+\nu-\alpha)-\alpha\nu)} \\
&= 0. \qquad (3.40)
\end{aligned}
$$

and so $(s^*, e^*, i^*) = (1, 0, 0)$. By a similar substitution of the value of β^* into Equation 3.33, it can also be verified that the coefficient $a_0 = 0$ whilst $a_1, a_2 > 0$, and the eigenvalues of the characteristic Equation 3.31 are $\xi_1 = 0$, $\xi_2 < 0$ and $\xi_3 < 0$ as indicated by case (ii) of the application of the Descartes' rule of signs to Equation 3.31 (see Appendix D).

Equation 3.40 shows that when $\beta^* = ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$, the endemic Q^* and disease-free Q_0 equilibrium points coincide at $(1, 0, 0)$. In effect at the threshold value of β^* as the disease-free state loses stability the endemic state gains stability and vice versa.

The discussions and results in Subsections 3.3.1 and 3.3.5 show that

i. If $\beta < \beta^*$, $R_0 < 1$ and the endemic equilibrium state is unstable whilst the disease-free state is asymptotically stable.

ii. If $\beta = \beta^*$, $R_0 = 1$ and both the endemic and disease-free equilibrium states coincide at the point $(1, 0, 0)$ where stability changes from one to the other.

iii. If $\beta > \beta^*$, $R > 1$ and the endemic equilibrium is asymptotically stable whilst the disease-free state is unstable.

In essence at any given time in the dynamical system, exactly one of the equilibrium states is stable; either the disease-free state Q_0 is stable or the endemic state Q^* is stable. The threshold value of $\beta^* = ((\lambda+\nu-\alpha)(\gamma+\lambda)-\alpha\nu)/\gamma$ defines a crossover point where the two equilibrium states coincide.

3.3.6 Disease persistence

By Theorem 3, the global dynamics of Equation 3.6 in Σ is determined for $R_0 \leq 1$. From an epidemiological perspective, this result implies that the sum of the latent and infectious fractions which constitute the infected fraction of the population $e + i \longrightarrow 0$ as $t \longrightarrow \infty$ and so the disease tends to die out of the population. The opposite is the case when $R_0 > 1$ and so the disease is said to persist in the population. This occurs when the disease is endemic in that the infected fraction of the population persists above a certain critical value for a sufficiently long time. Endemicity of disease is therefore discussed under uniform persistence which is defined in Definition 1 [116]

Definition 1 *The system in Equation 3.6 is uniformly persistent if there exists a constant* $0 < c < 1$ *such that any solution* $(s(t), e(t), i(t))$ *with* $(s(0), e(0), i(0)) \in \mathring{\Sigma}$ *satisfies*

$$\min\{\lim_{t\to\infty} \inf s(t), \lim_{t\to\infty} \inf e(t), \lim_{t\to\infty} \inf i(t)\} \geq c$$

.

Uniform persistence of Equation 3.6 follows from Theorem 4.3 of [113]. In order to ease flow of discussion, Theorem 4.3 is briefly stated here whilst reference to detailed definitions including proof can be found in [113].

Let X be a metric space with the euclidean metric d, and let Ω be a closed subset of X with boundary $\partial\Omega$ and interior $\mathring{\Omega}$. Let $\mathcal{F} = (\Omega, \mathbb{R}, \pi)$ be a continuous flow defined on Ω so that $\partial\Omega$ is invariant under $\mathcal{F}$, where $\mathbb{R}$ is the set of real numbers, $\pi : \Omega \times \mathrm{R} \longrightarrow \Omega$ is a continuous map such that $\pi(x, 0) = x$ and $\pi(\pi(x, t), f) = \pi(x, t + f)$ for all $x \in \Omega$, $t, f \in \mathbb{R}$, and $\pi(\partial\Omega \times \mathbb{R}) \subset \partial\Omega$ [113, 124, 125]. Denote the restriction of the flow $\mathcal{F}$ of the dynamical system to the boundary $\partial\Omega$ of the set Ω by $\partial\mathcal{F}$. Define the positive/omega-limit set of the orbit of $\mathcal{F}$ through a point $x \in \Omega$ by $\Lambda^+_\omega(x) = \{y | y = \lim_{n\to\infty} \mathcal{F}_{t_n}(x), \text{with} \quad t_n \to +\infty\}$ [113, 124, 125]. Analogous to this is the negative/alpha-limit set which is defined as $\Lambda^-_\alpha(x) = \{y | y = \lim_{n\to\infty} \mathcal{F}_{t_n}(x), \text{with} \quad t_n \to -\infty\}$ [113, 124, 125]. The flow $\mathcal{F}$ is said to be point dissipative if for each $x \in \Omega$, $\Lambda^+_\omega(x) \neq \emptyset$ and the invariant set $\mathcal{F}_x = \cup_{x\in\Omega}\Lambda^+_\omega(x)$ has a compact closure [113, 126].

Next let N be the maximal invariant subset of $\partial\mathcal{F}$ on $\partial\Omega$. Suppose N is a closed invariant set and there exists a cover $\{N_i\}_{i\in A}$ of N, where $A = \{1, 2, \ldots, k\}$ is a nonempty index set, $N_i \subset \partial\Omega$, $N \subset \cup_{i\in A} N_i$ and $N_i (i \in A)$ are pairwise disjoint closed and isolated invariant sets. Furthermore, let $W^+(N_i) = \{x \in X : \Lambda^+_\omega(x) \neq \emptyset, \Lambda^+_\omega(x) \subset N_i\}$ denote a stable

manifold of N_i with $W^-(N_i)$ being the analogous unstable set. N_1 is chained to N_2, denoted by $N_1 \longrightarrow N_2$, if there exists $x \notin N_1 \cup N_2$ such that $x \in W^+(N_1) \cap W^-(N_2)$. A chain of isolated invariant sets is a finite sequence $N_1, N_2, ..., N_k$ with $N_1 \longrightarrow N_2 \longrightarrow \ldots \longrightarrow N_k$ is called a cycle if $N_k = N_1$. Applying the following hypothesis [113]:

(**H**)

(a) All N_i are isolated invariant sets of the flow $\mathcal{F}$.

(b) $\{N_i\}_{i\in A}$ is acyclic, that is, any finite subset of $\{N_i\}_{i\in A}$ does not form a cycle

(c) Any compact subset of $\partial\Omega$ contains at most finitely many sets of $\{N_i\}_{i\in A}$.

and defining $S[\partial\Omega, \epsilon] = \{x : x \in X, d(x, \partial\Omega) \leq \epsilon\}$ for any $\epsilon > 0$ and $\partial\Omega \subset X$, Theorem 4.3 of [113] is given as

Theorem 5 *Let Ω be a closed positively invariant subset of X on which a continuous flow $\mathcal{F}$ is defined. Suppose there is a constant $\epsilon > 0$ such that $\mathcal{F}$ is point dissipative on $S[\partial\Omega, \epsilon] \cap \mathring{\Omega}$ and the assumption* (**H**) *holds. Then the flow $\mathcal{F}$ is uniformly persistent if and only if*

$$W^+(N_i) \cap S[\partial\Omega, \epsilon] \cap \mathring{\Omega} = \emptyset$$

for any $i \in A$, where $W^+(N_i) = \{x \in X : \Lambda^+_\omega(x) \neq \emptyset, \Lambda^+_\omega(x) \subset N_i\}$ is the stable manifold of N_i.

The following proposition is made.

Proposition 1 *The system in Equation 3.6 is uniformly persistent in $\mathring{\Sigma}$ if and only if $R_0 > 1$.*

Proof. The proof of this proposition is based on Theorem 5. From Theorem 2 and also the fact that the asymptotic stability of Q_0 precludes any kind of persistence for $R_0 \leq 1$, it follows that $R_0 > 1$ is a necessary condition. It suffices to show that $R_0 > 1$ is also a sufficient condition for the system in Equation 3.6 to be uniformly persistent. This requires to show that the system in Equation 3.6 satisfies all the conditions of Theorem 5 when $R_0 > 1$. Following from Definition 1 and Theorem 5, given that $X = \mathbb{R}^3$, $\Omega = \Sigma$, and $x = (s, e, i) \in \Sigma$ is the component populations whose interactions are modelled by the flow $\mathcal{F}$, the singleton $N = \{Q_0\}$ is the maximal invariant subset of $\partial\mathcal{F}$ on $\partial\Sigma$ as established by the global stability results of the disease-free equilibrium in Subsection 3.3.2. Furthermore, Σ is a closed positively invariant subset of $\mathbb{R}^3$ and the positive s-axis, $N_s = \{(s, e, i) \in \Sigma | 0 \leq s \leq 1,$ e=i=0$\}$, which is the stable manifold $W^+(N_s)$ of

N_s of the flow $\mathcal{F}$ on $\partial\Sigma$, is a cover of $\{Q_0\}$. In fact the singleton $\{Q_0\}$ is the least cover of itself. Hence the hypothesis (**H**) holds for the system in Equation 3.6 in that $\{Q_0\}$ being a closed invariant set has a cover that is acyclic and any compact subset of $\partial\Sigma$ contains at most finitely many subsets of the cover. Thus when $R_0 > 1$, the result $W^+(N_s) \cap S[\partial\Sigma, \epsilon] \cap \mathring{\Sigma} = \emptyset$ holds. It was established in Subsection 3.3.5 of this study that exactly one of the equilibrium states is stable at any given time. In the absence of a periodic solution, the endemic equilibrium is the only attractor in $\mathring{\Sigma}$. In the setting of the system in Equation 3.6, it can be observed that the necessary and sufficient condition for uniform persistence is equivalent to the result that Q_0 is unstable. See the phase portrait of the dynamical system of Equation 3.6 displayed in Figure 5.7 of Chapter 5.

In conclusion, Theorem 3 and Proposition 1 establish R_0 as the epidemiological threshold parameter of the model in Equation 3.6; if $R_0 \leq 1$ the disease is kept under control or else if $R_0 > 1$ the disease persists in the population.

Chapter 4

Parameter estimation methodology

The parameters β, γ and ν (Figure 3.1) of the model in Equation 3.6 are critical in the calculation of the epidemiological threshold parameter R_0, in Equation 3.13, of an infectious disease epidemic in compartmental modelling. The inverse problem methodology is used to estimate a vector $\boldsymbol{\theta} = (\beta, \gamma, \nu) \in \mathbb{R}^3$, by minimising the difference between the model predictions and the observed data, using the least squares method [83, 127, 128]. The parameter estimation procedure for this study therefore involves solving a nonlinear least squares problem of the form

$$\min_{\boldsymbol{\theta} \in \mathbb{R}^3} L(\boldsymbol{\theta}), \qquad \boldsymbol{\theta} = (\beta, \gamma, \nu) \geq \mathbf{0} \tag{4.1}$$

where

$$L(\boldsymbol{\theta}) = \sum_{i=1}^{n} [Y_i - h(t_i, \boldsymbol{\theta})]^2 \tag{4.2}$$

is the sum of the squared difference between the model predicted cumulative incidence of hepatitis B

$$h(t_i, \boldsymbol{\theta}) = \int_0^{t_i} \frac{\beta SI}{N} dt \qquad i = 1, 2, ..., n$$

and the observed cumulative incidence of hepatitis B in year i

$$Y_i = \sum_{j=1}^{i} y_j$$

where y_j, $j = 1, ..., n$ is the observed incidence value of hepatitis B in month j. A hybrid method which combines a Genetic Algorithm (GA) and a modified Levenberg Marquardt (LM) algorithm is used to solve this nonlinear least squares optimisation problem [129].

The GA is applied first, and starts with a randomly generated population of candidate solutions $P_0 = \{\boldsymbol{\theta}_z\}_{z=1}^{K}$, K being the population size. These solutions are coded as binary strings of 0's and 1's which through processes of crossover, mutation, migration and elimination evolve a progressively better population of solutions. The GA, being a nongradient method, provides a global search of the solution space to identify solutions which are hoped to be close to optimal. Following the GA, a modified version of the LM algorithm which is a gradient method is applied to refine the solution generated by the GA. The flow diagram illustrating the process is displayed in Figure 4.1.

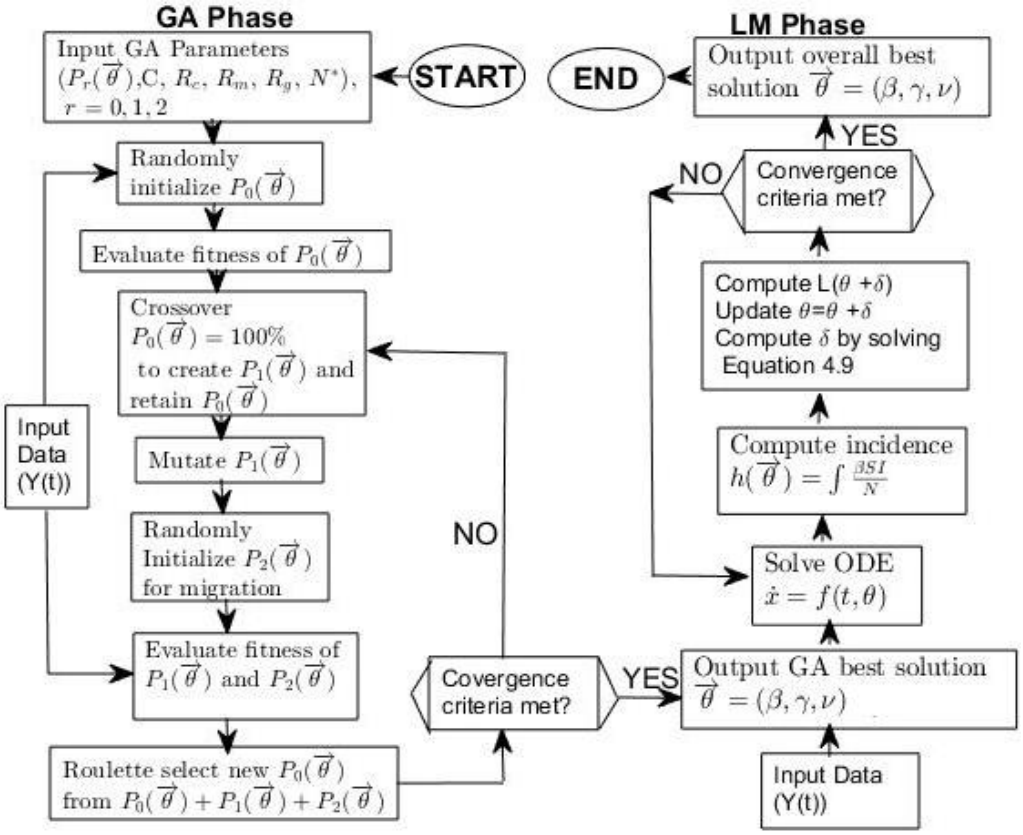


Figure 4.1: A flow chart illustrating a hybrid algorithm combining a Genetic Algorithm (GA) and a modified Levernberg-Marquardt Algorithm (LM).

4.1 Genetic algorithm overview

Genetic Algorithms (GA) are numerical randomised search processes which mimic the biological concept of evolution. The concept states that the survival of an organism is

by the rule "survival of the fittest" and it is implemented alongside the process of reproduction, crossover and mutation [130, 131]. Numerical optimisation adopts this concept to optimise an objective function of a physical problem. Potential solutions (satisfying problem constraints) are encoded as binary strings called chromosomes [130, 131]. A set of chromosomes is randomly defined at the start of the algorithm to form a population [130].

At each stage of the process, each new solution (chromosome) is passed through a fitness test using the objective function to assess the suitability or optimality of the solution with respect to the problem and to provide a basis for selecting which solutions to return for the next generation [130, 131]. Chromosomes in the population employ a process called crossover to produce new chromosomes called offspring whose genes are a combination of the parent chromosomes [131]. In a generation, some chromosomes also mutate in the genes. Crossover and mutation are respectively controlled by crossover and mutation rates defined by the user of the algorithm. Chromosomes with higher fitness value will have greater probability of being returned in the next generation and being selected for crossover [131]. The process runs through several generations until a predefined termination criterion, for example maximum number of generations or no improvement after a predefined number of generations, is satisfied. The most optimal solution from the final population is retained as the solution to the problem [130, 131]. It is however important to retain diversity in the population during the algorithm in order to avoid being trapped in local minima.

4.1.1 The GA phase of the hybrid method

The GA used in this study is a modification of a free version registered with GNU General Public License [132] in which a rate of migration is introduced and the rate of crossover is unrestricted (100%). In this study the input variables for the GA are population size P_0, chromosome length C, rate of mutation R_m, rate of crossover R_c, rate of migration R_g and number of generations N^* which are arbitrarily chosen.

The process of estimation by the GA can be summarised in the following steps:

1. Initialise population and evaluate fitness;
2. Generate new population or next generation by:
    i. Crossover or breeding of pairs of solutions (chromosomes).

ii. Mutation within sub-chromosomes (genes).

iii. Migration of new solutions (chromosomes) into algorithm.

iv. Evaluation of fitness values of new solutions (chromosomes).

v. Selection of solutions (chromosomes) for the next generation of the algorithm, by roulette method.

3. Repeat step 2 until algorithm terminates after a predetermined condition is satisfied and the best solution is returned.

The initialisation stage introduces the initial population of size P_0 made up of chromosomes $\boldsymbol{\theta} = (\beta, \gamma, \nu)$ expressed as binary strings of length C into the algorithm. A fitness value SSE^{-1}, which is the reciprocal of the sum of squares error (SSE), and the probability of selection, $P_{selection}(i) = \frac{fitness(i)}{\sum_{j=1}^{P_0} fitness(j)}$, of each of the chromosomes is computed using a fitness function $f(P)$ to end the initialisation process.

Parent chromosomes are selected randomly from the initial population of size P_0 according to the probability $P_{selection}$. Pairs of selected parent chromosomes are mated through crossover at the rate of (100%) to create new solutions (chromosome) called offspring. This process interchanges bits of genes in each pair of parent chromosomes at certain crossover (cut) points determined by random integers generated in the interval $[1, C]$. A new set of chromosomes (offspring) forming a population of size P_1 is generated as an addition to the existing population P_0.

The mutation process takes the population of size P_1 generated by crossover and randomly mutates some of the chromosomes at the rate R_m. This is done by first generating random numbers to correspond with each position of a bit of a gene in the population of size P_1. A bit of a gene is selected for mutation if its random number is less than the rate of mutation R_m. The mutation process replaces a 0 with a 1 and vice versa. A new set of solutions (chromosomes) forming the population of size P_2 is migrated at a rate of R_g to maintain variability in the population. The fitness values SSE^{-1} and probability of selection ($P(selection)$) of members of the two newly generated populations P_1 and P_2 are evaluated.

A new population of size equal to the initial population P_0 is then selected from the combined population $P_{comb} = P_0 \cup P_1 \cup P_2$ by a roulette method. The new population of solutions (chromosomes) is returned as the next generation of the algorithm. Steps 1

and 3 of the process are repeated until a predetermined convergence/termination criterion is met and the best solution $\boldsymbol{\theta} = (\beta, \gamma, \nu)$ in the final population is returned as the best solution of the problem. This solution is then passed on to the Levenberg-Marquardt phase of the algorithm as an initial parameter value $\boldsymbol{\theta} = (\beta, \gamma, \nu)$ for the next stage of the parameter estimation process.

4.2 The Levenberg Marquardt phase of the hybrid method

The LM algorithm combines two minimisation methods, the gradient-descent (GDM) and the Gaussian-Newton (GNM) methods. The GDM reduces the SSE by updating the parameters in the steepest descent direction whilst the GNM reduces the SSE iteratively by assuming that the least squares function is locally quadratic and finding the minimum of the quadratic, to solve a nonlinear least squares problem of the form

$$\min_{\boldsymbol{\theta} \in \mathbb{R}^3} L(\boldsymbol{\theta}), \qquad \boldsymbol{\theta} = (\beta, \gamma, \nu) \tag{4.3}$$

where $L(\boldsymbol{\theta})$ can be expressed in quadratic form as

$$\begin{aligned} L(\boldsymbol{\theta}) &= \sum_{i=1}^{n} (Y_i - h(t_i, \boldsymbol{\theta}))^2 \\ &= (Y - h(\boldsymbol{\theta}))^T (Y - h(\boldsymbol{\theta})) \\ &= Y^T Y - 2Y^T h(\boldsymbol{\theta}) + h(\boldsymbol{\theta})^T h(\boldsymbol{\theta}), \end{aligned} \tag{4.4}$$

$Y = (Y_1, Y_2, ..., Y_n)^T$ and $h(\boldsymbol{\theta}) = (h(t_1, \boldsymbol{\theta}), h(t_2, \boldsymbol{\theta}), ..., h(t_n, \boldsymbol{\theta}))^T$ [133, 134, 135, 136, 137].

The LM algorithm minimises Equation (4.4) iteratively starting from an initial guess of the parameter vector $\boldsymbol{\theta} = (\beta, \gamma, \nu)$. In each iteration step, $\boldsymbol{\theta}$ is replaced by a new estimate $\boldsymbol{\theta} + \boldsymbol{\delta}$. In order to determine the step vector $\boldsymbol{\delta}$ the cumulative incidence function $h(\boldsymbol{\theta})$ is linearised about $\boldsymbol{\theta}$ as

$$h(\boldsymbol{\theta} + \boldsymbol{\delta}) \approx h(\boldsymbol{\theta}) + J_{LM} \boldsymbol{\delta}$$

where J_{LM} is the Jacobian matrix of h defined by

$$J_{LM} = \frac{\partial h(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}$$

which represents the local sensitivity of the function $h(\boldsymbol{\theta})$ to variation in the parameter $\boldsymbol{\theta}$. Using the linearisation of $h(\boldsymbol{\theta})$, the sum of squares function L can be approximated about $\boldsymbol{\theta}$ as

$$L(\boldsymbol{\theta}+\boldsymbol{\delta}) \approx Y^T Y + h^T(\boldsymbol{\theta})h(\boldsymbol{\theta}) - 2Y^T h(\boldsymbol{\theta}) - 2(Y-h(\boldsymbol{\theta}))^T J_{LM}\boldsymbol{\delta} + \boldsymbol{\delta}^T J_{LM}^T J_{LM}\boldsymbol{\delta} \quad (4.5)$$

[133, 136, 137, 138]. Taking the derivative of L with respect to $\boldsymbol{\delta}$ and setting the result to zero results into the GNM

$$\frac{d}{d\boldsymbol{\delta}} L(\boldsymbol{\theta}+\boldsymbol{\delta}) = -2J_{LM}^T[Y - h(\boldsymbol{\theta}) - J_{LM}\boldsymbol{\delta}] = 0$$

so that

$$(J_{LM}^T J_{LM})\boldsymbol{\delta} = J_{LM}^T[Y - h(\boldsymbol{\theta})]. \quad (4.6)$$

The system of equations (4.6) when solved yields the step vector

$$\boldsymbol{\delta} = (J_{LM}^T J_{LM})^{-1} J_{LM}^T (Y - h(\boldsymbol{\theta})) \quad (4.7)$$

which specifies the length of the step that moves the parameter estimate $\boldsymbol{\theta}$ in the direction of greatest descent [134, 137, 139]. A damped version of equation (4.6)

$$(J_{LM}^T J_{LM} + \sigma I)\boldsymbol{\delta} = J_{LM}^T[Y - h(\boldsymbol{\theta})] \quad (4.8)$$

is the Levenberg algorithm [134, 139], where I is the identity matrix and σ is a non-negative damping factor.

The damping term is adjusted at each iteration to ensure a reduction in the SSE given by L. If the value of L has increased due to an update, the step is retracted (weights reset to the previous values) and σ is increased by a factor of ten. If the value of L has decreased as a result of an update however, the step is accepted (weights kept at their new values) and σ is decreased by a factor of ten.

With small values of σ, the step is close to the exact quadratic step which approximates the Gaussian-Newton update in Equation 4.7, whilst the matrix $(J_{LM}^T J_{LM} + \sigma I)$ will be nearly diagonal if σ is set to large values and so the step will choose the gradient descent update $\boldsymbol{\delta}$ approximately in the steepest descent direction $J_{LM}^T(Y - h(\boldsymbol{\theta}))$ [134, 137, 138]. The damping process also improves the condition of the Hessian matrix $J_{LM}^T J_{LM}$ (curvature matrix), by reducing the ratio of the largest eigenvalue to the smallest eigenvalue, thereby stabilising the process through regions of the parameter space where the Jacobian is rank deficient and so the Hessian matrix is singular [140].

Iteration stops when one of the following is achieved:

- The length of the calculated step $\boldsymbol{\delta}$ falls below predefined limits.
- The reduction of sum of squares from $\boldsymbol{\theta}$ to the latest parameter vector $\boldsymbol{\theta} + \boldsymbol{\delta}$ falls below predefined limits.
- The magnitude of the gradient $J_{LM}^T(Y - h(\boldsymbol{\theta}))$ falls below predefined limits.
- A maximum number of iterations is completed.

The last parameter vector $\boldsymbol{\theta} = (\beta, \gamma, \nu)$ is selected as the solution [133, 134].

The Levenberg algorithm however is limited in the sense that if the damping factor σ is large, the inverse of the matrix $(J_{LM}^T J_{LM} + \sigma I)$ is not used at all. The Levenberg algorithm in Equation (4.8) is thus modified into

$$(J_{LM}^T J_{LM} + \sigma \text{diag}(J_{LM}^T J_{LM}))\boldsymbol{\delta} = J_{LM}^T[Y - h(\boldsymbol{\theta})] \tag{4.9}$$

which is the Levenberg-Marquardt (LM) algorithm, where the identity matrix I is replaced with the diagonal matrix made up of the diagonal elements of $(J_{LM}^T J_{LM})$. By this modification, each component of the gradient is scaled according to the curvature of the slope [133, 136, 137, 139]. The LM algorithm is therefore more reliable than the Levenberg algorithm in obtaining appropriate solutions to nonlinear inverse problems. Furthermore, in contrast to the Gauss-Newton search direction, the LM search direction mainly has components in the direction of eigenvectors corresponding to the largest eigenvalues of the Hessian $(J_{LM}^T J_{LM})$ [137]. The LM, however, is a local gradient-based search method which does not include constraints. Hence the LM was modified to account for the nonnegativity constraint, $\boldsymbol{\theta} = (\beta, \gamma, \nu) \geq \mathbf{0}$, of Equation (4.1).

4.2.1 Nonnegativity modification to the LM

The standard LM algorithm determines the solution to Equation 4.1 without the nonnegativity constraint on $\boldsymbol{\theta} = (\beta, \gamma, \nu) \geq \mathbf{0}$, which is critical to this study. To address this limitation, the LM was modified to impose a nonnegativity constraint on the parameter estimates of $\boldsymbol{\theta}$. There are two main cases that are considered in the modification process. Given that $\boldsymbol{\theta}_i = (\beta_i, \gamma_i, \nu_i)$ and $\boldsymbol{\delta}_i = (\delta_i^{(1)}, \delta_i^{(2)}, \delta_i^{(3)})$, $i = 1, 2, 3, ...$ are the current solution and step respectively, let $\boldsymbol{\theta}_{i+1} = \boldsymbol{\theta}_i + \boldsymbol{\delta}_i$ be an update of $\boldsymbol{\theta}_i$ by a step of size $\boldsymbol{\delta}_i$ after the i^{th} iteration. Furthermore, let $\mathbf{U} = \{\boldsymbol{\theta} | \boldsymbol{\theta} \geq \mathbf{0}\}$ be the domain of interest such that its

compliment is $\mathbf{U}' = \{\boldsymbol{\theta} | \boldsymbol{\theta} \not\geq \mathbf{0}\}$ and its boundary is $\partial\mathbf{U} = \{\boldsymbol{\theta} : \theta_1 \times \theta_2 \times \theta_3 = 0\}$, then two modifications are made.

1. When the current solution is located on the boundary of the solution domain, $\boldsymbol{\theta}_i \in \partial\mathbf{U}$, and the current step $\boldsymbol{\delta}_i$ of the algorithm in Equation 4.9 places the new solution outside the solution domain, $\boldsymbol{\theta}_{i+1} \in \mathbf{U}'$, then the solution $\boldsymbol{\theta}_{i+1}$ is projected back onto the boundary $\partial\mathbf{U}$ by setting $\boldsymbol{\delta}_i = \boldsymbol{\delta}_i^*$, where $\boldsymbol{\delta}_i^* = \text{proj}_{\partial\mathbf{U}}\boldsymbol{\delta}$, in order for the new solution $\boldsymbol{\theta}_i + \boldsymbol{\delta}_i$ to remains inside the solution domain (see Figure 4.2).

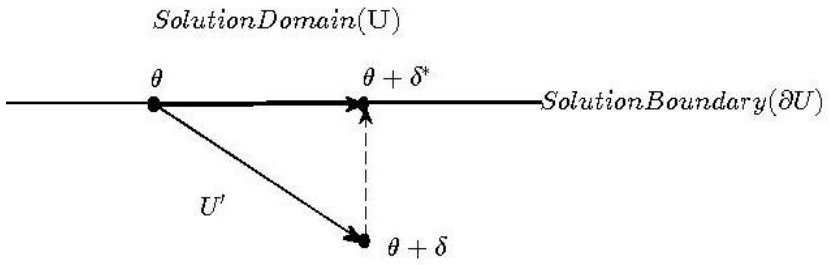


Figure 4.2: Diagrammatic illustration of projecting back solution onto the boundary of solution domain

2. When the current solution lies in the interior of the solution domain $\boldsymbol{\theta}_i \in \mathbf{U} \backslash \partial\mathbf{U}$, and the current step $\boldsymbol{\delta}_i$ of the algorithm in Equation 4.9 places the new solution outside the solution domain, $\boldsymbol{\theta}_{i+1} \in \mathbf{U}'$, then the current step $\boldsymbol{\delta}_i$ is rescaled back onto the boundary $\partial\mathbf{U}$ by a factor $\boldsymbol{\delta}_i^{**} = \min(t_{\delta i^{(1)}}, t_{\delta i^{(2)}}, t_{\delta i^{(3)}})\boldsymbol{\delta}_i$ where $t_{\delta i} = -\theta_i/\delta_i$ and $i = 1, 2, 3, ...$ so that the search direction is retained and the solution $(\boldsymbol{\theta_i} + \boldsymbol{\delta_i^{**}})$ remains in the solution domain (Figure 4.3).

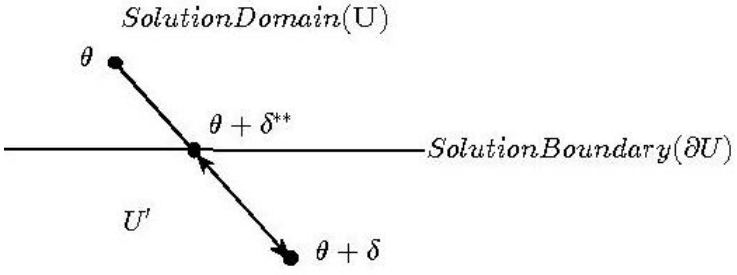


Figure 4.3: Diagrammatic illustration of rescaling back solution onto the boundary of solution domain.

4.2.2 Summary

This chapter discussed a hybrid optimisation method applied to the incidence data to estimate the parameters vector $\boldsymbol{\theta} = (\beta, \gamma, \nu)$ of the model in Equation 3.6. The hybrid method consists of a GA and a modified LM algorithm. The GA being a randomised global search method was applied first to identify solutions from the solution space of the model in Equation 3.6, solutions which are hoped to be close to optimal. The modified LM algorithm was applied after the GA to refine the solution randomly generated by the GA. The LM algorithm was modified to impose a nonnegativity constraint which is critical to this study but is absent in the standard LM algorithm. The GA as a randomised search process might not find the most optimal solution to the defined problem and so it may be difficult to have a good solution that reflects what the algorithm is expected to achieve. The nonnegativity restriction included in the LM algorithm may also impact the accuracy of refining the solution generated by the GA. However, the impact of these limitations are minimised by the combined GA and LM algorithm complementing each other although the computational cost may be high.

Chapter 5

Application of the $SEIR$ model to hepatitis B data of Ghana

5.1 Introduction

The $SEIR$ model which incorporates latent period and vertical transmission was applied to study the transmission and spread of hepatitis B in Ghana. In the study, hepatitis B incidence data obtained from the Regional Health Informant Units (RHIU) and Centre for Health Information Management (CHIM) of the Ghana Health Service (GHS) and demographic data from the Ghana Statistical Service (GSS) were used.

In this chapter, the descriptive statistics of the national data are presented showing the time series and cumulative incidence plots of the data to give an overall idea of the structure of the data. The process of estimating the model parameters applying the methods described in Chapter 4 is presented. For the estimated parameters, the epidemiological threshold parameter R_0 and its corresponding herd immunity threshold value H are computed and used to predict the state of hepatitis B in Ghana and the estimated percentage of the population needed to be immune to control the disease. Discussion of the behaviour of the dynamical system of the model, with respect to the disease-free and the endemic equilibrium states, is aided by plots of the predictions of the proportions of the state variables s, e and i and phase portraits of the dynamical system of the model. Sensitivity of the model stability to the key parameters and their impact on the epidemiological threshold parameter R_0 is discussed.

5.2 National data description

The main data for the study consist of reported monthly incidence cases of hepatitis B, categorised into cases of persons aged less than 5 years that are assumed to be vertically transmitted and those aged 5 years and above that come from horizontal routes of transmission. These age brackets were based on existing categorisation as provided by the data management systems of GHS and the data were available from 2008 to 2014. The data for the period 2008 to 2014 were aggregated and deidentified for the ten regions of Ghana. Summary statistics of the data are displayed in Table 5.1.

Table 5.1: Summary of monthly hepatitis B incidence data collected during $2008 - 2014$.

	Monthly incidence				Standard	Total
Region	Min.	Max.	Mean	Median	deviation	incidence
Ghana	372	$2,789$	$1,368.18$	$1,371$	630.54	$114,927$
Vertical Transmission (Incidence aged< 5)	28	323	103.93	83	68.51	$8,730$
All other routes (Incidence aged≥ 5)	341	$2,611$	$1,264.25$	$1,288.5$	579.6	$106,197$

A total of $114,927$ hepatitis B incidence cases consisting of $8,730$ cases assumed to be vertically transmitted and $106,197$ cases from horizontal transmission, were recorded for the study period $2008 - 2014$. The data range from 372 cases a month to $2,789$ cases a month with a mean monthly value of $1,368.18$ and standard deviation of 630.54. The time series plot of the incidence data displayed in Figure 5.1 shows a fluctuating but increasing trend over the stated period $2008 - 2014$. The corresponding cumulative incidence plot of the data displayed in Figure 5.2 also shows an increasing rate of monthly incidence numbers.

Inherent challenges associated with capturing and compiling hepatitis B data in poorly-resourced countries globally often leads to underestimation and under-reporting of the true cases and limits utility of such case reporting data [50]. Ghana is not an exception to these challenges in data compilation due to the inefficient tools used by the health systems in disease surveillance as cited in Section 1.4 of this thesis. The Ghana Health Service in its annual report of 2014 indicated that $7,581$ out of $51,052$ suspected viral hepatitis cases were laboratory confirmed [59]. This observation translates into approximately 1 in every

7 persons reporting an incidence of viral infection to a designated health facility to be captured into an official database. In order to address these limitations in data collection and make meaningful conclusions, the data used in this estimation process were scaled by a factor of 7.

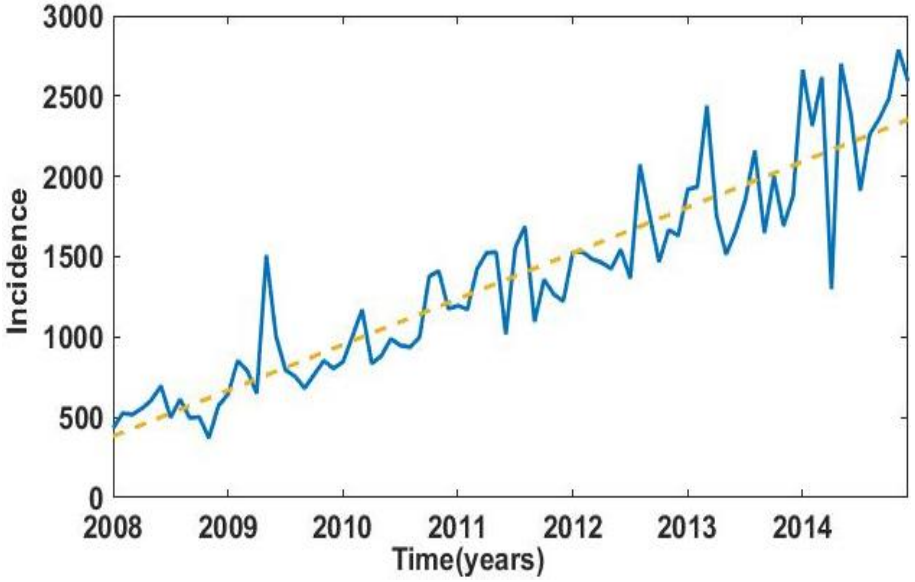


Figure 5.1: Time series plot of hepatitis B incidence data from 2008 to 2014.

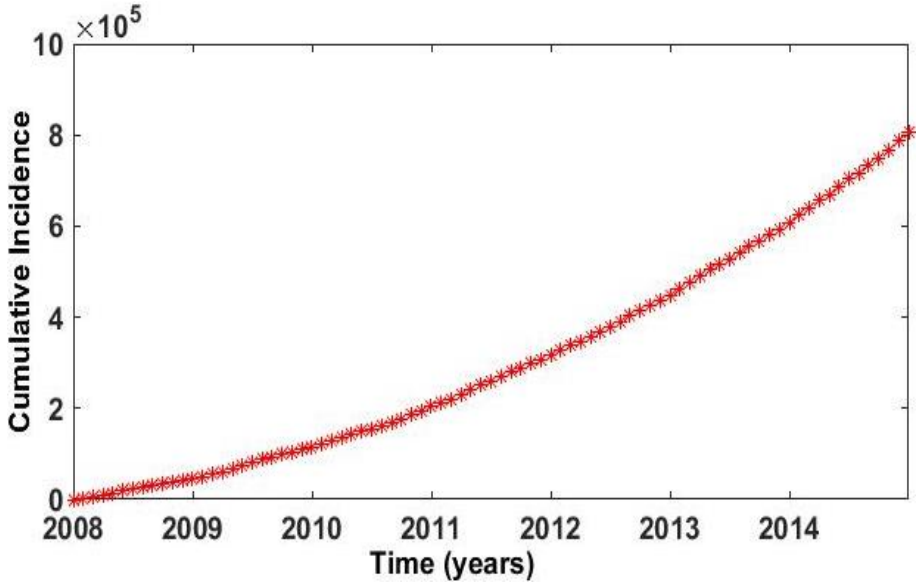


Figure 5.2: Cumulative incidence plot of hepatitis B incidence data from 2008 to 2014.

In addition to the hepatitis B incidence data, demographic parameter constants of projected total population $N = 27,075,827$ (2014), birth rate $\lambda = 24.9$ per $1,000$ population and death rate $\mu = 6.6$ per $1,000$ population were obtained from the Ghana Statistical Service (GSS) [141]. Vertical transmission rate which represents the number of newborns per $1,000$ population who present with hepatitis B was estimated by

$$\alpha = \frac{\text{incidence(aged} < 5)}{\text{total} \quad \text{incidence}} \times \lambda = 0.076\lambda,$$

where incidence age less than 5 represents the number of incidence cases via vertical transmission whilst total incidence from data, (incidence ($aged < 5$) + incidence ($aged \geq 5$)) corresponds to total infection ($I + E$) in the model.

5.3 Parameter estimation for national hepatitis B data

The initial state (s_0, e_0, i_0) of (s, e, i) for the estimation process was not known and needed to be estimated. Preliminary sensitivity analysis performed showed that varying the initial condition (s_0, e_0, i_0) in the model produces varying parameter estimates which impacts on model predictions. The initial condition was therefore estimated by generating combinations of (s_0, e_0, i_0) from ranges of values of $s_0 \in [0.4, 0.8]$, $e_0 \in [0.1, 0.5]$ and $i_0 \in [0.005, 0.045]$ increasing in steps of 0.05, 0.05 and 0.005 respectively, and applied to the nonlinear least squares method discussed in Chapter 4 to fit the model in Equation 3.6 to the observed cumulative hepatitis B incidence data. The choice of the intervals for the initial values of s_0, e_0 and i_0 was based on the values obtained from the preliminary sensitivity analysis of the parameter estimation process, assuming that not less than 40% of population were susceptible at the start of the study when prevalence was estimated between $10 - 15\%$.

In each fitting, the hybrid method was used to identify an optimal set of parameters (β, γ, ν) yielding a least-squares error between the resulting model predictions and the observed data. For each combination of the initial state variables (s_0, e_0, i_0), this optimisation process was run 20 times to increase the likelihood of approximating the true optimum set of parameters (β, γ, ν) since the GA is a random search method. The estimated initial susceptible, exposed and infectious proportions obtained by the fitting process were 0.55, 0.40 and 0.04 respectively.

Using the methodology in Chapter 4, the parameters estimated for the model are $\beta = 0.0480$, $\gamma = 0.1254$ and $\nu = 0$. The mean latent and infectious periods were calcu-

lated as 6.7 months and 40.2 months respectively. A birth rate of $\lambda = 24.9$ per $1,000$ population and vertical transmission rate $\alpha = 0.076\lambda$ per $1,000$ population were estimated from demographic and incidence data discussed in Section 5.2. The epidemiological threshold parameter was calculated as $R_0 = 1.6854$ and so the endemic equilibrium $Q^* = (0.5741, 0.0706, 0.3553)$ was found to be asymptotically stable. This means the spread of hepatitis B in the population is increasing with time. The herd immunity threshold value was calculated as $H = 0.4067$ which means that approximately 41% of the population is required to be immune in order to keep the disease under control. Figure 5.3 shows a plot of the model fitted to the cumulative hepatitis B incidence data from 2008 to 2014.

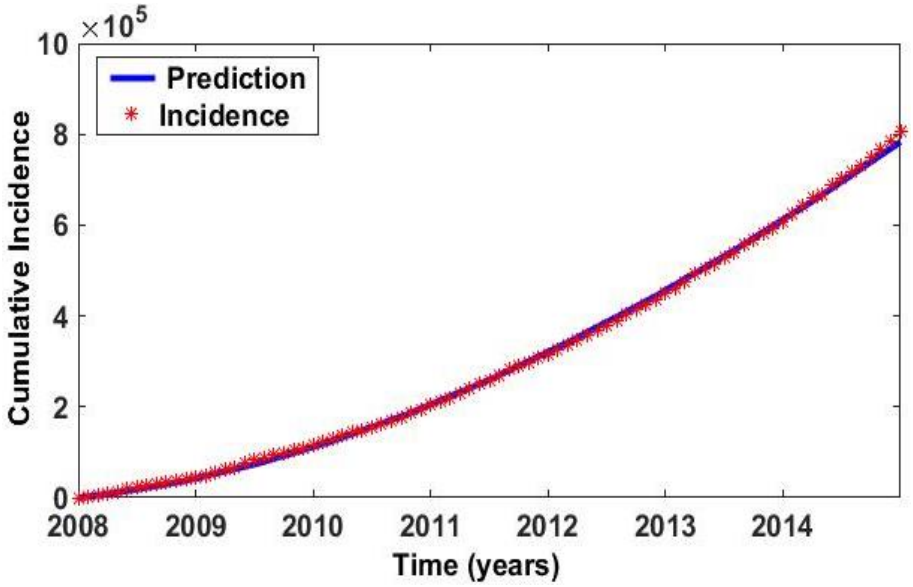


Figure 5.3: Model fit to cumulative hepatitis B incidence data.

In validating the estimation process for the national parameters of (β, γ, ν), the model was fitted to the first 5 years of cumulative incidence data, based on which prediction of the last 2 years of study period was evaluated. The root-mean-square error between the the data and the model predictions for the last was calculated as 1.0904×10^4. Figure 5.4 displays the fitted plot where the portion marked red represents the cumulative incidence for the first 5 years whilst the portion marked green is for the predicted cumulative incidence for the last 2 years of study period.

The model predictions of the state variables s, e and i over a period of 36 months, that is 3 years, based on their estimated values for the study period of 84 months or 7 years is

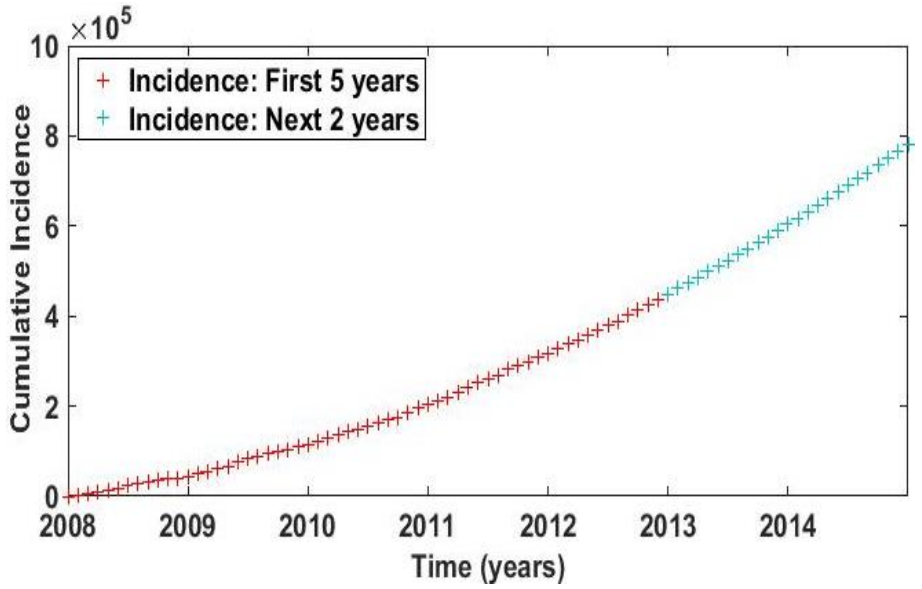


Figure 5.4: Model validation of estimation process: Fit for the first 5 years (red) used in predicting the last 2 years (green).

displayed in Figure 5.5.

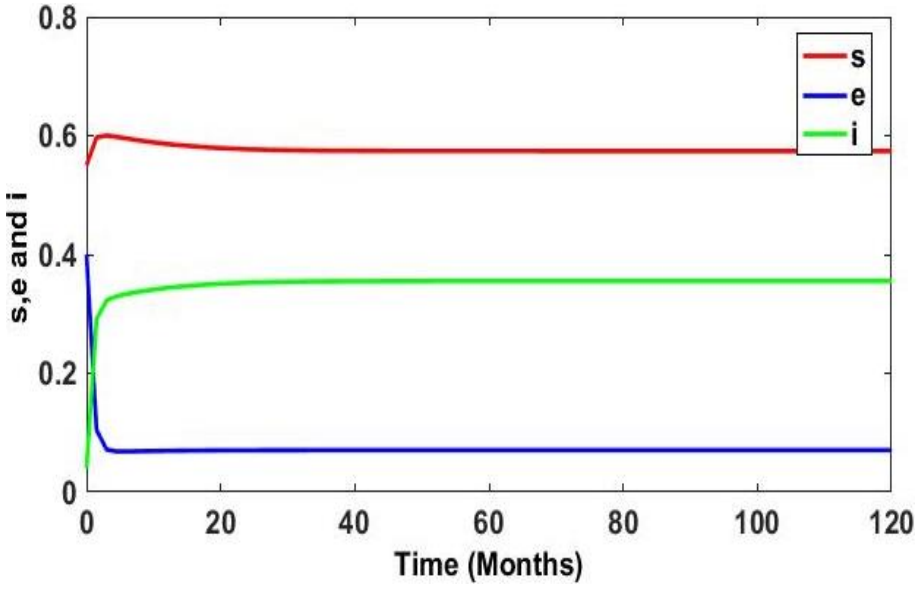


Figure 5.5: Disease curves of s, e and i for the study period of 84 months and the next 36 months of model predictions.

Figure 5.5 displays the path traced by the state variables s, e and i of the model over a total of 120 months or 10 years, which consists of the first 84 months (7 years) of estimation based on the incidence data and the next 36 months (3 years) of prediction. Starting from the initial state $(s_0, e_0, i_0) = (0.55, 0.4, 0.04)$, the exposed proportion e declines whilst the infectious i and susceptible s proportions increase within about 7 months of latent period from the start of the study. The sharp decrease in the exposed proportion is influenced by the sharp increase in the infectious proportion, which causes the susceptible proportion increase during the latent period. This describes the stage immediately after infection, when rapid viral replication takes place, leading to an individual becoming infectious as prescribed in the dynamics of the transmission of hepatitis B. The susceptible proportion peaks thereafter and begins to decrease gently whilst the infectious proportion continues to increase until the end of the infectious period in about month 40 when the three variables stabilise at the endemic state $Q^*(s^*, e^*, i^*) = (0.5741, 0.0706, 0.3553)$. From Figure 5.5, the disease is predicted to remain persistent in the population with time unless an intervention is applied to control it.

5.4 Sensitivity of model stability to key parameters

Let each of the estimated parameters $(\beta, \gamma, \nu) = (0.0480, 0.1254, 0)$ and the parameter constants $\lambda = 0.0249$ and $\alpha = 0.0019$ of the model in Equation 3.6 be designated as the baseline values denoted by $\tilde{\theta}_{baseline}$, and let $\tilde{\theta}_{threshold}$ denote the corresponding threshold values. Note that the threshold parameters were calculated from Equations 3.21 and 3.22 using the estimated parameters of the model. For each of the estimated parameters, $\tilde{\theta}_{baseline}$, the percentage difference from the corresponding threshold value $\tilde{\theta}_{threshold}$ was computed as displayed in Table 5.2 by the formula

$$\%\triangle\tilde{\theta} = \frac{\triangle\tilde{\theta}}{\tilde{\theta}_{baseline}} \times 100, \qquad \text{where} \quad \triangle\tilde{\theta} = \tilde{\theta}_{threshold} - \tilde{\theta}_{baseline},$$

to examine the quantum of change in each of the model parameters needed to shift model stability from endemic state to disease-free state. Note that " $-$ " in percent change means a decrease whilst " $+$ " means increase.

From Table 5.2, the contact rate β, latent rate γ and vertical transmission rate α need decreases of about 42.59%, 81.74% and 901.91% respectively to shift the endemic state Q^* of the model from stability to instability. Conversely, the birth rate λ needs an increase of 55.08% to change the endemic state from stability to instability whilst the required

percentage increase in the recovery rate ν cannot be quantified. In terms of percentage change from the baseline values, the model stability is more sensitive to changes in the values of β, γ and λ compared to ν and α, but β, γ and α require decreases whilst ν and λ require increases. The negative threshold value of $\alpha = -0.0152$ cannot be achieved since $\alpha \geq 0$, that is the endemic state would be stable even with $\alpha = 0$.

Table 5.2: Percentage differences in baseline parameters.

Key model parameter	Threshold value ($\tilde{\theta}_{threshold}$)	Baseline value ($\tilde{\theta}_{baseline}$)	Percentage change in Baseline value
β	0.0276	0.0480	-42.59
γ	0.0229	0.1254	-81.74
ν	0.0173	0	∞
λ	0.0386	0.0249	55.08
α	-0.0152	0.0019	-901.91

Note: "$-$" in percentage change means decrease and "$+$" otherwise.

From Table 5.2 the contact rate β, latent rate γ and vertical transmission rate α need decreases of about 42.59%, 81.74% and 901.91% respectively to shift the endemic state Q^* of the model from stability to instability. Conversely, the birth rate λ needs an increase of 55.08% to change the endemic state from stability to instability whilst the required percentage increase in the recovery rate ν cannot be quantified. In terms of percentage change from the baseline values, the model stability is more sensitive to changes in the values of β, γ and λ compared to ν and α, but β, γ and α require decreases whilst ν and λ require increases. The negative threshold value of $\alpha = -0.0152$ cannot be achieved since $\alpha \geq 0$, that is, the endemic state would be stable even with $\alpha = 0$.

Table 5.3: Rates of change in $Q^* = (s^*, e^*, i^*)$ with respect to β, γ, ν, λ and α.

Key model parameters	Rates s^*	e^*	i^*	Magnitude of change (Euclidean Norms)
β	-11.95	1.98	9.97	15.69
γ	-0.76	-0.34	1.10	1.38
ν	24.64	-4.08	-34.82	42.86
λ	28.77	-2.40	-26.37	39.10
α	-24.95	4.13	20.82	32.76

Note: " $-$ " means decrease in rates and " $+$ " otherwise.

The partial derivatives of the endemic proportion variables $Q^* = (s^*, e^*, i^*)$ with respect to the model parameters, β, γ, ν, α and λ, calculated at the baseline values and the corresponding magnitudes of change (Euclidean norms) as displayed in Table 5.3, were used to examine how rapidly the equilibrium state changes to impact model stability as the parameters change. In this instance, the signs " - " and " + " mean a decrease and an increase respectively. The following were the results:

- Unit increases in β, γ and α cause a decrease in the susceptible population and an increase in the infectious population and tend to shift equilibrium towards the endemic state Q^*. The magnitudes of change in the endemic state Q^* per unit changes in β, γ and α are 15.69, 1.38 and 32.76 respectively. A unit increase in α has the biggest impact on the shift in equilibrium towards the endemic state Q^* followed by β and then γ.

- Conversely, unit increases in ν and λ cause an increase in the susceptible population and a decline in the infectious population and tend to shift equilibrium towards disease-free state Q_0 more rapidly. The magnitudes 42.86 and 39.10 of change in Q^* per unit changes in ν and λ respectively indicate that an increase in ν shifts equilibrium towards the disease-free state Q_0 more rapidly than λ.

5.5 Sensitivity analysis of the epidemiological threshold parameter R_0

The impact of the model parameters α, β, γ, ν and λ on the epidemiological threshold parameter R_0 was examined. This was to investigate the sensitivity of the threshold parameter R_0 to each of the model parameters. The baseline parameters $\beta = 0.0480$,

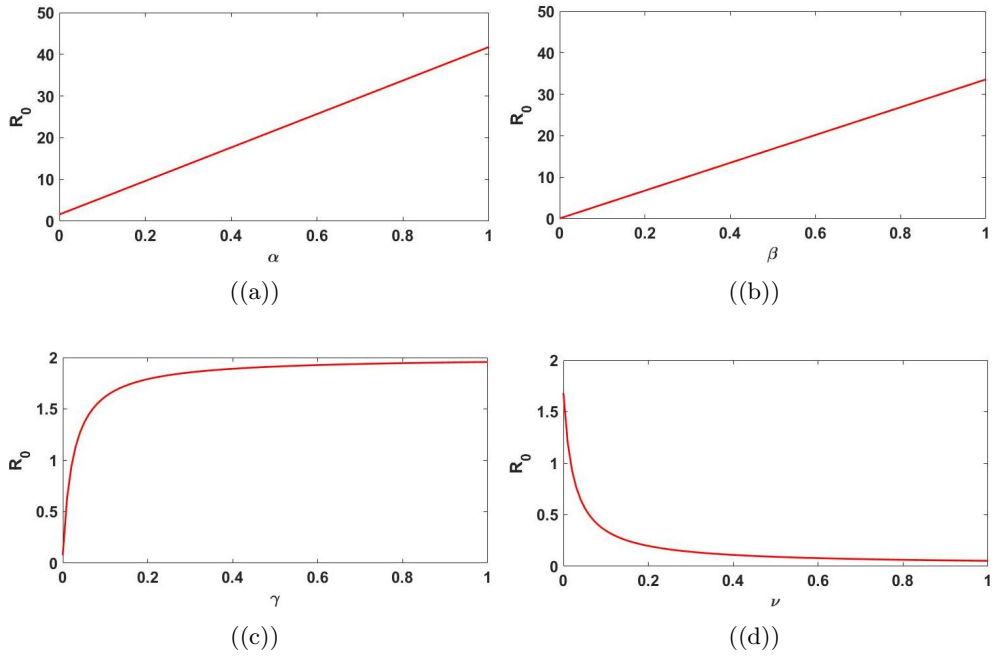


Figure 5.6: Sensitivity of R_0 to model parameters: (a) R_0 versus α; (b) R_0 versus β; (c) R_0 versus γ; (d) R_0 versus ν.

$\gamma = 0.1254$, $\nu = 0$, $\lambda = 0.0249$ and $\alpha = 0.0019$ were held fixed in Equation 3.13, whilst each of the model parameters was varied in turn over the interval $[0, 1]$ to produce a corresponding set of values for R_0. Figure 5.6 displays the plots of each of the parameters against R_0.

From Figures 5.6(a) and 5.6(b), R_0 varies linearly as α and β with positive slopes of 30 and 40 respectively. The slope of 40 in the variation of R_0 with respect to α compared to the slope of 30 in the variation of R_0 with respect to β, displayed in Figures 5.6(a) and 5.6(b) respectively, indicate that α has a larger impact on R_0 than β for a given magnitude of change. This means R_0 is relatively more sensitive to α than β. Hence any intervention targeted at reducing the rate α of vertical transmission would have much more impact in reducing the epidemiological threshold parameter R_0, that is used to determine how widespread hepatitis B is in the population, relative to the rate β of transmission through all other routes.

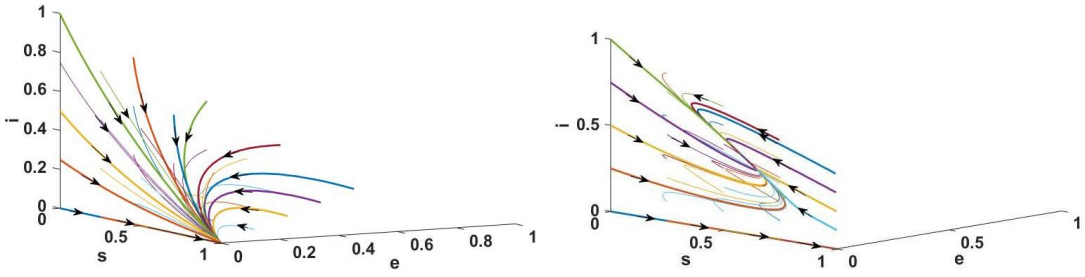
In Figures 5.6(c) and 5.6(d), R_0's relation to γ and ν is hyperbolic. As γ increases R_0 increases sharply for $\gamma \in [0, 0.2]$ until it begins to level off close to $R_0 = 2$. As ν increases

however, R_0 decreases steeply for $\nu \in [0, 0.2]$ and begins to level off close to $R_0 = 0$. Although R_0 increases with respect to γ, the overall impact of γ on R_0 compared to that of α and β, discussed in the last paragraph and illustrated in Figures 5.6(a) and 5.6(b) respectively, is less due to its tendency to stabilise the value of R_0 with time. Invariably, the rate of change of R_0 with respect to γ reduces to approximately zero when R_0 is stabilised at $R_0 \approx 2$. The effect of the latent rate γ on the epidemiological threshold parameter R_0 relative to the other parameters of the model is significant, although the impact is seen to be greater only if $\gamma < 0.2$. This indicates that the latent rate γ and so the latent period is important in modelling hepatitis B in a population. The decrease in the epidemiological threshold parameter R_0 with respect to the rate of recovery ν, relative to the other parameters of the model, surely reflects the natural dynamics of any disease including hepatitis B. In fact the key intervention to control an epidemic of a disease in a population requires the increase of the rate of recovery ν that tend to populate the immune class R and deplete the infectious class I of the model.

5.6 Phase portraits

Phase portraits of the $SEIR$ model in Equation 3.6 were produced using the estimated parameters to examine the flow of the dynamical system in relation to the disease-free and endemic equilibrium states. Figure 5.7(a) displays a phase portrait for the threshold parameters $\beta^* = 0.0276$, $\gamma^* = 0.0229$ and $\nu^* = 0.0173$ of the model indicated in Table 5.2. Note that the threshold parameters were calculated from Equations 3.13 and 3.22 using the estimated parameters of the model. Figure 5.7(b) displays a phase portrait for the estimated parameters $\beta = 0.0480$, $\gamma = 0.1254$ and $\nu = 0$ of the model. The dynamics of the model in the neighbourhood of the two equilibrium points were examined using the two plots, with the initial state of $(s_0, e_0, i_0) \in \Sigma = \{(s, e, i) \in \mathbb{R}^3_+ | 0 \leq s + e + i \leq 1\}$.

Figure 5.7(a) shows that if the model parameters are at the threshold, all solutions (s, e, i) starting from the interior of the closed positive set Σ are attracted to the disease-free equilibrium point $Q_0 = (1, 0, 0)$. Figure 5.7(b) however shows that all solutions (s, e, i) starting from within the closed positive set Σ tend to the endemic equilibrium point $Q^*(s^*, e^*, i^*) = (0.5741, 0.0706, 0.3553)$, except those starting on the invariant s-axis that tend to remain on the axis and ultimately approach the disease-free equilibrium point Q_0. It is worth mentioning from in Figure 5.7(b), that even solutions starting sufficiently close to the disease-free equilibrium point Q_0 move away and are attracted to the endemic equilibrium Q^*.



((a)) ((b))

Figure 5.7: Phase portraits of the $SEIR$ model (a) Threshold and below $R_0 \leq 1$ (Disease-free state). (b) Above threshold $R_0 > 1$ (Endemic state).

In the case when $\beta^* \leq 0.0276$, all solutions starting from within the closed positive set Σ approach the disease-free equilibrium state Q_0 and thereby make it stable whilst the endemic state Q^* is infeasible and unstable. In the opposite case where $\beta^* > 0.0276$, all solutions starting from within the closed positive set Σ approach the endemic equilibrium state Q^*, which now is valid and stable whilst the disease-free equilibrium state Q_0 becomes unstable. The parameter value of $\beta^* = 0.0276$ therefore is a threshold of the crossover from stability to instability between the two equilibrium states Q_0 and Q^*. Although this threshold value of $\beta^* = 0.0276$ may be low in terms of the epidemiology of hepatitis B, it reflects the incidence of the disease in the population of Ghana based on the incidence data used in the study. The threshold value of $\beta^* = 0.0276$ describes a point in the modelling process where stability shifts between the disease-free and endemic equilibrium states.

5.7 Discussion

A basic reproduction number of $R_0 = 1.6854$ indicates that the expected proportion of infection caused by a single infective in the population is greater than one and so the transmission and spread of hepatitis B in the population is increasing with time. This result is consistent with reports by WHO, GHS and MOHG of increasing spread of hepatitis B and the associated burden in Ghana and by extension the Sub-Saharan Africa and emphasises the need to control it. A herd immunity threshold value of 0.4067 was calculated, which means that a critical proportion of about 41% of the population is needed to be immune to hepatitis B in order to bring the disease under control. Furthermore, the latent period of $6.7 \approx 7$ months agrees with literature on the incubation period of the HBV which spans between 30 to 180 days or more depending on the viral load of the

infected person.

Stability analysis of the model indicates that the endemic proportion equilibrium of $Q^* = (0.5741, 0.0706, 0.3553)$ is asymptotically stable, which means hepatitis B is at a state where about 57.4% of the population are susceptible, 7.1% are exposed and 35.5% are infectious. The 0% recovery rate indicates that none of the infected persons could clear hepatitis B at the acute stage. Otherwise, it could also be possible that recovery was significantly low as to be rounded zero or could be a numerical artefact in the parameter estimation process. Stability, however, switches between the disease-free Q_0 and endemic Q^* states at a threshold contact rate of $\beta = 0.0276 \approx 0.028$. In essence if the contact rate through effective vaccination was reduced to 0.028, or below, it would provide adequate measure of protection for individuals in the population who are not immune thereby reducing the spread of hepatitis B in the population.

Sensitivity analysis of the model in Equation 3.6 with respect to quantum of change from the baseline parameters indicates that stability is most sensitive to the hepatitis B contact rate β followed by birth rate λ, latent rate γ and vertical transmission rate α whereas that of the recovery rate cannot be quantified. Apart from the birth rate which requires an increase of 55.08%, the contact rate, latent rate and vertical transmission rate need to decrease by 42.59%, 81.74% and 901.91% respectively to shift stability from endemic state to the disease-free state. A higher birth rate is not desirable due to its socioeconomic and cultural implications on a society. However, a greater proportion of the population can be immunised to disrupt chains of infection that would reduce the chances of contact with infectious individuals to keep the disease from spreading. This strategy targets reducing the contact rate β and vertical transmission rate α.

Rates of change of endemic proportion variables $Q^*(s^*, e^*, i^*)$ with respect to model parameters indicate that unit increases in contact rate β, latent rate γ and vertical transmission rate α increase the infectious population and decrease the susceptible population and tend to shift equilibrium to the endemic state Q^*. Sensitivity analysis of the epidemiological threshold parameter R_0 with respect to the model parameters further indicated that R_0 is most sensitive to the rate of change in the vertical transmission rate α. The sensitivity analysis indicated that the rate of vertical transmission α has a linear relationship with the epidemiological threshold parameter R_0 with the greatest positive slope, compared to the rest of the model parameters. Vertical transmission was found to have the most impact of shifting the model to the endemic state, followed by the contact rate and latent

rate. This means that the rate at which newborns are infected with hepatitis B at birth is higher than infection through the other modes of transmission.

Vertical transmission of hepatitis B most likely occurs during birth when there is a break in the maternal-foetal barrier, and so can be reduced if screening and immunisation of women of child-bearing age are effectively conducted to ensure that the HBV is not passed on to the child at birth. Conversely, the rates show that unit increases in birth rate λ and recovery rate ν increase the susceptible population and decrease the infectious population and tend to drive equilibrium towards the disease-free state more rapidly, although control of both of them may not be practically achievable.

5.8 Summary

In summary, the results of the study show that hepatitis B is increasing with time in Ghana and that emphasises the need to control it. This is consistent with reports by WHO, GHS and MOHG, and also agrees with studies of parts of Ghana and Sub-Saharan Africa of the disease burden in those regions. The contact rate, latent rate and vertical transmission rate have been identified as driving the disease spread in the population. Mother-to-child transmission was found to have a larger impact on the spread of hepatitis B in Ghana, compared to other routes of transmission, due to its high impact on stability shift towards endemic state. Policy intervention must therefore target reducing vertical transmission rate although horizontal transmission driven by the disease contact rate should not be neglected.

To control the spread of the disease, an estimated critical proportion (Herd immunity threshold) of about 41% of the population needs to be immune to effectively disrupt chains of infection. This would reduce the number of effective contacts between infectious and susceptible individuals in the population, reduce the spread and hence bring the disease under control. Since there is no known cure for hepatitis B, national policy intervention should aim at nationwide mass screening and immunisation designed to factor in the latent period of the disease, complemented with antiviral treatment of chronic carriage to reduce disease complications and liver damages.

The intervention programmes are recommended to target each member of the population, particularly women of child-bearing age and newborns in order to prevent mother-to-child transmission and eradicate the chronic carriage state of hepatitis B from the population

with time. It is also recommended that these intervention programmes for hepatitis B should be included in the national health insurance scheme (NHIS) of Ghana, which hitherto was not part, to ensure affordability and accessibility to all.

Chapter 6

Application of the $SEIR$ model to regional hepatitis B data in Ghana

6.1 Introduction

Analysis of the incidence and spread of hepatitis B in Ghana as a whole, based on the $SEIR$ model used in Chapter 4 of this work, indicated that the disease persists but did not show the individual regional burden. Ghana is made up of ten administrative regions as displayed in Figure 1.2 which also consist of districts, metropolitans and municipalities that see to the implementation of government policies and programmes. Varying but limited resource allocation to the various regions demands varying strategies at building preventive and control measures suitable to the local disease epidemiological profile. The report in this chapter presents an analysis of the incidence and spread of hepatitis B in terms of its distribution in the ten regions of Ghana, using the $SEIR$ model in Equation 3.6. It is expected that the knowledge about the burden of hepatitis B in the various regions in Ghana would be useful in formulating an informed policy to manage the distribution of health resources, particularly in the implementation of hepatitis B control interventions, to meet the health needs of each region.

In this chapter, the formulated model was applied to the various regional data to analyse the dynamics of the incidence and spread of hepatitis B in order to examine the impact of the disease on each region. This involved estimating the key model parameters for each region, applying the methods outlined in Chapter 4, and using them to calculate the corresponding epidemiological threshold parameters R_0 and their herd immunity threshold values H. These threshold parameters were used to examine the differences in transmission

and spread of hepatitis B within the regions of Ghana thereby showing the trend across the country. A simple correlation analysis was performed to examine the association between the trend of transmission and spread of hepatitis B and poverty inequalities across the country. The incidence and spread of the disease was also analysed with respect to disparities in health resource allocation across the country and the prevalence differentials of hepatitis B between Ghana and its neighbouring countries. A summary of the findings concludes the chapter.

6.2 Regional data description

Recall that the national hepatitis B incidence data of Ghana were formed by aggregating the deidentified regional data. The regional data consist of reported monthly incidence cases of hepatitis B, categorised into cases of persons aged less than 5 years and cases of persons aged 5 years and above, that covers the period from 2008 to 2014. The data were obtained from the Regional Health Informant Units (HIU) and Centre for Health Information Management (CHIM) of the Ghana Health Service (GHS). The data summary is displayed in Table 6.1.

Table 6.1: Summary of regional monthly hepatitis B incidence data collected during 2008 − 2014.

	Monthly incidence				Standard	Total
Region	Minimum	Maximum	Mean	Median	deviation	incidence
Greater Accra	6	745	129.2	98.5	139.34	10,853
Brong Ahafo	10	404	145.06	122.5	81.31	12,185
Upper East	10	586	103.12	69	99.49	8,661
Upper West	24	869	173.32	104	188.36	14,559
Ashanti	21	949	181.29	154.5	137.92	15,228
Eastern	32	428	143.74	128.5	87.81	12,074
Western	28	743	173.39	152	108.99	14,565
Central	22	769	136.95	91.5	146.44	11,504
Northern	29	327	108.25	90.5	55.32	9,093
Volta	8	535	73.87	36.5	101.25	6,205

From Table 6.1 Ashanti region recorded the highest number of 15,228 incidence cases over

the $2008 - 2014$ period, with a mean monthly incidence of 181 cases. Next to Ashanti are Western and Upper West with $14,565$ and $14,559$ cases respectively, both regions recording a mean monthly incidence of approximately 173. The least number of $6,205$ incidence cases was recorded for Volta region with a mean monthly incidence of about 74. Followed closely are Upper East region with $8,661$ incidence cases and monthly mean of 103 and Northern region with $9,093$ cases and monthly mean of 108. The overall monthly minimum of 6 and a maximum of 949 incidence cases were recorded for Greater Accra and Ashanti regions respectively, which show similar variability of monthly incidence cases with standard deviation of 139 for Greater Accra and 138 for Ashanti. The largest monthly incidence variability, measured in terms of standard deviation, of 188 was recorded for Upper West region and the least of 55 was recorded for Northern region.

The time series plots of hepatitis B incidence data for each region are displayed in Figure 6.1. The time series plots generally show an increasing but fluctuating trend although the specific features differ from region to region across the country. There is no regular pattern except for Northern, Western and Brong Ahafo regions where the time plots show a steady increase. In the case of Upper West and Central regions, the time plots show sharp and drastic increase in 2014 after levelling off from 2008. These sharp increases in incidence cases in the Western and Central region may be as a result of increased reporting or increased awareness about HB. The plot for Eastern region shows a steady increase until 2014 when it dipped down sharply whilst those of the remaining regions show gentle and irregular but fluctuating increase over the period $2008 - 2014$.

Due to the effect of inadequacies in data collection and compilation in Ghana as in other poorly-resourced countries [50], the data were scaled in order to minimise these limitations and to make meaningful conclusions. The scaling was done to reflect the assumption made with respect to reporting rates of hepatitis B incidence cases of the regions, given in the Ghana Health Service (GHS) annual reports of 2014 on viral hepatitis as displayed in Table 6.2 [59]. The scale factors were calculated as a ratio of suspected cases of hepatitis B to number of laboratory confirmed cases reported by GHS for each region, except in the case of Northern region which did not have any records and so the national values were applied. These ratios are assumed for lack of better data statistics to represent and reflect the reporting rates of hepatitis B in the regions of Ghana. The calculated values of the scale factors are displayed together with other input parameters for the parameter estimation process later in Table 6.4 of Section 6.3 of this work.

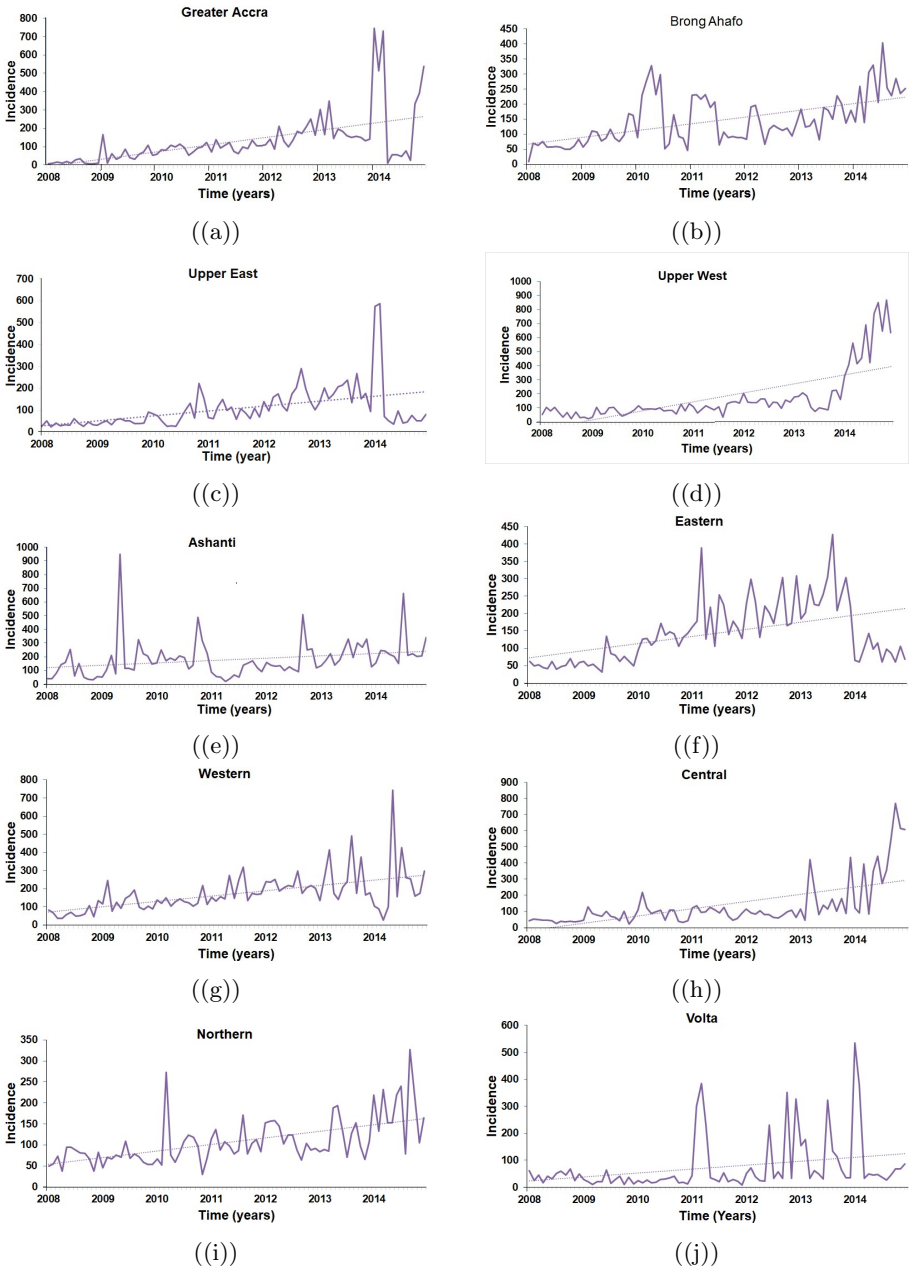


Figure 6.1: Time series plot of hepatitis B incidence data for the regions of Ghana 2008 – 2014.

Table 6.2: Reported viral hepatitis cases and deaths by region, Ghana 2014

Region	Suspected cases	Laboratory Confirmed cases	Deaths	CFR
Greater Accra	14791	878	14	0.1
Brong-Ahafo	2413	1339	47	1.9
Upper East	1583	212	11	0.7
Upper West	8812	1784	17	0.2
Ashanti	6117	698	3	0.0
Eastern	171	52	0	0.0
Western	5199	1062	9	0.2
Central	8003	902	7	0.1
Northern	-	-	-	-
Volta	3963	654	0	0.0
Ghana (Total)	51052	7581	108	0.2

Data source: GHS DHIMS2, 2014; CFR means Crude Fatality Rate

In addition to the incidence data, demographic data consisting of the projected annual regional population from 2008 to 2014 were obtained from the Ghana Statistical Service (GSS). Birth and death rates and poverty headcount by regions were also sourced from GSS' population and housing census and Ghana Living Standards Survey (GLSS6) of 2010. In the survey report, poverty head count was defined as the percentage of the population living below the national poverty line which was fixed at an income of GhC1, 314.00 (GhC - Ghana Cedis). Table 6.3 shows a summary of the poverty head count by region in Ghana.

From Table 6.3, the least poverty headcount of 6.6 by census and 5.6 by GLSS6 were recorded for Greater Accra region whilst the highest of 69.4 and 70.7 by the census and GLSS6 respectively were recorded for the Upper West region. The three highest poverty headcount values of 69.4, 45.9 and 44.2 were recorded for Upper West, Upper East and Northern regions respectively which constitute the three northern regions of Ghana. The four least poverty headcount values of 6.6, 13.6, 19.2 and 19.6 were recorded for Greater Accra, Ashanti, Western and Central regions respectively which are situated in the southern part of the country.

Figure 6.5(c) shows the regional distribution of poverty headcount in Ghana. The map shows high poverty levels in the three northern regions (namely Upper West, Upper East and Northern) and Volta region, but low to middle poverty levels in the southern regions

Table 6.3: Ghana poverty headcount (HC) by region (poverty line = GHC1,314.00).

	Census			GLSS6			
						95% CI	
Region	Poverty headcount	Std. Error	Absolute difference	Poverty headcount	Std. Error	lower limit	Upper limit
Greater Accra	6.6	0.0015	1.0	5.6	0.0151	2.65	8.57
Brong Ahafo	28.6	0.0036	0.7	27.9	0.0215	23.64	32.09
Upper East	45.9	0.0137	1.5	44.4	0.0388	36.8	52.01
Upper West	69.4	0.0102	1.3	70.7	0.0275	65.29	76.07
Ashanti	13.6	0.0035	1.2	14.8	0.0169	11.43	18.07
Eastern	22.0	0.0097	0.3	21.7	0.0242	16.91	26.4
Western	19.2	0.0040	1.7	20.9	0.0252	15.94	25.82
Central	19.6	0.0072	0.8	18.8	0.0223	14.44	23.19
Northern	44.2	0.0062	6.2	50.4	0.0318	44.12	56.59
Volta	33.3	0.0028	0.5	33.8	0.0343	27.12	40.57

Source: Ghana Statistical Service, 2010 Population and Housing Census and GLSS6.

and regions in the middle belt respectively.

6.3 Regional parameters estimation

The initial state variables (s_0, e_0, i_0) of the model in Equation 3.6 were estimated for each region, using a similar method applied to the process of estimating the national parameters of the model in Section 5.3. The method involved generating all combinations of (s_0, e_0, i_0) from ranges of values of $s_0 \in [0.4, 0.8]$, $e_0 \in [0.1, 0.5]$ and $i_0 \in [0.005, 0.045]$ increasing in steps of 0.05, 0.05 and 0.005 respectively, and applying the combined Genetic algorithm (GA) and a Levenberg-Marquardt (LM) algorithm to fit the model to each regional data set. In order to improve the estimation of the parameters (β, γ, ν), the optimisation process was run 20 times for each combination of initial state variables (s_0, e_0, i_0) for each region.

The vertical transmission rate α for each of the regions was calculated by the equation

$$\alpha = \frac{\text{incidence(aged} < 5)}{\text{total} \quad \text{incidence}} \times \lambda,$$

using the various regional data. A summary of the estimated initial state variables (s_0, e_0, i_0) and the calculated values of α and other demographic input parameters for

each region that were used for the regional estimation process are displayed in Table 6.4. The demographic data consisting of regional population and birth rates were obtained from the Ghana Statistical Service.

Table 6.4: Summary of input parameters for estimation

	Population			Initial values			
Region	projections	λ	α	s_0	e_0	i_0	Scale
Greater Accra	$4,416,861$	22.7	0.065788λ	0.55	0.4	0.02	16
Brong Ahafo	$2,547,144$	26.3	0.101436λ	0.5	0.35	0.02	2
Upper East	$1,170,820$	22.7	0.058538λ	0.55	0.4	0.04	7
Upper West	$758,725$	23.1	0.043616λ	0.5	0.45	0.01	5
Ashanti	$5,175,581$	25.7	0.075584λ	0.55	0.15	0.03	9
Eastern	$2,899,417$	25.4	0.074623λ	0.55	0.35	0.015	3
Western	$2,763,926$	26.8	0.074974λ	0.5	0.15	0.02	5
Central	$2,276,168$	26.5	0.081798λ	0.55	0.4	0.04	9
Northern	$2,736,822$	24.0	0.08831λ	0.55	0.15	0.03	7
Volta	$2,330,363$	24.2	0.12087λ	0.55	0.15	0.04	6
Ghana	$27,075,827$	24.9	0.076λ	0.55	0.40	0.04	7

$*\lambda$ is birth rate per $1,000$ population; $*\alpha$ is vertical transmission rate per $1,000$ population.

Using the methodology described in Section 5.3 and the input parameters in Table 6.4, the parameters β, γ and ν of the model in Equation 3.6 were estimated for each region. These estimated parameters were then used to calculate the corresponding epidemiological threshold parameters R_0 and herd immunity threshold values H for the various regions. Table 6.5 displays the values of the estimated parameters β, γ and ν, their epidemiological threshold parameters R_0 and herd immunity threshold values H by region.

From Table 6.5, the maximum value of $R_0 = 3.7212$ and the corresponding maximum value of $H = 0.7312$ were calculated for Upper West region whilst the least values of $R_0 = 1.3669$ and $H = 0.2684$ were calculated for Volta region. The range between the least and the maximum of the threshold values R_0 and H across the regions are 2.3543 and 0.4628 respectively, which represent a percentage difference of about 172% relative to the lowest value in both cases. All the regions except Western region had an estimated recovery rate of $\nu = 0$. A recovery rate of $\nu = 0.0378$ was estimated for Western region. The highest hepatitis B contact rate of $\beta = 0.1308$ was estimated for Western region whilst

the minimum of $\beta = 0.0359$ was estimated for Volta region. Upper West, Upper East and Western regions have high values whilst Volta region has a low value with respect to R_0, H and β most likely because they are all border points with either high or low incidence country. Similarly, the highest latent rate of $\gamma = 0.7698$ was estimated for the Northern region whilst the minimum rate of $\gamma = 0.1255$ was estimated for Volta region.

Table 6.5: Summary of regional parameters estimated

	Estimated parameters				
Region	β	γ	ν	R_0	H
Greater Accra	0.0416	0.2744	0	1.7595	0.4316
Brong Ahafo	0.0475	0.2894	0	1.7572	0.4309
Upper East	0.0602	0.3413	0	2.5456	0.6071
Upper West	0.0899	0.3925	0	3.7212	0.7312
Ashanti	0.0404	0.2672	0	1.5119	0.3386
Eastern	0.0422	0.3083	0	1.6104	0.3790
Western	0.1308	0.1848	0.0378	1.8057	0.4462
Central	0.0603	0.1234	0	1.9580	0.4892
Northern	0.0422	0.7698	0	1.7940	0.4426
Volta	0.0359	0.1255	0	1.3669	0.2684
Ghana	0.0480	0.1254	0	1.6854	0.4067

Plots of the model fitted to the cumulative incidence data were produced for each region and are displayed in Figure 6.2.

6.4 Regional model predictions

The model values of the state proportion variables s, e and i for each of the ten regions were examined over a period of ten years (120 months), which include the first 7 years (84 months) of study period and the next 3 years (36 months) of prediction. Figure 6.3 displays the plots for the model values of s, e and i against time, based on the respective estimated parameters for the ten regions. Starting from the initial state values s_0, e_0 and i_0 presented in Table 6.4 for the various regions, the plots illustrate changes in s, e and i for latent periods varying from 1 to 7 months until after infectious periods varying between 15 to 44 months when the three variables finally stabilise at the respective endemic states values $Q^* = (s^*, e^*, i^*)$ displayed in Table 6.6.

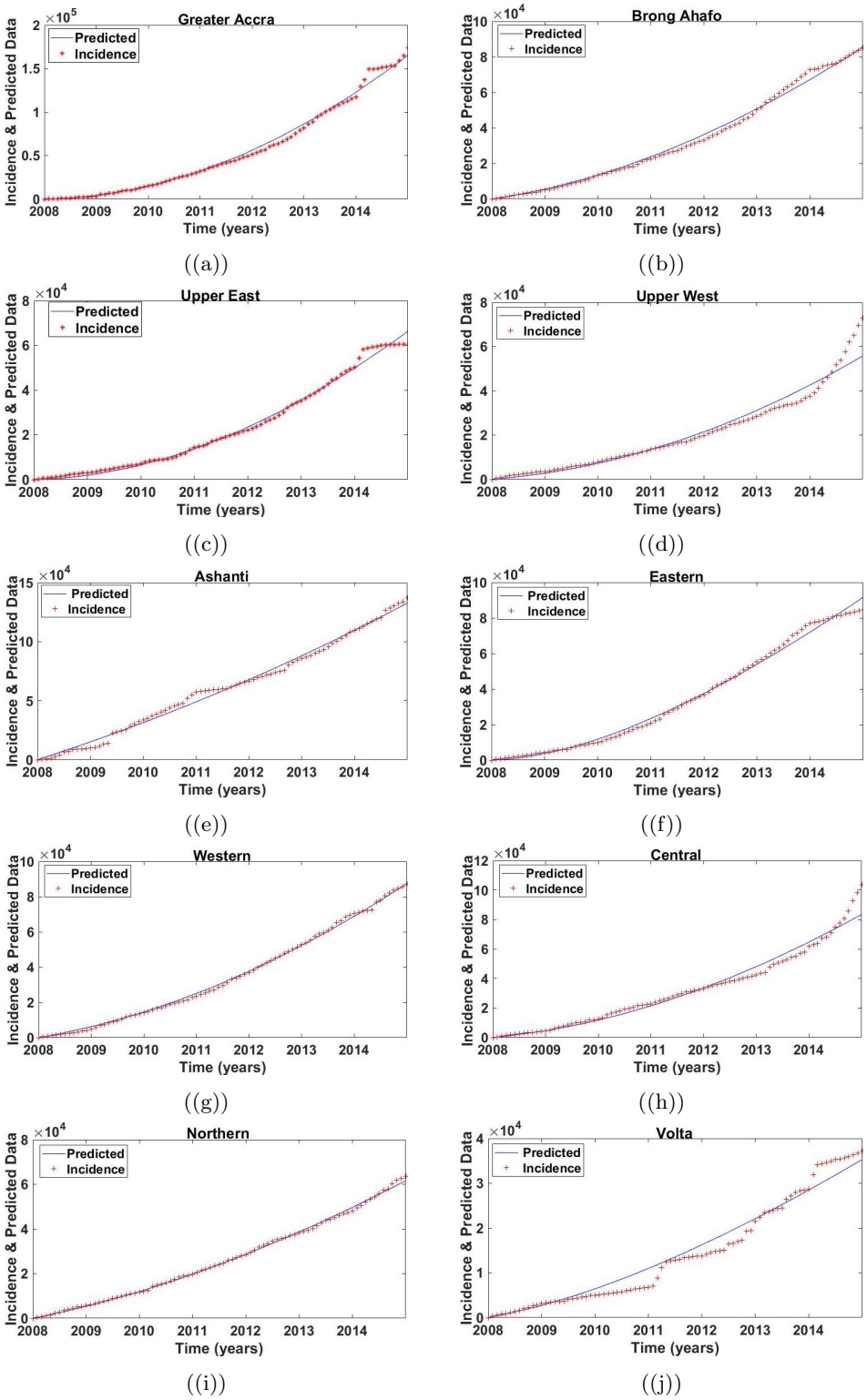


Figure 6.2: Model fit to regional cumulative HB incidence data (2008 - 2014).

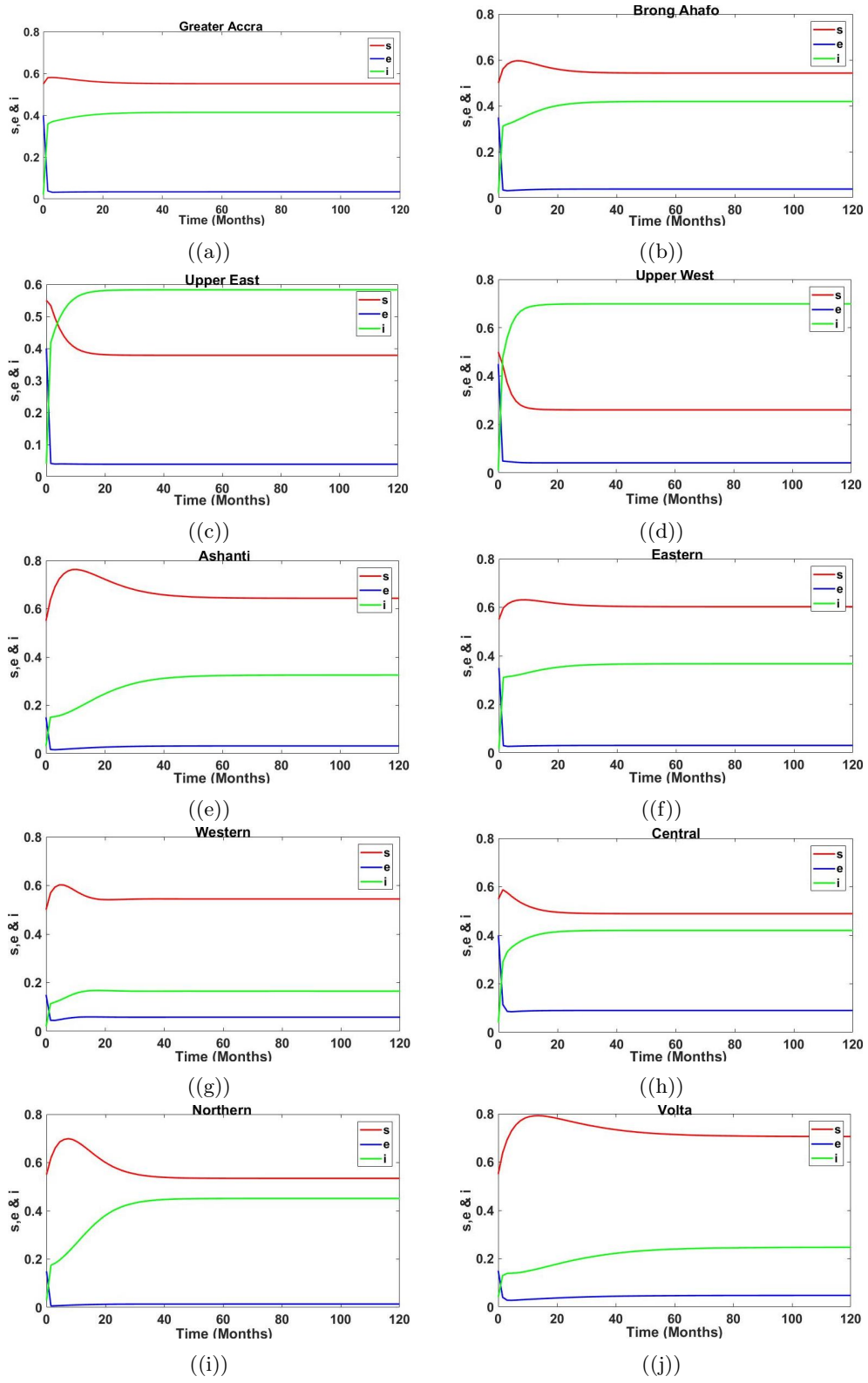
From Table 6.6, the endemic susceptible proportions s^* range from 0.2601 to 0.7055, the endemic exposed proportions e^* range from 0.01407 to 0.0902 and the endemic infectious proportions i^* range from 0.2468 to 0.6988. Regions with higher proportions of susceptible endemic state values have lower proportions of infectious state values and vice versa. Volta region has the highest endemic susceptible proportion of $s^* = 0.7055$ and therefore the least endemic infectious proportion of $i^* = 0.2468$, whilst Upper West region has the least endemic susceptible proportion of $s^* = 0.2601$ and so the highest infectious endemic proportion of 0.6988.

Figures 6.5(d) and 6.5(e) show the distribution of infectious and latent periods of hepatitis B respectively across Ghana. Whilst the infectious periods are high in the three northern regions (Upper East, Upper West and Northern), Volta and Greater Accra regions, the latent periods are low in the three northern regions with Volta and Central regions showing the highest latent period. The middle belt and the southern regions show low infectious periods but high latent periods in contrast to the pattern shown with respect to the three northern regions. Volta and Central regions show the highest latent periods whilst Upper East and Greater Accra regions show the highest infectious periods. With the exception of Volta, Central and Greater Accra regions, the distribution of the infectious and latent periods show a reverse trend with respect to each other. Whilst the infectious period shows an increase from south to north, the latent period shows a decrease from south to north across the regions of Ghana.

The regional distribution of the endemic susceptible, exposed and infectious proportions are displayed in Figures 6.5(f), 6.5(h) and 6.5(g) respectively. The three northern regions show relatively high endemic infectious proportions, but relatively low endemic susceptible proportions. The trend of endemic infectious proportions decrease from north to south whilst that of the endemic susceptible proportions increase from north to south across the regions of Ghana. Unlike the endemic susceptible and infectious proportions, the distribution of the endemic exposed proportions of the regions displayed in Figure 6.5(h) shows no definite pattern.

6.5 Regression analysis

Linear regression analysis was used to examine the relationship among R_0, H, poverty and the state variables s, e and i of the model in Equation 3.6, using the simple linear regression model.



((a)) ((b)) ((c)) ((d)) ((e)) ((f)) ((g)) ((h)) ((i)) ((j))

Figure 6.3: Regional model predictions of the state variables s, e and i over 120 months.

Table 6.6: Regional endemic state values with corresponding latent and infectious periods.

	Endemic values			Latent	Infectious
Region	s^*	e^*	i^*	period	period
Greater Accra	0.551559	0.034255	0.414186	3.4	44.1
Brong Ahafo	0.542686	0.038095	0.419219	3.2	38.0
Upper East	0.378539	0.038749	0.582712	2.7	44.1
Upper West	0.260055	0.041124	0.698821	2.4	43.3
Ashanti	0.643577	0.031266	0.325157	3.4	38.9
Eastern	0.602528	0.03025	0.367222	3.0	39.4
Western	0.544531	0.057686	0.165009	4.7	15.5
Central	0.489379	0.090266	0.420355	6.7	37.7
Northern	0.534483	0.014075	0.451443	1.3	41.7
Volta	0.70554	0.047582	0.246878	6.7	41.3
Ghana	0.5741	0.0706	0.3553	6.7	40.2

$$\hat{y} = \beta_0 + \beta_1 x + \epsilon \tag{6.1}$$

where $\hat{y}$ is the dependent/response variable, x the independent variable, β_0 the intercept, β_1 the slope and ϵ the error or noise, testing the hypothesis

$$H_0 : \beta_1 = 0, \quad H_a : \beta_1 \neq 0.$$

In addition to the estimated statistics of the analysis, correlation coefficients for each pair of variables were computed. The summary of the results is displayed in Table 6.7.
The p-values of 0.0257, 0 and 0.0027 for categories H versus poverty, H versus s^* and H versus i^* respectively in Table 6.7 are less than the significance level $p < 0.05$, which indicates that there is association between herd immunity H and poverty, H and s^* and H and i^* respectively. The correlation coefficients of 0.6948, -0.9993 and 0.8341 for the relation between H and poverty, H and s^* and H and i^* respectively, indicate that there is a positive correlation between H and poverty and H and i^* whilst the correlation between H and s^* is negative. This implies that H increases with increases in poverty and i^*, but H declines as s^* increases and vice versa. The associations between H and poverty, H and s^* and H and i^* are illustrated in Figures 6.4(a), 6.4(c) and 6.4(e) respectively.

Similarly in Table 6.7, R_0 shows a positive linear relationship with poverty and i^* and a negative linear relationship with s^*, as indicated by the statistics ($p = 0.0064$, correlation $=$

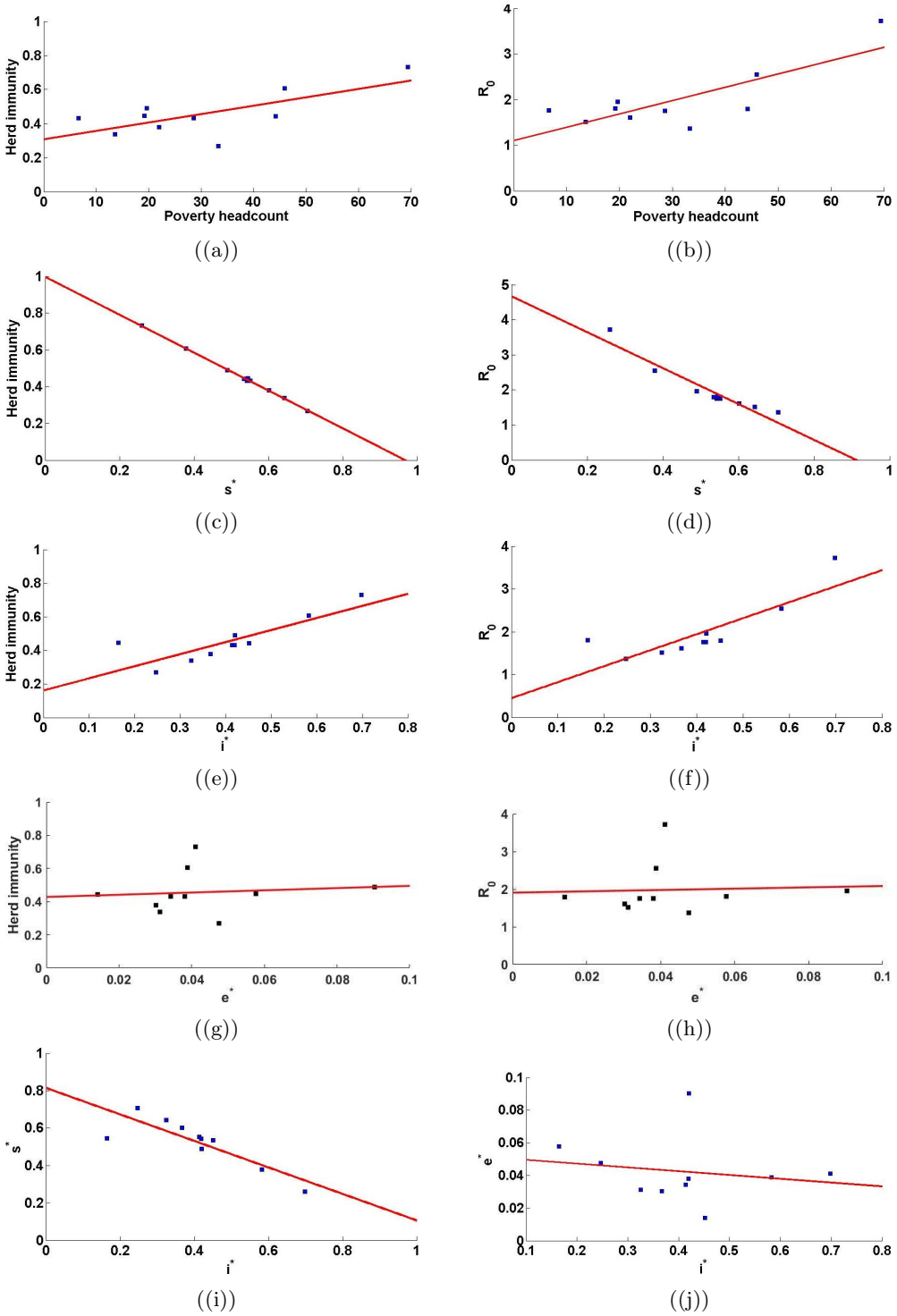


Figure 6.4: Linear regression of (a) Herd immunity on Poverty. (b) R_0 on Poverty. (c) Herd immunity on s^*. (d) R_0 on s^*. (e) Herd immunity on i^*. (f) R_0 on i^*. (g) Herd immunity on e^*. (h) R_0 on e^*. (i) s^* on i^*. (j) e^* on i^*.

Table 6.7: Calculated correlation coefficient values and summary statistics of regression analysis among Herd immunity threshold (H), poverty headcount (poverty), epidemiological threshold parameter R_0 and the endemic state proportion variables s^*, e^* and i^*.

Category	Correlation coefficient	Coefficient (β_1)	Standard Errors	t-values	p-values	df
H on Poverty	0.6948	0.0049	0.0018	2.7325	0.0257	8
H on s^*	-0.9993	-0.9700	0.0137	-75.1973	< 0.0001	8
H on i^*	0.8341	0.7176	0.1678	4.2765	0.0027	8
H on e^*	0.1034	0.0160	2.2761	0.2941	0.7762	8
R_0 on Poverty	0.7912	0.0292	0.0080	3.6594	0.0064	8
R_0 on s^*	-0.9530	-5.1214	0.5754	-8.9009	< 0.0001	8
R_0 on i^*	0.8327	3.7374	0.8787	4.2536	0.0028	8
R_0 on e^*	0.0520	0.0015	11.9212	0.1474	0.8865	8
s^* on i^*	-0.8469	-0.7074	0.1570	-4.5049	0.0020	8
s^* on e^*	-0.1034	-0.6499	2.2095	-0.2941	0.7761	
e^* on i^*	-0.1740	-0.0231	0.0463	-0.4999	0.6306	8

0.7912), ($p = 0.0028, \text{correlation} = 0.8327$) and ($p = 0, \text{correlation} = -0.9530$) respectively. The correlations between R_0 and poverty, R_0 and s^* and R_0 and i^* are illustrated in Figures 6.4(b), 6.4(d) and 6.4(f) respectively, in which R_0 increases as poverty and i^* increase and R_0 declines as s^* increase and vice versa. There is no significant statistical evidence of association between H and e^*, R_0 and e^* and e^* and i^* as indicated by the p-values of 0.8865, 0.7762 and 0.6306, and illustrated by Figures 6.4(g), 6.4(h) and 6.4(j) respectively. However there is a negative correlation between s^* and i^* with ($p = 0.0020, \text{correlation} = -0.8469$) and illustrated in Figure 6.4(i).

The correlation results above indicate that the spread and burden of hepatitis B in the population of Ghana is associated with the poverty levels of the people, since the two variables have a positive correlation. Regions with high levels of poverty would experience increased spread of hepatitis B compared to less poor regions. The results also indicate that regions which require higher levels of herd immunity to control hepatitis B have increasing percentage of infectious population and so there is declining percentage of susceptible population. Regions which have decreasing percentage of infectious population would have increasing percentage of susceptible population and so require lower herd immunity to keep the disease under control.

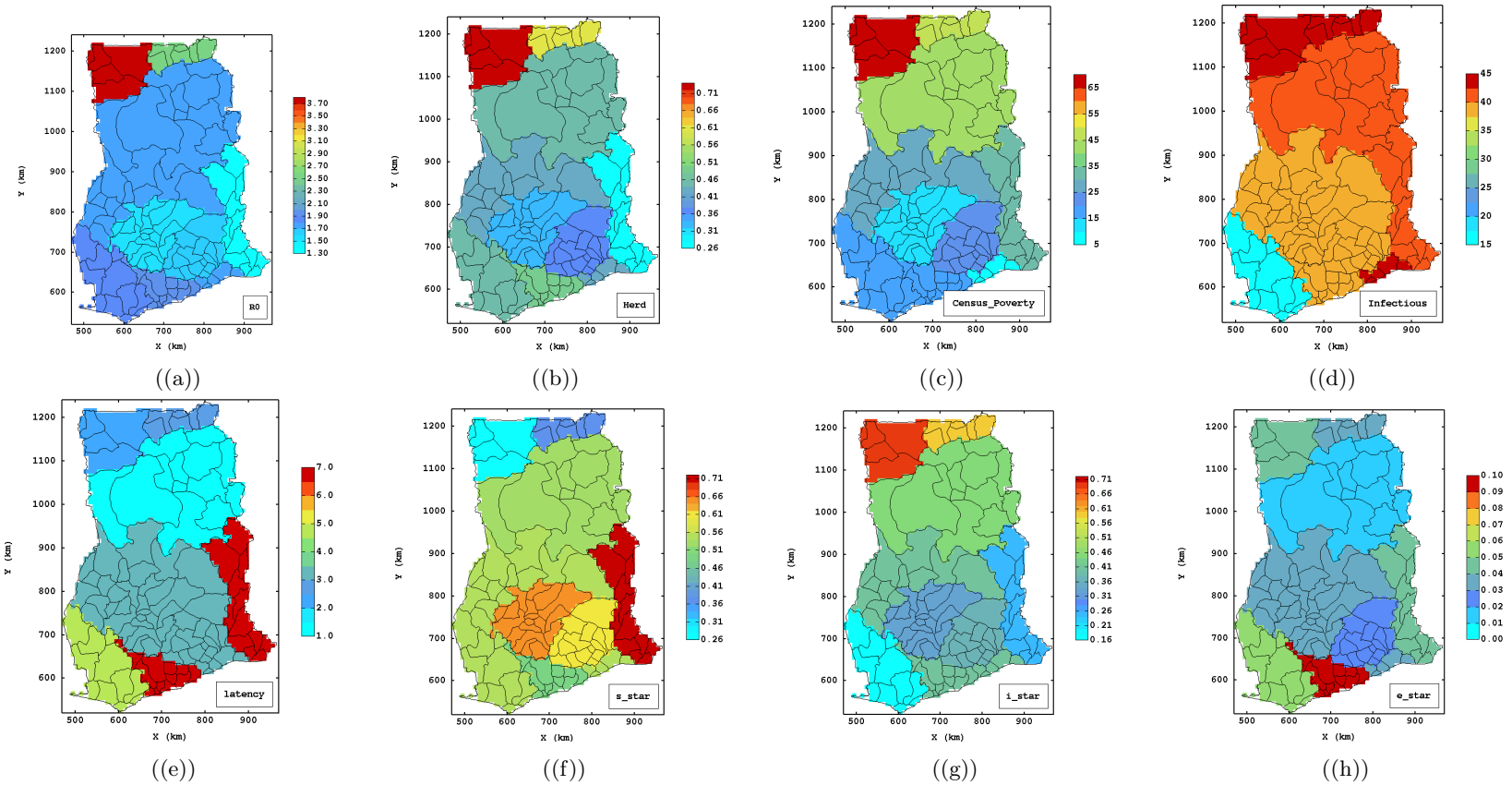
6.6 Discussion of results

6.6.1 The threshold parameters and their implications on the trend of disease

The computed regional values of the epidemiological threshold parameter R_0 are all greater than unity, which indicates that hepatitis B persists in all ten regions of Ghana. With a minimum value of $R_0 = 1.3669$ and a maximum of $R_0 = 3.7212$, the threshold value R_0 shows a variability, in terms of range, of 2.3543 which represents a percentage change of about 172% across Ghana. The extent of variability of R_0 indicates that the intensity of incidence and spread of hepatitis B vary significantly from region to region across the country. The corresponding herd immunity threshold values H also show that controlling the disease requires different percentages of the population to be immune in each region across the country. The value of H ranges from a minimum of 0.2684 to a maximum of 0.7312 across the regions of Ghana.

Apart from Volta, Ashanti and Eastern regions with values of $R_0 = 1.3669$, $R_0 = 1.5119$ and $R_0 = 1.6104$ respectively that are lower than the overall national value of $R_0 = 1.6854$, the values of the remaining seven regions are greater than the national value. The Greater Accra and Brong Ahafo regions have an approximate value of $R_0 = 1.76$ which indicates that the spread and burden of the disease in the two regions are similar. The epidemiological threshold parameters R_0 and herd immunity threshold values H, calculated for the regions, show that the spread of the disease and its associated burden is highest in Upper West region ($R_0 = 3.7212, H = 0.7312$) and lowest in Volta region ($R_0 = 1.3669, H = 0.2684$).

The values of the threshold parameters and their herd immunity values also show an increasing trend from south to north of Ghana, indicating that the spread of the disease and the associated burden increase from the south to the north across the three main ecological zones, i.e. Coastal savanna, Rain forest and Northern savanna, of the country [142]. Although Western and Central regions are situated in the southern part of the country, they have high values of ($R_0 = 1.8057, H = 0.4462$) and ($R_0 = 1.9580, H = 0.4892$) respectively that deviate from this increasing trend of disease from south to north. Apart from the Western region which showed some recovery of disease of 0.0378, the rest of the regions have zero recovery indicating that none of the infected persons could clear the disease at the acute stage [71, 143].



((a)) ((b)) ((c)) ((d))

((e)) ((f)) ((g)) ((h))

Figure 6.5: Regional distributions of (a)Epidemiological threshold parameter R_0; (b) Herd immunity threshold value H; (c) Poverty inequality (by poverty headcount); (d) Infectious period; (e) Latent period; (f) Estimated endemic susceptible proportion s^*; (g) Estimated endemic infectious proportion i^*. (h) Estimated endemic exposed proportion e^*;

Although this may be a numerical artefact, studies on the characteristics of the dynamics of hepatitis B however indicate that the disease can be cleared at the acute stage without the need for intervention or antiviral treatment. The clearance of hepatitis B at the acute stage according to studies depend on the age and immune competence of the infected individual at the time of infection [29, 92]. A visual representation of the regional distribution of the incidence and spread of hepatitis B with respect to the epidemiological threshold parameters R_0 and herd immunity threshold values H across the country is displayed in Figures 6.5(a) and 6.5(b) respectively.

6.6.2 Influence of poverty and health sector inequalities on trend of disease

Poverty and health sector inequalities influence the pattern of incidence and spread of hepatitis B across the regions of Ghana, as poverty and ill-health are generally intertwined [144, 145, 146]. Since poverty is characterised by a lack of essential goods and services and also low levels of education and awareness, poor people tend to have worse health outcomes than otherwise better-off people [144]. This for example is evident in the longer term illness indicators such as long standing illness and self-assessed health, as in the case of chronic hepatitis and hepatocellular carcinoma, complicated with high levels of morbidity and mortality which show inequality to the disadvantage of the poor [144]. The various factors that have direct influence on health outcomes in a population generally tend to be worse in poorer communities.

The Ghana poverty and inequality report indicated that the highest poverty rates continue to be observed in the Northern, Upper East and Upper West regions [147]. Table 6.3, sourced from GSS population and housing census and GLSS6 of 2010, displays the estimates of poverty headcount of Ghana by region. Figure 6.5(c) illustrates the regional poverty inequality distribution, based on the estimates of poverty headcount of Ghana presented in Table 6.3. Figure 6.5(c), shows that poverty levels reduce from north to south of the country. Volta region however deviates from this trend since it is among the top five poorest regions by virtue of its poverty headcount, although it is situated in the south-eastern part of the country.

The location of health facilities as well as the availability of health personnel to man these facilities also affects the pattern of incidence and spread of hepatitis B in Ghana. Health staff concentration in urban areas especially Kumasi and Accra and inadequate supply of

logistics to health care facilities across the country remain a challenge to health delivery particularly in the vast rural settings [59]. The Ghana Health Service (GHS) acknowledged challenges of provision of accessible, affordable and quality health care to regions in the north of the country [59, 71].

The poor by their predisposition to illnesses tend to use health services more than the better-off, but it turns out mostly that the utilisation of the health service is insufficient for their greater medical needs due to unavailability or inaccessibility of health facilities, services and logistics [144]. Access to medical care and cost of screening, diagnosis and treatment of viral hepatitis compound the challenges in hepatitis and liver cancer management in poor communities. In fact surveillance programs and routine HBV screening for the general population are virtually absent in poor communities which usually form the vast rural areas of Sub-Saharan Africa [148]. For example, poor children in poor communities are typically far less likely to be immunised against an infectious disease than better-off children [144].

The transmission and spread of hepatitis B increase from south to north as shown by the distribution of the epidemiological threshold parameters and herd immunity threshold values in Figures 6.5(a) and 6.5(b) respectively, reflects the poverty and health sector differentials across the country. It is however worth noting that although Volta region is not the richest region, it presents the least incidence and spread of hepatitis B whilst Western and Central regions are not rated among the poorest regions but the intensity of hepatitis B is considerably high. This shows that the incidence and spread of hepatitis B in Ghana is not determined by poverty and health sector inequalities alone.

6.6.3 Prevalence differentials of hepatitis B between Ghana and neighbouring countries

Apart from poverty inequalities across the country, differentials in prevalence of hepatitis B between Ghana and the neighbouring countries most likely contribute to the pattern of incidence and spread of the disease in Ghana. Some studies have indicated that migration across health and disease disparities influence the epidemiology of certain diseases globally and in communities receiving migrants [3, 149, 150, 151]. Granted that specific disease-based outcomes may vary between migrant groups, yet by general epidemiological principles moving a population from the risk environment or establishing disease transmission outside of the usual environmental constraints impact on the epidemiology of the

condition in the receiving region and on the local community [149]. The health characteristics of migrants usually reflect their place and country of origin and thus carry with them most of these characteristics when they move, although they are also subject to other prevalent conditions that affect their health [3].

Some studies indicated that increased volumes of movement of people across regions of different hepatitis B prevalence have changed the hepatitis B epidemiology between both immigration and emigration countries [150]. In recent years, hepatitis B prevalence has been a major public health concern to countries which hitherto did not have such concerns mostly due to increased migration from high or intermediate hepatitis B prevalence regions [150, 151]. Ghana is bounded on the north by Burkina Faso, on the east by Togo and on the west by Ivory Coast. Global infection rates of hepatitis B reviewed in 2006 by WHO's National Centres for Disease Control and Prevention (CDCP) indicated that hepatitis B prevalence for Burkina Faso, Ghana, Ivory Coast and Togo were 12%, 12%, 12% and 8% respectively [152]. However, other reports indicated that hepatitis B is hyperendemic in Burkina Faso with prevalence of around 14.5% whereas Ivory Coast is considered intermediate endemicity [152].

Volta and Western regions provide the main official exits to Togo and Ivory Coast respectively where much interaction with respect to socioeconomic activities take place among people travelling on either side of the borders. Lower prevalence of hepatitis B in Togo could most likely be an influence on a lower transmission and spread of the disease in Volta region compared to a considerably higher prevalence in Ivory Coast, which could also impact a higher transmission and spread in Western region with respect to the epidemiological threshold parameters of the two regions. Since Upper East and Upper West are also the main official exits to Burkina Faso where similar interactions of people moving to and from both countries across the border, the high spread of hepatitis B would most likely be attributable to the hepatitis B hyperendemicity status of Burkina Faso.

6.7 Summary

The epidemiological threshold parameter R_0, calculated for each of the ten regions of Ghana, is greater than unity. This indicates that hepatitis B is persistent throughout Ghana, although the incidence and spread and the associated burden differs from region to region across the country. The corresponding herd immunity threshold values H for the various regions are also indicative that different immunity levels are required to bring

hepatitis B in each region under control. The incidence and spread and the associated burden of hepatitis B, based on the values of R_0, show a general increasing trend from south to north across the regions of Ghana. Exception to this trend are Western and Central regions which have relatively high values of R_0 but are situated in the southern part of Ghana. Values of R_0 for Eastern, Ashanti and Volta regions compared to the national value indicate that the incidence and spread of hepatitis B and the associated burden in the three regions is lower than that of broader Ghana. The remaining seven regions have higher values of R_0 and therefore experience higher burden compared to the national burden.

Poverty and health sector inequalities potentially impact the trend of incidence and spread of hepatitis B and the associated burden across the regions of Ghana. Poverty and ill-health are intertwined and poor people tend to have worse health outcomes. Ghana poverty and inequality report of 2010 indicated an increasing trend of poverty from south to north across the regions of Ghana. A simple correlation analysis between poverty headcount and values of both R_0 and H show a strong positive association. This implies that as poverty headcount increases, R_0 and H increase. Poor communities most likely face challenges of provision of accessible, affordable and quality health care due to the unavailability of health facilities and logistics and also health personnel. Poor communities are most likely disadvantaged with regards to access to medical care and cost of screening, diagnosis and treatment of hepatitis B and thus are the most vulnerable to advanced liver disease and death due to late reporting.

Differentials in prevalence of hepatitis B is another area that potentially impact the pattern of incidence and spread of the disease across both regional and international borders of Ghana. Since the health characteristics of migrants usually reflect their region and country of origin, most of these characteristics are brought to bear on their new settlements. Potential interregional and international influences of disparities in prevalence of hepatitis B show in a subtle way in the pattern of incidence and spread of the disease in regions of Ghana that have direct economic and/or social border activities with neighbouring countries. For example, border activities between Upper East and Upper West regions of Ghana and Burkina Faso, which is reported to be a hepatitis B hyperendemic country, most likely have a relative influence on the high incidence and spread pattern of the disease in the three northern regions of Ghana. Similarly, the intermediate endemicity status of Ivory Coast potentially influences the relatively high pattern of incidence and spread of hepatitis B in Western, Central and Brong-Ahafo regions on the western border with Ivory

Coast. It is also most likely that the low to intermediate hepatitis B prevalence in Togo impact the relatively low pattern of incidence and spread of the disease in Volta, Greater Accra and eastern regions on the eastern border of Ghana with Togo.

Chapter 7

Impact of vaccination on the hepatitis B model $(SEIR)$ of Ghana

7.1 Introduction

Global control of the prevalence of hepatitis B is a major goal of WHO, with a special emphasis on prevention of the disease in Africa which is an endemic region [148]. Although there are other forms of intervention for the control and prevention of hepatitis B, vaccination is known to be the major and most effective one, especially when universally incorporated in national infant immunisation programmes [12, 148, 153, 154]. The depth of hepatitis B prevalence is determined by the depth of chronic infection existing in a population, and infected infants have the highest risk of developing chronic infection [154]. There is no treatment for acute hepatitis B. Treatment for chronic hepatitis B, although available and important, will keep down viral replications and slow the progression of cirrhosis, reduce incidence of liver cancer and sustain long term survival of the infected person but it does not prevent the development of the disease [12, 153]. The key to preventing the spread of hepatitis B therefore is to ensure that fresh or new incidence of the infection is completely cut off from a population, essentially at the early stages of life where there is a high likelihood of developing into chronic infection. In fact WHOs recommendation with respect to the WHAs resolution in 2010, that calls for public health intervention to prevent and control viral hepatitis, emphasised the need to administer hepatitis B vaccine to all infants as soon as possible after birth [12, 153].

In this chapter, vaccination as an intervention was introduced into the $SEIR$ model with vertical transmission, to examine its impact on the incidence and spread of hepatitis B and the associated burden on the population of Ghana. The $SEIR$ model of hepatitis B for Ghana in Equation 3.1 was modified to include a vaccination component that moves vaccinated susceptible members directly into the recovered compartment R. The epidemiological threshold parameter R_{v0} of the modified model was analytically determined. Sensitivity of R_{v0} to the rate of vaccination was performed to examine the impact of vaccination on the incidence and spread of hepatitis B, in the case of Ghana and also for each of the ten regions of Ghana. Stability analysis of the modified model was discussed analytically with respect to the equilibrium states of the model. A summary of the results concludes the chapter.

7.2 The vaccination model

The vaccination model is a modification of the $SEIR$ model in which a vaccination component determined by the rate of vaccination k is introduced. Progression of infection through the modified model is similar to that of the existing model in Equation 3.1, except that now vaccinated susceptible individuals are transferred directly into the recovered class by gaining immunity. In essence, a nonvaccinated susceptible individual moves into the exposed class after being exposed to the pathogen, the exposed individual then moves into the infectious class and finally moves into the recovered class by permanent immunity, or may die naturally in the course of progression through the model. Birth fluxes of $\lambda N - \alpha(E+I)$ and $\alpha(E+I)$ via the susceptible and exposed classes respectively are recruited into the model, where α is the rate of vertical transmission. The disease progression in the model is illustrated by the flow diagram in Figure 7.1.

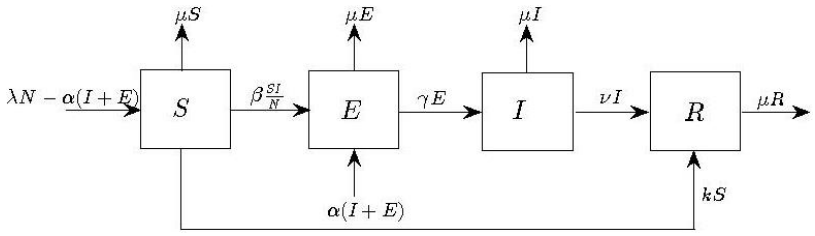


Figure 7.1: A model for transmission of hepatitis B with vaccination.

The vaccination model is represented by the system of nonlinear ordinary differential equations

$$\begin{aligned}
\frac{dS}{dt} &= \lambda N - \alpha(I+E) - \beta\frac{SI}{N} - \mu S - kS \\
\frac{dE}{dt} &= \beta\frac{SI}{N} + \alpha(I+E) - \mu E - \gamma E \\
\frac{dI}{dt} &= \gamma E - \mu I - \nu I \\
\frac{dR}{dt} &= \nu I + kS - \mu R, \qquad (7.1)
\end{aligned}$$

subject to $S(t), E(t), I(t), R(t) \geq 0$, $S(t)+E(t)+I(t)+R(t) = N(t)$ and $\frac{dN}{dt} = (\lambda - \mu)N$, where $k \geq 0$ is the rate of vaccination. The remaining parameters are defined as in the original model in Equation 3.1 stated in Chapter 3 of this thesis. Using the proportions of the state variables $S(t)$, $E(t)$, $I(t)$ and $R(t)$ in $N(t)$ and by determining r from $r = 1-(s+e+i)$, the system in Equation 7.1 becomes

$$\begin{aligned}
\frac{ds}{dt} &= \lambda - \alpha(i+e) - \beta si - ks - s\lambda \\
\frac{de}{dt} &= \beta si + \alpha(i+e) - \gamma e - e\lambda \\
\frac{di}{dt} &= \gamma e - \nu i - i\lambda \qquad (7.2)
\end{aligned}$$

defined on the closed positively invariant set, $\Sigma = \{(s,e,i) \in \mathbb{R}^3_+ | 0 \leq s+e+i \leq 1\}$ [112]. The vaccination model, like the original $SEIR$ model, is also well-posed because any solution of the system in Equation 7.2 with initial state of $(s_0, e_0, i_0) \in \Sigma$ remains in Σ, that is invariant. The model has two equilibrium states; a disease-free equilibrium $Q_{v0} = (\lambda/(\lambda+k), 0, 0)$ and an endemic equilibrium $Q^*_v = (s^*_v, e^*_v, i^*_v)$, where

$$\begin{aligned}
s^*_v &= \frac{(\lambda+\gamma)(\lambda+\nu) - \alpha(\lambda+\gamma+\nu)}{\beta\gamma} \\
e^*_v &= \frac{\beta\gamma\lambda + \alpha(\lambda+k)(\lambda+\gamma+\nu) - (\lambda+k)(\gamma+\lambda)(\lambda+\nu)}{\beta\gamma(\gamma+\lambda)} \\
i^*_v &= \frac{\beta\gamma\lambda + \alpha(\lambda+k)(\lambda+\gamma+\nu) - (\lambda+k)(\gamma+\lambda)(\lambda+\nu)}{\beta(\lambda+\gamma)(\lambda+\nu)}. \qquad (7.3)
\end{aligned}$$

The assumptions of the model include all the assumptions of the original model from Chapter 3. In addition, the susceptible proportion of the population is assumed to be vaccinated at the rate $k \geq 0$ with a vaccine efficacy of 100%. This means that the effect of

the vaccine is not expected to wane within the period of study and so the entire vaccinated susceptible proportion moves into the recovered class.

7.3 The epidemiological threshold parameter R_{v0} of the vaccination model

The threshold parameter R_{v0} is defined as the spectral radius of the next generation matrix AB^{-1} evaluated at the disease-free state $Q_{v0} = (\lambda/(\lambda+k), 0, 0)$. From Equation 3.6, the rate of appearance of new infection $\mathscr{A}$ into the infected compartments and the rate of transfer into $\mathscr{B}^+$ and transfer out $\mathscr{B}^-$ of the infected compartments by all other means, i.e. $\mathscr{B} = \mathscr{B}^+ - \mathscr{B}^-$ are respectively

$$\mathscr{A} = \begin{bmatrix} \beta si + \alpha(i+e) \\ 0 \end{bmatrix}, \qquad \mathscr{B} = \begin{bmatrix} \gamma e + e\lambda \\ -\gamma e + \nu i + \lambda i \end{bmatrix} \tag{7.4}$$

Note that the transfer from E to I is not considered to be new infection, but rather the progression of an infected person through the various compartments. Hence the partial derivatives of $\mathscr{A}$ and $\mathscr{B}$ with respect to e and i, evaluated at the disease-free state $Q_{v0} = (\lambda/(\lambda+k), 0, 0)$, are respectively

$$A = \begin{bmatrix} \alpha & \alpha + \frac{\beta\lambda}{\lambda+k} \\ 0 & 0 \end{bmatrix}, \qquad B = \begin{bmatrix} \gamma+\lambda & 0 \\ -\gamma & \nu+\lambda \end{bmatrix} \tag{7.5}$$

and so

$$B^{-1} = \frac{1}{(\lambda+\gamma)(\lambda+\nu)} \begin{bmatrix} \lambda+\nu & 0 \\ \gamma & \lambda+\gamma \end{bmatrix}. \tag{7.6}$$

Hence the next generation matrix is

$$AB^{-1} = \begin{bmatrix} \frac{\alpha(\lambda+k)(\lambda+\nu)+\alpha\gamma(\lambda+k)+\beta\gamma\lambda}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} & \frac{\alpha(\lambda+k)+\beta\lambda}{(\lambda+k)(\lambda+\nu)} \\ 0 & 0 \end{bmatrix} \tag{7.7}$$

The spectral radius of the next generation matrix AB^{-1} is obtained from the eigenvalues of AB^{-1} given by

$$\xi_1 = 0, \quad \xi_2 = \frac{\alpha(\lambda+k)(\lambda+\nu) + \alpha\gamma(\lambda+k) + \beta\gamma\lambda}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}$$

Therefore the epidemiological threshold parameter R_{v0} is the dominant eigenvalue ξ_2 of the next generation matrix FV^{-1} given by [105]

$$R_{v0} = \frac{\beta\gamma\lambda + \alpha(\lambda + k)(\lambda + \gamma + \nu)}{(\lambda + k)(\lambda + \gamma)(\lambda + \nu)}. \tag{7.8}$$

Regardless of the presence of vaccination in the model, the disease is said to die off in the population when the epidemiological threshold parameter $R_{v0} < 1$. When $R_{v0} > 1$, the disease is said to persist. Recall also that in the absence of the intervention, $k = 0$ and so R_{v0} reverts to the threshold parameter of the original model without vaccination

$$R_0 = \frac{\beta\gamma + \alpha(\lambda + \gamma + \nu)}{(\lambda + \gamma)(\lambda + \nu)}. \tag{7.9}$$

The herd immunity threshold of the vaccination model is given by

$$H_v = 1 - \frac{(\lambda + k)(\lambda + \gamma)(\lambda + \nu)}{\beta\gamma\lambda + \alpha(\lambda + k)(\lambda + \gamma + \nu)} \tag{7.10}$$

7.4 Stability analysis of the vaccination model

The Jacobian of the system in Equation 7.2 is

$$J(s, e, i) = \begin{bmatrix} -(\beta i + \lambda + k) & -\alpha & -(\alpha + \beta s) \\ \beta i & \alpha - \lambda - \gamma & \alpha + \beta s \\ 0 & \gamma & -(\lambda + \nu) \end{bmatrix}, \tag{7.11}$$

the eigenvalues of which are then used to discuss the stability of the model in Equation 7.2 at the two equilibrium solutions, namely the disease-free state $Q_{v0} = \left(\frac{\lambda}{\lambda+k}, 0, 0\right)$ and the endemic state $Q_v^* = (s_v^*, e_v^*, i_v^*)$.

The disease-free and endemic equilibrium solutions of the vaccination model in the entire stability analysis will refer to disease eradication and persistence with respect to the infected proportions e and i of the population and not the absolute cases E and I respectively as indicated for the original model in chapter 3 [114].

7.4.1 Stability of the disease-free state

At the disease-free equilibrium state $Q_{v0} = \left(\frac{\lambda}{\lambda+k}, 0, 0\right)$ the Jacobian of the system in Equation 7.2 is given by

$$J\left(\frac{\lambda}{\lambda+k},0,0\right)=\begin{bmatrix} -(\lambda+k) & -\alpha & -\left(\alpha+\beta\frac{\lambda}{\lambda+k}\right) \\ 0 & \alpha-\lambda-\gamma & \alpha+\beta\frac{\lambda}{\lambda+k} \\ 0 & \gamma & -(\lambda+\nu) \end{bmatrix} \tag{7.12}$$

The characteristic equation of the Jacobian is

$$\begin{aligned} (\lambda+k+\xi)\left[((\alpha-\lambda-\gamma)-\xi)((\lambda+\nu)+\xi)+\gamma\left(\beta\frac{\lambda}{\lambda+k}+\alpha\right)\right] &= 0 \\ \Rightarrow (\lambda+k+\xi)\left[\xi^2+(2\lambda+\nu+\gamma-\alpha)\xi+(\lambda+\nu)(\lambda+\gamma-\alpha)-\gamma\left(\alpha+\frac{\beta\lambda}{\lambda+k}\right)\right] &= 0 \end{aligned} \tag{7.13}$$

Hence the eigenvalues of the disease-free state are

$$\begin{aligned} \xi_1 &= -(k+\lambda) \\ \xi_2 &= \frac{(\lambda+k)(\alpha-2\lambda-\gamma-\nu)+\sqrt{\triangle_v}}{2(\lambda+k)} \\ \xi_3 &= \frac{(\lambda+k)(\alpha-2\lambda-\gamma-\nu)-\sqrt{\triangle_v}}{2(\lambda+k)} \end{aligned} \tag{7.14}$$

where

$$\triangle_v=(\lambda+k)[(\lambda+k)(\alpha+\nu-\gamma)^2+4\gamma(\alpha\lambda+k\alpha+\beta\lambda)] \tag{7.15}$$

From Equation 7.14, $\xi_1<0$ and $\xi_3<0$ since $\alpha<\lambda$ and $\alpha,\beta,\gamma,\nu,\lambda\geq 0$, but $\xi_2=0$ if

$$\begin{aligned} (\lambda+k)^2(2\lambda+\gamma+\nu-\alpha)^2 &= (\lambda+k)[(\lambda+k)(\alpha+\nu-\gamma)^2+4\gamma(\alpha\lambda+k\alpha+\beta\lambda)] \\ \Longrightarrow \qquad k &= \frac{\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)]}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma} \end{aligned}$$

This defines a threshold value of

$$k^*=\frac{\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)]}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma} \tag{7.16}$$

such that $\xi_2<0$ if $k>k^*$ and $\xi_2>0$ if $k<k^*$. It follows from the above analysis that the eigenvalues of the disease-free state Q_{v0} are:

i. All negative, that is, $\xi_1 < 0$, $\xi_2 < 0$ and $\xi_3 < 0$, if $k > k^*$ which means that the disease-free state Q_{v0} is asymptotically stable;

ii. One zero and two negative, that is, $\xi_1 < 0$, $\xi_2 = 0$ and $\xi_3 < 0$, if $k = k^*$;

iii. One positive and two negative, that is, $\xi_1 < 0$, $\xi_2 > 0$ and $\xi_3 < 0$, if $k < k^*$, which means the disease-free state Q_{v0} is unstable.

When the vaccination rate is $k = k^*$, the epidemiological threshold parameter from Equation 7.8 becomes

$$\begin{aligned}
R_{v0} &= \frac{\beta\gamma\lambda + \alpha\left(\lambda + \frac{\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)]}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}\right)(\lambda+\gamma+\nu)}{\left(\lambda + \frac{\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)]}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}\right)(\lambda+\gamma)(\lambda+\nu)} \\
&= \frac{\beta\gamma\lambda + \frac{\alpha(\lambda(\lambda+\nu)(\lambda+\gamma-\alpha)-\lambda\alpha\gamma-\lambda(\lambda+\nu)(\lambda+\gamma-\alpha)+\lambda\gamma(\alpha+\beta))(\lambda+\gamma+\nu)}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}}{\frac{(\lambda(\lambda+\nu)(\lambda+\gamma-\alpha)-\lambda\alpha\gamma-\lambda(\lambda+\nu)(\lambda+\gamma-\alpha)+\lambda\gamma(\alpha+\beta))(\lambda+\nu)(\lambda+\gamma)}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}} \\
&= \frac{\beta\gamma\lambda + \frac{\alpha\beta\gamma\lambda(\lambda+\gamma+\nu)}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}}{\frac{\lambda\gamma\beta(\lambda+\gamma)(\lambda+\nu)}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}} \\
&= \frac{\beta\gamma\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma] + \alpha\lambda\gamma\beta(\lambda+\gamma+\nu)}{\lambda\gamma\beta(\lambda+\gamma)(\lambda+\nu)} \\
&= \frac{\beta\gamma\lambda[(\lambda+\nu)(\lambda+\gamma)-\alpha(\lambda+\gamma+\nu)] + \alpha\lambda\beta\gamma(\lambda+\gamma+\nu)}{\lambda\gamma\beta(\lambda+\gamma)(\lambda+\nu)} \\
&= \frac{\beta\gamma\lambda(\lambda+\nu)(\lambda+\gamma)}{\beta\gamma\lambda(\lambda+\nu)(\lambda+\gamma)} \\
&= 1
\end{aligned} \tag{7.17}$$

In conclusion, if the vaccination rate $k = k^*$, $R_{v0} = 1$ as expected. The disease-free equilibrium state $Q_{v0} = \left(\frac{\lambda}{\lambda+k}, 0, 0\right)$ is stable if the vaccination rate $k > k^*$. The disease-free equilibrium state is however unstable if the vaccination rate $k < k^*$. Moreover from Equation 7.16, if $k > k^*$

$$k > \frac{\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)]}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}$$

Since $\lambda > \alpha$, it implies that $(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma > 0$ and so

$$\begin{aligned}
k[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma] &> \lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)] \\
\implies k[(\lambda+\nu)(\lambda+\gamma)-\alpha(\lambda+\gamma+\nu)] &> -\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]+\beta\gamma\lambda \\
\implies k[(\lambda+\nu)(\lambda+\gamma)-\alpha(\lambda+\gamma+\nu)] &> -\lambda[(\lambda+\nu)(\lambda+\gamma)-\alpha(\lambda+\gamma+\nu)+\lambda\gamma\beta \\
\implies (\lambda+k)(\lambda+\nu)(\lambda+\gamma) &> \lambda\gamma\beta+\alpha(\lambda+k)(\lambda+\gamma+\nu) \\
\implies \frac{\lambda\gamma\beta+\alpha(\lambda+k)(\lambda+\gamma+\nu)}{(\lambda+k)(\lambda+\nu)(\lambda+\gamma)} &< 1 \\
\implies R_{v0} &< 1 \qquad (7.18)
\end{aligned}$$

Hence if $k > k^*$, the epidemiological threshold parameter $R_{v0} < 1$. The same analogy can be used to show that if $k < k^*$, $R_{v0} > 1$. From the above discussions, the following conclusions can be made, that

- If $k > k^*$, $R_{v0} < 1$ and the disease-free equilibrium is asymptotically stable;
- If $k = k^*$, $R_{v0} = 1$; and
- If $k < k^*$, $R_{v0} > 1$ and the disease-free is unstable.

7.4.2 Global stability of the disease-free equilibrium state

In Section 7.4.1, the stability of the disease-free proportion equilibrium Q_{v0} for the vaccination model was established on the basis that the real parts of all the eigenvalues of the Jacobian in Equation 7.11 are negative for $k > k^*$. It was therefore concluded that the disease-free equilibrium state is asymptotically stable if $R_{v0} < 1$. In this section, discussion of the global stability of the disease-free equilibrium state of the vaccination model also follows from the methods applied to the model without vaccination in Chapter 3. The methods are applied to show that the restriction on the threshold parameter $R_{v0} < 1$ also guarantees the global stability of the disease-free equilibrium state Q_{v0} of the vaccination model in the closed positive set Σ in the sense of Lyapunov and LaSalle if $R_{v0} \leq 1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}$. In this regard, Theorem 3 can be restated and used to prove this result as follows:

Theorem 6 *The disease-free equilibrium $Q_{v0} = (\frac{\lambda}{\lambda+k}, 0, 0)$ of the vaccination model in Equation 7.2 is globally asymptotically stable in Σ if $R_{v0} \leq 1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}$.*

Proof. Let $R_{v0} \leq 1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}$ and choose the scalar function $V(s(t), e(t), i(t), k(t))$ $= \gamma e + (\lambda + \gamma - \alpha)i$, where $V : \mathbb{R}^3_+ \longrightarrow \mathbb{R}$ has continuous derivatives in $\mathbb{R}$. Then from Equations 3.24, 7.2 and 7.8

$$\begin{aligned}
\dot{V}(s,e,i) &= i[\gamma\beta s + \alpha(\lambda+\gamma+\nu) - (\lambda+\gamma)(\lambda+\nu)] \\
&= i\left[\frac{\beta\gamma s - \frac{\beta\gamma(\lambda+k)}{\lambda+k} + \frac{\beta\gamma(\lambda+k)}{\lambda+k} + \alpha(\lambda+\gamma+\nu) - (\lambda+\gamma)(\lambda+\nu)}{(\lambda+\gamma)(\lambda+\nu)}\right](\lambda+\gamma)(\lambda+\nu) \\
&= i\left[\frac{\beta\gamma s(\lambda+k) - \beta\gamma(\lambda+k)}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} + \frac{\beta\gamma(\lambda+k) + \alpha(\lambda+k)(\lambda+\gamma+\nu)}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} - 1\right] \\
&\times (\lambda+\gamma)(\lambda+\nu) \\
&= i\left[\frac{\beta\gamma(\lambda+k)(s-1)}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} + \frac{\beta\gamma\lambda + \beta\gamma k + \alpha(\lambda+k)(\lambda+\gamma+\nu)}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} - 1\right] \\
&\times (\lambda+\gamma)(\lambda+\nu) \\
&= i\left[\frac{\beta\gamma(s-1)}{(\lambda+\gamma)(\lambda+\nu)} + \frac{\beta\gamma\lambda + \alpha(\lambda+k)(\lambda+\gamma+\nu)}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} + \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)} - 1\right] \\
&\times (\lambda+\gamma)(\lambda+\nu) \\
&= i\left[\frac{\beta\gamma(s-1)}{(\lambda+\gamma)(\lambda+\nu)} + R_{v0} - \left(1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}\right)\right](\lambda+\gamma)(\lambda+\nu) \\
&= i\left[\beta\gamma(s-1) + \left(R_{v0} - \left(1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}\right)\right)(\lambda+\gamma)(\lambda+\nu)\right].
\end{aligned} \tag{7.19}$$

But since $R_{v0} \leq 1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}$ and $s \leq 1$ then

$$\beta\gamma(s-1) + \left(R_{v0} - \left(1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}\right)\right)(\lambda+\gamma)(\lambda+\nu) \leq 0 \tag{7.20}$$

It follows that for $i \geq 0$

$$\dot{V}(s,e,i) \leq 0 \qquad \forall (s,e,i) \in \Sigma. \tag{7.21}$$

From Equation 7.19, $i = 0$ is a necessary and sufficient condition for $\dot{V} = 0$, which means that $E = \{(s,e,i) \in \Sigma | i = 0\}$ is the set of all points in Σ such that $\dot{V} = 0$. However, from the vaccination model in Equation 7.2, if $i = 0$

$$\begin{aligned} s' &= \lambda - \alpha e - ks - s\lambda \\ e' &= \alpha e - \gamma e - e\lambda \\ i' &= \gamma e \end{aligned} \tag{7.22}$$

which means that if $e > 0$, $i' > 0$ and no solutions starting in the set $\{(s, e, i) \in \Sigma | i = 0, e > 0\}$ remains in $\{(s, e, i) \in \Sigma | i = 0, e > 0\}$. Thus the set $\{(s, e, i) \in \Sigma | i = 0, e > 0\}$ is not an invariant subset of E. If $e = i = 0$, Equation 7.22 further reduces to

$$\begin{aligned} s' &= \lambda - ks - s\lambda \\ e' &= 0 \\ i' &= 0 \end{aligned} \tag{7.23}$$

From Equation 7.23, if $s = \frac{\lambda}{\lambda+k}$, $s' = 0$ which implies that $\{(\frac{\lambda}{\lambda+k}, 0, 0)\}$ is an invariant subset of E. If $s \neq \frac{\lambda}{\lambda+k}$, then solving the first equation in Equation 7.23 subject to $s(0) = s_0$ gives

$$s = \frac{\lambda}{\lambda + k} + \left(s_0 - \frac{\lambda}{\lambda + k} \right) \exp\left(-(\lambda + k)t\right). \tag{7.24}$$

For $s < \frac{\lambda}{\lambda+k}$,

$$\lim_{t \longrightarrow -\infty} s = -\infty$$

whilst for $s > \frac{\lambda}{\lambda+k}$

$$\lim_{t \longrightarrow -\infty} s = \infty$$

Hence the set $\{(s, e, i) | s \neq \frac{\lambda}{\lambda+k}, e = 0, i = 0\}$ is only positively invariant and not invariant. Thus the singleton $\{Q_{v0}\}$ is the maximum invariant subset of Σ. Using a similar argument in Subsection 3.3.2, by setting $\Omega = \Sigma$, $M = Q_{v0}$ and $D = \mathbb{R}^3_+$ in Theorem 2

$$\lim_{t \to \infty} ||(s(t), e(t), i(t)) - Q_{v0}|| = 0.$$

Hence Q_{v0} is globally asymptotically stable in Σ when $R_{v0} \leq 1 - \frac{\beta\gamma k}{(\lambda+k)(\lambda+\gamma)(\lambda+\nu)}$.

7.4.3 Stability of the endemic equilibrium state

At the endemic equilibrium state $Q^* = (s_v^*, e_v^*, i_v^*)$, where the coordinates s_v^*, e_v^* and i_v^* are defined by Equation 7.3, the Jacobian of the vaccination model in Equation 7.2 is given by

$$J(s_v^*, e_v^*, i_v^*) = \begin{bmatrix} -(\lambda + k + \beta i_v^*) & -\alpha & -(\alpha + \beta s_v^*) \\ \beta i_v^* & (\alpha - \lambda - \gamma) & \beta s_v^* + \alpha \\ 0 & \gamma & -(\lambda + \nu) \end{bmatrix}. \tag{7.25}$$

The characteristic equation of the model is

$$\begin{aligned} &\xi^3 + \xi^2(-\alpha + \gamma + k + 3\lambda + \nu + \beta i_v^*) \\ &+ \xi(-\alpha\gamma - \alpha k - 2\alpha\lambda - \alpha\nu + \gamma k + 2\gamma\lambda + \gamma\nu + 2\lambda k + \nu k + 2\lambda\nu + 3\lambda^2 + \beta\gamma i_v^* + 2\beta\lambda i_v^* \\ &+ \beta\nu i_v^* - \beta\gamma s_v^*) - \beta\gamma\lambda s_v^* - \beta\gamma k s_v^* + \beta\gamma\nu i_v^* + \beta\gamma\lambda i_v^* - \alpha\lambda\nu - k\alpha\nu - k\alpha\lambda - \alpha\gamma\lambda - k\alpha\gamma \\ &+ \beta\lambda\nu i_v^* + \beta\lambda^2 i_v^* + k\lambda\nu + \gamma\lambda\nu + \gamma\nu + k\gamma\lambda - \alpha\lambda^2 + \lambda^3 + \lambda^2\nu + k\lambda^2 + \gamma\lambda^2) = 0 \end{aligned} \tag{7.26}$$

which is of the form

$$\xi^3 + a_2\xi^2 + a_1\xi + a_0 = 0 \tag{7.27}$$

where the coefficients a_2, a_1 and a_0 are given by

$$\begin{aligned} a_2 &= \frac{\gamma^2\lambda + \gamma^2\nu + 3\gamma\lambda^2 + 4\gamma\lambda\nu + \beta\gamma\lambda + \gamma\nu^2 - \alpha\gamma\nu + k\alpha\gamma + 2\lambda^3 + 3\lambda^2\nu + \lambda\nu^2}{(\gamma + \lambda)(\lambda + \nu)} \\ &\quad + \frac{k\alpha\lambda + k\alpha\nu}{(\gamma + \lambda)(\lambda + \nu)} \\ a_1 &= \frac{\alpha\lambda^3 + k\alpha\gamma^2 + 2\alpha\gamma\lambda^2 + \alpha\gamma^2\lambda + 2\beta\gamma\lambda^2 + \beta\gamma^2\lambda + k\alpha\lambda^2 + k\alpha\nu^2 + \alpha\lambda\nu^2 + 2\alpha\lambda^2\nu}{(\gamma + \lambda)(\lambda + \nu)} \\ &\quad + \frac{k\alpha\gamma\nu + \alpha\gamma\lambda\nu + \beta\gamma\lambda\nu + 2k\alpha\lambda\nu + 2k\alpha\gamma\lambda}{(\gamma + \lambda)(\lambda + \nu)} \\ a_0 &= \alpha\lambda^2 - \gamma\lambda^2 - k\lambda^2 - \lambda^2\nu - \lambda^3 + k\alpha\gamma + \alpha\gamma\lambda + \beta\gamma\lambda + k\alpha\lambda + k\alpha\nu + \alpha\lambda\nu - k\gamma\lambda \\ &\quad - k\gamma\nu - \gamma\lambda\nu - k\lambda\nu \end{aligned} \tag{7.28}$$

From Equation 7.28, $a_2 > 0$ and $a_1 > 0$ since $\alpha, \beta, \gamma, \nu, \lambda, k \geq 0$ and $\alpha < \lambda$, but $a_0 = 0$ if

$$a_0 = \alpha\lambda^2 - \gamma\lambda^2 - k\lambda^2 - \lambda^2\nu - \lambda^3 + k\alpha\gamma + \alpha\gamma\lambda + \beta\gamma\lambda + k\alpha\lambda + k\alpha\nu + \alpha\lambda\nu \tag{7.29}$$

$$- k\gamma\lambda - k\gamma\nu - \gamma\lambda\nu - k\lambda\nu = 0 \tag{7.30}$$

$$\implies \quad k = \frac{\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)+\gamma(\alpha+\beta)]}{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma} = k^* \tag{7.31}$$

That is the threshold value of the rate of vaccination for the disease-free equilibrium state Q_{v0} of the model. Furthermore from Equations 7.3 if $k = k^*$, the endemic state coordinates are $e_v^* = i_v^* = 0$ and

$$\begin{aligned}
s_v^* &= \frac{(\lambda+\nu)(\lambda+\gamma)-\alpha(\lambda+\gamma+\nu)}{\beta\gamma} \\
&= \frac{(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma}{\beta\gamma} \\
&= \frac{\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]}{\lambda\beta\gamma} \\
&= \frac{\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]}{\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]-\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]+\lambda\beta\gamma} \\
&= \frac{\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]}{\lambda[(\lambda+\nu)(\lambda+\gamma-\alpha)-\alpha\gamma]+\lambda[(\lambda+\nu)(\alpha-\lambda-\gamma)]+\gamma(\alpha+\beta)} \\
&= \frac{\lambda}{\lambda+k}
\end{aligned} \tag{7.32}$$

Hence if $k = k^*$, $Q_v^* = Q_{v0} = (\frac{\lambda}{\lambda+k}, 0, 0)$ is a common threshold point where stability changes between the endemic equilibrium and the disease-free equilibrium states of the vaccination model in Equation 7.2. It can also be shown that $a_0 > 0$ if $k < k^*$, $a_0 < 0$ if $k > k^*$ and $a_0 = 0$ if $k = k^*$. It follows from the discussion above, that the coefficients of the characteristic equation in Equation 7.27 are

i. All positive, that is, $a_2 > 0$, $a_1 > 0$ and $a_0 > 0$, if $k < k^*$.

ii. One zero and two positive, that is $a_2 > 0$, $a_1 > 0$ and $a_0 = 0$, if $k = k^*$.

iii. One negative and two positive, that is, $a_2 > 0$, $a_1 > 0$ and $a_0 < 0$, if $k > k^*$, and

Using the methods described in Subsection 3.3.3, it can be numerically verified for $\beta, \gamma, \nu \geq 0$ conditional upon

$$\frac{q^2}{4} + \frac{p^3}{27} < 0, \tag{7.33}$$

that the characteristic Equation 7.27 has three distinct real roots.

Applying the Descartes' rule for polynomials in Theorem 4 [155] to Equation 7.27 , it follows that

- If $k < k^*$, all the eigenvalues are negative, that is, $\xi_1 < 0$, $\xi_2 < 0$ and $\xi_3 < 0$ and so the endemic state is asymptotically stable.
- If $k = k^*$, One eigenvalue is zero and two are negative, that is, $\xi_1 < 0$, $\xi_2 = 0$ and $\xi_3 < 0$ and there is stability crossover between the endemic and disease-free states.
- If $k > k^*$, one eigenvalue is positive and two are negative, that is, $\xi_1 < 0$, $\xi_2 > 0$ and $\xi_3 < 0$ and so the endemic state is unstable.

In conclusion, the endemic proportion equilibrium state $Q_v^* = (s_v^*, e_v^*, i_v^*)$ of the model is stable if the vaccination rate $k < k^*$ and unstable if the vaccination rate $k > k^*$. Furthermore, using Equations 7.8 and 7.16, it can be shown that $R_{v0} > 1$ if $k < k^*$

From Sections 7.4.1 and 7.4.3, it has been established that the vaccination model has two equilibrium solutions, namely the disease-free state $Q_{v0} = \left(\frac{\lambda}{\lambda+k}, 0, 0\right)$ and the endemic state $Q_v^* = (s_v^*, e_v^*, i_v^*)$. The disease-free equilibrium state Q_{v0} is global asymptotically stable if the vaccination rate k is greater than a threshold value k^* and $R_{v0} \leq 1$, where all the eigenvalues of the characteristic equation in Equation 7.13 are negative, whilst the endemic equilibrium state Q_v^* is unstable. The endemic state Q_v^* is asymptotically stable if the vaccination rate k is less than the threshold value k^* where all the eigenvalues of the characteristic equation in Equation 7.26 are negative and $R_{v0} > 1$, whilst the disease-free state Q_{v0} is unstable. If the vaccination rate k is equal to the threshold value k^*, the dynamical system of the vaccination model is at a crossover point where stability shifts between the disease-free equilibrium and the endemic equilibrium states. At this threshold value of k^*, the epidemiological threshold parameter $R_{v0} = 1$.

7.5 The threshold parameter R_{v0} as a function of the vaccination rate k

The plot of the threshold parameter R_{v0} as a function of the vaccination rate of $k \geq 0$ was produced, using Equation 7.8, to examine the impact of k on R_{v0}. The national and

regional plots were produced based on the national and regional parameters respectively, estimated from the model without the vaccination component in Chapters 5 and 6. These plots are displayed in Figures 7.2 and 7.3. In all the plots as k increases over the interval $[0, 1]$, R_{v0} declines until it flattens off beyond the estimated herd immunity threshold values H.

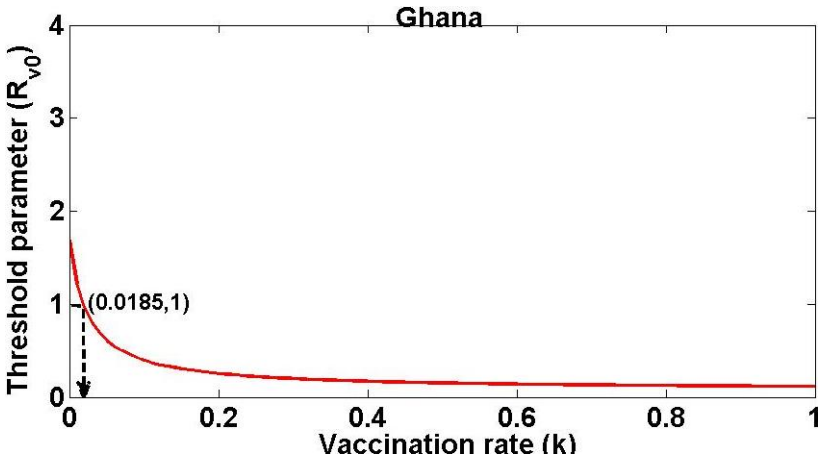


Figure 7.2: Vaccination rate versus basic reproduction number.

For the national plot in Figure 7.2, the fixed parameters were $\beta = 0.0480$, $\gamma = 0.1254$ and $\nu = 0$. The birth rate $\lambda = 0.249$ and vertical transmission rate $\alpha = 0.076\lambda$ were also the same values used in the parameter estimation of the model without the vaccination component. As k increases from 0, the threshold parameter R_{v0} drops sharply from the national value of $R_{v0} = 1.6854$ until it levels off at a vaccination rate of about $k = 0.4$, which is analogous to having achieved the herd immunity threshold of the population. By achieving a vaccination rate of about $k = 0.4$, that is higher than the estimated contact rate, the threshold parameter would be stabilised at a value way below unity, which indicates that the spread of hepatitis B is under control in the population. At the value of $R_{v0} = 1$, the rate of vaccination k attains a threshold value $k^* = 0.0185$ that is a crossover point of the model where stability shifts from the endemic equilibrium state Q_v^* to the disease-free equilibrium state Q_{v0}. This means that when the vaccination rate is $k > 0.0185$, the epidemiological threshold parameter is $R_{v0} < 1$ and the transmission and spread of the disease would decline in the population. However when the vaccination rate is $k < 0.0185$, the threshold parameter is $R_{v0} > 1$ which means that the transmission and spread of the disease would increase in the population.

For the regional plots in Figure 7.3, the fixed parameters β, γ, ν, λ and α used as input values for the simulation process, herd immunity values H and the threshold values of k^* are shown in Table 7.1. The threshold values k^* for the regions range from a minimum of 0.01 for Volta region to a maximum of 0.0657 for Upper West region. Three regions namely Volta, Ashanti and Eastern have threshold values of $k^* = 0.01$, $k^* = 0.0142$ and $k^* = 0.0167$ respectively that are less than the national value of $k^* = 0.0185$. This is consistent with the herd immunity threshold values of $H = 0.2684$, $H = 0.3386$ and $H = 0.3790$ for Volta, Ashanti and Eastern regions respectively that are also less than the national herd immunity threshold value of $H = 0.4067$.

Table 7.1: Input parameters for regional $R_{v0} - k^*$ plots and vaccination threshold k^* and herd immunity threshold H values.

	Input parameters					Threshold values	
Region	β	γ	ν	λ	α	k^*	H
Greater Accra	0.0416	0.2744	0	22.7	0.065788λ	0.0184	0.4316
Brong Ahafo	0.0475	0.2894	0	26.3	0.101436λ	0.0222	0.4309
Upper East	0.0602	0.3413	0	22.7	0.058538λ	0.0373	0.6071
Upper West	0.0899	0.3925	0	23.1	0.043616λ	0.0657	0.7312
Ashanti	0.0404	0.2672	0	25.7	0.075584λ	0.0142	0.3386
Eastern	0.0422	0.3083	0	25.4	0.074623λ	0.0167	0.3790
Western	0.1308	0.1848	0.0378	26.8	0.074974λ	0.0223	0.4462
Central	0.0603	0.1234	0	26.5	0.081798λ	0.0276	0.4892
Northern	0.0422	0.7698	0	24.0	0.08831λ	0.0209	0.4426
Volta	0.0359	0.1255	0	24.2	0.12087λ	0.0100	0.2684
Ghana	0.0480	0.1254	0	24.9	0.076λ	0.0185	0.4067

Note: λ and α are per $1,000$ population.

The values of k^* for the rest of the regions are above the national value as is the case of their corresponding values of H, except for Greater Accra region whose vaccination threshold value approximates the national value of $k^* = 0.0185$. Comparing the two quantities, a simple linear regression analysis showed that there is a positive correlation between H and k^* with p-value less than 0.0001 and a correlation coefficient of 0.9599. The result of the regression analysis and the coefficient of correlation indicate that the herd immunity threshold value H increases as the vaccination threshold k^* increases. This

means that a region with high herd immunity threshold value requires a high vaccination threshold and vice versa. For each of the regions, the value of R_{v0} levels off way below unity when the rate of vaccination $k > k^*$ is also in excess of the corresponding disease contact rate β which can be seen in Figure 7.3. Clearly in Table 7.1, the disease contact rate β for each region is greater than the corresponding threshold vaccination rates k^*. The stabilisation of the value of R_{v0} way below unity indicates that the disease is under control in the population. This also indicates that if the rate of vaccination k was greater than the contact rate β, the disease would be kept under control with time. It may not therefore be sufficient to achieve a rate of vaccination of $k > k^*$, but also to ensure that the rate of vaccination exceeds a value, which is likely to be the contact rate $k > \beta$, that is equivalent to having achieved the herd immunity threshold of the population in order to bring the disease under control.

7.6 Summary

Vaccination is the most important measure of intervention regarding prevention of hepatitis B in a population. In fact there is no cure for hepatitis B. Although acute hepatitis B has no treatment, treatment of chronic hepatitis B keeps down viral replication and slows progression of cirrhosis and liver damage, and thus sustains the life of an individual who is chronically infected. Since the depth of the prevalence of hepatitis B is a function of the depth of chronic infection in a population, it suffices to focus the attention of policy makers on vaccination that targets a complete cut off of the disease from a population. In view of this importance, a vaccination component was included in the original $SEIR$ model to examine the impact of vaccination on the transmission and spread of hepatitis B in Ghana.

In the modified model, vaccinated susceptible individuals are progressed directly into the recovered compartment by gaining immunity. The vaccine was assumed to have a 100% efficacy and was not expected to wane within the period of study. All other conditions pertaining to the original model were maintained in the new model, in addition to a vaccination rate of $k \geq 0$. Stability analysis of the vaccination model in Equation 7.2 indicated that the modified model has a disease-free equilibrium state $Q_{v0} = (\frac{\lambda}{\lambda+k}, 0, 0)$ that is globally asymptotically stable when the epidemiological threshold parameter $R_{v0} \leq 1$ and a unique endemic equilibrium state $Q_v^* = (s^*, e^*, i^*)$ when $R_{v0} > 1$. The stability analysis further indicated that there exists a certain threshold value of the rate of vaccination k^* such that if $k > k^*$, the threshold parameter $R_{v0} < 1$ and the disease-free equilibrium

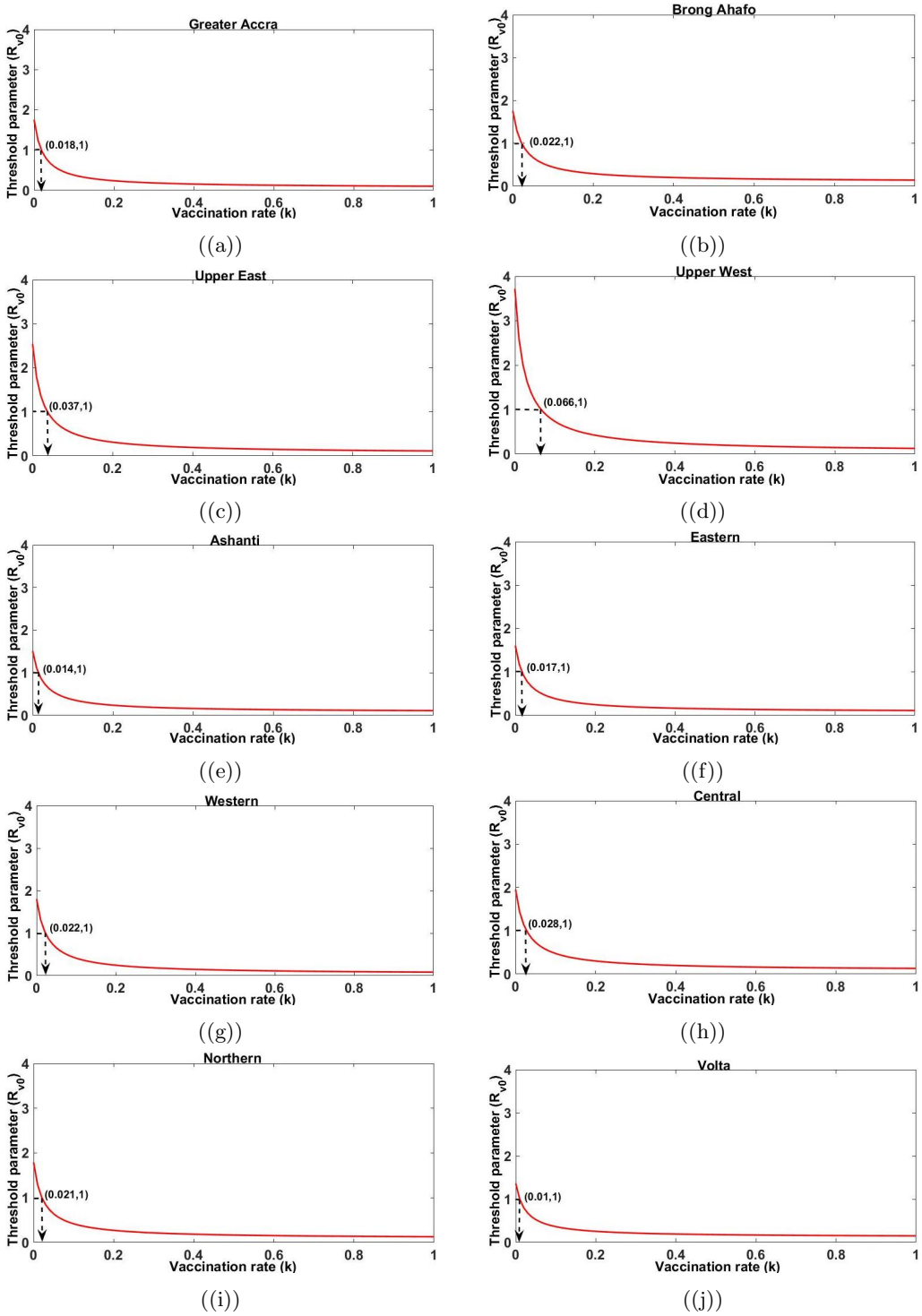


Figure 7.3: Regional plots of basic reproduction number against vaccination rate

state Q_{v0} is stable whilst the endemic equilibrium state Q^* is unstable; and if $k < k^*$, $R_{v0} > 1$ and the disease-free equilibrium state is unstable whilst the endemic equilibrium state is stable. If $k = k^*$, $R_{v0} = 1$ and there is a crossover point in the dynamics of the model in Equation 7.2 where the disease-free and endemic equilibrium states coincide and stability shifts between the two equilibrium states.

The impact of vaccination on the model was examined based on the impact of the rate of vaccination k on the epidemiological threshold parameter R_{v0}. By holding the key parameters β, γ, ν, α and λ in the vaccination model fixed at the values estimated for the original model, the epidemiological threshold parameter R_{v0} was varied for $0 \leq k \leq 1$ and a plot of R_{v0} as a function of k was produced for Ghana as a whole and also for each of the ten regions of Ghana. Variation in R_{v0} with respect to $k \geq 0$ traces a path resembling a hyperbola starting from the value calculated for R_{v0} in the original model and declining until it flattens off way below unity when k is greater than the disease contact rate β for Ghana and each of the ten regions of Ghana.

In conclusion, the vaccination model is well-posed in that any solution starting within the set Σ remains in the set Σ. The system has a disease-free equilibrium state Q_{v0}, that is global asymptotically stable for $R_{v0} \leq 1$, and a unique endemic equilibrium state Q_v^* for $R_{v0} \leq 1$ and $R_{v0} > 1$ respectively. Thus the disease is said to be decreasing in the population when $R_{v0} \leq 1$ and is increasing when $R_{v0} > 1$. An increase in the rate of vaccination k in excess of a threshold value k^* causes R_{v0} to decline below unity, so that the disease free equilibrium state Q_{v0} becomes stable and the disease is under control. When k is greater than the disease contact rate β, the value of R_{v0} levels off and disease begins to die off in the population. A rate of vaccination k below the threshold value of k^* invariably causes R_{v0} to remain above unity, so that the endemic equilibrium state is stable and so the disease persists in the population. On the basis of the incidence data used the following recommendation

1. An effective vaccination intervention regarding prevention and control of hepatitis B in Ghana must target at the national disease contact rate of $\beta = 0.0480$, way in excess of the national vaccination threshold value of $k^* = 0.0185$ with regional values as displayed in Figure 7.1. A vaccination rate greater than the threshold value of the vaccination rate k^* would cause the decline of the disease, but achieving a vaccination rate in excess of the disease contact rate would adequately reduce the contact rate β, vertical transmission rate α and the latent rate γ that have been

indicated as driving the transmission and spread of hepatitis B and bring the disease under control in Ghana.

2. A vaccination intervention must target at the following groups of people who are often described as priority population [64, 156].

    a. All women at child bearing age; in order to prevent transmission of hepatitis B from mother to child. In this regard, screening of pregnant women for hepatitis B is therefore crucial. Especially those who have been diagnosed with the chronic infection must be referred to clinicians with the requisite expertise to manage the disease condition during the entire period of gestation.

    b. Infants soon after birth to prevent the newborn from contracting the disease during birthing. After completing the course of vaccination, any child born to a mother who is diagnosed of chronic hepatitis B must be referred to a paediatric service with expertise in viral hepatitis to be assessed and managed for chronic hepatitis B.

    c. Unvaccinated adults who are at higher risk of infection. These include, but are not limited to, men who have sex with men, sex workers, people who inject drugs, partners and other household and intimate contacts of people diagnosed with chronic hepatitis B infection, people in custodial settings and people diagnosed with HIV and/or hepatitis C infection.

    d. Healthcare workers and emergency services workers.

    e. People travelling to and from high prevalence countries and communities.

    f. Vulnerable populations, including the homeless and people with mental health issues.

Chapter 8

Conclusion and recommendations

8.1 Summary of analysis and conclusion

High prevalence of hepatitis B and its associated burden, constitute a major public health concern to Ghana in the Sub-Saharan Africa. In spite of the serious threat posed to life and socioeconomic development, very little attention has been given to control and prevent hepatitis B in this West African country. Apart from the significant gaps reported in the evidence quantifying the burden of the disease on Ghana, there are many misconceptions leading to stigmatisation and public outcry for national policy attention. Although through WHO's assistance, tools and resources are available for the prevention and control of hepatitis B, Ghana faces challenges to build capacity towards extending these interventions country-wide. These challenges as outlined in the GHS annual report of 2014 include, but are not limited to, lack of a working policy on hepatitis B, lack of health infrastructure and equipment, inadequate health financing and financial arrangements, inadequate and disproportionate concentration of human resources for the health sector, poor health information system and inadequate collaboration of the health sector with other relevant sectors of the economy of Ghana.

As a contribution, this thesis sought to formulate an epidemiological model to study the transmission and spread of hepatitis B in Ghana in order to provide knowledge to address some of the challenges that constrain the implementation of available interventions. The Hepatitis B incidence data used in the study were obtained from HIU and CHIMG of the GHS. Due to inherent inadequacies in the collection and compilation of the hepatitis B incidence data from a poorly-resourced country like Ghana, the national and regional data were scaled by a factor corresponding to the regional disease reporting rates presented in

the 2014 report of the GSS in order to make meaningful conclusions. The main objectives of the study were:

1. To formulate an appropriate compartmental model, which incorporates the limitations identified in models previously applied to hepatitis B in Ghana, to estimate model parameters using hepatitis B incidence data from Ghana, and to use the model to examine the transmission and spread of the pandemic of the disease in Ghana.

2. To subject the formulated model to sensitivity and stability analysis to assess its veracity and to examine how robust the model will be in the face of perturbation.

3. To predict the future of the national hepatitis B pandemic on the basis of the model developed and further examine the regional burden.

4. To investigate the impact of vaccination on the incidence and spread of hepatitis B, and interpret the results in a way that will be useful to policy makers in taking informed decisions towards the prevention and control of the disease in the public health setting of an economy.

Generally, the disease was found to persist in Ghana with the disease intensity increasing from south to north across the ten regions of the country. This trend of the disease was found to have a significant association with poverty inequalities and health sector differentials across the regions of the country. Other possible factors that are widely believed to have impacted the disease pattern include, but are not limited to, the intra and interregional and also international hepatitis B prevalence disparities mainly driven by migration of the population. The introduction of a vaccination component in the model showed that an increase in vaccination rate reduces the epidemiological threshold parameter way below unity, indicative of a significant impact of vaccination on the transmission and spread of hepatitis B in the population of Ghana. In the ensuing sections, a summary of discussions and conclusion of results of the study, as well as, some limitations and recommendations for possible future work on hepatitis B in Ghana and by extension the Sub-Saharan Africa are presented.

8.1.1 The formulated compartmental model

A $SEIR$ deterministic compartmental model that incorporates vertical transmission and the proportionate mass-action term was employed to model the transmission and spread of hepatitis B in Ghana. The model was defined by a system of ordinary differential

equations which divided the population N(t) into $S(t)$ - susceptible, $E(t)$ - exposed, $I(t)$ - infectious and $R(t)$ - recovered compartments such that $S(t) + E(t) + I(t) + R(t) = N(t)$. With a fraction α of births presenting with hepatitis B, birth fluxes of $\alpha(I + E)$ and $\lambda N - \alpha(I + E)$ due to vertical transmission were recruited into the model through the exposed and susceptible compartments of the model respectively. In addition to vertical transmission and the mass-action term, the model also addressed the latent period which many studies have indicated as a very important feature in modelling hepatitis B.

The model has two equilibrium solutions, namely the disease-free $Q_0 = (1, 0, 0)$ and endemic equilibrium $Q^* = (s^*, e^*, i^*)$ states, where s^*, e^* and i^* are given in Equation 3.7. Stability analysis of the model was in terms of the proportions of the population instead of the absolute numbers and disease persistence meant uniformly persistence. Both the proportionate and absolute numbers of the population can be used to predict the spread of infectious diseases in a population in the same manner although the same outcome cannot be guaranteed. The stability analysis indicated that the disease-free equilibrium state Q_0 is globally asymptotically stable when $R_0 \leq 1$ and unstable when $R_0 > 1$, and the unique endemic equilibrium state Q^* is asymptotically stable when $R_0 > 1$ and unstable when $R_0 \leq 1$. A threshold contact rate β^* defines a crossover point in the dynamical system where stability shifts between the disease-free and endemic equilibrium states. The disease-free equilibrium is stable whilst the endemic equilibrium is unstable if the contact rate $\beta < \beta^*$, and the disease-free state is unstable whilst the endemic state is stable if $\beta > \beta^*$. The endemic and the disease-free states coincide when $\beta = \beta^*$

8.1.2 Parameter estimation

The model parameters $(\beta, \gamma, \nu) \in \mathbb{R}^3_+$ were estimated by minimising the difference between the observed and predicted data by a least squares approach. This nonlinear least squares optimisation problem was solved using a hybrid method that combines a GA and a modified LM algorithm. As a nongradient randomised search method, the GA is applied first to provide a global search of the solution space and identify solutions that are closed to optimal. The LM algorithm, being a gradient method, is then applied to refine the solution generated by the GA. The initial state variables (s_0, e_0, i_0) were estimated as part of the process of estimating the model parameters (β, γ, ν). This was because the initial state variables were not known, and preliminary sensitivity analysis showed some variations in the model predictions due to the choice of the initial conditions.

8.1.3 Analysis of national and regional results

The initial state variables estimated for Ghana (national) were $(s_0, e_0, i_0) = (0.55, 0.40, 0.04)$, which indicated that at the start of the study in 2008, the estimated initial susceptible, exposed and infectious percentages of the population were 55%, 40% and 4% respectively. Apart from Upper East and Central regions, the estimated initial state variables of the remaining regions were different compared with the national values. Whilst the estimated initial susceptible proportions were either 0.55 or 0.5, the exposed and infectious proportions ranged from 0.15 to 0.45 and 0.01 to 0.4 respectively. The national parameters estimated for the contact rate β, latent rate γ and recovery rate ν for disease transmission were 0.0480, 0.1254 and 0 respectively. The regional parameters estimated for the contact rate β and latent rate γ range from 0.0359 to 0.1308 and 0.1234 to 0.7698 respectively whilst the recovery rate ν for all the regions was 0, except Western region whose recovery rate was 0.0378. The 0 recovery rate indicated that none of the infected persons was able to clear the disease at the acute stage as characterised by the dynamics of the disease. Otherwise, the 0 recovery rate could also be a numerical artefact resulting from with the estimation process.

From an initial state of $(s_0, e_0, i_0) = (0.55, 0.40, 0.04)$, the national disease is predicted to stabilise at the endemic proportion equilibrium state $Q^* = (0.5741, 0.0706, 0.3553)$ with time, where about 57.4% of the population are estimated to be susceptible, 7.1% are exposed and 35% are infectious. A threshold contact rate of $\beta^* = 0.0276$ was calculated, where crossover of stability occurs between the endemic and the disease-free equilibrium states. Furthermore, the national herd immunity threshold value was calculated as $H = 0.4067$ which indicated that if about 41% of the population was immune hepatitis B in Ghana would be brought under control. The national value of the epidemiological threshold parameter was calculated as $R_0 = 1.6854$. Apart from Ashanti, Eastern and Volta regions whose values of R_0 were less than the national value, the remaining seven regions had values that were greater than the national value. This indicated that the intensity and burden of hepatitis B in Ashanti, Eastern and Volta regions is below the national average, whilst it is higher in the case of the remaining seven regions. Greater Accra and Brong Ahafo regions had an approximate value of $R_0 = 1.76$ which indicated a similar intensity and burden of hepatitis B in the two regions. The least and greatest values of $R_0 = 1.3669$ and $R_0 = 3.7212$ were calculated for Volta and Upper East regions respectively.

8.1. Summary of analysis and conclusion

The national and regional values of the epidemiological threshold parameters R_0 calculated were all greater than unity, which indicated that hepatitis B persists in all ten regions of Ghana. A percentage difference of about 172%, representing a range of 2.3543, between the least and the greatest regional epidemiological threshold parameters R_0 shows significant variability in the values, which indicated that there are significant disease differentials across the regions of Ghana. These disease disparities obviously come with different disease burdens across the ten regions of the country and certainly require different control strategies. Interestingly, the calculated regional epidemiological threshold parameters R_0 and the corresponding regional herd immunity threshold values H are linearly related. Thus regions with higher values of R_0, which signifies higher transmission and spread of hepatitis B, require higher proportions H of the population to be immune in order to control the disease. With the exception of the Central and Western regions, the values of R_0 for the regions show an increasing trend from south to the north across Ghana. This indicated that the transmission and spread of hepatitis B and its associated burden increase from south to the north across the regions of the country, although the Central and Western regions deviate from the trend.

The threshold parameter R_0 increases as the vertical transmission α and contact β rates increase, although α has a larger impact on R_0 compared to β. This indicated that vertical transmission has a larger impact on the disease transmission compared to transmission through horizontal routes. Reducing transmission of hepatitis B from mother to child would have much more impact on controlling the disease, although the other routes of transmission must not be neglected. Variation of R_0 with respect to the latent γ and recovery ν rates is hyperbolic in shape. As γ increases, R_0 increases until it peaks above unity and levels off after $\gamma = 0.4$. The latent period is therefore important in modelling hepatitis B in the population due to its impact on R_0. As ν increases however, R_0 drops until after $\nu = 0.4$ when it levels off below unity. This indicated that with an intervention that adequately increases the recovery rate would reduce the disease transmission and spread in the population.

The quantum of change in each of the model parameters from the baseline values, needed to shift stability from the endemic state to the disease-free state, indicated that the contact rate β requires the least change compared to the birth rate λ, latent rate γ and vertical transmission rate α. Furthermore, the rate of change of endemic proportion variables $Q^* = (s^*, e^*, i^*)$ with respect to the model parameters, indicated that unit increases in contact β, latent γ and vertical transmission α rates increase the infectious population and

decrease the susceptible population and tend to shift model stability towards the endemic state Q^*. A unit increase in α has a larger impact on the shift in equilibrium towards the endemic state Q^* compared to β and γ. Unit increases in birth rate λ and recovery rate ν however increase the susceptible population and decrease the infectious population and tend to shift stability towards the disease-free state Q_0. A higher birth rate is not desirable due to its socioeconomic and cultural implications on the society. However, a greater proportion of the population can be immunised to disrupt many chains of infection and reduce the likelihood of a contact with an infectious individual to keep the disease from spreading. A policy intervention to control the transmission and spread of hepatitis B in the population is recommended to aim at reducing the contact, vertical transmission and the latent rates. A recommended intervention that is considered to be optimal is vaccination backed by treatment of chronic hepatitis B.

A simple regression analysis performed on the regional values of R_0 and H, poverty headcount and the endemic proportions variables s^*, e^* and i^* showed a positive correlation between poverty and the threshold values R_0 and H, a positive correlation between i^* and the threshold values R_0 and H, and a negative correlation between s^* and i^*. This indicated that regions with high threshold values of R_0 and H tend to have high poverty levels and high proportions of infectious population, and therefore increased transmission and spread of hepatitis B. This result also indicated that regions with high levels of infectiousness tend to have low susceptible proportions as expected. In relation to the GSS's living standard survey report of 2010, which indicated that poverty levels increase from south to north of Ghana, it can be concluded that transmission and spread of hepatitis B generally increases from south to north across the regions of Ghana. Interregional and international hepatitis B prevalence disparities is another phenomenon that potentially impact the pattern of transmission and spread of the disease, mainly through migration of people, across the regions of the country.

8.1.4 The vaccination model

In the absence of complete cure, vaccination is the single most effective intervention with respect to the control of hepatitis B [12, 148, 153, 154]. To examine the impact of this intervention on the transmission and spread of hepatitis B in Ghana, the original $SEIR$ model in Equation 3.6 was modified to include a vaccination component that directly transfers the vaccinated susceptible population into the immune class R of the model at the rate $k \geq 0$. Stability analysis of the model indicated that the disease-free equilibrium state

is globally asymptotically stable when its epidemiological threshold parameter $R_{v0} \leq 1$ and unstable when $R_{v0} > 1$, whilst the unique endemic equilibrium state is stable when $R_{v0} > 1$ and unstable when $R_{v0} \leq 1$. The model has a threshold value of k^* such that if the vaccination rate is equal to k^*, then $R_{v0} = 1$ and there is stability crossover between the disease-free and the endemic equilibrium states. If $k > k^*$, then $R_{v0} < 1$ and the disease-free equilibrium state is globally asymptotically stable whilst the endemic equilibrium state is unstable, and if $k < k^*$, $R_{v0} > 1$ and the unique endemic equilibrium Q_v^* is asymptotically stable whilst the disease-free equilibrium state Q_{v0} is unstable.

In the national and all the regional cases, the plots of R_{v0} as a function of k showed a hyperbolic relationship consistent with Equation 7.8. At $k = 0$ when there is no vaccination intervention, the model is reduced to the original model in Equation 3.6 and so the value of $R_{v0} = R_0$. As k was increased from 0 to 1, the value of R_{v0} dropped from the value of R_0 until it levelled off at a value less than unity when the value of k exceeded the disease contact rate β. This indicated the disease would be brought under control, if the rate of vaccination k was increased in excess of the contact rate β.

8.2 Policy recommendation

The discussions and conclusions indicate that hepatitis B persists in Ghana. Vertical transmission was found to be the major driver of the transmission and spread of the disease in Ghana, although transmission through horizontal routes cannot be neglected. The results of the study are indicative of the fact that hepatitis B can be prevented through vaccination. Other studies have indicated that vaccination, when backed by treatment of chronic hepatitis, gives the best result [90]. Notwithstanding the competing priorities and short term focus of policy makers and/or governments, the following recommendations are made in line with the key findings of this study to inform policy formulation and guidance for the control and prevention of hepatitis B in Ghana. In all of these considerations, cost remains a key barrier especially in the acquisition of vaccines and antiviral therapy and other logistics and resources [156, 157].

The key to achieving significant successes in prevention, treatment and control is to formulate a national action plan, in a framework of a strategic policy, that reflects the experience and aspirations of the affected people at the community, regional and national levels [156, 157, 158]. This requires a broad consultative process led by a team of experts from the healthcare sector and involving relevant governmental agencies and NGOs, and a

cross-section of the affected people. It also requires identification and collection of quality data that adequately describe the public health situation, as well as the personal impact of hepatitis B on the population of Ghana [156, 157]. The goals of the national action plan must therefore include, but not be limited to, reducing transmission, morbidity and mortality and minimise the personal and social impact of persons living with hepatitis B [156, 157, 158, 159].

8.2.1 Prevention of hepatitis B transmission

In the absence of complete cure to hepatitis B, prevention is the most important consideration for the control of the disease [157]. Unlike other viral hepatitis infections, HIV and sexually transmitted infections (STI) that can be prevented by adopting and maintaining protective behaviours, the most effective means to prevent the transmission of hepatitis B is vaccination. Vaccination is particularly important in newborns and children, because of the risk of vertical transmission and disease progression to the chronic stage with its associated complications [10, 35]. Nevertheless, the impact of vaccination on adults who are at higher risk of infection through other routes of transmission cannot be overemphasised. Childhood vaccination becomes relevant when it is included in the national immunisation programme and is universally accessible [156, 157, 160]. In view of the above and on the basis of the findings of this study, it is recommended that:

1. On the basis of the parameters estimated for the model, given the hepatitis B incidence dataset used in the study

    i. Vertical transmission rate has a greater impact on transmission and spread of hepatitis B in Ghana compared to horizontal transmission (routes other than vertical transmission). Hence an immunisation intervention targeted at reducing transmission of hepatitis B from mother to child (vertical transmission) will have much more impact on controlling the disease compared to horizontal transmission, although horizontal transmission must not be neglected.

    ii. A national vaccination rate exceeding a threshold value of $k^* = 0.0185$, with regional threshold values displayed in Table 7.1, will cause the transmission and spread of hepatitis B to decline in Ghana.

    iii. Achieving a national herd immunity threshold value of $H = 0.4067$, with the regional values displayed in Table 7.1, would bring the disease under control in Ghana.

iv. Any immunisation intervention targeted at reducing the transmission and spread of hepatitis B in Ghana should aim at reducing the contact rate to below a national threshold value of $\beta^* = 0.0276$.

2. A comprehensive national vaccination programme is tailored to cover the following as a matter of priority [156, 157, 160].

   i. All women at child bearing age including pregnant women, to prevent mother-to-child transmission. Screening of pregnant women for hepatitis B is therefore crucial and those who are diagnosed with the chronic infection must be referred to clinicians with the requisite expertise to manage the disease condition during the entire period of gestation.

   ii. Infants soon after birth, preferably within 24 hours, to prevent the newborn from contracting the disease during birthing; Any child born to a mother who is diagnosed of chronic hepatitis B must have the HBV vaccine in conjunction with the hepatitis B immune globulin ($HBIG$), to reduce the likelihood of contracting the disease at birth. Such infants must be referred immediately to a paediatric service with expertise in viral hepatitis to be assessed and managed for chronic hepatitis B.

   iii. Unvaccinated adults especially those who are at higher risk of infection, to prevent horizontal transmission of hepatitis B; These include, but are not limited to:

      – Men who have sex with men, sex workers, people who inject drugs, partners and other household and intimate contacts of people diagnosed with chronic hepatitis B infection, people in custodial settings and people diagnosed with HIV and/or hepatitis C infection.
      – Healthcare workers and emergency services workers.
      – People travelling to and from high prevalence countries and communities.
      – Vulnerable populations, including the homeless and people with mental health issues.

3. Routine mass screening and laboratory diagnosis be made affordable and accessible through funding from the National Health Insurance Scheme (NHIS) and provision of well-resourced laboratories at the community, district and regional levels. This should include provision of opportunistic hepatitis B testing and vaccination [156, 157, 160]:

i For pregnant women during antenatal care.

ii. For young people who may have missed vaccination at birth.

iii. For adults at their routine health checks.

iv. In association with recruitment activities involving public institutions as part of medical examination requirements.

v. For health care professionals and emergency services workers.

vi. At the instance of clinicians in primary healthcare at all levels of health delivery.

4. Research, public advocacy and general education on hepatitis B should be promoted at the community, regional and national levels to [156, 157, 160]:

   i. Provide an evidence base for effective public health attention and response to the disease pandemic.

   ii. Increase the understanding of hepatitis B and the support available to persons who are infected, in order to reduce the burden of the disease and improve health outcomes.

   iii. Increase knowledge among sex workers and people who inject drugs.

   iv. Increase public awareness and reduce misconception about the disease that leads to stigmatisation and discrimination against infected persons.

   v. Develop and strengthen effective collaboration between communities and all levels of government and NGOs, as well as among medical, healthcare, research and scientific communities at local, regional and national levels.

8.2.2 Treatment of chronic hepatitis B

Essentially, a vaccination programme backed by a treatment regimen for chronic hepatitis B is highly recommended as the optimal strategy to control transmission and spread of hepatitis B [90, 156, 157, 158, 159]. Although there is no specific treatment for acute hepatitis B, there are effective antiviral drugs for treatment of chronic hepatitis B that keep down viral replications and reduce risk of progression to liver disease and death of an infected person [157]. Persons who are diagnosed with chronic hepatitis B should be referred to designated health facilities for clinical management and treatment. A key barrier to treatment for a resource-constrained setting like Ghana, has always been the cost of medicines, diagnostic and monitoring facilities and staff. The following recommendations are made based on the admission by the GHS and MOHG in annual reports of 2011 and

2014 regarding challenges of inadequate provision and supply of standard health facilities, staff and logistics across the country, especially in the vast rural settings [16, 59]:

1. In view of the high cost of treatment of chronic hepatitis B, it is recommended that acquisition of antiviral drugs is funded through the NHIS and with support from NGOs and other developing partners.

2. The complexity of the HBV makes treatment regimens for chronic hepatitis B often complicated [156, 157]. Thus, the level of awareness and knowledge of general practitioners and primary care doctors needs consistent improvement and upgrading regarding management of persons with hepatitis B. All healthcare workers involved in chronic hepatitis B care must be given a standardised training in administering the antiviral therapy in addition to regular in-service training and seminars to keep them abreast with options for treatment of chronic hepatitis B.

3. The government, with support from its developing partners, must provide funding for adequate provision and resourcing of health facilities at all levels of service delivery for chronic hepatitis B care and treatment. This must provide increased access to adequate clinic infrastructure, healthcare staff, a referral system, laboratory and diagnostic services, reliable and affordable supply of antiviral medicines to enhance disease surveillance and ensure effective ways to collect and compile adequate database that would facilitate monitoring and follow-ups for treatment and care of hepatitis B at all levels especially in the poor communities.

8.3 Limitations of study

The study sought to formulate an epidemiological model based on hepatitis B incidence data, to examine the transmission and spread of hepatitis B pandemic in Ghana. The study was conducted to achieve a set of targeted objectives listed in Section 1.6 that served as a guide. Although the set targets were achieved, there were some constraints that could potentially have had some adverse effect on the outcomes obtained. These limitations include the following:

1. The hepatitis B incidence data used in the study constitute only cases that had been reported to the RIUs and CHIMs of the GHS. The GHS's admission of lack of the needed tools and personnel to effectively collect and compile data on viral hepatitis is an indication of underestimation and under-reporting of the true incidence cases

of hepatitis B in Ghana. In Ghana, the existing health emergency preparedness and response plan is targeted at communicable diseases like malaria, HIV and more recently ebola and given high national attention at the expense of equally threatening diseases like viral hepatitis. A survey on risk communication of health emergency conducted indicated that most of the information is churned out by media [71]. These are significant gaps in the evidence quantifying the burden of hepatitis B on individuals, the healthcare system and the community. Although the data were scaled, this limitation could potentially have affected the conclusions of this work.

2. Hepatitis incidence for cases of persons aged< 5 were assumed to represent vertical transmission and were used in the computation of the vertical transmission fraction α in the model [23]. The risk of vertical transmission of HBV, especially in poorly-resourced settings like Ghana, is quite a complicated issue. Although the standard way of measuring the risk of vertical transmission largely depends on maternal HBeAg positivity, it is acknowledged that the size of maternal viral load is also an important determinant [7, 93]. Vertical transmission of HBV most likely occurs during birth due to the nature of the virus, although it may also occur postpartum [7, 93]. In the vast rural settings of Sub-Saharan Africa and in particular Ghana, screening and testing of neonates and mothers for HBV is not a mandatory health policy due to lack of a requisite health facility and/or the unaffordable cost of service [102]. HBV infection of these categories of persons most likely would not normally be detected immediately after birth as routinely done in the developed world [7, 93]. Such cases may be reported and captured in the national database later during early childhood and categorised based on some medical history as indicated in [102]. This is noted as a constraint that could potentially have affected the findings of this work.

8.4 Research contribution

Although theoretical analysis of deterministic compartmental modelling and its application to infectious disease epidemiology has been widely studied, application of this modelling technique to specific incidence data to study a particular disease epidemiology in a population is not common, especially, in the Sub-Saharan Africa and in particular Ghana. A review of literature indicated a few applications of the SIR deterministic compartmental modelling to hepatitis B incidence data in Ghana, that neglect the latent period. In this study, the latent period was found to be important in modelling the dynamics of hepatitis B in a population and cannot be ignored. Using the $SEIR$ model, the findings indicated

that an increase in the latent rate, relative to the other parameters of the model, tend to increase the infected population and a decrease in the susceptible population. The findings also indicated that the epidemiological threshold parameter R_0 is sensitive to the latent rate. An increase in the latent rate, relative to the other model parameters, tend to increase R_0 until it stabilises above unity, an indication that the disease persists in a population. Apart from the latent period, the commonly used pseudo mass-action incidence factor βSI was also replaced with the standard proportionate incidence term $\frac{\beta SI}{N}$ which is more appropriate in dealing with a population that varies in size with time [75, 76].

Vertical transmission of hepatitis B is another important area that has not been adequately studied, particularly with the application of deterministic compartment modelling to existing infectious disease data in the Sub-Saharan African region and Ghana. Clinical surveys and systematic reviews of the global burden of hepatitis B have indicated that vertical transmission is a major route of transmission of hepatitis B in the endemic regions. In this study, birth fluxes of $\alpha(I + E)$ and $\lambda N - \alpha(I + E)$, where α is the fraction of the infected population due to vertical transmission, was introduced into the $SEIR$ model to examine the impact of vertical transmission on the population as applied to a hepatitis B incidence data. The findings indicated that the model stability and so the disease persistence was most sensitive to the vertical transmission rate, relative to the other model parameters.

For disease modelling involving deterministic compartment models, estimation of parameters is an important process leading to a full determination of the health outcomes. It is for this reason that an application of a hybrid optimisation process, which combined a nongradient method (GA) and a gradient method (LM algorithm), is unique and transparent in the parameter estimation of this study. Whilst the GA provides a global search of the solution space to identify solutions which are assumed to be close to optimal, the LM algorithm refines the solution generated by the GA by increasing the likelihood of approximating the optimal solution. Based on the estimated parameters, the findings indicated that hepatitis B persists in Ghana and the intensity and burden increase from south to north across the regions of the country. The incidence and spread is higher in poorer communities compared to the nonpoor due to health sector differentials from south to north across the regions of Ghana. Prevalence disparities along interregional and international boundaries also potentially impacts the hepatitis B epidemiology in the population of Ghana.

8.5 Recommendation for future work

The study applied a $SEIR$ deterministic compartmental model with vertical transmission to existing incidence data, to examine the transmission and spread of hepatitis B in Ghana. The deterministic model considered the individuals in the population to be more interdependent and the health outcomes were fully determined by the estimated parameter values and the initial conditions without any element of randomness. A stochastic approach which considers the population as independent units of observation, may be employed to estimate the probability distribution of potential health outcomes based on the random variations of the input data with time. The element of randomness and chance fluctuations in such a process could be modelled using time series or maximum likelihood estimation processes, to mention but a few.

The global epidemiology of HBV is changing partly because of the impact of migration between high- and low-prevalence populations. Migration across health and disease differentials significantly influences the epidemiology of hepatitis B globally and in particular the recipient nations. This study discussed migration impact on hepatitis B in the population of Ghana on the basis of prevalence differentials between regions and with neighbouring countries, but did not incorporate migration in the model due to lack of data on hepatitis B related to migration. The $SEIR$ model could be modified to include a migration compartment to examine migration effect of hepatitis B on the Ghanaian population if adequate data is available.

A modification of the $SEIR$ model could also be made to split the infectious class into acute and chronic compartments to examine the effects of each of these two stages of hepatitis B on the model and also in a population. Age is an important factor in determining the risk of progression to chronic hepatitis B and that could be studied using a $SEIR$ model. Another possible area of study would be to examine the impact of HBV coinfection with other blood borne diseases like $HIV/AIDS$, HCV and HDV in a population. These suggested areas of studies would be possible if there is an availability of relevant and adequate data.

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Appendix A

Parameter estimation codes

A.1 Main combination

```
clear
% Combined Genetic Algorithm followed by Gradient Approach.
global lambda alpha beta mu gamma nu time sick T_max y0
   N_current
format long
% Data
temp=xlsread('datafile.xlsx');
%temp=xlsread('Book115_Adjusted1.xlsx');
%temp=xlsread('Artificial_Data_I_incidence.xlsx'); % Change
   the IC.
time = [0; temp(:,1)]'; % Insert the zeros time.
sick=zeros(1,size(temp,1)+1);
for i=2:size(temp,1)+1
    time(i)=time(i)/12; % Convert time to units of years.
    sick(i) = sum(temp(1:i-1,4)); % Sum incidence data to get
        accumulation.
end
% Inputs
% N_current=25758108;
N_current=Total_population; % Current Population.
lambda = Birth_rate;
alpha = (vertical_transmission_fraction)*lambda;
```

```
mu = Death_rate;
T_max=max(time);
y0=[0.6 0.35 0.05]; % Initial susceptible, exposed and
   infectious fractions
                    %respectively.
% Also need to consider the range for the parameter exponents
    in
% 'gene_to_values.m' and the ga input arguments.
[P, best,best_val] = ga_SR(100, 300, 0.01, 150,0.1); % Note
   that second
                                          % argument must be a
                                             multiple of 3.
[beta, gamma, nu] = gene_to_values(best);
SSE=1/best_val;
display(beta)
display(gamma)
display(nu)
display(SSE)
[t, y] = ode15s('seir', [0 T_max], y0);
% Need to calculate the incidence h and population size N.
   Use the Trapezoid rule and
% interpolate s, i and N linearly.
h=zeros(size(t,1),1);
N=zeros(size(t,1),1);
for j=1:size(t,1)
    N(j)=N_current * (1+lambda-mu)^(t(j)-7); % 7 - period of
       study in years
end
% Note - t is NOT uniform.
for j=2:size(t,1)
    h(j)=h(j)+beta/2*(y(1,1)*y(1,3)*N(1)*(t(2)-t(1))+y(j,1)*y
       (j,3)*N(j)*(t(j)-t(j-1)));
    if j>2
        for k=2:j-1
            h(j)=h(j)+beta/2*y(k,1)*y(k,3)*N(k)*(t(k)-t(k-1))
```

```
                +beta/2*y(k,1)*y(k,3)*N(k)*(t(k+1)-t(k));
        end
    end
end
figure
plot(t, h, time, sick, 'rs')
figure
plot(t, y(:,1), 'b', t, y(:,2), 'r', t, y(:,3), 'g')
% Gradient Method
options = statset('Display', 'iter','TolFun',10^(-16));
[values,r] = nlinfit_nneg_v2(time, sick, 'infection', [beta
   gamma nu], options);
% r = residuals
SSE=r*r';
display(values)
display(SSE)
% Set beta and delta to the values found by nlinfit
beta = values(1);
gamma = values(2);
nu = values(3);
% Evaluate the ODE with the new values for beta and delta
[t, y] = ode15s('seir', [0 T_max], y0);
% Need to calculate the incidence h and population size N.
   Use the Trapezoid rule and
% interpolate s, i and N linearly.
h=zeros(size(t,1),1);
N=zeros(size(t,1),1);
for j=1:size(t,1)
    N(j)=N_current * (1+lambda-mu)^(t(j)-7);
end
% Note - t is NOT uniform.
for j=2:size(t,1)
    h(j)=h(j)+beta/2*(y(1,1)*y(1,3)*N(1)*(t(2)-t(1))+y(j,1)*y
       (j,3)*N(j)*(t(j)-t(j-1)));
    if j>2
```

```
        for k=2:j-1
            h(j)=h(j)+beta/2*y(k,1)*y(k,3)*N(k)*(t(k)-t(k-1))
               +beta/2*y(k,1)*y(k,3)*N(k)*(t(k+1)-t(k));
        end
    end
end
% Display the results
figure
plot(t, h, time, sick, 'r*')
figure
plot(t, y(:,1), 'b', t, y(:,2), 'r', t, y(:,3), 'g')
```

A.2 Squared error

```
% squared_error(data_time, data_points, fn_time, fn_points)
%   Calculates the squared error between a set of data points
    and a
% series of points representing a function output.
% Inputs:
%   data_time   - A 1D array containing the time points of
   the data
%   data_points - A 1D array of the data values
%   fit_time    - A 1D array of the time points for the
   function output
%   fit_points  - A 1D array of the function values
% Output:
%   error = the sum of the squared residuals of the data vs.
   the function
function error = squared_error(data_time, data_points,
   fn_time, fn_points)
    % Intepolate the fit to match the time points of the data
    fn_values = interp1(fn_time, fn_points, data_time);
    % Square the error values and sum them up
    error = sum((fn_values - data_points).^2);
```

A.3 SEIR

```
% seir.m
% Implements an SEIR infection model
% dS/dt = lambda N - alpha (I + E) - beta SI/N - mu S
% dE/dt = beta SI/N + alpha (I + E) - mu E - gamma E
% dI/dt = gamma E - mu I - nu I
% dR/dt = nu I - mu R,  Not needed since S+E+I+R=1
% Inputs:
% t - Time variable: not used here because our equation
%     is independent of time, or 'autonomous'.
% x - Independent variable: this contains four
%     populations (S, E, I, and R)
% Output:
% dx - First derivative: the rate of change of the
   populations
function dx = seir(t, x)
  global lambda alpha beta mu gamma nu;
  dx = [0; 0; 0];
  dx(1) = lambda - alpha * (x(3) + x(2)) -beta * x(1) * x(3)
     - mu *x(1) - x(1) * (lambda - mu);
  dx(2) = beta * x(1) * x(3) + alpha * (x(3) + x(2)) - mu * x
     (2) - gamma * x(2) - x(2) * (lambda - mu);
  dx(3) = gamma * x(2) - mu * x(3) - nu * x(3) - x(3) * (
     lambda - mu);
```

A.4 Nonlinear fit

```
function [beta,r,J,Sigma,mse] = nlinfit_nneg_v2(X,y,model,
   beta,options)
% Version 2 corrects an error in the original nneg
   modification.
if nargin < 4
    error('stats:nlinfit:TooFewInputs','NLINFIT requires four
        input arguments.');
elseif ~isvector(y)
    error('stats:nlinfit:NonVectorY','Requires a vector
       second input argument.');
```

```
end
if nargin < 5
    options = statset('nlinfit');
else
    options = statset(statset('nlinfit'), options);
end
% Check sizes of the model function's outputs while
   initializing the fitted
% values, residuals, and SSE at the given starting
   coefficient values.
model = fcnchk(model);
try
    yfit = model(beta,X);
catch
    [errMsg,errID] = lasterr;
    if isa(model, 'inline')
        error('stats:nlinfit:ModelFunctionError',...
              ['The inline model function generated the
                 following ', ...
               'error:\n%s'], errMsg);
    elseif strcmp('MATLAB:UndefinedFunction', errID) ...
                && ~isempty(strfind(errMsg, func2str(model)))
        error('stats:nlinfit:ModelFunctionNotFound',...
              'The model function ''%s'' was not found.',
                 func2str(model));
    else
        error('stats:nlinfit:ModelFunctionError',...
              ['The model function ''%s'' generated the
                 following ', ...
               'error:\n%s'], func2str(model),errMsg);
    end
end
if ~isequal(size(yfit), size(y))
    error('stats:nlinfit:WrongSizeFunOutput', ...
          'MODELFUN should return a vector of fitted values
```

```
            the same length as Y.');
end
% Find NaNs in either the responses or in the fitted values
   at the starting
% point.  Since X is allowed to be anything, we can't just
   check for rows
% with NaNs, so checking yhat is the appropriate thing.
   Those positions in
% the fit will be ignored as missing values.  NaNs that show
   up anywhere
% else during iteration will be treated as bad values.
nans = (isnan(y(:)) | isnan(yfit(:))); % a col vector
r = y(:) - yfit(:);
r(nans) = [];
n = numel(r);
p = numel(beta);
sse = r'*r;
funValCheck = strcmp(options.FunValCheck, 'on');
if funValCheck && ~isfinite(sse), checkFunVals(r); end
% Set the level of display
switch options.Display
    case 'off',    verbose = 0;
    case 'notify', verbose = 1;
    case 'final',  verbose = 2;
    case 'iter',   verbose = 3;
end
maxiter = options.MaxIter;
if strcmp(options.Robust,'off')
    % display format for non-robust fit
    if verbose > 2 % iter
        disp(' ');
        disp('              Norm of  Norm of');
        disp('Iteration SSE Gradient Step ');
        disp('  -------------------------');
        disp(sprintf('      %6d    %12g',0,sse));
```

```
    end
    [beta,J,lsiter,cause] = LMfit(X,y, model,beta,options,
       verbose,maxiter);
else
    % Do a preliminary fit just to get residuals and leverage
        from the
    % least squares coefficient.  We won't count this against
        the iteration
    % limit.
    [beta_ls,J] = LMfit(X,y, model,beta,options,0,maxiter);
    res = y - model(beta_ls,X);
    res(isnan(res)) = [];
    ols_s = norm(res) / sqrt(max(1,length(res)-length(beta)))
       ;

    % display format for robust fit
    % Please note there are two loops for robust fit. It
       would be very
    % confusing if we display all iteration results. Instead,
        only the last
    % step of each inner loop (LM fit) will be output.
    if verbose > 2 % iter
        disp(' ');
        disp('Displaying iterations that re-calculate the
           robust weights');
        disp(' ');
        disp('   Iteration             SSE ');
        disp('  ----------------------------');
        disp(sprintf('      %6d    %12g',0,sse));
    end
    [beta,J,sig,cause] = nlrobustfit(X,y,beta,model,J,ols_s,
       options,verbose,maxiter);
end;
switch(cause)
    case 'maxiter'
```

```
            warning('stats:nlinfit:IterationLimitExceeded', ...
                    'Iteration limit exceeded.  Returning results
                        from final iteration.');
        case 'tolx'
            if verbose > 1 % 'final' or 'iter'
                disp('Iterations terminated: relative norm of the
                    current step is less than OPTIONS.TolX');
            end
        case 'tolfun'
            if verbose > 1 % 'final' or 'iter'
                disp('Iterations terminated: relative change in
                   SSE less than OPTIONS.TolFun');
            end
        case 'stall'
            warning('stats:nlinfit:UnableToDecreaseSSE', ...
                    'Unable to find a step that will decrease SSE
                       .  Returning results from last iteration.'
                      );
    end
    % If the Jacobian is ill-conditioned, then two parameters are
        probably
    % aliased and the estimates will be highly correlated.
       Prediction at new x
    % values not in the same column space is dubious.  NLPARCI
       will have
    % trouble computing CIs because the inverse of J'*J is
       difficult to get
    % accurately.  NLPREDCI will have the same difficulty, and in
        addition,
    % will in effect end up taking the difference of two very
       large, but nearly
    % equal, variance and covariance terms, lose precision, and
       so the
    % prediction bands will be erratic.
    [Q,R] = qr(J,0);
```

```
if n <= p
    warning('stats:nlinfit:Overparameterized', ...
            ['The model is overparameterized, and model
               parameters are not\n' ...
             'identifiable.  You will not be able to compute
                confidence or ' ...
             'prediction\nintervals, and you should use
                caution in making predictions.']);
elseif condest(R) > 1/(eps(class(beta)))^(1/2)
    warning('stats:nlinfit:IllConditionedJacobian', ...
            ['The Jacobian at the solution is ill-conditioned
               , and some\n' ...
             'model parameters may not be estimated well (
                they are not ' ...
             'identifiable).\nUse caution in making
                predictions.']);
end
if nargout > 1
    % Return residuals and Jacobian that have missing values
       where needed.
    yfit = model(beta,X);
    r = y - yfit;
    JJ(~nans,:) = J;
    JJ(nans,:) = NaN;
    J = JJ;
end
if nargout > 3
    if strcmp(options.Robust,'off')
        % We could estimate the population variance and the
           covariance matrix
        % for beta here as
        mse = sum(abs(r(~nans)).^2)/(n-p);
    else
        mse = sig.^2;
    end
```

```
    Rinv = inv(R);
    Sigma = Rinv*Rinv'*mse;
end
%-------------------------------------------------------------
function  [beta,J,iter,cause] = LMfit(X,y, model,beta,options
   ,verbose,maxiter)
% Levenberg-Marquardt algorithm for nonlinear regression
% Set up convergence tolerances from options.
betatol = options.TolX;
rtol = options.TolFun;
fdiffstep = options.DerivStep;
funValCheck = strcmp(options.FunValCheck, 'on');
% Set initial weight for LM algorithm.
lambda = .01;
% Set the iteration step
sqrteps = sqrt(eps(class(beta)));
p = numel(beta);
% treatment for nans
yfit = model(beta,X);
r = y(:) - yfit(:);
nans = (isnan(y(:)) | isnan(yfit(:))); % a col vector
r(nans) = [];
sse = r'*r;
zerosp = zeros(p,1,class(r));
iter = 0;
breakOut = false;
cause = '';
while iter < maxiter
    iter = iter + 1;
    betaold = beta;
    sseold = sse;
    % Compute a finite difference approximation to the
       Jacobian
    J = getjacobian(beta,fdiffstep,model,X,yfit,nans);
    % Levenberg-Marquardt step: inv(J'*J+lambda*D)*J'*r
```

```
diagJtJ = sum(abs(J).^2, 1);
if funValCheck && ~all(isfinite(diagJtJ)), checkFunVals(J
   (:)); end
Jplus = [J; diag(sqrt(lambda*diagJtJ))];
rplus = [r; zerosp];
step = Jplus \ rplus;
% Check if current beta contains any zero values and step
    will force
% the new beta to violate non-negativity. If it does then
    we
% modify the step direction to essentially project onto
   the boundary by
% making the component in the relevant direction 0.
alpha_b=ones(size(beta,2),1);
for j=1:size(beta,2)
    if beta(j)+step(j)<0
        alpha_b(j)=max(beta(j),0)/abs(step(j));
        if alpha_b(j)<0 || alpha_b(j)>1
            display('We have a problem')
        end
    end
end
if min(alpha_b)==0
    % If the point is on the boundary we need to allow
       the algorithm to
    % move along the boundary.
    step_temp=step;
    for j=1:size(alpha_b,1)
        if alpha_b(j)==0
            step_temp(j)=0;
            alpha_b(j)=1;
        end
    end
    step1=min(alpha_b)*step_temp;
else
```

```
    % If the point is off the boundary then we simply
       scale back the
    % search direction so that it stops on the boundary.
    step1=min(alpha_b)*step;
end
beta(:) = max(beta(:) + step1, zeros(size(beta,2),size(
   beta,1)));
%beta(:) = beta(:) + step;
% Evaluate the fitted values at the new coefficients and
% compute the residuals and the SSE.
yfit = model(beta,X);
r = y(:) - yfit(:);
r(nans) = [];
sse = r'*r;
if funValCheck && ~isfinite(sse), checkFunVals(r); end
% If the LM step decreased the SSE, decrease lambda to
   downweight the
% steepest descent direction.  Prevent underflowing to
   zero after many
% successful steps; smaller than eps is effectively zero
   anyway.
if sse < sseold
    lambda = max(0.1*lambda,eps);
% If the LM step increased the SSE, repeatedly increase
   lambda to
% upweight the steepest descent direction and decrease
   the step size
% until we get a step that does decrease SSE.
else
    while sse > sseold
        lambda = 10*lambda;
        if lambda > 1e16
            breakOut = true;
            break
        end
```

```
Jplus = [J; diag(sqrt(lambda*sum(J.^2,1)))];
step = Jplus \ rplus;
% Check if current beta contains any zero values
   and step will force
% the new beta to violate non-negativity. If it
   does then we
% modify the step direction to essentially
   project onto the boundary by
% making the component in the relevant direction
   0.
alpha_b=ones(size(beta,2),1);
for j=1:size(beta,2)
    if beta(j)+step(j)<0
        alpha_b(j)=max(beta(j),0)/abs(step(j));
        if alpha_b(j)<0 || alpha_b(j)>1
            display('We have a problem')
        end
    end
end
if min(alpha_b)==0
    % If the point is on the boundary we need to
       allow the algorithm to
    % move along the boundary.
    step_temp=step;
    for j=1:size(alpha_b,1)
        if alpha_b(j)==0
            step_temp(j)=0;
            alpha_b(j)=1;
        end
    end
    step1=min(alpha_b)*step_temp;
else
    % If the point is off the boundary then we
       simply scale back the
    % search direction so that it stops on the
```

```
                    boundary.
                step1=min(alpha_b)*step;
            end
            beta(:) = max(betaold(:) + step1, zeros(size(beta
                ,2),size(beta,1)));
            yfit = model(beta,X);
            r = y(:) - yfit(:);
            r(nans) = [];
            sse = r'*r;
            if funValCheck && ~isfinite(sse), checkFunVals(r)
                ; end
        end
    end
    if verbose > 2 % iter
        disp(sprintf('      %6d    %12g    %12g    %12g', ...
                    iter,sse,norm(2*r'*J),norm(step)));
    end
    % Check step size and change in SSE for convergence.
    if norm(step) < betatol*(sqrteps+norm(beta))
        cause = 'tolx';
        break
    elseif abs(sse-sseold) <= rtol*sse
        cause = 'tolfun';
        break
    elseif breakOut
        cause = 'stall';
        break
    end
end
if (iter >= maxiter)
    cause = 'maxiter';
end
%-----------------------------------------------------------
function checkFunVals(v)
% check if the functin has the finite output
```

```
if any(~isfinite(v))
    error('stats:nlinfit:NonFiniteFunOutput', ...
          'MODELFUN has returned Inf or NaN values.');
end
%-----------------------------------------------------------
function [beta,J,sig,cause]=nlrobustfit(x,y,beta,model,J,
   ols_s,options,verbose,maxiter)
% nonlinear robust fit
tune = options.Tune;
WgtFun = options.WgtFun;
[eid,emsg,WgtFun,tune] = statrobustwfun(WgtFun,tune);
if ~isempty(eid)
    error(sprintf('stats:nlinfit:%s',eid), emsg);
end
yfit = model(beta,x);
fullr = y(:) - yfit(:);
ok = ~isnan(fullr);
r = fullr(ok);
Delta = sqrt(eps(class(x)));
% Adjust residuals using leverage, as advised by DuMouchel &
   O'Brien
% Compute leverage based on X, the Jacobian
[Q,ignore]=qr(J,0);
h = min(.9999, sum(Q.*Q,2));
% Compute adjustment factor
adjfactor = 1 ./ sqrt(1-h);
radj = r .* adjfactor;
% If we get a perfect or near perfect fit, the whole idea of
   finding
% outliers by comparing them to the residual standard
   deviation becomes
% difficult.  We'll deal with that by never allowing our
   estimate of the
% standard deviation of the error term to get below a value
   that is a small
```

```
% fraction of the standard deviation of the raw response
   values.
tiny_s = 1e-6 * std(y);
if tiny_s==0
    tiny_s = 1;
end
% Main loop of repeated nonlinear fits, adjust weights each
   time
totiter = 0;
w = repmat(NaN,size(y));
while maxiter>0
    beta0=beta;
    s = madsigma(radj, length(beta)); % robust estimate of
       sigma for residual
    % Compute robust weights based on current residuals
    w(ok) = feval(WgtFun, radj/(max(s,tiny_s)*tune));
    % this is the weighted nlinfit
    sw = sqrt(w);
    yw = y .* sw;
    modelw = @(b,x) sqrt(w).*model(b,x);
    [beta,J1,lsiter,cause] = LMfit(x,yw,modelw,beta0,options
       ,0,maxiter); % 6th arg always silences display
    totiter = totiter + lsiter;
    maxiter = maxiter - lsiter;
    yfit = model(beta,x);
    fullr = y - yfit;
    r = fullr(ok);
    radj = r .* adjfactor;
    % if there is no change in any coeffcienct, the
       iterations stop.
    if  all(abs(beta-beta0) < Delta*max(abs(beta),abs(beta0))
       )
        break;
    end
    if verbose > 2 % iter
```

```
        disp(sprintf('      %6d    %12g', ...
                     totiter, r'*r));
    end
end
% this is a warning about the non-convergence
if maxiter<=0
    cause = 'maxiter';
end
% We need the Jacobian at the final coefficient estimates,
   but not the J1
% version returned by LMfit because it has robust weights
   included
fdiffstep = options.DerivStep;
J = getjacobian(beta,fdiffstep,model,x,yfit,~ok);
% Compute MAD of adjusted residuals after dropping p-1
   closest to 0
p = numel(beta);
n = length(radj);
mad_s = madsigma(radj, p);
% Compute a robust scale estimate for the covariance matrix
sig = statrobustsigma(WgtFun,radj,p,mad_s,tune,h);
% Be conservative by not allowing this to be much bigger than
    the ols value
% if the sample size is not large compared to p^2
sig = max(sig, ...
          sqrt((ols_s^2 * p^2 + sig^2 * n) / (p^2 + n)));
%---------------------- Robust estimate of sigma
function s = madsigma(r,p)
%MADSIGMA    Compute sigma estimate using MAD of residuals
   from 0
n = length(r);
rs = sort(abs(r));
s = median(rs(max(1,min(n,p)):end)) / 0.6745;
% --------------------- Jacobian
function J = getjacobian(beta,fdiffstep,model,X,yfit,nans)
```

```
p = length(beta);
delta = zeros(size(beta));
for k = 1:p
    if (beta(k) == 0)
        nb = sqrt(norm(beta));
        delta(k) = fdiffstep * (nb + (nb==0));
    else
        delta(k) = fdiffstep*beta(k);
    end
    yplus = model(beta+delta,X);
    dy = yplus(:) - yfit(:);
    dy(nans) = [];
    J(:,k) = dy/delta(k);
    delta(k) = 0;
end
```

A.5 Infection

```
% infection.m
% Returns expected incidence values given a set of time
   points and
%   coefficients
% Inputs:
% a   List of free parameter values
% x   List of time points of interest
% Output:
% y   A list of expected cummulative incidence of Hep-B for
   each time
%     point in  x .
function y = infection(a, x)
  % Define beta, gamm and nu as globals so we can pass the
     values into the
  %  seir  function. Also pass the fixed model parameters y0,
     lambda, mu
  % and N_current.
  global beta gamma nu y0 lambda mu N_current;
```

```
  beta = a(1);
  gamma = a(2);
  nu = a(3);
  % Solve our model. Run the model until the
  % last time point we are concerned about.
  % (we are assuming x is ordered).
  [t, yy] = ode15s('seir', [0 x(end)], y0);
  % Calculate the incidence
  y=zeros(1,size(x,2));
  I=zeros(size(x,2),1);
  S=zeros(size(x,2),1);
  N=zeros(size(x,2),1);
  for j=1:size(x,2)
      I(j) = interp1(t, yy(:,3), x(j));
      S(j) = interp1(t, yy(:,1), x(j));
      N(j) = N_current*(1+lambda-mu)^(x(j)-7);
  end
  % Note - x may not be uniform.
  for j=2:size(x,2)
      y(j)=y(j)+beta/2*(I(1)*S(1)*N(1)*(x(2)-x(1))+I(end)*S(
         end)*N(end)*(x(end)-x(end-1)));
      if j>2
          for k=2:j-1
              y(j)=y(j)+beta/2*I(k)*S(k)*N(k)*(x(k)-x(k-1))+
                 beta/2*I(k)*S(k)*N(k)*(x(k+1)-x(k));
          end
      end
  end
end
```

A.6 GA modified

```
function [P,best,best_val] = ga_SR(pop_size,chrom_len,pm,
   max_gen,migration)
 % Modified by Steven Richardson
%-------------------------------------------------------------
```

```
% Copyright (C) 2009  George Bezerra
% This program is free software: you can redistribute it and/
   or modify
% it under the terms of the GNU General Public License as
   published by
% the Free Software Foundation, either version 3 of the
   License, or
% (at your option) any later version.
% This program is distributed in the hope that it will be
   useful,
% but WITHOUT ANY WARRANTY; without even the implied warranty
    of
% MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE.  See
   the
% GNU General Public License for more details.
% You should have received a copy of the GNU General Public
   License
% along with this program.  If not, see <http://www.gnu.org/
   licenses/>.
%-------------------------------------------------------------
% Inputs:
% pop_size  => population size
% chrom_len => chromosome length
% pm        => probability of mutation
% pc        => probability of crossover
% max_gen   => maximum number of generations
% Outputs:
% P    => population
% best => best individual of the population
% best_val => max fittness value
% suggested run: [P,best] = ga(100,100,0.01,0.5,200);
% INITIALIZE POPULATION
P = initialize(pop_size,chrom_len);
gen = 1;
max_fit=zeros(max_gen,1);
```

```
mean_fit=zeros(max_gen,1);
while gen<=max_gen
    % BREAD SOLUTIONS - CROSSOVER
    Pb = two_point_crossover(P,1);
    % MUTATION
    Pb = point_mutation(Pb,pm);
    % MIGRATION
    Pm = initialize(round(migration*pop_size),chrom_len);
    % Combine P, Pb and Pm
    Pcomb=[P; Pb; Pm];
    % EVALUATION
    if gen==1
        fitc = fitness(Pcomb);
    else
        fitc = [fitv; fitness([Pb; Pm])];
    end
    % SELECTION - Pick pop_size solutions from Pc using
      roulette selection. Must ensure top solution is
      retained.
    [P,fitv] = roulette_selection(Pcomb,fitc,pop_size);
    % record data
    max_fit(gen) = max(fitv);
    mean_fit(gen) = mean(fitv);
    % display information
    disp_info(gen,max_fit(gen));
    gen = gen+1;
end
disp(sprintf('Generation: %d',gen));
disp(sprintf('Best fitness: %d\n',max_fit(end)));
% plot evolution curve
plot(1:length(max_fit), max_fit,'b');
hold on;
plot(1:length(mean_fit), mean_fit,'g');
hold off;
xlabel('Generations');
```

```
ylabel('Fitness');
legend('Best fitness','Average fitness','Location','SouthEast
    ');
% output best individual
[m,ind] = max(fitv);
best = P(ind,:);
best_val=max(fitv); % Modified by Steven Richardson.
function [P] = initialize(pop_size,chrom_length)
P = round(rand(pop_size,chrom_length));
function [P_new] = tournament_selection(P,fitv,tourn_size)
for i=1:size(P,1)
    t = ceil(rand(1,tourn_size)*size(P,1));
    [max_fit,winner] = max(fitv(t));
    P_new(i,:) = P(t(winner),:);
end
function [P_new] = two_point_crossover(P,pc)
mating_list = randperm(size(P,1));
P_new = [];
while ~isempty(mating_list)
    pair = mating_list(1:2);
    mating_list(1:2) = [];
    if rand<pc
        crossover_points = ceil(rand(1,2)*(size(P,2)));
        point1 = min(crossover_points);
        point2 = max(crossover_points);
        individual1 = P(pair(1),:);
        individual2 = P(pair(2),:);
        individual1(point1:point2) = P(pair(2),point1:point2)
            ;
        individual2(point1:point2) = P(pair(1),point1:point2)
            ;
        P_new = [P_new;individual1;individual2];
    else
        P_new = [P_new;P(pair,:)];
    end
```

```
end
function [P_new] = point_mutation(P,pm)
r = rand(size(P));
mutation_list = find(r<pm);
P_new = P;
P_new(mutation_list(find(P(mutation_list)==1))) = 0;
P_new(mutation_list(find(P(mutation_list)==0))) = 1;
function [] = disp_info(gen,fitv)
if mod(gen,10)==0
    disp(sprintf('Generation: %d',gen));
    disp(sprintf('Best fitness: %d\n',fitv));
end
function [P_new,fit_new] = roulette_selection(P,fitv,pop_size
   )
P_new = zeros(pop_size,size(P,2));
fit_new = zeros(pop_size,1);
[fit_max,index_max] = max(fitv);
P_new(1,:) = P(index_max,:); % Ensure that top solution is
   selected.
fit_new(1)=fit_max;
fitv(index_max) = min(fitv);
for i=2:pop_size
    fit1 = (fitv - min(fitv)).^2;
    fit1 = cumsum(fit1);
    fit1 = fit1/max(fit1);
    f = find(fit1>rand);
    P_new(i,:) = P(f(1),:);
    fit_new(i)=fitv(f(1));
    fitv(f(1)) = min(fitv);
end
```

A.7 Converting gene to value

```
% gene_to_values(gene)
%   Given a binary array chromosome, returns real values for
   beta, gamma
```

```
%   and nu.
% Inputs:
%   gene  - A 1D binary array, the first third representing
   beta, the
%           second third representing gamma, and the third
   third
%           representing nu.
% Output:
%   beta  - The value for beta
%   gamma - The value for gamma
%   nu    - The value for nu
%
function [beta, gamma, nu] = gene_to_values(gene)
% Set the min and max ranges for the exponents (base 10)
beta_min_exponent = -10;
beta_max_exponent = 2;
gamma_min_exponent = -10;
gamma_max_exponent = 2;
nu_min_exponent = -10;
nu_max_exponent = 2;
% The length of a gene within the chromosome is one third the
    total length
gene_len = size(gene,2)/3;
% Use bi2de to convert binary arrays to decimal numbers
beta_decimal = bi2de(gene(1:gene_len));
gamma_decimal = bi2de(gene(gene_len+1:2*gene_len));
nu_decimal = bi2de(gene(2*gene_len+1:3*gene_len));
% Convert the decimal values to real numbers inside the
% ranges established above.
beta_exponent = beta_min_exponent + ...
                  ((beta_max_exponent-beta_min_exponent) * ...
                   beta_decimal / 2^gene_len);
gamma_exponent = gamma_min_exponent + ...
                  ((gamma_max_exponent-gamma_min_exponent) *
                     ...
```

```
                    gamma_decimal / 2^gene_len);
nu_exponent = nu_min_exponent + ...
                   ((nu_max_exponent-nu_min_exponent) * ...
                    nu_decimal / 2^gene_len);
% We are using base 10 exponents
beta = 10^beta_exponent;
gamma = 10^gamma_exponent;
nu = 10^nu_exponent;
```

A.8 Fitness

```
% fitness(P)
%   Returns a vector with the fitness scores for each member
   of the
%   population, P
% Inputs:
%   P - A 2D array of the population genomes
% Output:
%   fit = A 1D array of fitness scores
function fit = fitness(P)
% Use globals so we can send the values into our sir.m
   funciton
global beta gamma lambda mu nu time sick T_max y0 N_current
% I like to initialize any arrays I use
fit = zeros(size(P,1), 1);
% Loop through each individual in the population
for i=1:size(P,1)
    % Convert the current chromosome to real values.  I chose
       to interperet
    % the chromosome as three binary representations of
       numbers.  You may
    % also want to consider a Grey Code representation (or
       others).
    [beta, gamma, nu] = gene_to_values(P(i,:));
    % Get the model output for the given values of beta gamma
       and nu.
```

```
    [t, y] = ode15s('seir', [0 T_max], y0);
    % Need to calculate the incidence h and population size N
       . Use the Trapezoid rule and
    % interpolate s, i and N linearly.
    h=zeros(1,size(time,2));
    I=zeros(size(time,2),1);
    S=zeros(size(time,2),1);
    N=zeros(size(time,2),1);
    for j=1:size(time,2)
        I(j) = interp1(t, y(:,3), time(j));
        S(j) = interp1(t, y(:,1), time(j));
        N(j) = N_current*(1+lambda-mu)^(time(j)-7);
    end
    % Note - x may not be uniform.
    for j=2:size(time,2)
        h(j)=h(j)+beta/2*(I(1)*S(1)*N(1)*(time(2)-time(1))+I(
           end)*S(end)*N(end)*(time(end)-time(end-1)));
        if j>2
            for k=2:j-1
                h(j)=h(j)+beta/2*I(k)*S(k)*N(k)*(time(k)-time
                   (k-1))+beta/2*I(k)*S(k)*N(k)*(time(k+1)-
                   time(k));
            end
        end
    end

    error = squared_error(time , sick, time, h);
    % The GA maximizes values, so we return the inverse of
       the error to
    % trick the GA into minimzing the error.
    fit(i) = error^-1;
end
```

Appendix B

Stability of the endemic equilibrium; Routh-Hurwitz criterion approach

Although other tools like the Descartes' rule for polynomials, discussed in Subsection 3.3.4, can be used to analyze the stability of the endemic state of dynamical systems, the Routh-Hurwitz criterion is the more generally accepted and routinely used approach. For the benefit of other users of this thesis, the Routh-Hurwitz criterion is reviewed in this section. This important criterion provides a necessary and sufficient condition for all the roots of a characteristic polynomial, with real coefficients, to lie in the left half of the complex plane. The criterion is given in the following theorem.

Theorem 7 (Routh-Hurwitz Criterion) *Given the polynomial,*

$$P(x) = p_0 x^n + p_1 x^{n-1} + ... + p_{n-1} x + p_n,$$

where the coefficients p_i, $i = 1, 2, ..., n$ are real constants, define the n^{th} Routh-Hurwitz array using the coefficients p_i of the characteristic polynomial by

$$\begin{bmatrix} p_1 & p_3 & p_5 & p_7 & \dots & 0 \\ p_0 & p_2 & p_4 & p_6 & \dots & 0 \\ 0 & p_1 & p_3 & p_5 & \dots & 0 \\ 0 & p_0 & p_2 & p_4 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 \end{bmatrix} \tag{B.1}$$

with $H_1 = p_1$,

$$H_2 = \begin{bmatrix} p_1 & p_3 \\ p_0 & p_2 \end{bmatrix}, \quad H_3 = \begin{bmatrix} p_1 & p_3 & p_5 \\ p_0 & p_2 & p_4 \\ 0 & p_1 & p_3 \end{bmatrix}, \ldots \quad H_n = \begin{bmatrix} p_1 & p_3 & p_5 & p_7 & \ldots & 0 \\ p_0 & p_2 & p_4 & p_6 & \ldots & 0 \\ 0 & p_1 & p_3 & p_5 & \ldots & 0 \\ 0 & p_0 & p_2 & p_4 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \ldots & 0 \end{bmatrix}$$

where $p_j = 0$ *if* $j > n$. *All of the roots of the polynomial* $P(x)$ *are negative or have negative real part if and only if the determinants of all Hurwitz matrices are positive:*

$$detH_j > 0, \quad j = 1, 2, 3, ..., n.$$

Applying this criteria to the characteristic polynomial in Equation 3.31 of the Jacobian of the endemic state of the model where

$$\begin{aligned} a_2 &= \frac{(\lambda+\nu)(\gamma\nu+\lambda\nu+\gamma^2+2\lambda^2)+\gamma\lambda(3\lambda+\beta)+2\gamma\lambda\nu+\gamma\nu(\lambda-\alpha)}{(\gamma+\lambda)(\lambda+\nu)}, \\ a_1 &= \frac{\lambda(\alpha\gamma^2+\alpha\lambda^2+\beta\gamma^2+\alpha\nu^2+\beta\gamma\nu+\alpha\gamma\nu+2\alpha\gamma\lambda+2\beta\gamma\lambda+2\alpha\nu\lambda)}{(\lambda+\nu)(\gamma+\lambda)}, \\ a_0 &= \lambda(\beta\gamma+\alpha\nu)-\lambda(\lambda+\nu-\alpha)(\lambda+\gamma) \end{aligned}$$

it can be shown that $a_1 > 0$ and $a_2 > 0$, since the natural birth rate always exceeds the rate newborns present with hepatitis B, $\lambda > \alpha$. Note that the subscript convention of the polynomial $P(x)$ in Theorem 7 is opposite that in Equation 3.31

The Routh-Hurwitz array of the characteristic polynomial in Equation 3.31 is

$$\begin{bmatrix} a_2 & a_0 & 0 \\ 1 & a_1 & 0 \\ 0 & a_2 & a_0 \end{bmatrix} \tag{B.2}$$

where

$$H_1 = a_2, \quad H_2 = \begin{bmatrix} a_2 & a_0 \\ 1 & a_1 \end{bmatrix}, \quad \text{and} \quad H_3 = \begin{bmatrix} a_2 & a_0 & 0 \\ 1 & a_1 & 0 \\ 0 & a_2 & a_0 \end{bmatrix}. \tag{B.3}$$

The endemic state Q^* is stable when $\det H_1 = a_2 > 0$, $\det H_2 = a_2a_1 - a_0 > 0$ and $\det H_3 = a_0(a_2a_1 - a_0) > 0$ or unstable otherwise. Stability of the endemic state is therefore achieved if $a_2a_1 - a_0 > 0$, and so $a_2a_1 > a_0$ for $a_0 > 0$. The endemic state Q^* is unstable if $a_2a_1 - a_0 < 0$ and so $a_2a_1 < a_0$ for $a_0 > 0$, or else if $a_0 < 0$ and so $a_0(a_2a_1 - a_0) < 0$. Thus if $a_0 > 0$, $a_2a_1 \nleq a_0$ which follows that $a_0(a_2a_1 - a_0) > 0$ and so the endemic state is stable. The endemic state is therefore unstable only if $a_0 < 0$ and so $a_0(a_2a_1 - a_0) < 0$.

In conclusion, since $a_1, a_2 > 0$, $\det H_1 = a_2 > 0$, $\det H_2 = a_2a_1 - a_0 > 0$ and $\det H_3 = a_0(a_2a_1 - a_0) > 0$ if $a_2a_1 > a_0$ for $a_0 > 0$, and so the endemic equilibrium state Q^* of the model in Equation 3.6 is stable. If $a_0 < 0$, $\det H_3 = a_0(a_2a_1 - a_0) < 0$ and so the endemic equilibrium state Q^* is unstable. The above conditions that underpins this approach are usually difficult to verify analytically and make the approach technically difficult to use.

Appendix C

Stability of the endemic equilibrium - Spectral properties of second additive compound matrix approach

Stability of the endemic equilibrium $Q^* = (s^*, e^*, i^*)$ was shown by establishing that all the eigenvalues of the Jacobian matrix 7.12 have negative real parts using the Descartes' rule of signs of a polynomial instead of the Routh-Hurwitz conditions which is routinely used. Note that the Routh-Hurwitz criterion for the stability of Q^* is usually technically very difficult to use when the coefficients of the resulting characteristic equation of the Jacobian matrix is hard to come by [116]. Stability of the endemic equilibrium can also be discussed using another criterion applied in [116] that uses the spectral properties of the second additive compound matrix $A^{[2]}$ of a matrix A. A matrix A is generally known to be stable if all its eigenvalues have negative real parts. The following definitions and proposition are relevant for the purpose of this discussion [116].

Definition 2 *The second additive compound matrix* $A^{[2]}$ *of a* 3×3 *matrix* $A = (a_{ij})$, *i.e. for* $m = 3$ *is defined as*

$$A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}$$

Let $\rho(A) = \{\xi_j : j = 1, 2, ..., m\}$ be the spectrum of A [116]

Proposition 2 *The spectrum of* $A^{[2]}$, $\rho(A^{[2]}) = \{\xi_{j1} + \xi_{j2} : 1 \leq j1 < j2 \leq m\}$

The spectral properties of the second additive compound matrix is now used to prove the following result.

Lemma 2 *Let* A *be a* $m \times m$ *matrix with real entries. For* A *to be stable, it is necessary and sufficient that*

(i) The second compound matrix $A^{[2]}$ *is stable.*

(ii) $(-1)^m \det(A) > 0$.

To prove this Lemma, the definition of the second additive compound matrix of the Jacobian $J(Q)$ in Equation 7.12 at the point $Q = (s, e, i)$, by Definition 2 is

$$J^{[2]}(Q) = \begin{bmatrix} -2\lambda - \beta i - \gamma + \alpha & \alpha + \beta s & \alpha + \beta s \\ \gamma & -2\lambda - \nu - \beta i & -\alpha \\ 0 & \beta i & \alpha - 2\lambda - \nu - \gamma \end{bmatrix} \tag{C.1}$$

Proof. It requires to show that the Jacobian J (Equation 7.12) satisfies conditions (i) and (ii) of Lemma 2. For $Q^* = (s^*, e^*, i^*)$ and the diagonal matrix $T = \text{diag}(i^*, e^*, s^*)$, the matrix $J^{[2]}$ is similar to

$$TJ^{[2]}(Q^*)T^{-1} = \begin{bmatrix} -2\lambda - \beta i^* - \gamma + \alpha & \frac{i^*}{e^*}(\alpha + \beta s^*) & \frac{i^*\alpha}{s^*} + \beta i^* \\ \frac{e^*\gamma}{i^*} & -2\lambda - \nu - \beta i^* & \frac{\alpha e^*}{s^*} \\ 0 & \frac{\beta i^* s^*}{e^*} & \alpha - 2\lambda - \nu - \gamma \end{bmatrix} \tag{C.2}$$

By the similarity property of matrices, the matrix $J^{[2]}(Q^*)$ is stable if and only if $TJ^{[2]}(Q^*)T^{-1}$ is stable since similarity preserves the eigenvalues. The diagonal elements of the matrix $TJ^{[2]}(Q^*)T^{-1}$ are negative since $\lambda > \alpha$. Geršgorin discs shows that $TJ^{[2]}(Q^*)T^{-1}$ is stable if it is diagonally dominant in rows. To show that $TJ^{[2]}(Q^*)T^{-1}$ is diagonally dominant is to show that $\psi = \max\{u_1, u_2, u_3\} < 0$ where

$$\begin{aligned} u_1 &= \alpha - \gamma - 2\lambda - \beta i^* + \frac{\alpha i^*}{s^*} + \beta i^* + \frac{(\alpha + \beta s^*)i^*}{e^*} \\ &= \alpha - \gamma - 2\lambda + \frac{\alpha i^*}{s^*} + \frac{(\alpha + \beta s^*)i^*}{e^*} \\ u_2 &= \frac{\gamma e^*}{i^*} - 2\lambda - \beta i^* - \nu - \frac{\alpha e^*}{s^*} \\ u_3 &= \frac{\beta i^* s^*}{e^*} + \alpha - \gamma - 2\lambda - \nu \end{aligned} \tag{C.3}$$

Rearranging the homogeneous part of Equation 3.6 gives

$$\begin{aligned}\frac{\lambda-\alpha(i^*+e^*)}{s^*} &= \beta i^* + \lambda \\ \frac{(\beta s^*+\alpha)i^*}{e^*} &= \gamma+\lambda-\alpha \\ \frac{\gamma e^*}{i^*} &= \nu+\lambda \end{aligned} \tag{C.4}$$

By substituting Equation C.4 into Equation C.3, the set ψ becomes

$$\psi = \max\left\{-\lambda+\frac{\alpha i^*}{s^*}, -\lambda-\frac{\alpha e^*}{s^*}-\beta i^*, -\lambda-\nu-\frac{\alpha i^*}{e^*}\right\} < 0$$

since $0 < i^* < 1$ and $\lambda > \alpha$ and so $\frac{i^*}{s^*} < \frac{\lambda}{\alpha}$. This result implies the diagonal dominance claim and so satisfies the condition (i) of Lemma 2. Furthermore, by Equation C.4 the determinant of the Jacobian matrix Equation C.1 is

$$\det(J(Q^*)) = \begin{vmatrix} -\frac{\lambda-\alpha(i^*+e^*)}{s^*} & -\alpha & -\frac{e^*}{i^*}(\gamma+\lambda-\alpha) \\ \beta i & -\frac{i^*}{e^*}(\beta s^*+\alpha) & \alpha+\beta s \\ 0 & \gamma & -\frac{\gamma e^*}{i^*} \end{vmatrix} \tag{C.5}$$

$$\begin{aligned} &= -\frac{\lambda-\alpha(i^*+e^*)}{s^*}\left[\frac{\gamma e^*}{i^*}\left(\frac{i^*}{e^*}(\beta s^*+\alpha)\right)-\gamma(\alpha+\beta s^*)\right]+\alpha\left(-\frac{\gamma e^*}{i^*}\beta i^*\right)-\frac{e^*}{i^*}\gamma\beta i^*(\gamma+\lambda-\alpha) \\ &= -\frac{\lambda-\alpha(i^*+e^*)}{s^*}[\gamma(\alpha+\beta s^*)-\gamma(\alpha+\beta s^*)]-\alpha\beta\gamma e^*-\beta\gamma e^*(\lambda+\gamma-\alpha) \\ &= -\alpha\beta\gamma e^*-\beta\gamma e^*(\lambda+\gamma-\alpha) \\ &= -\alpha\beta\gamma e^*+\alpha\beta\gamma e^*-\beta\gamma e^*(\lambda+\gamma) \\ &= -\beta\gamma e^*(\lambda+\gamma) < 0 \end{aligned} \tag{C.6}$$

which satisfies condition (ii) of Lemma 2 and thus completes the proof.
The following theorem summarizes the parameter restriction $R_0 > 1$ on the stability of the endemic equilibrium Q^*.

Theorem 8 *If $R_0 > 1$, then the system in Equation 3.6 has a unique equilibrium Q^* in $\mathring{\Sigma}$ and Q^* is asymptotically stable.*

Appendix D

Verification of the values of a_0, a_1 and a_2 at the crossover value of β^*

At the crossover value of β^*, the values of a_2, a_1 and a_0 are

$$
\begin{aligned}
a_2 &= \frac{\gamma-\alpha+3\lambda+\nu+(\lambda(\gamma\lambda-\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu+\lambda\nu+\lambda^2)-\lambda(\gamma+\lambda)(\lambda+\nu)}{(\gamma+\lambda)(\lambda+\nu)} \\
&+ \frac{\alpha\lambda(\gamma+\lambda+\nu))}{(\gamma+\lambda)(\lambda+\nu)} = \gamma-\alpha+3\lambda+\nu \\
a_1 &= \frac{2\gamma\lambda-2\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu+2\lambda\nu+\alpha(\gamma+\lambda+\nu)-(\gamma+\lambda)(\lambda+\nu)+3\lambda^2}{(\gamma+\lambda)(\lambda+\nu)} \\
&+ \frac{(\gamma(\lambda(\gamma\lambda-\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu+\lambda\nu+\lambda^2)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu)))}{(\gamma+\lambda)(\lambda+\nu)} \\
&+ \frac{(2\lambda(\lambda(\gamma\lambda-\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu+\lambda\nu+\lambda^2)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu)))}{(\gamma+\lambda)(\lambda+\nu)} \\
&+ \frac{(\nu(\lambda(\gamma\lambda-\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu+\lambda\nu+\lambda^2)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu)))}{(\gamma+\lambda)(\lambda+\nu)} \\
&= \lambda(\gamma-\alpha+2\lambda+\nu) \\
a_0 &= \frac{\lambda(\alpha(\gamma+\lambda+\nu)-(\gamma+\lambda)(\lambda+\nu))+(\lambda+\nu)((\lambda+(\lambda(\gamma\lambda-\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu)}{(\gamma+\lambda)(\lambda+\nu)} \\
&+ \frac{+\lambda\nu+\lambda^2-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu))}{(\gamma+\lambda)(\lambda+\nu))}(\gamma-\alpha+\lambda) \\
&+ \frac{(\alpha(\lambda(\gamma\lambda-\alpha\lambda-\alpha\nu-\alpha\gamma+\gamma\nu+\lambda\nu+\lambda^2)-\lambda(\gamma+\lambda)(\lambda+\nu)+\alpha\lambda(\gamma+\lambda+\nu)))}{(\gamma+\lambda)(\lambda+\nu))} \\
&- \alpha\gamma\lambda = 0. \qquad \text{(D.1)}
\end{aligned}
$$

respectively. Hence Equation 3.31 becomes

Appendix D. Verification of the values of a_0, a_1 and a_2 at the crossover value of β^*

$$\xi^3 + (\gamma - \alpha + 3\lambda + \nu)\xi^2 + \lambda(\gamma - \alpha + 2\lambda + \nu)\xi = 0$$

and so the eigenvalues are

$$\begin{aligned}
\xi_1 &= 0 \\
\xi_{2\&3} &= \frac{-(\gamma - \alpha + 3\lambda + \nu) \pm \sqrt{(\gamma - \alpha + 3\lambda + \nu)^2 - 4\lambda(\gamma - \alpha + 2\lambda + \nu)}}{2} \\
&= \frac{\alpha - \gamma - \nu - 3\lambda \pm \sqrt{(\gamma + \lambda + \nu - \alpha)^2}}{2} \\
&= \frac{(\alpha - \gamma - \nu - 3\lambda) \pm (\gamma + \lambda + \nu - \alpha)}{2}
\end{aligned}$$

from which it follows that

$$\begin{aligned}
\xi_1 &= 0 \\
\xi_2 &= \frac{-2\lambda}{2} = -\lambda < 0 \\
\xi_3 &= \alpha - \gamma - \nu - 2\lambda < 0
\end{aligned} \tag{D.2}$$