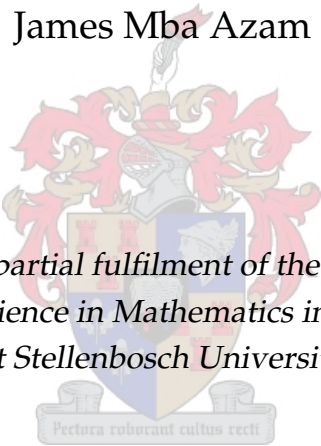# Mathematical Modelling of the Possible Elimination of Hepatitis B in sub-Saharan Africa: A Focus on the Impact of Vaccination and Treatment on the Long Run Dynamics of the Disease.

by

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Thesis presented in partial fulfilment of the requirements for the degree of Master of Science in Mathematics in the Faculty of Science at Stellenbosch University

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September 2016

Declaration

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Abstract

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the abstract goes here

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Dedications

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Publications

The following publications are extracts from this thesis. They are appended at the end of the thesis.

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Chapter 1

Introduction

Of all chronic viral infections in the world, hepatitis B (HBV), a liver disease, is arguably the most popular. In some parts of the world, particularly, in most parts of Asia and sub-Saharan Africa, hepatitis B is highly endemic. A systematic review by [5] has estimated HBV to have caused over 600,000 deaths in the past. It is a common cause for liver cancer, liver cirrhosis, and some other liver-related diseases. The WHO has consequently listed HBV as part of its major health priorities due to its high mortality and morbidity rates.

HBV is acquired through contact with blood, serum, or bodily fluids of highly viremic individuals. This is termed horizontal transmission. It can also be transmitted from a mother to her child(vertical) either prenatally, or neonatally. The infection transmission dynamics is such that, mother-to-child(vertical) transmission is the most common[13]. Some authors, for instance, [1, 13] have posited that, in order to reduce the burden of the disease, it is important to reduce the number of infections arising from the vertical transmission route. Also, chronic hepatitis B is inversely related to the age at which individuals acquire the infection[13] . It is therefore pertinent that vertical transmission is reduced so as to further deplete the number of chronically infected individuals in the long run.

The disease is not evenly distributed across the globe, as it is almost rare in most advanced countries whilst remaining highly endemic in sub-Saharan Africa and parts of Asia[4]. The World Health Organization (W.H.O) has made it a priority to reduce the prevalence of the disease to certain levels within the next decade in the highly endemic regions of the world. Several countries have recognised the health impact of the disease and are continually implementing revised strategies geared towards reducing the hepatitis B prevalence. China, for instance, has a target of reducing its HBV prevalence

below 1% within the next decade [9]. Countries in sub-Saharan Africa, however, have not yet put in effective measures to reduce the impact of the disease as this is evident in the results of studies like [5] which estimated the prevalence of the disease by world regions.

HBV vaccination has been present since the early 1980's [11]. Studies have shown there has been a noticeable reduction in the disease prevalence and this can be attributed to the introduction of childhood immunization. In many low-income countries, the vaccine is usually administered in three doses from week 6, after birth, till week 14. Studies have shown that, this routine vaccination strategy is only efficient if the infants remain uninfected till the 6th week after birth. However, to infants born to chronic HB positive mothers, vaccination will only be effective if it is administered at the time of birth, or within 24 hours after birth. Other researchers have corroborated this strategy through their studies. It has further been established that a first dose at birth, combined with the routine vaccination between weeks 6 to 14 without delay, will provide approximately 97% efficiency in protecting the infants [11, 13].

In the quest to prevent HBV mother-to-child transmission, the risk factors involved in the process must be thoroughly investigated. One of such factors is the maternal DNA which has won the highest mention in articles over the years [6, 13].

Studies like [12, 13] have predicted that the risk of hepatitis b vertical transmission could be reduced if more efficient methods, for example, antiviral therapy, are put in place to reduce the HBV DNA levels below the established level of 10^7 IU/mL. A high level of maternal DNA can be inferred from most studies to mean any level above 10^7 IU/mL or $8 \log_{10}$ copies/mL. At high maternal DNA levels, it has been noticed that vertical transmission begins to increase with a positive correlation. A recent cohort trial by [7] has produced very convincing results that seem to affirm the stance that, a reduced maternal DNA level below 10^7 IU/mL, combined with administering a birth vaccine, as well as, the routine vaccine starting at week 6 after birth, is likely to produce desirable results in the quest to reduce mother-to-child transmission as a way to eventually eradicate HBV globally.

In conclusion, a campaign for the eradication of HBV mother-to-child transmission has been long standing. Various prevention strategies have been proposed towards the amelioration of vertical transmission of HBV in the bid to eradicate the disease. This thesis therefore aims to provide a mathematical point of view in contribution to the ongoing discourse. For this to be achieved, this work shall answer the questions that follow:

1.0.1 Research Question

This study aims to answer the question and sub-questions:

1. Can Hepatitis B be eradicated from Sub-Saharan Africa (SSA) within a couple of generations, given the intervention is limited to:

   (a) treatment of the mothers only,

   (b) administering a combination of the birth vaccine and the routine vaccine to the infants only,

   (c) a combination of sub-questions

1.0.2 Aim and Objectives of the Research

By answering the research question, this thesis will aim to serve as a mathematical backing in the prevailing campaign towards considering the revision of the hepatitis B prevention strategies in sub-Saharan Africa and other parts of the world where the disease remains a burden.

In this thesis, our objectives include:

1. to examine hepatitis B vertical transmission which captures interventions applied to both the mothers and their newborns,

2. to investigate whether the proposed interventions affect the population dynamics of the infected infants,

3. determine the contribution of the infected infants to the disease dynamics in the general population over time,

4. provide recommendations towards further research aimed at eradicating the disease.

1.1 Background on the hepatitis B virus

1.2 Background on the hepatitis B virus Elimination

Chapter 2

Literature Review

Under this section, we analyse the various studies which have been performed in relation to our research question. The section has been split into various "themes" pertaining to our research question. The "themes" include, but are not limited to: studies on Mother-to-child transmission risk factors, studies on the interventions applied to the mothers only, the discourse on the interventions applied to infants only, discourses on a combined intervention approach to both mothers and infants, and the evolution of HBV vertical transmission modeling, with vaccination and treatment, over time.

2.1 Hepatitis B Mother-to-child Transmission

2.1.1 HBV Mother-to-Child Transmission Risk Factors

According to [6], an efficient way to prevent vertical transmission of hepatitis B is to profile the risk factors of this mode of transmission, and further, to identify the mothers who possess the most risk so as to administer the interventions to prevent HBV MTCT. Eventually, they listed: maternal level of HBV DNA $> 200,000$ IU/mL, positive test(s) for the HB envelope Antigen(HBeAg) and HB surface Antigen(HBsAg), pregnancy complications such as threatened pretem labour, or prolonged labour, and failure of the immunoprophylaxis in children who had received it, as the risk factors to consider. Other authors such as [14] have agreed with [6] in terms of maternal DNA levels being one of the most important risk factors.

2.2 HBV Mother-to-child Transmission Interventions

2.2.1 Infant Vaccination

Several authors for instance, those of [1, 10, 13, 15], have posited that it will be prudent to concentrate on preventing mother-to-child transmission of hepatitis B if eradication is to be achieved in the near future. On the said matter, the authors of [6] conducted a systematic review of articles published between $1975 - 2011$ on HBV mother-to-child transmission. They deduced that by administering Hb immunoglobulin alongside the Hb vaccine between the time of birth and at most 12 hours after exposure, combined with the routine vaccination regimen between $6 - 12$ months, to an infant, will provide an approximate 95% chance of preventing the perinatal transmission of HBV from their HBsAg-positive pregnant mother. Other studies have also shown that mother-to-child transmission is not totally preventable, even though, by combining strategies such as antiviral therapy to highly viremic mothers, alongside a full vaccination strategy of a birth vaccine and the routine vaccine administered to infants can provide better protection to the infants[13] in preventing the infection. Authors of the paper [13] provided a more enlightening HBV mother-to-child transmission strategy thus: for babies at high risk of perinatal infection from HBeAg infected mothers, a birth dose alongside the routine vaccine may provide enough protection. However, for babies born to HBsAg positive mothers, HB immunoglobulin should be included in the birth regimen. Furthermore, it has been suggested that the second dose must be administered in time, as a study by [11] has proven that a delay in receiving the subsequent vaccines might cause a reduction in the protection of the infants against HBV transmission.

These interventions under study in our research question in Section 1.0.1 are therefore worth our attention since research spanning over at least the past $2 - 3$ decades seem to be corroborating the same assertion.

2.2.2 Treatment of Infected Mothers

Several drugs have been under use to suppress HB viral replication. Telbuvindine, Lamivudine and Tenofivir are some of such examples. Viral replication is a key factor in MTCT. Concerning the use of tenofovir as immunoprophylaxis for reducing HBV MTCT, a recent study in the paper [7] has concluded that it might be a good option in the future, as predicted by the authors in [15]. The same primary author, in a different trial, the results of which were published in [8], revealed that telbuvindine is a safe drug for the suppression of vertical transmission in a group of pregnant women with HBeAg positive status.

Chapter 3

Mathematical Model

We will apply quantitative methods in order to achieve the objectives listed. Since we intend to study the contribution of the birth dose and treatment of infected mothers to the transmission dynamics of the disease, we will employ population-based deterministic ordinary differential equations(ODE) models which we will adapt and modify from the existing literature. Population-based deterministic models are proper at this stage since we are only interested in how the infected population structure behaves when the suggested interventions are applied. Other tools which are appropriate in achieving the objectives could include: delay differential equation models so as to introduce a delay in terms of various events such as the kick-start of immunity, a delay in taking the routine vaccination, and so on, or partial differential equations so as to set up our model implicitly in terms of age and/or time. However, this is outside the scope of our research question.

The model formulation process will take two "stages": In the first stage, an appropriate model from the literature will be adapted (and/or modified) to capture the contributions of the various interventions under investigation in our research questions 1a, 1b and 1c. The interventions in questions 1a and 1b will be applied separately, and then combined, in order to answer question 1c. This will help in identifying individual contributions of the interventions, as well as, the synergistic contribution. These models will be simulated separately just as they have been described. A simulation of the three separate models over time will then produce outputs which will be fed into the second stage.

At stage two of the process, a sort of a "reservoir" will be created to keep track of the number of infants who remain infected after these interventions have been put in place. This output will flow into a larger population model for sub-Saharan Africa for

simulation over several generations. The total contribution of HBV+ children into the larger population will thus be the foundation on which the hypothesis of eradication will be shown in this work.

3.0.1 Model Framework

We formulate a mathematical model to study the long term contribution of infected neonates to the general population-level infection dynamics. Our model studies the impact of the administration of a birth and routine vaccine to infants, as well as treatment to infected pregnant women in sub-Saharan Africa where HBV is highly endemic.

In our model, we assume that infants destined to take their first dose within 24 hours and the full routine vaccination within the next 6 months. This model serves as a feeder into a larger population model. It will feed the number of infants who remain infected (acute and chronic), after several iterations, into the population model we shall develop.

To the best of our knowledge, not many models which consolidate HBV vertical transmission and two stages of vaccination have been published. In particular, none has been published, which studies the long term impact of combining a birth dose vaccine and a routine vaccine in the same model.

To answer our research questions, we modify the models by [2, 17] by amalgamating ideas from the models in those papers. Of particular interest is the age-structured model by [2]. We adapt the equation set (1) in [2] for infants aged $0 - 1.25$ years since it captures the age structure of the neonates we intend to study, and modify it by including an extra dose of vaccination denoting the routine vaccination. For sub-question 1b, we assume that there are two types of immunity induced in the infants for each stage of vaccination: for the birth dose, the infants acquire a temporary immunity which wanes. However, they acquire long term immunity if they proceed to receive the routine vaccination. The work by [3] extrapolated the vaccine-induced immunity period to be an average of 22.2 years from data which was collected over a period of 7 years. This vaccine-induced immunity acquired by these infants, we assume, is comparable to that acquired by the carrier individuals who clear the infection. This assumption is in contradiction to that of the model of [17]. Our assumption is, however, justifiable since we only intend to simulate our model over a number of generations which amounts to a time period less than the average vaccine-induced immunity duration. It is therefore safe to equate the two types of acquired immunities described in our model and classify those two groups of individuals into the same epidemiological group. Again, in agreement with [16], we assume that all infants born infected will be classified as chronic carriers. Finally, in

accordance with [2], our model assumes that HBV-related deaths in the birth cohort in totality are negligible.

The model flowchart in Figure 3.1 describes a modified SIR type model. The model consists of the following class of individuals, all of whom are neonates within their first 24 hours of birth: susceptible babies, S_b, infants who receive the routine vaccine, V_b, chronically infected babies, I_b, and those with full immunity either by receving the vaccine or through natural clearance, R_b .

3.1 Model Assumptions

The following simplifying assumptions were made in the model below:

1. There are constant inflows or births.

2. Babies are either born infected or susceptible. We classify all infected babies as chronic in agreement with [16].

3. There is an existing routine vaccination in place.

4. Babies are only infected through vertical transmission, either before or after birth. Horizontal transmission is ignored at this stage.

5. Since the time it takes for infants to become chronic is very short compared to the time span of infected, it is assumed all the infected infants are chronic.

6. The routine vaccine provides permanent immunity.

7. All the babies are at equal risk of acquiring the infection.

8. There is no HBV related mortality at that stage.

3.1.0.1 Flowchart Description

Neonates are either born susceptible or infected and that is how *S* and *I* are populated. A proportion of the susceptible individuals receive the routine vaccine after birth, moving to *V* . The rest get infected vertically and move to *I*. The infants who receive the routine vaccine will populate the *R* compartment with full protection after immunity kicks in. The infants who clear the infection naturally will move to *R* as well.

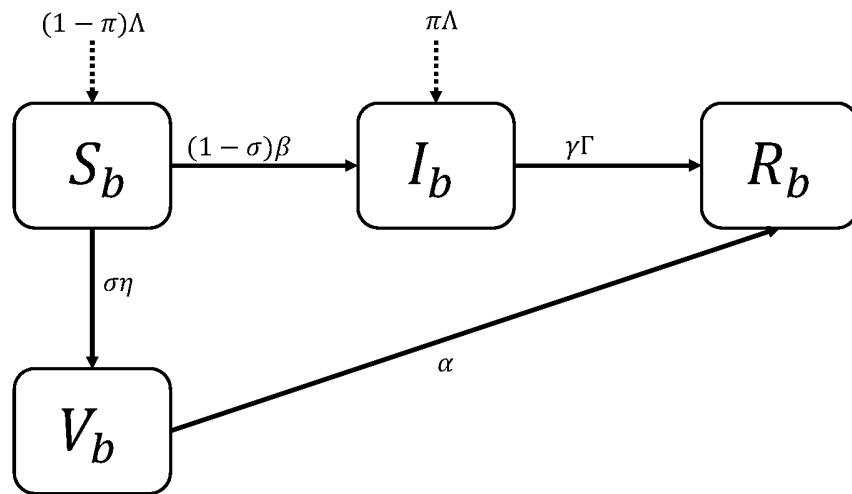The model flow diagram is represented in Figure 3.1.

Figure 3.1: the SVIR model structure indicating vertical transmission. The solid arrows indicate movement of the individuals, whiles the dashed arrows represent initial inflows.

The systems of ordinary differential equations representing the dynamics described

above are as follows:

$$\frac{dS}{dt} = (1 - \pi)\Lambda - \beta S_b (\frac{I_m + C_m}{N_m}) - \sigma \eta - mu S_b,$$

$$\frac{dV}{dt} = \sigma \eta S_b - (\mu + \alpha) V_b$$

$$\frac{dI}{dt} = \beta S_b (\frac{I_m + C_m}{N_m}) + \pi \Lambda - \gamma \Gamma - \mu I_b,$$

$$\frac{dR}{dt} = \sigma \eta S - (\mu + \alpha) V_b.$$

(3.1.1)

The various parameters used in our model are described the following table:

Parameter	Description	Source
Λ	Total births per year	
μ	natural death rate	
β	mother-to-child contact rate	
γ	rate of natural clearance of infection	
α	rate of acquiring vaccine-induced permanent immunity	
η	routine vaccination rate	
σ	proportion of infants who receive the routine vaccine	
Γ	Proportion of infected babies who clear naturally	

Table 3.1: Model parameters and their descriptions

Group	Description
S	Susceptible to the infection
V	Infants with the routine vaccination
I	Chronically infected babies
R	Fully immune individuals

Table 3.2: Description of epidemiological grouping

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