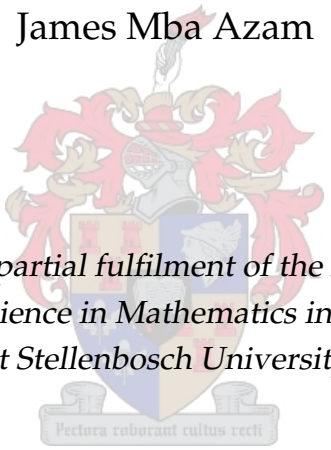
Mathematical Modelling of the Possible Eradication of Hepatitis B in sub-Saharan Africa: A Focus on the Impact of Vaccination and Treatment on the Long Run Dynamics of the Disease.

by

James Mba Azam



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

Department of Mathematical Sciences,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Supervisor: Dr. Eben du Toit
Dr. Monique Ingrid Andersson
Prof. Martin Nieuwoudt

September 2016

Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature: .....
James Mba Azam

Date: September 12, 2016 .....

Abstract

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

James Mba Azam

Department of Mathematical Sciences,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Thesis: MSc. (Mathematics)

September 2016

the abstract goes here

Keywords: mother-to-child transmission, hepatitis B, hepatitis B eradication.

Abstract

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

James Mba Azam

Department of Mathematical Sciences,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Thesis: MSc. (Mathematics)

September 2016

.....

Keywords: mother-to-child transmission, hepatitis B, hepatitis B eradication.

Acknowledgements

I would like to express my sincere gratitude to the following people and organisations ...

Dedications

T..

Publications

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

1. .....
2. .....

Contents

List of Figures

List of Tables

Chapter 1

Introduction

In most parts of the world, hepatitis B(HBV) is causing a great health havoc. It has been estimated to have caused over 600,000 deaths in the past according to a systematic review by [6]. Hepatitis B is a common cause for liver cancer, liver cirrhosis, and some other liver-related diseases.

HBV is acquired through sexual contact, blood and serum, and after long exposures to the 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[14]. Some authors, for instance, [1, 14] 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[14] . 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 over the globe, as it is almost rare in most advanced countries whilst remaining highly endemic in sub-Saharan Africa and parts of Asia[5]. 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 [10]. 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 [6] which estimated the prevalence of the disease by world

regions.

Throughout the history of disease amelioration, vaccination and immunization have both played a dominant role. This can be attested to by the steps taken in eradicating diseases like small pox globally[2]. HBV vaccination has been present since the early 1980's [12]. In many low-income countries, It 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 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 [12, 14].

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 [7, 14].

Studies like [13, 14] had 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 critical level of 10^7 IU/mL. A recent cohort trial by [8] has produced very convincing results that seem to affirm the stance that, reducing maternal DNA levels below the critical level, 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. To do this, we 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 1a and 1b

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 to hepatitis B

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.

2.0.1 HBV Mother-to-Child Transmission Risk Factors

According to [7], 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 [15] have agreed with [7] in terms of maternal DNA levels being one of the most important risk factors.

2.0.2 Vaccination of Neonates

Several authors for instance, those of [1, 11, 14, 16], 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. Other studies, however, have 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 almost 97% protection to the infants[14] in preventing the infection. On the same matter, the authors of [7] did a 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. More importantly, it has been been suggested that the second dose must be administered in time, as a study by [12] has proven that a delay in receiving the subsequent vaccines might cause a reduction in the protection of the infants against the transmission of HBV. 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.

2.0.3 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 [8] has concluded that it might be a good option in the future, as predicted by the authors in [16]. The same primary author, in a different trial, the results of which were published in [9], 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 not the focus of our research question.

In applying the ODE models, our modelling process will take two “stages": In the first stage, we shall develop (or modify) several models from the literature. These models shall apply treatment independently to the infected mothers, and a combined strategy involving a birth dose alongside the routine vaccine to children. Here, the authors will assume that in reality, it will be done in primary health-care settings. These models will be simulated separately just as they have been described. Finally, we shall combine the two separate interventions we have described into a single model. A simulation of the three separate models over time will then produce outputs which will be fed into the second stage.

On the matter of stage two, we will only be interested in the number of infants who remain infected after these interventions have been put in place. This output will flow into a larger SSA birth/death model 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 Mathematical Modeling

We propose a mathematical model to study the long term contribution of the 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 all infants 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 [3, 18] by amalgamating ideas from the models in those papers. Of particular interest is the age-structured model by [3]. We adapt the equation set (1) in [3] 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 [4] 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 [18]. 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 [17], we assume that all infants born infected will be classified as chronic carriers. Finally, in accordance with [3], our model assumes that HBV-related deaths in the birth cohort in totality are negligible.

3.0.1.1 Model Framework

The model flowchart in figure 3.1 describes a modified SIR type model adopted from [18].

The model consists of the following class of individuals, all of whom are neonates within their first 24 hours of birth: susceptible individuals, S, infants with temporary protection from receiving the birth vaccine, V, exposed neonates, E, a class of individuals who have progressed from being exposed to having acute infections, I, the HBV carriers, C, and those with full immunity, R .

3.0.1.2 Flowchart Description

Neonates are either born susceptible or infected and that is how S and C are populated. We assume that all infected infants go directly into the carrier class. The number of infected infants born to infected mothers is controlled by the efficacy of the treatment administered to the mothers. The susceptible individuals receive their first dose immediately after birth, moving to V with temporary immunity. We, again, assume infants who receive the birth dose cannot be infected until after the vaccine wanes. We only allow waning of the birth vaccine for infants who will not proceed to receive the routine vaccine. The infants who receive the routine vaccine after the birth vaccine will populate the R compartment with full protection alongside those neonates who will clear their infection. The infants who do not receive the birth vaccine, but remain uninfected until they receive the routine vaccine in full dosage will move to R as well. The rest of the susceptible individuals either remain susceptible or go through the stages of being exposed to the infection from their mothers, and then, proceeding to the acute stage, and finally, the carrier phase. These infection stages described are only as a result of perinatal transmission as we assume horizontal transition is negligible at that age. We also assume hepatitis B related death to be negligible and so, in all the classes, mortality is only through natural death.

The model flow diagram is represented in Figure 3.1.

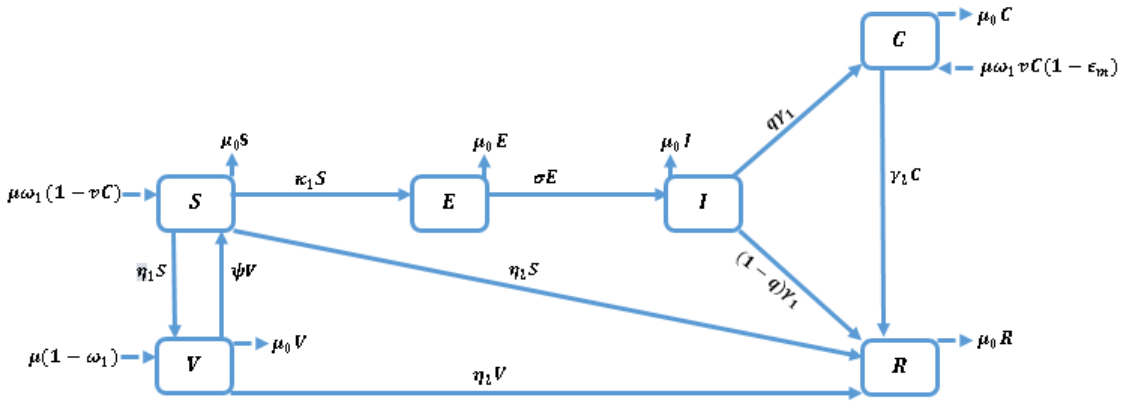


Figure 3.1: the model structure indicating vertical transmission and two stages of immunity, the first through the birth vaccine, and final through a sort of booster by routine vaccination. The solid arrows indicate movement of the individuals, whiles the dashed arrows represent initial inflows and deaths.

The systems of ordinary differential equations representing the dynamics described above are as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \mu\omega_1(1-\nu C) - (\mu_0+\kappa_1+\eta_2+\eta_1)S + \psi V \\
\frac{dV}{dt} &= \mu(1-\omega_1) + \eta_1 S - (\mu_0+\eta_2+\psi)V \\
\frac{dE}{dt} &= \kappa_1 S - (\mu_0+\sigma)E \\
\frac{dI}{dt} &= \sigma E - (\mu_0+\gamma_1)I \\
\frac{dC}{dt} &= (1-\epsilon_m)\mu\omega_1\nu C + q\gamma_1 I - (\mu_0+\gamma_2)C \\
\frac{dR}{dt} &= \gamma_2 C + (1-q)\gamma_1 I + \eta_2(S+V) - \mu_0 R
\end{aligned} \tag{3.0.1}$$

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

Parameter	Description
μ	birth rate
μ_0	natural death rate
κ_1	MTCT transmission coefficient
ϵ_m	efficacy of treatment of the infected mothers
σ	rate of progression from exposed state to acute state
γ_1	rate of moving from acute infection to carrier state
γ_2	rate of natural clearance of infection
ω_1	proportion of infants without successful birth vaccination
η_1	birth vaccination rate
η_2	routine vaccination rate
ψ	waning rate of the birth vaccine
ν	proportion of infants infected at birth
q	average probability that an infant proceeds to the carrier state due to inability to clear acute infection

Table 3.1: Model parameters and their descriptions

List of references

[1] Monique I Andersson, Ruma Rajbhandari, Michael C Kew, Sandro Vento, Wolfgang Preiser, Andy IM Hoepelman, Gerhard Theron, Mark Cotton, Jennifer Cohn, Dieter Glebe, et al. Mother-to-child transmission of hepatitis b virus in sub-saharan africa: time to act. *The Lancet Global Health*, 3(7):e358–e359, 2015.

[2] Frank Fenner. Global eradication of smallpox. *Review of Infectious Diseases*, 4(5):916–930, 1982.

[3] Joanne Mann and Mick Roberts. Modelling the epidemiology of hepatitis b in new zealand. *Journal of theoretical biology*, 269(1):266–272, 2011.

[4] Angela R Mclean and Baruch S Blumberg. Modelling the impact of mass vaccination against hepatitis bi model formulation and parameter estimation. *Proceedings of the Royal Society of London B: Biological Sciences*, 256(1345):7–15, 1994.

[5] Graham F Medley, Nathan A Lindop, W John Edmunds, and D James Nokes. Hepatitis-b virus endemicity: heterogeneity, catastrophic dynamics and control. *Nature medicine*, 7(5):619–624, 2001.

[6] JJ Ott, GA Stevens, J Groeger, and ST Wiersma. Global epidemiology of hepatitis b virus infection: new estimates of age-specific hbsag seroprevalence and endemicity. *Vaccine*, 30(12):2212–2219, 2012.

[7] Calvin Q Pan, Zhong-Ping Duan, Kalyan R Bhamidimarri, Huai-Bin Zou, Xiao-Feng Liang, Jie Li, and Myron J Tong. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis b virus. *Clinical Gastroenterology and Hepatology*, 10(5):452–459, 2012.

[8] Calvin Q Pan, Zhongping Duan, Erhei Dai, Shuqin Zhang, Guorong Han, Yuming Wang, Huaihong Zhang, Huaibin Zou, Baoshen Zhu, Wenjing Zhao, et al. Teno-

fovir to prevent hepatitis b transmission in mothers with high viral load. *New England Journal of Medicine*, 374(24):2324–2334, 2016.

[9] Calvin Q Pan, Guo-Rong Han, Hong-Xiu Jiang, Wei Zhao, Min-Kai Cao, Cui-Min Wang, Xin Yue, and Gen-Ju Wang. Telbivudine prevents vertical transmission from hbeag-positive women with chronic hepatitis b. *Clinical Gastroenterology and Hepatology*, 10(5):520–526, 2012.

[10] Jianhua Pang, Jing-an Cui, and Xueyong Zhou. Dynamical behavior of a hepatitis b virus transmission model with vaccination. *Journal of Theoretical Biology*, 265(4):572–578, 2010.

[11] Yusuke Shimakawa, Coumba Toure-Kane, Maimuna Mendy, Mark Thursz, and Maud Lemoine. Mother-to-child transmission of hepatitis b in sub-saharan africa. *The Lancet Infectious Diseases*, 16(1):19–20, 2016.

[12] Piyanit Tharmaphornpilas, Aim-orn Rasdjarmrearnsook, Saowanee Plianpanich, Pattaratida Sa-nguanmoo, and Yong Poovorawan. Increased risk of developing chronic hbv infection in infants born to chronically hbv infected mothers as a result of delayed second dose of hepatitis b vaccination. *Vaccine*, 27(44):6110–6115, 2009.

[13] Chloe L Thio, Nan Guo, Chan Xie, Kenrad E Nelson, and Stephan Ehrhardt. Global elimination of mother-to-child transmission of hepatitis b: revisiting the current strategy. *The Lancet Infectious Diseases*, 15(8):981–985, 2015.

[14] TRAM T Tran. Management of hepatitis b in pregnancy: weighing the options. *Cleveland Clinic journal of medicine*, 76:S25–9, 2009.

[15] Wan-Hsin Wen, Mei-Hwei Chang, Lu-Lu Zhao, Yen-Hsuan Ni, Hong-Yuan Hsu, Jia-Feng Wu, Pei-Jer Chen, Ding-Shinn Chen, and Huey-Ling Chen. Mother-to-infant transmission of hepatitis b virus infection: significance of maternal viral load and strategies for intervention. *Journal of hepatology*, 59(1):24–30, 2013.

[16] Yuanyong Xu, Huihui Liu, Yong Wang, Rongzhang Hao, Zhenjun Li, and Hongbin Song. The next step in controlling hbv in china. *Bmj*, 347:f4503, 2013.

[17] Suxia Zhang and Yicang Zhou. The analysis and application of an hbv model. *Applied Mathematical Modelling*, 36(3):1302–1312, 2012.

[18] Lan Zou, Weinian Zhang, and Shigui Ruan. Modeling the transmission dynamics and control of hepatitis b virus in china. *Journal of Theoretical Biology*, 262(2):330–338, 2010.