Hepatitis D virus among immigrants in Canada: an estimation of the prevalence and a cost-effectiveness analysis of screening and treatment

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.

Abstract

Background: Hepatitis D virus (HDV) is an important health concern in Canada. HDV is a viral infection can cause a rapid progression to inflammatory response in the liver, resulting in liver cirrhosis, hepatocellular carcinoma (HCC) and liver-related death. HDV is a derivative viral infection of hepatitis B virus (HBV). HDV infections can be acute or chronic. Chronic infections can lead to long term illness, liver cirrhosis or liver death. HDV infections can happen simultaneously, HBV and HDV infections happen at the same time, known as coinfection. HDV infections can also occur chronologically, patients already infected with Chronic hepatitis B (CHB) will then be infected with HDV, known as superinfection. Currently, no known cure for HDV infection, only available treatment is pegylated interferon alfa. Various new therapies are being developed due to limited effectiveness of pegylated interferon alfa. Bulevirtide (BLV) is a treatment that has shown promising efficacy.

Objective: The objectives of this thesis are to: (1) estimate the overall prevalence of HDV among immigrants in Canada. (2) assess the cost-effectiveness of HDV screening and treating patients with bulevirtide, pegylated interferon alfa-2a and combined therapy compared to no screening for HDV.

Methodology: A literature review was conducted to gather all relevant data on HDV. The prevalence estimation for HDV among immigrants in Canada was calculated based on a weighted average analysis by estimating the HBV population in Canada and then estimating HDV population using the HBV population estimation. A state transition model representing the natural progression of CHB and HDV was developed in TreeAge Pro to assess the cost-effectiveness of three screening and treating strategies. Analyses were performed from a public payer perspective with a lifetime time horizon and a 1.5% annual discount rate. One way sensitivity analysis and probabilistic analysis have been conducted to assess uncertainty.

Results: Estimated HDV prevalence among HBV infected immigrants in Canada in 2021 was to be 7.7%. This is equivalent to an overall HDV prevalence rate of 0.24%, around 20,102 immigrants. HDV screening and treating with pegylated interferon alfa-2a monotherapy is cost-effective. Our analysis resulted in mean cost of $288,062 and a 22.96 QALY for screening and treating with pegylated interferon alfa-2a monotherapy versus $283,716 and 22.76 QALY for no HDV screening and treatment. With an ICER of $21,808/QALY. However, HDV screening and treating with BLV monotherapy and HDV screening and treating with combined therapy (BLV plus pegylated interferon alfa-2a) were both not cost-effective compared to no HDV screening and treatment. Our analysis resulted in ICER values of $329,015/QALY and $199,841/QALY for screening and treating with BLV and screening and treating with combined therapy, respectively. From a clinical perspective, all screen and treat HDV strategies showed a reduction in cases of liver related outcomes in decompensated cirrhosis, hepatocellular carcinoma and liver death.

Conclusion: The estimated prevalence of HDV showed that a reasonable number of immigrants living in Canada with HDV remain undiagnosed. The results of cost-effectiveness study showed that screening for HDV and treating can increase clinical benefits. The results of the thesis can provide policy makers with actionable recommendation in re-assessing the current HDV screening recommendation in Canada among our immigrant population.

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List of Abbreviations

ACM – All cause mortality

CHB – Chronic Hepatitis B

HDV – Hepatitis D virus

HBeAg – Hepatitis B e Antigen

ALT – Alanine transaminase

CDA-AMC – Canada's drug agency L'Agence des Médicaments du Canada

IT – Immune tolerant

CC – Compensated cirrhosis

HCC – Hepatocellular carcinoma

DC – Decompensated cirrhosis

LT – Liver transplant

PLT – Post liver transplant

ICER – Incremental cost-effectiveness ratio

PHAC – Public Health Agency of Canada

PSA – Probabilistic sensitivity analysis

QALY – Quality-adjusted life years

WHO – World Health Organization

WTP – Willingness-to-pay

BLV – Bulevirtide

IgG – Immunoglobulin G

IgM – Immunoglobulin M

HIE – Healthy Immigrant Effect

Chapter 1
Introduction and Background

Hepatitis D

Hepatitis D is a viral infection caused by the hepatitis delta virus (HDV).[1] It triggers an inflammatory response in the liver and results in liver cirrhosis, hepatocellular carcinoma (HCC) and liver-related death.[1] It is considered as a satellite virus because HDV is a derivative viral infection of the hepatitis B virus (HBV).[1]

HDV was first discovered in 1977 by Rizzetto et al. through an immunofluorescence detection of a new antigen-antibody system associated with HBV.[2] Since the initial discovery of this virus, HDV has not received any widespread attention until recently (i.e., in the late 2010s), when epidemiology studies found that the prevalence of HDV was previously underestimated and that the disease posed a greater burden than previously anticipated.[3,4]

Natural History of Hepatitis D

HDV is a virus that requires the HBV virus to replicate within the body and spread between individuals.[1] The key components of HDV are that it is a type of ribonucleic acid (RNA) virus, structurally comprising the hepatitis D antigen and a lipoprotein envelope derived from HBV.[1] For any type of HDV infection to occur, HDV requires HBV surface antigens as its envelope protein to facilitate with its own infections.[1]

HDV infections can be acute or chronic.[5] Acute hepatitis D is a short-term illness that can last up to six months.[6] Chronic HDV lasts more than six months and can lead to serious long-term illness, resulting in liver cirrhosis or liver death.[6] HDV is an infection that can happen simultaneously with HBV, where patients become infected with HBV and HDV at the same time. This is known as coinfection.[5] The clinical presentation of a coinfected patient is similar to that of a patient with acute HBV.[7] Coinfections resolve spontaneously over time.[5]

Infections can also occur chronologically, where patients will be already infected with chronic hepatitis B (CHB) and then eventually infected with HDV. This is known as superinfection.[5] Patients who are diagnosed with CHB may develop a superinfection and present as severe acute hepatitis or an exacerbation of pre-existing chronic HBV.[7] Superinfections can result in rapid progression of liver cirrhosis, liver failure and HCC.[5] For individuals with superinfections, progression of cirrhosis occurs within 2-10 years (5 years on average) for 70-80% of cases[4,8], while HCC tends to develop within 10 years of infection.[4] The majority of HDV-related deaths come from infected individuals progressing to cirrhosis and HCC, making HDV a global health concern.[9]

There are three primary ways that HDV can be spread, and these are similar to the modes in which HBV is transmitted: percutaneous, sexual and perinatal.[5] The first mode of transmission is percutaneous, which is HBV being transmitted through puncture of the skin that comes into contact with an individual infected blood or bodily fluid.[10] The second mode of transmission is sexual; HBV can be transmitted from person to person through semen and other bodily fluids.[11] The third and most common mode of HBV transmission in endemic countries is perinatal.[12] Perinatal transmission is when an infected pregnant mother infects a child.[12] Children who are born with HBV-infected mothers have a greater than 90% chance of developing chronic hepatitis B (CHB) if they are not appropriately treated at birth.[12]

Diagnosis, prevention, treatment and cure for Hepatitis D

Anti-HDV immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies are the main serological markers for identifying an HDV infection.[13] Following a positive IgG or IgM result, an active infection is confirmed by conducting HDV RNA tests.[14] These tests, which are also used to monitor response to antiviral therapy, are not standardized and result in varying test outcomes.[14]

There is no known cure for HDV infections, and prior to 2024, pegylated interferon alpha (pegylated IFN-α), a therapeutic class of biological response modifier, was the only available HDV treatment for infected patients.[14] However, pegylated IFN-α has many associated mild to severe side effects, including flu-like symptoms, fatigue, headache, injection site reactions, gastrointestinal issues, depression, and anxiety.[15] Moreover, only 20% of patients will likely demonstrate notable clinical improvement because of this treatment.[16] At the same time, this treatment is not recommended for patients with decompensated cirrhosis, mental health conditions and autoimmune diseases.[5]

New therapies are being developed because pegylated IFN-α has limited effectiveness, although it will likely limit disease progression.[5,17,18] One such treatment that is first-in-class as an entry inhibitor for HDV is called Bulevirtide (BLV).[19] This new treatment has shown promising efficacy when 2mg is administered for 24 or 48 weeks as a monotherapy or combined with pegylated IFN-α in clinical trials and in the real world.[19] BLV combined with pegylated IFN-α is 41% more effective than pegylated IFN-α alone.[20] BLV, as a monotherapy, compared to pegylated interferon alpha, is 18% more effective.[20] Unfortunately, the Food and Drug Administration (FDA) has not approved this new treatment due to manufacturing and delivery concerns that have yet to be disclosed.[21] However, the European Medicines Agency (EMA) approved the usage of BLV for HDV patients in 2023.[22]

Other emerging forms of therapy, such a lonafarnib and interferon lambda polymers are in the pipeline showing promising results.[17,18] However, we focused on BLV because it is more established and well-studied compared with other emerging treatment options.

There is a consensus that HBV vaccination is an effective strategy to prevent HDV infection, given the replicative nature of HDV.[5,8,16] Targeting individuals at high risk of HBV would, therefore, control the spread of both HBV and HDV.[8] However, vaccination is less effective if a patient is already infected with HBV.[5,16] While the World Health Organization does not have an official recommendation for HDV, universal infant vaccination for hepatitis B is recommended by other authorities.[23]

Prevalence of Hepatitis D

While it is estimated that HDV affects millions of people globally[24], the actual global prevalence rate is unknown. There are three meta-analyses that attempted to estimate the global prevalence of HDV: Stockdale et al 2020, Miao et al 2020, and Chen et al 2019.[4,24,25] For Stockdale et al 2020, it was estimated that the global HDV prevalence among hepatitis B surface antigens (HBsAg) infected individuals was 4.5%, with an overall HDV prevalence of 0.16%, which corresponds to an estimated total prevalence of 12 million cases.[24] For Miao et al 2020, they estimated that the global HDV prevalence among HBsAg infected individuals was 13.02%, with an overall HDV prevalence of 0.8%, which corresponds to an estimated total prevalence of 48 to 60 million cases.[26] Meanwhile, in Chen et al 2019, the estimated global HDV prevalence rate was 10.58% among HBsAg carriers, with an estimated overall HDV prevalence of 0.98% globally which was associated with a total of 72 million cases.[25]

These meta-analyses are not without notable limitations, making their estimates unreliable. Firstly, these estimates are markedly different ranging from 12 million to 72 million cases.[4,24,25] The main reason for this disparity is that there were limited data collected on HDV prevalence and treatment in specific regions, mainly North America, Latin America, Southern Africa and most of Asia.[4,24] Additionally, researchers explained that the study quality, data sources and study population could be potential causes of bias in the estimate of the HDV prevalence rate.[4,24]

HDV in Canada

HDV is an important public health concern in Canada.[27] However, the true national prevalence of HDV is also uncertain. This uncertainty is because of a lack of standardized testing and the absence of routine screening.[23] Nevertheless, a national prevalence rate of 3.0% in 2020 was reported by Razavi-Shearer, D. et al[28], and approximately 2-20% of cases are expected to die.[23] Although Canada is considered one of the low-endemic countries in the world (with an HDV prevalence < 2%)[29,30], there is concern that the growing immigrant population contributes to maintaining the prevalence rate as many individuals from within this group originate from countries with high HDV and HBV endemicity.[29,31,32] There is further concern that the proportion of undiagnosed individuals remains unknown because only 50% of HBV-positive cases are tested for HDV infection.[32]

Given the link between HBV and HDV, interventions aimed at preventing the spread of HBV would also curtail the transmission of HDV. In Canada, various HBV interventions are in place across the country.[29] For example, screening for HBV is recommended for specific patient groups, including but are not limited to, pregnant women, inmates, patients with chronic renal failure needing dialysis, and those with signs of liver disease or other infectious diseases like Hepatitis C, among others.[33]

Vaccines are 95% to 100% effective in preventing HBV infections.[29] Canada's current vaccination policy focuses on routine immunization of children, including adolescents and preadolescents.[33] However, in Ontario, HBV vaccines are given at grade 7 instead of at birth, which leaves children with the chance of being infected with the disease.[34] In other provinces, new mothers are screened to identify whether their babies would be likely candidates for vaccinations.[34] Other eligible groups for vaccination include, persons who were exposed to blood or bodily fluids containing HBV, individuals in household where HBV is present, and individuals who have had sexual contact with an acute or chronic HBV carrier.[29] There is currently no formal screening program for immigrants in Ontario.[34]

HBV treatment options are generally effective and lifelong lasting.[35] All approved HBV treatments in Ontario are adefovir, entecavir, tenofovir, lamivudine, telbivudine and pegylated interferon-2b. However, the latter two treatment options are not funded by the Ontario public drug program.[35]

Meanwhile, current HDV-specific recommendations call for screening the following candidates in Canada: HBV positive patients in HDV endemic regions, persons with a history of injection drug use, persons with abnormal Alanine Transaminase (ALT), persons with advanced liver disease.[33] The recommended screening process include the utilization of an approved HDV antibody assay for HDV detection and an HDV RNA test to confirm active infections.[33] However, in Ontario, Public Health Ontario only has serology HDV tests available.[36] These test are performed on Hepatitis B surface antigen (HBsAg) positive samples.[36] In terms of treatment, weekly doses of 180 µg of pegylated IFN-α for 48 weeks are also recommended.[33]

Knowledge Gap

We have identified several gaps based on a review of the literature on HDV in Canada. We summarize them here. Although the true prevalence of HDV is unknown, Canada is a relatively low HDV-endemic country, with a large migrant population from high HBV-HDV-endemic countries.[29] Available estimates of HDV prevalence in Canada are unreliable because of methodological limitations.[27] The current treatment therapy for HDV is not fully effective, but new ones show greater promise, yet they are not readily available.[32] The cost-effectiveness of screening and treating diagnosed individuals with more effective treatment options in Canada is also unknown. Additionally, to our knowledge, there is no decision model that assesses screening or treatment of HDV in Canada. These gaps were also echo by Coffin et al in their call for research to provide further evidence on HDV epidemiology, natural history, and the effectiveness of new treatments.[33]

This study intends to bridge these gaps in the literature. We posit that knowledge of the true prevalence of the disease and the cost-effectiveness of care is important in informing and funding appropriate policy interventions to mitigate the spread and burden associated with HDV.

Objectives

Given the knowledge gap, our study seeks to answer two major questions: (1) what is the true prevalence of HDV in Canada, and (2) is screening-and-treating HDV-positive migrants in Canada cost-effective? The goal of this study is to answer these questions. The first objective is to estimate the overall prevalence of hepatitis D among immigrants in a Canadian setting. The second objective is to assess the cost-effectiveness of HDV screening and treating patients with BLV, pegylated interferon alfa-2a and combined therapy compared with no screening for HDV. To achieve the second objective, this study also intends to develop a state-transition model of the natural history of HDV that can be used to estimate the potential incidence of HDV in Canada. This analysis allows us to assess the health and economic impact of modifying treatment in the Canadian population.

Chapter 2
Estimation of the Prevalence of HDV among Canadian immigrants in Canada in 2021

Introduction

In this chapter, we estimate the prevalence of HDV among the immigrant population in Canada for the year 2021. As highlighted in the previous chapter, the true prevalence of HDV is unknown. This uncertainty stems from limited awareness of the disease, the lack of routine testing of HBV-positive individuals in clinical practice, and the lack of standardized HDV RNA tests that produce varying results.[37,38] Country-level studies estimating the national HDV prevalence rate are also rare. One recent study estimated HDV prevalence to be 3% of the Canadian population in 2021.[32] A few provincial studies can be identified in the literature, with prevalence rates ranging from 0% to 1.6%.[39,40] Researchers, however, cautioned that these estimates might be unreliable because they were based on limited available data, restricted inclusion criteria and small sample sizes.[37] Even further, little is known of the undiagnosed proportion of the HDV population. The contribution of the immigrant population to the total disease burden is also unknown.

Accurately estimating the prevalence of HDV, including the prevalence among the immigrant population in Canada, is critical to inform appropriate interventions around screening, treatment and prevention to lessen the burden of the disease. It will also guide funding decisions related to these interventions.[24] Understanding the prevalence rate of HDV among the immigrant population is also crucial because this group represents a substantial portion of the total number of HDV cases in Canada.[41] Over the period 1970 – 2021, Canada received a total of 8,359,155 immigrants, most of whom emigrated from Western Africa, Central Africa, and Southeast Asia: regions known to have a high prevalence of CHB cases.[42,43] These individuals also have an increased chance of developing HDV compared with Canadian-born residents.[24] Therefore, in this chapter, we developed and executed a unique methodology to estimate the prevalence of HDV among the immigrant population in Canada.

Methodology

Study Design

To estimate the prevalence of HDV among the immigrant population in Canada, we conducted a literature review and a weighted average analysis. The literature review was performed to identify suitable studies with relevant data on HDV prevalence from countries around the world. These studies estimated the prevalence of HDV among HBV-infected populations. We also estimated the prevalence of HBV among Canadian immigrants using data on migration from Statistics Canada and regional HBV data across the world from Sheena et al.[9] We then combined the data on HBV prevalence with data on HDV prevalence from countries where migrants originated to estimate the prevalence of HDV among Canadian immigrants using a weighted average analysis.

Search strategy for HDV prevalence studies

To identify all relevant literature, we conducted literature searches in PubMed and Embase. This included a combination of keywords and controlled vocabulary (dependent on database availability) related to Hepatitis D, HDV prevalence, and geographical locations, including specific countries and regions. These terms were used individually and together, separated by the logical operators 'and' or 'or' for each respective database. The specific search terms are provided in the appendix. Only literature published between 2000 and 2023 were considered because they are more recent and more likely to represent-current HDV prevalence rates.[44]

Search strategy for HBV prevalence

Regional HBV prevalence rates were taken from a recent systematic review that estimated the burden of the disease across the world.[9]

Eligibility criteria, study selection and data extraction

Studies eligible for inclusion were those that reported HDV prevalence in the general population of a specific country or studies that reported HDV prevalence based on HBV-infected populations of a specific country of origin. Studies that did not report on HDV prevalence after the year 2000 were excluded. Abstracts were not included because of concerns about the quality of the method provided. We only included studies that were written in English.

The author screened all the titles and abstracts based on the aforementioned inclusion-exclusion criteria. Those that met these criteria were selected for full-text review. During this process, the author further assessed whether the studies were eligible for final review based on the inclusion-exclusion criteria.

All relevant data from the final selection of HDV studies were extracted by the author. For each study, data were extracted on the country/region of focus, HDV prevalence, and on each articles reference.

Immigrant Data

Data on the Canadian immigrant population by country of birth and year of entry were sourced from the Statistics Canada census for the year 2021.[43] We created a data analysis spreadsheet with every country listed, grouping them by specific geographic regions. We identified 47 countries from which individuals emigrated. The specific regions of focus were North America, Central America, the Caribbean, South America, Western Europe, Eastern Europe, Northern Europe, Southern Europe, Western Africa, Eastern Africa, Northern Africa, Central Africa, Southern Africa, West Central Asia and the Middle East, Eastern Asia, Southeast Asia, Southern Asia, and Oceania.[45]

Data synthesis and analysis

Given that HDV research is very limited for countries that do not have published data, we assumed that the HDV prevalence for such countries was equal to the average of that specific region.

To calculate the prevalence of HDV among the Canadian immigrant population, we first estimated the number of immigrants with HBV residing in Canada in 2021. This was done by multiplying the number of people who immigrated to Canada from each country of origin by the prevalence of HBV in the corresponding country. We then multiplied the estimated number of immigrants infected with HBV by the HDV prevalence rate of each country of origin. To estimate the prevalence of HDV among immigrants in Canada, we divided the total number of immigrants with HDV by the total immigrant population. These formulae provided below.

$$IMM^{HBV} = \sum_{i=1}^{n}(HBV_i^P \times IMM_i)$$

$$IMM^{HDV} = \sum_{i=1}^{n}(HDV_i^P \times IMM_i^{HBV})$$

$$HDV_{IMM}^P = \frac{IMM^{HDV}}{\sum_{i=1}^{n} IMM_i}$$

Where,

IMM^{HBV} – Estimated number of immigrants in Canada with an HBV infection

HBV_i^P – Prevalence of HBV in source country *i*

IMM_i – Number of immigrants to Canada from source country *i*

HDV_i^P – Proportion of HDV among infected HBV individuals in source country *i*

IMM^{HDV}– Estimated number of immigrants in Canada with an HDV infection

HDV_{IMM}^P – Estimated prevalence of HDV among immigrants in Canada

i – individual source countries, where *i* =1, …,n.

Twenty-five studies that reported country-specific HDV prevalence rates were selected from 1,895 studies identified from the search strategy. Figure 1 presents the study selection process. The countries that had at least one study reporting HDV prevalence were the United States, Romania, Italy, Spain, Uzbekistan, Afghanistan, China, Pakistan, India, Japan, Mongolia, Vietnam, Malaysia, Kiribati, Cuba, Uganda, Austria, Bulgaria, Finland, Germany, Netherlands, Norway, Sweden, United Kingdom, Australia, New Zealand, Argentina, Brazil, Taiwan, Thailand, Peru, Malawi, France, Denmark, Greenland, Nigeria, Mali, Senegal, Burkina Faso, Ghana, Somalia, Ethiopia, Libya, Algeria, Egypt, Tunisia, Cameroon, and Mexico. When there were multiple studies reporting HDV prevalence for a specific country, we selected the most recent study for that specific country to reflect the most recent prevalence.

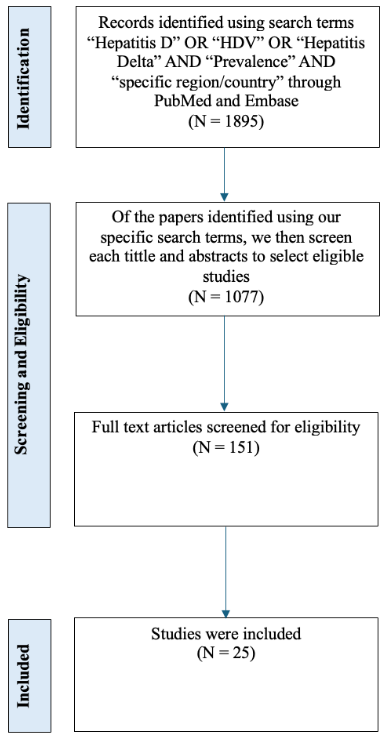


Figure 1: Flow Chart of study selection for literature review

Results

The overall prevalence of HBV among all immigrants in Canada in 2021 was estimated to be 3.1% (95% CI: 2.8% - 3.5%), which was equivalent to 259,897 immigrants.

The distribution of HBV cases by source region is as follows:

Americas (North, Central, and South combined) 0.85% (95% CI: 0.67% - 0.10%), Europe (Western, Eastern, Northern and Southern combined) 0.72% (95% CI: 0.62% - 0.80%), Africa (Western, Eastern, Central, Northern and Southern combined) 5.01% (95% CI: 4.39% - 5.60%), Asia and the Middle East (Eastern, Southeast, and Southern combined) 4.48% (95% CI: 4.00% - 4.99%), and Oceania 2.56% (95% CI: 2.24% - 2.87%). See Table 1 below.

The top 5 source countries with the highest HBV infections were the Philippines 8.2% (95% CI: 7.2% - 9.4%), China 6.5% (95% CI: 5.8% - 7.1%), India 2.9% (95% CI: 2.6% - 3.3%), Vietnam 6.6% (95% CI: 6.3% - 6.9%), and Nigeria 9.9% (95% CI: 8.6% - 11.3%). See Table 2 below.

Among the immigrants infected with HBV, we estimated that 7.7% (95% CI: 5.7% - 9.7%) were also infected with HDV. This corresponded to an overall HDV prevalence rate of 0.24% (95% CI: 0.15% - 0.33%), which was equivalent 20,102 immigrants.

Looking at the HDV prevalence per continent, we were able to estimate the distribution of HDV cases based on source regions as follows:

America (North, Central, and South combined) 0.015% (95% CI: 0.009% - 0.026%), Europe (Western, Eastern, Northern and Southern combined) 0.041% (95% CI: 0.026% - 0.058%), Africa (Western, Eastern, Central, Northern and Southern combined) 0.62% (95% CI: 0.37% - 0.86%) Asia and the middle east (Eastern, Southeast, and Southern combined) 0.32% (95% CI: 0.21% - 0.44%), and Oceania 0.23% (95% CI: 0.15% - 0.33%). See Table 1 below.

The top 5 source countries with the highest HDV infections were the Philippines 0.59% (95% CI: 0.39% - 0.85%), China 0.45% (95% CI: 0.30% - 0.61%), India 0.22% (95% CI: 0.15 – 0.31%), Vietnam 1.02% (95% CI: 0.72% - 1.33%) and Congo 3.46% (95% CI: 2.76% - 4.21%). See Table 2 below.

Table 1: Overall prevalence for HBV and HDV based on regions

Countries/Region	Immigrant population	HBV Prevalence (%)	HBV population	HDV Prevalence among HBV population (%)	HDV population	Overall HDV Prevalence
All Immigrants	8,359,155	3.1 (2.8 – 3.5)	259897	7.73 (5.67-9.66)	20102	0.24 (0.15 – 0.33)
Americas	1,200,895	0.8 (0.7 – 0.9)	10209	1.76 (1.22 – 2.65)	182	0.015 (0.009 – 0.026)
Europe	1,967,620	0.7 (0.6 – 0.8)	14158	6.86 (5.18 – 8.57)	977	0.04098 (0.02624 – 0.05831)
Africa	821,735	5.0 (4.4 – 5.6)	41191	12.43 (8.52 – 15.38)	5116	0.62254 (0.37005 – 0.85645)

Asia and the Middle East	4,307,000	4.5 (3.9 – 5.0)	192756	7.09 (5.33 – 8.87)	13684	0.317709 (0.213357 – 0.441975)
Oceania	61,905	2.6 (2.2 – 2.9)	1583	9.08 (6.83 – 11.33)	144	0.232224 (0.150633 – 0.329413)

Table 2: Overall prevalence for HBV and HDV among Canadian immigrants in 2021

Countries/Region	**Immigrant population**	**HBV Prevalence (%)**	**HBV population**	**HDV Prevalence among HBV population (%)**	**HDV population**	**Overall HDV Prevalence**
All Immigrants	8,359,155	3.1 (2.8 – 3.5)	259897	7.73 (5.67-9.66)	20102	0.24 (0.15 – 0.33)
Americas	1,200,895	0.8 (0.7 – 0.9)	10209	1.76 (1.22 – 2.65)	182	0.015 (0.009 – 0.026)
North America	**256,465**	**0.3 (0.3 – 0.4)**	**772**	**3.39 (2.54 – 4.24)**	**26**	**0.010 (0.008 – 0.017)**
Greenland	25	1.4 (1.1 – 1.7)	0	1.1 (0.83 – 1.38)	0	0.0154 (0.009 – 0.023)
Saint Pierre and Miquelon	355	0.85 (0.7 – 1.1)	3	2.25 (1.69 – 2.81)	0	0.019 (0.012 – 0.029)
United States of America	256,090	0.3 (0.3 – 0.4)	768	3.4 (2.55 – 4.25)	26	0.010 (0.008 – 0.017)
Central America	**187,250**	**0.5 (0.4 – 0.6)**	**976**	**4.0 (3.0 – 5.0)**	**39**	**0.021 (0.013 – 0.029)**
Belize	2,015	0.6 (0.5 – 0.6)	12	4.0 (3.0 – 5.0)	0	0.024 (0.015 – 0.030)
Costa Rica	4,660	0.7 (0.6 – 0.9)	33	4.0 (3.0 – 5.0)	1	0.028 (0.018 – 0.045)
El Salvador	49,450	0.7 (0.5 – 0.8)	346	4.0 (3.0 – 5.0)	14	0.028 (0.015 – 0.040)

Guatemala	18,035	1.2 (1 – 1.4)	216	4.0 (3.0 – 5.0)	9	0.048 (0.030 – 0.070)
Honduras	8,980	1.1 (0.9 – 1.3)	99	4.0 (3.0 – 5.0)	4	0.044 (0.027 – 0.065)
Mexico	90,585	0.2 (0.2 – 0.2)	181	4.0 (3.0 – 5.0)	7	0.008 (0.006 – 0.010)
Nicaragua	10,735	0.7 (0.7 – 0.8)	75	4.0 (3.0 – 5.0)	3	0.028 (0.021 – 0.040)
Panama	2,800	0.5 (0.4 – 0.6)	14	4.0 (3.0 – 5.0)	1	0.020 (0.012 – 0.030)
Caribbean and Bermuda	**402,780**	**0.7 (0.5 – 0.8)**	**3341**	**0.34 (0.10 – 1.25)**	**13**	**0.003 (0.0006 – 0.012)**
Anguilla	85	0.6 (0.5 – 0.7)	1	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Antigua and Barbuda	2,430	0.5 (0.5 – 0.5)	12	0.39 (0.11 – 1.44)	0	0.00195 (0.00044 – 0.0072)
Aruba	480	0.6 (0.5 – 0.7)	3	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Bahamas	2,145	0.5 (0.5 – 0.6)	11	0.39 (0.11 – 1.44)	0	0.00195 (0.00044 – 0.00864)
Barbados	13,665	0.6 (0.5 – 0.7)	82	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.0072)
Bermuda	1,795	0.5 (0.5 – 0.6)	9	0.39 (0.11 – 1.44)	0	0.00195 (0.00044 – 0.00864)
Cayman Islands	170	0.6 (0.5 – 0.7)	1	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Cuba	19,545	0.6 (0.5 – 0.7)	117	0.39 (0.11 – 1.44)	0	0.00234 (0.00033 – 0.0072)
Dominica	2,905	0.6 (0.5 – 0.7)	17	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)

Dominican Republic	13,360	0.7 (0.5 – 0.8)	94	0.39 (0.11 – 1.44)	0	0.00273 (0.00066 – 0.01152)
Grenada	9,895	0.6 (0.5 – 0.7)	59	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Guadeloupe	650	0.6 (0.5 – 0.7)	4	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Haiti	99,945	1.6 (0.5 – 1.9)	1599	0.39 (0.11 – 1.44)	6	0.00624 (0.00143 – 0.02736)
Jamaica	145,360	0.6 (0.5 – 0.7)	872	0.39 (0.11 – 1.44)	3	0.00117 (0.00022 – 0.00432)
Martinique	700	0.6 (0.5 – 0.7)	4	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Montserrat	580	0.6 (0.5 – 0.7)	3	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Netherlands Antilles		0.6 (0.5 – 0.7)	0	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Puerto Rico	490	0.6 (0.5 – 0.7)	3	0.39 (0.11 – 1.44)	0	0.00234 (0.00033 – 0.0072)
Saint Kitts and Nevis	2,030	0.6 (0.5 – 0.7)	12	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Saint Lucia	6,730	0.6 (0.5 – 0.7)	40	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Saint Vincent and the Grenadines	13,930	0.5 (0.5 – 0.6)	70	0.39 (0.11 – 1.44)	0	0.00195 (0.00044 – 0.00864)
Trinidad and Tobago	65,035	0.5 (0.5 – 0.6)	325	0.39 (0.11 – 1.44)	1	0.00195 (0.00044 – 0.00864)
Turks and Caicos Islands	90	0.6 (0.5 – 0.7)	1	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)
Virgin Islands, British	95	0.6 (0.5 – 0.7)	1	0.39 (0.11 – 1.44)	0	0.00234 (0.00055 – 0.01008)

Virgin Islands, US	80	0.6 (0.5 – 0.7)	0	0.39 (0.11 – 1.44)	0	0.00234 (0.00044 – 0.0072)
South America	**354,395**	**1.4 (1.2 – 1.7)**	**5120**	**2.02 (1.42 – 2.87)**	**104**	**0.029236 (0.01747 – 0.04805)**
Argentina	19,530	0.3 (0.3 – 0.4)	59	0.27 (0.21 – 0.33)	0	0.00081 (0.00063 – 0.00132)
Bolivia	3,835	0.6 (0.5 – 0.6)	23	2.27 (1.71 – 2.83)	1	0.01362 (0.00855 – 0.01698)
Brazil	48,450	3.4 (3.0 – 3.8)	1647	1.29 (0.97 – 1.61)	21	0.04386 (0.0291 – 0.06118)
Chile	27,755	0.5 (0.4 – 0.6)	139	2.27 (1.71 – 2.83)	3	0.01135 (0.00684 – 0.01698)
Colombia	80,570	2.5 (2.1 – 2.9)	2014	2.27 (1.71 – 2.83)	46	0.05675 (0.03591 -0.08207)
Ecuador	16,320	0.5 (0.4 – 0.4)	82	2.27 (1.71 – 2.83)	2	0.01135 (0.00684 – 0.01415)
Falkland Islands (Malvinas)	15	1.1 (0.9 – 1.3)	0	2.27 (1.71 – 2.83)	0	0.02497 (0.01539 – 0.03679)
French Guiana	175	1.1 (0.9 – 1.3)	2	2.27 (1.71 – 2.83)	0	0.02497 (0.01539 – 0.03679)
Guyana	85,530	0.7 (0.6 – 0.6)	599	2.27 (1.71 – 2.83)	14	0.01589 (0.01026 – 0.02264)
Paraguay	6,085	3.0 (2.4 – 3.5)	183	2.27 (1.71 – 2.83)	4	0.0681 (0.04104 – 0.09905)
Peru	31,420	0.5 (0.5 – 0.6)	157	5.26 (0.64 – 17.74)	8	0.0263 (0.0032 – 0.10644)
Suriname	960	0.6 (0.5 – 0.7)	6	2.27 (1.71 – 2.83)	0	0.01362 (0.00855 – 0.01981)
Uruguay	6,435	0.3 (0.2 – 0.3)	19	2.27 (1.71 – 2.83)	0	0.00681 (0.00342 – 0.00849)

Venezuela	27,320	0.7 (0.6 – 0.9)	191	2.27 (1.71 – 2.83)	4	0.01589 (0.01026 – 0.02547)
Europe	**1,967,620**	**0.7 (0.6 – 0.8)**	**14158**	**6.86 (5.18 – 8.57)**	**977**	**0.04098 (0.02624 – 0.05831)**
Western Europe	**375,105**	**0.9 (0.7 – 0.9)**	**3244**	**0.91 (0.69 – 1.14)**	**30**	**0.0079 (0.00508 – 0.01024)**
Austria	13,840	0.8 (0.6 – 0.9)	111	0.55 (0.42 – 0.68)	1	0.0044 (0.00252 – 0.00612)
Belgium	18,650	0.5 (0.5 – 0.6)	93	0.86 (0.65 – 1.07)	1	0.0043 (0.00325 – 0.00642)
France	121,525	1.4 (1.3 – 1.4)	1701	0.85 (0.64 – 1.06)	14	0.0119 (0.00832 – 0.01484)
Germany	126,470	0.4 (0.3 – 0.4)	506	1.2 (0.9 – 1.5)	6	0.0048 (0.0027 – 0.006)
Liechtenstein	15	0.8 (0.7 – 0.9)	0	0.86 (0.65 – 1.07)	0	0.00688 (0.00455 – 0.00963)
Luxembourg	455	0.8 (0.6 – 0.9)	4	0.86 (0.65 – 1.07)	0	0.00688 (0.0039 – 0.00963)
Monaco	130	0.7 (0.5 – 0.8)	1	0.86 (0.65 – 1.07)	0	0.00602 (0.00325 – 0.00856)
Netherlands	75,830	0.9 (0.7 – 1.0)	682	0.94 (0.70 – 1.18)	6	0.00846 (0.0049 – 0.0118)
Switzerland	18,185	0.8 (0.7 – 0.9)	145	0.86 (0.65 – 1.07)	1	0.00688 (0.00455 – 0.00963)
Eastern Europe	**512,350**	**0.5 (0.4 – 0.6)**	**2490**	**16.30 (12.45 – 20.35)**	**412**	**0.04713 (0.03034 – 0.06611)**
Bulgaria	19,170	2.4 (2.3 – 2.5)	460	1.4 (1.05 – 1.75)	6	0.0336 (0.02415 – 0.04375)
Czech and Slovak Federal Republic, Former	32,505	1.1 (0.9 – 1.2)	209	11.92 (8.98 – 14.87)	25	0.0766 (0.05093 – 0.10658)

Czech Republic	19,550	0.9 (0.8 – 1)	176	8.9 (6.7 – 11.1)	16	0.0801 (0.0536 – 0.111)
Slovakia	12,955	0.8 (0.7 – 0.9)	104	8.9 (6.7 – 11.1)	9	0.0712 (0.0469 – 0.0999)
Czechoslovakia, N.O.S		0.9 (0.8 – 1)	0	8.9 (6.7 – 11.1)	0	0.0801 (0.0536 – 0.111)
Hungary	31,050	0.7 (0.6 – 0.7)	217	8.9 (6.7 – 11.1)	19	0.0623 (0.0402 – 0.0777)
Poland	135,030	0.4 (0.4 – 0.5)	540	8.9 (6.7 – 11.1)	48	0.0356 (0.0268 – 0.0555)
Romania	86,770	1 (0.8 – 1.1)	868	16.4 (12.3 – 20.5)	142	0.164 (0.0984 – 0.2255)
USSR, Former (European Component)	207,840	0.03 (0.02 – 0.04)	56	8.9 (6.7 – 11.1)	171	0.00022 (0.00009 – 0.00046)
Baltic Republics, Former Soviet	12,605	0.5 (0.4 – 0.6)	63	8.9 (6.7 – 11.1)	6	0.0445 (0.0295 – 0.0666)
Estonia	2,600	0.5 (0.4 – 0.6)	13	8.9 (6.7 – 11.1)	1	0.0445 (0.0268 – 0.0666)
Latvia	5,075	0.5 (0.4 – 0.6)	25	8.9 (6.7 – 11.1)	2	0.0445 (0.0335 – 0.0666)
Lithuania	4,930	0.5 (0.4 – 0.6)	25	8.9 (6.7 – 11.1)	2	0.0445 (0.0268 – 0.0666)
Eastern Europe Republics, Former Soviet	195,235	1.0 (0.8 – 1.1)	1860	8.9 (6.7 – 11.1)	166	0.08478 (0.05365 – 0.12076)
Belarus	12,190	0.6 (0.5 – 0.6)	73	8.9 (6.7 – 11.1)	6	0.0534 (0.0335 – 0.0666)
Moldova, Republic of	20,070	1.2 (1.0 – 1.3)	241	8.9 (6.7 – 11.1)	21	0.1068 (0.067 – 0.1443)
Russian Federation	81,840	0.6 (0.5 – 0.7)	491	8.9 (6.7 – 11.1)	44	0.0534 (0.0335 – 0.0777)

Ukraine	81,135	1.3 (1.1 – 1.5)	1055	8.9 (6.7 – 11.1)	94	0.1157 (0.0737 – 0.1665)
USSR, n.o.s		0.9 (0.8 – 1.0)	0	8.9 (6.7 – 11.1)	0	0.0801 (0.0536 – 0.111)
Northern Europe	**524,995**	**0.7 (0.6 – 0.8)**	**3656**	**2.73 (2.05 – 3.42)**	**100**	**0.01903 (0.01222 – 0.02721)**
Ireland	29,300	0.6 (0.5 – 0.7)	176	1.95 (1.46 – 2.44)	3	0.0117 (0.0073 – 0.01708)
Scandinavia	30,595	0.8 (0.6 – 0.9)	231	1.24 (0.93 – 1.56)	3	0.0094 (0.00601 – 0.01372)
Denmark	11,000	0.9 (0.7 – 1.0)	99	0.7 (0.52 – 0.88)	1	0.0063 (0.00364 – 0.0088)
Finland	8,420	0.9 (0.7 – 1.0)	76	0.94 (0.7 – 1.18)	1	0.00846 (0.0049 – 0.0118)
Iceland	650	0.6 (0.5 – 0.8)	4	1.95 (1.46 – 2.44)	0	0.0117 (0.0073 – 0.01952)
Norway	3,845	0.5 (0.4 – 0.6)	19	2.47 (1.85 – 3.09)	0	0.01235 (0.0074 – 0.01854)
Sweden	6,680	0.5 (0.5 – 0.6)	33	2.78 (2.08 – 3.48)	1	0.0139 (0.0104 – 0.02088)
United Kingdom	464,135	0.7 (0.6 – 0.8)	3249	2.88 (2.16 – 3.6)	94	0.02016 (0.01296 – 0.0288)
Southern Europe	**555,170**	**0.9 (0.7 – 1.0)**	**4768**	**9.13 (6.84 – 11.42)**	**435**	**0.07841 (0.05002 – 0.11299)**
Albania	17,825	0.6 (0.6 – 0.7)	107	8.05 (6.04 – 10.06)	9	0.0483 (0.03624 – 0.07042)
Andorra	55	0.9 (0.7 – 1.1)	0	8.05 (6.04 – 10.06)	0	0.07245 (0.04228 – 0.11066)
Gibraltar	200	0.8 (0.7 – 1.0)	2	8.05 (6.04 – 10.06)	0	0.0644 (0.04228 – 0.1006)

Greece	54,715	1.8 (1.6 – 2.0)	985	8.05 (6.04 – 10.06)	79	0.1449 (0.09664 – 0.2012)
Holy See (Vatican City)	0	0.8 (0.7 – 1.0)	0	8.05 (6.04 – 10.06)	0	0.0644 (0.04228 0 0.1006)
Italy	204,065	0.7 (0.6 – 0.8)	1428	11.9 (8.9 – 14.9)	170	0.0833 (0.0534 – 0.1192)
Malta	6,300	0.6 (0.5 – 0.7)	38	8.05 (6.04 – 10.06)	3	0.0483 (0.0302 – 0.07042)
Portugal	128,795	0.9 (0.7 – 1.1)	1159	8.05 (6.04 – 10.06)	93	0.07245 (0.04228 – 0.11066)
San Marino	0	0.7 (0.6 – 0.8)	0	8.05 (6.04 – 10.06)	0	0.05635 (0.03624 – 0.08048)
Spain	11,510	0.8 (0.7 – 0.8)	92	4.2 (3.15 – 5.25)	4	0.0336 (0.02205 – 0.042)
Yugoslavia, Former [14]	123,235	0.8 (0.7 – 0.9)	957	8.05 (6.04 – 10.06)	77	0.062516 (0.04087 – 0.08875)
Bosnia and Herzegovina	35,925	0.6 (0.5 – 0.7)	216	8.05 (6.04 – 10.06)	17	0.0483 (0.0302 – 0.07042)
Croatia	36,675	1.1 (1.0 – 1.2)	403	8.05 (6.04 – 10.06)	32	0.08855 (0.0604 – 0.12042)
Macedonia	10,195	0.8 (0.7 – 0.9)	82	8.05 (6.04 – 10.06)	7	0.0644 (0.04228 – 0.09054)
Serbia and Montenegro	33,505	0.6 (0.5 – 0.7)	201	8.05 (6.04 – 10.06)	16	0.0483 (0.0302 – 0.07042)
Slovenia	6,935	0.8 (0.7 – 1.0)	55	8.05 (6.04 – 10.06)	4	0.0644 (0.04228 – 0.1006)
Yugoslavia, n.o.s [16]		0.8 (0.7 – 1.0)	0	8.05 (6.04 – 10.06)	0	0.0644 (0.04228 – 0.1006)
Africa	**821,735**	**5.0 (4.4 – 5.6)**	**41191**	**12.43 (8.52 – 15.38)**	**5116**	**0.62254 (0.37005 – 0.85645)**

Western Africa	**166,155**	**9.1 (7.9 – 10.1)**	**15149**	**7.06 (5.28 – 8.83)**	**1069**	**0.64337 (0.42013 – 0.89412)**
Benin	3,885	7.6 (6.2 – 8.8)	295	5.48 (4.11 – 6.85)	16	0.41648 (0.25482 – 0.6028)
Burkina Faso	2,935	12.1 (10.1 – 14.1)	358	3.4 (2.55 – 4.25)	12	0.4148 (0.25755 – 0.59925)
Cape Verde	250	6.5 (5.0 – 7.6)	16	5.48 (4.11 – 6.85)	1	0.3562 (0.2055 – 0.5206)
Cote d'lvoire	18,865	7.9 (6.7 - 7.9)	1490	5.48 (4.11 – 6.85)	82	0.43292 (0.27537 – 0.4795)
Gambia	850	3.0 (2.9 – 3.1)	26	5.48 (4.11 – 6.85)	1	0.1644 (0.1192 – 0.2124)
Ghana	25,755	9.1 (8.3 – 9.9)	2344	11.3 (8.47 – 14.13)	265	1.0283 (0.70301 – 1.39887)
Guinea	6,205	11.7 (9.5 – 13.6)	726	5.48 (4.11 – 6.85)	40	0.64116 (0.39045 – 0.9316)
Guinea-Bissau	110	10.8 (9.0 – 12.4)	12	5.48 (4.11 – 6.85)	1	0.59184 (0.3699 – 0.8494)
Liberia	2,640	10.0 (8.2 – 11.8)	264	5.48 (4.11 – 6.85)	14	0.548 (0.337 – 0.808)
Mali	2,835	5.0 (3.9 – 6.0)	142	2.7 (2.1 – 3.3)	4	0.135 (0.082 – 0.198)
Mauritania	1,245	11.7 (11.5 – 11.9)	146	5.48 (4.11 – 6.85)	8	0.64116 (0.47265 – 0.81515)
Niger	1,235	8.7 (8.4 – 9)	107	5.48 (4.11 – 6.85)	6	0.47676 (0.34524 – 0.6165)
Nigeria	81,290	9.9 (8.6 – 11.3)	8048	7.1 (5.3 – 8.9)	571	0.7029 (0.4558 – 1.0057)
Saint Helena	20	8.4 (7.2 – 9.4)	2	5.48 (4.11 – 6.85)	0	0.46032 (0.29592 – 0.6439)

Senegal	10,045	6.4 (5.3 – 7.6)	643	2.9 (2.17 – 3.63)	19	0.1856 (0.11501 – 0.27588)
Sierra Leone	3,120	9.2 (7.1 – 10.7)	287	5.48 (4.11 – 6.85)	16	0.50416 (0.29191 – 0.73295)
Togo	4,885	5.0 (4.4 – 5.7)	244	5.48 (4.11 – 6.85)	13	0.274 (0.181 – 0.390)
Eastern Africa	**243,405**	**4.8 (4.3 – 5.4)**	**11767**	**13.62 (3.58 – 20.01)**	**1603**	**0.6585 (0.1523 – 1.0581)**
Burundi	13,050	2.1 (2.1 – 2.2)	274	8.8 (6.6 – 11.0)	24	0.1848 (0.1386 – 0.242)
Comoros	225	4.5 (3.6 – 5.5)	10	8.8 (6.6 – 11.0)	1	0.396 (0.238 – 0.605)
Djibouti	3,245	5.2 (4.2 – 6.4)	169	8.8 (6.6 – 11.0)	15	0.4576 (0.2772 – 0.704)
Eritrea	31,385	4.3 (3.5 – 5.2)	1350	8.8 (6.6 – 11.0)	119	0.3784 (0.231 – 0.572)
Ethiopia	41,720	3.8 (3.3 – 4.4)	1585	1.5 (1.0 – 1.9)	24	0.057 (0.033 – 0.0836)
Kenya	29,235	3.0 (2.6 – 3.3)	877	8.8 (6.6 – 11.0)	77	0.264 (0.1716 – 0.363)
Madagascar	4,295	4.6 (4.0 – 5.2)	198	8.8 (6.6 – 11.0)	17	0.4048 (0.264 – 0.572)
Malawi	795	7.9 (6.5 – 9.3)	63	1.5 (1.0 – 1.9)	1	0.1185 (0.065 – 0.1767)
Mauritius	18,140	2.9 (2.4 – 3.3)	526	8.8 (6.6 – 11.0)	46	0.2552 (0.1584 – 0.363)
Mayotte	0	5.1 (4.4 – 5.8)	0	8.8 (6.6 – 11.0)	0	0.4488 (0.2904 – 0.638)
Mozambique	1,250	8.0 (6.6 – 9.4)	100	8.8 (6.6 – 11.0)	9	0.704 (0.4356 – 1.034)

Reunion	415	5.1 (4.4 – 5.8)	21	8.8 (6.6 – 11.0)	2	0.4488 (0.2904 – 0.638)
Rwanda	7,955	3.8 (3.1 – 4.5)	302	8.8 (6.6 – 11.0)	27	0.3344 (0.2046 – 0.495)
Seychelles	965	3.2 (2.7 – 3.8)	31	8.8 (6.6 – 11.0)	3	0.2816 (0.1782 – 0.418)
Somalia	32,500	11.1 (10.1 – 12.0)	3608	28.99 (16.38 – 45.96)	1046	3.21789 (0.01654 – 5.5152)
Tanzania, United Repubwluc of	21,595	3.5 (3.4 – 3.7)	756	8.8 (6.6 – 11.0)	67	0.308 (0.2244 – 0.407)
Uganda	15,120	4.8 (4.3 – 5.2)	726	3.2 (2.4 – 4.0)	23	0.1536 (0.1032 – 0.208)
Zambia	3,470	6.7 (5.4 – 8.0)	232	8.8 (6.6 – 11.0)	20	0.5896 (0.3564 – 0.88)
Zimbabwe	12,050	7.8 (7.5 – 8.0)	940	8.8 (6.6 – 11.0)	83	0.06864 (0.495 – 0.88)
Northern Africa	**283,895**	**2.7 (2.4 – 3.0)**	**7561**	**2.74 (2.06 – 3.42)**	**207**	**0.073071 (0.047691 – 0.103062)**
Algeria	79,660	2.4 (2.0 – 2.8)	1912	5.3 (4.0 – 6.6)	101	0.1272 (0.08 – 0.1848)
Egypt	73,710	3.6 (3.4 – 3.8)	2654	1.27 (0.95 – 1.59)	34	0.04572 (0.0323 – 0.06042)
Libya	8,305	1.7 (1.5 – 1.9)	141	1.7 (1.3 – 2.1)	2	0.0289 (0.0195 – 0.0399)
Morocco	81,770	1.5 (1.4 – 1.5)	1227	2.57 (1.93 – 3.21)	32	0.03855 (0.02702 – 0.04815)
Sudan	16,025	6.5 (5.2 – 8.1)	1042	2.57 (1.93 – 3.21)	27	0.16705 (0.10036 – 0.26001)
Tunisia	24,425	2.4 (2.2 – 2.7)	586	2.0 (1.5 -2.5)	12	0.048 (0.033 – 0.0675)

Western Sahara	0	3.0 (2.6 – 3.5)	0	2.57 (1.93 – 3.21)	0	0.0771 (0.05028 – 0.11235)
Central Africa	**73,535**	**6.5 (5.6 – 7.3)**	**4783**	**46.74 (44.52 – 48.97)**	**2236**	**3.03978 (2.49758 – 3.59802)**
Angola	3,515	12.0 (10.4 – 13.6)	422	46.73 (44.51 – 48.96)	197	5.6076 (4.62904 – 6.65856)
Cameroon	28,755	4.2 (3.8 – 4.5)	1208	46.73 (44.51 – 48.96)	564	1.96266 (1.69138 – 2.2032)
Central African Republic	1,700	9.5 (9.2 – 9.8)	162	46.73 (44.51 – 48.96)	76	4.43935 (4.09492 – 4.79808)
Chad	1,950	12.4 (9.9 – 14.5)	242	46.73 (44.51 – 48.96)	113	5.79452 (4.40649 – 7.0992)
Congo, Democratic Republic of the	33,110	7.4 (6.2 – 8.6)	2450	46.73 (44.51 – 48.96)	1145	3.45802 (2.75962 – 4.21056)
Congo, Republic of the	3,070	7.4 (6.5 – 8.3)	227	46.73 (44.51 – 48.96)	106	3.45802 (2.89315 – 4.06368)
Equatorial Guinea	45	1.3 (1.1 – 1.4)	1	46.73 (44.51 – 48.96)	0	0.60749 (0.48961 – 0.68544)
Gabon	1,370	5.2 (4.7 – 5.7)	71	46.73 (44.51 – 48.96)	33	2.42996 (2.09197 – 2.79072)
Sao Tome and Principe	20	7.4 (6.5 – 8.3)	1	46.73 (44.51 – 48.96)	0	3.45802 (2.89315 – 4.06368)
Southern Africa	**54,740**	**3.5 (3.1 – 3.9)**	**1930**	**0.05 (0 – 1.78)**	**1**	**0.001763 (0 – 0.69885)**
Botswana	1,145	4.6 (3.3 – 5.5)	53	0.05 (0 – 1.78)	0	0.0023 (0 – 0.0979)
Lesotho	175	6.9 (5.5 – 8.3)	12	0.05 (0 – 1.78)	0	0.00345 (0 – 0.14774)
Namibia	1,420	4.2 (4.1 – 4.2)	60	0.05 (0 – 1.78)	0	0.0021 (0 – 0.07476)

South Africa	51,590	3.5 (3.1 – 3.9)	1806	0.05 (0 – 1.78)	1	0.00175 (0 – 0.06942)
Swaziland		4.8 (4.0 – 5.5)	0	0.05 (0 – 1.78)	0	0.0024 (0 – 0.0979)
Asia and the Middle East	**4,307,000**	**4.5 (3.9 – 5.0)**	**192756**	**7.09 (5.33 – 8.87)**	**13684**	**0.317709 (0.213357 – 0.441975)**
West Central Asia and the Middle East	**749,415**	**2.2 (2.0 – 2.5)**	**16785**	**2.09 (1.59 – 2.59)**	**352**	**0.047035 (0.031838 – 0.064688)**
Afghanistan	62,450	2.9 (2.7 – 3.2)	1811	2.1 (1.6 – 2.6)	38	0.0609 (0.0432 – 0.0832)
Cyprus	4,110	0.7 (0.7 – 0.7)	29	2.1 (1.6 – 2.6)	1	0.0147 (0.0112 – 0.0182)
Iran	182,940	1.5 (1.3 – 1.7)	2744	2.1 (1.6 – 2.6)	58	0.0315 (0.0208 – 0.0442)
Middle East	423,845	2.4 (2.1 – 2.7)	10251	2.09 (1.59 – 2.59)	215	0.050789 (0.034233 – 0.069577)
Bahrain	2,815	2.6 (2.3 – 3.0)	73	2.1 (1.6 – 2.6)	2	0.0546 (0.0368 – 0.078)
Iraq	84,130	2.0 (1.6 – 2.3)	1683	2.1 (1.6 – 2.6)	35	0.042 (0.0256 – 0.0598)
Israel	29,395	0.5 (0.4 – 0.6)	147	2.1 (1.6 – 2.6)	3	0.0105 (0.0064 - 0.0156)
Jordan	17,530	3.4 (3.3 – 3.5)	596	2.1 (1.6 – 2.6)	13	0.0714 (0.0528 – 0.091)
Kuwait	17,655	1.2 (1.0 – 1.4)	212	2.1 (1.6 – 2.6)	4	0.0252 (0.016 – 0.0364)
Lebanon	95,730	2.8 (2.4 – 3.2)	2680	2.1 (1.6 – 2.6)	56	0.0588 (0.0384 – 0.0832)

Oman	2,240	2.5 (2.1 – 2.9)	56	2.1 (1.6 – 2.6)	1	0.0525 (0.0336 – 0.0754)
Palestine/West bank/Gaza strip [22]	8,960	1.5 (1.2 – 1.7)	134	2.1 (1.6 – 2.6)	3	0.0315 (0.0192 – 0.0442)
Qatar	4,110	1.4 (1.3 – 1.6)	58	2.1 (1.6 – 2.6)	1	0.0294 (0.0208 – 0.0416)
Saudi Arabia	29,585	2.7 (2.3 – 3.1)	799	2.1 (1.6 – 2.6)	17	0.0567 (0.0368 – 0.0806)
Syria	97,595	3.1 (3.0 – 3.2)	3025	2.1 (1.6 – 2.6)	64	0.0651 (0.048 – 0.0832)
United Arab Emirates	29,405	1.8 (1.5 – 2.1)	529	2.1 (1.6 – 2.6)	11	0.0378 (0.024 – 0.0546)
Yemen	4,695	5.5 (4.9 – 6.0)	258	2.1 (1.6 – 2.6)	5	0.1155 (0.0784 – 0.156)
Turkey	35,270	2.4 (2.3 – 2.6)	846	2.1 (1.6 – 2.6)	18	0.0504 (0.0368 – 0.0676)
USSR, Former (Asian Component) [24]	40,825	2.7 (2.3 – 3.1)	1104	2.1 (1.6 – 2.6)	23	0.056782 (0.036834 – 0.079549)
Central Asian Republics, former Soviet	27,245	2.9 (2.4 – 3.3)	781	2.1 (1.6 – 2.6)	16	0.06021 (0.03866 – 0.08497)
Kazakhstan	13,965	2.3 (1.8 – 2.6)	321	2.1 (1.6 – 2.6)	7	0.0483 (0.0288 – 0.0676)
Kyrgyzstan	3,945	2.5 (2.1 – 2.9)	99	2.1 (1.6 – 2.6)	2	0.0525 (0.0336 – 0.0754)
Tajikistan	1,590	2.5 (2.1 – 2.9)	40	2.1 (1.6 – 2.6)	1	0.0525 (0.0336 – 0.0754)
Turkmenistan	670	2.6 (2.2 – 3.0)	17	2.1 (1.6 – 2.6)	0	0.0546 (0.0352 – 0.078)

Uzbekistan	7,075	4.3 (3.9 – 4.9)	304	2.1 (1.6 – 2.6)	6	0.0903 (0.0624 – 0.1274)
Transcaucasian Republics, former soviet	13,580	2.4 (2.1 – 2.6)	323	2.1 (1.6 – 2.6)	7	0.0499 (0.03317 – 0.06868)
Armenia	5,065	2.1 (1.7 – 2.4)	106	2.1 (1.6 – 2.6)	2	0.0441 (0.0272 – 0.0624)
Azerbaijan	5,210	3.2 (2.8 – 3.6)	167	2.1 (1.6 – 2.6)	4	0.0672 (0.0448 – 0.0936)
Georgia	3,305	1.5 (1.5 – 1.5)	50	2.1 (1.6 – 2.6)	1	0.0315 (0.024 – 0.039)
Eastern Asia	**1,172,170**	**5.6 (5.1 – 6.1)**	**66026**	**5.92 (4.45 – 7.38)**	**3906**	**0.333216 (0.224688 – 0.453323)**
China and Special Administrative regions	935,010	6.0 (5.3 – 6.5)	55724	6.59 (4.97 – 8.23)	3676	0.0393191 (0.26421 – 0.53554)
China	715,835	6.5 (5.8 – 7.1)	46529	6.9 (5.2 – 8.6)	3211	0.4485 (0.3016 – 0.6106)
Hong Kong, Special Administrative Region	213,855	6.5 (5.8 – 7.1)	13901	3.27 (2.45 -4.09)	455	0.21255 (0.1421 – 0.29039)
Macau, Special Administrative Region	5,320	6.5 (5.8 – 7.1)	346	3.27 (2.45 – 4.09)	11	0.21255 (0.1421 – 0.29039)
Japan	30,870	3.0 (2.7 – 3.4)	926	1.7 (1.3 – 2.1)	16	0.051 (0.0351 – 0.0714)
Korea, North	775	10.7 (9.1 – 12.3)	83	3.27 (2.45 – 4.09)	3	0.34989 (0.22295 – 0.50307)
Korea, South	138,355	2.9 (2.8 – 3.1)	4012	3.27 (2.45 -4.09)	131	0.09483 (0.0686 – 0.12679)

Mongolia	1,810	6.5 (5.8 – 7.1)	118	14.3 (10.7 – 17.9)	17	0.9295 (0.6206 – 1.2709)
Taiwan	65,365	7.9 (7.5 – 8.2)	5164	1.22 (0.91 – 1.53)	63	0.09638 (0.06825 – 0.12546)
Southeast Asia	**1,023,540**	**7.4 (6.6 – 8.4)**	**76156**	**8.43 (6.32 – 10.54)**	**6419**	**0.627092 (0.422355 – 0.87562)**
Brunei Darussalam	4,525	2.1 (1.8 – 2.4)	95	7.21 (5.41 – 9.01)	7	0.15141 (0.09738 – 0.21624)
Cambodia	23,065	6.6 (5.5 – 7.6)	1522	7.21 (5.41 – 9.01)	110	0.47586 (0.29755 – 0.68476)
East Timor	30	4.1 (3.3 – 4.9)	1	7.21 (5.41 – 9.01)	0	0.29561 (0.17853 – 0.44149)
Indonesia	16,025	3.6 (3.2 – 4.0)	577	7.21 (5.41 – 9.01)	42	0.25956 (0.17312 – 0.3604)
Laos	13,955	8.7 (7.3 – 10.0)	1214	7.21 (5.41 – 9.01)	88	0.62727 (0.39493 – 0.901)
Malaysia	25,060	1.3 (1.1 – 1.4)	326	4.9 (3.7 – 6.1)	16	0.0637 (0.0407 – 0.0854)
Myanmar	9,235	2.4 (2.0 – 2.7)	222	7.21 (5.41 – 9.01)	16	0.17304 (0.1082 – 0.24327)
Philippines	719,580	8.2 (7.2 – 9.4)	59006	7.21 (5.41 – 9.01)	4254	0.59122 (0.38952 – 0.84694)
Singapore	12,560	2.7 (2.5 – 2.9)	339	7.21 (5.41 – 9.01)	24	0.19467 (0.13525 – 0.26129)
Thailand	17,410	4.8 (4.4 – 5.1)	836	1.34 (1.0 – 1.68)	11	0.06432 (0.044 – 0.0856)
Viet Nam	182,095	6.6 (6.3 – 6.9)	12018	15.4 (11.5 – 19.3)	1851	1.0164 (0.07245 – 1.3317)
Southern Asia	**1,361,875**	**2.5 (2.2 – 2.8)**	**33789**	**8.89 (6.65 – 11.15)**	**3007**	**0.220788 (0.146416 – 0.313909)**

Bhutan	3,990	2.6 (2.5 – 2.7)	104	11.1 (8.3 – 13.9)	12	0.2886 (0.2075 – 0.3753)
India	898,050	2.9 (2.6 – 3.3)	26043	7.5 (5.6 – 9.4)	1953	0.2175 (0.1456 – 0.3102)
Maldives	25	2.9 (2.4 – 3.4)	1	11.1 (8.3 -13.9)	0	0.3219 (0.1992 – 0.4726)
Nepal	19,370	1.1 (1.0 – 1.2)	213	11.1 (8.3 – 13.9)	24	0.1221 (0.083 – 0.1668)
Pakistan	234,105	2.3 (2.0 – 2.6)	5384	14.7 (11.0 – 18.4)	791	0.3381 (0.22 – 0.4784)
Sri Lanka	136,240	1.5 (1.3 – 1.7)	2044	11.1 (8.3 – 13.9)	227	0.1665 (0.1079 – 0.2363)
Oceania	**61,905**	**2.6 (2.2 – 2.9)**	**1583**	**9.08 (6.83 – 11.33)**	**144**	**0.232224 (0.150633 – 0.329413)**
Samoa	120	5.4 (4.5 – 6.3)	6	14.1 (10.6 – 17.6)	1	0.7614 (0.477 – 1.1088)
Australia	25,200	2.1 (1.9 – 2.3)	529	0.77 (0.58 – 0.96)	4	0.01617 (0.01102 – 0.02208)
Cook Islands	0	3.3 (2.7 – 3.7)	0	14.1 (10.6 – 17.6)	0	0.4653 (0.2862 – 0.6512)
Fiji	24,710	3.6 (3.1 – 4.1)	890	14.1 (10.6 – 17.6)	125	0.5076 (0.3286 – 0.7216)
French Polynesia	270	4.6 (3.8 – 5.3)	12	14.1 (10.6 – 17.6)	2	0.6486 (0.4028 – 0.9328)
Guam	55	5.0 (4.3 – 5.9)	3	14.1 (10.6 – 17.6)	0	0.705 (0.4558 – 1.0384)
Kiribati	15	7.5 (6.1 – 8.9)	1	37.0 (27.75 – 46.25)	0	2.775 (1.69275 – 4.11625)
Marshall Islands	10	4.2 (3.5 – 4.9)	0	14.1 (10.6 – 17.6)	0	0.5922 (0.371 – 0.8624)

Micronesia	20	3.6 (3.1 – 4.0)	1	14.1 (10.6 – 17.6)	0	0.5076 (0.3286 – 0.704)
Nauru	35	4.8 (3.9 – 5.7)	2	14.1 (10.6 – 17.6)	0	0.6768 (0.4134 – 1.0032)
New Caldeonia	175	4.6 (3.8 – 5.3)	8	14.1 (10.6 – 17.6)	1	0.6485 (0.4028 – 0.9328)
New Zealand	10,675	0.9 (0.8 – 1.0)	96	4.54 (3.40 – 5.68)	4	0.04086 (0.0272 – 0.0568)
Palau	0	4.3 (3.6 – 5.0)	0	14.1 (10.6 – 17.6)	0	0.6063 (0.3816 – 0.88)
Papua New Guinea	330	6.2 (5.8 – 6.5)	20	14.1 (10.6 – 17.6)	3	0.8742 (0.6148 – 1.144)
Pitcairn	0	4.6 (3.8 – 5.3)	0	14.1 (10.6 – 17.6)	0	0.6486 (0.4028 – 0.9328)
Samoa	120	5.2 (4.3 – 6.3)	6	14.1 (10.6 – 17.6)	1	0.7332 (0.4558 – 1.1088)
Solomon Islands	15	6.3 (4.9 – 7.4)	1	14.1 (10.6 – 17.6)	0	0.8883 (0.5194 – 1.3024)
Tonga	120	4.0 (3.2 – 4.6)	5	14.1 (10.6 – 17.6)	1	0.564 (0.3392 – 0.8096)
Tuvalu	0	5.8 (4.8 – 6.7)	0	14.1 (10.6 – 17.6)	0	0.8178 (0.5088 - 1.1792)
Vanuatu	30	5.2 (4.2 – 6.2)	2	14.1 (10.6 – 17.6)	0	0.7332 (0.4452 – 1.0912)
Wallis and Futuna	15	4.6 (3.8 – 5.3)	1	14.1 (10.6 – 17.6)	0	0.6486 (0.4028 – 0.9328)

Discussion

This chapter sought to estimate the prevalence of HDV among migrants in Canada. The overall prevalence of HDV among Canadian immigrants was estimated to be 0.24% (0.15% - 0.33%). This was equivalent to 20,102 individuals. Our findings indicate that migrants originate mainly from regions such as Southeast Asia and East Asia, with the highest migrant flows coming from countries such as the Philippines and China. These countries are known to have either intermediate or high HDV prevalence rates.[41]

One recent Canadian-based study also attempted to estimate HDV prevalence among the general population and the foreign-born population in the country.[27] This study estimated an HDV prevalence rate of 5.19% among HBV-infected immigrant population in Canada.[27] Although this study adopted a meta-analysis, it shares similar methodological characteristics to our present study. These include multiplying pooled country-specific HDV rates by the number of foreign-born individuals with CHB in Canada in 2021,[27] using a weighted average calculation procedure, and relying on immigration data from Statistics Canada. Where our study differs is in the search terms used to identify relevant literature. For example, Wong et al. included search terms such as HDAg, anti-HD, and anti-HDV, which were not included in our search strategy.[27] Rather we used, broad descriptors such as Hepatitis Delta and HDV. This discrepancy may account for the differences in HDV prevalence data collected. We also adopted a less computationally complex method to estimate HDV prevalence compared to the Wong et al. study.

Another study by Osiowy et al. also estimated HDV prevalence rate among immigrants in Canada to be 4.8%[32], which is comparable to our estimate of 7.7%. The difference between our rates and other studies like Wong et al, and Osiowy et al. could be due to how our HDV data were collected and included in the analysis. The inclusion-exclusion criteria were different in each study which can result in different literature paper obtained and used in the analysis. Given these differences, further research needs to be done to accurately access the prevalence among Canadian immigrants.

Knowledge of the likely prevalence rate is important in evaluating the feasibility of establishing an HDV screening program in Canada. Currently, mandatory HDV screening does not exist, but given the prevalence and severity of this disease, this position warrants reconsideration. The Public Health Agency of Canada (PHAC) has noted that due to the increased interest in HDV research, more accurate data on HDV prevalence is needed and this can only be generated through routine screening of HBV-positive individuals.[23] In fact, the National Microbiology Laboratory (NML) of the PHAC, in collaboration with the Canadian HBV Network (CanHepB Network), conducts viral hepatitis testing, including HDV testing, for all referred patients in Canada.[32] While this is a positive step, greater effort is needed to also capture undiagnosed individuals who are less likely to seek health services. Targeting the immigrant population in Canada for HDV testing may be a practical option given that this group usually originates from high-endemic regions and is usually less willing to engage public health services.[46] The cost-effectiveness of such an intervention is explored in the next chapter.

There are a number of limitations; the first limitation is that we are assuming that the prevalence of HBV and HDV among immigrants in Canada is equivalent to the overall prevalence in each country. This is a limitation because the prevalence of HBV and HDV would most likely be lower among immigrant groups because immigrants usually have a lower chance of being infected with diseases, as they are most likely highly educated individuals with no health problems.[47] This is known as a healthy immigrant effect (HIE).[47] HIE suggests that immigrants immigrating to Canada are often healthier due to the selection process and the medical screening.[47] Another limitation is the assumption made when country-specific HDV and HBV prevalence rates were unknown. In some countries, we were not able to obtain the prevalence of HBV and HDV from published literature review papers. We had to assume the prevalence for those countries equated to the average prevalence in the surrounding region or continent. Given this assumption, the limitation is that some unknown country's prevalence could be lower or higher than expected.

Conclusion

This chapter provides an estimate of HDV prevalence based on literature reviews among Canadian immigrant population and provides us with the relevant data needed for the next chapter to conduct a cost-effectiveness analysis on screening and treating HDV-positive individuals in Canada. The study concluded that there is a notable number of HDV-infected individuals among the immigrant population. However, there is still a lot of research that needs to be done on HDV due to very limited data on the prevalence worldwide.

Chapter 3

Cost-utility analysis for hepatitis D screening and treatment among immigrants in Canada

Introduction

Canada has a relatively low HDV endemicity with an estimated national prevalence rate of 3.0%, nonetheless, the immigrant population contributes notably to the prevalence of disease in the country.[41] In Chapter 2, we estimated that 7.7% of migrants with HBV might also be infected with HDV, and this was equivalent to 20,102 immigrants in Canada in 2021. Wong et al. provided a more conservative yet significant estimate of 5.19% among HBV-infected immigrants.[27] Further compounding the disease burden, approximately 2-20% of individuals with HDV in Canada are expected to die.[16] Liver-related death is usually linked to accelerated liver cirrhosis and an increased propensity to develop HCC.[1]

Although HDV is a satellite virus of HBV, mandatory screening of HBV-positive patients is not practiced in Canada. Currently, approximately 50% of HBV-positive patients are referred to HDV testing.[32] However, recommendations state that all CHB-positive patients must be evaluated.[33] Currently, there are HDV-specific screening recommendations for the following groups in Canada: HBV-positive individuals from HDV endemic regions, persons with a history of injection drug use, persons with abnormal ALT levels, and persons with advanced liver diseases.[33] In Ontario, Public Health Ontario only has serology HDV tests available for HBsAg positive samples.[36]

While there is no cure for HDV, pegylated interferon alfa-2a (administered for at least 48 weeks) is the only approved treatment option in Canada for patients with HDV.[16] However, this form of therapy is not effective, with only 20-30% of HDV cases clearing infection when this treatment is administered, and many experience a relapse of infection over time.[33] Oral nucleoside analogues such as lamivudine, ribavirin, famciclovir, adefovir, and entecavir, which are all used to treat CHB, are even less successful in treating HDV infections.[48–53]

Bulevirtide (BLV) is a new form of treatment that has shown potential to improve the clinical outcomes of individuals with HDV. Although, BLV has not received approval from the Food and Drug Administration (FDA) or Health Canada, it is currently under review by the Canada's Drug Agency L'Agence des medicaments du Canada (CDA-AMC). The results from phase 2 and 3 clinical trials revealed favorable responses in HDV-RNA undetectability (< limit of detection), a decrease of ≥2 log10 IU/mL from baseline and normalization of ALT levels 24 and 48 weeks after treatment was administered.[22,54] Outcomes in real-world settings were also promising.[17] Even with these likely favorable outcomes, the cost-effectiveness of BLV for HDV-positive patients has not been extensively explored in the literature. However, one study that examined this intervention found that it was more effective at preventing cases of DC and HCC than pegylated IFN-α.[55]

Generally, early screening and treatment of HDV would likely prevent the advancement of DC, HCC and even death.[56] However, currently no studies exist on the cost-effectiveness of screening and treating HDV-positive patients in Canada. Consequently, the health and economic benefits of such interventions are unknown. The goal of this chapter is to evaluate the cost-utility of screening HBV-positive immigrants in Canada for HDV and subsequently treating those who are HDV-positive with either BLV, pegylated interferon alfa-2a, or BLV plus pegylated interferon alfa-2a compared with no screening and treatment. The cost-utility analysis will provide health officials with much needed information to guide decisions on implementing HDV screening and treatment programs in Canada.

Methodology

Study design

A state-transition model representing the natural history of hepatitis D was developed to conduct the cost-utility analysis of screening and treating HDV among Canadian immigrants with CHB versus no screening. The construction of the model and the cost-utility analysis followed the guidelines for economic evaluations provided by Canada's Drug Agency L'Agence des medicaments du Canada (CDA-AMC).

The analysis was performed from a Canadian public payer perspective with a lifetime horizon. The cost and health parameters were all discounted at an annual rate of 1.5% as per the CDA-AMC recommendation. Each cycle was set to a one-year duration, and all costs were adjusted for inflation to 2023 Canadian dollars. The primary outcome of interest was the total costs, total quality-adjusted life years (QALY) and their corresponding incremental cost-effectiveness ratio (ICER) between screening interventions and no screening interventions. The ICER value is determined by calculating the ratio of the difference in total cost and the difference in the QALYs. The secondary outcomes of interest were clinical in nature and included decompensated cirrhosis, hepatocellular carcinoma, liver-related deaths and liver related deaths prevented.

Cohort

A theoretical cohort of Canadian immigrants diagnosed with CHB was considered in the model. For the base case analysis, we focused on patients aged 45 with a broader age range of 35-55 years in the sensitivity analysis. The subjects were modelled from the start of their respective diagnosis and followed until they progressed to liver-related death.

Screening strategies

We adopted the intervention strategies investigated in a phase 2b randomized controlled trial conducted by Asselah et al.[57] These strategies included two monotherapies: BLV and pegylated interferon alfa-2a, respectively, as well as one combination therapy that incorporates these treatment options.[57] The outcome of this trial revealed that HDV RNA was undetectable 48 weeks after the end of treatment for 12%, 25%, and 46% of individuals who received BLV only, pegylated interferon alfa-2a only, and the combination therapy of 10mg BLV and pegylated interferon alfa-2a, respectively.[57]

In the present analysis, the following interventions were modelled.

(1) No screening for HDV: Individuals in this group are expected to progress through the natural history of HDV superinfection. They enter the model with CHB but will not be screened nor treated for HDV. As a result, they will progress rapidly to HCC, DC, and LD.
(2) HDV screening and treatment with BLV: Individuals in this group enter the model with a CHB infection. However, they will be screened once for HDV infection, and BLV treatment will be administered to those with a positive test result. These individuals will receive 10mg daily of BLV subcutaneously for 96 weeks as a form of monotherapy.
(3) HDV screening and treatment with pegylated interferon alfa-2a: Individuals in this group also enter the model with CHB infection. They will also be screened once for HDV infection, and those with a positive test result will be treated subcutaneously with

180 μg of pegylated interferon alfa-2a weekly for 48 weeks as an alternative monotherapy.

(4) HDV screening and treatment with BLV and pegylated interferon alfa-2a combined therapy: Individuals in this group will also enter the model with a CHB infection and be screened once for HDV. Those with an HDV diagnosis will be treated with a combination of BLV and pegylated interferon alfa-2a. Specifically, they will receive 10mg of BLV daily for 96 weeks and 180 μg of pegylated interferon alfa-2a weekly for 48 weeks. Both therapies will be administered subcutaneously.

Decision Model

A state-transition model was developed and implemented in TreeAge Pro Healthcare 2023 decision analysis software to evaluate the long-term outcomes of HDV screening and treatment. This model simplifies the clinical cascade of CHB and HDV superinfection among immigrants in Canada. Figure 2 is a further simplified representation of the proposed model. The model consists of 21 health states identified below.

Chronic HBV, Immune tolerant (HBeAg$^+$), HBeAg$^+$ Chronic HBV, Inactive Chronic HBV (HBeAg$^-$), HBeAg$^-$ Chronic HBV, Immune tolerant HDV, HBeAg$^+$ Chronic HBV and HDV, Inactive Chronic HBV (HBeAg$^-$) and HDV, HBeAg$^-$ Chronic HBV and HDV, HBeAg$^+$ Compensated Cirrhosis (CC), Inactive CC HBeAg$^-$, HBeAg$^-$ CC, HBeAg$^+$ CC and HDV, Inactive CC HBeAg$^-$ and HDV, HBeAg$^-$ CC and HDV, Natural Immunity, Decompensated Cirrhosis (DC), Hepatocellular carcinoma (HCC), Liver Transplant (LT), Post-liver Transplant (PLT), Liver-related Death (LD), and All-Cause Mortality (ACM).

The immune tolerant health state is characterized by high levels of viral replication without any signs of liver damage.[58] HBeAg$^+$ health states indicate both high viral replication and an increased risk of viral transmission of the hepatitis B e antigen.[59] In contrast, HBeAg$^-$ health states signify a less contagious and comparatively less active phase of infection.[59] Inactive health states are identified by normal liver function coupled with low levels of viral replication.[60] Compensated Cirrhosis represents the end-stage of liver disease wherein liver function remains intact, yet symptoms of liver disease are present and observable.[61] Natural immunity develops when the body successfully clears the infection and produces antibodies that provide protection against future infections.[62] The term "post-liver transplant" pertains to the period following liver transplantation surgery. Liver-related mortality encompasses all fatalities resulting from liver diseases, while all-cause mortality refers to deaths caused by any illness or injury.

Individuals may enter the model at any one of the CHB mono-infection health states. These are Immune tolerant, $HBeAg^+$ Chronic HBV, Inactive Chronic HBV ($HBeAg^-$), $HBeAg^-$ Chronic HBV. Meanwhile, those with a positive HDV result after screening and testing may enter the model at one of three HDV superinfection health states. These are $HBeAg^+$ Chronic HBV HDV, Inactive Chronic HBV ($HBeAg^-$) HDV, and $HBeAg^-$ Chronic HBV HDV. Individuals may also progress directly to CC from their respective CHB health states. These CC health states are $HBeAg^+$ CC, Inactive CC $HBeAg^-$, $HBeAg^-$ CC. Likewise, those diagnosed with HDV infection may also transition to CC health states, namely, $HBeAg^+$ CC + HDV, Inactive CC ($HBeAg^-$) + HDV, and $HBeAg^-$ CC + HDV. See Figure 2 below.

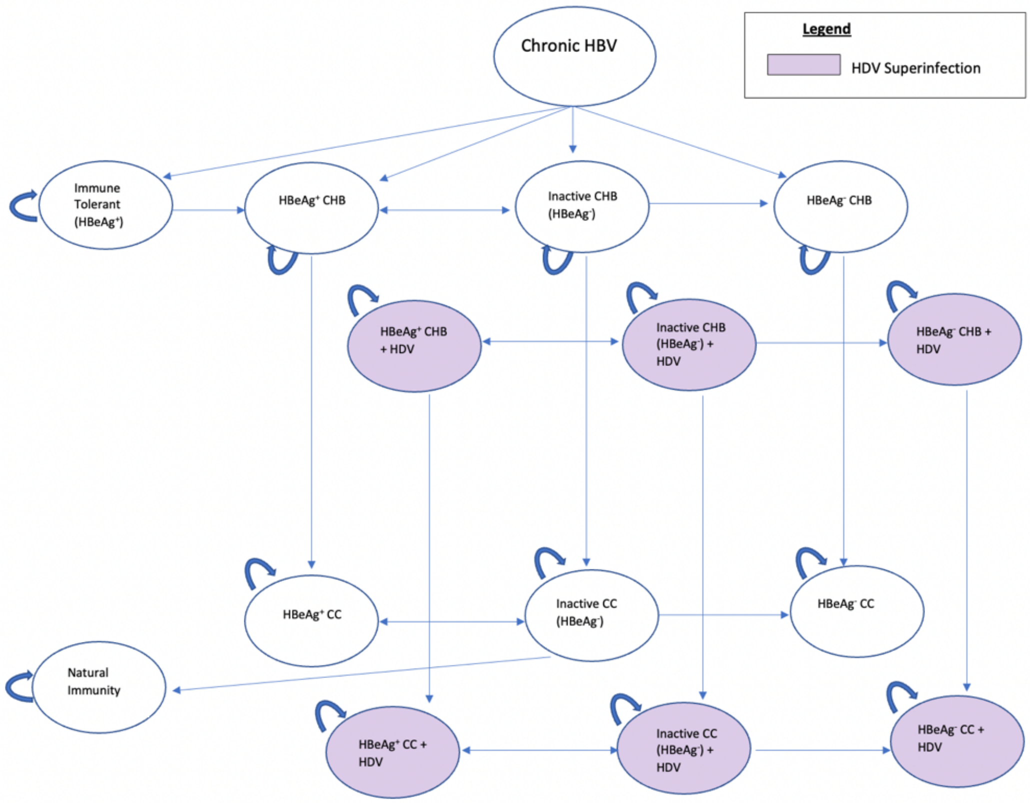
Our model also assumes that individuals with initial CHB or CHB-CC health states, as illustrated in Figure 2A, will receive standard CHB treatment. These individuals may clear infection with treatment or progress to other liver-related complications, namely, DC, HCC, and liver-related death. For individuals who test positive for HDV, one of the three treatment strategies will be administered depending on the treatment group assigned to that individual. Individuals treated for HDV may progress similarly to those treated for CHB.

Figure 2B further shows that individuals may develop hepatocellular carcinoma (HCC) from any CHB or CHB-CC health state. They may subsequently transition sequentially to liver transplant (LT), and liver death (LD). Following an LT, individuals flow into the post-liver transplant (PLT) health state.

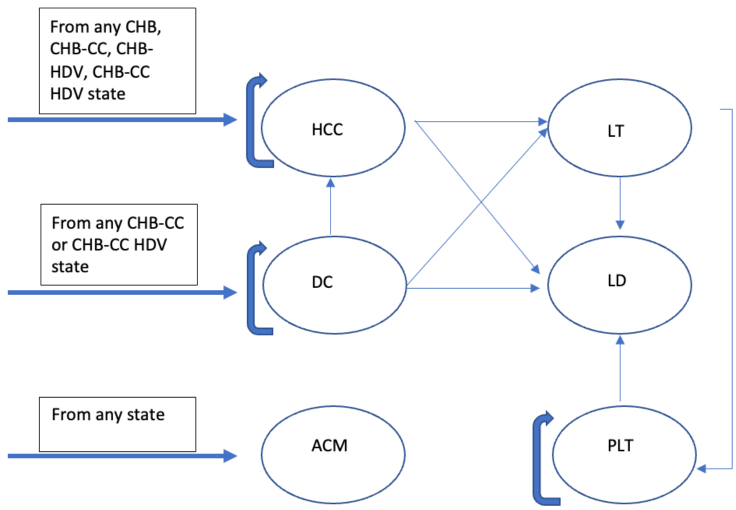
Individuals may also die from any one of the following health states: DC, HCC and LT. Subjects can progress to DC from any CHB-CC health state, after which they can follow the same progression as a CHB patient. Subjects can end up in ACM from any of the health states in the model. See Figure 2 below.

Figure 2: Conceptual diagram of CHB and HDV infections

A



B



Abbreviations: HCC – Hepatocellular Carcinoma, LT – Liver Transplant, DC – Decompensated Cirrhosis, LD – Liver Death, ACM – All Cause Mortality, PLT – Post Liver Transplant, CHB – Chronic Hepatitis B, HDV – Hepatitis D Virus, CC – Compensated Cirrhosis, HBeAg – Hepatitis B e Antigen

Model Input

a. All the transition probabilities associated with CHB were obtained from relevant literature. The progression rate/transition probabilities for HDV were obtained from a relevant literature paper and applied to both HDV progression and CHB progression. We assumed that based on HDV superinfection progresses faster towards end-stage liver disease at an odds ratio 2.42 compared to CHB mono-infection.[63] The prevalence of HDV estimated in Chapter 2 of this thesis was also incorporated in our current cost-effectiveness model. All epidemiological parameters are summarized in Table 3.

b. Cost data were obtained from various Canadian sources and inflated to 2023 Canadian dollars. The cost of individual health states was derived from a cost-effectiveness study on implementing a universal birth hepatitis B vaccination program in Ontario, Canada.[64]. The estimated annual cost of BLV was $193,012, as reported by Meds Entry Watch Canada.[65] The estimated annual cost of pegylated interferon alfa-2a was $19,008, as reported by CDA-AMC. The cost of an anti-HDV test ($15) and an HDV RNA test ($100) were assumed to be the same as other respective viral hepatitis tests in Canada as reported by blood tests Canada. All adverse events cost related to treatment were also obtained from relevant literature studies.[66,67] The costs associated with adverse events such as decreases in neutrophils, white blood cells, and platelets were $466, $466, and $6,397, respectively.[66,67] All cost parameters are summarized in Table 4.

c. All utility parameters were derived from the same study from which the cost parameters were obtained.[64] This paper also reported on the progression of hepatitis B and provided estimates of the utility associated with each related health state.[64] All disutility associated with adverse events were obtained from the same studies from which the costs of adverse events were obtained from.[66,67] All estimates of utilities are presented in Table 5.

Table 3: Epidemiological parameter estimates

Parameter	Point Estimate	Lower Limit	Upper Limit
Prevalence of HDV	7.73%	5.67%	9.66%
Pr of IT to HCC	0.0003	0	0.0004
Pr of IT to $HBeAg^+$ CHB	0.1423	0.12	0.16
Pr of $HBeAg^+$ CHB to HCC	0.008	0.004	0.016
Pr of $HBeAg^+$ CHB to $HBeAg^+$ CC	0.044	0.022	0.088
Pr of $HBeAg^+$ CHB to Inactive CHB	0.0225	0.0079	0.0551
Pr of $HBeAg^+$ CHB HDV to HCC	0.0191	0.0144	0.0239
Pr of $HBeAg^+$ CHB HDV to $HBeAg^+$ CC HDV	0.1002	0.0752	0.1253
Pr of $HBeAg^+$ CHB HDV to Inactive CHB HDV	0.0527	0.0395	0.0659
Pr of $HBeAg^+$ CC to DC	0.0756	0.035	0.1

Pr of HBeAg$^+$ CC to HCC	0.034	0.01	0.12
Pr of HBeAg$^+$ CC to Inactive CC	0.1112	0.0840	0.1399
Pr of HBeAg$^+$ CC HDV to DC	0.1651	0.1239	0.2064
Pr of HBeAg$^+$ CC HDV to HCC	0.0785	0.0589	0.0981
Pr of HBeAg$^+$ CC HDV to Inactive CC CHB HDV	0.2338	0.1754	0.2923
Pr of Inactive (HBeAg$^-$) CHB to HCC	0.003	0.0015	0.006
Pr of Inactive (HBeAg$^-$) CHB to Inactive CC	0.001	0.001	0.002
Pr of Inactive (HBeAg$^-$) CHB to HBeAg$^-$ CHB	0.0256	0.02	0.05
Pr of Inactive (HBeAg$^-$) CHB HDV to HCC	0.0072	0.0054	0.0090
Pr of Inactive (HBeAg$^-$) CHB HDV to Inactive CC HDV	0.0024	0.0018	0.0030
Pr of Inactive (HBeAg$^-$) CHB HDV to HBeAg$^-$ CHB HDV	0.0598	0.0449	0.0748
Pr of Inactive CC to DC	0.0082	0.004	0.016
Pr of Inactive CC to HCC	0.022	0.011	0.044
Pr of Inactive CC to HBeAg$^-$ CC	0.0254	0.02	0.05
Pr of Inactive CC HDV to DC	0.0195	0.0146	0.0245
Pr of Inactive CC HDV to HCC	0.0516	0.0387	0.0645
Pr of Inactive CC HDV to HBeAg$^-$ CC HDV	0.0614	0.0460	0.0767
Pr of HBeAg$^-$ CHB to HCC	0.008	0.004	0.012

Pr of HBeAg$^-$ CHB to HBeAg$^-$ CC	0.0292	0.015	0.058
Pr of HBeAg$^-$ CHB HDV to HCC	0.008	0.004	0.012
Pr of HBeAg$^-$ CHB HDV to HBeAg$^-$ CC HDV	0.0679	0.0509	0.0849
Pr of HBeAg$^-$ CC to DC	0.0758	0.035	0.1
Pr of HBeAg$^-$ CC to HCC	0.037	0.01	0.12
Pr of HBeAg$^-$ CC HDV to DC	0.1656	0.1242	0.2070
Pr of HBeAg$^-$ CC HDV to HCC	0.4286	0.3214	0.5358
Pr of HCC to LT	0.15	0.05	0.4
Pr of HCC to LD	0.4129	0.181	0.451
Pr of DC to HCC	0.0772	0.01	0.113
Pr of DC to LT	0.0605	0	0.4
Pr of DC to LD	0.173	0.058	0.221
Pr of LT to LD	0.142	0.124	0.159
Pr of PLT to LD	0.034	0.024	0.043
Pr transition to treatments	0.2366	0.1775	0.2958

PR - Probability, PR are on an annual basis, CHB - Chronic Hepatitis B, HDV - Hepatitis D Virus, IT - Immune Tolerant, CC - Compensated Cirrhosis, DC - Decompensated Cirrhosis, HCC - Hepatocellular Carcinoma, LT - Liver Transplant, PLT - Post Liver Transplant, LD - Liver Death,

Table 4: Cost parameter estimates

Parameter	Point Estimate	Lower Limit	Upper Limit
Cost of HBV Treatment	1,843	1,382	2,306
Cost of BLV Treatment	193,012	144,759	241,265
Cost of pegylated interferon alfa-2a	19,008	14,256	23,760
Cost of Anti HDV Test	15	11	19
Cost of HDV RNA	100	75	125
Cost of Pegylated Interferon alfa-2a	19,008	14,256	23,760
Cost of being in Immune Tolerant	687	544	842
Cost of $HBeAg^+$ CHB	9,322	6,992	11,653
Cost of $HBeAg^+$ CHB and HDV	9,322	6,992	11,653
Cost of $HBeAg^+$ Compensated Cirrhosis	9,322	6,992	11,653
Cost of $HBeAg^+$ Compensated Cirrhosis and HDV	9,322	6,992	11,653
Cost of Inactive ($HBeAg^-$) CHB	7,455	5,591	9,319
Cost of Inactive ($HBeAg^-$) CHB and HDV	7,455	5,591	9,319
Cost of Inactive ($HBeAg^-$) Compensated Cirrhosis	7,455	5,591	9,319
Cost of Inactive ($HBeAg^-$) Compensated Cirrhosis and HDV	7,455	5,591	9,319
Cost of $HBeAg^-$ CHB	9,322	6,992	11,653
Cost of $HBeAg^-$ CHB and HDV	9,322	6,992	11,653
Cost of $HBeAg^-$ Compensated Cirrhosis	9,322	6,992	11,653

Cost of HBeAg$^-$ Compensated Cirrhosis and HDV	9,322	6,992	11,653
Cost of HCC	9,322	6,992	11,653
Cost of DC	9,322	6,992	11,653
Cost of LT	49,614	46,344	52,883
Cost of PLT	54,467	47,123	67,087
Cost of Neutrophils Decreased	466	350	583
Cost of White Blood Cells Decreased	466	350	583
Cost of Platelets Decreased	6397	4,797	7,997

CHB - Chronic Hepatitis B, HDV - Hepatitis D Virus, CC - Compensated Cirrhosis, DC - Decompensated Cirrhosis, HCC - Hepatocellular Carcinoma, LT - Liver Transplant, PLT - Post Liver Transplant, Cost for each parameter is our annual cost

Table 5: Utility parameter estimates

Parameter	Point Estimate	Lower Limit	Upper Limit
HBeAg$^+$ CHB Health State	0.87	0.85	0.88
HBeAg$^+$ CC Health State	0.81	0.75	0.86
Inactive CHB Health State	0.87	0.85	0.88
Inactive CC Health State	0.81	0.75	0.86
HBeAg$^-$ CHB Health State	0.87	0.85	0.88
HBeAg$^-$ CC Health State	0.81	0.75	0.86
DC Health State	0.49	0.37	0.61
HCC Health State	0.85	0.76	0.95
IT Health State	0.87	0.85	0.88

LT Health State	0.72	0.60	0.83
PLT Health State	0.72	0.60	0.83
Neutrophils Decreased	-0.2	-0.25	-0.15
White Blood Cells Decreased	-0.2	-0.25	-0.15
Platelets Decreased	-0.19	-0.24	-0.14

CHB - Chronic Hepatitis B, CC - Compensated Cirrhosis, DC - Decompensated Cirrhosis, HCC - Hepatocellular Carcinoma, IT - Immune Tolerant, LT - Liver Transplant, PLT - Post Liver Transplant

Modelling Assumptions

A number of assumptions were made in the implementation of the state-transition model. First, the estimate of the prevalence of HDV among Canadian immigrants derived from the previous chapter has the same inherent limitations discussed earlier, including the assumption that HDV prevalence rate among immigrants in Canada is equal to the average prevalence of HDV among source countries. The second assumption we made in our model is on the cost and utilities of each health state. In particular, we assumed that the costs and utilities associated with HDV are equal to those associated with CHB. This assumption is made because there is limited information on the natural history of HDV, and the costs and utility estimates for each HDV health state are not readily available in published literature. For treatment related adverse events, the costs and disutility were assumed to be the same as for chronic cancers as there is limited information published regarding the adverse events for HDV patients.[66,67] The third assumption we made is the progression probability for HDV health states. HDV superinfection progresses faster at an odds ratio of 2.42 compared to CHB mono-infection.[63] The odds ratio is applied to CHB mono-infection to represent the HDV progression rate towards end-stage liver diseases.[63] The fourth assumptions we made is the progression probability for treatment health states with HDV. These probability progressions were derived from a ratio calculation. We assumed that someone receiving treatment for CHB will progress at a similar rate as someone receiving treatment for HDV. Likewise, we assumed that someone not receiving treatment for CHB will progress at a similar rate as someone not receiving treatment for HDV. For the fifth assumption, we did not model the transition from mono-infection CHB to HDV superinfection. We assumed that immigrants enter the model with at least a CHB infection or with HDV superinfection once screened and diagnosed. Sixthly, we assumed 100% screening compliance and 100% treatment adherence for those in the intervention arms of our model. Lastly, for our sensitivity analysis, most parameters did not provide a confidence interval value, therefore we had to assume a ± 25% for our sensitivity analysis.

Analytic Strategy

A base-case analysis was conducted to determine the ICER for no screening HDV compared with screening and treating HDV. In compliance with CDA-AMC guidelines, a probabilistic sensitivity analysis was performed for the base-case analysis. Univariate sensitivity analysis was also performed to determine the impact of each parameter on the model's overall outcome. A probabilistic sensitivity analysis was performed using a Monte Carlo simulation of 10,000 to test the robustness of the model. Cost-effectiveness was evaluated at two willingness to pay (WTP) thresholds: $50,000 per QALY based on CDA-AMC recommendation and $100,000 per QALY which is the maximum threshold that healthcare system is willing to pay for per QALY.[68,69] We also assessed the clinical effects of the three screening strategies by conducting an individual-level microsimulation of 100,000 iterations in TreeAge Pro Healthcare 2023 to assess the differences in health outcomes such as DC, HCC, and LD between the screen-and-treat group and the no-screening group.

Model Validation

The model was validated by comparing the estimated risk of developing HCC and LD to published real-world evidence on similar data based on a risk stratification study of HBV-infected patients.[70] To validate our model, we performed a microsimulation of 10,000 trials along the HBV branch of our state-transition model to risk of the aforementioned health outcomes.

Results

Model Validation

We found the risk of developing HCC in our model to be 25.05%. This estimate falls within the range highlighted in the literature. Previous studies have shown that the risk of HBV carriers developing HCC ranges from 15% to 40%.[70]

Projection of clinical outcomes

In the base case analysis, the intervention strategy of HDV screening and treating with BLV resulted in a decrease in HDV-related deaths compared with no screening for HDV. Our analysis showed that screening for HDV and treatment with BLV would prevent around 1,372 liver deaths per 100,000 patients screened over the lifetime of the cohort.

The intervention strategy of HDV screening and treating with pegylated interferon alfa-2a resulted in a decrease in HDV-related deaths compared with no screening for HDV. Our analysis showed that HDV screening and treat with pegylated interferon alfa-2a would prevent around 1,513 liver deaths per 100,000 patients screened over the lifetime of the cohort.

The intervention strategy of HDV screening and treating with BLV plus pegylated interferon alfa-2a resulted in a decrease in HDV-related deaths when compared with no screening for HDV. Our analysis showed that HDV screening and treat with BLV plus pegylated interferon alfa-2a would prevent around 2,152 liver deaths per 100,000 patients screened over the lifetime of the cohort.

Our results show that HDV screening and treating with BLV plus pegylated interferon alfa-2a prevented the most HDV related deaths when compared to HDV screen and treat with BLV and HDV screen and treat with pegylated interferon alfa-2a strategies. See Table 6.

Table 6: Baseline population outcomes per 100,000 screened

Strategy	Number of DC	Number of HCC	Number of HDV related liver death	Number of HDV related deaths prevented
No screen HDV	8,753	14,760	17,624	-
HDV screening and treat with BLV	8,034	13,641	16,252	1,372
HDV screening and treat with pegylated interferon alfa-2a	7,885	13,663	16,111	1,513
HDV screening and treat with BLV plus pegylated interferon alfa-2a	7,661	13,008	15,472	2,152

HDV – Hepatitis D Virus, DC – Decompensated Cirrhosis, HCC – Hepatocellular Carcinoma, BLV – Bulevirtide

Base Case Analysis

For screening and treating with BLV versus the no screening strategy, results had shown that the no screening arm had a mean cost of $283,716, while the mean cost of the screen-and-treat with BLV strategy was $348,329 resulting in a mean difference of $64,613 The no-screening strategy had an average effectiveness of 22.76 QALY compared, while the screen-and-treat strategy had an average effectiveness of 22.95 QALY, which resulted in a difference of 0.19 QALYs. Ultimately, the ICER associated with screening HDV and treating HDV-positive individuals with BLV is not cost-effective (ICER: $329,015/QALY) at a WTP threshold of $100,000/QALY. See Table 7.

For screening and treating with pegylated interferon alfa-2a versus the no screening strategy, results had shown that the no screening arm had a mean cost of $283,716, while the mean cost of the screen-and-treat with pegylated interferon alfa-2a was $288,062 resulting in a mean difference of $4,346. The no-screening strategy had an average effectiveness of 22.76 QALY compared, while the screen-and-treat with pegylated interferon alfa-2a had an average effectiveness of 22.96 QALY, which resulted in a difference of 0.20 QALYs. As a result, the ICER associated with screening HDV and treating positive individuals with pegylated interferon alfa-2a is cost-effective (ICER: $21,808/QALY) when compared to the WTP threshold of $50,000/QALY and $100,000/QALY. See Table 7.

For screening and treating with BLV combined with pegylated interferon alfa-2a versus the no screening strategy, results had shown that the no screening arm had a mean cost of $283,716, while the mean cost of the screen-and-treat with BLV combined with pegylated interferon alfa-2a was $331,859, resulting in a mean difference of $48,140. The no-screening strategy had an average effectiveness of 22.76 QALY compared, while the screen-and-treat with BLV combined with pegylated interferon alfa-2a had an average effectiveness of 23.00 QALY, which resulted in a difference of 0.24 QALYs. As a result, the ICER associated with screening HDV and treating positive individuals with BLV and pegylated interferon alfa-2a is not cost-effective (ICER: $199,841/QALY) when compared to the WTP threshold of $100,000/QALY. See Table 7.

The costs associated with BLV monotherapy, pegylated interferon alfa-2a monotherapy and the combination therapy (of BLV and pegylated interferon alfa-2a) were $348,329, $288,062, and $331,859, respectively. The associated QALYs for each intervention were 22.95, 22.96 and 23.00, respectively. Meanwhile, the cost and QALY associated with no HDV screening were $283,716 and 22.76, respectively. The base case analysis therefore demonstrated that HDV screening and pegylated interferon alfa-2a monotherapy was cost-effective (ICER $21,808/QALY) at a WTP threshold of $100,000/QALY. However, HDV screening and treatment with BLV monotherapy and combined treatment (BLV and pegylated interferon alfa-2a) were both not cost-effective at the same WTP threshold, with estimated ICER values of $329,015/QALY and $199,841/QALY, respectively.

Table 7: Base Case Analysis Screen-and-Treat with three different treatment strategies

Strategy	Cost	QALYs	ΔCost	ΔQALYs	ICER
No Screen HDV	$283,716	22.76	-	-	-
HDV screening and treat with BLV	$348,329	22.95	$64,613	0.19	$329,015
HDV screening and treat with pegylated interferon alfa-2a	$288,062	22.96	$4,346	0.20	$21,808
HDV screening and treat with BLV combined with pegylated interferon alfa-2a	$331,859	23.00	$48,143	0.24	$199,841

Note: All the values for ΔQALYs and ICER for the screening interventions in the table above were all compared to no screen HDV

Sensitivity analysis

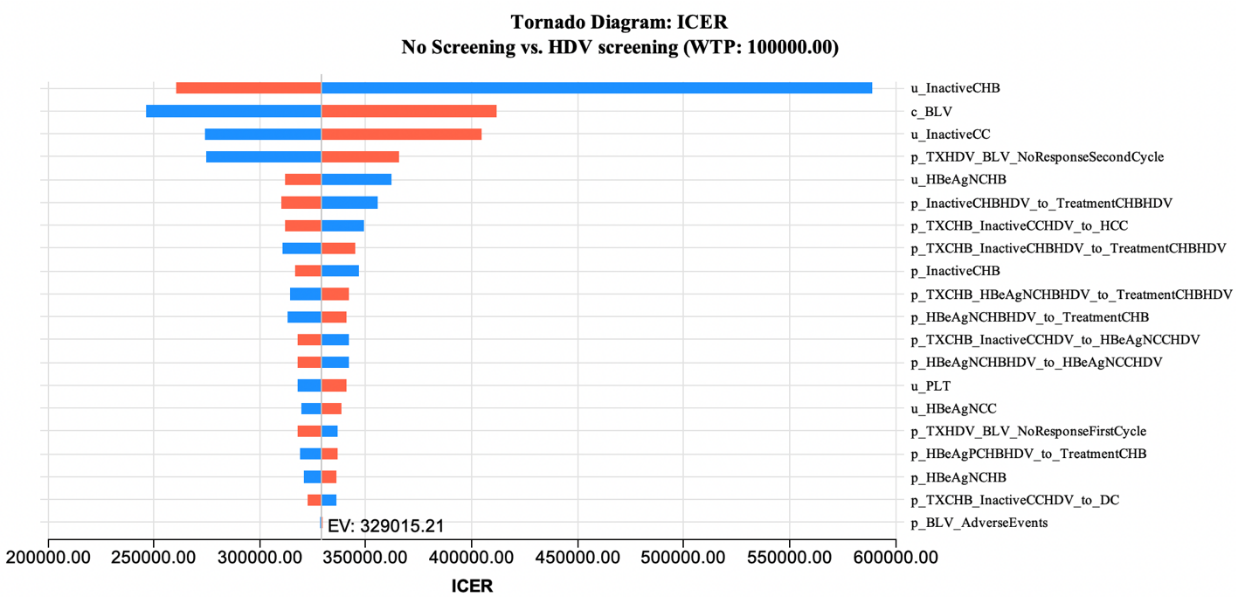
The results of the twenty most sensitive parameters are summarized in the tornado diagrams in Figure 3. A tornado diagram was derived from each respective intervention.

The tornado diagrams in parts A through C in Figure 3 show that the utility of inactive CHB health state is the most sensitive parameter for all strategies. It should be noted that the models for BLV monotherapy and combined therapy prove to be not cost-effective. If the utility value were closer to 1, then the ICER would be closer to the WTP of $100,000/QALY. The cost of BLV was another sensitive variable. The tornado diagrams in Figure 3A and 3C suggest that if the cost of BLV were to decrease notably, then ICER would decrease significantly, tending below the WTP of $100,000/QALY. The efficacy of treatment was to be more effective than it will decrease the ICER values, making it more cost-effective when compared to WTP of $100,000/QALY.

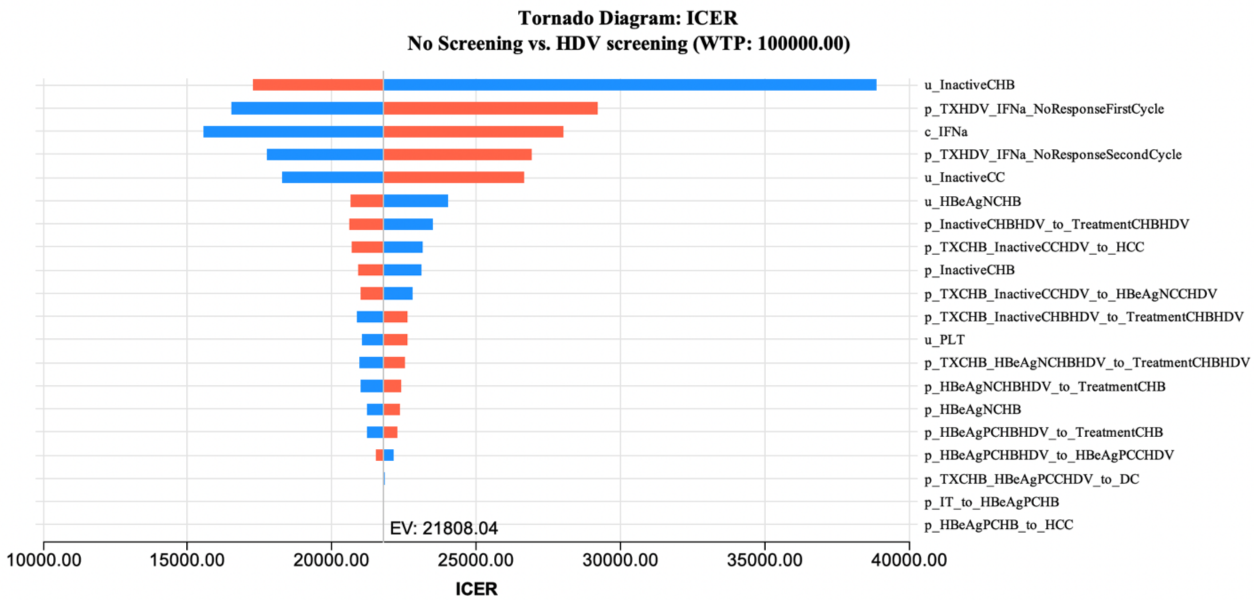
A threshold analysis was performed on the cost of BLV. For the screening and treating with BLV monotherapy, discounting the cost of BLV by 69% to $59,737 will make this strategy cost-effective at a WTP threshold of $100,000/QALY. A threshold analysis was also performed on the cost of BLV in the combination therapy strategy. For this strategy, discounting the cost of BLV by 51% to $94,048 will make it cost-effective at a WTP threshold of $100,000/QALY.

Figure 3: Tornado diagrams for our 20 most sensitive parameters

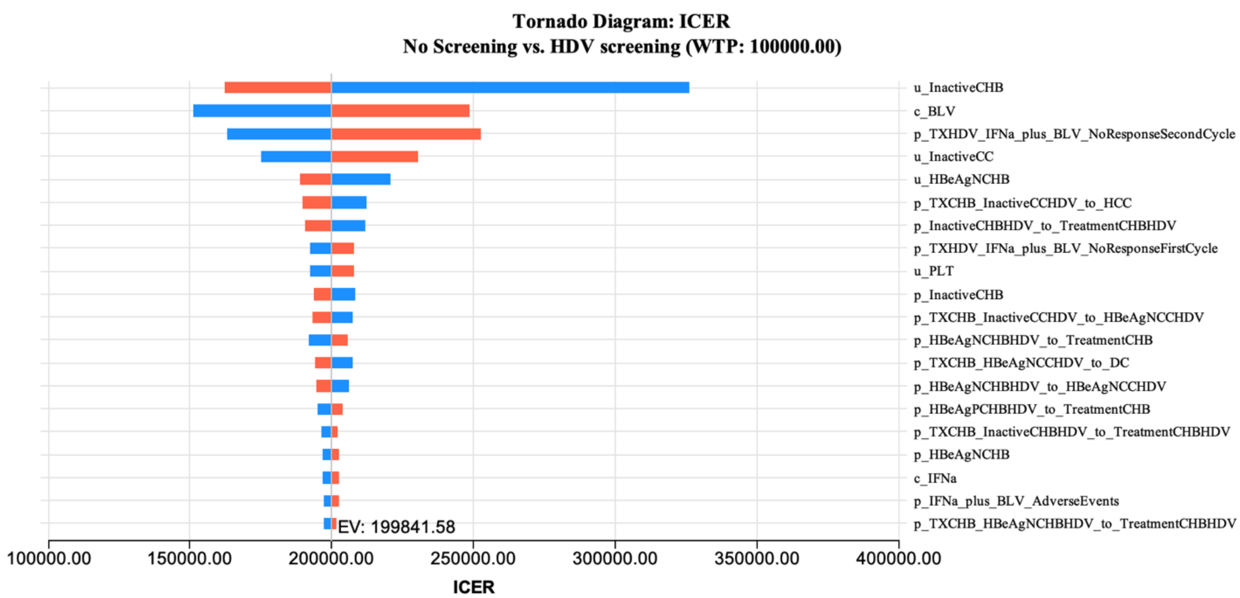
a) Screen and treat with Bulevirtide



b) Screen and treat with pegylated interferon alfa-2a



c) Screen and treat with buleviride and pegylated interferon alfa-2a (combined therapy)



Abbreviations: CHB – Chronic Hepatitis B, IT – Immune Tolerant, CC – Compensated Cirrhosis, HCC – Hepatocellular Carcinoma, HBeAg – Hepatitis B e Antigen, HDV – Hepatitis D Virus, BLV – Bulevirtide, IFNa – Pegylated Interferon alfa-2a, u_InactiveCHB – utility of being in CHB health state, c_BLV – Cost of BLV treatment, u_InactiveCC – utility of being in CC health state, p_TXHDV_BLV_NoResponseSecondCycle – probability of people that do not respond to BLV treatment in the second cycle, u_HBeAgNCHB – utility of being in HBeAg negative CHB health state, p_InactiveCHBHDV_to_TreatmentCHBHDV – probability of people in Inactive CHB HDV health state progressing to treatment for CHB HDV, p_TXCHB_InactiveCCHDV_to_HCC – probability of people in Inactive CC HDV progressing to HCC with CHB treatment, p_TXCHB_InactiveCHBHDV_to_treatmentCHBHDV – probability of inactive CHB and HDV progressing to treatment CHB and HDV with CHB treatment, p_InactiveCHB – probability of people starting off in inactive CHB health state, p_TXCHB_HBeAgNCHBHDV_to_TreatmetnCHBHDV - Probability of HBeAg negative CHB and HDV progressing to treatment CHB and HDV with CHB treatment only, p_HBeAgNCHB_to_TreatmentCHB – probability of HBeAg negative CHB progressing to treatment with CHB only, p_TXCHB_InactiveCCHDV_to_HBeAgNCCHDV – probability of inactive CC HDV progressing to HBeAg negative CC HDV health state with CHB treatment, p_HBeAgNCHBHDV_to_HBeAgNCCHDV – probability of HBeAg negative HDV progressing to HBeAg negative CC HDV health state, u_PLT – utility of being in post liver transplant health state, u_HBeAgNCC – utility of being in HBeAg negative CC health state, p_TXHDV_BLV_NoResponseFirstCycle – probability of people not responding to BLV treatment in the first cycle, p_HBeAgNCHB – probability of initially starting off in HBeAg negative CHB health state, p_TXCHB_InactiveCCHDV_to_DC – probability of Inactive CC HDV progressing to DC with treatment CHB, p_BLV_AdverseEvents – probability of developing adverse events while on BLV treatment, p_TXHDV_IFNa_NoResponseFirstCycle – probability of people not responding to IFNa treatment in the first cycle, c_IFNa – cost of IFNa treatment, p_TXHDV_IFNa_NoResponseSecondCycle – probability of people no responding to IFNa treatment in the second cycle, p_IT_to_HBeAgPCHB – probability of IT progressing to HBeAg positive CHB health state, p_TXHDV_IFNa_plus_BLV_NoResponseSecondCycle – probability of people not responding to combined therapy in the first cycle, p_TXHDV_IFNa_plus_BLV_NoResponseSecondCycle – probability of people not responding to combined therapy in the second cycle, p_IFNa_plus_BLV_AdverseEvents – probability people on combined therapy developing adverse events

Cost-effectiveness scatter plots of 10,000 iterations and 1,000 outcomes of the probabilistic sensitivity analysis were generated for all three strategies. These are shown below in Figures 4-6. The probabilistic sensitivity analysis for HDV screening and treating with BLV showed that this strategy was not cost-effective at a WTP of $100,000/QALY in 100% of the iterations. Meanwhile, HDV screening and treating with pegylated interferon alfa-2a was cost-effective at a WTP threshold of $50,000/QALY in 100% of the iterations. Lastly, the analysis showed that for HDV screening and treating with BLV plus pegylated interferon alfa-2a was not cost-effective at a WTP of $100,000/QALY in 99% of the iterations.

Figure 4: Incremental cost-effectiveness scatterplot of HDV screening vs no screening (Bulevirtide)

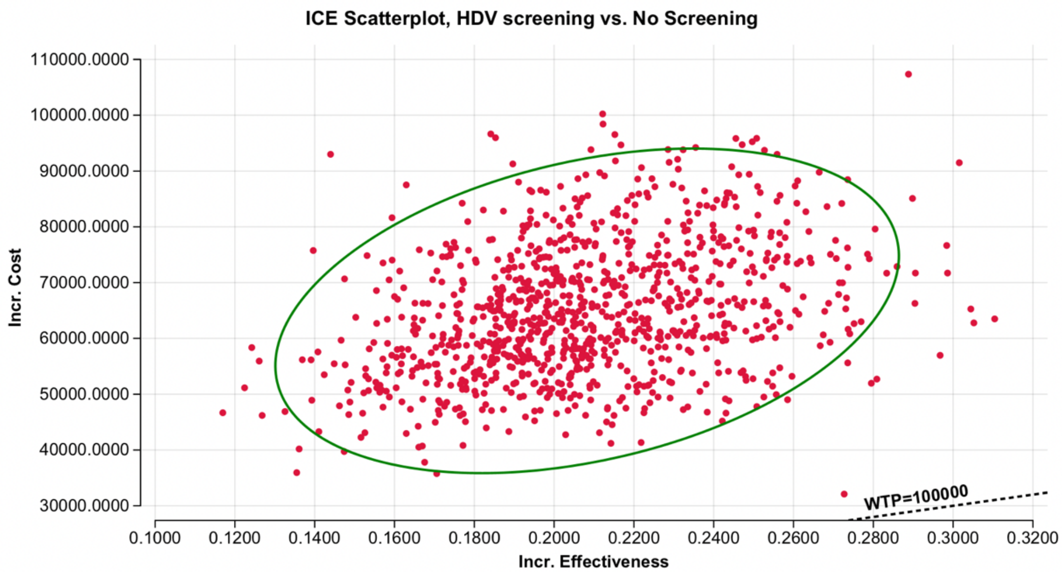


Figure 5: Incremental cost-effectiveness scatterplot of HDV screening vs no screening (Pegylated interferon alfa-2a)

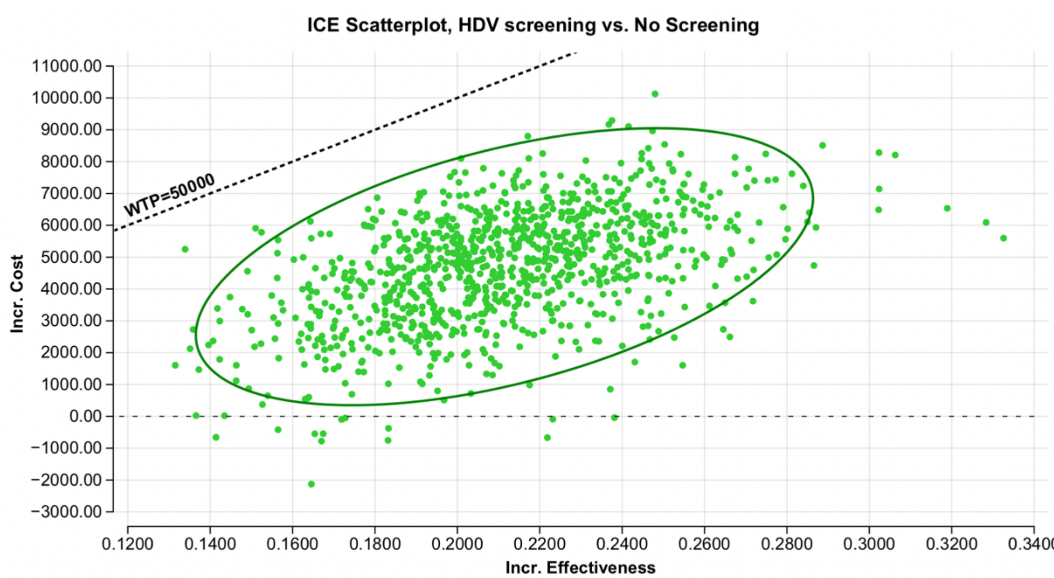
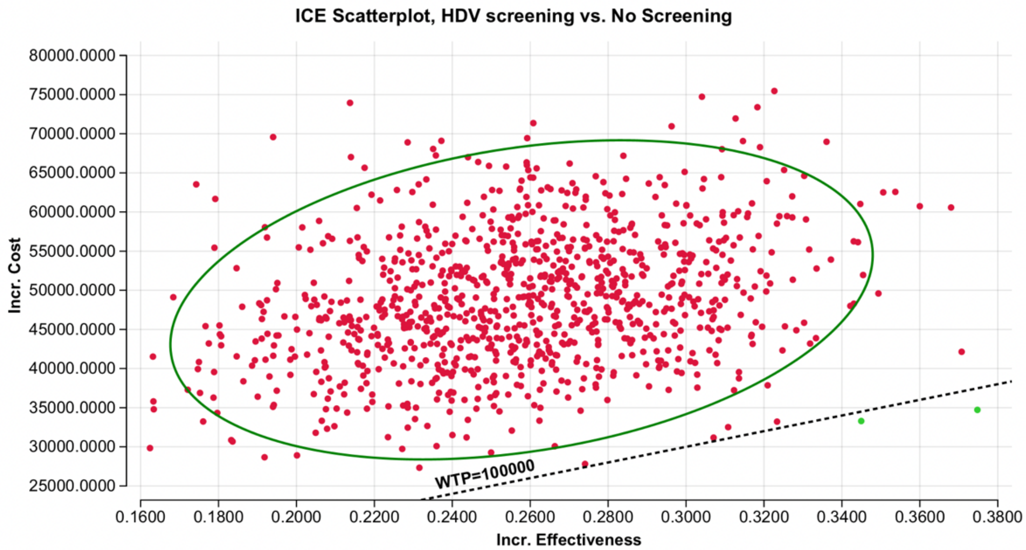


Figure 6: Incremental cost-effectiveness scatterplot of HDV screening vs no screening (Bulevirtide plus pegylated interferon alfa-2a)



Discussion

This chapter assessed the cost-effectiveness of screening and treating HDV-positive immigrants in Canada versus no screening. This assessment was conducted for three interventions: screening and treating with two monotherapies, BLV and pegylated interferon alfa-2a, separately, and a combination treatment of both BLV and pegylated interferon alfa-2a. The results of the study revealed that screening and treating with pegylated interferon alfa-2a is the most cost-effective strategy at the proposed WTP threshold of $50,000/QALY and $100,000/QALY. Nonetheless, from a clinical perspective, all the screening and treatment strategies were associated with lower numbers of cases of liver-related complications, namely DC, HCC, and LD, with the combination therapy showing most favourable outcomes in this regard. Such reductions are important to note although BLV treatment is not currently approved for use by the FDA or Health Canada. However, conditional approval has been granted by the European Medicines Agency. Meanwhile, pegylated interferon alfa-2a has notable side-effects.[15]

Previous economic evaluation studies also demonstrated that HDV screening and treatment was cost-effective.[55,71] One study showed that entecavir and pegylated interferon alpha were cost-effective approximately 80% and between 20-40% of the time, respectively, from a societal perspective, at a WTP threshold of $12,000 (2015 USD), for a hypothetical cohort consisting of patients with HBV and HDV infections.[71] It should be noted that this study preceded the introduction of BLV. Meanwhile, a

Spanish-based study revealed that 48 weeks of BLV treatment was associated with notably fewer lifetime cases of DC (152), HCC (113), liver transplant (11), and liver-related deaths (321) compared to pegylated interferon alpha.[55] Cost-saving of over €11,837,044 (2024 €) was also estimated for BLV from a national healthcare system perspective. This contradicting result that favors BLV over pegylated interferon as a monotherapy likely stemmed from the adoption of a more restricted treatment protocol, i.e. 48 weeks of treatment, although the results of longer-term treatment and efficacy rates are known.[57,72] These longer-term clinical outcomes, however, were incorporated into this present study.

While we demonstrated that BLV can likely reduce liver-related complications, especially in combination with pegylated interferon alfa-2a, neither BLV monotherapy nor BLV combination therapy were cost-effective. Even further, from an implementation point of view, these results suggest that it would be challenging for public health authorities to fund BLV because of its exorbitant cost, which is one of the primary factors contributing to it not being cost-effective. Other sensitive variables in our model included the utility of the inactive CHB health state, and the efficacy of each treatment option.

Reducing the cost of HDV treatment, especially the cost of BLV, through more efficient production methods and/or government subsidies may help improve cost-effectiveness even further. Specially, in Canada, it may be beneficial for public health officials to subsidize the cost of BLV, so that HDV-infected individuals may be able to receive an additional effective therapy option. Furthermore, this will help lower transmission and prevalence rates within Canadian communities, especially among migrant groups.

It may also be beneficial to implement mandatory HDV screening and treatment among immigrants to curtail rapid progression towards liver-related diseases. This can be achieved by screening potential legal migrants to Canada either before immigrating or at points of entry into Canada. However, this will likely have sociocultural implications if such an intervention is implemented.[46] For this and other reasons, full screening and treatment adherence is seldom achieved in the real world. In fact, the WHO have reported that adherence among patients in developed countries averages to be around 50%, and being even lower in developing countries.[73]

A number of limitations exist in the study. First, the cost and utilities associated with the HDV health states are assumed to be equal to those of HBV. This is a limitation because the pathogenesis of HDV is still relatively unknown. With the absence of the true cost and utilities, it is difficult to accurately reflect real-world practices and estimate the potential economic and health impacts of each intervention. Second, the prevalence of HDV applied in our model was derived from estimated in Chapter 2. The estimation method assumed that the HDV prevalence rate among immigrants in Canada was equivalent to the average prevalence of HDV-infected individuals among countries of origin. This is an assumption because in most cases, country-specific immigrant population would most likely have a lower prevalence rate as the immigrant population are usually healthy individuals with a high level of education based on the healthy immigrant effect (HIE).[47] The third limitation is the lack of data on HDV transition rates. With this limitation, we had to assume in our model that there was no infection going from CHB to HDV.

Conclusion

This study concluded that among immigrants in Canada, HDV screening and treatment with pegylated interferon alfa-2a monotherapy was cost-effective. However, HDV screening and treatment with bulevirtide or combination therapy consisting of bulevirtide and pegylated interferon alfa-2a were not cost-effective. It was also observed that compared to no intervention, screening and treatment generally resulted in more favourable clinical outcomes with respect to reduced cases of decompensated cirrhosis, hepatocellular carcinoma, and liver-related deaths. In this regard, HDV screening and combination therapy demonstrated the greatest benefits. However, reducing the cost of bulevirtide is likely to improve its cost-effectiveness as a monotherapy or combination therapy with pegylated interferon alfa-2a. Future studies on HDV interventions may benefit from updated HDV epidemiology, cost-related, and utility data.

Chapter 4

This thesis recognizes that HDV is a serious public health challenge, and although endemicity is relatively low in Canada, there is concern that continued migrant flows may be sustaining HDV prevalence rates in the country.[29] Even with this concern, the true prevalence of HDV in the country is still unknown, and available estimates may not be accurate because of challenges with methodologies used to calculate these estimates.[37] Additionally, the cost-effectiveness of screening and treating eligible individuals is still understudied in Canada even as new therapies become available.

Recognizing the issues mentioned above, this thesis sought to (1) estimate the prevalence of HDV among the migrant population in Canada, and (2) estimate the cost-effectiveness of screening and treating HDV-positive individuals with either pegylated interferon alpha, BLV or pegylated interferon alpha and BLV combined compared with no screening and no treatment.

Summary of results/thesis contribution

Chapter 2 of this thesis outlines and executes a methodological approach that incorporated a literature review of HBV and HDV prevalence rates in foreign countries and a weighted average analysis to estimate the prevalence of HDV among the migrant population in Canada. The prevalence of HDV among the HBV-positive Canadian immigrant population was estimated to be 7.7%, which is equivalent to an overall prevalence of 0.24% or 20,102 immigrants. This estimate is similar to that calculated by Wong et al which was 5.19%.[27]

The estimate of HDV prevalence and the methodology used to calculate this estimate can add to the limited data on HDV and inform HDV intervention policy making in Canada. The lack of true HDV prevalence data in Canada makes it difficult to emphasize the importance of this virus not just in Canada, but worldwide. Crucially, understanding the true prevalence of this disease will help public health officials to determine whether more intensive HDV screening program among immigrants in Canada would be more appropriate to prevent transmission.

The second major contribution of this thesis was to evaluate the cost-effectiveness of screening and treating HDV-positive patients versus no screening and treatment. This was done in Chapter 3 using a cost-utility analysis based on a state-transition model of the natural history of HDV. This model is another contribution of this dissertation, and it can potentially be used wholly or adapted to assess the health and economic impacts of screening and treating eligible HDV-positive candidates in other countries.

In Chapter 3, we showed that HDV screening and treating with BLV among Canadian immigrants is not cost-effective using a WTP of $100,000, when compared to the no screening for HDV strategy. In our base-case analysis the results showed that screen for HDV and treat with BLV costed $348,329 and 22.95 QALY versus no screen for HDV costed $283,716 and 22.76 QALY. The difference in cost between the two strategies were $64,613 and 0.19 QALY, which results in an ICER value of $329,915, exceeding the WTP of $100,000/QALY resulting in screen and treat with BLV not cost-effective. For screen HDV and treat with pegylated interferon alfa-2a, results showed that this strategy costed $288,062 and 22.96 QALY versus no screen for HDV costed $283,716 and 22.76 QALY. The difference in cost between the two strategies were $4,346 and 0.20 QALY, which results in an ICER value of $21,808, which is within the WTP of $50,000/QALY and WTP $100,000/QALY resulting in screen and treat with pegylated interferon alfa-2a cost-effective. For screen HDV and treat with BLV combined with pegylated interferon alfa-2a, results showed that this strategy costed $331,859 and 23.00 QALY versus no screen for HDV costed $283,716 and 22.76 QALY. The difference in cost between the two strategies were $48,143 and 0.24 QALY, which results in an ICER value of $199,841, which exceeds the WTP of $100,000/QALY, making this strategy not cost-effective. This means that HDV screening and treat with pegylated interferon monotherapy provides the clinical benefits and is within the WTP threshold of $50,000/QALY and $100,000/QALY.

Our model was successfully validated using HBV literature outcomes, notwithstanding the limited HDV data available. Previous studies have shown that the risk of HBV carriers developing HCC ranges from 15% to 40%. A microsimulation of 10,000 trials showed that the risk of developing HCC in our model was 25.05%, which falls within the range of literature.

This cost-effectiveness analysis in Chapter 3 assessing the four-screening strategy, no screen for HDV versus HDV screening and treat with BLV, HDV screening and treat with pegylated interferon alfa-2a, and HDV screening and treat with BLV plus pegylated interferon alfa-2a, has the potential to significantly impact public health policy towards implementing a screening strategy for HDV. Specifically, the results indicate that screening and treating with pegylated interferon alfa-2a was the only cost-effective intervention, and the policy makers can be guided by this outcome. Our results also suggest that implementing screening and treatment for HDV among immigrants in Canada will significantly improve their health outcomes, but the cost of effective treatment interventions like BLV is prohibitive.

As discussed in Chapter 1, given the link between HBV and HDV, HBV prevention measures, which are currently in place, can indirectly prevent HDV from developing. At the same time, existing recommendations call for HDV screening among: HBV positive patients in HDV endemic regions, persons with a history of injection drug use, persons with abnormal Alanine Transaminase (ALT), persons with advanced liver disease.[33] It is important to implement a screening strategy for HDV among immigrants in Canada because they account of a notable proportion of total HDV cases in the country, and screening and treatment would delay the rapid progression of disease.

Overall, this study aimed to bridge the gaps in the literature by providing a more reliable estimate of the HDV prevalence rate among immigrants in Canada and assessing the cost-effectiveness of screening and treating these individuals. Again, we reiterate that knowledge of the true prevalence of the disease and the cost-effectiveness of care is important in informing and funding appropriate policy interventions to mitigate the spread and burden associated with HDV.

Future work

Firstly, future work is needed to bridge the gaps in HDV prevalence data, specifically from countries where no HDV prevalence data currently exists. For example, in our model, we were only able to obtain 47 countries that reported country-specific HDV prevalence rates. There were 148 countries in our model without any prevalence rate reported, and in order for us to estimate our prevalence rate, we had to assume the prevalence for those countries equated to the average prevalence in the surrounding region. Due to this assumption, the limitation is that some unknown country prevalence could be lower or higher than our base assumption. To circumvent this limitation, screening and reporting of HDV infections are encouraged, especially in high endemic counties.

Secondly, in our cost-effectiveness model, we made several assumptions. We made assumptions on the cost, utility, and transition probabilities of each health state. To accurately assess the cost-effectiveness of no screening versus screening and treating for HDV, it is imperative to obtain reliable values of critical parameter estimates.

Third, a cost-effectiveness analysis of other treatment options for HDV would be of great interest. As discussed in Chapter 1, there are various HDV-specific treatment options being developed, such as lonafarnib and interferon lambda polymers, which are showing promising results.[17,18] Conducting a cost-effectiveness analysis that includes additional treatment options that are both viable and effective would be of great value to decision makers.

Lastly, an analysis focusing on identifying the prevalence of disease among the Canadian-born population would also be of interest, as would an assessment of the cost-effectiveness of screening and treating this cohort. It would be appropriate to explore these areas given the public health challenge that this infection poses.

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Appendix A

Hepatitis B

Hepatitis B virus (HBV) is a viral infection that has caused a severe global health concern.[74] As of 2022, the global prevalence for HBV infected individuals is 3.2% which corresponds to 258 million individuals who are positive for HBV.[28] This disease has resulted in 550, 000 deaths globally.[9] Majority of the deaths have come from infected individuals progressing to cirrhosis and hepatocellular carcinoma (HCC), this makes HBV a global health concern.[9]

In Canada there are various treatments and preventative measures put in place for Canadian across the country.[29] Fortunately, Canada is considered as one of the low endemic countries.[29] It has been estimated that less than 5% of Canadians have the Hepatitis B surface antigens and less than 0.5% are carriers.[29] Even though various preventative measures exist in Canada, HBV an infectious disease in Canada. Majority of the people who are infected with HBV in Canada are immigrants. [29] The Public Health Agency of Canada (PHAC) in 2021 reported that there were 3,524 cases of HBV from all 13 provinces and territories, with a rate of 9.2 per 100,000 people living in Canada.[75] The rate of HBV per 100,000 people living in Canada is slowly decreasing as in 2019 it was reported to be as 13.1 per 100,000 people living in Canada.[76]

HBV is such a big concern in Canada is related to its mode of transmission. There are three significant ways that HBV can be spread: percutaneous, sexual and perinatal. The first mode of transmission is percutaneous, which is HBV being transmitted through puncture of the skin that comes into contact with an individual infected blood or bodily fluid.[10] The second mode of transmission is sexual; HBV can be transmitted from person to person through semen and other bodily fluids.[11] The third and most common mode of HBV transmission in endemic countries is perinatal.[12] Perinatal transmission is when an infected pregnant mother infects a child.[12] Children who are born with HBV-infected mothers have a greater than 90% chance of developing chronic hepatitis B (CHB) if they are not appropriately treated at birth.[12] This mode of HBV transmission is relevant in Canada because currently Canada is a very popular immigration destination among families from highly endemic countries with higher HBV prevalence.

Natural History of Hepatitis B

HBV is a double stranded DNA virus with multiple markers that allow medical professionals to detect whether or not a person is infected.[74] HBV can be categorized into two either acute HBV or chronic HBV.[77] Acute HBV is usually considered when a person's infection with HBV last within the first three months.[77] A chronic HBV infection usually last more than six months, where the patients' symptoms are still present for a long period of time.[77] CHB can lead to serious liver disease and or liver death.[77]

The progression of CHB can be described in four phases. Immune tolerance (HBeAg positive chronic infection), Immune clearance (HBeAg positive chronic hepatitis), Inactive phase, and Immune control (HBeAg negative chronic infection).[78,79] The first phase, the immune tolerance phase, also known as HBeAg positive chronic infection, is characterized by a high viral load but a low inflammatory phase, with near-normal liver level.[78] The second phase is the immune clearance phase, also known as HBeAg-positive chronic hepatitis, which will mostly occur in the third or fourth decade of life in patients who are infected with HBV.[78] This phase is characterized by a decrease in HBV DNA levels but an increase in alanine transaminase (ALT) levels.[78] The third phase the inactive phase, in this phase the virus is still present in the body but it will not be actively replicating.[79] Usually blood test will show normal levels of ALT, which means there is little to no inflammation in the liver.[79] The fourth phase is the immune control phase, also known as HBeAg negative chronic infection, and is characterized by low levels of HBV DNA and low levels of ALT.[78] Some patients in this phase will undergo seroconversion of HBeAg, where antibodies against HBeAg known as anti-HBeAg develop and HBeAg is lost.[78]

In Canada, vaccination policy is effective in preventing transmission between people, but Ontario's vaccine policy makes young kids unprotected, which may not be effective.[34] In Ontario, HBV vaccines are given at grade 7, which leaves children with the chance of being infected with the disease.[34] There is currently no formal screening program for immigrants in Ontario, but there is parental screening.[34] Treatment is effective but lifelong.[35] All approved HBV treatments in Ontario are adefovir, entecavir, tenofovir, and lamivudine except telbivudine and pegylated interferon are funded by Ontario public drug programs.[35]

Appendix B

Table AB1: List of all the search terms used in the literature review

Regions	Search terms
North America	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("North America*" OR "Greenland*" OR "Saint Pierre and Miquelon*" OR "United States of America*")
Central America	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Central America*" OR "Belize*" OR "Costa Rica*" OR "El Salvador*" OR "Guatemala*" OR "Honduras*" OR "Mexico*" OR "Nicaragua*" OR "Panama*")
Carribbean and Bermuda	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Caribbean*" OR "Anguilla*" OR "Antigua and Barbuda*" OR "Aruba*" OR "Bahamas*" OR "Barbados*" OR "Bermuda*" OR "Cayman Islands*" OR "Cuba*" OR "Dominica*" OR "Dominican Republic*" OR "Grenada*" OR "Guadeloupe*" OR "Haiti*" OR "Jamaica*" OR "Martinique*" OR "Montserrat*" OR "Netherlands Antilles*" OR "Puerto Rico*" OR "Saint Kitts and Nevis*" OR "Saint Lucia*" OR "Saint Vincent and the Grenadines*" OR "Trinidad and Tobago*" OR "Turks and Caicos Islands*" OR "Virgin Islands, British*" OR "Virgin Islands, US*")
South America	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("South America*" OR "Argentina*" OR "Bolivia*" OR "Brazil*" OR "Chile*" OR "Colombia*" OR "Ecuador*" OR "Falkland Islands

	(Maldvinas)*" OR "French Guiana*" OR "Guyana*" OR "Paraguay*" OR "Peru*" OR "Suriname*" OR "Uruguay*" OR "Venezuela*")
Western Europe	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Western Europe*" OR "Austria*" OR "Belgium*" OR "France*" OR "Germany*" OR "Liechtenstein*" OR "Luxembourg*" OR "Monaco*" OR "Netherlands*" OR "Switzerland*")
Eastern Europe	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Eastern Europe*" OR "Czech Republic*" OR "Hungary*" OR "Poland*" OR "USSR*" OR "Estonia*" OR "Latvia*" OR "Lithuania*" OR "Belarus*" OR "Moldova*" OR "Russian Federation*" OR "Ukraine*")
Northern Europe	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Northern Europe*" OR "Ireland*" OR "Scandinavia*" OR "Denmark*")
Southern Europe	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Southern Europe*" OR "Albania*" OR "Andorra*" OR "Gibraltar*" OR "Greece*" OR "Vatican City*" OR "Malta*" OR "Portugal*" OR "San Marino*")
Western Africa	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Western Africa*" OR "Benin*" OR "Burkina Faso*" OR "Cape Verde*" OR "Cote d'lvoire*" OR "Gambia*" OR "Ghana*" OR

	"Guinea*" OR "Guinea-Bissau*" OR "Liberia*" OR "Mali*" OR "Mauritania*" OR "Niger*" OR "Nigeria*" OR "Saint Helena*" OR "Senegal*" OR "Sierra Leone*" OR "Togo*")
Eastern Africa	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Eastern Africa*" OR "Burundi*" OR "Comoros*" OR "Djibouti*" OR "Eritrea*" OR "Ethiopia*" OR "Kenya*" OR "Madagascar*" OR "Malawi*" OR "Mauritius*" OR "Mayotte*" OR "Mozambique*" OR "Renuion*" OR "Rwanda*" OR "Seychelles*" OR "Somalia*" OR "Tanzia*" OR "Uganda*" OR "Zambia*" OR "Zimbabwe*")
Northern Africa	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Northern Africa*" OR "Algeria*" OR "Egypt*" OR "Libya*" OR "Morocco*" OR "Sudan*" OR "Tunisia*" OR "Western Sahara*")
Central Africa	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Central Africa*" OR "Angola*" OR "Cameroon*" OR "Chad*" OR "Congo*" OR "Equatorial Guinea*" OR "Gabon*" OR "Sao Tome and Principle*")
Southern Africa	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Southern Africa*" OR "Botswana*" OR "Lesotho*" OR "Namibia*" OR "South Africa*" OR "Swaziland*")
Eastern Asia	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Eastern Asia*" OR "China*" OR "Japan*" OR "Korea North*" OR "Korea South*" OR "Mongolia*" OR "Taiwan*")

Southeast Asia	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Southeast Asia*" OR "Brunei Darussalam*" OR "Cambodia*" OR "East Timor*" OR "Indonesia*" OR "Laos*" OR "Malaysia*" OR "Myanmar*" OR "Philippines*" OR "Singapore*" OR "Thailand*" OR "Viet Nam*")
Southern Asia	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Bhutan*" OR "India*" OR "Maldives*" OR "Nepal*" OR "Pakistan*" OR "Sri Lanka*")
Oceania	("Hepatitis D" OR "HDV" OR "Hepatitis Delta") AND Prevalence AND ("Oceania*" OR "Samoa*" OR "Australia*" OR "Cook Islands*" OR "Fiji*" OR "French Polynesia*" OR "Guam*" OR "Kiribati*" OR "Marshall Islands*" OR "Micronesia*" OR "Nauru*" OR "New Caledonia*" OR "New Zealand"* OR "Palau"* OR "Papua New Guinea"* OR "Pitcairn"* OR "Solomon Islands"* OR "Tonga"* OR "Tuvalu"* OR "Vanuatu"* OR "Wallis and Futuna"*)