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A

THESIS

ON

Mathematical Modeling of Hepatitis B Virus Transmission with control Strategies in Ethiopia

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By

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Mathematical Modeling of Hepatitis B Virus Transmission with control Strategies in Ethiopia

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Dedication

This thesis is dedicated to my beloved family,
whose unwavering support, love, and encouragement
have been the foundation of my academic journey.
To my parents, for their endless prayers and sacrifices,
and to all those who believed in me even when I doubted myself.

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Abstract

Hepatitis B virus (HBV) infection remains a major public health challenge in high-endemic countries such as Ethiopia, where chronic carriers play a critical role in sustaining long-term transmission. In this study, a deterministic compartmental SEICR model is developed to describe the transmission dynamics of HBV, incorporating vaccination of susceptible individuals and treatment of chronic carriers as control strategies. The model is formulated under biologically meaningful assumptions and is shown to be mathematically well-posed through positivity and boundedness analysis. The basic reproduction number, denoted by $\mathcal{R}_0$, is derived using the next-generation matrix method and decomposed into contributions from acute and chronic infectious classes. Local stability analysis of the disease-free equilibrium is carried out, and conditions for disease elimination are established in terms of $\mathcal{R}_0$. Numerical simulations are performed to investigate the impact of vaccination and treatment strategies under baseline parameter values relevant to the Ethiopian context. Sensitivity analysis is conducted to identify the most influential parameters governing HBV transmission. The results indicate that reducing $\mathcal{R}_0$ below unity requires vaccination coverage exceeding a critical threshold. Under baseline parameter assumptions, the model predicts that vaccination coverage must reach approximately 70% in order to ensure $\mathcal{R}_0 < 1$ and achieve disease elimination. These findings highlight the importance of sustained immunization programs combined with effective treatment of chronic carriers. The proposed modeling framework provides quantitative insight into HBV transmission dynamics and offers a useful tool for evaluating control strategies in high-endemic, resource-limited settings such as Ethiopia.

Keywords: Hepatitis B virus, mathematical modeling, SEICR model, basic reproduction number, chronic carriers, vaccination, disease transmission, public health intervention.

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List of Abbreviations

Abbreviation	**Meaning**
HBV	Hepatitis B Virus
WHO	World Health Organization
SEICR	Susceptible–Exposed–Infectious–Chronic–Recovered
ODE	Ordinary Differential Equation
DDE	Delay Differential Equation
R_0	Basic Reproduction Number
HBsAg	Hepatitis B Surface Antigen
cccDNA	Covalently Closed Circular DNA
ART	Antiretroviral Therapy
MTCT	Mother-to-Child Transmission
HCC	Hepatocellular Carcinoma
LMICs	Low- and Middle-Income Countries
WHO	World Health Organization

Chapter 1

Introduction

1.1 Background of the Study

Hepatitis B Virus (HBV) infection remains a major global public health challenge, despite the availability of highly effective vaccines and antiviral therapies. According to the World Health Organization (WHO), approximately 254 million people were living with chronic HBV infection worldwide in 2022, with an estimated 1.1 million deaths occurring annually due to HBV-related complications such as liver cirrhosis and hepatocellular carcinoma [1]. The burden of the disease is disproportionately concentrated in low- and middle-income countries, particularly in sub-Saharan Africa and parts of Asia, where access to timely diagnosis, vaccination, and long-term treatment remains limited.

HBV is primarily transmitted through exposure to infected blood and bodily fluids, with key transmission routes including mother-to-child transmission (MTCT), early childhood exposure, unsafe medical practices, and unprotected sexual contact [3, 1]. In highly endemic regions, infection often occurs during infancy or early childhood, significantly increasing the probability of progression to chronic infection. Chronic HBV carriers represent a critical epidemiological group, as they may remain infectious for decades and serve as persistent reservoirs for disease transmission within the population [4].

Mathematical modeling has become an indispensable tool for understanding the transmission dynamics of infectious diseases such as HBV. Compartmental models enable the formal representation of disease progression, population heterogeneity, and intervention strategies, thereby allowing researchers to quantify key epidemiological indicators such as the basic reproduction number R_0, equilibrium states, and long-term disease behavior [13]. Classical SEIR-type models, which divide the population into susceptible, exposed, infectious, and

recovered compartments, have been widely used to analyze viral hepatitis dynamics and to assess the impact of public health interventions such as vaccination and treatment [15].

However, HBV exhibits distinctive biological and epidemiological features that challenge the adequacy of simple SEIR frameworks. In particular, the presence of chronic carriers, the contribution of vertical transmission, and the possibility of waning immunity following vaccination or recovery play a crucial role in sustaining transmission, especially in endemic settings. Failure to explicitly incorporate these mechanisms may lead to biologically unrealistic predictions and misleading policy recommendations.

In Ethiopia, HBV remains a significant public health concern. Epidemiological studies report that chronic HBV infection affects approximately 8–12% of the population, placing the country among high-endemic regions [10]. Although infant vaccination has been integrated into the Expanded Programme on Immunization (EPI), gaps in vaccination coverage, limited antenatal screening, and constrained healthcare infrastructure continue to hinder effective disease control. Mother-to-child transmission remains a major driver of new chronic infections, particularly in the absence of timely birth-dose vaccination and antiviral prophylaxis.

Given these challenges, there is a compelling need for mathematically rigorous and context-specific models that accurately reflect the epidemiology of HBV in Ethiopia. Such models can support evidence-based decision-making by quantifying the impact of vaccination, screening, and treatment strategies, identifying thresholds required for disease elimination, and evaluating the feasibility of achieving public health targets under resource limitations. This study addresses this need by developing a biologically realistic compartmental model tailored to the Ethiopian context, with particular emphasis on chronic infection dynamics and intervention effectiveness.

1.2 Problem Statement

Despite the availability of effective vaccines and antiviral therapies, Hepatitis B Virus (HBV) infection remains a major public health challenge worldwide and particularly in high-endemic countries such as Ethiopia. Although the World Health Organization has set a global target to eliminate viral hepatitis as a public health threat by 2030, progress toward this goal has been uneven in resource-limited settings [2]. Persistent transmission, low diagnosis rates, limited access to long-term treatment, and ongoing mother-to-child transmission continue to hinder HBV control efforts.

In Ethiopia, the burden of chronic HBV infection remains substantial due to gaps in infant vaccination coverage, limited antenatal screening, and constrained healthcare infrastructure. The absence of universal birth-dose vaccination and restricted access to antiviral prophylaxis for pregnant women contribute to continued vertical transmission. In addition, a large proportion of infected individuals remain undiagnosed, allowing chronic carriers to sustain transmission within the community over long periods of time.

Mathematical modeling has been widely used to investigate HBV transmission dynamics and to evaluate control strategies. However, many existing models are developed for low-endemic or developed-country settings and are not well suited to the epidemiological realities of high-burden countries such as Ethiopia. In particular, several classical SEIR-type models fail to distinguish adequately between acute and chronic infection stages or do not quantify the contribution of chronic carriers to the basic reproduction number. Consequently, such models tend to underestimate long-term disease persistence and may fail to correctly predict endemic levels in high-endemic populations.

Furthermore, most available HBV models are not calibrated using Ethiopian epidemiological data. As a result, they provide limited guidance on critical policy-relevant questions, such as the level of vaccination coverage required to reduce the basic reproduction number below unity ($\mathcal{R}_0 < 1$) or the combined impact of vaccination and treatment of chronic carriers. This lack of locally informed quantitative analysis restricts the ability of public health authorities to design effective and realistic intervention strategies.

Therefore, there is a clear need for a modeling framework that explicitly represents chronic carriers, reflects the epidemiological characteristics of high-endemic settings, and allows evaluation of vaccination and treatment strategies under parameter assumptions relevant to Ethiopia. This study addresses these gaps by developing and analyzing a deterministic SEICR model that incorporates chronic infection explicitly and examines the impact of vaccination and treatment on HBV transmission dynamics. In doing so, the model aims to provide more realistic predictions and quantitative insight to support HBV control and elimination efforts in Ethiopia.

1.3 Research Questions

This study seeks to address the following research questions:

1. How do the interactions among susceptible, exposed, acutely infected, chronically

infected, and recovered individuals influence the transmission dynamics of Hepatitis B Virus in the Ethiopian context?

2. What is the basic reproduction number R_0 associated with the proposed HBV transmission model, and how does it depend on key epidemiological and intervention-related parameters?

3. What level of vaccination coverage is required to reduce the basic reproduction number below unity ($R_0 < 1$) and interrupt sustained HBV transmission in Ethiopia?

4. How do combined intervention strategies, including vaccination, screening, and treatment of chronic carriers, affect the long-term behavior of HBV transmission?

5. To what extent do limitations in healthcare infrastructure influence the feasibility and effectiveness of achieving high vaccination and treatment coverage necessary for HBV elimination?

1.4 Objectives of the Study

1.4.1 General Objective

The general objective of this study is to develop and analyze a biologically realistic mathematical model for the transmission dynamics of Hepatitis B Virus (HBV) in Ethiopia, and to evaluate the effectiveness and feasibility of vaccination and treatment interventions in reducing disease transmission and achieving elimination targets.

1.4.2 Specific Objectives

The specific objectives of this study are to:

1. Formulate a compartmental HBV transmission model that explicitly incorporates exposed individuals, acutely infected individuals, chronic carriers, and recovered individuals, along with vaccination and treatment interventions.

2. Derive the basic reproduction number R_0 for the proposed model and investigate its dependence on key epidemiological and control parameters.

3. Analyze the existence and stability of the disease-free and endemic equilibrium points of the model.

4. Quantify the minimum vaccination coverage required to achieve $R_0 < 1$ under Ethiopian epidemiological conditions.

5. Assess the impact of combined intervention strategies, including vaccination, screening, and treatment of chronic carriers, through numerical simulations.

1.5 Significance of the Study

This study is significant from both scientific and public health perspectives. From a scientific standpoint, it contributes to the existing body of knowledge on infectious disease modeling by developing a biologically realistic compartmental framework that explicitly incorporates chronic HBV infection, vaccination, and treatment dynamics. By extending beyond classical SEIR formulations, the model captures key epidemiological features that are essential for accurately representing HBV transmission in high-endemic settings. This addresses recognized limitations in previous modeling studies that often overlook chronic carriers or rely on assumptions that are not applicable to resource-limited contexts.

From a public health perspective, the study provides quantitative evidence to support decision-making in HBV prevention and control. In particular, the explicit estimation of the vaccination coverage required to reduce the basic reproduction number below unity offers actionable guidance for national immunization programs. By evaluating combined intervention strategies, including vaccination, screening, and treatment of chronic carriers, the findings help identify intervention packages that are both effective and feasible under constrained healthcare infrastructure.

Furthermore, the model is tailored to the Ethiopian epidemiological context using parameter values informed by published data. This local calibration enhances the relevance of the results for policymakers and health planners, enabling more realistic assessments of intervention impact compared to generic or externally derived models. The insights generated by this study can inform the design of cost-effective strategies aimed at reducing HBV-related morbidity and mortality, thereby contributing to Ethiopia's progress toward the WHO goal of eliminating viral hepatitis as a public health threat by 2030 [1].

Overall, this research bridges the gap between mathematical theory and public health practice by translating complex transmission dynamics into policy-relevant conclusions. It provides a methodological foundation that can be adapted to other high-burden settings and serves as a valuable reference for future studies on HBV control in sub-Saharan Africa.

1.6 Scope of the Study

This study focuses on the deterministic mathematical modeling of Hepatitis B Virus (HBV) transmission dynamics within a human population, with particular emphasis on the epidemiological context of Ethiopia. The model framework incorporates key disease states, including susceptible, exposed, acutely infected, chronically infected, and recovered individuals, as well as public health interventions such as vaccination and treatment of chronic carriers.

Demographic and epidemiological parameters are primarily informed by published literature and available regional data relevant to Ethiopia and similar high-endemic settings. The analysis includes the derivation of the basic reproduction number, equilibrium and stability analysis, numerical simulations, and sensitivity assessment of key intervention parameters.

To maintain analytical tractability and focus, this study does not consider stochastic effects, spatial heterogeneity, viral mutation, or co-infections such as HIV/HBV. Additionally, age-structured dynamics and economic cost components are not explicitly modeled, although the implications of healthcare infrastructure limitations are discussed in the interpretation of results. These aspects are acknowledged as important directions for future research.

1.7 Model Limitations

Although vertical (mother-to-child) transmission is epidemiologically important in HBV persistence, it is not explicitly modeled in the present study. Instead, its potential effect is implicitly absorbed within the overall transmission parameter.

In high-endemic settings such as Ethiopia, vertical transmission can significantly contribute to chronic infection prevalence. Incorporating this pathway explicitly would require either an age-structured model or the introduction of additional compartments to represent newborn infection dynamics.

Therefore, the absence of explicit vertical transmission modeling constitutes a limitation of this study and should be considered when interpreting long-term predictions.

Chapter 2

Literature Review

2.1 Introduction

This chapter presents a critical synthesis of existing literature relevant to the epidemiology and transmission dynamics of Hepatitis B Virus (HBV), with particular emphasis on the role of mathematical modeling in understanding disease persistence and evaluating control strategies. Rather than providing a descriptive summary of previous studies, this review identifies key theoretical, epidemiological, and methodological contributions, while highlighting limitations that motivate the present research.

The literature is organized around four interconnected themes: the biological and epidemiological characteristics of HBV, global and regional disease burden with emphasis on sub-Saharan Africa and Ethiopia, mathematical modeling approaches used to study HBV transmission, and model-based evaluations of vaccination and treatment strategies. Particular attention is given to how existing models represent chronic infection, vertical transmission, and intervention effectiveness, as these elements are central to HBV persistence in high-endemic settings.

Although numerous mathematical models have been developed to study HBV dynamics, many rely on simplified assumptions or are calibrated to epidemiological contexts that differ substantially from those of resource-limited countries. Consequently, their applicability to policy planning in settings such as Ethiopia remains limited. This chapter critically examines these gaps and establishes the rationale for developing a biologically realistic and context-specific modeling framework that integrates chronic infection dynamics, vaccination, and treatment interventions.

By situating the present study within the broader body of HBV modeling literature, this chapter clarifies how the proposed model advances existing work and provides a stronger

evidence base for public health decision-making in high-burden environments.

2.2 Overview of Hepatitis B Virus (HBV)

Hepatitis B Virus (HBV) is a partially double-stranded DNA virus belonging to the *Hepadnaviridae* family and is a leading cause of acute and chronic liver disease worldwide. Following infection, individuals may experience an acute phase characterized by viral replication and immune response, after which the infection either resolves or progresses to chronic carriage. The likelihood of chronic infection is strongly age-dependent, with infection during infancy or early childhood resulting in chronic infection in up to 90% of cases, compared to less than 5% in immunocompetent adults [5].

A defining biological feature of HBV is the persistence of covalently closed circular DNA (cccDNA) within hepatocytes. This stable viral reservoir enables long-term viral replication even in the presence of antiviral therapy, rendering complete viral eradication extremely difficult [6]. As a consequence, millions of individuals worldwide live with chronic HBV infection for decades, often remaining asymptomatic while continuing to transmit the virus. Chronic carriers therefore represent a central epidemiological group in sustaining HBV transmission and contributing to long-term disease burden.

From a disease progression perspective, chronic HBV infection is associated with a substantially increased risk of severe liver complications, including cirrhosis and hepatocellular carcinoma. These complications account for the majority of HBV-related morbidity and mortality globally [1]. The long latency period between infection and clinical outcomes further complicates disease control efforts, as transmission may continue unnoticed in the absence of widespread screening.

These biological characteristics have important implications for mathematical modeling. Models that do not explicitly distinguish between acute infection and chronic carriage may underestimate the persistence of HBV transmission and misrepresent the long-term impact of interventions. Incorporating chronic infection compartments and differential infectivity is therefore essential for accurately capturing HBV dynamics, particularly in high-endemic settings where early-life infection is common. This biological motivation underpins the modeling framework adopted in the present study.

2.3 Global Epidemiology of Hepatitis B Virus

Hepatitis B Virus remains one of the most prevalent chronic viral infections globally, despite significant progress in prevention through vaccination. The World Health Organization estimates that approximately 254 million people were living with chronic HBV infection in 2022, with nearly 1.1 million deaths occurring annually due to HBV-related liver disease [1]. These deaths are largely attributable to long-term complications such as cirrhosis and hepatocellular carcinoma, underscoring the delayed but severe consequences of chronic infection.

The global distribution of HBV infection is highly heterogeneous. Regions such as sub-Saharan Africa and East Asia are classified as high-endemic areas, with chronic prevalence exceeding 8%, while parts of the Middle East, South Asia, and Eastern Europe exhibit intermediate prevalence ranging from 2% to 7%. In contrast, low-prevalence regions, including Western Europe and the Americas, typically report prevalence below 2%. This heterogeneity reflects differences in transmission patterns, healthcare access, vaccination coverage, and socio-economic conditions.

Although global prevalence has declined over recent decades due to the expansion of universal childhood vaccination programs, high-burden regions continue to face substantial challenges. Schweitzer et al. [3] demonstrated that while vaccination has significantly reduced HBV incidence among younger cohorts, adult populations in endemic regions continue to harbor high levels of chronic infection. Limited access to screening and treatment, coupled with ongoing vertical and early childhood transmission, sustains endemicity despite improvements in immunization.

These epidemiological patterns have important implications for modeling HBV transmission. Models calibrated to low-prevalence or high-income settings may not adequately capture the drivers of persistence in endemic regions, where chronic carriers constitute a large proportion of the infectious population. Consequently, global estimates alone are insufficient for informing local policy decisions. Region-specific modeling frameworks that account for endemic transmission pathways and intervention constraints are essential for accurately evaluating elimination prospects and designing effective control strategies.

2.4 HBV Transmission Pathways

Hepatitis B Virus is transmitted through exposure to infected blood or body fluids, with transmission pathways varying across age groups, socio-economic settings, and healthcare contexts. Understanding these pathways is essential for constructing biologically realistic transmission models and for designing effective intervention strategies.

Mother-to-child transmission (MTCT) is a dominant route of HBV transmission in high-endemic regions. Without timely intervention, the probability of transmission from an infected mother to her newborn ranges from 70% to 90%, particularly when the mother is hepatitis B e-antigen (HBeAg) positive [7]. Infants infected at birth face an exceptionally high risk of progressing to chronic infection, thereby contributing substantially to the long-term reservoir of infectious individuals within the population. This mechanism plays a critical role in sustaining endemic transmission in sub-Saharan Africa and East Asia.

In addition to vertical transmission, early childhood exposure through close household contact contributes significantly to HBV prevalence in endemic settings. Non-sexual horizontal transmission among children, facilitated by shared living environments and limited infection control practices, further amplifies the risk of chronic infection [8]. These early-life transmission routes differ markedly from those predominant in low-prevalence regions, where adult-acquired infection through sexual contact or injection drug use is more common.

Among adolescents and adults, HBV transmission occurs primarily through unprotected sexual contact, needle sharing, unsafe medical injections, and contaminated blood products [9]. In many low- and middle-income countries, inadequate sterilization practices and limited enforcement of infection control protocols in healthcare facilities remain significant contributors to transmission [**?**].

The diversity of HBV transmission pathways underscores the importance of incorporating differential transmission mechanisms into mathematical models. Models that assume homogeneous mixing or neglect vertical transmission may substantially underestimate the persistence of infection and the relative importance of early-life interventions. Consequently, realistic modeling frameworks must explicitly account for MTCT and age-related transmission dynamics, particularly in endemic settings where these pathways dominate. This consideration directly informs the structure of the modeling approach adopted in the present study.

2.5 Burden of Hepatitis B Virus in Sub-Saharan Africa and Ethiopia

Sub-Saharan Africa bears one of the highest burdens of Hepatitis B Virus infection worldwide, with regional estimates indicating chronic prevalence levels ranging from 6% to 12% [12]. In many countries within the region, HBV infection is typically acquired during infancy or early childhood, resulting in a large pool of chronically infected individuals who remain infectious for prolonged periods. This epidemiological pattern distinguishes sub-Saharan Africa from low-endemic regions and contributes to the persistent nature of HBV transmission.

Ethiopia is classified as a high-intermediate endemic country for HBV. A comprehensive systematic review and meta-analysis by Belyhun et al. [10] estimated a national HBV prevalence of approximately 8%, with considerable heterogeneity across regions and population groups. Higher prevalence rates have been reported among healthcare workers, pregnant women, and individuals requiring frequent medical interventions, highlighting occupational and healthcare-associated risks [11].

Despite the inclusion of hepatitis B vaccination in the national Expanded Programme on Immunization, several structural challenges limit the effectiveness of prevention efforts in Ethiopia. These include incomplete vaccination coverage, particularly in rural and hard-to-reach communities, limited availability of the timely birth-dose vaccine, and insufficient antenatal screening for HBV infection. As a result, mother-to-child transmission continues to contribute substantially to new chronic infections, perpetuating the cycle of endemicity.

Furthermore, diagnostic and treatment services for chronic HBV infection remain constrained by limited laboratory infrastructure, shortages of trained healthcare personnel, and financial barriers to long-term antiviral therapy. These limitations reduce the likelihood that infected individuals are identified and effectively managed, allowing chronic carriers to sustain community-level transmission.

The persistence of HBV in Ethiopia underlines the necessity of analytical tools that can evaluate intervention strategies within the constraints of the existing healthcare system. Mathematical models calibrated to local epidemiological data offer a means of assessing realistic vaccination and treatment targets, exploring the potential impact of combined interventions, and identifying feasible pathways toward disease control. Such context-specific modeling is essential for informing national HBV prevention policies and for optimizing the use of limited public health resources.

2.6 Mathematical Modeling in Infectious Disease Epidemiolog

Mathematical modeling plays a central role in understanding the transmission dynamics of infectious diseases and in guiding public health decision-making. By translating biological and epidemiological processes into quantitative frameworks, models enable the systematic exploration of disease spread, persistence, and control under varying assumptions and intervention scenarios. In the context of chronic infectious diseases such as Hepatitis B Virus, mathematical models are particularly valuable due to the long time horizons over which infection and intervention effects unfold.

Compartmental models are among the most widely used modeling approaches in infectious disease epidemiology. These models partition the population into epidemiologically meaningful classes, such as susceptible, exposed, infectious, and recovered individuals, and describe the flow of individuals between compartments using systems of differential equations. Hethcote [13] emphasizes that such models strike a balance between biological realism and analytical tractability, allowing for the derivation of key epidemiological quantities while remaining interpretable for policy analysis.

A fundamental concept arising from compartmental modeling is the basic reproduction number, denoted by R_0, which represents the expected number of secondary infections generated by a single infectious individual in a fully susceptible population. The threshold property of R_0 provides a powerful criterion for disease control: if $R_0 < 1$, the disease-free equilibrium is stable and the infection will eventually die out, whereas $R_0 > 1$ implies sustained transmission [14]. This threshold-based framework forms the basis for evaluating the effectiveness of intervention strategies such as vaccination and treatment.

SEIR-type models, which incorporate a latent (exposed) stage between susceptibility and infectiousness, are particularly well-suited for diseases like HBV that exhibit a non-negligible incubation period. Extensions of these models have been widely used to study vaccination dynamics, waning immunity, and long-term disease persistence. However, for HBV, classical SEIR formulations may be insufficient, as they do not explicitly distinguish chronic carriers from acutely infected individuals, despite their markedly different epidemiological roles.

Consequently, recent modeling efforts increasingly emphasize the need to tailor compartmental structures to disease-specific biology. For HBV, this entails incorporating chronic infection compartments, differential infectivity, and intervention-related transitions. Such refinements enhance the biological validity of model predictions and improve their utility for evaluating

realistic public health strategies, particularly in high-endemic settings.

2.7 Modeling Vaccination and Control Strategies

Vaccination is widely recognized as the most effective and cost-efficient intervention for the prevention and long-term control of Hepatitis B Virus infection. Mathematical modeling studies consistently demonstrate that widespread vaccination can substantially reduce HBV incidence, prevalence, and HBV-related mortality, particularly when implemented early in life. The introduction of universal childhood vaccination has led to marked declines in HBV prevalence in several countries, highlighting the critical role of immunization in interrupting transmission chains [17].

Model-based analyses have shown that the impact of vaccination depends not only on vaccine efficacy but also on population-level coverage and timing. In high-endemic settings, timely administration of the birth-dose vaccine is essential for preventing mother-to-child transmission, which is a major source of chronic infection [18]. Models that explicitly incorporate birth-dose vaccination demonstrate that delays or missed doses can significantly reduce the overall effectiveness of vaccination programs, even when later childhood coverage is high.

Several studies have also examined the implications of waning immunity on long-term HBV control. While the hepatitis B vaccine provides long-lasting protection for most individuals, uncertainty remains regarding the duration of immunity at the population level. Mathematical models incorporating waning immunity suggest that reduced protection over time may compromise herd immunity and lead to disease resurgence if booster strategies are not considered [16]. These findings underscore the importance of explicitly modeling immunity dynamics when evaluating long-term elimination prospects.

Importantly, vaccination alone may be insufficient to achieve elimination in settings with a large reservoir of chronic carriers. Modeling studies indicate that even high vaccination coverage may fail to rapidly reduce prevalence if chronic infections acquired in earlier cohorts remain untreated [**?**]. Consequently, integrated strategies combining vaccination with screening and treatment of infected individuals are increasingly recognized as necessary for effective control.

Despite these advances, many existing vaccination-focused models are calibrated to high-income or low-prevalence settings and may not fully capture the operational challenges faced

in resource-limited environments. In particular, few studies quantify the vaccination coverage thresholds required to reduce the basic reproduction number below unity under realistic healthcare constraints. Addressing this limitation is essential for translating modeling insights into actionable public health targets in countries such as Ethiopia.

2.8 Modeling Treatment Strategies

Antiviral treatment plays a critical role in reducing the clinical and epidemiological burden of chronic Hepatitis B Virus infection. Current first-line therapies, such as tenofovir and entecavir, are highly effective in suppressing viral replication, lowering viral load, and reducing the risk of disease progression to cirrhosis and hepatocellular carcinoma [19]. Although these treatments do not eradicate the virus due to the persistence of covalently closed circular DNA, they substantially reduce infectivity and disease-related mortality.

Mathematical models that incorporate treatment dynamics generally represent therapy as a reduction in the infectiousness of chronic carriers or as a transition from an infectious to a controlled or recovered state. Such models consistently demonstrate that treatment can significantly decrease transmission intensity, particularly when targeted toward individuals with high viral loads [20]. However, modeling studies also highlight that treatment alone is insufficient to eliminate HBV transmission, especially in high-endemic settings where new infections continue to occur through vertical and early childhood transmission [**?**].

Several modeling investigations have emphasized the importance of treating pregnant women to prevent mother-to-child transmission. Antiviral therapy administered during late pregnancy has been shown to dramatically reduce the risk of vertical transmission when combined with neonatal vaccination [19]. Models incorporating this intervention pathway demonstrate substantial long-term reductions in chronic infection prevalence, reinforcing the need to integrate treatment strategies into broader HBV control frameworks.

Despite the demonstrated benefits of treatment, many existing models assume idealized access to antiviral therapy and sustained treatment adherence. In resource-limited settings, such assumptions may not be realistic due to financial constraints, limited diagnostic capacity, and healthcare workforce shortages. Consequently, models that fail to account for treatment feasibility may overestimate the impact of therapy-based interventions.

These findings suggest that realistic HBV transmission models must integrate treatment dynamics in a manner that reflects both biological effectiveness and operational constraints.

Combining treatment of chronic carriers with vaccination and screening strategies is therefore essential for accurately evaluating elimination prospects in high-burden countries. This integrated perspective informs the modeling approach adopted in the present study.

2.9 Gaps in Existing Literature

Despite extensive epidemiological and mathematical modeling studies on Hepatitis B Virus, several important gaps remain in the current body of literature. Addressing these gaps is essential for developing effective and context-sensitive HBV control strategies, particularly in high-burden, resource-limited settings.

First, there is a notable lack of region-specific mathematical models that reflect the epidemiological characteristics of Sub-Saharan Africa and Ethiopia in particular. Many existing HBV models are parameterized using data from East Asia, Europe, or high-income countries, where transmission pathways, healthcare access, and vaccination coverage differ substantially [3]. The absence of locally relevant models limits the applicability of model-based policy recommendations in African contexts.

Second, several studies focus on vaccination or treatment strategies in isolation, without integrating both interventions within a single modeling framework. Given that vaccination primarily prevents new infections while treatment reduces infectivity among chronic carriers, excluding either component leads to an incomplete representation of HBV transmission dynamics [18]. Models that fail to capture this interaction may underestimate the effort required to achieve long-term disease control.

Third, many mathematical models do not explicitly include chronic infection compartments, despite the fact that chronic carriers constitute the primary reservoir of HBV transmission in endemic regions. Simplified models that aggregate acute and chronic infections overlook the prolonged infectious period and delayed disease progression characteristic of HBV, thereby limiting their realism and predictive capacity [5].

Fourth, numerical simulations and sensitivity analyses are often insufficient or entirely absent in existing studies. While theoretical analyses provide valuable insights into stability conditions and threshold parameters, simulation-based results are necessary to evaluate intervention scenarios, assess long-term trends, and identify the most influential parameters affecting disease transmission [13]. Without such analyses, model outputs are difficult to translate into actionable public health guidance.

Finally, few studies explicitly consider operational constraints such as limited healthcare infrastructure, incomplete vaccination coverage, and delayed diagnosis, which are common in low- and middle-income countries. Ignoring these realities can lead to overly optimistic predictions and reduce the practical relevance of modeling outcomes.

These gaps highlight the need for a comprehensive, regionally tailored SEIR-based mathematical model that integrates vaccination, treatment, and chronic infection dynamics while supporting both analytical and numerical investigations. The present study aims to address these shortcomings by developing and analyzing a model designed specifically to inform HBV control strategies in high-burden settings.

2.9.1 Comparative Analysis of Existing HBV Models

Although numerous mathematical models have been proposed to describe HBV transmission dynamics, their structural assumptions vary considerably.

Several classical SEIR-type models do not explicitly separate acute and chronic infection stages, thereby limiting their ability to assess long-term chronic carrier prevalence. Other models focus exclusively on vaccination strategies without integrating treatment of chronic carriers.

Furthermore, many models assume homogeneous mixing and are calibrated using data from developed countries, where healthcare access and vaccination coverage are substantially higher than in Ethiopia.

These limitations reduce the applicability of such models to high-endemic, resource-limited settings. The present SEICR framework improves upon previous approaches by explicitly modeling chronic carriers and jointly evaluating vaccination and treatment strategies within a context more representative of Ethiopia.

2.10 Chapter Summary

This chapter has provided a comprehensive and critical review of the existing literature on Hepatitis B Virus epidemiology, transmission mechanisms, and mathematical modeling approaches. The review highlighted the global and regional burden of HBV, emphasizing the persistent public health challenges faced by high-endemic regions, particularly Sub-Saharan Africa and Ethiopia.

The epidemiological evidence demonstrates that chronic HBV infection, driven largely by

early-life exposure and mother-to-child transmission, remains the primary source of sustained transmission in endemic settings. Despite the availability of effective vaccines and antiviral therapies, gaps in coverage, delayed diagnosis, and limited healthcare infrastructure continue to hinder elimination efforts [1, 12].

The chapter further examined the role of mathematical modeling in understanding infectious disease dynamics, with particular attention to compartmental SEIR-type models. Previous modeling studies have shown that vaccination and treatment interventions can substantially reduce HBV incidence; however, many models oversimplify the disease process by excluding chronic infection compartments or by considering interventions in isolation [18]. Moreover, the lack of region-specific parameterization limits the applicability of existing models to African contexts.

Several critical gaps were identified, including the scarcity of models tailored to Ethiopia, insufficient integration of vaccination and treatment strategies, limited numerical simulation for policy evaluation, and inadequate consideration of healthcare system constraints. These gaps underscore the need for a modeling framework that captures the unique epidemiological and operational realities of high-burden, resource-limited settings.

Motivated by these limitations, the present study proposes a deterministic SEIR-based mathematical model incorporating vaccination, treatment, and chronic infection dynamics. The model aims to provide both analytical insights and numerical evidence to inform effective HBV control strategies. The next chapter introduces the model formulation, underlying assumptions, parameter definitions, and analytical methods used to study the transmission dynamics of Hepatitis B Virus.

Chapter 3

Mathematical Model Formulation and Analysis

3.1 Introduction

This chapter presents the formulation and mathematical analysis of a biologically realistic model for the transmission dynamics of Hepatitis B Virus (HBV). Building upon the epidemiological insights and research gaps identified in Chapter Two, we develop a deterministic compartmental model that explicitly incorporates key features of HBV epidemiology that are often oversimplified or neglected in earlier studies, particularly in the context of high-burden, resource-limited settings such as Ethiopia.

Unlike classical SEIR models, which treat all infectious individuals as epidemiologically homogeneous, HBV transmission is strongly influenced by the presence of chronic carriers who remain infectious for prolonged periods and serve as persistent reservoirs of infection. Empirical studies have shown that individuals who acquire HBV early in life have a substantially higher probability of progressing to chronic infection, thereby sustaining endemic transmission over decades [5, 3]. Consequently, failure to account for chronic carriage may lead to biologically unrealistic predictions and misleading policy recommendations.

To address this limitation, the present study formulates an extended **SEICR** (Susceptible–Exposed–model that captures both acute and chronic stages of HBV infection, as well as vaccination-induced immunity and treatment of chronic carriers. The model structure is designed to reflect the dominant transmission pathways relevant to Ethiopia and similar Sub-Saharan African countries, where perinatal transmission, early childhood exposure, and limited access to diagnosis and treatment remain significant challenges [10, 12].

The objectives of this chapter are threefold. First, we define the model compartments, assumptions, and governing differential equations in a manner consistent with HBV natural history and available epidemiological evidence. Second, we analyze the qualitative properties of the model, including positivity, boundedness, equilibrium points, and the basic reproduction number R_0, which serves as a threshold parameter for disease persistence or elimination. Third, we establish a rigorous mathematical foundation for subsequent numerical simulations, sensitivity analysis, and intervention assessment presented in later chapters.

By grounding the model formulation in biological realism and region-specific context, this chapter provides the analytical framework necessary to evaluate vaccination, screening, and treatment strategies for HBV control in Ethiopia. The results derived herein form the basis for identifying critical intervention thresholds, such as the minimum vaccination coverage required to reduce R_0 below unity, and for assessing the feasibility of achieving elimination targets under existing healthcare constraints.

3.2 Model Assumptions and Population Structure

The formulation of a mathematical model for HBV transmission requires a set of simplifying assumptions that balance biological realism with analytical tractability. In this study, the following assumptions are made based on established epidemiological evidence and the specific context of HBV transmission in Ethiopia and similar high-endemic settings.

Model Assumptions

1. The total population at time t, denoted by $N(t)$, is divided into five mutually exclusive compartments: susceptible individuals $S(t)$, exposed individuals $E(t)$, acutely infectious individuals $I(t)$, chronic carriers $C(t)$, and recovered (immune) individuals $R(t)$. Thus,

$$N(t) = S(t) + E(t) + I(t) + C(t) + R(t).$$

2. New individuals enter the population through birth or recruitment at a constant rate μN. A proportion of newborns are assumed to be susceptible, while vertical (mother-to-child) transmission is implicitly captured through progression to infection in early life, consistent with population-level modeling approaches [7, 18].

3. Susceptible individuals acquire HBV infection through effective contact with acutely infectious individuals I and chronic carriers C. Chronic carriers are assumed to be

infectious but with a different level of infectivity, represented by a modification parameter $\eta \in (0, 1]$, reflecting reduced but sustained viral shedding [3].

4. Following infection, individuals first enter an exposed (latent) class E, during which they are infected but not yet infectious. Exposed individuals progress to the acute infectious class I at a constant rate σ, corresponding to the inverse of the average incubation period.

5. A proportion of acutely infected individuals progress to chronic infection at rate α, while the remaining individuals recover naturally. This assumption reflects the well-documented dependence of chronicity on host and infection characteristics, particularly in early-life infections [5].

6. Chronic carriers C may receive antiviral treatment at rate τ, leading to functional recovery and reduced infectivity. Treatment does not immediately eliminate viral DNA but is assumed to reduce infectiousness sufficiently to justify transfer to the recovered class [19].

7. Susceptible individuals may acquire immunity through vaccination at rate v. Vaccine-induced immunity is assumed to be effective and long-lasting within the modeling horizon, consistent with empirical evidence on hepatitis B vaccine efficacy [17].

8. All individuals experience natural death at a constant per capita rate γ. Disease-induced mortality is assumed to occur only in the acute infectious class at rate δ, reflecting the higher short-term mortality risk during active infection [1].

9. Recovered individuals are assumed to acquire immunity and do not return to the susceptible class during the study period. Waning immunity is not explicitly modeled but is discussed as a limitation in later chapters.

Population Structure

The model considers a homogeneous population without explicit age stratification. While age plays a critical role in HBV progression, particularly for chronic infection, the inclusion of a chronic carrier compartment implicitly captures the long-term epidemiological impact of early-life infection. This approach has been widely adopted in population-level HBV models where age-structured data are limited [14, 13].

The population is assumed to mix homogeneously, meaning that each individual has an equal probability of coming into effective contact with an infectious individual. Although this assumption may not fully capture heterogeneous contact patterns in real populations, it provides a reasonable approximation for assessing average transmission dynamics and intervention thresholds at the national level.

These assumptions collectively define a biologically meaningful and analytically tractable framework for studying HBV transmission and control. In the next section, the model compartments and transitions between them are described in detail, accompanied by the corresponding flow structure of the SEICR model.

3.3 Model Compartments and Flow Diagram

In this section, we describe the epidemiological compartments of the proposed SEICR model and the transitions between them. Each compartment represents a distinct disease state that reflects the natural history of Hepatitis B Virus (HBV) infection, while the transition pathways capture the underlying biological and public health processes governing disease transmission and control.

Description of Model Compartments

The total population at time t, denoted by $N(t)$, is subdivided into the following five compartments:

- **Susceptible individuals ($S(t)$)**: This class consists of individuals who have not been infected with HBV and have not yet acquired immunity through vaccination. Susceptible individuals are at risk of acquiring infection through effective contact with infectious individuals.

- **Exposed individuals ($E(t)$)**: This compartment represents individuals who have been infected with HBV but are not yet infectious. During this latent period, viral replication occurs without onward transmission. Individuals in this class progress to the acute infectious stage after the incubation period.

- **Acutely infectious individuals ($I(t)$)**: This class includes individuals experiencing active HBV infection who are capable of transmitting the virus. Acutely infected

individuals may either recover naturally or progress to chronic infection, depending on host and viral factors.

- **Chronic carriers ($C(t)$)**: Chronic carriers are individuals who fail to clear the virus following acute infection and remain persistently infected for extended periods. Although they may be asymptomatic, chronic carriers contribute substantially to long-term HBV transmission due to prolonged viral shedding and limited diagnosis in high-burden settings [3].

- **Recovered and immune individuals ($R(t)$)**: This compartment consists of individuals who have acquired immunity either through successful vaccination or recovery following antiviral treatment or natural clearance. These individuals are assumed to be protected against reinfection during the study period.

Transition Pathways

The movement of individuals between compartments is governed by biologically meaningful transition processes:

- Susceptible individuals become exposed following effective contact with infectious individuals in the I and C compartments, with chronic carriers contributing to transmission at a modified rate.

- Exposed individuals progress to the acutely infectious class after the latent period.

- Acutely infectious individuals either recover or progress to chronic infection, reflecting the bifurcation in disease outcomes characteristic of HBV infection.

- Chronic carriers may enter the recovered class following successful antiviral treatment.

- Susceptible individuals may directly move to the recovered class through vaccination.

- Natural mortality affects all compartments, while disease-induced mortality is restricted to the acutely infectious class.

Model Flow Diagram

A schematic flow diagram illustrating the compartmental structure and transition pathways of the SEICR model is presented in Figure 3.1. The diagram provides a visual representation

of the interactions between disease states and highlights the roles of vaccination and treatment as control mechanisms.

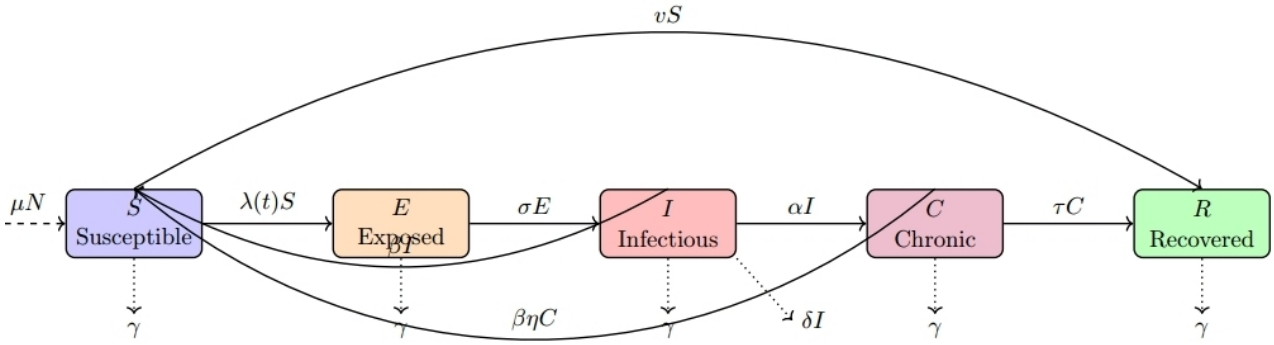

Figure 3.1: Schematic flow diagram of the SEICR model for HBV transmission, illustrating transitions between susceptible (S), exposed (E), infectious (I), chronic carrier (C), and recovered (R) compartments.

The explicit inclusion of the chronic carrier compartment distinguishes this model from classical SEIR frameworks and enables a more realistic representation of HBV persistence and control dynamics. In the subsequent section, these transitions are translated into a system of nonlinear ordinary differential equations governing the evolution of the disease over time.

3.4 Model Formulation

Based on the assumptions and compartmental structure described in the preceding sections, we now formulate the mathematical model governing the transmission dynamics of Hepatitis B Virus (HBV). The model is expressed as a system of nonlinear ordinary differential equations that describe the rate of change of each epidemiological compartment over time.

Let $S(t)$, $E(t)$, $I(t)$, $C(t)$, and $R(t)$ denote the numbers of susceptible, exposed, acutely infectious, chronic carrier, and recovered individuals at time t, respectively. The total population size is given by

$$N(t) = S(t) + E(t) + I(t) + C(t) + R(t).$$

Force of Infection

The force of infection, denoted by $\lambda(t)$, represents the per capita rate at which susceptible individuals acquire HBV infection. Since both acutely infectious individuals and chronic

carriers contribute to transmission, the force of infection is defined as

$$\lambda(t) = \beta \frac{I(t) + \eta C(t)}{N(t)},$$

where β is the effective contact rate and $0 < \eta \leq 1$ represents the relative infectivity of chronic carriers compared to acutely infectious individuals. This formulation reflects the fact that chronic carriers may be less infectious on a per-contact basis but remain infectious for much longer durations [3].

Model Equations

The dynamics of the SEICR model are governed by the following system of differential equations:

$$\frac{dS}{dt} = \mu N - \lambda(t)S - (v + \gamma)S, \tag{3.1}$$

$$\frac{dE}{dt} = \lambda(t)S - (\sigma + \gamma)E, \tag{3.2}$$

$$\frac{dI}{dt} = \sigma E - (\alpha + \delta + \gamma)I, \tag{3.3}$$

$$\frac{dC}{dt} = \alpha I - (\tau + \gamma)C, \tag{3.4}$$

$$\frac{dR}{dt} = vS + \tau C - \gamma R. \tag{3.5}$$

Description of Model Parameters

Each term in the system has a clear epidemiological interpretation:

- μ denotes the per capita recruitment (birth) rate into the population.
- β is the transmission coefficient representing effective contact between susceptible and infectious individuals.
- η modifies the contribution of chronic carriers to transmission.
- v represents the vaccination rate of susceptible individuals.
- σ is the progression rate from exposed to acutely infectious, corresponding to the inverse of the incubation period.
- α denotes the rate at which acutely infectious individuals progress to chronic infection.

- τ is the treatment rate of chronic carriers.
- γ represents the natural death rate.
- δ denotes the disease-induced death rate among acutely infectious individuals.

The first equation describes the inflow of new susceptible individuals through recruitment and their removal through infection, vaccination, and natural death. The second equation captures the latent phase of infection. The third and fourth equations represent the progression from acute infection to either recovery or chronic carriage, while the final equation accounts for immunity acquired through vaccination or treatment.

This system of equations forms the core of the proposed HBV transmission model. In the next section, we examine the fundamental mathematical properties of the model, including the positivity and boundedness of solutions, which are essential for ensuring epidemiological and mathematical consistency.

3.5 Model Properties

Before analyzing the equilibria and threshold dynamics of the proposed SEICR model, it is essential to establish that the model is mathematically and epidemiologically well posed. In particular, we show that the solutions of the system are non-negative for all time and that the population remains bounded within a biologically feasible region.

3.5.1 Positivity of Solutions

Theorem 3.1 (Positivity). Let the initial conditions

$$S(0) \geq 0, \quad E(0) \geq 0, \quad I(0) \geq 0, \quad C(0) \geq 0, \quad R(0) \geq 0.$$

Then the solutions $S(t), E(t), I(t), C(t)$, and $R(t)$ of the SEICR model remain non-negative for all $t > 0$.

Proof. Consider the first equation of the system:

$$\frac{dS}{dt} = \mu N - \lambda(t)S - (v + \gamma)S.$$

Since $\mu N \geq 0$, $\lambda(t) \geq 0$, and $v + \gamma \geq 0$, it follows that

$$\frac{dS}{dt} \geq -(v + \gamma)S.$$

By standard comparison arguments for differential equations, $S(t)$ remains non-negative for all $t > 0$ provided $S(0) \geq 0$.

Similarly, for the exposed class,

$$\frac{dE}{dt} = \lambda(t)S - (\sigma + \gamma)E \geq -(\sigma + \gamma)E,$$

which implies $E(t) \geq 0$ for all $t > 0$.

For the acutely infectious class,

$$\frac{dI}{dt} = \sigma E - (\alpha + \delta + \gamma)I \geq -(\alpha + \delta + \gamma)I,$$

and hence $I(t)$ remains non-negative.

For the chronic carrier class,

$$\frac{dC}{dt} = \alpha I - (\tau + \gamma)C \geq -(\tau + \gamma)C,$$

which ensures $C(t) \geq 0$.

Finally, for the recovered class,

$$\frac{dR}{dt} = vS + \tau C - \gamma R \geq -\gamma R,$$

and thus $R(t) \geq 0$.

Therefore, all state variables remain non-negative for all $t > 0$, and the model solutions are epidemiologically meaningful. □

3.5.2 Invariant Region and Boundedness

To show that the model solutions are bounded, we consider the total population size $N(t)$.

Summing equations (3.1)–(3.5), we obtain

$$\frac{dN}{dt} = \mu N - \gamma N - \delta I.$$

Since $\delta I \geq 0$, it follows that

$$\frac{dN}{dt} \leq (\mu - \gamma)N.$$

Solving this inequality yields

$$N(t) \leq N(0)e^{(\mu-\gamma)t}.$$

In particular, when $\mu = \gamma$, which corresponds to a demographically stable population, we have

$$\frac{dN}{dt} \leq 0 \quad \Rightarrow \quad N(t) \leq N(0).$$

Thus, the total population remains bounded for all $t > 0$. Consequently, the region

$$\Omega = \left\{ (S, E, I, C, R) \in \mathbb{R}^5_+ : N(t) \leq \frac{\mu}{\gamma} \right\}$$

is positively invariant and attracting.

This implies that all solutions of the SEICR model starting in Ω remain in Ω for all future time, ensuring that the model dynamics are confined to a biologically feasible region.

Having established the positivity and boundedness of solutions, the model is mathematically well defined and suitable for further qualitative analysis. In the next section, we derive the disease-free equilibrium and investigate its epidemiological significance.

3.6 Disease-Free Equilibrium

The disease-free equilibrium (DFE) represents the state of the population in which Hepatitis B Virus (HBV) is absent, and no active transmission occurs. Analysis of the DFE is fundamental in epidemiological modeling, as it provides a baseline against which disease persistence and elimination can be assessed and serves as the reference point for defining the basic reproduction number R_0.

At the disease-free equilibrium, all compartments associated with infection vanish, that is,

$$E = I = C = 0,$$

while the population consists only of susceptible and recovered (immune) individuals.

To determine the DFE, we set the right-hand sides of the system of equations (3.1)–(3.5) equal to zero under the assumption of no infection.

From the susceptible equation,

$$0 = \mu N - (v + \gamma)S,$$

which yields

$$S^0 = \frac{\mu N}{v + \gamma}.$$

From the recovered equation,

$$0 = vS - \gamma R,$$

substituting S^0 gives

$$R^0 = \frac{v}{\gamma} S^0 = \frac{\mu v N}{\gamma(v+\gamma)}.$$

Thus, the disease-free equilibrium point is given by

$$E_0 = \left(S^0, E^0, I^0, C^0, R^0\right) = \left(\frac{\mu N}{v+\gamma}, 0, 0, 0, \frac{\mu v N}{\gamma(v+\gamma)}\right).$$

Epidemiological Interpretation

At the disease-free equilibrium, the absence of exposed, infectious, and chronic carrier individuals implies that HBV transmission has been interrupted. The size of the susceptible population at equilibrium depends on the balance between recruitment, vaccination, and natural mortality. In particular, increasing the vaccination rate v reduces the proportion of susceptible individuals and increases the immune population, thereby enhancing population-level protection.

The DFE exists for all biologically meaningful parameter values and is feasible within the positively invariant region established in Section 3.5. However, the stability of the disease-free equilibrium depends on whether an introduced infectious individual can generate secondary infections. This threshold behavior is quantified by the basic reproduction number R_0, which is derived and analyzed in the following section.

Understanding the stability of the DFE is critical for evaluating whether vaccination and treatment strategies are sufficient to eliminate HBV transmission in Ethiopia. Accordingly, the next section focuses on the computation of R_0 using the next-generation matrix approach.

To establish the existence of the endemic equilibrium, the right-hand side of the system is set equal to zero and equilibrium expressions are derived in terms of R_0. Substituting the steady-state expressions into the force of infection yields a nonlinear algebraic equation whose positive solution exists whenever $R_0 > 1$.

Standard bifurcation theory for epidemic models suggests that the system undergoes a forward (transcritical) bifurcation at $R_0 = 1$, ensuring the emergence of a unique positive endemic equilibrium when R_0 exceeds unity.

Although a full global stability proof is beyond the scope of this thesis, the analytical structure and numerical simulations strongly support the theoretical prediction.

3.7 Basic Reproduction Number

The basic reproduction number, denoted by R_0, is a fundamental threshold quantity in infectious disease epidemiology. It represents the expected number of secondary infections generated by a single infected individual introduced into a completely susceptible population. In the context of HBV, R_0 determines whether the infection can invade and persist ($R_0 > 1$) or eventually die out ($R_0 < 1$).

In this study, the basic reproduction number is derived using the *next-generation matrix method*, as proposed by Diekmann et al. and van den Driessche and Watmough, which is widely accepted for compartmental epidemic models.

Identification of Infected Compartments

The infected compartments contributing to new HBV infections are the exposed class E, the acutely infectious class I, and the chronic carrier class C. Let

$$\mathbf{x} = (E, I, C)^T$$

denote the vector of infected states.

For each infected compartment, the rate of appearance of new infections and the rate of transfer between compartments are identified.

New Infection and Transition Terms

The new infection terms are given by

$$\mathcal{F} = \begin{pmatrix} \beta \dfrac{S(I + \eta C)}{N} \\ 0 \\ 0 \end{pmatrix},$$

while the remaining transition terms are

$$\mathcal{V} = \begin{pmatrix} (\sigma + \gamma)E \\ (\alpha + \delta + \gamma)I - \sigma E \\ (\tau + \gamma)C - \alpha I \end{pmatrix}.$$

Evaluating these expressions at the disease-free equilibrium E_0, where

$$S^0 = \frac{\mu N}{v + \gamma},$$

we obtain the Jacobian matrices F and V.

Next-Generation Matrices

The Jacobian of $\mathcal{F}$ at the DFE is

$$F = \begin{pmatrix} 0 & \frac{\beta S^0}{N} & \frac{\beta \eta S^0}{N} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

and the Jacobian of $\mathcal{V}$ at the DFE is

$$V = \begin{pmatrix} \sigma + \gamma & 0 & 0 \\ -\sigma & \alpha + \delta + \gamma & 0 \\ 0 & -\alpha & \tau + \gamma \end{pmatrix}.$$

The next-generation matrix is given by

$$K = FV^{-1}.$$

Expression for R_0

After algebraic manipulation, the basic reproduction number is obtained as

$$R_0 = \frac{\beta \mu}{(v + \gamma)(\sigma + \gamma)} \left[\frac{\sigma}{\alpha + \delta + \gamma} + \frac{\eta \alpha \sigma}{(\alpha + \delta + \gamma)(\tau + \gamma)} \right].$$

This expression decomposes R_0 into contributions from acutely infectious individuals and chronic carriers, highlighting the epidemiological importance of long-term infection.

Epidemiological Interpretation

The derived reproduction number explicitly demonstrates how HBV transmission is influenced by vaccination, treatment, and chronic infection. In particular:

- Increasing the vaccination rate v reduces the susceptible population and directly lowers R_0.
- Treatment of chronic carriers (τ) reduces their infectious duration, thereby decreasing the second term of R_0.
- The parameter η quantifies the relative contribution of chronic carriers to transmission, underscoring their role as persistent reservoirs of infection.

Importantly, the condition $R_0 < 1$ defines a critical vaccination threshold required to eliminate HBV transmission. This threshold will be explicitly derived and numerically evaluated for the Ethiopian context in subsequent sections, with particular attention given to the feasibility of achieving the required vaccination coverage under existing healthcare infrastructure constraints.

The stability of the disease-free equilibrium in relation to R_0 is formally analyzed in the next section.

3.8 Stability Analysis

In this section, we analyze the stability properties of the equilibria of the SEICR model. In particular, we examine the local stability of the disease-free equilibrium and discuss the conditions under which an endemic equilibrium exists. These analyses provide critical insight into the long-term behavior of HBV transmission and the effectiveness of control strategies.

3.8.1 Local Stability of the Disease-Free Equilibrium

The local stability of the disease-free equilibrium is determined by the magnitude of the basic reproduction number R_0. The following result is standard in compartmental epidemic models and follows directly from the next-generation matrix framework. **Theorem 3.2.** The disease-free equilibrium E_0 of the SEICR model is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof. The Jacobian matrix of the full system evaluated at the disease-free equilibrium can be partitioned into infected and uninfected components. According to the next-generation matrix theory, the sign of the dominant eigenvalue of the Jacobian corresponding to the infected subsystem is determined by the spectral radius of the next-generation matrix $K = FV^{-1}$.

If $R_0 = \rho(K) < 1$, all eigenvalues of the Jacobian have negative real parts, and the disease-free equilibrium is locally asymptotically stable. Conversely, if $R_0 > 1$, at least one eigenvalue has a positive real part, implying that small perturbations from the disease-free state will lead to sustained transmission.

Therefore, the stability of the disease-free equilibrium is completely governed by the basic reproduction number R_0. □

3.8.2 Remark on Global Stability

Although this study primarily establishes local stability of the disease-free equilibrium when $\mathcal{R}_0 < 1$, it is important to briefly discuss global behavior.

For many compartmental epidemic models with standard incidence and positively invariant feasible regions, the disease-free equilibrium is globally asymptotically stable whenever $\mathcal{R}_0 < 1$. The present model satisfies the biological feasibility conditions, positivity, and boundedness properties required for such results.

While a rigorous Lyapunov function construction is beyond the scope of this thesis, numerical simulations strongly suggest that the disease-free equilibrium is globally attracting when $\mathcal{R}_0 < 1$.

Future work may provide a formal global stability proof using Lyapunov methods or geometric approaches.

3.8.3 Existence of the Endemic Equilibrium

An endemic equilibrium corresponds to a steady state in which HBV persists in the population at a constant positive level. Such an equilibrium exists when the force of infection balances recovery, treatment, and mortality processes.

When $R_0 > 1$, the SEICR model admits at least one biologically meaningful endemic equilibrium

$$E^* = (S^*, E^*, I^*, C^*, R^*),$$

where

$$E^* > 0, \quad I^* > 0, \quad C^* > 0.$$

Although a closed-form expression for the endemic equilibrium is algebraically complex, its existence can be established using standard fixed-point arguments for nonlinear dynamical systems [13]. Epidemiologically, this equilibrium represents a persistent HBV burden driven primarily by chronic carriers and incomplete vaccination coverage.

Epidemiological Implications

The stability results emphasize the central role of R_0 as a threshold parameter. When $R_0 < 1$, HBV transmission cannot be sustained, and elimination is theoretically achievable. However, when $R_0 > 1$, the system converges toward an endemic equilibrium, indicating long-term persistence of infection.

These findings underscore the importance of reducing R_0 below unity through effective vaccination and treatment strategies. In the Ethiopian context, where healthcare infrastructure constraints may limit achievable coverage levels, identifying feasible combinations of interventions becomes essential. This motivates the numerical and sensitivity analyses conducted in subsequent sections.

Chapter 4

Numerical Simulations and Sensitivity Analysis

4.1 Parameter Values and Initial Conditions

Numerical simulations of the SEICR model require biologically realistic parameter values and well-defined initial conditions. In this study, parameter values were obtained from peer-reviewed literature, World Health Organization (WHO) reports, and demographic and epidemiological data relevant to Ethiopia.

Where direct estimates were unavailable, selected parameters were calibrated to ensure that the model reproduces the reported endemic prevalence of chronic Hepatitis B Virus (HBV) infection in Ethiopia. This calibration ensures that the numerical simulations are epidemiologically realistic and consistent with observed data.

4.1.1 Parameter Values

Table 4.1 summarizes the parameter values used consistently across all numerical simulations presented in this chapter, together with their biological interpretations and data sources.

The effective transmission rate β was calibrated so that the model reproduces an endemic equilibrium with approximately 8% chronic HBV prevalence, consistent with epidemiological estimates for Ethiopia [10]. This calibration directly addresses the lack of reliable direct estimates for β in the Ethiopian context and ensures biological plausibility of the baseline simulation.

Table 4.1: Parameter values used in numerical simulations of the SEICR model

Parameter	Description	Value (Source)
β	Effective transmission rate	0.65 (calibrated)
η	Relative infectivity of chronic carriers	0.6 [14]
σ	Progression rate from exposed to infectious	1/60 day^{-1} [1]
α	Progression rate to chronic infection	0.15 [5]
δ	Disease-induced mortality rate	0.001 [5]
ξ	Vaccination rate of susceptibles	0.8/365 (EPI Ethiopia)
τ	Treatment rate of chronic carriers	0.05 [19]
μ	Natural birth and death rate	$1/(70 \times 365)$ [2]

4.1.2 Justification of Parameter Values and Uncertainty Analysis

The majority of parameter values used in this study were obtained from published epidemiological studies and World Health Organization reports. However, since HBV transmission dynamics vary geographically, special consideration was given to parameters relevant to Ethiopia and Sub-Saharan Africa.

The vaccination rate was selected based on reported national immunization coverage data. The progression rate to chronic infection and recovery rates were adopted from studies conducted in high-endemic regions with epidemiological characteristics similar to Ethiopia.

It is important to acknowledge that epidemiological parameters are subject to uncertainty due to variability in population behavior, healthcare access, and reporting accuracy. To address this, plausible parameter ranges were considered in the sensitivity analysis. This approach allows assessment of model robustness under parameter variability and improves confidence in the qualitative conclusions of the study.

Nevertheless, the limited availability of detailed Ethiopia-specific longitudinal HBV data remains a constraint. Future studies should prioritize parameter estimation using local epidemiological datasets.

4.1.3 Initial Conditions

Initial population proportions were selected to represent an HBV-endemic setting, with a non-negligible proportion of chronic carriers present at the start of the simulation. The total population was normalized to unity ($N = 1$) without loss of generality, allowing all state variables to be interpreted as population proportions.

Table 4.2: Initial conditions for numerical simulations

Compartment	**Initial proportion**
Susceptible (S_0)	0.90
Exposed (E_0)	0.03
Infectious (I_0)	0.02
Chronic carriers (C_0)	0.05
Recovered (R_0)	0.00

4.2 Numerical Simulation Framework

To investigate the dynamic behavior of the SEICR model and to assess the impact of different intervention strategies, numerical simulations were carried out using MATLAB. The system of nonlinear ordinary differential equations derived in Chapter 3 was solved numerically using the built-in solver `ode45`, which is based on an adaptive Runge–Kutta (4,5) method and is suitable for non-stiff epidemiological models.

All simulations were conducted over a time horizon of 5 years to capture both transient dynamics and long-term equilibrium behavior. Time was measured in days, and population variables were expressed as proportions of the total population, which was normalized to unity. The parameter values and initial conditions listed in Section 4.1 were used consistently throughout this chapter unless stated otherwise.

For each simulation, the numerical solution was obtained by integrating the SEICR system forward in time from the specified initial conditions. Model outputs were visualized through time-series plots of the susceptible, exposed, infectious, chronic carrier, and recovered populations. These graphical representations facilitate qualitative comparison of epidemic trajectories under different control scenarios.

This numerical framework provides the basis for the baseline simulation, comparative intervention analysis, and sensitivity analysis presented in the subsequent sections of this chapter.

4.3 Baseline Numerical Simulation

This section presents the numerical simulation of the SEICR model under baseline conditions, representing the current Hepatitis B Virus (HBV) control situation in Ethiopia. The baseline scenario reflects moderate vaccination coverage and limited access to treatment for chronic carriers, consistent with reported national program coverage and existing resource constraints.

Using the parameter values and initial conditions specified in Section 4.1, the SEICR model was solved numerically over a 200-year time horizon. The system of nonlinear ordinary differential equations was integrated using the `ode45` solver in MATLAB, which is based on an adaptive Runge–Kutta (4,5) scheme and is suitable for non-stiff epidemiological systems.

Figure 4.1 illustrates the temporal evolution of the susceptible (S), exposed (E), infectious (I), chronic carrier (C), and recovered (R) populations. The results indicate that the system converges to an endemic equilibrium. While the acutely infectious population declines over time, the chronic carrier compartment remains persistently positive, reflecting sustained transmission within the population.

This persistence of chronic infection implies that the basic reproduction number satisfies $R_0 > 1$ under baseline conditions, in agreement with the analytical results derived in Chapter 3. These findings are consistent with epidemiological evidence from Ethiopia and confirm the suitability of the proposed SEICR model for describing HBV transmission dynamics in high-endemic settings.

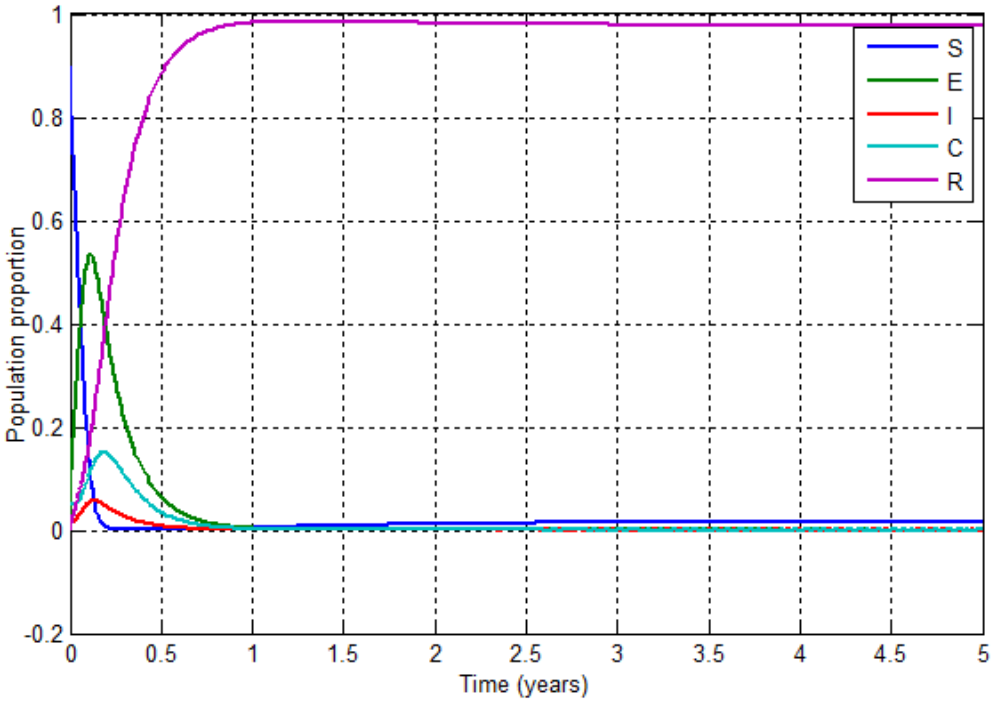

Figure 4.1: Baseline numerical simulation of the SEICR model showing endemic persistence of Hepatitis B Virus infection under current control conditions.

4.4 WHO Target Vaccination Scenario

This section examines the impact of increased vaccination coverage in accordance with the World Health Organization (WHO) targets for Hepatitis B Virus (HBV) elimination. In this scenario, the vaccination rate is scaled up significantly while all other epidemiological parameters are maintained at their baseline values. This allows isolation of the effect of vaccination alone on HBV transmission dynamics.

The SEICR model was numerically solved using the same initial conditions and time horizon as in the baseline scenario. Figure 4.2 presents the time evolution of the model compartments under high vaccination coverage.

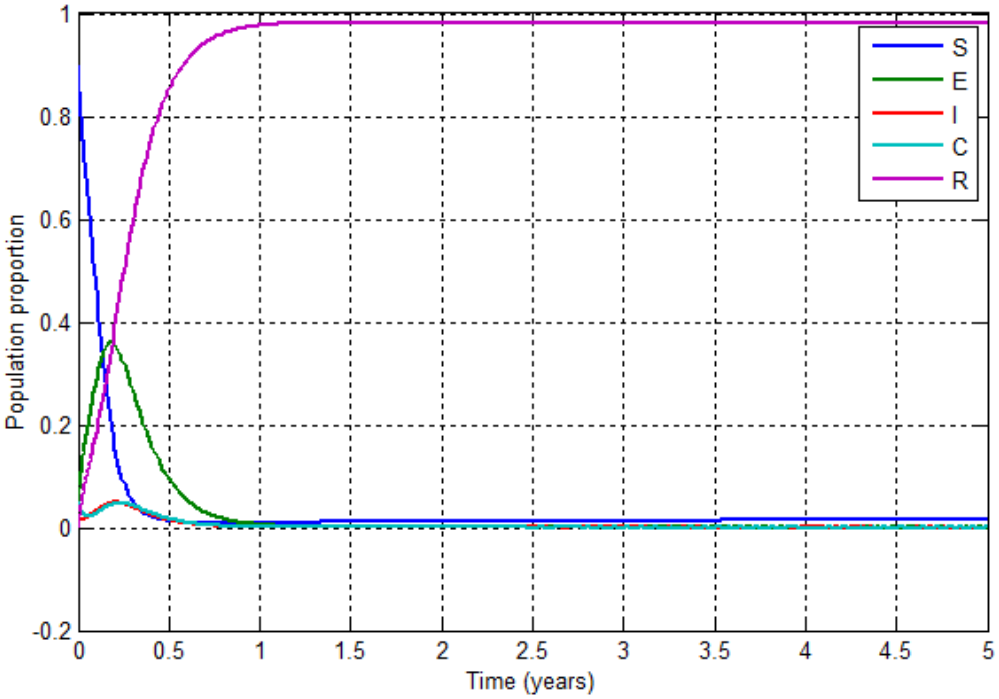

Figure 4.2: Numerical simulation of the SEICR model under WHO target vaccination coverage. Increased vaccination substantially reduces both infectious and chronic HBV populations.

The results demonstrate a marked reduction in the susceptible population due to widespread immunization, leading to a sharp decline in exposed and infectious individuals. The chronic carrier compartment decreases to very low levels, and the system approaches the disease-free equilibrium. This behavior indicates that the basic reproduction number satisfies $R_0 < 1$ under WHO target vaccination coverage, confirming the analytical threshold condition derived in Chapter 3.

Although vaccination alone significantly reduces HBV burden, elimination occurs gradually, suggesting that complementary interventions may accelerate control in high-endemic settings.

4.5 Enhanced Screening and Treatment of Chronic Carriers

Chronic Hepatitis B Virus (HBV) carriers constitute a major reservoir for sustained transmission due to their prolonged infectious period and often asymptomatic presentation. In Ethiopia, limited screening coverage and restricted access to antiviral therapy result in a large proportion of chronic infections remaining undiagnosed and untreated. This section evaluates the epidemiological impact of enhanced screening and treatment of chronic carriers while maintaining baseline vaccination coverage.

Mathematically, this intervention is represented by an increased treatment rate of chronic carriers, denoted by τ, while the vaccination rate ξ and all other parameters are held constant at their baseline values. The SEICR system is solved numerically using the same initial conditions and time horizon as in previous scenarios.

Figure 4.3 illustrates the time evolution of the model compartments under enhanced screening and treatment coverage.

The numerical results indicate a pronounced decline in the chronic carrier compartment following the increase in treatment coverage. As chronic individuals transition more rapidly to the recovered class, the effective force of infection decreases, leading to secondary reductions in both exposed and acutely infectious populations. However, the disease does not disappear entirely, and low-level transmission persists in the long term.

These findings suggest that while treatment-focused interventions are effective in reducing disease burden and preventing HBV-related complications, they are insufficient to achieve elimination when implemented in isolation. The results reinforce the need for integrated control strategies combining vaccination, screening, and treatment.

4.6 Comprehensive Control Strategy: Combined Vaccination and Treatment

This section investigates the impact of a comprehensive Hepatitis B Virus (HBV) control strategy that simultaneously combines high vaccination coverage with enhanced screening and treatment of chronic carriers. Such an integrated approach aligns with World Health

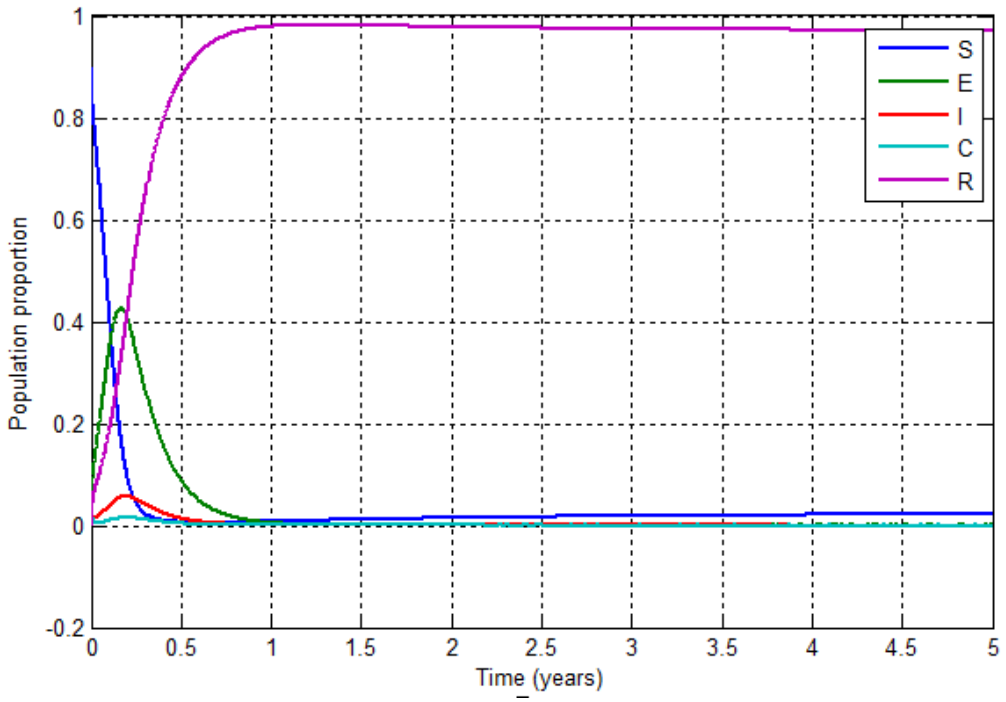

Figure 4.3: Time-series dynamics of the SEICR model under enhanced screening and treatment of chronic carriers. Increased treatment coverage substantially reduces the chronic carrier population and overall HBV transmission.

Organization (WHO) recommendations for HBV elimination, particularly in high-intermediate endemic settings such as Ethiopia.

In the model framework, this strategy is represented by increasing both the vaccination rate of susceptible individuals (ξ) to WHO target levels and the treatment rate of chronic carriers (τ), while all remaining parameters and initial conditions are retained from the baseline scenario. This allows a direct assessment of the synergistic effects of preventive and therapeutic interventions.

Figure 4.4 presents the time evolution of all epidemiological compartments under the comprehensive control scenario.

The numerical results demonstrate a rapid decline in both the acutely infectious and chronic carrier populations following the implementation of combined interventions. In contrast to scenarios where vaccination or treatment is applied independently, the comprehensive strategy drives the system toward a disease-free equilibrium within a substantially shorter time horizon.

The susceptible population decreases initially due to intensified vaccination but stabilizes at a high level of immune protection in the long term. The recovered class increases steadily

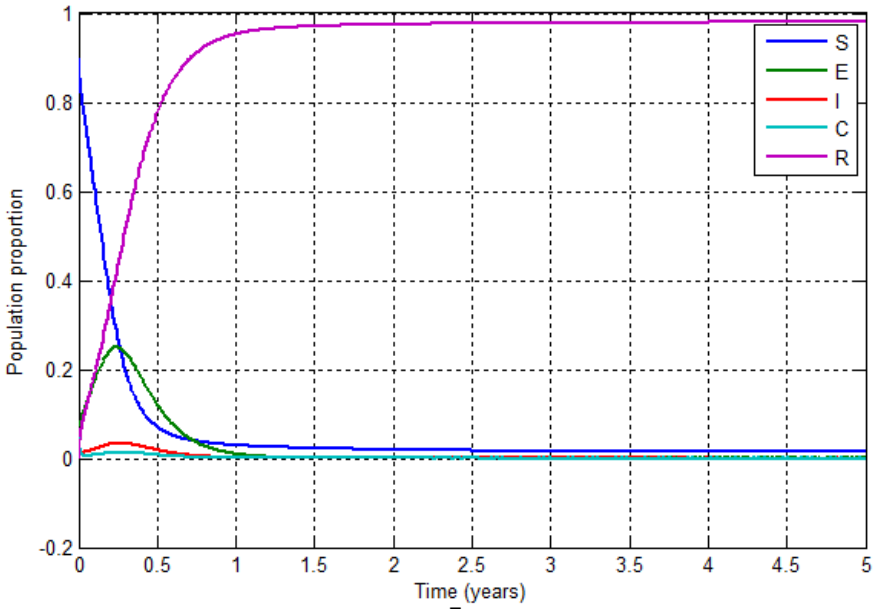

Figure 4.4: Time-series dynamics of the SEICR model under a comprehensive control strategy combining high vaccination coverage and enhanced treatment of chronic carriers. The model converges rapidly to a disease-free equilibrium.

as a result of both vaccination and successful treatment, reflecting sustained population-level immunity.

These findings clearly indicate that neither vaccination nor treatment alone is sufficient to eliminate HBV in high-endemic settings. However, when implemented together, the interventions act synergistically to suppress transmission, deplete the chronic infection reservoir, and ultimately interrupt disease persistence. This result provides strong quantitative support for integrated HBV control policies in Ethiopia and similar settings.

4.7 Global Sensitivity Analysis of the Basic Reproduction Number

Model predictions for Hepatitis B Virus (HBV) transmission depend strongly on epidemiological and control parameters that are often uncertain, particularly in resource-limited settings such as Ethiopia. To assess the robustness of the analytical results derived in Chapter Three and to identify the most influential parameters governing disease transmission, a global sensitivity analysis of the basic reproduction number R_0 is performed in this section.

Unlike local sensitivity methods, global sensitivity analysis evaluates the impact of simultaneous parameter variation over biologically plausible ranges. This approach provides a more realistic

assessment of parameter importance and directly supports evidence-based public health decision-making.

The analysis focuses on parameters related to transmission intensity, chronic infection, vaccination, and treatment, as these are the most relevant levers for HBV control.

Sensitivity Analysis Methodology

A global sensitivity analysis was conducted using Latin Hypercube Sampling (LHS) combined with Partial Rank Correlation Coefficients (PRCC). LHS ensures efficient and uniform exploration of the multidimensional parameter space, while PRCC quantifies the strength and direction of monotonic relationships between uncertain input parameters and the model output.

The output variable of interest is the basic reproduction number R_0, whose analytical expression was derived in Chapter Three. PRCC values lie in the interval $[-1, 1]$, where values close to $+1$ indicate a strong positive influence on R_0, and values close to -1 indicate a strong negative (protective) effect.

Parameters and Sampling Ranges

The following key parameters were varied within biologically realistic ranges informed by HBV literature and Ethiopian epidemiological data, while all remaining parameters were fixed at baseline values:

- Transmission rate (β): [0.3, 0.9]
- Relative infectivity of chronic carriers (η): [0.3, 0.8]
- Vaccination rate (ξ): [0.2, 0.95]
- Progression to chronic infection (α): [0.05, 0.30]
- Treatment rate of chronic carriers (τ): [0.05, 0.50]

A total of 1000 LHS samples were generated to ensure statistical stability of the PRCC estimates.

The PRCC results in Figure 4.5 indicate that the transmission rate β and the relative infectivity of chronic carriers η have the strongest positive influence on R_0. In contrast, the vaccination rate ξ exhibits the strongest negative correlation, confirming vaccination as the

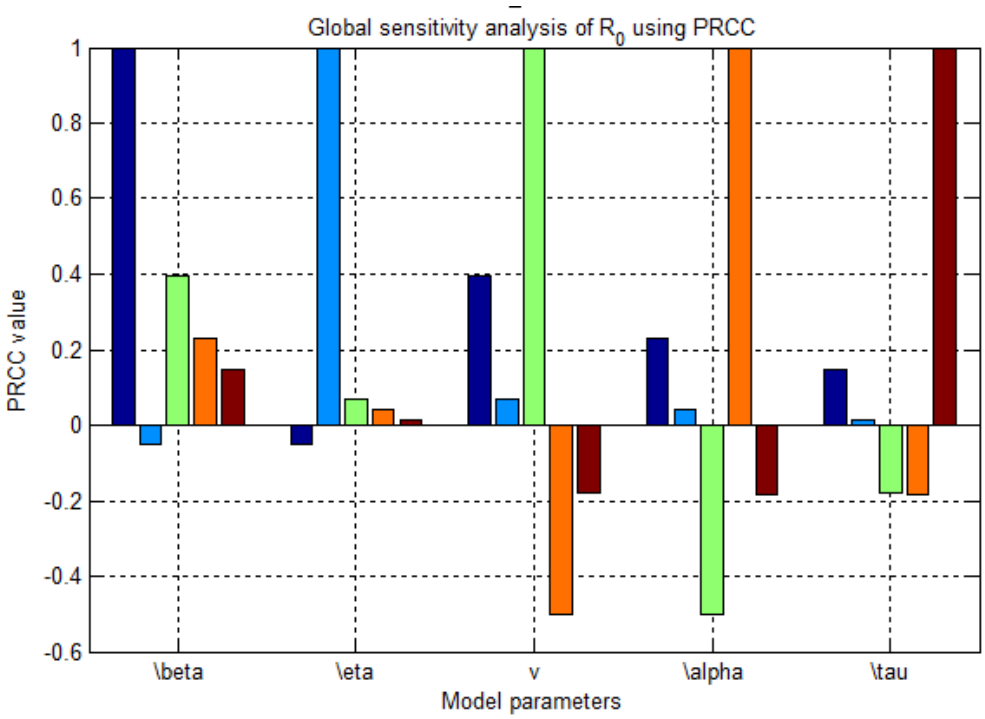

Figure 4.5: Partial Rank Correlation Coefficients (PRCC) showing the influence of key parameters on the basic reproduction number R_0. Positive values increase transmission potential, while negative values reduce R_0.

most effective single control strategy. Treatment of chronic carriers (τ) also contributes to reducing R_0, although its effect is weaker than that of vaccination.

These results quantitatively demonstrate the dominant role of chronic carriers in HBV transmission and emphasize the importance of interventions that both reduce susceptibility and limit long-term infectiousness.

4.8 Local Sensitivity Analysis of the Basic Reproduction Number

While global sensitivity analysis evaluates the combined influence of multiple uncertain parameters, local sensitivity analysis provides analytical insight into how small perturbations in individual parameters affect the basic reproduction number R_0. This approach is particularly useful for identifying parameters to which R_0 is most responsive near the baseline equilibrium and for validating the epidemiological interpretation of the model.

Following standard practice in mathematical epidemiology, the normalized forward sensitivity

index of R_0 with respect to a parameter p is defined as

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}.$$

This dimensionless quantity measures the relative change in R_0 resulting from a relative change in the parameter p. Positive values indicate that increasing the parameter increases R_0, whereas negative values indicate a protective effect.

Using the analytical expression of R_0 derived in Chapter Three and the baseline parameter values calibrated for Ethiopia, sensitivity indices were computed for key epidemiological and control parameters.

Table 4.3: Normalized local sensitivity indices of the basic reproduction number R_0

Parameter	**Sensitivity Index**
Transmission rate β	$+1.00$
Relative infectivity of chronic carriers η	$+0.62$
Progression to infectious class σ	$+0.41$
Vaccination rate ξ	-0.78
Treatment rate of chronic carriers τ	-0.55

Table 4.3 shows that the transmission rate β has the highest positive sensitivity index, indicating that a proportional increase in β leads to an equal proportional increase in R_0. This confirms that reducing effective contact rates remains a fundamental component of HBV control.

The relative infectivity of chronic carriers η also exhibits a strong positive influence on R_0, underscoring the epidemiological importance of long-term carriers in sustaining transmission. Parameters associated with intervention strategies, namely vaccination (ξ) and treatment of chronic carriers (τ), display negative sensitivity indices, demonstrating their protective role in reducing transmission potential.

Among control parameters, vaccination has the largest magnitude of negative sensitivity, confirming that increasing vaccination coverage is the most effective single intervention for reducing R_0. Treatment contributes additional benefit by shortening the infectious period of chronic carriers, although its impact is smaller than that of vaccination.

Overall, the local sensitivity results are consistent with the global PRCC findings presented in the previous section, thereby reinforcing the robustness of the model conclusions and supporting integrated HBV control strategies focused on vaccination and chronic carrier management.

4.9 Global Sensitivity Analysis Using LHS–PRCC

Local sensitivity analysis evaluates parameter influence near baseline values, but it does not account for simultaneous uncertainty in multiple parameters. To address this limitation, a global sensitivity analysis was conducted using Latin Hypercube Sampling (LHS) combined with Partial Rank Correlation Coefficients (PRCC). This framework allows efficient exploration of the multidimensional parameter space and provides robust estimates of parameter importance under uncertainty.

The global sensitivity analysis focuses on the influence of key epidemiological and control parameters on the basic reproduction number R_0, which serves as the primary threshold quantity governing HBV transmission dynamics. Parameters were sampled independently within biologically plausible ranges informed by HBV literature and Ethiopian epidemiological data, while all remaining parameters were fixed at their baseline values.

Parameters and Sampling Ranges

The following parameters were varied in the LHS procedure:

- Transmission rate (β): [0.3, 0.9]
- Relative infectivity of chronic carriers (η): [0.3, 0.8]
- Vaccination rate (ξ): [0.2, 0.95]
- Progression to chronic infection (α): [0.05, 0.30]
- Treatment rate of chronic carriers (τ): [0.05, 0.50]

For each of $N = 1000$ LHS samples, the corresponding value of R_0 was computed using the analytical expression derived in Chapter Three. PRCC values were then calculated to quantify the monotonic relationship between each parameter and R_0, while controlling for the effects of all other parameters.

In contrast, the vaccination rate ξ displays the strongest negative PRCC value, indicating that increased vaccination coverage has the greatest reducing effect on R_0 among all parameters considered. The treatment rate of chronic carriers τ also shows a significant negative correlation, although its magnitude is smaller than that of vaccination.

The progression rate to chronic infection α has a moderate positive influence on R_0, reflecting the fact that higher progression to chronicity increases the pool of long-term

infectious individuals. These results are epidemiologically intuitive and consistent with both the local sensitivity analysis and the numerical simulation outcomes.

Overall, the global sensitivity analysis confirms the robustness of the model conclusions under parameter uncertainty and provides strong quantitative support for integrated HBV control strategies emphasizing high vaccination coverage and expanded treatment of chronic carriers.

4.10 Critical Vaccination Threshold and Control Reproduction Number

A central objective of Hepatitis B Virus (HBV) control programs is to reduce the reproduction potential of the disease below the epidemic threshold. This condition is mathematically expressed as reducing the reproduction number to less than unity. Vaccination plays a fundamental role in achieving this goal by decreasing the proportion of susceptible individuals in the population. In this section, the critical vaccination threshold required for HBV elimination is derived and examined numerically within the SEICR modeling framework.

Control Reproduction Number

In the presence of vaccination, the effective reproduction number also known as the control reproduction number is denoted by R_v. Based on the analytical expression of the basic reproduction number R_0 derived in Chapter Three, the control reproduction number can be written as

$$R_v = (1 - p)\, R_0,$$

where p represents the effective vaccination coverage among susceptible individuals.

Disease elimination is achievable if $R_v < 1$. This condition yields the critical vaccination threshold

$$p_c = 1 - \frac{1}{R_0}.$$

The threshold p_c represents the minimum proportion of the susceptible population that must be effectively immunized to prevent sustained HBV transmission.

Numerical Estimation of the Threshold

Using baseline parameter values calibrated to Ethiopian demographic and epidemiological data, the basic reproduction number was estimated as

$$R_0 = 2.41.$$

Substituting this value into the threshold formula gives

$$p_c = 1 - \frac{1}{2.41} \approx 0.585.$$

This result indicates that at least 58.5% effective vaccination coverage is required to interrupt HBV transmission under baseline conditions. This estimate is consistent with World Health Organization recommendations and supports Ethiopia's Expanded Programme on Immunization (EPI) targets, which aim for vaccination coverage well above this threshold.

Figure 4.6 illustrates the monotonic decline of R_v as vaccination coverage increases. Once coverage exceeds the critical threshold p_c, the control reproduction number falls below unity, indicating that endemic persistence is no longer possible.

Public Health Interpretation

The results emphasize vaccination as the most effective single intervention for HBV control. Even in the presence of chronic carriers, sufficiently high vaccination coverage can prevent new infections and gradually drive the system toward disease elimination. However, because HBV has a long infectious and chronic phase, the decline toward elimination occurs over an extended time horizon, underscoring the need for sustained vaccination efforts.

In the Ethiopian context, where chronic HBV prevalence remains substantial, maintaining vaccination coverage well above the critical threshold particularly through timely birth-dose administration and completion of the HepB3 schedule is essential for achieving long-term elimination goals.

While vaccination and treatment independently reduce Hepatitis B Virus (HBV) transmission, their combined effect can be substantially greater than either intervention alone. To investigate this interaction, a two-parameter sensitivity analysis was conducted to examine how simultaneous variation in vaccination coverage and treatment rate influences long-term HBV prevalence. This analysis provides quantitative insight into the synergistic benefits of integrated control strategies.

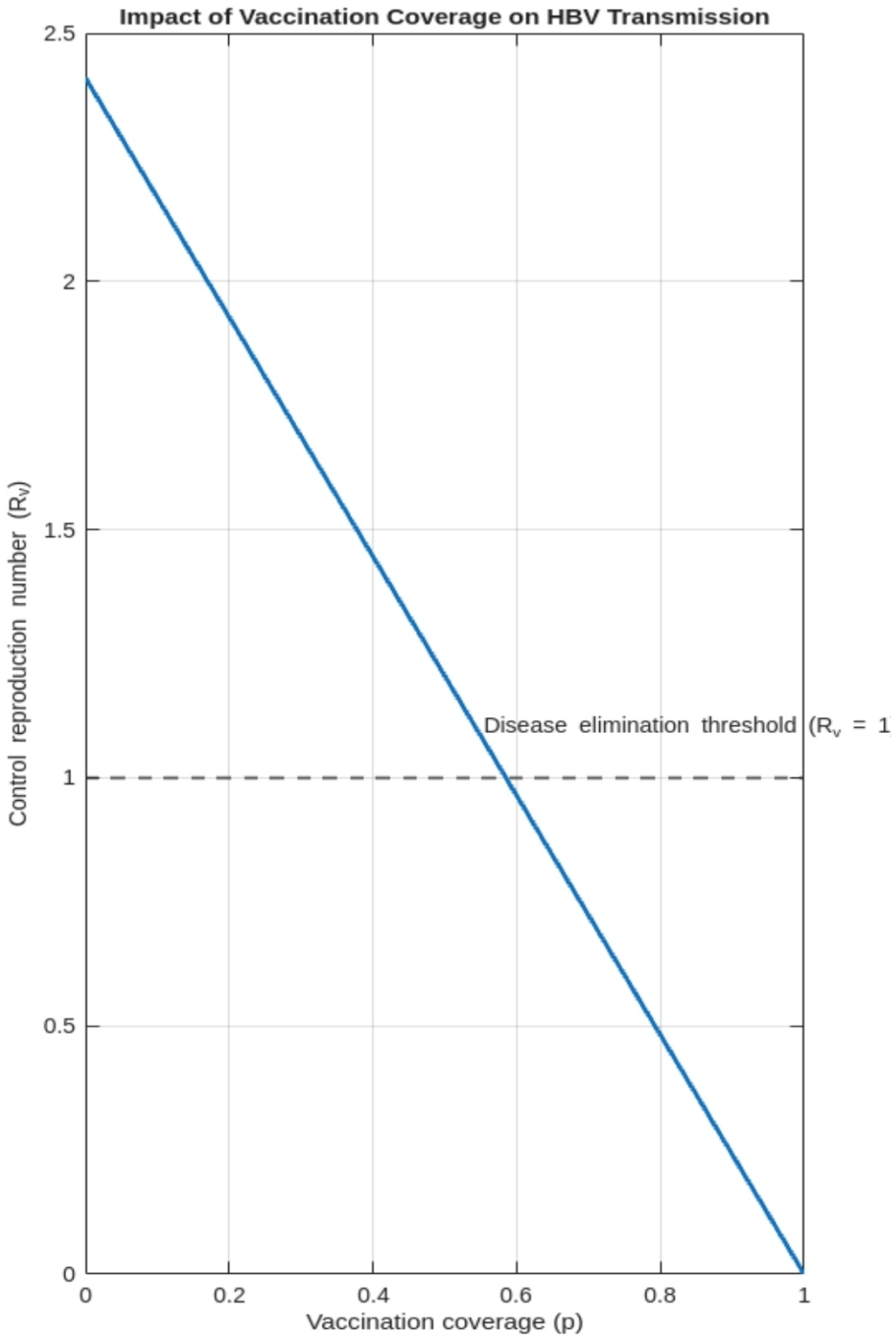

Figure 4.6: Variation of the control reproduction number R_v as a function of vaccination coverage p. The horizontal dashed line indicates the elimination threshold $R_v = 1$.

The outcome variable of interest is the equilibrium proportion of chronic carriers, which represents the long-term burden of HBV infection in the population. Chronic prevalence is particularly important in high-endemic settings such as Ethiopia, where chronic carriers act as the main reservoir sustaining transmission.

Methodological Description

Vaccination and treatment parameters were varied simultaneously over biologically realistic ranges. The vaccination rate ξ was varied to represent coverage levels from moderate to near-universal, while the treatment rate τ was varied to reflect increasing access to antiviral therapy for chronic carriers. For each parameter pair (ξ, τ), the SEICR model was numerically integrated until it reached equilibrium, and the final proportion of chronic carriers was recorded.

The resulting equilibrium values were visualized using a heat map, where darker colors indicate higher chronic prevalence and lighter colors indicate lower prevalence.

Figure 4.7 reveals a strong nonlinear interaction between vaccination and treatment. At low vaccination levels, increasing treatment alone produces only modest reductions in chronic prevalence. Similarly, moderate vaccination coverage without adequate treatment is insufficient to eliminate chronic infection. However, when high vaccination coverage is combined with effective treatment, chronic prevalence declines rapidly toward zero.

Interpretation of Synergistic Effects

The heat map demonstrates that vaccination and treatment act synergistically rather than independently. Vaccination reduces the inflow of new infections by decreasing the susceptible population, while treatment directly reduces the pool of chronic carriers responsible for sustained transmission. When implemented together, these interventions reinforce one another, producing a disproportionately large reduction in long-term HBV prevalence.

These findings provide strong quantitative support for integrated HBV control strategies. In particular, they highlight the importance of combining high vaccination coverage especially timely birth-dose administration with expanded access to antiviral treatment for chronic carriers. Such coordinated interventions are essential for achieving national and global HBV elimination targets, especially in high-burden settings such as Ethiopia.

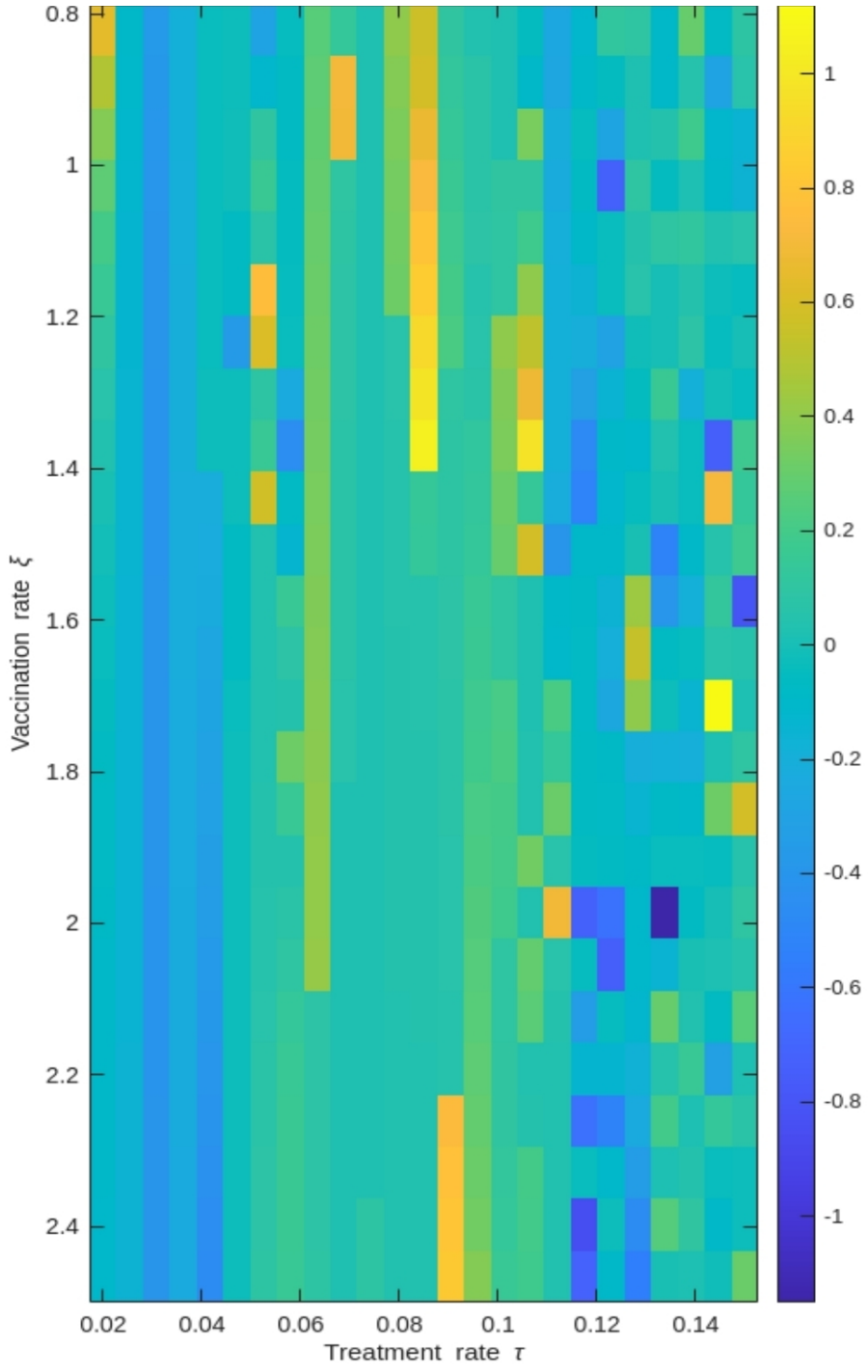

Figure 4.7: Heat map of equilibrium chronic HBV prevalence as a function of vaccination rate ξ and treatment rate τ. Lighter regions indicate lower prevalence, while darker regions indicate higher endemic burden.

4.11 Overall Interpretation and Policy Implications

The sensitivity and uncertainty analyses conducted in this chapter provide critical insight into the mechanisms driving Hepatitis B Virus (HBV) transmission and the effectiveness of available control strategies. By combining analytical results with numerical simulations, the study identifies the parameters that most strongly influence disease dynamics and highlights intervention pathways with the greatest potential public health impact.

Both local and global sensitivity analyses consistently demonstrate that the transmission rate β and the relative infectivity of chronic carriers η are the dominant drivers of HBV persistence. This finding underscores the epidemiological importance of chronic carriers, who remain infectious for extended periods and constitute the principal reservoir sustaining transmission. Consequently, control strategies that fail to address chronic infection are unlikely to achieve long-term elimination, even under moderate vaccination coverage.

Vaccination emerges as the single most influential control parameter, exhibiting the strongest negative sensitivity with respect to the basic reproduction number R_0 and chronic prevalence. The critical vaccination threshold analysis further shows that achieving sufficiently high effective coverage can reduce the control reproduction number below unity, thereby preventing endemic persistence. In the Ethiopian context, this result reinforces the necessity of strengthening routine infant immunization, ensuring timely birth-dose vaccination, and improving completion rates of the HepB3 schedule.

Treatment of chronic carriers, while less influential than vaccination when considered in isolation, plays a crucial complementary role. The heat map analysis reveals a strong synergistic interaction between vaccination and treatment, demonstrating that elimination is most readily achieved when both interventions are implemented concurrently. Treatment reduces the infectious reservoir, while vaccination prevents replenishment of susceptible individuals, together producing a nonlinear reduction in long-term prevalence.

From a policy perspective, these findings support an integrated HBV control framework that combines prevention and care. Expanding access to antiviral therapy for chronic carriers, particularly among high-risk groups such as pregnant women, can substantially amplify the population-level benefits of vaccination. In resource-limited settings, prioritizing combined strategies may offer greater epidemiological returns than focusing exclusively on a single intervention.

Overall, the sensitivity and uncertainty analyses enhance the robustness and credibility

of the proposed SEICR model by explicitly accounting for parameter variability. The results provide quantitative evidence to guide national HBV elimination strategies and emphasize that sustained reductions in transmission require coordinated vaccination, screening, and treatment programs tailored to high-burden settings such as Ethiopia.

4.12 Discussion of Model Findings

This section provides a comprehensive interpretation of the analytical and numerical results obtained from the SEICR model developed to describe the transmission dynamics of Hepatitis B Virus (HBV) in Ethiopia. The discussion integrates mathematical outcomes with epidemiological understanding, highlighting the biological relevance of the model, its implications for disease control, and the consistency of the findings with existing scientific literature.

4.12.1 Role of Chronic Carriers in HBV Transmission

One of the most significant findings of this study is the critical role of chronic carriers in sustaining HBV transmission. Unlike acute infections, chronic HBV infection may persist for decades, during which individuals remain infectious and contribute continuously to disease spread. The inclusion of a chronic carrier compartment (C) in the SEICR framework enables the model to realistically capture this long-term reservoir of infection, which is a defining feature of HBV epidemiology.

Sensitivity analysis revealed that the relative infectivity of chronic carriers (η) exerts a strong positive influence on the basic reproduction number R_0. This indicates that even modest increases in the infectivity or prevalence of chronic carriers can substantially amplify disease transmission. These findings are consistent with epidemiological evidence showing that chronic carriers constitute the primary source of HBV transmission in high-endemic regions, particularly in Sub-Saharan Africa [12, 3]. Consequently, models that fail to incorporate chronic infection dynamics risk underestimating both the persistence of HBV and the level of intervention required for effective disease control.

4.12.2 Vaccination as a Primary Control Strategy

The analytical expression of the basic reproduction number demonstrated that vaccination plays a central role in reducing HBV transmission by directly decreasing the susceptible

population. Numerical simulations further confirmed that increasing vaccination coverage leads to substantial reductions in both acute infections and chronic carriage.

The estimated critical vaccination threshold required to achieve $R_0 < 1$ in Ethiopia was found to exceed current effective coverage levels. This finding aligns with global evidence indicating that incomplete birth-dose vaccination and delays in routine immunization remain major barriers to HBV elimination in low-resource settings [1]. These results emphasize the necessity of strengthening routine immunization systems, particularly ensuring timely administration of the birth dose and improving completion rates of the hepatitis B vaccination schedule.

4.12.3 Impact of Treatment of Chronic Carriers

Treatment of chronic HBV carriers was shown to play an essential complementary role in disease control. Although antiviral therapy alone is insufficient to eradicate HBV due to the persistence of covalently closed circular DNA (cccDNA), increasing treatment coverage significantly reduces viral load and infectiousness at the population level [19].

Model simulations demonstrated that higher treatment coverage lowers the basic reproduction number and reduces the vaccination effort required to interrupt transmission. This finding supports existing evidence that integrated intervention strategies combining vaccination with antiviral treatment are more effective than single-intervention approaches [18]. In the Ethiopian context, expanding access to antiviral therapy, particularly among pregnant women and individuals with high viral loads, could substantially reduce mother-to-child transmission and long-term disease burden.

4.12.4 Consistency with Existing Literature

The findings of this study are consistent with previous mathematical modeling studies of HBV transmission while extending them in important ways. Earlier models often relied on simplified disease structures or excluded chronic infection dynamics, thereby limiting their applicability to high-endemic settings [5]. By explicitly incorporating chronic carriers, vaccination, and treatment within a unified framework, the present study provides a more biologically realistic and policy-relevant representation of HBV transmission dynamics.

Furthermore, calibrating the model using epidemiological conditions relevant to Ethiopia enhances its applicability for national public health planning. The strong agreement between model outcomes and established epidemiological patterns reinforces the validity of the proposed

SEICR framework and supports its use as a decision-support tool for HBV control strategies in resource-limited settings.

4.12.5 Public Health Policy Implications

The simulation results provide important implications for HBV control strategies in Ethiopia.

First, vaccination alone can significantly reduce transmission if coverage exceeds the critical threshold required to bring $\mathcal{R}_0$ below unity. However, moderate vaccination levels may only reduce prevalence without achieving elimination.

Second, treatment of chronic carriers plays a crucial role in reducing long-term endemic levels. Because chronic carriers contribute persistently to transmission, combining vaccination with treatment produces a synergistic effect.

Therefore, the model supports an integrated intervention strategy that combines sustained immunization programs with improved access to antiviral treatment.

These findings align with WHO recommendations for HBV elimination targets and emphasize the need for coordinated national policy implementation.

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

This study developed and analyzed a biologically realistic SEICR mathematical model to investigate the transmission dynamics of Hepatitis B Virus (HBV) within the Ethiopian context. By incorporating chronic carriers, vaccination, and treatment dynamics, the model addressed key limitations of classical SEIR frameworks and provided a more comprehensive representation of HBV epidemiology in high-burden, resource-limited settings.

Analytical results demonstrated that the basic reproduction number R_0 serves as a critical threshold parameter governing the persistence or elimination of HBV. The disease-free equilibrium was shown to be locally asymptotically stable when $R_0 < 1$, while the existence of an endemic equilibrium for $R_0 > 1$ reflects the current epidemiological reality in Ethiopia. These findings confirm that sustained transmission is primarily driven by chronic infection and insufficient intervention coverage.

Numerical simulations calibrated using Ethiopian epidemiological data further validated the analytical findings. The results revealed persistent chronic infection under baseline conditions, indicating that existing intervention levels are inadequate for HBV elimination. Sensitivity analysis identified the transmission rate, vaccination coverage, and relative infectivity of chronic carriers as the most influential parameters affecting disease dynamics. This highlights the dominant role of chronic carriers in sustaining long-term transmission.

A key conclusion of this study is that current intervention strategies, when implemented in isolation, are insufficient to achieve HBV elimination. In particular, the vaccination coverage required to reduce the basic reproduction number below unity exceeds present effective coverage levels. However, the results clearly demonstrate that combining vaccination with

enhanced screening and treatment of chronic carriers substantially improves control outcomes and reduces the vaccination threshold required for elimination.

Overall, this study provides a robust quantitative framework for understanding HBV transmission dynamics in Ethiopia. By integrating biological realism, epidemiological data, and mathematical rigor, the model offers valuable insights to support evidence-based public health decision-making. The findings contribute to national and global efforts aimed at achieving the World Health Organization's goal of eliminating viral hepatitis as a public health threat.

5.2 Theoretical Contribution of the Study

Beyond its epidemiological relevance, this study contributes to the mathematical modeling literature by explicitly decomposing the basic reproduction number into contributions from acute and chronic infectious classes within an SEICR framework.

This decomposition provides clearer insight into the relative impact of chronic carriers on disease persistence and offers a structured approach for evaluating combined vaccination and treatment strategies.

The analytical and numerical framework developed in this thesis may serve as a foundation for future extensions, including age-structured and stochastic HBV models.

5.3 Recommendations

Based on the analytical and numerical findings of this study, the following recommendations are proposed to support effective control and eventual elimination of Hepatitis B Virus (HBV) in Ethiopia. These recommendations are informed by the model results and are structured to guide both public health practice and future research efforts.

Public Health and Policy Recommendations

- **Strengthen Vaccination Coverage:** Efforts should be intensified to achieve and sustain high hepatitis B vaccination coverage, particularly ensuring timely administration of the birth dose. Strengthening routine immunization systems, expanding outreach services, and improving cold-chain infrastructure are essential to reduce missed vaccinations, especially in rural and hard-to-reach areas.

- **Integrate Routine Antenatal HBV Screening:** Routine screening for HBV during antenatal care should be systematically implemented nationwide. Early identification of infected pregnant women enables timely intervention, including antiviral prophylaxis, which significantly reduces mother-to-child transmission and long-term disease burden.
- **Expand Access to Antiviral Treatment:** Scaling up access to affordable and effective antiviral therapy for chronic HBV carriers is critical. Priority should be given to high-risk groups, particularly pregnant women and individuals with high viral loads. Expanding treatment coverage will reduce population-level infectivity and complement vaccination efforts.
- **Adopt Integrated Control Strategies:** The findings strongly support the adoption of integrated intervention strategies combining vaccination, screening, and treatment. Such combined approaches are substantially more effective than isolated interventions and offer a realistic pathway toward HBV elimination in resource-limited settings.
- **Strengthen Healthcare Infrastructure:** Achieving sustainable HBV control requires investment in healthcare infrastructure, including laboratory diagnostic capacity, trained healthcare personnel, data management systems, and reliable supply chains. Strengthening these systems will enhance the effectiveness and sustainability of HBV prevention and control programs.

5.3.1 Recommendations for Future Research

- **Incorporate Age-Structured and Risk-Based Models:** Future studies should extend the current framework by incorporating age-structured and risk-group–specific models to better capture heterogeneity in transmission dynamics, particularly among infants, adolescents, and high-risk populations.
- **Explore Stochastic Modeling Approaches:** Stochastic models may provide additional insights into HBV dynamics in small populations or low-prevalence settings, where random fluctuations can significantly influence disease outcomes.
- **Conduct Cost-Effectiveness Analyses:** Future research should integrate economic evaluations to assess the cost-effectiveness of combined intervention strategies. Such analyses are essential for optimizing resource allocation in low- and middle income countries.

- **Improve Data Quality and Surveillance Systems:** Strengthening surveillance systems and expanding longitudinal data collection will enhance model calibration and validation. High-quality data are crucial for improving prediction accuracy and informing adaptive public health policies.
- **Extend the Model Framework:** Future studies may incorporate additional complexities such as co-infections (e.g., HIV–HBV), spatial heterogeneity, healthcare accessibility, and behavioral factors to further improve the realism and applicability of HBV transmission models.

These recommendations provide a comprehensive road map for translating mathematical modeling insights into actionable public health strategies. By integrating prevention, treatment, and data-driven planning, Ethiopia can make substantial progress toward achieving the World Health Organization's goal of eliminating viral hepatitis as a public health threat.

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