Model-Based Estimation of the Prevalence of Chronic Hepatitis B in Canada and Cost-Effectiveness Analysis of Implementing a Universal Birth Hepatitis B Vaccination Program in Ontario, Canada

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Chapter 2 of the thesis has been previously presented as a conference abstract at the 43rd Annual North American Meeting of the Society for Medical Decision Making and at the 2021 CADTH Symposium. This work was awarded the Best Poster Award at the 2021 CADTH Symposium.

Chapter 3 of the thesis has been previously presented as a conference abstract at the 2022 Canadian Liver Meeting.

ABSTRACT

Background Hepatitis B is a potentially life-threatening acute or chronic disease that is caused by hepatitis B virus (HBV). The development of chronic disease is age-dependent, with the highest risk in the infant population. As such, the World Health Organization recommends universal hepatitis B vaccination within the first 24 hours of birth. Yet, hepatitis B vaccination is provided at age 12 years in Ontario, Canada. Chronic hepatitis B (CHB) is also characterized by the lack of symptoms until progression to end-stage liver disease, making it difficult identify infected patients early in the disease. This has resulted in uncertainties regarding the true prevalence and the impact of CHB in Canada.

Objectives The objectives of this thesis are to: 1) assess the cost-effectiveness of implementing a universal hepatitis B vaccination program in newborns versus adolescents in Ontario, and 2) estimate the true prevalence of CHB and the proportion of undiagnosed cases in Canada.

Methodology Two models were developed to achieve the study objectives. First, a state-transition model representing the natural history of acute and chronic hepatitis B was developed in TreeAge Pro to assess the cost-effectiveness of two hepatitis B vaccine schedules. Analyses were performed from a public payer perspective with a lifetime time horizon and a 1.5% annual discount rate. Second, a modified version of the natural history model was adopted to create a prevalence model in MATLAB to estimate the prevalence of CHB using Markov Chain Monte Carlo. Model input data were obtained from peer-reviewed literature and publicly available databases from Statistics Canada and Public Health Agency of Canada.

Results Birth vaccination was found to be cost-saving compared to the current adolescent vaccination strategy in Ontario. Probabilistic analysis resulted in a mean cost of $317,261 and

43.36 QALYs for birth vaccination versus $317,735 and 43.18 QALYs for adolescent vaccination. A microsimulation showed that the birth vaccination strategy leads to decreases in liver-related cases by 15.96% in acute hepatitis B, 44.27% in CHB, 47.45% in compensated cirrhosis, 47.54% in hepatocellular carcinoma, 56.44% in decompensated cirrhosis, 50.00% in liver transplant, and 51.16% in liver death

In Canada, the model estimated both the prevalence of CHB and proportion of undiagnosed cases to have trended downwards in the total population from 2011 to 2017. Overall, when all age cohorts were combined, CHB prevalence was estimated to be 0.85% and the undiagnosed proportion was estimated to be 32.77%. The model-generated estimate for CHB prevalence of 0.85% was approximately doubled the previously estimated seroprevalence of 0.4% from a national seroprevalence study.

Conclusion The results of the study indicate that by switching to a birth hepatitis B vaccination program, the Ontario government can save healthcare spendings while increasing clinical benefits. The results of the study provide policy makers with actionable recommendations on re-assessing the current hepatitis B vaccination schedule in Ontario. The second model also showed that the prevalence of CHB may be much higher than previously estimated and that a significant proportion of patients remain undiagnosed. The prevalence model demonstrates a feasible framework for future analyses using administrative databases to more accurately identify the true burden of CHB in Canada.

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LIST OF ABBREVIATIONS

ACM – all-cause mortality

AHB – acute hepatitis B

ALT – alanine transaminase

CADTH – Canadian Agency for Drugs and Technologies in Health

CASL – Canadian Association for the Study of the Liver

CC – compensated cirrhosis

CDC – US Centers for Disease Control and Prevention

CHB – chronic hepatitis B

DC – decompensated cirrhosis

DSA – deterministic sensitivity analysis

HBeAg – hepatitis B e antigen

HBsAg – hepatitis B surface antigen

HBV – hepatitis B virus

HCC – hepatocellular carcinoma

HCV – hepatitis C virus

ICER – incremental cost-effectiveness ratio

IT – immune tolerant

LD – liver death

LT – liver transplant

LVI – lost vaccine immunity

MCMC – Markov Chain Monte Carlo

MH – Metropolis-Hastings

NACI – National Advisory Committee on Immunization

NI – natural immunity

PHAC – Public Health Agency of Canada

PHO – Public Health Ontario

PLT – post-liver transplant

PSA – probabilistic sensitivity analysis

QALY – quality-adjusted life year

UK – United Kingdom

VII – vaccine-induced immunity

WHO – World Health Organization

WTP – willingness-to-pay

CHAPTER 1

Introduction and Background

i. Viral Hepatitis

Viral hepatitis is an inflammatory disease of the liver that is caused by viral pathogens.[1] Most cases of viral hepatitis are caused by hepatitis A, B, C, D, or E viruses, although adenovirus, cytomegalovirus, Epstein-Barr virus, among others, can also rarely cause viral hepatitis.[1] Characterized by both non-specific and specific symptoms such as fever, fatigue, dark urine, and jaundice, the disease has a wide spectrum of symptom severity ranging from asymptomatic disease to life-threatening cases from complications such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[2-3]

Broadly, hepatitis can be categorized as acute or chronic infection. About 95% and 15-40% of acute hepatitis B and C infection, respectively, in adults is self-resolving, does not require antiviral therapy, and can be managed simply through supportive care.[1] Chronic infection is characterized by the presence of virus in the blood for at least six months and increases the patient's risk of more severe liver diseases such as decompensated cirrhosis (DC) and HCC.[4] Of the five hepatitis viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV) have the highest risk of causing chronic infection, while hepatitis A, D, and E viruses are unable to, or have minimal risk of, causing chronic infection.[1]

ii. Hepatitis B

Estimates from the World Health Organization (WHO) in 2015 suggest that 257 million people are chronically infected with HBV globally, resulting in approximately 800,000 deaths

annually.[5] Majority of the deaths stem from cirrhosis and HCC, making hepatitis B a major global health concern.[6] Fortunately, due to advancements in, and access to, preventative and treatment methods, Canada is considered a low endemic (defined as <8% hepatitis B surface antigen prevalence) hepatitis B country.[7] Yet, hepatitis B still remains to be a burdensome disease with a national incidence of 13.0 per 100,000 for chronic hepatitis B (CHB).[7] In 2018, 4,783 cases of HBV were reported in Canada.

Part of the reason why hepatitis B remains a concern in Canada is related to its modes of transmission. HBV can be spread through three major ways: percutaneous, sexual, and perinatal.[4] Perinatal transmission, from mother to child, is typically the most common mode of transmission in highly endemic countries.[8] However, perinatal transmission is still important in low endemic countries like Canada where transmission occurs mostly in children of mothers who are HBV-positive but did not receive recommended prophylactic therapy which can sometimes occur due to incomplete prenatal screening coverage, as evidenced in a Canadian study by Biondi *et al*.[4,9] Perinatal transmission is also an important factor especially considering the fact that Canada is a popular destination country for immigrant families from high HBV endemic countries such as China and South Korea.[6,9]

iii. Natural History of Hepatitis B

Different phases of hepatitis B are defined not by the symptoms but rather by the status of viral DNA and liver function tests. Following an acute hepatitis B (AHB) infection, a patient may develop CHB if they are unable to mount a sufficient adaptive immune response which will lead to viral persistence in the body.[10] The risk of developing CHB is age-dependent with the highest risk being in infants at 80-90% compared to only about 5% in adults.[6] The persistence of hepatitis B surface antigen (HBsAg), a biomarker used to indicate current infection, for at least six months

defines CHB.[4] It is important to understand that HBV generally does not directly kill hepatocytes.[10] But rather, it is the immune response-mediated inflammation and the resulting cirrhosis that causes complications in a chronic infection.[10]

The natural history of CHB can be described in three phases: hepatitis B e antigen (HBeAg)-positive chronic infection, HBeAg-positive chronic hepatitis, and HBeAg-negative chronic infection.[11] The three phases have also been more commonly referred in the literature as immune tolerance, immune active/clearance, and immune control/residual phases, respectively.[11] HBeAg is an important biomarker in the assessment of CHB patients because positive HBeAg is associated with high HBV DNA levels and so it can be used as a surrogate marker for viral replication.[12-13]

The HBeAg-positive chronic infection phase, or the immune tolerance phase, is the first phase of CHB. It is characterized as a highly replicative but low inflammatory phase.[10] Viral DNA levels are observed to be high while alanine transaminase (ALT) levels remain below the upper limit of normal.[10] As such, antiviral treatment in this stage is not indicated.[10]

The HBeAg-positive chronic hepatitis phase, or the immune active/clearance phase, is characterized by a decrease in viral DNA level and an increase in ALT level.[10] The reduction in viral DNA and increase in ALT is a function of host-mediated immune response against HBV-infected hepatocytes.[10] Depending on the intensity of the immune response, the changes in the viral DNA and ALT levels can fluctuate.[10] Antiviral treatment is typically indicated in this phase.[14]

The HBeAg-negative chronic infection phase, or the immune control/residual phase, is characterized by low levels of both viral DNA and ALT.[10] An important aspect of this phase is the seroconversion of HBeAg in some patients where antibodies against HBeAg, named anti-HBe,

develop and HBeAg is lost.[10] HBeAg seroconversion is an important endpoint for antiviral treatment as it is associated with disease remission in majority of patients.[8] Earlier seroconversion is also associated with longer duration of remission, lower rate of reversion back to HBeAg-positive phase, and slower disease progression.[8] Inactive carriers typically do not require treatment and are monitored routinely, whereas active carriers will treatment.

iv. Hepatitis B: A Silent Disease

Arguably the most lethal and problematic characteristic of the natural progression of hepatitis B is the fact that it is a silent disease. It is estimated that approximately 50% of adults and 90% of children under the age of five with AHB are asymptomatic.[15-17] Such high rates of asymptomatic cases are concerning for various reason. First, many AHB patients who develop CHB will be unaware of their disease until they have progressed to symptomatic end-stage liver disease such as DC or HCC at which point the prognosis will be poor.[18,19] This makes it difficult for patients and clinicians to identify the disease early and treat it appropriately to prolong disease remission. Second, the asymptomatic nature of the disease creates an epidemiological problem. Because many patients will be unaware of their disease and remain undiagnosed, it is difficult to understand the true prevalence of the disease and the true impact on the society. The lack of knowledge on such fundamental epidemiological data then naturally makes it difficult to design and implement public health measures against the disease.

v. Prevalence of Chronic Hepatitis B

In 2013, Statistics Canada, in partnership with the Public Health Agency of Canada (PHAC), published the results of the Canadian Health Measures Survey which looked to produce nationally representative estimates of the seroprevalence of hepatitis B and C virus infections.[20]

Seroprevalence is the prevalence of a disease determined based on a blood sample. As such, the PHAC study collected blood samples from the study participants to run serology tests and identify their infection status.[20] Looking at the data from 2007 to 2011, the authors found the seroprevalence of current HBV infection in the 14 – 79 years old population to be 0.4% which represents approximately 111,800 individuals.[20] Yet, in 2017, only 192 cases of AHB, 4,086 cases of CHB, and 627 cases of unspecified cases were reported in Canada through the Canadian Notifiable Disease Surveillance System for a total of 4,905 known cases of hepatitis B.[21] Considering the fact that a large proportion of hepatitis B patients are asymptomatic and possibly undiagnosed, these reported numbers are likely gross underestimations of the true prevalence of the disease. In Canada, hepatitis B is not considered to be a highly prevalent disease but because of the asymptomatic nature of the disease, questions remain regarding how much of the infected population is not being captured through the currently narrow screening program. As such, understanding the true prevalence of the disease and the proportion of undiagnosed patients will be critically important in informing public health officials on whether it makes sense to implement a broader screening program.

vi. Current Policies on Hepatitis B

A number of policies surrounding hepatitis B vaccination, screening, and treatment are in place in Canada. For disease screening, the 2018 Canadian guidelines for the management of HBV infection recommends a list of patient groups that should be screened for hepatitis B including, but not limited to, pregnant women, inmates, patients with chronic renal failure needing dialysis, those with signs of liver disease or other infectious diseases like hepatitis C, among others.[30] In Ontario, the Ministry of Health and Long-Term Care recommends screening for pregnant women for each

pregnancy, individuals from countries with high prevalence of HBV, and adopted children from countries with high prevalence of infection and persons in high risk groups.[31]

In terms of vaccination, all provinces and territories in Canada have long provided routine vaccination against hepatitis B. Vaccination schedules vary by province with most provinces and territories following one of three schedules: two-dose series beginning at birth, three-dose series beginning in infancy, or two-dose series in grades six or seven.[29]

Table 1: Hepatitis B Vaccination Recommendations by Province

BC, PEI, YT	AB	SK, MB, NL	ON, NS	QC	NB	NT	NU
Infancy: provided as a 3-dose combination vaccine of DTaP-HB-IPV-Hib	Grade 6 (3-dose)	Grade 6 (2-dose)	Grade 7 (2-dose)	Infancy: provided in a combination vaccine of DTaP-HB-IPV-Hib Adolescence: HAHB	At birth, 2, 6 mos	At birth, 1, 6 mos	At birth, 1, 9 mos

Abbreviations: DTaP, diphtheria tetanus acellular pertussis; HB, hepatitis B; IPV, inactivated polio vaccine; Hib; Hemophilus influenzae; HAHB, hepatitis A hepatitis B.

OBJECTIVES

Cost-Utility Analysis of Implementing Hepatitis B Vaccination in Newborns in Ontario

i. Knowledge Gap

In Ontario, hepatitis B vaccines are routinely given to Grade 7 students on a two-dose schedule through a publicly funded program. Several agencies around the world, including the Canadian Association for the Study of the Liver (CASL), World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) recommend that hepatitis B vaccines be given as a birth dose within 24 hours of birth. Many economic analyses have assessed the cost-effectiveness of implementing a birth vaccination strategy compared to no vaccination. However, to the best of our knowledge, no study has compared birth and adolescent vaccination strategies in Ontario. As such, a state-transition model detailing the natural history of AHB and CHB was developed to perform a cost-effectiveness analysis comparing universal hepatitis B vaccination in adolescents (status quo) versus newborns in Ontario, Canada.

ii. Objective

The objective of this work was to assess the health and economic impact of modifying the current vaccination schedule in Ontario to be aligned with evidence-based recommendations from a clinical perspective with a penultimate goal of the data being used to aid decision-makers. Our hypothesis is that the implementation of a birth vaccination program will be a cost-effective method in Ontario.

Model-Based Estimation of the Prevalence of CHB and Proportion of Undiagnosed CHB Cases in Canada Between 2011 and 2017

i. Knowledge Gap

In Canada, there is a lack of a widely accepted estimate on the prevalence of CHB. This is complicated by the fact that many patients with CHB are asymptomatic. Considering the similar disease characteristics between CHC and CHB, and recent findings suggesting that a significant proportion of CHC patients may remain undiagnosed in Canada, there is a need to delineate the true prevalence of CHB and better understand its true impact in Canada. As such, a model-based approach, using data from Statistics Canada and PHAC as core model input data, was taken to estimate the true prevalence (e.g., diagnosed and undiagnosed) of CHB in Canada.

ii. Objective

The objective of this work was to develop a framework to assess the feasibility of using a model to estimate the prevalence of CHB and to allow future analyses with administrative databases. Ultimately, the goal of the study is to provide relevant stakeholders, such as clinicians and public health officials, with a better understanding of the epidemiology of the disease. Our hypothesis is that a model-based estimation of the prevalence leveraging historic data will be greater than what has been reported through surveillance systems in Canada.

CHAPTER 2

Cost-Utility Analysis of Implementing Hepatitis B Vaccination in Newborns in Ontario

INTRODUCTION

While widespread implementation of hepatitis B screening is currently not part of Canada's public health strategy against CHB, another fundamental public health measure is currently in place – vaccination. Notably, Ontario, the largest province in Canada by population, has adopted a two-dose schedule provided to grade seven students.[29] However, CASL and world-renowned public health agencies like the WHO and the US CDC recommend that hepatitis B vaccine series be started within 24 hours of birth.[30,33,34] Such a recommendation is largely stemmed from the fact that the risk of developing CHB from AHB is age-dependent. Evidence suggests that infants infected with HBV have 80 to 90% chance of developing CHB, while the risk for adults is less than 5%.[6] Despite this knowledge and the strong recommendations from CASL, WHO and CDC, Ontario continues to vaccinate children over a decade later than the recommended timeframe.

Part of the reason why Ontario has adopted an adolescent vaccination strategy is because there were concerns in the past that the protective effects of hepatitis B vaccines would wane after ten to fifteen years.[35] Considering that hepatitis B is a sexually transmittable disease and children can start to become more sexually active in their teenage years, concerns of waned vaccine protection during sexually-active teenage years were raised. However, more recent evidence has suggested that such drastic vaccine waning effect may not be true. In fact, a recent study by Bruce *et al*. demonstrated that the protective effect of hepatitis B vaccine is stable over 30 years.[36]

A number of barriers are often present when it comes to implementing change in a publicly driven healthcare system. One of the most prominent barriers is typically the financial barrier. In many instances, when there is an intervention available that can provide improved health outcomes, it is typically one of great financial burden. When considering that Canada's public health and vaccine expenditures are less than 6% and 0.3% of the total health expenditure, respectively, any proposal to the changes in vaccination programs is likely a challenging one even with a prospect of better health outcomes.[37] Economic evaluations become especially important in such circumstances where the incremental cost per additional health outcome can be quantified. Economic evaluations use computer models informed by scientific evidence to produce results that play an important role in providing decision-makers and key stakeholders with actionable policy recommendations.

Many research groups have studied the cost-effectiveness of various hepatitis B vaccination strategies, such as selective vaccination versus universal vaccination.[38,39] One group in the United Kingdom (UK) has conducted an economic evaluation of hepatitis B vaccination in infants or adolescents compared to no vaccination.[40] The UK study concluded that, compared to no vaccination, universal infant vaccination program would be more cost-effective than an adolescent vaccination program.[40] However, infant and adolescent programs were not directly compared to each other in the study.[40] In Ontario, there is also no research to directly demonstrate the clinical and economic impact of providing universal vaccination at birth compared to adolescents.

The role of cost-effectiveness studies in updating vaccine schedules may be particularly important in Ontario, as evidenced by past examples in other diseases. In February 2018, following extensive reports of real-world evidence in the US and UK, the National Advisory Committee on

Immunization (NACI), Canada's highest recommendation body on immunization, published a new statement recommending universal pertussis vaccination in every pregnancy as a method of reducing infant morbidity and mortality due to pertussis.[41] By March 2021, three years following the updated recommendation, every province and territory in Canada now publicly funds maternal pertussis immunization in pregnancy with the sole exception of Ontario. In an October 2018 report from the Public Health Ontario (PHO) in response to the 2018 NACI statement, PHO explicitly stated that even though they acknowledge maternal immunization to be a highly effective intervention from a clinical perspective, economic evaluation should be assessed as part of the decision-making process on updating vaccine programs.[42] Such inaction by Ontario decision-makers, despite strong clinical evidence to support a policy change, provides a level of insight on the importance of economic evaluation when trying to provide an actionable policy recommendation to decision-makers.

METHODOLOGY

i. Study Design

A state-transition model representing the natural history of acute and chronic hepatitis B was developed to conduct a cost-effectiveness analysis of universal hepatitis B vaccination at birth versus adolescence (status quo) in Ontario, Canada. The construct of the model and the analyses of the results followed the guidelines for economic evaluation by the Canadian Agency for Drugs and Technologies in Health (CADTH).[43] Analyses were performed from a Canadian public payer perspective with a lifetime model time horizon. Health outcome and cost parameters were discounted at an annual rate of 1.5%, as per the CADTH recommendation.[43] Each cycle was set to be one-year in duration and all costs were adjusted for inflation to 2021 Canadian dollars. The

primary outcome of interest was the incremental cost-effectiveness ratio (ICER) of vaccinating newborns versus adolescents. The ICER value was determined by calculating the ratio of the difference in total cost and the difference in the quality-adjusted life years (QALYs).

ii. Vaccination Strategies

Two vaccination strategies were considered in the study:

(1) *Universal vaccination during adolescence (status quo)*: Subjects in this arm were assumed to receive vaccination for hepatitis B at age 12 years based on the vaccine coverage rate in Ontario, in accordance with the standard school-based vaccination schedule followed in Ontario, Canada.[7] To reflect the current hepatitis B vaccination practices in Ontario for adolescents, subjects in this group received two doses to complete the vaccination series, instead of the typical three-dose series for infants.[7] Subjects in this arm had a higher risk of hepatitis B infection during the first 12 years of life until vaccination, after which the risk was comparable to those vaccinated in the newborn arm.

(2) *Universal vaccination at birth*: Subjects in this arm were assumed to receive vaccination for hepatitis B at birth, as recommended by WHO, based on the adolescent hepatitis B vaccine coverage rate in Ontario in the base-case analysis.[44] Subjects in this treatment group received three doses to complete the vaccination series.

Prenatal HBsAg screening was accounted for as per the Ontario screening rate described by Biondi *et al*.[9] Meaning, in both vaccination strategies, it was assumed that prenatal screening of HBsAg would continue regardless of timing of vaccination and that infants born to mothers who are found to be HBsAg-positive would then receive appropriate treatment.

iii. Cohort

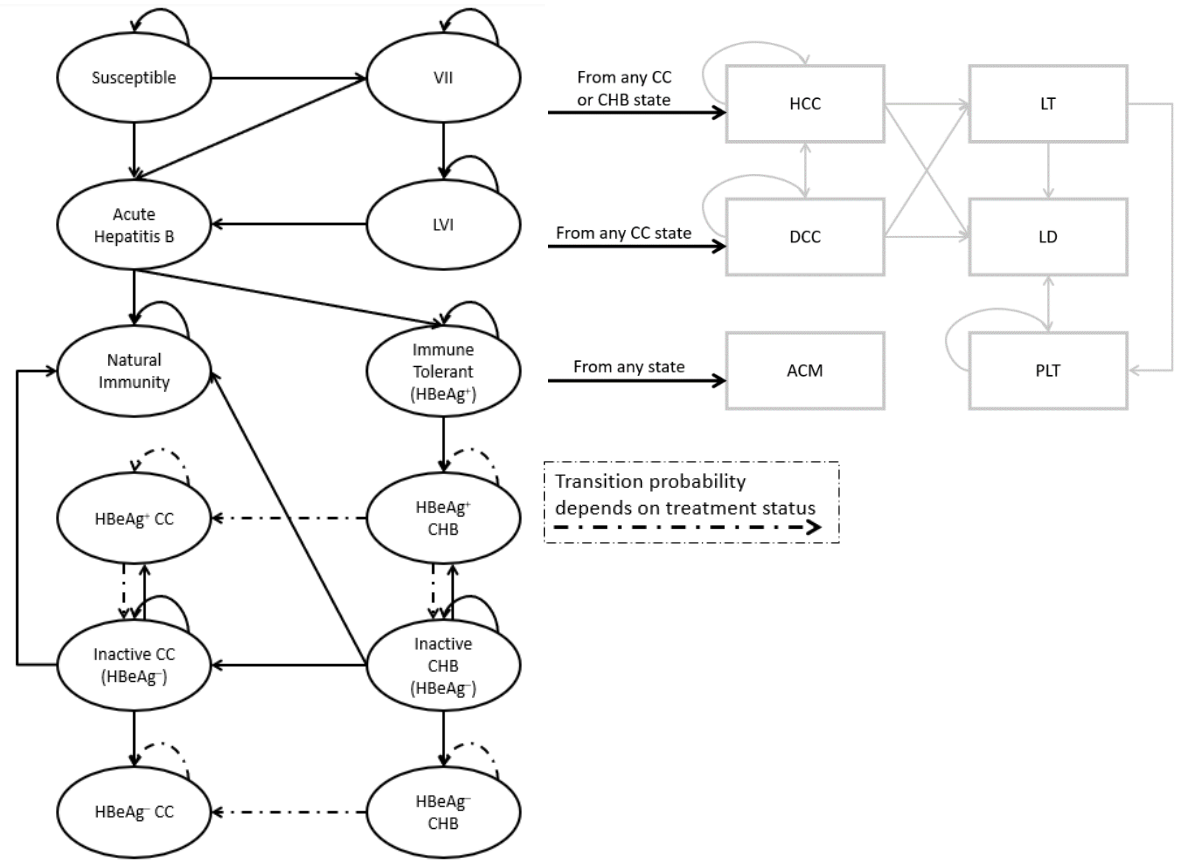
Two theoretical cohorts of children were implemented in the model. The characteristics of the two cohorts were assumed to be identical, with the exception of the timing of vaccination, and Canadian demographic data was applied to emulate the Canadian population. Subjects were modelled from birth, in order to capture disease incidents starting from age 0, and were followed until all subjects have deceased.

iv. Decision Model

A state-transition model was implemented using TreeAge Pro Healthcare 2020 decision analysis software.[45] A state-transition model was appropriate for this analysis because it is optimal for models where timing and recurrence of events need to be considered.[46] They are particularly useful when modelling long-term outcomes, which is appropriate for the present study considering the chronic nature of hepatitis B.[46]

Eighteen health states were implemented to represent the natural progression of hepatitis B and the state-transition model is illustrated in Figure 1: *Susceptible, Vaccine-Induced Immunity (VII), Lost Vaccine Immunity (LVI), Acute Hepatitis B (AHB), Natural Immunity (NI), Immune Tolerant (HBeAg-positive; IT), HBeAg-positive CHB, Inactive CHB (HBeAg-negative), HBeAg-negative CHB, HBeAg-positive compensated cirrhosis (CC), Inactive CC (HBeAg-negative), HBeAg-negative CC, Decompensated Cirrhosis (DC), Hepatocellular Carcinoma (HCC), Liver Transplant (LT), Post-Liver Transplant (PLT), Liver-Related Death (LD), and All-Cause Mortality (ACM).*

Figure 1: State-transition model of hepatitis B disease progression



Abbreviations: VII, vaccine-induced immunity; LVI, lost vaccine immunity; HBeAg, hepatitis B e antigen; CC, compensated cirrhosis; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; DCC, decompensated cirrhosis; ACM, all-cause mortality; LT, liver transplant; LD, liver death; PLT, post-liver transplant

Susceptible state represents healthy subjects who are not vaccinated and are at higher risk of HBV infection. To account for perinatal transmission, a portion of patients were born into the *IT* state, while the rest of the newborn subjects were assumed to begin in the *Susceptible* state where they may transition to *VII*, *AHB*, or remain in the *Susceptible* state. *VII* state represents subjects who have been vaccinated and are at reduced risk of acquiring HBV infection. Subjects in this state may remain in *VII*, or transition to *LVI* corresponding to waning vaccine effect, while

a small fraction may still transition to *AHB*. Subjects in the *LVI* state were assumed to have the same risk of developing acute hepatitis B as those in the *Susceptible* state. In the *AHB* state, subjects could either transition to *NI* or *IT* at an age-dependent proportion. Those who transition to *NI* were assumed to be immune from HBV and remained in this state until natural death from any cause. Subjects in the *IT* state could remain in the same state or, progress to *HCC* or *HBeAg-positive CHB*. From *HBeAg-positive CHB*, subjects could progress to *HCC*, *HBeAg-positive CC*, seroconvert to *Inactive CHB*, or remain in *HBeAg-positive CHB*. Similarly, in *HBeAg-negative CHB*, subjects could progress to *HCC* or *HBeAg-negative CC*, or remain in *HBeAg-negative CHB*. From *Inactive CHB*, subjects could progress to *HCC* or *Inactive CC*, revert back to *HBeAg-positive CHB*, reactivate to *HBeAg-negative CHB*, develop immunity (*NI*), or remain in *Inactive CHB*. Subjects in the *HBeAg-positive CC* state could progress to *HCC* or *DC*, seroconvert to *Inactive CC*, or remain in *HBeAg-positive CC*. Similarly, in the *HBeAg-negative CC*, subjects could progress to *HCC* or *DC*, or remain in *HBeAg-negative CC*. In the *Inactive CC* state, subjects could progress to *HCC* or *DC*, revert back to *HBeAg-positive CC*, reactivate to *HBeAg-negative CC*, develop immunity (*NI*), or remain in *Inactive CC*. Subjects who progress to *DC* could develop *HCC*, require *LT*, remain in DC, or decease from *LD.* Similarly, subjects in the *HCC* state could require *LT*, remain in *HCC*, or decease from *LD.* Patients requiring *LT* progressed to the *PLT* state where they could remain in the state or decease from *LD*. Patients could decease from *ACM* at any point in the model. Additionally, a minor proportion of subjects in *HBeAg-positive CHB, HBeAg-negative CHB, HBeAg-positive CC,* or *HBeAg-negative CC* received antiviral treatment slowing down the disease progression.

v. Model Input

a) Transition Probability

a. All transition probabilities were obtained from relevant peer-reviewed literature or publicly available provincial databases with the exception of the prevalence of CHB. The prevalence of CHB was estimated through a model-based approach in Chapter 3 of this thesis and was subsequently used to inform the current cost-effectiveness model. Of note, the age-specific probabilities of acquiring AHB without vaccination was obtained from a recent study from Ontario, Canada and the probability of acquiring AHB with vaccination was assumed to be the product of the probability without vaccination and vaccine effectiveness.[9] All transition parameters are summarized in Table 2.

b) Cost

a. Cost data were obtained from Canadian sources and inflated to 2021 Canadian dollars using the consumer price index from Statistics Canada.[48] Notably, the per person cost of vaccines for the infant arm was set at $119.79 (3-dose series) and $79.86 (2-dose series) for the adolescent arm.[47] Costs of individual health state were derived from a study by Nanwa *et al*. which was a matched cohort study assessing the mean attributable health care costs associated with hepatitis B in Ontario. In all health states, the average Canadian cost of health care of $6,768.08 was applied as a baseline, as per Statistics Canada. All cost parameters are summarized in Table 3.

c) Utility

a. All utility parameters were derived from a Canadian study by Woo *et al.* The study measured utility values based on 433 patients who were 16 years and older from four tertiary care hospitals in Ontario, Canada between 2007 and 2009. All utility parameters are summarized in Table 4.

Table 2: Transition probability parameters

Parameter	Point Estimate	Lower Limit	Upper Limit	Source
Prevalence of CHB [1]	0.0082	0.0078	0.0085	Chapter 3
Pr of prenatal HBsAg screening	0.073	–	–	9
Pr of perinatal transmission [2]	0.3780	0	0.5	60
Perinatal transmission rate	[1] × [2]	–	–	–
Pr of all-cause mortality	Life Table			61
Vaccine coverage rate[a]	0.692	–	–	44
Pr of AH without vaccine [3]	0 – 3 y: 0.006 4 – 7 y: 0.008 8 – 120 y: 0.011	–	–	9
Vaccine effectiveness [4]	0.9	0.6750	1	40
Pr of AH with vaccine	[3] × [4]	–	–	–
Vaccine waning effect	0	–	–	40, 49
Pr of AH to IT	0 y: 0.9 1 – 5 y: 0.5 6 – 120 y: 0.05	–	–	6
Pr of IT to HBeAg+ CHB	0.1423	0.12	0.16	62
Pr of HBeAg+ CHB to HBeAg+ CC	0.044	0.022	0.088	47, 63-65
Pr of HBeAg+ CHB to Inactive CHB	0.0213	0.0079	0.0551	66, 67
Pr of Inactive CHB to Inactive CC	0.001	0.001	0.002	47, 63, 68
Pr of Inactive CHB to HBeAg+ CHB	0.0048	0.004	0.018	47, 63, 68
Pr of Inactive CHB to HBeAg– CHB	0.0254	0.02	0.05	47, 68, 69
Pr of Inactive CHB to NI	0.008	0.005	0.02	47, 63, 70
Pr of HBeAg– CHB to HBeAg– CC	0.029	0.015	0.058	47, 68, 71, 72

Pr of HBeAg+ CC to Inactive HBeAg– CC[b]	0.1	0.07	0.13	73
Pr of Inactive CC to HBeAg+ CC	0.0048	0.008	0.018	47, 63, 70
Pr of Inactive CC to HBeAg– CC	0.0254	0.02	0.05	47, 68, 69
Pr of Inactive CC to NI	0.008	0.0005	0.02	47, 63, 70
Pr of HBeAg+ CHB to Inactive CHB with treatment	0.0809	0.0434	0.1422	66, 67
Pr of IT to HCC	0.0003	0	0.0004	74
Pr of HBeAg+ CHB to HCC	0.008	0.004	0.016	63, 75, 76
Pr of Inactive CHB to HCC	0.003	0.0015	0.006	63, 68
Pr of HBeAg– CHB to HCC	0.008	0.004	0.012	68, 72, 76, 77
Pr of HBeAg+ CC to HCC	0.034	0.01	0.12	47, 78-80
Pr of Inactive CC to HCC	0.022	0.011	0.044	47, 63, 81
Pr of HBeAg– CC to HCC	0.037	0.01	0.12	47, 76, 78-80
Pr of DC to HCC	0.06	0.01	0.113	47, 76, 82, 83
Pr of DC to LD	0.173	0.058	0.221	47, 82, 83
Pr of DC to LT	0.05	0	0.4	47, 82, 83
Pr of HCC to LT	0.15	0.05	0.4	47, 82, 83
Pr of HCC to LD	0.351	0.181	0.451	47, 82, 83
Pr of LT to LD	0.142	0.124	0.159	84
Pr of PLT to LD	0.034	0.024	0.043	84
Pr of HBeAg+ CC to DC	0.073	0.035	0.1	47, 80, 85, 86
Pr of Inactive CC to DC	0.008	0.004	0.016	47, 63, 81
Pr of HBeAg– CC to DC	0.073	0.035	0.1	47, 80, 85, 86
Pr of receiving treatment[c,d]	0.2366	0.1775	0.2958	87
Pr of HBeAg+ CC to Inactive CC with treatment[e]	0.18	0.12	0.3	88, 89
RR of CHB to CC for treatment vs. no treatment	0.308	0.231	0.385	90
RR of CC to DC for treatment vs. no treatment	0.5209	0.3910	0.6510	90
RR of CC to HCC for treatment vs. no treatment[d]	0.3857	0.2892	0.4821	91, 92
RR of CHB to HCC for treatment vs. no treatment	0.37	0.15	0.91	91

[a]Subjects in the Newborn arm were vaccinated at birth while subjects in the Adolescence arm were vaccinated at age 12. [b]Assumed to be same as non-cirrhotic CHB. [c]Calculated using the probability of being diagnosis and probability of treatment uptake after diagnosis. [d]Range is ±25%. [e]Assumed to be same as probability of HBeAg+ CHB to HBeAg– CHB with treatment.

Abbreviations: HBsAg, hepatitis B surface antigen; Pr, probability; AH, acute hepatitis B; IT, immune tolerant; HBeAg, hepatitis B e antigen; CHB, chronic hepatitis B; CC, compensated cirrhosis; NI, natural immunity; HCC, hepatocellular carcinoma; DC, decompensated cirrhosis; LD, liver-related death; LT, liver transplant; PLT, post-liver transplant; RR, relative risk.

Table 3: Cost parameters

Parameter	Point Estimate	Lower Limit	Upper Limit	Source
Cost of vaccine (3-dose; infants)	119.79	60.93	247.85	47
Cost of vaccine (2-dose; adolescents)	79.86	40.62	165.23	47
Susceptibility state[a]	6,768.08	5,076.06	8,460.09	93
Cost of VII state[a]	6,768.08	5,076.06	8,460.09	93
LVI state[a]	6,768.08	5,076.06	8,460.09	93
Additional cost of AH state	709.02	455.45	1,061.06	47
NI state[a]	6,768.08	5,076.06	8,460.09	93
Additional cost of IT state	687.17	544.55	842.76	97
Additional cost of HBeAg+ CHB state	2,554.21	1,905.93	3,264.07	97
Additional cost of Inactive CHB state	687.17	544.55	842.76	97
Additional cost of HBeAg– CHB state	2,554.21	1,905.93	3,264.07	97
Additional cost of HBeAg+ CC state	2,554.21	1,905.93	3,264.07	97
Additional cost of Inactive CC state	687.17	544.55	842.76	97
Additional cost of HBeAg– CC state	2,554.21	1,905.93	3,264.07	97
Additional cost of DC state	2,554.21	1,905.93	3,264.07	94
Additional cost of HCC state	2,554.21	1,905.93	3,264.07	98
Additional cost of LT state	142,267.15	135,462.98	153,421.23	94
Additional cost of PLT state	54,468	47,123.27	67,087.13	98
Annual cost of treatment (TDF)	1,843.24	1427.65	2,379.42	95

All costs are adjusted to 2021 Canadian dollars. All costs are annual costs except for the cost of vaccine which is a one-time cost. [a]Cost of baseline average healthcare cost

Abbreviations: VII, vaccine-induced immunity; LVI, lost vaccine immunity; AH, acute hepatitis B; NI, natural immunity; IT, immune tolerant; HBeAg, hepatitis B e antigen; CHB, chronic hepatitis B; CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PLT, post-liver transplant; TDF, tenofovir disoproxil fumarate.

Table 4: Utility parameters

Parameter	Point Estimate	Lower Limit	Upper Limit	Source
Susceptible state[a]	0.93	0.85	1.00	96
VII state[a]	0.93	0.85	1.00	96
LVI state[a]	0.93	0.85	1.00	96
AH state	0.87	0.85	0.88	96
NI state[a]	0.93	0.85	1.00	96
IT state	0.87	0.85	0.88	96
HBeAg+ CHB state	0.87	0.85	0.88	96
Inactive CHB state	0.87	0.85	0.88	96
HBeAg– CHB state	0.87	0.85	0.88	96
HBeAg+ CC state	0.81	0.75	0.86	96
Inactive CC state	0.81	0.75	0.86	96
HBeAg– CC	0.81	0.75	0.86	96
DC state	0.49	0.22	0.75	96
HCC state	0.85	0.76	0.95	96
LT state	0.72	0.60	0.83	96
PLT state	0.72	0.60	0.83	96

[a]Utility value for the average Canadian population

Abbreviations: VII, vaccine-induced immunity; LVI, lost vaccine immunity; AH, acute hepatitis B; NI, natural immunity; IT, immune tolerant; HBeAg, hepatitis B e antigen; CHB, chronic hepatitis B; CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PLT, post-liver transplant.

vi. Modelling Assumptions

A number of modelling assumptions were made in the implementation of the model. First, although the vaccine coverage rate for adolescents is available through Public Health Ontario[44], what the coverage rate for birth vaccination would be in Ontario is unknown. As such, although a higher coverage rate with a birth vaccination strategy may be expected, it was assumed that the vaccine coverage rate in newborns will be identical to that of adolescents in the base-case analysis because an assumption of higher coverage rate in the newborn arm is one that could significantly favour the newborn arm and such a strong assumption could potentially unfairly bias the results. However, this assumption was challenged in a scenario analysis by applying the vaccine coverage rate from British Columbia, where an infant vaccination strategy is already implemented. Second,

while the diagnosed prevalence of AHB in Ontario is quantified for children between ages 0 to 11 years[9], age-specific prevalence values for older children and adults were not available. As such, it was assumed that the prevalence in the ≥12 years population would be equal to the prevalence in 11-year-olds as identified by Biondi *et al*.[9] Lastly, it was assumed that the protective effect of hepatitis B vaccine was consistent and life-long. Previously, the potential waning effect of hepatitis B vaccine was a major concern and a key driver in delaying vaccination until adolescence.[35] However, a recent study has demonstrated that hepatitis B vaccine may produce protection up to 30 years.[36]

vii. Analytic Strategy

A base-case analysis was performed to identify the ICER value of vaccinating at birth compared to during adolescence from a public payer perspective with a lifetime time horizon. In compliance with the CADTH guidelines, a probabilistic analysis was performed for the base-case analysis.[43] A deterministic sensitivity analysis (DSA) was done to test the robustness of the model and to delineate the impact of individual model parameters on the overall outcome. A probabilistic analysis was performed using a Monte Carlo simulation of 10,000 replications to determine the cost-effectiveness of vaccinating at birth at a willingness-to-pay (WTP) threshold of $50,000 per QALY. To assess the clinical effects of the two vaccination strategies, a microsimulation in TreeAge Pro Healthcare 2020 was performed to assess the differences in the incidence of liver outcomes such as AHB, CHB, CC, DC, HCC, LT, and LD.

viii. Model Validation

The model was validated by comparing the model-produced risk of developing HCC and the proportion of liver-related mortality due to HCC to real-world evidence of HBV infected patients.[49-51]

RESULTS

i. Model Validation

Previous studies have shown that the risk of HBV carriers to develop HCC ranges from 15% to 40%.[49,50] To ensure the validity of our model, we performed a microsimulation of 10,000 trials and found the risk of developing HCC in our model to be 32.8% which falls within the range observed in the literature. Furthermore, a European review of the burden of liver disease indicated that about 46% of liver-related deaths could be attributed to liver cancer.[51] Similarly, our model projected that 50.6% of liver-relates deaths were from HCC, further validating our model.

ii. Base Case Analysis

In the base case analysis, universal hepatitis B vaccination at birth was compared to vaccination during adolescence by performing a PSA of 10,000 iterations (Table 5). Vaccination at birth had a mean cost of $317,261 while the mean cost during adolescence was $317,735, resulting in a mean difference of –$474. Considering the effectiveness of the two strategies, vaccination at birth had a mean effectiveness of 43.36 QALYs compared to 43.18 QALYs for adolescents, resulting in a mean difference of 0.18 QALY. As such, the base case analysis concluded that universal hepatitis B vaccination at birth dominated vaccination during adolescence.

Table 5: Base-case analysis

Vaccination Strategy	Cost ($)	ΔCost ($)	QALY	ΔQALY	ICER	Cost-Effective	Cost-Saving
Adolescent Vaccination	317,735	–	43.18	–	–	–	–
Birth Vaccination	317,261	–474	43.36	0.18	Dominant	100%	79.39%

The base case analysis is performed using 10,000 iterations of probabilistic sensitivity analysis. Cost-effectiveness was assessed at willingness-to-pay threshold of $50,000 per QALY. All costs are adjusted to 2021 Canadian dollars.

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; –, not applicable

A microsimulation of 10,000 iterations indicated that hepatitis B vaccination at birth leads to reductions in CHB and other liver-related outcomes. Compared to the status quo, birth vaccination led to decreases in cases by 15.96% in AHB, 44.27% in CHB, 47.45% in CC, 47.54% in HCC, 56.44% in DC, 50.00% in LT, and 51.16% in LD. A full list of projections on the clinical impact of birth vaccination is summarized in Table 6.

Table 6: Comparison of health events between vaccination strategies

Health Event	% Change, if Birth Vaccination Implemented
Acute Hepatitis B	–15.96%
Immune Tolerant	–42.14%
Natural Immunity	–13.00%
Total CHB	–44.27%
HBeAg+ CHB	–43.08%
HBeAg– CHB	–49.15%
Inactive CHB	–45.08%
Total CC	–47.45%
HBeAg+ CC	–49.09%

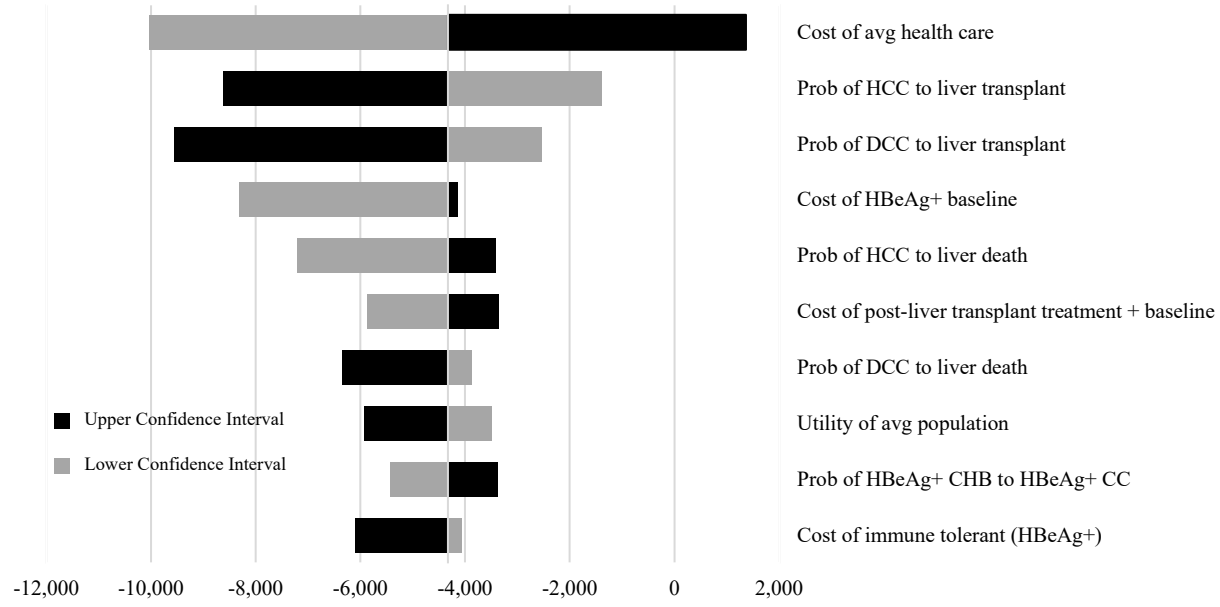
HBeAg– CC	–48.28%
Inactive CC	–43.96%
Hepatocellular Carcinoma	–47.54%
Decompensated Cirrhosis	–56.44%
Liver Transplant	–50.00%
Liver-Related Death	–51.16%

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; CC, compensated cirrhosis

iii. Sensitivity Analyses

To assess for the impact of individual model parameter on the outcome of the study, a DSA was performed and the results of the ten most sensitive parameters are summarized as a tornado diagram in Figure 2. Of the ten parameters, five were transition probabilities, four were cost parameters, and one was a utility parameter. Cost of baseline healthcare was the most sensitive parameter.

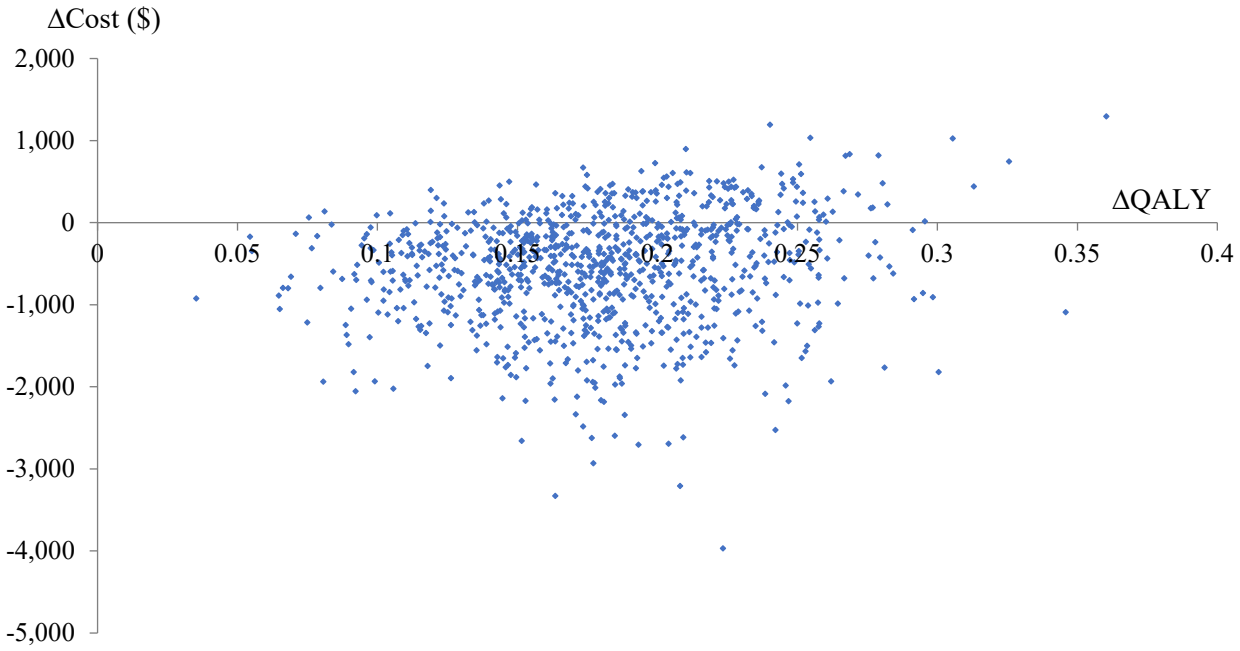
Figure 2: Tornado diagram of deterministic sensitivity analysis



Abbreviations: Pr, probability; HCC, hepatocellular carcinoma; LT, liver transplant; DCC, decompensated cirrhosis; LD, liver death; HBeAg+ CHB, hepatitis B e antigen positive chronic hepatitis B; PLT, post-liver transplant; IT, immune tolerant; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

A cost-effectiveness scatterplot of 10,000 iterations of a probabilistic analysis is shown in Figure 3. The probabilistic analysis results indicated that a universal birth vaccination strategy would be cost-effective at a WTP threshold of $50,000 per QALY in 100% of the model iterations and cost-saving in 79.39% of the iterations (Table 5).

Figure 3: Incremental cost-effectiveness scatterplot of vaccination at birth versus adolescence



10,000 replications were performed in the probabilistic analysis and 1,000 outcomes were randomly generated and plotted in a scatterplot to visually represent the likelihood of vaccination at birth being cost-effective compared to vaccination at adolescence. Each dot represents an iteration of the analysis and those that fall within the bottom-right quadrant are cost-saving

iv. Scenario Analysis

In the base case analysis, it was assumed that the vaccine coverage rate between the two intervention arms would be identical based on the current coverage rate amongst adolescents in Ontario, Canada. A scenario analysis was performed to assess impact of changing vaccine coverage rate for the birth vaccination strategy. When a coverage rate of 84% was used, as per the infant vaccination rate in British Columbia, the birth vaccination strategy remained 100% cost-effective and cost-saving in 81.37% of the iterations (Table 7). Even when the birth vaccine coverage rate was reduced to 50%, it remained cost-saving compared to the adolescent vaccination strategy.

Table 7: Scenario analysis of varying vaccine coverage rate

Vaccine Coverage Rate	Vaccination Strategy	Cost ($)	ΔCost ($)	QALY	ΔQALY	Cost-Effective[c]	Cost-Saving
69.2%	Adolescent Vaccination	317,735	–	43.18	–	–	–
50%	Birth Vaccination	317,502	–233	43.29	0.11	100%	72.68%
69.2%	Adolescent Vaccination	317,735	–	43.18	–	–	–
69.2%[a]	Birth Vaccination	317,261	–474	43.36	0.18	100%	79.39%
69.2%	Adolescent Vaccination	317,735	–	43.18	–	–	–
84%[b]	Birth Vaccination	317,074	–661	43.41	0.23	100%	81.37%

[a]Base case analysis; 69.2% based on the current hepatitis B vaccine coverage rate in Ontario
[b]84% based on vaccine coverage rate from British Columbia where a birth vaccination strategy is implemented[99]
[c]Cost-effective at a willingness-to-pay threshold of $50,000 per QALY

DISCUSSION

The results of the study indicate that a universal hepatitis B vaccination program at birth is cost-saving compared to the status quo of vaccination during adolescence. More importantly, from a clinical perspective, the birth vaccination strategy was projected to lead to reductions in cases of

CHB and other liver-related outcomes. Such reductions are important because, when consider the fact that over 90% of AHB cases in children under the age of 5 years are asymptomatic,[17] many infected children may progress to chronic disease without awareness until they develop advanced liver disease such as HCC or DC at which point the prognosis remains poor.[52] As such, it is important to minimize the risk of infection in this population in order to reduce the incidence of chronic infection and end-stage liver diseases.

As reported in a recent study by Biondi *et al.*, the current vaccination strategy in Ontario has a number of issues that may potentially leave Ontarians at an unnecessary risk of developing acute and/or chronic hepatitis B infection.[9] First, the current adolescent vaccination strategy relies on screening and treating infants born to mothers with hepatitis B infection. However, as illustrated by Biondi *et al.*, the current routine screening process has failed to screen over 7% of pregnancies in Ontario between 2012 and 2016, creating missed opportunities in providing early and effective treatment measures for newborns. Second, while a child may be born without hepatitis B infection, there is a risk of horizontal transmission before vaccination during adolescence. While the risk of horizontal transmission in young children may be low, the probability of progressing to a chronic infection in infants and young children is disproportionately higher making early vaccination an important, necessary and achievable intervention.[6]

From an implementation perspective, changing from an adolescent to birth vaccination schedule may be challenged by the fact that infants born in Canada currently follow a relatively complex and crowded vaccination schedule.[29] While a hexavalent vaccine containing hepatitis B, diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, and *Haemophilus influenzae* type B is currently licensed in Canada for pediatric use, it is used in children over the age of 6 weeks.[53] As such, a separate monovalent hepatitis B vaccine would need to be given at birth and possibly

finish the series through the hexavalent vaccine, or a three-dose monovalent hepatitis B series in addition to a pentavalent vaccine series may be needed, both of which increase the number of injections an infant may receive, further complicating an already-complex vaccination schedule.

While the current study was aimed at assessing the cost-effectiveness of a birth hepatitis B vaccination strategy in Ontario, clinicians and policy makers in all Canadian provinces and territories may benefit from assessing their current hepatitis B vaccination schedules. Considering the possibility of families with infants and young children moving between provinces, it is possible for a child to be neglected of a potentially life saving hepatitis B vaccine. For instance, if a child born in a province providing hepatitis B vaccination during adolescence relocates to a province that provides vaccination at birth, they may not receive the vaccine and be at a higher risk of developing the disease. Hence, this provides an additional layer of the importance of not only a provincial but a national strategy on providing universal hepatitis B vaccination at birth.

A number of limitations exist in the study. First, a static approach to vaccination was applied in the model. It was assumed that, in the newborn and adolescent arms of the model, subjects will be vaccinated at a particular coverage rate exclusively at ages 0 and 12 years, respectively. However, in practice, although the proportions are unknown, some patients receive hepatitis B vaccination outside the recommended timeframe. Therefore, such static approach to the vaccination rate may not accurately reflect real-world practices and potentially have an impact on the magnitude of the economic or clinical benefits seen with birth vaccination. Second, the model assumed that hepatitis B vaccine would provide consistent and life-long protection. Meaning, the effects of the vaccine will not wane over time. Although recent studies appear to suggest that hepatitis B vaccines may provide long-term protection against the virus,[36] a level of

uncertainty regarding the true duration and level of protection remains. As such, a scenario analysis considering different levels of vaccine waning effect may provide a more robust conclusion.

CONCLUSION

The study concluded that hepatitis B vaccination at birth may be cost-saving compared to vaccination during adolescence in Ontario, Canada. In addition, the birth vaccination strategy was projected to lead to clinical benefits through the reductions in cases of AHB, CHB, CC, HCC, DC, LT, and LD. The study outcomes are in alignment with recommendations from CASL, CDC and WHO, and provide an actionable change to consider for policy makers.

CHAPTER 3

Model-Based Estimation of the Prevalence of CHB and Proportion of Undiagnosed CHB Cases in Canada Between 2011 and 2017

INTRODUCTION

For diseases that are difficult to diagnose due to a lack of overt presentation, one of the most fundamental and effective epidemiological strategies in disease-control is screening. Disease screening can be especially effective and useful in the case of hepatitis B because clinicians know exactly what biomarker to test for in order to diagnose hepatitis B reliably and also because screening and identifying HBV-positive patients early on can allow clinicians and patients to implement appropriate interventions to delay progression to end-stage liver disease as CHB is associated with 25% chance of death from cirrhosis of HCC if left undiagnosed or without appropriate treatment.[28] On a population level, early detection of disease may lead to reductions in end-stage liver diseases and HBV-related deaths while potentially being a cost-effective measure for the government. However, despite understanding the potential benefits of disease screening, it is difficult to make the decision to implement a nation-wide, or even a province-wide, screening strategy with a broad eligibility criteria without fully understand the true prevalence of the disease and its impact. Most notably, a publicly funded screening program capturing a large proportion of the population will add a significant financial burden on the system. As such, it is difficult to rationalize broadening the current screening program without a sound scientific justification to show that the current program may be leading to high rates of patients being undiagnosed. Otherwise, it does not make clinical and financial sense to invest additional funds only to get minimal returns. As such, it is critically important to understand the true prevalence of

CHB and the proportion of undiagnosed cases in order to assess the feasibility and necessity of such a program.

A recent Canadian modelling study estimated that 27.1% of the chronic hepatitis C infected population in Canada remains undiagnosed, leaving a large gap in missed opportunity for early care.[22] Considering the similar natural history of hepatitis B and C, where patients are often asymptomatic until they reach end-stage liver disease, it is reasonable to question whether a significant proportion of CHB patients also remain undiagnosed in Canada. In fact, a national seroprevalence study by Statistics Canada found that 54.5% of those with HBV infection were not aware of their infection.[20] Unfortunately, there are currently no widely accepted estimate on the true prevalence of CHB in Canada. This gap in knowledge is critical in not only understanding the true burden of CHB in Canada but also in informing public health officials to take an evidence-based approach in re-assessing public health programs for hepatitis B.

In the US, studies have estimated the proportion of undiagnosed CHB population in several ways. A recent study by Ogawa *et al.* used a large national claims database of over 100 million patients to compare the number of patients with CHB diagnoses and the number of patients who should have been diagnosed based on their HbsAg test result to estimate the true prevalence of the disease and found only 18.6% of privately insured patients with CHB were diagnosed.[23] Another study by Moore *et al*. used a surveillance-based approach to estimate the prevalence of CHB in New York City by utilizing data from routine surveillance over a 16-year period and incorporated an estimation of the number of undiagnosed persons based on a modelling study to estimate the true prevalence of the disease.[24] They also found that a large proportion of patients remain undiagnosed with the diagnosed CHB prevalence being 1.5% while the prevalence for both diagnosed and undiagnosed patients was estimated to be 2.7%.[24] Lastly, multiple studies have also

used cross-sectional community-based hepatitis B screening process to estimate the prevalence of CHB.[25-28]

As mentioned in Chapter 1, the only estimate on the prevalence of CHB in Canada is from a seroprevalence study by Statistics Canada.[20] For diseases like CHB that are often asymptomatic and remain undiagnosed, a back-calculation based modelling approach has frequently been used in the literature to estimate the true prevalence of a disease. Such method has successfully been implemented in several disease states like CHC and HIV.[22,100] In this chapter, a similar back-calculation method was implemented to estimate the prevalence of diagnosed and undiagnosed CHB in Canada.

METHODOLOGY

i. Study Design

A back-calculation based model framework was developed to estimate the prevalence of diagnosed and undiagnosed CHB cases in Canada between 2011 and 2017. The back-calculation approach used in this study has been successfully implemented in several studies in the past like chronic hepatitis C and HIV.[22,100] In essence, back-calculation is a technique that uses known outcome values to infer the unknown values that would have led to the known outcomes. Back-calculation approach is often used when the unknown values are unobservable. In this model, the known outcomes values were the observed number of cases of CHB and HCC from PHAC and Statistics Canada while the inferred unknown values were the historical prevalence of CHB that consists of both diagnosed and undiagnosed cases. The inference was done through a calibration method based on the Bayesian Markov Chain Monte Carlo Metropolis-Hastings (MCMC-MH)

algorithm. Through a process of repeated sampling of five million iterations, the algorithm calibrated the model generated outcomes against the known outcome values (observed number of CHB and HCC cases) to generate a probability distribution of the historical prevalence of CHB. A detailed mathematical description of the method is presented in the appendix. The model focused on three birth cohorts: patients born before 1938, patients born between 1938 and 1967, and patients born after 1967. The three birth cohorts were chosen based on seroprevalence data from a Statistics Canada study by Rotermann *et al*. which showed that there was higher seroprevalence for HBV among the 50- to 79-year-old age group.[20] Using 2017 as the base year, the age of the birth cohorts to be used in the prevalence model then correspond to ≤49 years, 50 to 79 years, and ≥80 years. 2017 was chosen as the base year as it is the most recent year with comprehensive hepatitis B-related data available from Statistics Canada and PHAC.

ii. Model Input Data

Model input data were gathered mainly from the literature and public databases. Most of the transition probabilities used were identical to the values used in the vaccination model in Chapter 2 (Table 2). Likelihood data for model calibration were obtained from public databases: the number of reported cases of hepatitis B from PHAC, the Canadian population size from Statistics Canada, and the number of HCC cases from Statistics Canada.[54-56] HCC cases from Statistics Canada were reported as the total cases from any cause and thus, the data was adjusted to reflect HCC caused by hepatitis B. It is estimated that approximately 9% of primary liver cancers are caused by hepatitis B.[57] As such, HCC values from Statistics Canada were multiplied by 9% to estimate the number of HCC cases caused by hepatitis B. Relevant datapoints were obtained and adjusted for years 1992 to 2017; however, only data for years 2011 to 2017 were implemented

in the model because these were the years with the most accurate data (Table 8). Of note, the reported cases of hepatitis B from PHAC does not distinguish acute and chronic hepatitis B cases.

Table 8: Diagnosis data for prevalence model calibration

Year	Birth Year ≥ 1968			1938 ≤ Birth Year ≤ 1967			Birth Year ≤ 1937		
	HCC[56,57]	HepB[54]	Population[55]	HCC[56,57]	HepB[54]	Population[55]	HCC[56,57]	HepB[54]	Population[55]
1992	≤5	449	9,867,028	11	1,330	12,778,419	49	174	5,627,114
1993	≤5	435	10,371,025	11	1,136	12,746,765	52	161	5,464,560
1994	≤5	441	10,841,479	13	1,076	12,754,303	58	155	5,299,150
1995	≤5	413	11,272,581	16	880	12,797,943	56	107	5,123,127
1996	≤5	388	11,717,853	17	735	12,840,623	56	99	4,939,927
1997	≤5	357	12,142,793	23	591	12,904,468	57	70	4,743,663
1998	≤5	314	12,609,983	23	557	12,852,209	59	67	4,573,906
1999	≤5	273	13,042,822	25	473	12,834,027	57	54	4,400,882
2000	≤5	271	13,474,052	30	423	12,859,140	60	46	4,223,994
2001	≤5	205	13,941,472	39	349	12,899,809	61	41	4,179,621
2002	≤5	212	14,414,518	42	332	12,956,177	61	33	3,989,384
2003	≤5	241	14,911,850	42	298	12,901,335	60	48	3,830,843
2004	≤5	416	15,389,683	54	442	12,883,290	57	65	3,667,681
2005	≤5	697	15,849,042	62	662	12,897,264	63	90	3,497,447
2006	≤5	817	16,325,577	70	639	12,914,783	61	99	3,330,814
2007	≤5	1,559	16,828,672	81	1,238	12,923,613	61	163	3,136,740
2008	≤5	1,864	17,421,853	83	1,443	12,840,506	61	172	2,984,759
2009	≤5	1,938	18,003,477	94	1,385	12,795,460	56	154	2,829,958
2010	6	1,891	18,557,778	99	1,265	12,776,234	60	152	2,670,876
2011	≤5	3,369	19,093,076	125	1,996	12,745,288	64	212	2,500,964
2012	≤5	3,429	19,673,366	140	2,011	12,724,543	64	232	2,316,313
2013	8	3,371	20,288,292	151	2,087	12,618,784	64	248	2,175,878
2014	8	3,211	20,868,392	164	1,841	12,537,885	54	206	2,031,157
2015	9	3,113	21,361,116	184	1,674	12,470,086	57	170	1,871,707
2016	12	3,302	21,988,721	175	1,656	12,403,606	48	156	1,717,159
2017	11	3,188	22,660,628	176	1,567	12,336,713	40	138	1,547,954

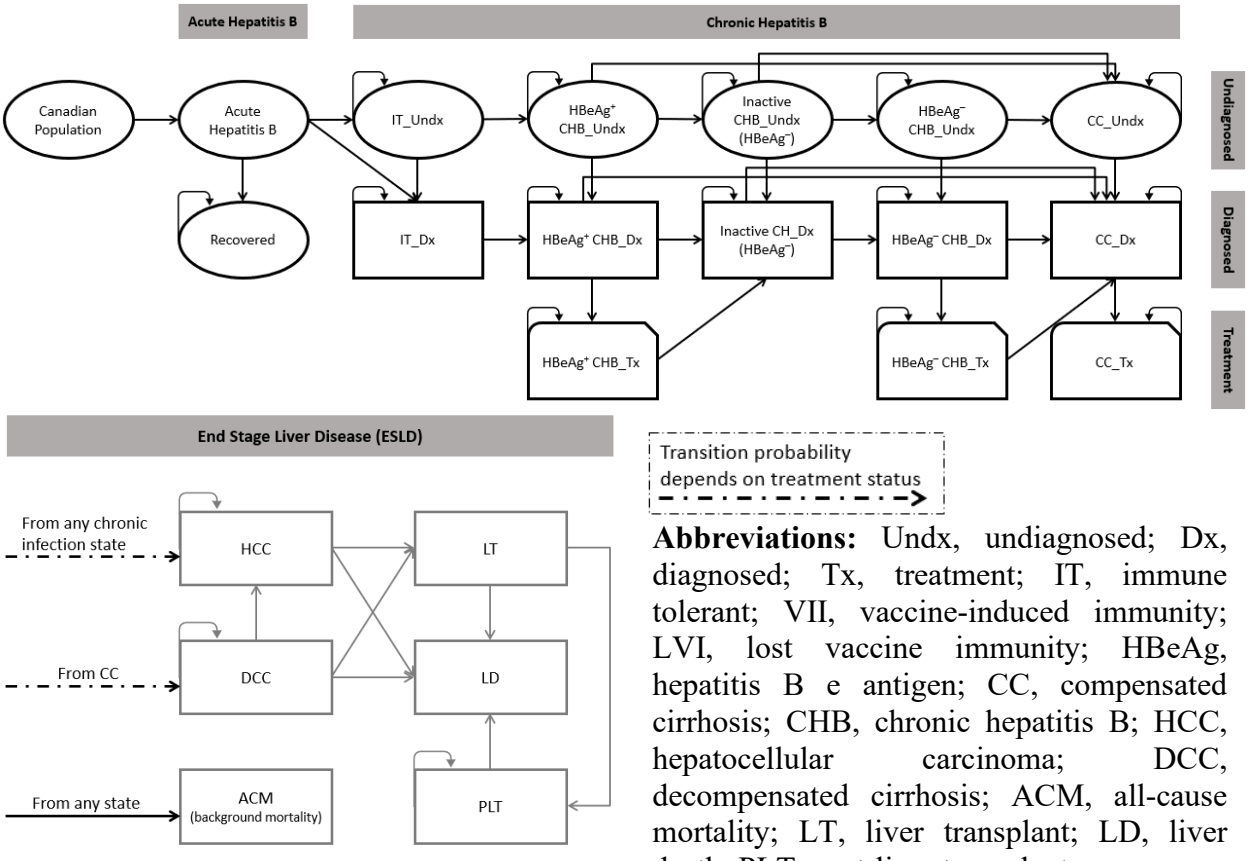
HCC values are adjusted to reflect cases caused by hepatitis B

iii. Natural History Model of Hepatitis B

The prevalence model utilized parts of the hepatitis B natural progression model that was developed as part of the cost-effectiveness model in Chapter 2 of the thesis. Specifically, a modified version of the CHB segment of the vaccination model was utilized in the prevalence model (Figure 4). This modified state-transition model describes the movement of CHB patients based on the same transition probabilities utilized in the vaccination model (Table 2). Broadly, the model can be categorized into three groups: AHB, CHB, and end-stage liver disease (ESLD). The model assumes that patients may be diagnosed in either acute or chronic stages of the disease.

Newly infected patients are assumed to have an opportunity to clear the infection and develop natural immunity in the acute phase of the disease. If the virus is not cleared, the disease is assumed to progress to the chronic phase. Individuals who have CHB but are undiagnosed were grouped into X_0 (IT), X_1 (HBeAg+ CHB), X_2 (inactive CHB), X_3 (HBeAg- CHB), and X_4 (CC). Those who have diagnosed CHB but not receiving treatment were grouped into D_0 (IT), D_1 (HBeAg+ CHB), D_2 (inactive CHB), D_3 (HBeAg- CHB), and D_4 (CC). Those in HBeAg+ CHB, HBeAg- CHB, and CC states receiving treatment were categorized into T_1, T_3, and T_4, respectively. From any stage of the disease, patients could advance to ESLD: HCC, DCC, LT, PLT, and LD. A detailed illustration of the model is shown in the appendix Figure A1 and a more simplified, illustrative version of the same model is shown in Figure 4.

Figure 4: Modified state-transition model of hepatitis B disease progression for prevalence estimation



Abbreviations: Undx, undiagnosed; Dx, diagnosed; Tx, treatment; IT, immune tolerant; VII, vaccine-induced immunity; LVI, lost vaccine immunity; HBeAg, hepatitis B e antigen; CC, compensated cirrhosis; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; DCC, decompensated cirrhosis; ACM, all-cause mortality; LT, liver transplant; LD, liver death; PLT, post-liver transplant

iv. Outcomes of Measure

The study measured four main outcomes. First, model-estimated values for the number of HCC and CHB diagnoses were plotted. The model-generated plots were overlayed with the time-series data obtained from PHAC and Statistics Canada to assess whether the model estimates fall within the real-world data points. Then, model-estimated values of CHB prevalence and the percentage of undiagnosed CHB were plotted in time-series for the three birth cohorts as well as the combined overall population group.

v. Sensitivity Analysis

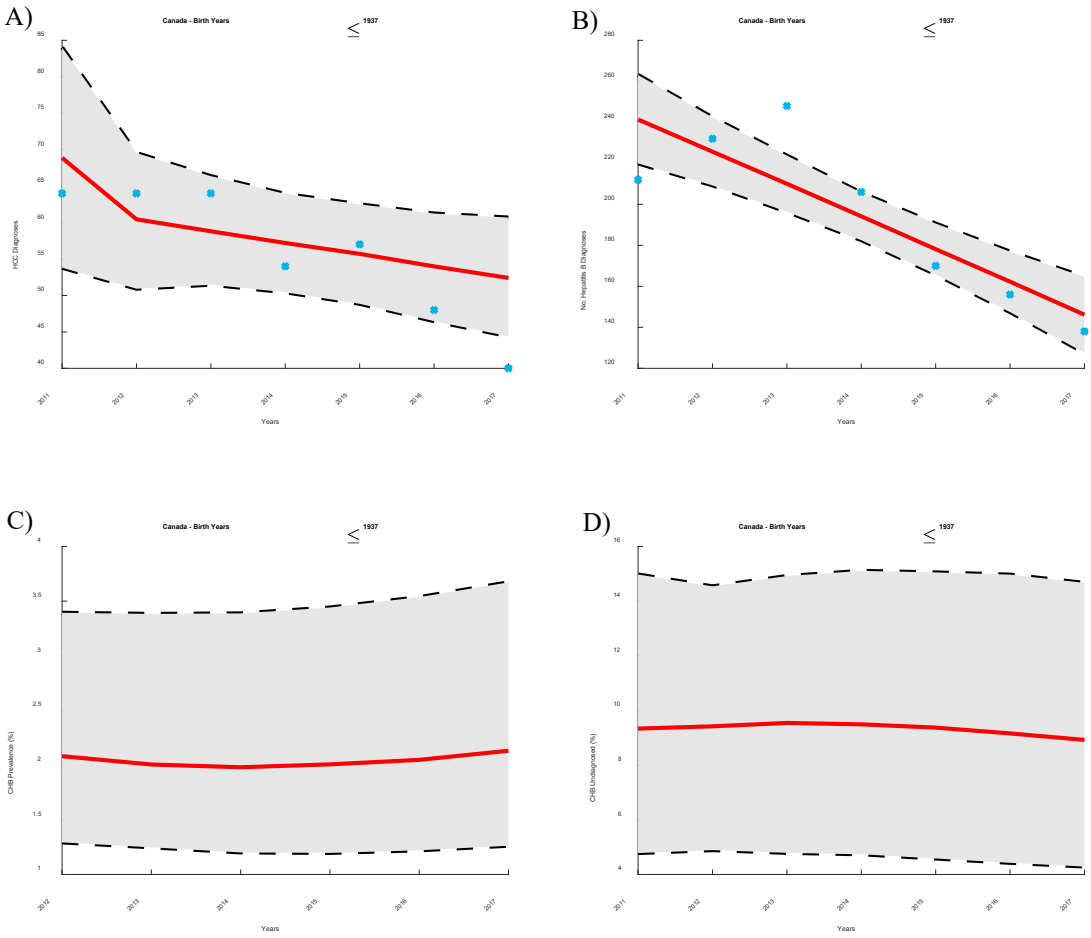
A deterministic sensitivity analysis (DSA) was performed in order to identify the variables that have the greatest impact on the outcomes. DSA was performed for both the prevalence and undiagnosed proportion outcomes in the combined cohort.

RESULTS

i. Birth years ≤ 1937

For the oldest age cohort of birth years ≤ 1937, Figures 5A and 5B show the numbers of HCC and hepatitis B diagnoses, respectively, from 2011 to 2017. The figures show the publicly reported data from PHAC and Statistics Canada in blue and model generated estimates are shown in red. The model generated estimates fit the reported HCC diagnosis data with $R^2 = 0.60$ and hepatitis B diagnosis data with $R^2 = 0.73$. Figure 5C shows the model generated estimate of CHB prevalence rate in 2017 as 2.13% (95% CI: 1.26% – 3.67%) and Figure 6D shows the estimated proportion of undiagnosed CHB cases in 2017 as 8.92% (95% CI: 4.29% – 14.67%).

Figure 5: Model estimates for patients born ≤ 1937



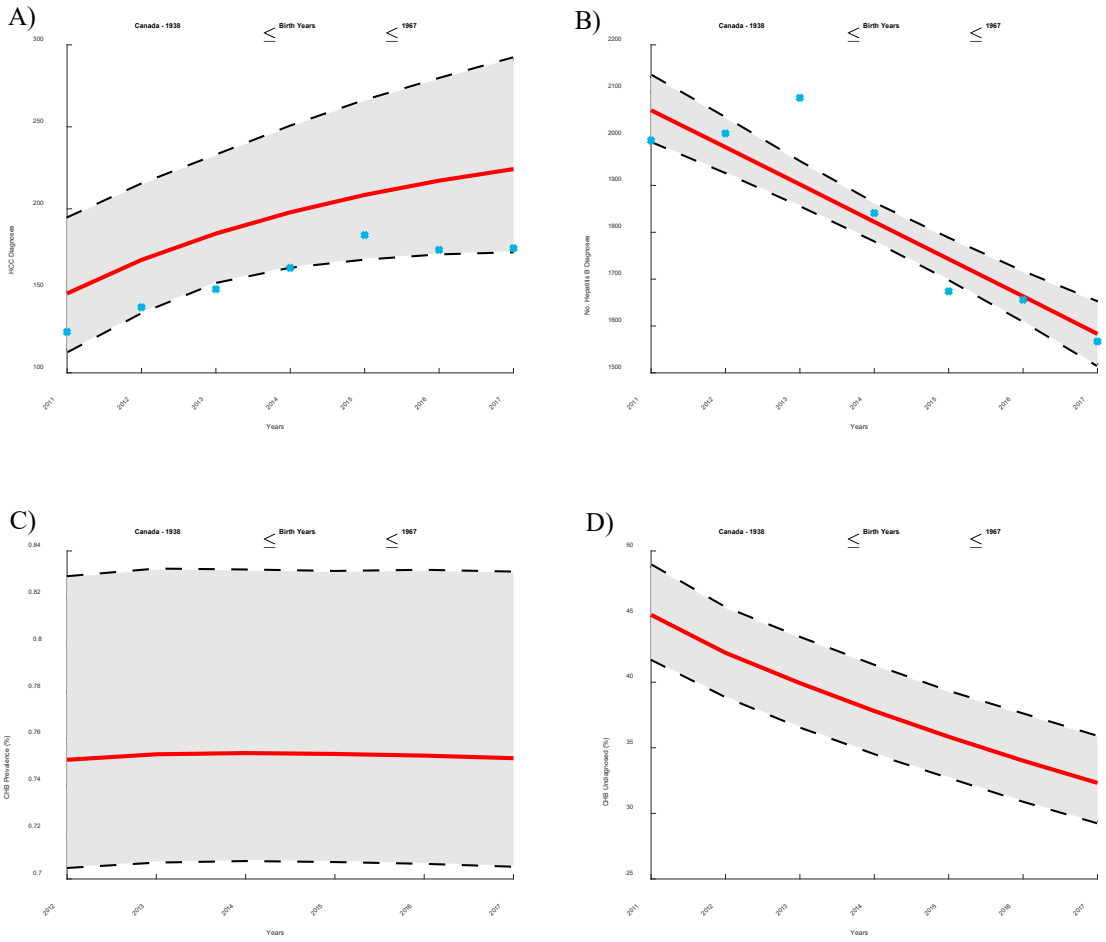
A) Model generated estimates for HCC diagnoses (red line) and Statistics Canada reported HCC diagnoses (blue dots); B) Model generates estimated for hepatitis B diagnoses (red line) and PHAC reported hepatitis B diagnoses (blue dots); C) Model generated estimates for CHB prevalence; D) Model generated estimates for the proportion of undiagnosed CHB cases

ii. Birth years between 1938 and 1967

For the cohort with birth years between 1938 and 1967, Figures 6A and 6B show the numbers of HCC and hepatitis B diagnoses, respectively, from 2011 to 2017. The model generated estimates fit the reported HCC diagnosis data with $R^2 = 0.92$ and hepatitis B diagnosis data with $R^2 = 0.83$. Figure 7C shows the model generated estimate of CHB prevalence rate in 2017 as 0.75%

(95% CI: 0.71% – 0.83%) and Figure 7D shows the estimated proportion of undiagnosed CHB cases in 2017 as 32.32% (95% CI: 29.32% – 35.83%).

Figure 6: Model estimates for patients born between 1938 and 1967

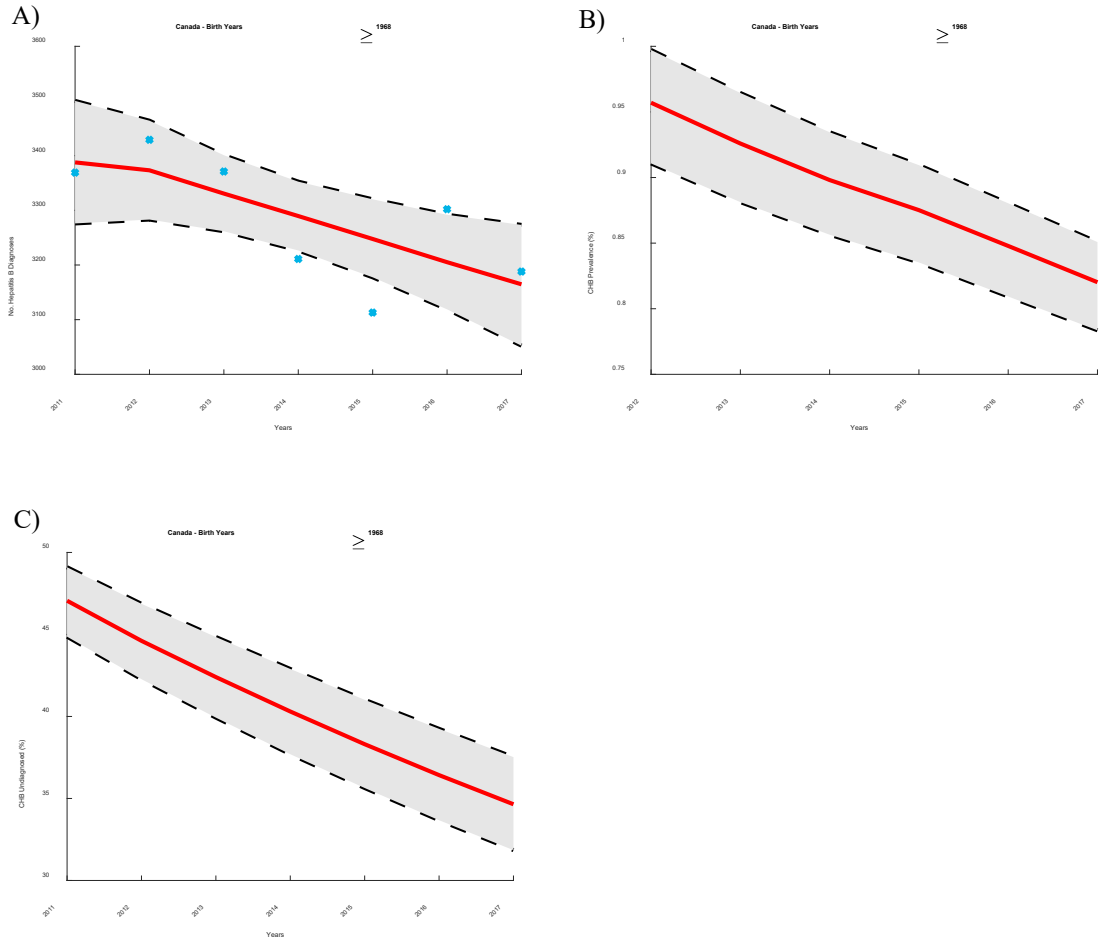


A) Model generated estimates for HCC diagnoses (red line) and Statistics Canada reported HCC diagnoses (blue dots); B) Model generates estimated for hepatitis B diagnoses (red line) and PHAC reported hepatitis B diagnoses (blue dots); C) Model generated estimates for CHB prevalence; D) Model generated estimates for the proportion of undiagnosed CHB cases

iii. Birth years ≥ 1968

For the youngest cohort of birth years ≥ 1968, Figure 7A shows the number of hepatitis B diagnoses from 2011 to 2017. The model generated estimates fit the reported hepatitis B diagnosis data with R^2 = 0.51. Figure 8C shows the model generated estimate of CHB prevalence rate in 2017 as 0.82% (95% CI: 0.78% – 0.85%) and Figure 8D shows the estimated proportion of undiagnosed CHB cases in 2017 as 34.65% (95% CI: 31.85% – 37.52%). For the youngest cohort, HCC diagnoses were not generated by the model due to near-zero observed cases in this age cohort because HCC is often diagnosed in the latter stages of life. As such, model calibration for this age cohort was primarily done against the CHB data only.

Figure 7: Model estimates for patients born after 1968

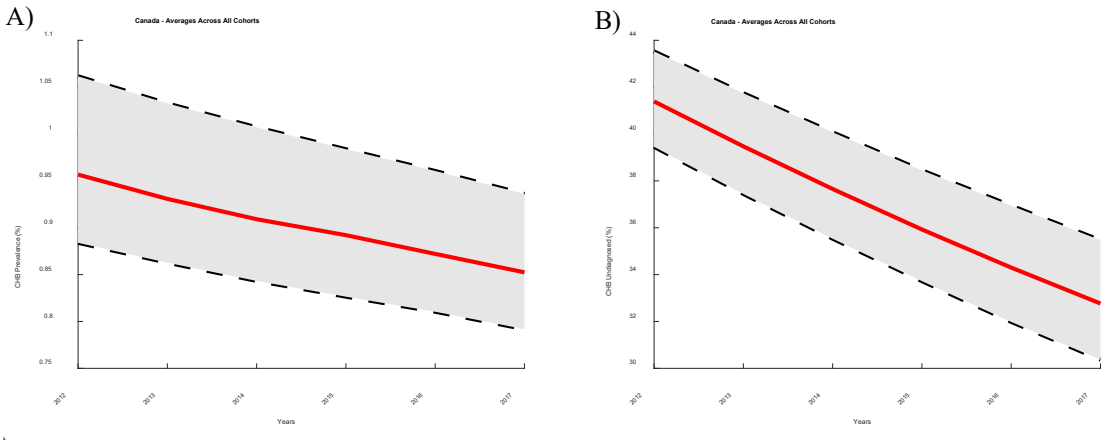


A) Model generated estimated for hepatitis B diagnoses (red line) and PHAC reported hepatitis B diagnoses (blue dots); B) Model generated estimates for CHB prevalence; C) Model generated estimates for the proportion of undiagnosed CHB cases

iv. Combined cohort

Overall, when all age cohorts were combined, Figure 8A shows the model generated estimates of CHB prevalence rate in 2017 as 0.85% (95% CI: 0.79% – 0.94%) and Figure 8B shows the estimated proportion of undiagnosed CHB cases in 2017 as 32.77% (95% CI: 30.37% – 35.47%).

Figure 8: Model estimates for all age cohorts combined



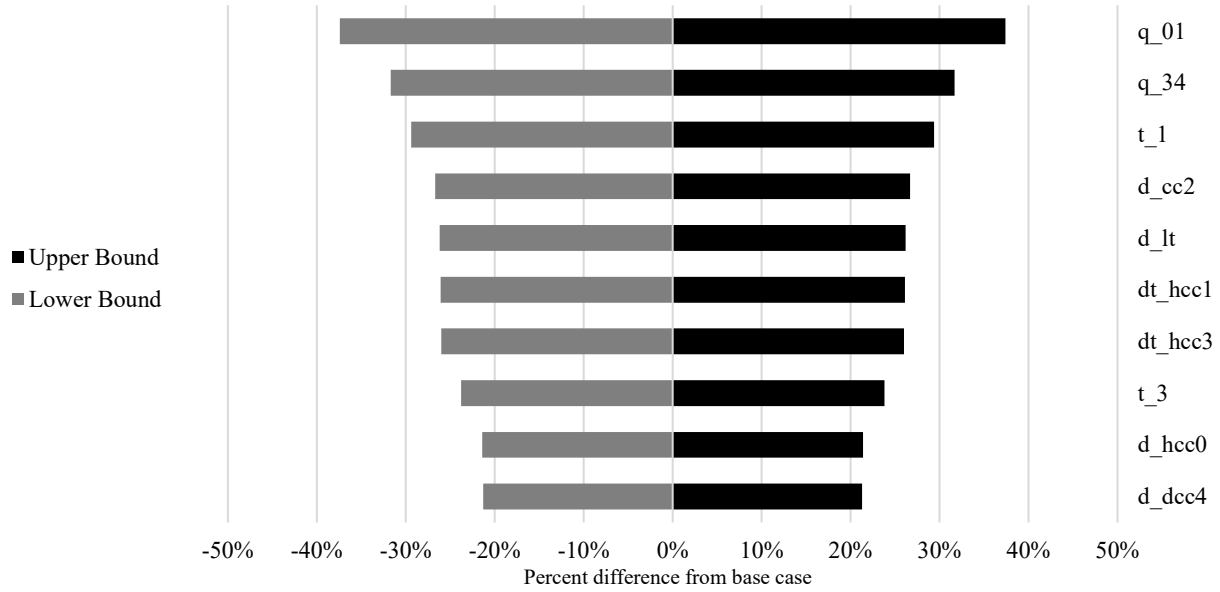
A) Model generated estimates for CHB prevalence; B) Model generates estimated for the proportion of undiagnosed CHB cases

v. Sensitivity analysis

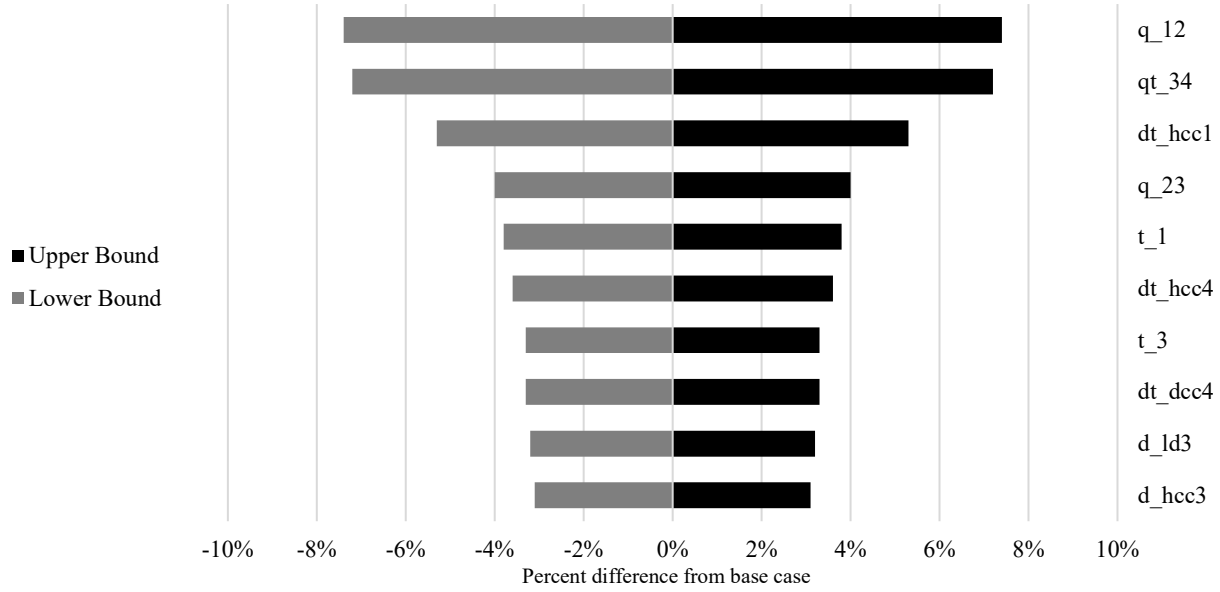
DSA identified the ten most sensitive parameters for both the prevalence and undiagnosed proportion outcomes in the combined cohort. For the prevalence outcome, q_01 (annual probability that an undiagnosed individual in X_0/D_1 (IT) will progress to X_0/D_1 (CHB+)) was the most sensitive parameter. For the undiagnosed proportion outcome, q_12 (annual probability that an undiagnosed individual in X_1/D_1 (CHB+) will progress to X_2/D_2 (inactive CHB)) was the most sensitive parameter. The results are summarized as tornado diagrams in Figure 9.

Figure 9: Deterministic sensitivity analysis

A) Prevalence



B) Undiagnosed Proportion



Abbreviations: q_01, annual probability that an undiagnosed individual in X_0/D_0 (IT) will progress to X_1/D_1 (+CHB); q_34, annual probability that an undiagnosed individual in X_3/D_3 (+CHB) will progress to X_4/D_4 (Inactive CHB); t_1, annual probability of treatment for individuals in D_1 (+CHB); d_cc2, annual probability of progression to X_4/D_4 (CC) from stages X_2/D_2 (Inactive CHB); d_lt, annual probability of LT for individuals with HCC; dt_hcc1, annual probability of progression to HCC from T_1 (+CHB); dt_hcc3, annual probability of progression to HCC from T_3 (-CHB); t_3, annual probability of treatment for

individuals in D_3 (-CHB); d_hcc0, annual probability of progression to HCC from x_0/D_0 (IT); d_dcc4, annual probability of progression to DCC from x_4/D_4 (CC); q_12, annual probability that an undiagnosed individual in X_1/D_1 (+CHB) will progress to X_2/D_2 (Inactive CHB); qt_34, annual probability that a treated individual in T_3 (-CHB) will transit to D_4 (CC); q_23, annual probability that an undiagnosed individual in X_2/D_2 (Inactive CHB) will progress to X_3/D_3 (-CHB); dt_hcc4, annual probability of progression to HCC from T_4 (CC); dt_dcc4, annual probability of progression to DCC from T_4 (CC); d_ld3, annual probability of LD for individuals in LT; d_hcc3, annual probability of progression to HCC from x_3/D_3 (-CHB)

DISCUSSION

The results of this study show that although the prevalence of CHB and the proportion of undiagnosed patients appear to be trending downwards, a large proportion of CHB patients remain undiagnosed. In the oldest cohort of patients born ≤ 1937, although the number of HCC and hepatitis B diagnoses appear to be decreasing, the prevalence and the undiagnosed proportion remain relatively unchanged from 2011 to 2017. The decreasing absolute number of cases in this age cohort is likely related to the overall decreasing population from both liver-related and all-cause mortality. In both the birth cohorts between 1938 and 1967 and ≥ 1968, the proportion of undiagnosed CHB appears to also be trending downwards consistently. Overall, when combining all age groups, both the CHB prevalence and undiagnosed proportions appear to be decreasing, with an estimated CHB prevalence of 0.85% and undiagnosed proportion of 32.77% in 2017. Notably, there were significant differences in the proportion of undiagnosed cases in the older cohort versus the younger cohorts. In the oldest cohort, it was estimated that only 8.92% of cases remain undiagnosed whereas in the two younger cohorts, 32.32% (birth years between 1938 and 1967) and 34.65% (birth years ≥ 1968) of cases were estimated to be undiagnosed. This suggests that a lot more of the younger CHB patients are not being identified which aligns with the known characteristics of CHB where it is largely a silent disease until the disease progresses to more severe and overt stages later on in life. Considering that disease progression and severity of disease

can be well-controlled with earlier treatment, this finding of significantly higher proportion of undiagnosed cases in the younger cohorts suggests that with a broader screening strategy in the younger population, it may be feasible to identify a large number of patients earlier on in their disease and initiate drug therapy to better control their disease progression.

In Canada, the most recent and relevant study looking at the prevalence of CHB is the seroprevalence study performed by Statistics Canada and PHAC.[20] As noted in Chapter 1, the authors of the study gathered data from 14 – 79 years old population from 2007 to 2011 through household questionnaires and blood sample collection.[20] The authors concluded that the seroprevalence of present HBV infection in this population was 0.4%.[20] Although the timeframe differed between the seroprevalence study and our model-based approach, when comparing similar age groups of <49 years old and 50 – 79 years old populations, our approach estimated the prevalence to be 0.82% and 0.75%, respectively. Meaning, our study estimates the CHB prevalence to be approximately twice as high compared to the seroprevalence study indicating that the issue of CHB on a population level may be far greater than previously estimated. Additionally, considering the fact that our model estimated that 32.77% of CHB cases remained undiagnosed in 2017, the true extent of the impact of CHB on Canadians is likely severely underestimated.

As noted in Chapter 1, CASL recommends a list of patient groups that should be screened for hepatitis B including, but not limited to, pregnant women, inmates, patients with chronic renal failure needing dialysis, those with signs of liver disease or other infectious diseases like hepatitis C, among others.[30] The current recommendations indicate screening of high-risk groups to reduce the risk of transmission of disease.[30] However, given that our study suggests a much higher CHB prevalence than previously estimated, almost a third of CHB cases may remain undiagnosed, and

Canada has endorsed WHO's strategy to eliminate viral hepatitis by 2030, a possible revision to the screening recommendations may be warranted to allow it to be more broad. Early screening is also recognized by PHAC in their report *"pan-Canadian Framework for Action: Reducing the Health Impact of Sexually Transmitted and Blood-Borne Infections in Canada by 2030"* to be a critical tool in reducing the risk of long-term effects of disease and prevent further transmission.[101]

Several limitations exist with the study. The current model is heavily dependent on publicly available databases from PHAC and Statistics Canada. While these databases provide a good source of country-level data, public databases are often subject to under-reporting, reporting bias, inconsistency in reporting practices between provinces and years, changes in disease definition and classification, among others. Thus, this creates an inherent limitation to the accuracy of the model generated data. Specifically, the HCC diagnosis numbers from Statistics Canada does not specify the cause of the cancer and so manual manipulation of the data was required to estimate hepatitis B-related HCC cases. Using a more accurate data on hepatitis B-related HCC as a calibration factor will allow for a more accurate estimation. Additionally, hepatitis B cases reported from PHAC does not differentiate between acute and chronic cases and there were some discrepancies in reporting practices between provinces.

CONCLUSION

The study provides a model-based approach to estimating the prevalence of CHB and the proportion of undiagnosed CHB cases in Canada by birth cohorts. The study concluded that in the overall population, both the prevalence of CHB and the undiagnosed proportion of CHB cases have decreased between 2011 and 2017, but the undiagnosed proportion remain high at an

estimated 32.77% in 2017. Considering the limitations of the model-based approach, the results should be interpreted in conjunction with other data when making policy decisions.

CHAPTER 4

SUMMARY OF RESULTS

In Chapter 2, we showed that hepatitis B vaccination at birth is a cost-saving alternative to the current practice of adolescent vaccination in Ontario – meaning, the new strategy provides more clinical benefits while costing less. The model was successfully validated against literature values for HCC risk and mortality risk. In the base case analysis, the PSA of 10,000 iterations resulted in a mean cost of $317,261 and 43.36 QALYs for newborn vaccination versus $317,735 and 43.18 QALYs for adolescent vaccination. A microsimulation showed that the birth vaccination program leads to decreases in liver-related cases by 15.96% in AHB, 44.27% in CHB, 47.45% in CC, 47.54% in HCC, 56.44% in DC, 50.00% in LT, and 51.16% in LD.

In Chapter 3, we showed that both the prevalence of CHB and the proportion of undiagnosed cases have trended downwards in the total population from 2011 to 2017. In the oldest age cohort of birth years $\leq$ 1937, CHB prevalence in 2017 was estimated to be 2.13% while prevalence was estimated to be 0.75% and 0.82% in birth years between 1938 and 1967 and birth years $\geq$ 1968, respectively. Proportion of undiagnosed cases was estimated to be much lower in the oldest cohort at only 8.92% while the proportions were 32.32% and 34.65% in the two younger cohorts. Overall, when all age cohorts were combined, CHB prevalence was estimated to be 0.85% and the undiagnosed proportion was estimated to be 32.77%.

THESIS CONTRIBUTION

The cost-effectiveness analysis assessing two hepatitis B vaccination scenarios has the potential to significantly impact policymaking on vaccination schedules in Ontario, Canada. As discussed in Chapter 1, the current hepatitis B vaccination schedule in Ontario is based on outdated evidence and does not align with national and global recommendations. Our data suggest that switching the vaccination timing from adolescence to birth will not only improve health outcomes, but also decrease costs for the government. In fact, CASL provides a strong recommendation that all provinces and territories should harmonize hepatitis B vaccination policy with universal, preferably neonatal or infant, vaccination and the results of our analysis supports the implementation of this recommendation.[30] Such cost-saving policy alternatives are rare and will provide decision-makers with a possibly attractive choice that will be beneficial for the general population. Additionally, considering the current global spotlight on vaccines in general, a cost-saving vaccination policy may be better received now than ever by many internal and external stakeholders.

The prevalence model is anticipated to make an important contribution to the hepatology field and policy making capacity in Canada. The lack of an established prevalence data in Canada makes it incredibly difficult to implement or modify any public health intervention with confidence as the true burden of disease, and therefore the need for an intervention, cannot be accurately assessed. Notably, better understanding the true prevalence of the disease can enable public health officials to determine whether a broad or a targeted hepatitis B screening program would be more appropriate in Canada. Our data indicating nearly doubled the previously estimated prevalence and a high proportion of undiagnosed cases will provide public health officials with additional data to

support their decision-making process, particularly when it comes to population-level interventions like screening programs.

FUTURE WORK

Several variations of model analysis and model adjustment could be of interest in the future. First, for both the cost-effectiveness and prevalence models, additional analyses with a more defined population may be warranted in the future. For example, both models can easily be adapted to provide province-specific data. This flexibility is particularly important in Canada where health care is largely administered on a provincial level but also important because hepatitis B prevalence varies by province, partly due to different patterns of immigration. As such, understanding the epidemiology on a more granular level will allow for targeted interventions on a provincial level. Second, analyses of special population would also be of great interest. For example, considering that Canada is home to a significant Asian immigrant population and there is higher prevalence of hepatitis B in Asian countries like China and South Korea, studies looking at the cost-effectiveness of vaccinating all immigrants or estimating the prevalence of CHB in those born in Canada versus foreign countries may provide additional insights to support decision makers in developing unique vaccination strategies like requiring vaccination from those immigrating from high hepatitis B prevalence countries. Third, conducting a cost-effectiveness analysis comparing the current hepatitis B screening strategy to a broader strategy in the younger population would also be beneficial. Such study would utilize data from the current prevalence study and would provide additional practical data to decision makers. Lastly, utilizing health administrative data will likely strengthen the estimates generated by the prevalence model. As mentioned previously, the prevalence model is currently heavily dependent on the input data from Statistics Canada and PHAC. However, both databases have several limitations and are likely not as accurate and

granular as health administrative databases like the ICES Data Repository. As such, incorporating data from health administrative database could improve the accuracy of the model-generated estimates.

REFERENCES

1. Dale C and Yim C. Viral hepatitis, acute. In: Compendium of Therapeutic Choices. Canadian Pharmacists Association. Updated May 24, 2018. Accessed April 4, 2021. https://myrxtx-ca.proxy.lib.uwaterloo.ca/search.
2. What is viral hepatitis? Centers for Disease Control and Prevention. Updated July 28, 2020. Accessed April 4, 2021. https://www.cdc.gov/hepatitis/abc/index.htm.
3. Hepatitis B – Get the Facts. Public Health Agency of Canada. Updated September 22, 2014. Accessed April 4, 2021. https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/hcai-iamss/bbp-pts/hepatitis/pdf/hepb-eng.pdf.
4. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560- 1599.
5. World Health Organization. (2017). Global hepatitis report 2017. World Health Organization. https://apps.who.int/iris/handle/10665/255016. License: CC BY-NC-SA 3.0 IGO
6. Hepatitis B. World Health Organization. Updated July 27, 2020. Accessed April 4, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.
7. Hepatitis B vaccine: Canadian immunization guide, Public Health Agency of Canada. Updated February 13, 2020. Accessed April 4, 2021. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-7-hepatitis-b-vaccine.html#a2.
8. Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int. 2009;3(3):425-433. Doi: 10.1007/s12072-009-9140-3.

9. Biondi MJ, Marchand-Austin A, Cronin K, *et al.* Prenatal hepatitis B screening, and hepatitis B burden among children, in Ontario: a description study. *Can Med Assoc J.* 2020;193:E1299-305. Doi: 10.1503/cmaj.200290.
10. Yuen MF, Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, et al. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:1-20. Doi: 10.1038/nrdp.2018.35.
11. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J. Hepatol. 67, 370–398 (2017).
12. Wen WH, Chang MH, Zhao LL, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol. 2013; 59:24–30.
13. Xu DZ, Yan YP, Choi BC, et al. Risk factors and mechanism of transplacental transmission of hepatitis B virus: a case-control study. J Med Virol. 2002; 67:20–6.
14. Dale C and Yim C. Viral hepatitis, chronic. In: Compendium of Therapeutic Choices. Canadian Pharmacists Association. Updated November 1, 2018. Accessed April 4, 2021. https://myrxtx-ca.proxy.lib.uwaterloo.ca/search.
15. Fattovich G. Natural history of hepatitis B. J Hepatol. 2003;39:S50-S58. Doi: 10.1016/S0168-8278(03)00139-9.
16. Centre for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases: Hepatitis B. https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html. Updated April 15, 2019. Accessed October 20, 2020.
17. Public Health Agency of Canada. Brief Report: Hepatitis B Infection in Canada. Accessed December 4, 2020. https://www.phac-aspc.gc.ca/id-mi/pdf/hepB-eng.pdf.

18. Llovet JM, Fuster J, Bruix J. Prognosis of hepatocellular carcinoma. *Hepatogastroenterology*. 2002;49(43):7-11.

19. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver Int.* 2012;32(9):1407-1414. Doi: 10.1111/j.1478-3231.2012.02830.x.

20. Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Reports. 2013;24(11):3-13.

21. Report on hepatitis B and C in Canada: 2017. Public Health Agency of Canada. Published July 2019. Accessed April 4, 2021. https://www.canada.ca/en/services/health/publications/diseases-conditions/report-hepatitis-b-c-canada-2017.html.

22. Hamadeh A, Feng Z, Krahn M, Wong WWL. A model-based framework for chronic hepatitis C prevalence estimation. PLoS ONE. 2019;14(11):e0225366. Doi: https://doi.org/10.1371/journal.pone.0225366.

23. Ogawa E, Yeo YH, Dang N, Le MH, Jeong D, Tran S, et al. Diagnosis rates of chronic hepatitis B in privately insured patients in the United States. JAMA Netw Open. 2020;3(4):e201844. Doi: 10.1001/jamanetworkopen.2020.1844.

24. Moore MS, Bocour A, Winters A. Surveillance-based estimate of the prevalence of chronic hepatitis B virus infection, New York City, 2016. Public Health Rep. 2019;134(6):695-702. Doi: 10.1177/0033354919882962.

25. Navarro N, Lim, N, Kim J, Joo E, Che K, Runyon BA, *et al*. Lower than expected hepatitis B virus infection prevalence among first generation Koreans in the U.S.: results of HBV

screening in the Southern California Inland Empire. *BMC Infect Dis*. 2014;14:269. Doi: https://doi.org/10.1186/1471-2334-14-269.

26. Li S, Sim SC, Lee L, Pollack HJ, Wyatt LC, Trinh-Shevrin C, *et al.* Hepatitis B screening and vaccination behaviours among a community-based sample of Chinese and Korean Americans in New York City. *Am J Health Behav*. 2017;41(2):204-214. Doi: 10.5993/AJHB.41.2.12.
27. Screening for chronic hepatitis B among Asian/Pacific Islander populations --- New York City, 2005. MMWR Weekly. Published May 12, 2006. Accessed Apr 4, 2021. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5518a2.htm.
28. Lin SY, Chang ET, So SK. Why we should routinely screen Asian American adults for hepatitis B: A cross-sectional study of Asians in California. *Hepatology*. 2007;46(4):1034-1040. Doi: https://doi.org/10.1002/hep.21784.
29. Public Health Agency of Canada. Provincial and territorial routine and catch-up vaccination schedule for infants and children in Canada. Updated June 2020. Accessed December 4, 2020. https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information/provincial-territorial-routine-vaccination-programs-infants-children.html.
30. Coffin CS, Fung SK, Alvarez F, Cooper CL, Doucette KE, Fournier C, et al. Management of hepatitis B virus infection: 2018 guidelines from the Canadian Association for the Study of the Liver and Association of Medical Microbiology and Infectious Disease Canada. Can Liv J. 2018;1(4):156-217. Doi: https://doi.org/10.3138/canlivj.2018-0008.
31. Ontario Ministry of Health and Long-Term Care. Appendix A: Disease-specific chapters: Hepatitis B. Published February 2019. Accessed April 2021.

https://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/hep_b_chapter.pdf.

32. Ontario Ministry of Health and Long-Term Care. Notice from the Executive Officer: Funding of hepatitis B drugs under the Ontario Drug Benefit Program. Published February 2018. Accessed April 2021. https://www.health.gov.on.ca/en/pro/programs/drugs/opdp_eo/notices/exec_office_20180221.pdf.
33. World Health Organization. Hepatitis B. Updated January 24, 2018. Accessed December 4, 2020. https://www.who.int/immunization/diseases/hepatitisB/en/
34. Centers for Disease Control and Prevention. Hepatitis B Vaccination of Infants, Children, and Adolescents. Updated November 8, 2019. Accessed December 4, 2020. https://www.cdc.gov/hepatitis/HBV/VaccChildren.htm
35. Lu CY, Chiang BL, Chi WK, Chang MH, Ni YH, Hsu HM. Waning immunity to plasma-derived hepatitis B vaccine and the need for booster 15 years after neonatal vaccination. Hepatology. 2004;40(6):1415-1420. Doi: 10.1002/hep.20490.
36. Bruce MG, Bruden D, Hurlburt D, *et al*. Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. *J Infec Dis*. 2016;214:16-22. Doi: 10.1093/infdis/jiv748.
37. BIOTECanada Vaccine Industry Committee. Building on the legacy of vaccines in Canada: value, opportunities, and challenges. The current Canadian vaccine environment. 2010.
38. Lee D and Park SM. Cost-effectiveness analysis of hepatitis B vaccination strategies to prevent perinatal transmission in North Korea: selective vaccination vs. universal vaccination. *PLoS One*. 2016;11(11):e0165879. doi: 10.1371/journal.pone.0165879.

39. Tilson L, Thornton L, O'Flanagan D, et al. Cost effectiveness of hepatitis B vaccination strategies in Ireland: an economic evaluation. *Eur J Public Health*. 2008;18(3):275-82. doi: https://doi.org/10.1093/eurpub/ckm123.

40. Siddigui MR, Gay N, Edmunds WJ, and Ramsay M. Economic evaluation of infant and adolescent hepatitis B vaccination in the UK. *Vaccine*. 2011;29:466-475. Doi: 10.1016/j.vaccine.2010.10.075.

41. Update on immunization in pregnancy with Tdap vaccine. Public Health Agency of Canada. Published February 2018. Accessed April 4, 2021. https://www.canada.ca/en/public-health/services/publications/healthy-living/update-immunization-pregnancy-tdap-vaccine.html.

42. Pertussis immunization in pregnancy in Ontario: scientific and technical considerations. Public Health Ontario. Published October 2018. Accessed April 4, 2021. https://www.publichealthontario.ca/-/media/documents/P/2018/pertussis-immunization-pregnancy.pdf?la=en.

43. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf. Published March 2017. Accessed January 27, 2019.

44. Public Health Ontario. Immunization Coverage Report for School Pupils in Ontario: 2017-18 School Year. https://www.publichealthontario.ca/en/health-topics/immunization/vaccine-coverage. Published May 2019. Accessed October 20, 2020.

45. TreeAge Pro 2020, R2. *TreeAge Software, Williamstown, MA; software available at http://www.treeage.com*.

46. Gray AM, Clarke PM, Wolstenholme JL, and Wordsworth S. *Applied Methods of Cost-effectiveness Analysis in Health Care*. Oxford, UK: Oxford University Press; 2011.
47. Wong WWL, Woo G, Heathcote EJ, Krahn M. Cost effectiveness of screening immigrants for hepatitis B. *Liver Int*. 2011;31(8):1179-1190. Doi: https://doi.org/10.1111/j.1478-3231.2011.02559.x.
48. Statistics Canada. Consumer Price Index, annual average, not seasonally adjusted. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501. Updated December 7, 2020. Accessed December 7, 2020.
49. Lin CL, Kao JH. Risk stratification for hepatitis B virus related hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2012;28(1):10-17. Doi: https://doi.org/10.1111/jgh.12010.
50. Hepatitis B Foundation. Risk Factors. https://www.hepb.org/research-and-programs/liver/risk-factors-for-liver-cancer/. Accessed December 7, 2020.
51. Blachier M, Leleu H, Peck-Radosavljevic M, *et al*. The burden of liver disease in Europe: A review of available epidemiological data. *J Hepatol*. 2013;58(3):593-608. Doi: https://doi.org/10.1016/j.jhep.2012.12.005.
52. Potosek J, Curry M, Buss M, *et al*. Integration of palliative care in end-stage liver disease and liver transplantation. *J Palliat Med*. 2014;17(11):1271-1277. Doi: 10.1089/jpm.2013.0167.
53. GSK. Infanrix hexa product monograph. https://ca.gsk.com/media/537989/infanrix-hexa.pdf. Updated April 28, 2020. Accessed December 7, 2020.
54. Reported cases from 1924 to 2018 in Canada – Notifiable diseases on-line. Public Health Agency of Canada. Updated January 14, 2021. Accessed April 4, 2021. https://diseases.canada.ca/notifiable/charts?c=pl.

55. Population estimates on July 1st, by age and sex. Statistics Canada. Updated April 4, 2021. Accessed April 4, 2021. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501.

56. Number and rates of new cases of primary cancer, by cancer type, age group and sex. Statistics Canada. Updated April 4, 2021. Accessed April 4, 2021. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011101&pickMembers%5B0%5D=2.1&pickMembers%5B1%5D=3.1&pickMembers%5B2%5D=4.17&cubeTimeFrame.startYear=2013&cubeTimeFrame.endYear=2017&referencePeriods=20130101%2C20170101.

57. Canadian Liver Meeting 2021. Published May 2021. Accessed August 2021. https://hepatology.ca/education-events/canadian-liver-meeting/

58. Chan J, Kim JJ, Barrett BK, Hamadeh A, Feld JJ, Wong WWL. Cost-effectiveness analysis of sofosbuvir and velpatasvir in chronic hepatitis C patients with decompensated cirrhosis. J Viral Hep. 2020;28(2):260-267. Doi: https://doi.org/10.1111/jvh.13419.

59. Kim JJ, Tian AH, Pham L, Nakhla N, Houle SKD, Wong WWL, et al. Economic evaluation of pharmacists prescribing for minor ailments in Ontario, Canada: a cost-minimization analysis. Int J Pharm Prac. 2021;,riab006. Doi: https://doi.org/10.1093/ijpp/riab006.

60. Krahn M and Detsky AS. Should Canada and the United States universally vaccinate infants against hepatitis B? A cost-effectiveness analysis. *Med Decis Making*. 1993;13:4-20.

61. Statistics Canada. Life Tables, Canada, Provinces, and Territories, 1980/1982 to 2017/2019. https://www150.statcan.gc.ca/n1/en/catalogue/84-537-X. Updated November 26, 2020. Accessed December 7, 2020.

62. Chu CM, Liaw YF. Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implication of delayed HBeAg seroconversion. *J Viral Hepat* 2007; 14: 147–52.

63. Veenstra DL, Sullivan SD, Clarke L, et al. Cost effectiveness of entecavir versus lamivudine with adefovir salvage in HBeAg-positive chronic hepatitis B. *Pharmacoeconomics*. 2007;25:963–977.

64. Liaw YF, Tai DI, Chu CM, et al. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology.* 1988;8:493–496.

65. Lin S-M, Sheen I-S, Chien R-N, et al. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology.* 1999;29:971–975.

66. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, doubleblind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:185–195.

67. Wong WWL, Pechivanoglou P, Wong J, et al. Antiviral treatment for treatment-naïve chronic hepatitis B: systematic review and network meta-analysis of randomized controlled trials. Syst Rev. 2019;8:207.

68. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology*. 2002;35:1522–1527.

69. Gigi E, Lalla T, Orphanou E, et al. Long term follow-up of a large cohort of inactive HBsAg (+)/HBeAg (-)/ anti-HBe (+) carriers in Greece. *J Gastrointestin Liver Dis.* 2007;16:19–22.

70. Mcmahon BJ, Holck P, Bulkow L, et al. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. *Ann Intern Med.* 2001;135:759–768.

71. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology.* 2006;130:678–686.

72. Veenstra DL, Spackman DE, Bisceglie A, et al. Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: a cost-effectiveness analysis. *Aliment Pharmacol Ther.* 2008;27:1240–1252.

73. Tian F, Houle SKD, Alsabbagh MW, Wong WWL. Cost-effectiveness of tenofovir alafenamide for treatment of chronic hepatitis B in Canada. *Pharmacoeconomics*. 202;38:181-192. Doi: https://doi.org/10.1007/s40273-019-00852-y.

74. Wen WH, Chang MH, Hsu HY, Ni YH, Chen HL. The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. *J Pediatr.* 2004; 144: 397–9.

75. Liaw YF, Tai DI, Chu CM, et al. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. *Gastroenterology.* 1986; 90:263–7.

76. Papatheodoridis GV, Manolakopoulos S, Touloumi G, et al. Risk of Hepatocellular Carcinoma (HCC) in Chronic Hepatitis B (CHB) Patients With or Without Cirrhosis Treated With Oral Antivirals: Results of the Nationwide HEPNET. Greece Cohort Study. Boston, MA, USA: AASLD, 2009.

77. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295: 65–73.

78. Benvegnù L, Gios M, Boccato S, et al. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut.* 2004;53:744–749.

79. Fattovich G, Giustina G, Schalm SW, et al. Occurrence of hepatocellular carcinoma and decompensation in Western European patients with cirrhosis type B. *Hepatology*. 1995;21:77–82.

80. Kanwal F, Farid M, Martin P, et al. Treatment alternatives for hepatitis B cirrhosis: a cost effectiveness analysis. *Am J Gastroenterol.* 2006;101:2076–2089.

81. Fattovich G, Pantalena M, Zagni I, et al. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. *Am J Gastroenterol.* 2002;97:2886–2895.

82. Hutton DW, Tan D, So SK, et al. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. *Ann Intern Med.* 2007;147:460–469.

83. Kanwal F, Gralnek IM, Martin P, et al. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. *Ann Intern Med.* 2005;142:821–831.

84. Wong WWL, Lee KM, Singh S, et al. Drug therapies for chronic hepatitis C infection: a cost-effectiveness analysis. *CMAJ Open.* 2017;5:E97–E108.

85. Craxi A, Colombo P, D'Amico G, et al. Hepatitis B infection and liver cirrhosis: a reappraisal from the Mediterranean area. *Ann Ist Super Sanita.* 1987;24:257–265.

86. D'Amico G, Morabito A, Pagliaro L, et al. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci.* 1986;31:468–475.

87. The Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol*. 2018;3(6):383-403. Doi: 10.1016/S2468-1253(18)30056-6.

88. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and Entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and bayesian meta-analyses. *Gastroenterology*. 2010; 139: 1218–29.

89. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008; 359: 2442–55.

90. Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. *Value Heal*. 2010;13:922–933.

91. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology.* 2013;58:98–107.

92. Wong GL, Chan HL, Mak CW, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology.* 2013;58:1537–1547.

93. Canadian Institute for Health Information. Health Care in Canada. Ottawa, ON, Canada: Canadian Institute for Health Information, 2004.

94. Gagnon YM, Levy AR, Iloeje UH, et al. Treatment costs in Canada of health conditions resulting from chronic hepatitis B infection. *J Clin Gastroenterol.* 2004;38:S179–186.

95. Ontario Drug Benefit. eFormulary. Prices are effective as of November 30, 2020. http://www.health.gov.on.ca/en/pro/programs/drugs/odbf_eformulary.aspx. Accessed December 7, 2020.

96. Woo G, Tomlinson G, Yim C, et al. Health state utilities and quality of life in patients with hepatitis B. *Can J Gastroenterol.* 2012;26:445–451.

97. Nanwa N, Kwong J, Feld J, Wu C, Sander B. The mean attributable healthcare costs associated with hepatitis B virus in Ontario, Canada: a matched cohort study. *Can Liver J.* 2022. Doi: https://doi.org/10.3138/canlivj-2021-0029.

98. Wong WWL, Haines A, Bremner KE, et al. Health care costs associated with chronic hepatitis C virus infection in Ontario, Canada: a retrospective cohort study. *Can Med Assoc J Open.* 2021;9(1):E167-E174. Doi: https://doi.org/10.9778/cmajo.20200162

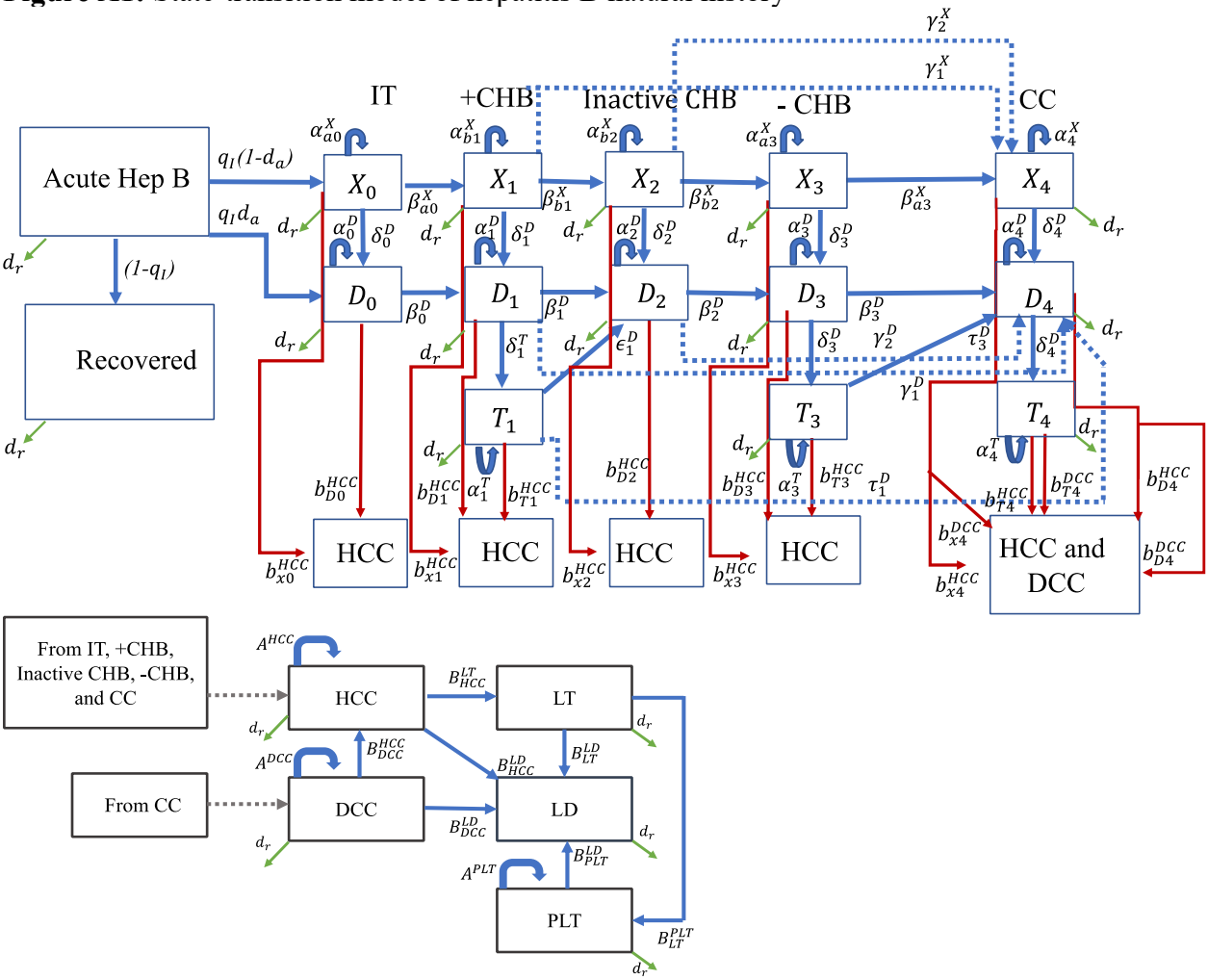
99. BC Centre for Disease Control. Immunization Coverage in Children by the Seventh Birthday: 2012-2020. Published March 23, 2021. Accessed April 30, 2022.

100. Brizzi F, Birrell PJ, Plummer MT, et al. Extending Bayesian back-calculation to estimate age and time specific HIV incidence. *Lifetime Data Anal.* 2019;25:757-780.

101. Public Health Agency of Canada. Reducing the health impact of sexually transmitted and blood-borne infections in Canada by 2030: A pan-Canadian STBBI framework for action. Updated July 9, 2018. Accessed April 30, 2022.

APPENDIX

Figure A1: State-transition model of hepatitis B natural history



Mathematical Formulation of the Natural History Model

The estimated number of patients in disease states X_i, D_i, T_i (i = 0, 1, 2, 3, 4), *DCC*, *HCC*, *LT*, *PLT*, and *LD* for the three age cohorts at year t are denoted by $X_i(t)$, $D_i(t)$, $T_i(t)$ (i = 0, 1, 2, 3, 4), *DCC(t)*, *HCC(t)*, *LT(t)*, *PLT(t)*, and *LD(t)*, respectively. *X, D,* and *T* represent undiagnosed, diagnosed, and treatment-receiving patients, respectively. The estimated number of patients at each state can then be shown by the following state vector *x(t)*:

$x(t) = [X(t), D(t), T(t), DCC(t), HCC(t), LT(t), PLT(t), LD(t)]$; where $X(t) = [X_0, X_1, X_2, X_3, X_4]$, $D(t) = [D_0, D_1, D_2, D_3, D_4]$, and $T(t) = [T_1, T_3, T_4]$.

The changes in the estimated number of patients ($x(t)$) over time is modelled using the state-transition model shown in the appendix Figure A1. Assuming $u(t)$ notates the number of new infections in year t, the vector $x(t + 1)$ can then be written as $x(t + 1) = Ax(t) + Bu(t)$, where A and B are defined below:

$$A = \begin{bmatrix} A_X(t) & 0_{5\times5} & 0_{5\times3} & 0 & 0 & 0 & 0 & 0 \\ B_D(t) & A_D(t) & C_D(t) & 0 & 0 & 0 & 0 & 0 \\ 0_{3\times5} & B_T(t) & A_T(t) & 0 & 0 & 0 & 0 & 0 \\ B_X^{DCC}(t) & B_D^{DCC}(t) & B_T^{DCC}(t) & A^{DCC}(t) & 0 & 0 & 0 & 0 \\ B_X^{HCC}(t) & B_D^{HCC}(t) & B_T^{HCC}(t) & B_{DCC}^{HCC}(t) & A^{HCC}(t) & 0 & 0 & 0 \\ 0_{1\times5} & 0_{1\times5} & 0_{1\times3} & 0 & B_{HCC}^{LT}(t) & 0 & 0 & 0 \\ 0_{1\times5} & 0_{1\times5} & 0_{1\times3} & 0 & 0 & B_{LT}^{PLT}(t) & A^{PLT}(t) & 0 \\ 0_{1\times5} & 0_{1\times5} & 0_{1\times3} & B_{DCC}^{LD}(t) & B_{HCC}^{LD}(t) & B_{LT}^{LD}(t) & B_{PLT}^{LD}(t) & 0 \end{bmatrix}$$

and

$$B(t) = \left[q_I(1-d_a)(1-d_r(t)), q_I d_a(1-d_r(t)), 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0\right]^T$$

where

$$A_X(t) = \begin{bmatrix} \alpha_{a0}^X(t) & 0 & 0 & 0 & 0 \\ \beta_{a0}^X(t) & \alpha_{b1}^X(t) & 0 & 0 & 0 \\ 0 & \beta_{b1}^X(t) & \alpha_{b2}^X(t) & 0 & 0 \\ 0 & 0 & \beta_{b2}^X(t) & \alpha_{a3}^X(t) & 0 \\ 0 & \gamma_1^X(t) & \gamma_2^X(t) & \beta_{a3}^X(t) & \alpha_4^X(t) \end{bmatrix}$$

$$A_D(t) = \begin{bmatrix} \alpha_0^D(t) & 0 & 0 & 0 & 0 \\ \beta_0^D(t) & \alpha_1^D(t) & 0 & 0 & 0 \\ 0 & \beta_1^D(t) & \alpha_2^D(t) & 0 & 0 \\ 0 & 0 & \beta_2^D(t) & \alpha_3^D(t) & 0 \\ 0 & \gamma_1^D(t) & \gamma_2^D(t) & \beta_3^D(t) & \alpha_4^D(t) \end{bmatrix}$$

$$A_T(t) = \begin{bmatrix} \alpha_1^T(t) & 0 & 0 \\ 0 & \alpha_3^T(t) & 0 \\ 0 & 0 & \alpha_4^T(t) \end{bmatrix}$$

$$C_D(t) = \begin{bmatrix} 0 & 0 & 0 \\ \epsilon_1^D(t) & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \tau_1^D(t) & \tau_3^D(t) & 0 \end{bmatrix}$$

$$B_D(t) = \begin{bmatrix} \delta_0^D(t) & 0 & 0 & 0 & 0 \\ 0 & \delta_1^D(t) & 0 & 0 & 0 \\ 0 & 0 & \delta_2^D(t) & 0 & 0 \\ 0 & 0 & 0 & \delta_3^D(t) & 0 \\ 0 & 0 & 0 & 0 & \delta_4^D(t) \end{bmatrix}$$

$$B_T(t) = \begin{bmatrix} 0 & \delta_1^T(t) & 0 & 0 & 0 \\ 0 & 0 & \delta_3^T(t) & 0 & 0 \\ 0 & 0 & 0 & \delta_4^T(t) & 0 \end{bmatrix}$$

$$B_X^{DCC}(t) = \begin{bmatrix} 0 & 0 & 0 & 0 & b_{X4}^{DCC} \end{bmatrix}$$

$$B_D^{DCC}(t) = \begin{bmatrix} 0 & 0 & 0 & 0 & b_{D4}^{DCC} \end{bmatrix}$$

$$B_T^{DCC}(t) = \begin{bmatrix} 0 & 0 & b_{T4}^{DCC} \end{bmatrix}$$

$$B_X^{HCC}(t) = \begin{bmatrix} b_{X0}^{HCC} & b_{X1}^{HCC} & b_{X2}^{HCC} & b_{X3}^{HCC} & b_{X4}^{HCC} \end{bmatrix}$$

$$B_D^{HCC}(t) = \begin{bmatrix} b_{D0}^{HCC} & b_{D1}^{HCC} & b_{D2}^{HCC} & b_{D3}^{HCC} & b_{D4}^{HCC} \end{bmatrix}$$

$$B_T^{HCC}(t) = \begin{bmatrix} b_{T1}^{HCC} & b_{T3}^{HCC} & b_{T4}^{HCC} \end{bmatrix}$$

The components of the matrices listed above are state-transition probabilities shown in the appendix Figure A1 and their descriptions are listed in Table A1.

Table A1: State-transition probabilities

Parameter formula	Description
$q_I(1-d_a)\sigma(t)$	Probability that an individual in state acute Hepatitis B in year t will go to Immune tolerant state and remain undiagnosed in year $t+1$.
$q_I d_a \sigma(t)$	Probability that an individual in state Acute Hepatitis B in year t will go to Immune tolerant state and will be diagnosed in year $t+1$.
$\alpha_{ai}^X(t) = (1-q_{ii+1})(1-d_{hcci}-d_i)\,\sigma(t)$	Probability that an individual in state X_i $(i=0,3)$ in year t will remain in state X_i in year $t+1$.

α_{bi}^{X}(t) = $(1 - q_{ii+1})(1 - d_{hcci} - d_{cci} - d_i)\ \sigma(t)$	Probability that an individual in state X_i $(i = 1, 2)$ in year t will remain in state X_i in year $t + 1$.
α_{4}^{X}(t) = $(1 - d_{hcc4} - d_{DCC4} - d_4)\ \sigma(t)$	Probability that an individual in state X_4 in year t will remain in state X_4 in year $t + 1$.
β_{ai}^{X}(t) = $q_{ii+1}(1 - d_{hcci} - d_i)\ \sigma(t)$	Probability that an individual in state X_i $(i = 0, 3)$ in year t will transit to state X_{i+1} in year $t + 1$.
β_{bi}^{X}(t) = $q_{ii+1}(1 - d_{hcci} - d_{cci} - d_i)\ \sigma(t)$	Probability that an individual in state X_i $(i = 1, 2)$ in year t will transit to state X_{i+1} in year $t + 1$.
$\gamma_{i}^{X}(t)$ = $(1 - q_{ii+1})d_{cci}\ \sigma(t)$	Probability that an individual in state X_i $(i = 1, 2)$ in year t will transit to state X_4 in year $t + 1$.
$\delta_{i}^{D}(t)$ = $(1 - q_{ii+1})d_i\ \sigma(t)$	Probability that an individual in state X_i $(i = 0, 1, 2, 3)$ in year t will be diagnosed, transitioning to state D_i in year $t + 1$.
$\delta_{4}^{D}(t)$ = $d_4\ \sigma(t)$	Probability that an individual in state X_4 in year t will be diagnosed, transitioning to state D_4 in year $t + 1$.
α_{0}^{D}(t) = $(1 - q_{01})(1 - d_{hcc0})\ \sigma(t)$	Probability that an individual in state D_0 (in year t will remain in state D_0 in year $t + 1$.
α_{1}^{D}(t) = $(1 - q_{12})(1 - d_{hcc1} - d_{cc1} - t_1)\ \sigma(t)$	Probability that an individual in state D_1 in year t will remain in state D_1 in year $t + 1$.
α_{2}^{D}(t) = $(1 - q_{23})(1 - d_{hcc2} - d_{cc2})\ \sigma(t)$	Probability that an individual in state D_2 in year t will remain in state D_2 in year $t + 1$.
α_{3}^{D}(t) = $(1 - q_{34})(1 - d_{hcc3} - t_3)\ \sigma(t)$	Probability that an individual in state D_3 in year t will remain in state D_3 in year $t + 1$.
α_{4}^{D}(t) = $(1 - d_{hcc4} - d_{DCC4} - t_4)\ \sigma(t)$	Probability that an individual in state D_4 in year t will remain in state D_4 in year $t + 1$.
β_{0}^{D}(t) = $q_{01}(1 - d_{hcc0})\ \sigma(t)$	Probability that an individual in state D_0 in year t will transit to state D_1 in year $t + 1$.
β_{1}^{D}(t) = $q_{12}(1 - d_{hcc1} - d_{cc1} - t_1)\ \sigma(t)$	Probability that an individual in state D_1 in year t will transit to state D_2 in year $t + 1$.
β_{2}^{D}(t) = $q_{23}(1 - d_{hcc2} - d_{cc2})\ \sigma(t)$	Probability that an individual in state D_2 in year t will transit to state D_3 in year $t + 1$.
β_{3}^{D}(t) = $q_{34}(1 - d_{hcc3} - t_3)\ \sigma(t)$	Probability that an individual in state D_3 in year t will transit to state D_4 in year $t + 1$.
γ_{1}^{D}(t) = $(1 - q_{12})d_{cc1}\sigma(t)$	Probability that an individual in state D_1 in year t will transit to state D_4 in year $t + 1$.
γ_{2}^{D}(t) = $(1 - q_{23})d_{cc2}\sigma(t)$	Probability that an individual in state D_2 in year t will transit to state D_4 in year $t + 1$.
$\delta_{i}^{T}(t)$ = $(1 - q_{ii+1})t_i\ \sigma(t)$	Probability that an individual in state D_i $(i = 1, 3)$ in year t will transit to state T_i in year $t + 1$.
$\delta_{4}^{T}(t)$ = $t_4\ \sigma(t)$	Probability that an individual in state D_4 in year t will transit to state T_4 in year $t + 1$.
α_{1}^{T}(t) = $(1 - qt_{12})(1 - dt_{hcc1} - dt_{cc1})\sigma(t)$	Probability that an individual in state T_1 in year t will remain in state T_1 in year $t + 1$.
α_{3}^{T}(t) = $(1 - qt_{34})(1 - dt_{hcc3})\sigma(t)$	Probability that an individual in state T_3 in year t will remain in state T_3 in year $t + 1$.
α_{4}^{T}(t) = $(1 - dt_{hcc4} - dt_{DCC4})\sigma(t)$	Probability that an individual in state T_4 in year t will remain in state T_4 in year $t + 1$.

$\epsilon_1^D(t) = qt_{12}(1 - dt_{hcc1} - dt_{cc1})\sigma(t)$	Probability that an individual in state T_1 in year t will transit to state D_2 in year $t+1$.
$\tau_1^D(t) = (1 - qt_{12})dt_{cc1}\sigma(t)$	Probability that an individual in state T_1 in year t will transit to state D_4 in year $t+1$.
$\tau_3^D(t) = qt_{34}(1 - dt_{hcc3})\sigma(t)$	Probability that an individual in state T_3 in year t will transit to state D_4 in year $t+1$.
$b_{X_i}^{HCC}(t) = (1 - q_{ii+1})d_{hcci}\,\sigma(t)$	Probability that an individual in state X_i $(i = 0,1,2,3)$ in year t will progress to state HCC in year $t+1$.
$b_{X_4}^{HCC}(t) = d_{hcc4}\,\sigma(t)$	Probability that an individual in state X_4 in year t will progress to state HCC in year $t+1$.
$b_{D_4}^{HCC}(t) = d_{hcc4}\,\sigma(t)$	Probability that an individual in state D_4 in year t will progress to state HCC in year $t+1$.
$b_{T_4}^{HCC}(t) = dt_{hcc4}\,\sigma(t)$	Probability that an individual in state T_4 in year t will progress to state HCC in year $t+1$.
$b_{D_i}^{HCC}(t) = (1 - q_{ii+1})d_{hcci}\,\sigma(t)$	Probability that an individual in state D_i $(i = 0,1,2,3)$ in year t will progress to state HCC in year $t+1$.
$b_{T_i}^{HCC}(t) = (1 - qt_{ii+1})dt_{hcci}\,\sigma(t)$	Probability that an individual in state T_i $(i = 1,3)$ in year t will progress to state HCC in year $t+1$.
$b_{X_4}^{DCC}(t) = d_{DCC4}\,\sigma(t)$	Probability that an individual in state X_4 in year t will progress to state DCC in year $t+1$.
$b_{D_4}^{DCC}(t) = d_{DCC4}\,\sigma(t)$	Probability that an individual in state D_4 in year t will progress to state DCC in year $t+1$.
$b_{T_4}^{DCC}(t) = dt_{DCC4}\,\sigma(t)$	Probability that an individual in state T_4 in year t will progress to state DCC in year $t+1$.
$A^{DCC}(t) = (1 - d_{hccdc})(\sigma(t) - d_{ld1})$	Probability that an individual in state DCC in year t will remain in state DCC in year $t+1$.
$A^{HCC}(t) = (1 - d_{lt})(\sigma(t) - d_{ld2})$	Probability that an individual in state HCC in year t will remain in state HCC in year $t+1$.
$A^{PLT}(t) = (\sigma(t) - d_{ld4})$	Probability that an individual in state PLT in year t will remain in state PLT in year $t+1$.
$B_{DCC}^{HCC}(t) = d_{hccdc}(\sigma(t) - d_{ld1})$	Probability that an individual in state DCC in year t will transit to state HCC in year $t+1$.
$B_{HCC}^{LT}(t) = d_{lt}(\sigma(t) - d_{ld2})$	Probability that an individual in state HCC in year t will transit to state LT in year $t+1$.
$B_{LT}^{PLT}(t) = (\sigma(t) - d_{ld3})$	Probability that an individual in state LT in year t will transit to state PLT in year $t+1$.
$B_{DCC}^{LD}(t) = (1\text{-}d_{hccdc})d_{ld1}$	Probability that an individual in state DCC in year t will transit to state LD in year $t+1$.
$B_{HCC}^{LD}(t) = (1\text{-}d_{lt})d_{ld2}$	Probability that an individual in state HCC in year t will transit to state LD in year $t+1$.
$B_{LT}^{LD}(t) = d_{ld3}$	Probability that an individual in state LT in year t will transit to state LD in year $t+1$.
$B_{PLT}^{LD}(t) = d_{ld4}$	Probability that an individual in state PLT in year t will transit to state LD in year $t+1$.

Here, we describe an example to show how the state transition probabilities are derived. Considering $d_r(t)$ to be the annual background probability, the annual probability that an individual will not die from CHB-related causes can be defined as $\sigma(t) = 1 - d_r(t)$. Moreover, q_I and d_a are assumed to be the probability that a new acute hepatitis B infection become chronic hepatitis B (immune tolerant), and the probability that an individual with an acute infection will be diagnosed before developing into immune tolerant state, respectively. Therefore, $q_I\ (1 - d_a\ )\ \sigma(t)$ is the probability that an individual with acute infection in year *t* will transition into the IT state and remain undiagnosed in year $t + 1$. In addition, assuming q_{01} is the annual probability that an undiagnosed individual in the IT state will progress to the HBeAg+ CHB state, d_0 is the annual probability that an undiagnosed individual in X_0 will be diagnosed with CHB, and d_{hcc0} is the annual probability that undiagnosed individual in X_0 will develop HCC, and as a result, $\alpha_{a0}^{X}(t)$=$(1 - q_{01}\ )(1 - d_{hcc0} - d_0)\ \sigma(t)$ is the probability that an individual in state X_0 will remain in the same state at year $t + 1$. Therefore, the number of patients who, at the beginning of the year 2011, were in stage X_0 can be estimated to be:

$$x_0(2011) = q_I\ (1 - d_a\ )\sigma(t)u(2010) + \alpha_{a0}^{X}(t)X_0(2010).$$

$q_I\ (1 - d_a\ )\sigma(t)u(2010)$ represents those who contracted HBV in 2010, survived and did not get diagnosed until 2011, and progressed to chronic disease through 2010. $\alpha_{a0}^{X}(t)X_0(2010)$ represents those who are at stage X_0 in 2010, survived until 2011, did not get diagnosed nor develop HCC through 2010, and progressed from IT stage to HBeAg+ CHB stage.

Model Calibration

As noted previously, a back calculation approach using Bayesian Markov Chain Monte Carlo based on the Metropolis-Hastings algorithm was implemented to estimate the prevalence of

CHB and proportion of undiagnosed cases. In the model, observed data on HBV-related events (numbers of CHB and HCC cases reported from PHAC and Statistics Canada) were used as the calibration targets to make inference about the number of CHB cases that would have had to have occurred in order to lead to the currently observed data. Below, a detailed approach to the model calibration is described.

In year k, patients with CHB in each age cohort can be in one of 18 disease states as previously described in Figures 4 and 5. Assuming $x_i(k)$ shows the number of individuals within each age cohort who are in state i ($i \in \{1, 2, \ldots, N\}$ at year k, we define the state vector $x(k)$ as the number of patients at each state i ($x_i(k)$). In addition, as previously described, $u(k)$ is defined as the number of new HBV infections in year k. It was assumed that the estimated number of CHB cases x in year $k + 1$ depends on the estimated CHB cases in year k as well as the number of new HBV infections u in year k. This relationship can then be formulated as below:

$x(k + 1) = A_k(m)x(k) + B_k(m)u(k)$; where m is a cohort specific vector of parameters, $A_k(m)$ is the state-transition matrix that includes the probabilities of transition from one state to another, and $B_k(m)$ is the probabilities that a newly infected individual will develop a chronic infection.

Considering an initial estimated CHB population of $x(0)$, parameter vector m, and newly infected patients $u(k)$ at years $k = 0, 1, \ldots, T - 1$ ($T > 0$), the estimated CHB population $x(k + 1)$ at years $k = 1, 2, \ldots, T$ can be assessed. Therefore, the estimated total CHB population $r(k)$, and the estimated undiagnosed CHB cases $d(k)$ can be expressed as a function of $x(k)$ as $r(k) = F_R x(k)$ and $d(k) = F_D x(k)$.

Initial estimate of CHB population $x(0)$, newly infected cases $u(0), \ldots, u(T-1)$, and cohort specific vectors of parameters m were combined into a vector $\boldsymbol{m}$. The elements of the vector $\boldsymbol{m}$ are unknown *a priori* but any preliminary knowledge of their likely values can be expressed in the form of a prior probability distribution $p(\boldsymbol{m})$.

The knowledge of $\boldsymbol{m}$ can be refined using observed evidence related to HBV events (i.e., calibration data from PHAC and Statistics Canada) and the number of different types of evidence is shown by M. For instance, M is equal to 2 if there is evidence about the number of HBV diagnosis and the number of CHB treatments initiated. Assuming $z_i(k)$ is the number of observations of type i (i = 1, …, M) in year k, one can define $z(k) = [z_1(k), \ldots, z_M(k)]^T$. Thus, $\boldsymbol{z}_{[0,T]} = [z(0), \ldots, z(T)]$ is the array of the observations for years k = 0, …, T and can be used to define the posterior distribution $p(\boldsymbol{m} \mid \boldsymbol{z}_{[0,T]})$, which satisfies the Bayes rule $p(\boldsymbol{m} \mid \boldsymbol{z}_{[0,T]}) \propto p(\boldsymbol{z}_{[0,T]} \mid \boldsymbol{m}) * p(\boldsymbol{m})$. Here, the likelihood function $p(\boldsymbol{z}_{[0,T]} \mid \boldsymbol{m})$ measures the goodness of fit of the model ($x(t) = [X(t), D(t), T(t), DCC(t), HCC(t), LT(t), PLT(t), LD(t)]$) to the data $\boldsymbol{z}_{[0,T]}$ for a given value of $\boldsymbol{m}$. This measure can then be evaluated by comparing data $z(k)$ with corresponding model estimate $y(k) = [y_1(k), \ldots, y_M(k)]^T$, which is given by: $y(k+1) = C_k(m)x(k) + D_k(m)u(k)$. Considering $\boldsymbol{y}_{[0,T]} = [y(0), \ldots, y(T)]$ to be the array of estimates of the observations $\boldsymbol{z}_{[0,T]}$ over the years k = 0, …, T, it is assumed that the number of observations $z_i(k)$ follows a Poisson process with rate $y_i(k)$ and consequently, $p(\boldsymbol{z}_{[0,T]} \mid \boldsymbol{m}) = \prod_{i=1}^{M} \prod_{k=0}^{T} \text{Poisson}(z_i(k) | y_i(k))$.

As noted earlier, the Metropolis-Hastings algorithm is used to sample the space of the unknown model parameters $\boldsymbol{m}$ and return the posterior distribution $p(\boldsymbol{m} \mid \boldsymbol{z}_{[0,T]})$. State vector $x(k)$, number of patients in the various health states, can be computed by repeatedly sampling from $p(\boldsymbol{m} \mid \boldsymbol{z}_{[0,T]})$ – five million times in this case. Then, the distributions of the populations in $x_0(2011) =$

$q_I\ (1 - d_a\ )\sigma(t)u(2010) + \alpha_{a0}^{X}(t)X_0(2010)$ can be obtained, using the values of *x(k)* for the samples from $p(\boldsymbol{m} \mid \boldsymbol{z}_{[0,T]})$. By normalizing the estimates of *r(k)* and *d(k)* with the appropriate reference populations, the prevalence and undiagnosed CHB rates can then be assessed.