Hepatitis B in Migrants: Burden of Infection and the Cost-Effectiveness of Interventions to Decrease Associated Morbidity and Mortality

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ABSTRACT

Background: Immigrants and refugees have increased morbidity and mortality from liver disease compared to host populations largely due to undetected chronic hepatitis B virus (HBV) infection. We conducted a systematic review of the seroprevalence of chronic HBV and prior immunity in migrants arriving in immigrant-receiving countries to identify the proportion who would benefit from HBV screening and vaccination programs. We then performed a cost-effectiveness analysis to identify the optimal intervention for adult immigrants and refugees arriving in Canada.

Methods: Four electronic databases were searched to identify studies that reported HBV surface antigen (HBsAg) and HBV surface antibodies (anti-HBs) in international migrants. Proportions for chronic HBV and prior immunity were transformed using the logit transformation and pooled using a random-effects model. A decision-analysis model was then developed to examine the cost-effectiveness of four screening and vaccination strategies, compared to no screening or vaccination: a) universal vaccination, b) anti-HBs screening and vaccination of susceptibles, c) HBsAg screening and antiviral treatment, d) combined HBsAg and anti-HBs screening. Model parameters for the seroprevalence of infection and immunity were obtained from the systematic review. Estimates for disease progression, medical costs and utilities were obtained from the published literature.

Results: The overall pooled seroprevalence of infection in international migrants was 7.2% (95% CI: 6.3% – 8.2%) and the proportion with prior immunity was 39.7% (95% CI: 35.7% – 43.9%). HBV seroprevalence differed significantly by

region of origin with migrants from East Asia and Sub-Saharan Africa at highest risk of infection and migrants from Eastern Europe at intermediate risk. None of the strategies were found to be cost-saving, but screening for HBsAg to identify chronically infected immigrants was found to be the most cost-effective strategy and would cost $37,675 per quality-adjusted life year (QALY) gained, compared to no intervention. Results were sensitive to the cost and effectiveness of antiviral therapy. A probabilistic sensitivity analysis demonstrated that the screen and treat strategy would have an 84% chance of having an incremental cost-effectiveness ratio of < $50,000 per QALY gained.

Conclusions: The seroprevalence of chronic HBV is high in migrants from most world regions, particularly among those from East Asia, Sub-Saharan Africa and Eastern Europe. Screening adult immigrants soon after arrival would be cost-effective and would reduce morbidity and mortality from HBV.

RÉSUMÉ

Contexte: Les immigrants et les réfugiés ont un taux élevé de mortalité par la maladie du foie par rapport aux populations d'accueil en grande partie en raison de la présence d'une infection par le virus de l'hépatite B (VHB) chroniquenon détectée. Nous avons effectué une révision systématique de la séroprévalence de l'hépatite B chronique et d'une immunité préalable aux migrants qui arrivent dans les pays qui accueillent des immigrants afin d'identifier ceux qui bénéficieraient d'un dépistage du VHB et des programmes de vaccination. Nous avons ensuite effectué une analyse coût-efficacité pour identifier l'intervention optimale pour les immigrants et les réfugiés adultes qui arrivent au Canada.

Méthodes: Des recherches ont été effectuées sur quatre bases de données afin d'identifier les études indiquant la prévalence de l'antigène de surface du VHB (AgHBs) et des anticorps du VHB (anti-HBs) chez les migrants internationaux. Les estimations de l'hépatite B chronique et de l'immunité préalable ont été transformées en utilisant la transformation *logit* et regroupées à l'aide d'un modèle à effets aléatoires. Un modèle d'analyse décisionnelle a ensuite été développé afin d'examiner le rapport coût-efficacité de quatre stratégies de dépistage et de vaccination: a) la vaccination universelle, b) le dépistage AgHBs et le traitement antiviral, c) le dépistage anti-HBs et la vaccination des sujets réceptifs, d) le dépistage combiné de AgHBs et anti-HBs, par rapport à l'absence de dépistage ou de vaccination. Les paramètres du modèle pour la séroprévalence de l'infection et l'immunité ont été obtenus à partir de la révision systématique. Les estimations pour la progression de la maladie, les frais médicaux et les services publics ont été obtenues à partir de la littérature publiée.

Résultats: La séroprévalence globale de l'infection était de 7.2% (IC 95%: 6.3% - 8.2%) et la proportion de l'immunité préalable était de 39.7% (IC 95%: 35.7% - 43.9%). La séroprévalence du VHB était considérablement différente par région d'origine. Les migrants de l'Asie de l'Est et de l'Afrique sub-saharienne étaient les plus à risque et les migrants de l'Europe de l'Est étaient à risque intermédiaire. Aucune de ces stratégies ne s'est avérée réduire les coûts, mais le dépistage AgHBs pour identifier les immigrants infectés chroniquement a été jugé le plus rentable et coûterait $37,675 par année de vie ajustée sur la qualité (QALY) gagnée, par rapport au status quo. Les résultats ont été sensibles au coût et à l'efficacité de la thérapie antivirale. Une analyse de sensibilité probabiliste a démontré que le dépistage et la stratégie de traitement aurait une chance de 84% d'avoir un rapport coût-efficacité de < $50,000 par QALY gagnée.

Conclusions: La séroprévalence de l'hépatite B chronique est élevée chez les migrants originaires de la plupart des régions du monde, en particulier pour ceux de l'Asie de l'Est, de l'Afrique subsaharienne et d'Europe de l'Est. Le dépistage d'AgHBs après l'arrivée des immigrants serait le plus rentable, quelle que soit la région d'origine des immigrants, et permettrait de réduire la morbidité et la mortalité causées par le VHB.

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Lastly, I would like to thank my parents, my brother and my fiancée, Stephanie, for all the support they have given me while I completed my research.
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CONTRIBUTIONS OF AUTHORS

The contents of this thesis originated from a research program developed by Dr. Chris Greenaway which aimed to investigate the epidemiology of viral hepatitis in Canadian immigrants in 2007-2008. I decided I would focus my attention on hepatitis B viral infections, the most common form of viral hepatitis found in immigrants and an important source of preventable liver disease in the foreign-born population of Canada. The results of my research at the Centre of Clinical Epidemiology and Community Studies of the Jewish General Hospital from April 2011 to April 2012 form the core of this thesis.

As first author of the two manuscripts included in this thesis, I, together with my supervisors, Dr. Chris Greenaway and Dr. Kevin Schwartzman, am responsible for the design of the studies and developing the specific research questions behind them. I was responsible for collecting the data and conducting all of the analysis included in the studies and produced the first draft of both manuscripts.

In addition to participating in the study conception and design of my research projects, Dr. Chris Greenaway and Dr. Kevin Schwartzman critically reviewed both manuscripts and provided timely feedback for my inquiries regarding the direction of the research. Dr. Ian Shrier and Dr. Guido Schwarzer provided methodological and statistical expertise for the meta-analysis component of my systematic review. Ms. Lee Marshall aided in the data extraction for the systematic review by serving as a second reader for the seroprevalence studies

that were reviewed. Ms. Sonya Cnossen and Dr. Marina Klein critical reviewed the manuscript for the systematic review. Dr. Olivia Oxlade provided methodological expertise for the cost-effectiveness modeling and computational expertise for the TreeAge Pro decision-analysis software.

Both of my supervisors assisted in revisions to this thesis and read the final version that is presented here.

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ABBREVIATIONS

AIC	Akaike information criterion
ALT	alanine aminotransferase
anti-HBc IgM	hepatitis B core antigen immunoglobulin M antibody
anti-HBs	hepatitis B surface antibodies
API	Asian and Pacific Islander
ARI	annual risk of infection
CCIRH	Canadian Collaboration for Immigrant and Refugee Health
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analyses
CI	confidence interval
CNDSS	Canadian Notifiable Disease Surveillance System
ELISA	enzyme-linked immunosorbent assay
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	Immigration Act
ICER	incremental cost-effectiveness ratio
IME	Immigration Medical Examination
MSM	men who have sex with men
NACI	National Advisory Committee on Immunization
OR	odds ratio
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
TB	tuberculosis
WHO	World Health Organization

CHAPTER 1: Introduction

1.1 Rationale

Hepatitis B viral infection is an important source of global morbidity and mortality. It is one of the world's leading causes of preventable illness and has affected the health of millions of people on every continent. Immigration from areas where hepatitis B is endemic has contributed to an increase in the prevalence of chronic hepatitis B infection and increased rates of cirrhosis and primary liver cancer in immigrant-receiving countries. In many such countries, such as Canada and the United States, there are no existing screening programs to detect immigrants or refugees who are chronically infected with hepatitis B virus (HBV) at the time of landing and there are no universal catch-up vaccination programs in place to provide immunity to susceptible individuals. As a result, many immigrants with, often asymptomatic, chronic HBV infections remain untreated and are at risk of developing liver disease. Furthermore, they continue to be infectious, while family members and close contacts, if susceptible, are at an increased risk of becoming infected with the virus.

1.2 Research Objectives

This research project had two major objectives. The first objective was to determine the burden of hepatitis B infection in migrant communities through a systematic review of the literature reporting the seroprevalence of HBV infection and prior immunity. The second objective was to evaluate the cost-effectiveness of four interventions for hepatitis B, using a decision-analysis model, in a hypothetical

cohort of new immigrants to Canada. Results obtained from the systematic review designed to meet the first objective were used to inform parameter estimates for the cost-effectiveness study.

The purpose of this research study was to determine what proportion of international migrants would benefit from targeted screening and vaccination programs and what the cost-effectiveness of introducing such programs would be for Canadian immigrants and refugees. Four different HBV screening, treatment and vaccination strategies were compared against the *status quo* strategy of no screening or vaccination for new immigrants during their first year in Canada. The first strategy consisted of universally vaccinating immigrants against HBV at the time of landing. The second strategy consisted of universally screening immigrants for prior immunity, and vaccinating only those found not to have serologic evidence of immunity. The third strategy consisted of screening immigrants for chronic HBV infection at the time of landing and providing appropriate antiviral treatment for those who it is indicated. The fourth strategy consisted of universally screening for both markers of HBV infection and prior immunity and then offering treatment for those indicated and vaccinating all immigrants found to susceptible.

With limited health-care resources, there exists a need to evaluate different health interventions designed to reduce morbidity and mortality associated with HBV in new immigrants and refugees to Canada. By implementing a large scale HBV screening program targeted at immigrants and refugees, public health officials may gain the ability to detect additional cases of asymptomatic chronic HBV infection in individuals, many of whom would benefit from antiviral treatment. Identifying these cases of chronic hepatitis B early and providing timely

preventative treatment may reduce the costs on the Canadian health-care system for treating patients with liver disease in the future and may also reduce the societal costs incurred through household and family expenditures for mild illness, time lost off work, and foregone income due to death or disability. In addition, the introduction of a catch-up vaccination program for immigrants and refugees can help prevent HBV transmission from chronically infected individuals to susceptible family members and close contacts, decreasing morbidity associated with HBV and reducing the need for costly antiviral treatment to manage chronic hepatitis B infections in the future.

1.3 Thesis Overview

Chapter 1 begins with a brief introduction to the research problem and describes the specific objectives of this thesis. Chapter 2 focuses on describing the population being studied and provides a review of the literature regarding both the local and global epidemiology of hepatitis B, as well as the natural history of the disease. It concludes by discussing interventions used to reduce the burden of hepatitis B and their cost-effectiveness in various immigrant populations.

Chapter 3 includes the manuscript entitled "Seroprevalence of Chronic Hepatitis B Virus Infection and Prior Immunity in Immigrants and Refugees: A Systematic Review and Meta-Analysis". This chapter addresses the first objective of systematically obtaining estimates for the seroprevalence of hepatitis B infection and immunity and determining the burden of HBV in international migrants.

Chapter 4 includes the manuscript entitled “Screening and Vaccination Strategies for Preventing Hepatitis B Related Morbidity and Mortality in Immigrants: A Cost-Effectiveness Analysis”. This chapter addresses the second objective of this thesis, which was to determine the cost-effectiveness of different health interventions designed to reduce the burden of HBV infection in the foreign-born population. This study incorporates results from the systematic review of seroprevalence surveys to inform parameter estimates in the decision-analysis model.

Chapter 5 and 6 include a discussion and an overall conclusion for the research presented in this thesis, respectively. An appendix follows the main body of the thesis which contains supplementary material related to the manuscripts presented in this thesis. An overall reference list is presented after the appendices and includes all the references cited in the body of this thesis and in the two manuscripts.

CHAPTER 2: Literature Review

2.1 Canadian Immigration

2.1.1 Canadian Immigration Policy and Processes

With increasing globalization, international travel, and immigration, the epidemiology of infectious diseases in developed countries are considerably becoming reflective of the current state of global health in the developing world. In Canada, the epidemiology of hepatitis B, as well as other infectious diseases, is driven by the importation of new infections linked with the changing immigrant patterns and immigration policies designed to attract highly-skilled and educated individuals from around the world.

Since 1976, Canadian immigration policies have been defined by the *Immigration Act* (IA).[1] The main objectives of the IA were to facilitate the selection of those individuals who best fit the economic and demographic needs of Canada, as well as to bring together existing immigration legislation designed to eliminate discrimination based on origin, race or religion. Over the last three and a half decades, Canadian immigration policy has focused on three main objectives: 1) encourage international migration of those able to contribute to enhancing the economic development of Canada, 2) reunite families of immigrants already in Canada and 3) protect refugees and vulnerable populations requiring humanitarian assistance.[2]

As a result of the three main objectives of the IA, permanent residents are classified into three distinct classes: the economic class, the family class, and the humanitarian class. Approximately 55-60% of permanent residents accepted into

Canada over the last five years were economic immigrants. Economic immigrants are selected based on their ability to enter the labour market in needed areas or can also be investors, entrepreneurs or live-in caregivers for children, the sick or the elderly. 20-25% of permanent residents are admitted as part of the family class and are reunited with immigrants or refugees previously admitted to Canada. Government-assisted refugees, selected from designated areas outside Canada, and privately-sponsored refugees constitute the humanitarian class, which accounts for 15% of permanent residents to Canada.[3]

In accordance with immigration legislation, all permanent residents, including those migrants selected or sponsored as refugees abroad, asylum seekers and certain temporary workers, who wish to immigrate to Canada are required to undergo the Immigration Medical Examination (IME).[4] The IME consists of a physical and mental examination, urinalysis, chest radiography for pulmonary tuberculosis (TB), and serology for syphilis and human immunodeficiency virus (HIV). Canadian immigration health policy has focused on excluding potential migrants who are a danger to public health and safety and migrants who are expected to place an excessive demand on health and social services. However, this approach has been criticized for being antiquated, as the IME focuses primarily on identifying those who are inadmissible on medical grounds for the drain they would have on public services, and does not provide health prevention or promotion activities, such as vaccination or mental health services.[5] Furthermore, up until 2002, the IME only screened for TB and syphilis, two infectious diseases that were common in immigrants from Western Europe during the early 20th century, and has

not changed to include other communicable illness that are common in new migrants from areas such as Eastern Europe, Africa and Asia.

Beginning in 2002, however, new immigration legislation mandated screening for HIV in order to be able to provide counselling and referral to HIV-positive migrants in an effort to improve the health of new arrivals to Canada.[6] The IME has the potential to be used to screen for further infectious disease and to provide health services to new Canadian immigrants and refugees, thus reducing the long-term burden of infectious diseases.

2.1.2 Canada's Immigrant Profile

Canada is one of the world's leading destinations for international migrants. Since 2001, an average of 250,000 immigrants and refugees became permanent residents of Canada, annually. Immigration continues to be an important source of demographic growth. From July 2009 to June 2010, immigration accounted for 62% of Canada's population growth.[7-9] Between 2001 and 2006, Canada's foreign-born population increased by 13.6%, a rate that was four times higher than the 3.3% growth rate of the Canadian-born population, during the same period.[10]

During the last 35 years, there has been a major shift in the source regions of immigrants to Canada. Prior to 1975, more than 100,000 immigrants from Western Europe arrived in Canada every year, constituting more than 40% of all new permanent residents. Last year, only 40,000 Europeans, mostly from Eastern Europe, settled in Canada, accounting for less than 15% of all new permanent residents. Conversely, the number of immigrants from Asia has increased from less than 50,000 a year, in the early 1980s, to 164,000 in 2010. Asian immigrants now

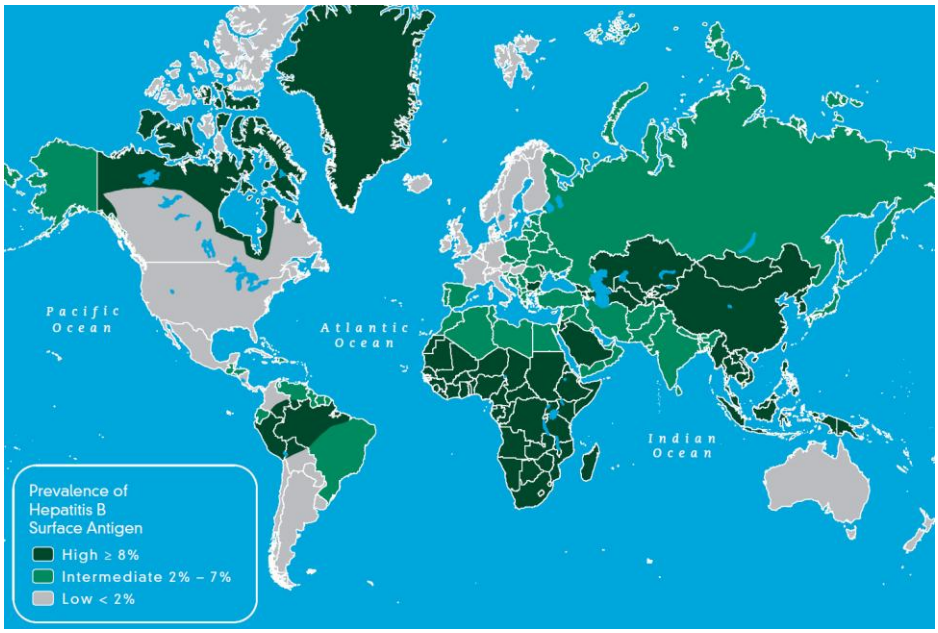
account for nearly 60% of new permanent residents to Canada. Similarly, there has also been an increase in immigrants from Africa, from approximately 4,000 annually, during the early 1980s, to 35,000 in 2010.[11]

2.2 Background of Hepatitis B

2.2.1 Global Epidemiology of Hepatitis B and Primary Liver Cancer

The World Health Organization (WHO) estimates that 350 million people, globally, are chronically infected with HBV.[12] Chronic HBV infection is defined by the serologic presence of the hepatitis B surface antigen (HBsAg) in the blood for more than six months.[13] The seroprevalence of this marker, which appears shortly after infection, is used to estimate the burden of chronic HBV worldwide (Figure 2.1). The seroprevalence of HBsAg is highest in East Asia and Sub-Saharan Africa, where more than 8% of the general population are chronically infected. In these regions, hepatitis B is considered to be highly endemic. It is estimated that nearly 45% of the world's population lives in areas of high HBV endemicity.[14] Intermediate HBV-endemic regions, such as Eastern Europe and South Asia, have HBsAg seroprevalences between 2% and 7%. Low HBV-endemic regions, such as North America and Western Europe have HBsAg seroprevalences of less than 2%, within the general population.

Figure 2.1: Global Prevalence of Hepatitis B Surface Antigen[15]



Chronic HBV infections are often asymptomatic and clinical symptoms usually occur only once an individual develops cirrhosis or hepatocellular carcinoma (HCC); two common liver disease sequelae that result from chronic HBV infection. Most of the disease burden associated with HBV occurs in chronically infected individuals. It is estimated that between 15% and 40% of people chronically infected will develop cirrhosis, liver failure, or HCC, over the course of their lifetime.[13,16] Chronic HBV infection is responsible for 500,000 to 1.2 million deaths annually, 320,000 of which are attributed to HCC.[16]

Age-adjusted incidence rates of primary liver cancer, of which HCC is the most frequent type, have been found to be greatest in those areas where HBV is highly endemic. In East Asia, for example, rates of liver cancer in males ranged between 30 and 98 cases per 100,000 person-years.[17] Similarly, incidence rates of primary liver cancer were high in Southeast Asia, where estimated rates in males

ranged from 20 to 35 cases per 100,000 person-years.[18] In Sub-Saharan Africa, rates of primary liver cancer were variable, but still elevated, and ranged between 7 and 40 cases per 100,000 person-years. In most areas, rates of liver cancer were between two and four times higher in males than in females, suggesting greater exposures to HBV and other carcinogens, or a role for androgenic hormonal activity or genetic susceptibility in predisposing males to liver cancer.[19,20] In HBV-endemic areas, age-specific rates of liver cancer were highest among younger age groups (40-49 year olds), compared to areas with low HBV endemicity, where incidence rates of liver cancer were highest among those > 75 years of age. This finding reflects the role that HBV plays as an etiologic cause of cancer and the fact that the infection is typically acquired early in life in HBV-endemic areas.[21] Typically, primary liver cancer develops 40 to 60 years after a chronic HBV infection has been established.[22]

2.2.2 Natural History of Hepatitis B Infection

HBV infection results from exposure to the hepatitis B virus, a partially double-stranded DNA virus classified in the *Hepadnaviridae* family. HBV is a blood-borne infection and is readily transmitted through percutaneous or mucosal exposure of infected blood or serum-derived bodily fluids and replicates inside liver tissue.[23]

There are several common transmission routes responsible for the spread of HBV. In areas of the world where HBV is endemic, such as Sub-Saharan Africa and East Asia, vertical perinatal transmission from an infected mother to her child, during child birth, accounts for the majority of viral transmission.[24] Horizontal

transmission from infected household family members to young children through contact with contaminated blood from scratching, biting, or sharing toothbrushes or household items, is also common.[25]

In areas where HBV endemicity is low (< 2%), such as North America and Western Europe, viral transmission most often occurs among adults who engage in high-risk behaviours, such as intravenous drug use or unprotected and unsafe sexual activity.[16,26] Vertical transmission, however, is relatively uncommon as prenatal screening programs are generally effective at identifying mothers who are infected and newborns are provided prophylaxis, in the form a HBV vaccination shortly after birth. Prior to routine vaccination against HBV in health care workers, HBV infection was also a common occupational hazard for those working in health care settings. Blood transfusions were once an important source of HBV transmission, but routine screening of donated blood for the virus has eliminated the pathogen from blood supplies in many low prevalence countries.[27]

HBV infections typically begin with an acute phase which precedes a chronic infection. Symptoms, which include nausea, abdominal pain and vomiting, are present in 33% to 50% of adults with an acute infection, but occur in less than 10% of acutely infected children.[23] Acute infections are rarely fatal and typically resolve within six months of exposure to HBV. In some circumstances, acute HBV infections may result in fulminant hepatitis, a condition characterized by rapid deterioration of liver function and encephalopathy, which may result in death.[28] Individuals who clear an acute infection typically generate long-lasting immunity against future infections through the development of hepatitis B surface antibodies (anti-HBs), which can be detected through serologic testing.

The risk of developing a chronic HBV infection following an acute infection is inversely related to the age at which an individual is infected.[29] The risk of developing a chronic infection is highest in infants born to hepatitis B e-antigen (HBeAg) positive mothers, where approximately 80% to 90% of neonates fail to resolve acute HBV infections and become chronic HBV carriers. The risk of becoming a chronic carrier is approximately 30% in children and decreases to less than 10% in immunocompetent adults. The risk of developing a chronic infection is higher in immunocompromised children and adults.[23] In HBV-endemic areas, where infection is commonly acquired very early in life and frequently progresses from an acute to a chronic infection, HBV is readily propagated from one generation to the next.

2.3 Epidemiology of Hepatitis B in Canada

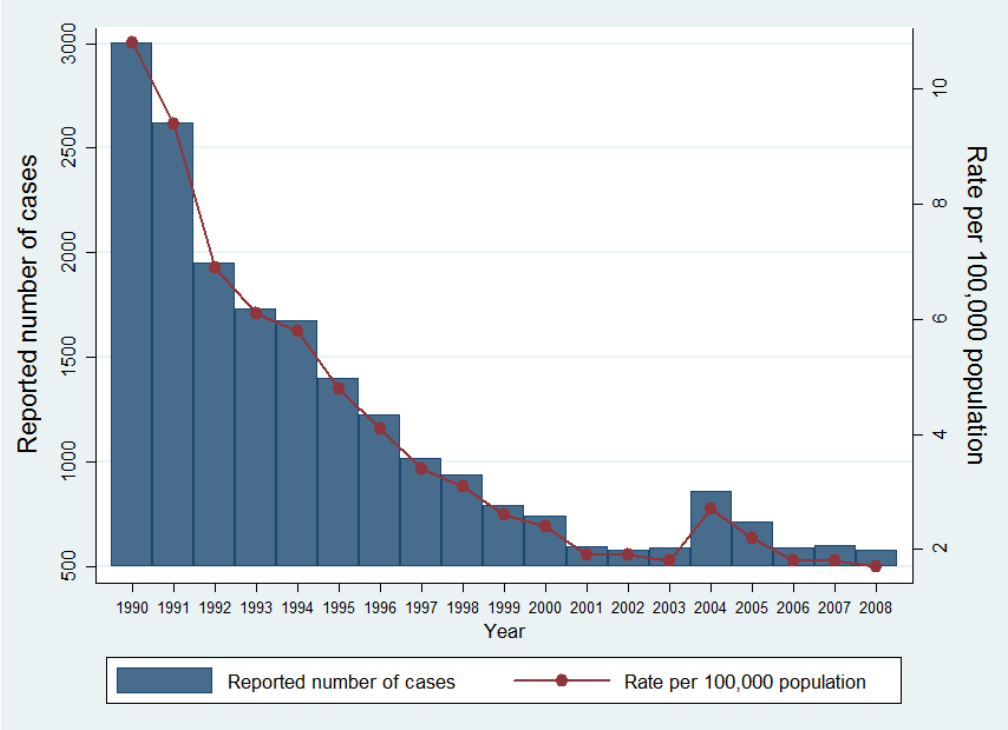
2.3.1 Hepatitis B Surveillance

In Canada, acute hepatitis B has been a notifiable disease since 1969. Any physician who clinically diagnoses acute HBV, with or without laboratory confirmation, must report case information to the local public health authorities.[30] If the reported case meets the definition for HBV, then it is reported to the provincial health departments, which in turn provide the information to the Canadian Notifiable Disease Surveillance System (CNDSS). Under the most recent case definition, a case is classified as a confirmed acute HBV case if either 1) a patient is both HBsAg positive and hepatitis B core antigen immunoglobulin M antibody (anti-HBc IgM) positive, or 2) a patient is HBsAg negative after being HBsAg

positive within the last six months.[31] A case is classified as probable if a patient presents with clinical symptoms and is epidemiologically linked to a confirmed case, but no serologic testing is performed.

Surveillance data from the CNDSS has shown that the overall incidence of confirmed and probable acute HBV infections has declined from 10.8 cases per 100,000 people to 1.7 cases per 100,000 people, between 1990 and 2008 (Figure 2.2). The largest decline in acute HBV incidence was reported in 10 to 19 year olds, where the annual incidence rate fell from 5.8 cases to 0.6 cases per 100,000 people, likely as a result of the pre-adolescent vaccination programs that were introduced, in 1992.[32] Age-specific incidence rates for acute HBV infection were highest in 20 to 39 year olds, however there has also been a substantial decline in HBV incidence in this high-risk age group. The average annual risk of acute HBV infection was two times greater in males than in females, likely as a result of greater exposure to risk factors such as intravenous drug use and unsafe sexual practices.[33] Since acute HBV infection may be asymptomatic, these reported rates underestimate the true incidence of HBV infection in Canada. Nonetheless, they are still useful in describing trends over time. No comparable data exists for the rate of newly acquired HBV infections in Canadian immigrants.

Figure 2.2: Number of Reported Cases and Incidence of Acute and Indeterminate Hepatitis B in Canada, 1990-2008 [32]



Although the CNDSS collects epidemiological data that can be used to examine acute HBV incidence rates in Canada, there are limits in using surveillance data to determine the burden of hepatitis B in Canadian communities. First, certain provinces have different reporting practices and do not all include probable or indeterminate classified cases.[30,34] Furthermore, since acute HBV infections can be asymptomatic, particularly in children and adolescents, routine surveillance data often underestimates the number of individuals developing an acute hepatitis B infection.[23] Lastly, and most importantly, few acute HBV infections progress to chronic HBV, where the greatest risk for liver disease and the largest potential for a public health intervention occur.

2.3.2 Seroprevalence of Hepatitis B in Canadian Communities

To determine the burden of HBV in Canadian communities, seroprevalence studies of representative populations have been utilized to ascertain the proportion of people who are chronic carriers.[35-37] These screening surveys have an advantage over using reported surveillance data because they capture infections in asymptomatic carriers in a community, but they are more costly to perform and require the cooperation of targeted populations. Seroprevalence surveys utilize enzyme-linked immunosorbent assays (ELISA) to screen for the presence of HBsAg in a subject's blood. Overall, in Canada, between 0.5% and 1.0% of the population (250,000 to 300,000 people) are estimated to be chronically infected with HBV.[38] This proportion has been found to be higher in certain at-risk groups, such as in street-involved youth (1.6%)[39], visitors of sexually transmitted disease clinics (2.7%)[40], men who have sex with men (MSM) (0.9% to 4.3%)[41,42], aboriginals (0.3% to 2.9%)[43-45], and the Inuit (3.9% to 6.9%).[43,46,47]

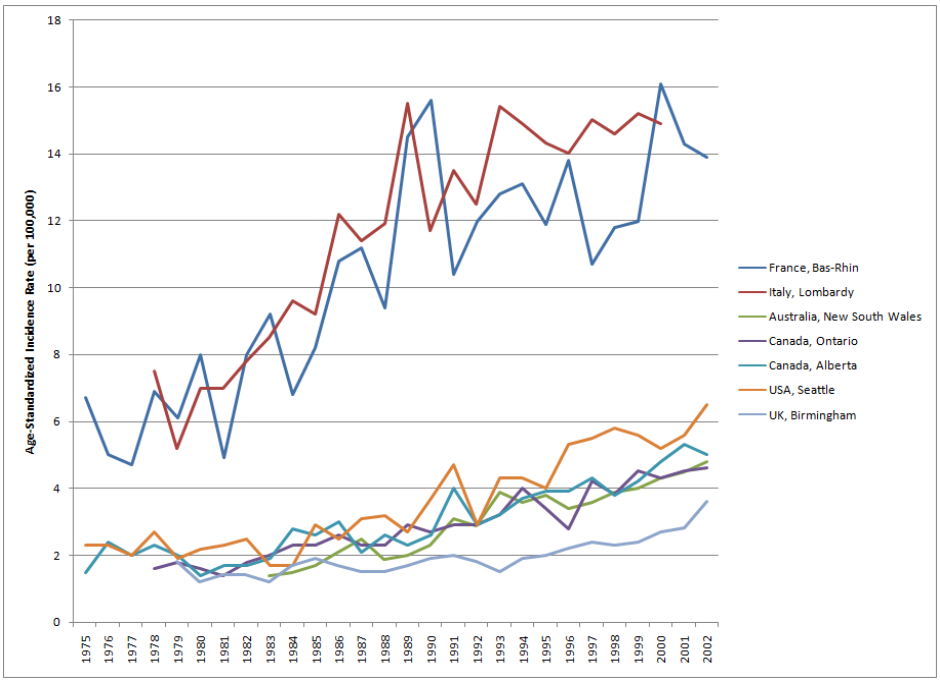
Among Canadian immigrants and refugees, very little information is available regarding the seroprevalence of chronic HBV. The largest hepatitis seroprevalence survey carried out in Canada occurred in Montreal and examined the prevalence of HBsAg in Vietnamese refugees arriving between 1979 and 1980.[48] Chaudhary et al. found that 11.6% of the 14,347 refugees were infected with HBV. The infection was significantly more prevalent in males, compared to females, and higher in middle-aged refugees compared to younger children, suggesting either declining levels of prenatal HBV exposure or ongoing horizontal transmission was a common mode of transmission among Vietnamese refugees. 48.9% of these refugees were found to be immune after resolving an acute infection. In a

seroprevalence survey of recent government-assisted refugees who settled in Canada, Pottie et al. found that 6.5% of Sub-Saharan African refugees were infected with HBV.[49] In both these surveys, estimates of chronic infection were similar to rates of infection in the migrants' region of origin.[50] This is not surprising as chronic HBV infection is often asymptomatic and does not reduce the ability of international migrants to travel to new countries.

2.3.3 Risk of Liver Disease in Canadian Immigrants

In developed countries, the incidence of primary liver cancers has been steadily increasing since the early 1970s. Figure 2.3 shows the age-adjusted incidence rates of primary liver cancer in seven cancer registries from 1975 to 2002 in males.[51] In Western Europe, increasing rates of HCC have been associated with a silent hepatitis C virus (HCV) epidemic that followed a childhood immunization campaign against vaccine-preventable diseases during the 1950s, which used inadequately sterilized reusable needles.[52] In North America, where liver cancer rates are lower than Europe, the increase in cancer incidence has been attributed to increase exposure to HBV and HCV from the use of shared needles for intravenous drug use, which was common during the 1970s.[53,54] Since liver cancer usually develops at least four decades after exposure to HBV or HCV, it is expected that rates of primary liver cancer will continue to increase in developed countries, particularly in North America, as a large at-risk population continues to live with chronic HBV and HCV infections.[55]

Figure 2.3: Age-Standardized Primary Liver Cancer Incidence Rates, Males, 1975-2002



Although it is unclear how much of the observed increase in primary liver cancer can be attributed to increased immigration from HBV-endemic countries, several population-based studies have shown that immigrants carry a disproportionate share of the HBV-associated disease burden in developed countries. In Canada, a linked national administrative database study found that immigrant men experienced 2.2 times (95% CI: 1.7 – 2.7) as many deaths from liver cancer, and immigrant women experienced 1.8 times (95% CI: 1.2 – 2.4) as many deaths, as would have been expected if they had the liver cancer mortality rates of the Canadian-born population.[56] A follow-up study, which examined the risk in developing liver cancer in specific immigrant groups, found that male East Asian immigrants were diagnosed with liver cancer 3.4 times more (95% CI: 2.5 – 4.4) than would have been expected if they had the liver cancer incidence rates of

the host population, and male refugees from Southeast Asia, who arrived to Canada following the Vietnam War, were diagnosed with liver cancer 6.8 times more (95% CI: 4.9 – 8.7) than would have been expected.[57] In the United States, Asian and Pacific Islander (API) populations were found to have HCC incidence rates that were four times higher than U.S. born Caucasians.[58]

2.4 Hepatitis B Interventions

2.4.1 Screening and Treatment for Chronic Hepatitis B

Despite the fact that most chronic HBV infections are asymptomatic and many infected individuals are unaware of their status, highly sensitive and specific serologic testing has been available as a diagnostic tool to determine the presence of hepatitis B markers in the blood.[59] In non-HBV endemic countries, serologic screening of blood supplies eliminated the risk of acquiring HBV through blood transfusions and screening of pregnant women for infection has had a major impact on reducing the risk of mother-to-child transmission of HBV.[60] In recent years, screening individuals who are at higher risk of being chronic carriers has become an important component of the public health response to reducing morbidity and mortality associated with HBV infection because of the new availability of effective nucleoside analogue antiviral therapy, which reduces the risk that someone with a chronic infection has of developing liver disease.[61]

Screening high risk populations for serologic markers of infection and immunity is important for three reasons. First, it allows for the timely identification of chronically infected individuals who can be referred to a liver specialist to

clinically determine if treatment is necessary to prevent or delay the onset of liver disease. Second, it enables infected individuals to adopt behaviours, such as notifying close contacts or assuring their blood does not come into contact with others, to reduce the risk of transmission. Finally, it allows the identification of susceptible individuals who are at risk and would benefit from highly-effective vaccination programs directed at eliminating new HBV cases.

Screening for HBV infection has been recommended for members of several high risk groups in Canada and the United States. Common risk groups include intravenous drug users, MSM populations, hemodialysis patients, HIV-positive patients, and patients requiring immunosuppressive therapy.[59] Recently, the Centers for Disease Control and Prevention (CDC) have recommend serologic testing of all immigrants, refugees, asylum seekers, and adopted children who arrive from regions where HBsAg seroprevalence is $\geq 2\%$, regardless of vaccination status in their country of origin.[62] The Canadian Collaboration for Immigrant and Refugee Health (CCIRH), a policy and advocacy organization dedicated to improving the health of immigrants and refugees through evidence-based medicine have also recommended that hepatitis B screening be expanded to adults and children from countries where the seroprevalence of hepatitis B infection is moderate or high.[63,64]

Despite these recommendations and efforts by community-based organizations and local clinics and hospitals to increase awareness and to provide serologic testing to high risk immigrants and refugees, to date there are no systematic HBV screening programs targeted at newly arriving immigrants and it is unclear what proportion of immigrants actually benefit from this intervention.[65] A recent review by Rein et al. found that nearly 22,000 high-risk individuals, most

who were Asian or Pacific Islander, were screened for HBV in the United States, a small fraction of the 16 million foreign-born living in the country.[66] One reason for the low levels of screening in foreign-born populations may be the result of a lack of awareness about the infection and the available interventions to diagnose and treat chronic HBV. Community-based interview surveys among East Asian populations residing in Canada and the United States have reported less than optimal levels of knowledge about HBV. For example, only between 35% and 75% of respondents reported knowing that there were health interventions available to reduce the risk of acquiring HBV and between 40% and 80% knew that chronic hepatitis B infection can result in serious liver disease and cancer. Among these populations between 48% and 67% self-reported being screened for HBV.[67-73]

2.4.2 Hepatitis B Immunization

Hepatitis B is a vaccine-preventable disease. Vaccination against HBV is the most effective method to prevent chronic infection and its sequelae, including cirrhosis, hepatic decompensation and liver cancer, in susceptible populations.[23,24] The first commercially-available HBV vaccines, which were introduced in 1982, were plasma-derived vaccines that used inactivated viral particles from the blood of HBsAg positive donors. In 1986, recombinant DNA technology allowed HBsAg to be synthetically prepared, without the need of blood products, and replaced the use of plasma-derived HBV vaccines in many countries.[25] Since the introduction of the vaccine, it has become one of the world's most utilized vaccines, with over one billion doses delivered since 1982.[12]

HBV vaccination consists of three intramuscular doses typically given at 0, 1 and 6 month intervals, for all age groups. Immunogenicity after completion of the three-dose HBV vaccination schedule is highest in infants (> 90%) and preadolescents (> 95%), but declines with age in adults ≥ 40 years of age.[74] A protective antibody response occurs in only 30% to 55% of adults, after the first dose, but exceeds 90% following completion of the three doses, highlighting the importance of completing the series of vaccinations in high-risk adult populations.[25] Vaccine booster doses are not required, as several long-term follow up studies of vaccinated cohorts have shown that adolescents maintained anamnestic responses 10 to 15 years after being vaccinated as an infant.[75-77]

As part of the strategy to eliminate HBV infection in Canada and in other non HBV-endemic countries, hepatitis B vaccination programs initially targeted individuals who were at greatest risk for acquiring new infections, such as health care workers, intravenous drug users, sex workers and children born to HBV infected mothers.[25] Beginning in 1992, the National Advisory Committee on Immunization (NACI) in Canada, as well as the CDC, began expanding their targeted vaccination strategy to include all infants and adolescents. In Canada, immunization is offered universally, either as part of the routine infant vaccination schedule or as part of a school-based program targeting pre-adolescents before they become exposed to HBV-related risk factors, such as sexual activity or intravenous drug use.

The NACI strategy to immunize and eliminate HBV in infants and adolescents has been successful in Canada. During the first decade of a 4th grade, school-based immunization program in Quebec, which began in 1994, vaccination

coverage of the three-dose series ranged from 85% to 95% and the incidence of acute HBV infection in 10-19 year olds decreased by 91%.[78] Similarly, in British Columbia, the province with the highest rates of acute HBV infection in adults, vaccine coverage was between 90% and 93% among 6th graders in school-based immunization program and the incidence of acute HBV infections declined from 1.7 to 0 per 100,000 among 12-20 year olds between 1992 and 2001.[79] Although rates of acute HBV infections have been declining in all age groups over the last two decades, the largest and most marked declines have occurred in cohorts of vaccinated children and adolescents.[32]

Despite the success that the universal immunization program has had in reducing the incidence of acute HBV in infants and adolescents, cases of acute HBV continue to be reported among immigrant children, suggesting that horizontal transmission from chronically infected close contacts is not uncommon in Canada. In Quebec, more than half (53%) of all reported cases of acute HBV in children ≤ 10 years of age were found in immigrant children.[78] Furthermore, in a surveillance study that covered several large metropolitan areas in Canada, 80% of reported acute HBV infections in children and adolescents were found among the foreign-born.[80] These findings highlight the need to prevent horizontal transmission of HBV infections in young foreign-born children before they are old enough to be vaccinated or have missed their vaccinations.

Similar to the screening-related guidelines, the CDC and CCIRH now recommend that all immigrants and refugees from areas where HBsAg seroprevalence ≥ 2% be targeted for vaccination against HBV, if found to be susceptible after serologic testing.[25,63,64] As with serologic testing, there are no

routine catch-up vaccination programs targeting immigrants or refugees, outside of the school-based vaccination program in Canada and it is unclear how many immigrants or refugees actual become immunized following landing in Canada.

2.5 Economic Evaluations of Hepatitis B Interventions in Immigrant Populations

2.5.1 Economic Evaluation of Health Care Programs

Economic evaluations of health care programs have been useful for helping decision-makers make choices about competing health care alternatives. A common question encountered by health planners is how to allocate scarce health resources to best maximize the health-related benefits gained. In order to answer questions related to costs and outcomes, health planners depend on results from cost-effectiveness analyses (CEA), a form of economic analysis that has its roots in decision analysis theory.[81] This type of epidemiological study provides a methodological foundation for systematically comparing alternative courses of action in terms of both their monetary costs and potential benefits to allow health planners to make important decisions.

During the last two decades, the number of published economic evaluations of hepatitis B screening and vaccination programs has more than doubled.[82] There are several reasons explaining the increase in the number of published cost-effectiveness studies. First, with increasingly limited resources available for public health programs, many decision makers are interested in determining the relative cost-effectiveness of different health programs and decision analysis techniques have become a popular tool for policy evaluation in this area. Secondly,

computational power has greatly increased, facilitating cost-effectiveness modeling as iterative calculations can be performed automatically using software such as TreeAge Pro. Finally, with the introduction of a highly effective vaccine and new antiviral treatments, health-care officials now have the means to both prevent HBV infections and reduce progression to advanced liver disease and they are interested in determining the most cost-effective way to reduce morbidity and mortality from this preventable and treatable disease in high-risk populations.

2.5.2 Cost-Effectiveness of Health Interventions

In 2007, Hutton et al. were the first to evaluate the cost-effectiveness of screening and vaccinating a foreign-born population for hepatitis B.[83] This study examined several screening and vaccination programs for Asian and Pacific Islander adults currently living in the United States. Hutton et al. recommended serologic testing and antiviral treatment for all API adults. Results were expressed in terms of the number of HBV-related deaths prevented and quality-adjusted life years (QALY) gained, as is typical for this type of study. This intervention was expected to cost $189,000 USD (2006) for every 10,000 APIs in the United States and would prevent 58 HBV-related deaths, compared to no targeted screening. The authors estimated that the intervention would be cost-effective and would cost $36,088 for every QALY gained. Targeted universal vaccination without serologic testing, however, was not found to be cost-effective.

This CEA does suffer from several critical shortcomings that contribute to undermine the results of the economic evaluation. First, in their model, Hutton et al. assumed that all those who tested positive for a chronic HBV would accept medical

management from specialist. In practice, this is rarely the case, as many immigrants face important barriers that limit their access to care, even if it is available. Chinese immigrants, for example, have reported language barriers, fear or stigmatization, and uncertainty about the need for antiviral treatment as self-reported barriers to care.[84] It is therefore conceivable that not all chronically infected immigrants who would benefit from antiviral treatment will receive it. By assuming that all eligible patients begin therapy, results of the CEA will be biased and the screening intervention will appear more cost-effective.

Next, Hutton et al. assumed that the annual risk of acute HBV infection in susceptible APIs was 4.8 cases per 100,000 people, which may be an underestimation. According to surveillance reports from the CDC, rates of clinically reported acute HBV for this population are close to 1.0 case per 100,000, but only one in ten cases of acute infection are believed to be reported because most cases of acute HBV appear asymptomatic and correct diagnoses may be missed by clinicians unfamiliar with this population.[85] Therefore, it is possible that the actual annual risk of infection (ARI) for susceptibles may be as high as 10 cases per 100,000 people. Underestimating the ARI will create less new infections in the model and is expected to bias the results in favour of the screening intervention because vaccinations will appear to have less benefit if fewer individuals become infected over their lifetimes.

Last, Hutton et al. failed to account for societal level costs associated with chronic HBV and liver disease, though they claim their CEA was carried out from a societal perspective. The authors erroneously concluded that their model incorporated societal level costs because they included publically paid health care

costs, but they did not include costs such as household expenditures, income lost from time off work, forgone annual income because of death or disability, or palliative care. Guidelines for performing CEA for HBV vaccination interventions recommend incorporating all relevant costs and taking an overall societal perspective when determining the cost-effectiveness of an intervention.[86,87]

A second study investigating the cost-effectiveness of interventions aimed at reducing morbidity and mortality from HBV in immigrant populations was completed by Veldhuijzen et al. in 2010.[88] This analysis examined the cost-effectiveness of a targeted screening strategy that invited all Dutch immigrants from intermediate and high HBV-endemic countries for serologic testing and compared it to passive screening that identifies chronically infected immigrants through existing opportunities for detection, such as at sexual health clinics or through prenatal screening of pregnant women. Results show that the screening program would cost €23.4 million ($30.8 million Canadian) and would prevent 108 HBV-related deaths over the lifetime of all immigrants living in the Netherlands. This strategy was deemed to be highly cost-effective and would cost €8,966 per QALY gained, compared to passive screening.

Unlike the study by Hutton et al., this study did not assume 100% compliance with medical management of patients who were found to be chronically infected and instead used estimates ranging between 39% and 75%, which are more reasonable estimates for this population which often faces difficulty accessing health care. For the status quo strategy, however, Veldhuijzen et al. assumed that 2.5% of chronically infected immigrants would be detected, annually, through passive screening, as 5,500 cases of chronic HBV were reported to the public health

authorities, over the last five years, out of an estimated 44,000 chronically infected immigrants. As no data currently exists that would accurately ascertain a baseline proportion of identified immigrants, it is uncertain if this is a reasonable estimate for this model parameter. The authors did not vary the value of this parameter in a sensitivity analysis, as is conventionally done when the value of parameter is uncertain or there exists a range of plausible values, to determine if it would affect the final results of the model.[81]

In 2011, a final study by Wong et al. examined the cost-effectiveness of two HBV interventions in Canadian immigrants and was published soon after the research plan for this thesis was conceived.[89] The investigators compared a screening and treatment strategy, as well as a strategy of screening, treatment and providing vaccination to susceptible individuals against the status quo of no targeted screening in the Canadian immigrant population. Similar to the aforementioned cost-effectiveness studies performed in this population, costs were not evaluated from a societal perspective, so they did not include the monetary value of patients' time or home care for advanced liver disease.

Wong et al. found the screening and treatment scenario to be only moderately cost-effective, compared to no systematic intervention. This strategy was estimated to cost the Canadian health-care system $1,665 more per person, compared to no screening, and was found to only increase the QALYs experienced by the cohort by 0.024 years. This resulted in an incremental cost-effectiveness ratio (ICER) of $69,209 per QALY gained, which is a moderate cost to increase one QALY.

This analysis has several limitations based on the way the decision-analysis model was parameterized. First, the investigators estimated that only 2.8% of the population in the model had natural HBV immunity that developed from clearing an acute infection. This is a very low baseline estimate, as previous seroprevalence surveys, including one performed in Canadian refugees, found that anti-HBs seroprevalences are greater than 10%.[48,90,91] Furthermore, Wong et al. attempted to use WHO data on HBV vaccine coverage to estimate the prevalence of vaccine-induced immunity in adult Canadian immigrants. This is problematic because vaccine coverage estimates are commonly obtained through childhood vaccination records in intermediate and high HBV-endemic countries, as infants are the most targeted subgroup for immunization.[12] Since this study sought to determine the cost-effectiveness of an intervention in adult immigrants currently living in Canada who may have immigrated more than twenty years ago, it is erroneous to use data on current childhood vaccine coverage to estimate the proportion of immigrants with vaccine-induced immunity. Finally, Wong et al. assumed that immigrants would comply with the intervention and would be screened for HBV. All those found to be HBsAg positive would be referred to specialists and all immigrants would start treatment, if offered. As discussed earlier, this is implausible and this study more likely estimates what the cost-effectiveness of the intervention would be under ideal circumstances and does not take into account other factors, such as barriers to health care access, which should be accounted for.

2.6 Summary of Literature Review

Over the last four decades, immigration to Canada has been increasing from intermediate and high HBV-endemic regions. The CDC estimates that more than 2% of the general population in Eastern Europe and South Asia, as well as more than 8% of the population of the Sub-Saharan Africa and East Asia are chronically infected with hepatitis B. To date, however, there has been no review that has synthesized information on the seroprevalence of HBV infection in international migrants in immigrant-receiving countries.

Chronically infected individuals are at increased risk of developing severe liver disease. Retrospective cohort studies on health outcomes in foreign-born populations living in Canada have highlighted the fact that immigrants and refugees are more likely to develop and die from liver cancer, compared to the Canadian-born population. This finding has been attributed to the increased prevalence of asymptomatic chronic HBV infection in this population, who are often unaware of their status and have little opportunity to undergo serologic testing.

HBV infections are both preventable and treatable. In Canada, a highly effective vaccine has been routinely administered to infants and school-aged children and has almost eliminated new infections in children, although acute HBV infections have been reported in children of foreign-born adults. Antiviral treatment, which has only been available during the last decade, has been demonstrated to reduce the risk of liver disease progression in chronically infected individuals. Coupled with serologic testing, immunization against HBV and

antiviral treatment has the potential to reduce the prevalence of HBV infection and improve the long-term health outcomes of people chronically infected with HBV.

Immigrants, however, are not routinely screened for, nor are vaccinated against HBV, despite their greater risk of acquiring an infection or developing liver disease after landing. The CCIRH and CDC have recommended that immigrants and refugees arriving from areas where the seroprevalence of HBV infection is 2% or greater be screened for HBV, and vaccinated, if found to susceptible to the virus. A small number of cost-effectiveness studies have evaluated the benefits of implementing targeted screening or vaccination programs designed to reduce morbidity and mortality from HBV, but have found slightly different results. These studies were limited by incorrect model parameter estimates and lack of sensitivity analysis on key estimates. Public health officials, who are interested in implementing interventions aimed at reducing HBV-related morbidity and mortality, would benefit from a cost-effectiveness study that incorporates barriers to health care and societal-level costs, as these will provide a more accurate estimation of how the costs and benefits of various HBV interventions are related.

CHAPTER 3: Systematic Review of the Hepatitis B Burden in International Migrants

3.1 Introduction

The first objective of this thesis was to perform a systematic review of the immigrant health literature to ascertain the seroprevalence of chronic HBV and the seroprevalence of prior immunity to the infection in international migrants who reside in traditional immigrant-receiving countries. This objective served two unique and novel purposes. First, there has yet to be a systematic review characterizing the prevalence of hepatitis B infection in new arrivals, who have been shown to be at greater risk of developing liver disease sequelae. Clinicians who serve increasingly large and diverse migrant populations would benefit from such a review to help identify the highest risk groups that may benefit from screening and immunization.

Second, results obtained from the meta-analysis, performed within the systematic review, can be used to inform model parameters within the cost-effectiveness analysis. Rather than estimate the value of a parameter from a single source, guidelines for cost-effectiveness analyses recommend using, when available, parameters that have been obtained from systematic reviews.[81] The results from the meta-analyses that pool together the seroprevalence of hepatitis B infection and prior immunity will be used as parameters for the proportion of new arrivals to Canada that are chronically infected and immune to infection, respectively, in the cost-effectiveness analysis.

The manuscript that follows was submitted for peer-review to PLoS One in June 2012.

3.2 Manuscript #1 – "Seroprevalence of Chronic Hepatitis B Virus Infection and Prior Immunity in Immigrants and Refugees: A Systematic Review and Meta-Analysis"

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Abstract:

Background: International migrants experience increased mortality from hepatocellular carcinoma compared to host populations, largely due to undetected chronic hepatitis B infection (HBV). We conducted a systematic review of the seroprevalence of chronic HBV and prior immunity to HBV in migrants arriving in low HBV-endemic countries to identify those at highest risk who may benefit from HBV screening and vaccination.

Methods: Four electronic databases (Medline, Medline In-Process, EMBASE and the Cochrane Database of Systematic Reviews) were searched from the earliest available date to November 1st, 2011. Studies that reported HBV surface antigen (HBsAg) or HBV surface antibodies (anti-HBs) in migrants were included. The proportion of migrants with chronic HBV and prior immunity were pooled by region of origin and immigrant class, using a random-effects model. A random-effects logistic regression was performed to further explore heterogeneity. The number of chronically infected migrants in each immigrant-receiving country was estimated using the pooled proportions of chronic HBV seroprevalence from this review and country-specific census data on the region of origin of immigrants received.

Findings: A total of 110 articles, representing 209,822 immigrants and refugees from all world regions over four decades were included. The overall pooled seroprevalence of infection was 7.2% (95% CI: 6.3% – 8.2%) and the proportion with prior immunity was 39.7% (95% CI: 35.7% – 43.9%). HBV seroprevalence

differed significantly by region of origin. Migrants from East Asia & the Pacific and Sub-Saharan Africa were at highest risk (> 10% HBsAg positive) and migrants from Eastern Europe & Central Asia were at an intermediate risk of infection (pooled seroprevalence of 5.8%). Region of origin, refugee status and decade of study were independently associated with infection in the adjusted random-effects logistic model. Almost 3.5 million migrants (95% CI: 2.8 – 4.5 million) living in immigrant-receiving countries are estimated to be chronically infected with HBV.

Interpretation: The seroprevalence of chronic HBV infection is high in migrants from most world regions, particularly in those from East Asia, Sub-Saharan Africa and Eastern Europe, and more than 50% were found to be susceptible to HBV. International migrants, who are at higher risk of infection from perinatal transmission, may benefit from chronic HBV screening programs and targeted HBV catch-up vaccination programs.

Introduction:

Hepatitis B virus (HBV) infection is an important global health problem. Approximately 350 million people are chronically infected with the virus worldwide, 25% of whom will die from liver disease, such as cirrhosis and hepatocellular carcinoma (HCC), resulting in 600,000 to one million deaths annually.[16,23] Morbidity and mortality from hepatitis B can be reduced through screening individuals at risk for chronic HBV infection, and offering appropriately timed antiviral therapy to those found to be positive.[13] Furthermore, an effective HBV vaccine to protect those who are susceptible has been available since the 1980s in most high-income countries.[25]

Over the past four decades, international migration has increased at an unprecedented rate and the majority of new immigrants arriving in high-income, low hepatitis B endemic countries [hepatitis B surface antigen (HBsAg) seroprevalence < 2%] have originated from intermediate (HBsAg seroprevalence between 2% - 7%) or high hepatitis B endemic countries (HBsAg seroprevalence ≥ 8%).[92] During this time period the prevalence of chronic HBV infection and the incidence and mortality rates of HCC have increased in North America and Western Europe, likely due in part to imported and undetected chronic HBV infection in the immigrant population, although, the rising incidence of HCC may also be attributable to chronic hepatitis C infection which increased due to exposure risks in the 1970s.[18,20,51,93,94] In these same countries, migrants have both higher incidence rates of chronic HBV infection and HCC and increased mortality from cirrhosis and HCC compared to host populations.[56-58,95-102] Screening immigrants for chronic

HBV infection and vaccinating at risk contacts has been shown to be cost-effective in certain situations.[83,88,89]

Despite these disparities, immigrants and refugees from hepatitis B intermediate and highly endemic countries are not routinely screened for HBV infection, nor is hepatitis B vaccination routinely given after arrival in most immigrant-receiving countries. We conducted a systematic review and meta-analysis of chronic hepatitis B infection and prior immunity in the immigrant and refugee population to identify groups at highest risk who would benefit the most from HBV screening and vaccination programs.

Methods:

Search Strategy and Study Selection

This review was prepared in accordance with PRISMA guidelines.[103] Medline, Medline In-Process, EMBASE, and the Cochrane Database of Systematic Reviews were searched for studies reporting the seroprevalence of chronic HBV infection and immunity in immigrants and refugees, using no initial language restrictions, from the earliest available date until November 1st, 2011. The search strategy that was used for all databases is shown in Table 1. Additional studies were identified by examining the reference lists of eligible studies and the bibliography of review articles. The titles and abstracts of all identified articles were reviewed by two authors (CR and CG). For those studies that met the pre-defined eligibility criteria, full-text articles were obtained. Reasons for exclusion were recorded for all full-text articles that were reviewed. Original studies published in English, French or Italian that reported data on the seroprevalence of chronic HBV infection and/or

HBV immunity in immigrants or refugees arriving in traditional immigrant-receiving countries were included. Only studies that recruited immigrants and refugees who were representative of the general migrant population were included. Studies that targeted migrant groups at increased risk for hepatitis B due to certain behaviours or circumstances were excluded (i.e. sex workers, intravenous drug users, prisoners, MSM populations or those being treated for liver disease[26,104]).

Data Extraction

Data were extracted independently and in duplicate, using a piloted and standardized data extraction form, by two authors (CR and LM) for all articles in English or French (See Appendix 1). For the one study reviewed that was published in Italian, data was extracted by one author (CR). Data were then entered independently and in duplicate into a Microsoft Access Database and imported into SAS (version 9.2, Cary, North Carolina) for comparing, cleaning and analysis. Discrepancies were corrected by consensus.

Study Outcomes and Variables

The primary study outcomes were 1) the proportion of subjects with chronic HBV infection among those screened and 2) the proportion of subjects with HBV immunity among those screened. Chronic HBV infection was defined as the presence of HBsAg, which is a serologic marker of either acute or chronic HBV infection. We assumed the presence of HBsAg represented imported chronic HBV infections rather than a new acute infection, given the fact that most immigrants and refugees from intermediate and high HBV-endemic countries acquire HBV

infection during the perinatal period or in early childhood.[25] HBV immunity was defined as the presence of hepatitis B surface antibody (anti-HBs), with or without hepatitis B core antibody (anti-HBc).[13] Anti-HBs are serologic markers that appear in individuals who have resolved an acute HBV infection and may also be found in individuals who have been immunized.

Data on study design, decade of study, country of landing, immigrant status, migrants' region of origin, mean or median age, gender distribution, co-morbidities, method of participant identification for study, and serologic testing method used were also extracted. The location of participant selection was categorized as occurring in reception centers at the time of arrival, in the context of a clinic or hospital visit, screening of pregnant women or other situations. Data on immigrant status was classified into the following categories: immigrants, refugees, asylum seekers, and adopted children. A dichotomous variable of immigrant status combined immigrants and adopted children into 'immigrants' and refugees and asylum seekers into 'refugees', because of the very small number of studies with adopted children or asylum seekers. Region of origin was classified according to the World Bank country classification and included the following regions: Latin America and the Caribbean, Eastern Europe and Central Asia, Middle East and North Africa, Sub-Saharan Africa, South Asia, and East Asia and the Pacific.[105] If a study contained migrants from more than one region, then seroprevalences for infection and immunity were obtained separately for each region of origin, if available.

Statistical Analysis

For each study, the seroprevalence of chronic HBV infection and HBV immunity was calculated by using the reported numbers of subjects positive for HBsAg and anti-HBs serologic markers, respectively, divided by the total number of people screened for each of these markers. Proportions were transformed with the logit transformation and pooled using a random-effects model to account for the expected high heterogeneity between studies.[106] The logit-transformed proportions were back-transformed and results were presented as percentages. The logit transformation was used to avoid studies with few events from being weighted too heavily in the random-effects model[107] and because the multivariate analysis, which used a random-effects logistic regression model, is also based on the logit transformation (see below). Overall heterogeneity among studies was assessed using the I^2 statistic and estimates were stratified by region of origin and immigration status, as these variables were believed *a priori* to be important predictors of HBV infection.[108] The data were not stratified by age or gender as few studies, 40% and 26% respectively, included any form of information on these variables. The meta-analysis was performed using the *metaprop* command of the meta package in R (version 2.13.1)[109]

Random-effects logistic regression, using the *glmer* command of the lme4 package to fit generalized linear mixed-models in R, was used to further explore heterogeneity and to compare the odds of being infected among migrants from the different regions of origin after adjusting for potential confounding by immigrant status and decade of study.[110] Three studies that did not report estimates separately for immigrants and refugees and 18 studies that did not report estimates separately

by region of origin were excluded from the random-effects logistic regression model.

To estimate the number of migrants who are chronically infected with hepatitis B in immigrant-receiving countries, data on the number of foreign-born residents from different regions of origin living in host countries was obtained from the national statistical agencies for each of these countries (Appendix 2 - Supplementary Table S1). This data and the pooled region-specific seroprevalence of chronic HBV infection in immigrants and refugees estimated in this review were multiplied to estimate the burden of chronic HBV infection in migrants living in traditional immigrant-receiving countries.

Results:

Search Results

A total of 1,456 citations were identified in the electronic search and an additional 11 citations were identified through hand searching (Figure 1). After duplicates were removed, 926 citations were screened with the title and abstract and 757 were excluded. A total of 169 articles were assessed with predefined eligibility criteria in the full-text review and 53 were excluded. An additional six articles were excluded because the full-text could not be retrieved despite assistance from a McGill University librarian. A total of 110 studies were included in the systematic review and meta-analysis (Supplementary Table S2).

Seroprevalence of Chronic Hepatitis B Infection in Migrants

All 110 studies reported the seroprevalence of HBV infection in immigrants or refugees, representing a total of 209,822 migrants from all world regions. Just over half of the seroprevalence studies of chronic HBV infection included refugees and asylum seekers (51.8%) and nearly a quarter studied migrants exclusively from East Asia and the Pacific, although almost half of all the studies screened migrants from more than one region (Table 2). All studies were conducted in the context of asymptomatic screening and almost 90% of study participants were recruited in settings with low risk for selection bias (i.e. mass screening in reception centers or in pregnant women). The number of studies published on the seroprevalence of HBV infection increased every decade after the initial studies first reported on the seroprevalence of infection in refugees from Southeast Asia.

The overall pooled seroprevalence of infection in all international migrants, among the 110 studies, was 7.2% (95% CI: 6.3% – 8.2%). Higher seroprevalences were found among refugees and asylum seekers, compared immigrants [9.6% (95% CI: 8.2% – 11.1%) vs. 5.1% (95% CI: 4.0% – 6.4%)] (Table 3). Pooled HBsAg seroprevalence estimates by region of origin differed from one another and were similar to global estimates from the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) and a recent systematic review of global seroprevalence of HBV infection.[12,15,50] These organizations divide the world into high (HBsAg seroprevalence ≥ 8%), intermediate (HBsAg seroprevalence between 2% – 7%) and low (< 2%) chronic hepatitis B endemic regions. Our region-specific pooled proportions for migrants fell within the same ranges for the HBV endemicity categories defined by the WHO and CDC (Figure 2).[12,15,50] Chronic HBV seroprevalence was high for migrants from East Asia and the Pacific

and from Sub-Saharan Africa [11.3% (95% CI: 10.3% – 12.4%) and 10.3% (95% CI: 9.1% – 11.8%), respectively], intermediate for migrants from Eastern Europe and Central Asia and from South Asia [5.8% (95% CI: 4.3% – 7.9%) and 4.6% (95% CI: 2.6% – 7.8%), respectively], and low for migrants from Latin America and the Caribbean and the Middle East and North Africa [1.7% (95% CI 1.1% – 2.7%) and 2.0% (95% CI: 1.6% – 2.9%), respectively].

Results from the random-effects logistic regression analysis showing both unadjusted and adjusted odds ratios of chronic HBV infection are reported in Table 4. Different models, with and without interaction terms, using traditional model selection criteria were explored using region of origin, immigrant status and decade of study as variables (Supplementary Table S3). The best model without interaction terms, as measured with the lowest *akaike information criterion* (AIC) value, included only the region of origin, however models including immigrant status and decade of study were very similar (odds ratio differences by ≤ 0.06). Models that included interactions between variables were also explored. Although there were some statistically significant interactions in some models, there was no consistent significant trend of interactions across models. The model with all three of these variables without interactions was chosen as we felt that this was the most relevant for clinicians working with migrant populations. In the final model, migrants from all world regions had significantly greater odds of being chronically infected with HBV as compared to migrants from Latin America and the Caribbean, the region with the lowest seroprevalence and the one most closely approximating the estimated prevalence in immigrant-receiving countries, after adjusting for immigrant status and decade of study. Refugees were found to have 1.42 (95% CI:

1.01 – 1.99) greater odds of being chronically infected compared to immigrants, after adjustment for region of origin and decade of study. Migrants in studies from the 1990s were found to have 1.58 (95% CI: 1.03 – 2.43) greater odds of being chronically infected, compared to migrants from studies reported in the 1980s, after adjusting for the other study-level covariates.

Seroprevalence of Hepatitis B Immunity in Migrants

Of the 110 studies included in this systematic review, 39 reported data on the seroprevalence of HBV immunity in immigrants or refugees and included data on 40,330 migrants from all world regions. As with studies reporting the seroprevalence of chronic HBV infection, just over half of the studies examining HBV immunity screened refugees (Table 5). The overall pooled seroprevalence of immunity to HBV was 39.7% (95% CI: 35.7% - 43.9%) and was highest in those regions that had the highest seroprevalence of chronic HBV infection (Table 6). Half of the migrants from East Asia & the Pacific [50.2% (95% CI: 45.8% - 54.6%)] and almost half of Sub-Saharan Africa migrants [41.7% (95% CI: 37.6% - 45.9%)] were immune to HBV. The seroprevalence of immunity was lower in regions where the seroprevalence of chronic HBV infection was lowest. The number of subjects screened for anti-HBs from the Middle East and North Africa (n=131), South Asia (n=364) and Latin America and the Caribbean (n=29) were very small and results from these regions were imprecise. There were too few studies to examine differences in immunity between immigrants and refugees for each specific region of origin.

Burden of Chronic Hepatitis B Infection in Migrants

Almost 3.5 million immigrants and refugees (95% CI: 2.8 – 4.5) living immigrant-receiving countries were estimated to be chronically infected with HBV (Table 7 and Figures 3 and 4). The proportion of all migrants chronically infected ranged from 3.7% to 9.7% in the different host countries with the largest number residing in the United States (~1.6 million), Canada (~285,000), Germany (~284,000), Italy (~201,000), the United Kingdom (~193,000), and Australia (~176,000).

Discussion:

The results from this study suggests that migrants originating from intermediate or high hepatitis B endemic countries and living in traditional immigrant receiving-countries are an important risk group for chronic HBV infection. Refugees were found to be a sub-group at particularly increased risk. We estimated that the prevalence of chronic HBV in the international migrant population (ranging from 3.7% to 9.7%) living in immigrant-receiving countries was higher than native populations (< 1%) in all host countries, leading to an estimate of 3.5 million chronically infected migrants in these countries.[38,50] These findings suggest that screening for asymptomatic chronic infection may be worthwhile in this population, as the risk of chronic carriage for HBV is relatively high. Furthermore, over half of all migrants were found to be susceptible to the infection and could potentially benefit from HBV immunization programs.

The pooled seroprevalence estimates of chronic hepatitis B in international migrants estimated in our study reflected the prevalence in the regions from which

they originated. Migrants from East Asia and the Pacific and Sub-Saharan Africa had the highest seroprevalence of chronic HBV infection (≥ 10% HBsAg positive), migrants from Eastern Europe and Central Asia and South Asia had intermediate seroprevalence (4% - 6%) and those from the Middle East & North Africa and Latin America and the Caribbean regions had low seroprevalence (≤ 2%). Migrants from East Asia and the Pacific and Sub-Saharan Africa are more commonly recognized risk groups for chronic HBV infection. Migrants from the Eastern Europe and Central Asian region, however, were found to have an intermediate prevalence of chronic HBV, a fact that may be underappreciated by clinicians caring for these populations.

Overall pooled estimates of chronic HBV seroprevalence were higher in refugees compared to immigrants. This same trend was also seen in all world regions except for migrants from Eastern Europe and Central Asia. In addition, refugees were found to have 42% greater odds of being chronically infected with HBV as compared to immigrants after adjusting for region of origin and decade of study in the random-effects logistic model. The increased risk of chronic HBV infection among refugees is plausible given the findings of a recent Canadian study in which male refugees had a significantly higher standardized mortality ratio (reference was Canadian-born males) from primary liver cancer than male immigrants, compared with the same reference group.[56] The higher seroprevalence of HBV in refugees is likely due to greater exposure to hepatitis B through experiencing violence and warfare, or from living in crowded conditions in refugee camps, all which promote horizontal transmission of the virus.[111,112] It was also noted that without adjusting for the other study covariates, the odds of having a

chronic HBV infection decreased with decade of study. However, after adjusting for region of origin and immigrant status, this observation no longer appears. We suspect that the relationship between study period and infection was likely being confounded by refugee status, as refugees had higher odds of infection and most of the earliest seroprevalence surveys in the 1980s were in refugee populations. This assumption is supported by statistical evidence that shows that the adjusted odds ratios for region of origin do not change, but the odds ratio for refugee change substantially in the multivariate model.

HBV immunity was found to be highest among those migrants who originated from areas where HBsAg seroprevalence was highest. However, more than 50% remained susceptible to HBV. This finding highlights the importance of testing all immigrants from intermediate or high hepatitis B endemic countries for immunity and to vaccinate those found to be susceptible. This is critical as these individuals can be at an increased risk of HBV exposure within their households, if they live with someone with an asymptomatic chronic HBV infection or if they travel back to their countries of origin to visit family or friends.[113-115] Acquisition of new HBV infection in the household of an undetected chronically infected individual with HBV was shown to be 1% - 2% in young children during the first decade of life.[113,114,116] Furthermore, exposure and transmission of new HBV infections may be substantial for immigrants travelling to HBV-endemic countries as was demonstrated in a study of acute cases of HBV in the Netherlands where 67% (18/27) of cases in immigrants were acquired while travelling back to hepatitis B endemic countries.[115] The modes of transmission in these cases were through sexual contact, high-risk medical practices (i.e. circumcision and injections) and

inadvertent percutaneous or mucosal contact with blood or infectious fluids, through the sharing of personal items. Although there are no known epidemiological studies comparing the attributable risk of incident acute HBV episodes between immigrant travelers and families, incident rates of new acute HBV episodes in immigrant travelers was reported at 4.5 cases per 100,000 travelers, which was similar to the incidence rate in the general U.S. immigrant population, which was about 5.0 per 100,000, after accounting for under-reporting.[115,117]

There are no systematic screening programs for chronic HBV infection in any of the low hepatitis B endemic, immigrant-receiving countries, nor is hepatitis B vaccination routinely given to all high risk immigrants. Only a small proportion of the foreign-born population have been screened or vaccinated for HBV, even though screening interventions have been shown to be at least moderately cost-effective.[83,88,89] Barriers to screening and vaccination are due to both low knowledge of HBV in the immigrant population and lack of awareness of this issue by health care workers in immigrant-receiving countries.[118,119] The importance of under detection of chronic HBV was highlighted in a recent US study that showed that although there were an estimated 1.4 to 2 million cases of chronic HBV, fewer than 50,000 people received prescriptions for HBV antiviral medication per year.[59] The CDC and the Canadian Collaboration for Immigrant and Refugee Health have recently made recommendations to screen immigrants from intermediate and high hepatitis B endemic countries for chronic hepatitis B and to vaccinate those found to be susceptible.[25,62,63] This is an important step towards increasing awareness for health care workers in low hepatitis B endemic countries and promoting health care

policy designed to reduce the burden of chronic liver disease in foreign-born populations. Novel programs to increase screening for chronic HBV and HBV vaccination coverage however, will clearly be required to decrease this health burden in the migrant population.[66]

One of the major strengths of this systematic review was that it included a very large number of migrants arriving from all world regions over a 40-year period to several different immigrant-receiving countries. This study captured seroprevalence estimates from several different cohorts of migrants, including movements of refugees from Southeast Asia in the 1980s, immigrants and refugees from the Balkans and Eastern Europe who arrived in the first decade of the 21st century and more recent movements of individuals from different countries in Sub-Saharan Africa. We believe this review encapsulated a representative cross-section of international migrants and provides valid estimates for the seroprevalence of HBV infection and immunity in the general immigrant and refugee populations.

Our systematic review and meta-analysis has several limitations. One major limitation of this study was the lack of data on the age and gender of included subjects. Less than half the studies reported mean or median age, and only 26% reported the proportion of subjects who were female. Consequently, we were not able to stratify the data by these variables nor were we able to adjust for them in the logistic model. This is important because children may have a lower seroprevalence of chronic HBV, compared to adults, given that they had less years of cumulative exposure. Without adjusting for age, we may have underestimated the seroprevalence of infection in migrants. Similarly, males have higher rates of chronic HBV and HCC, compared to females, for reasons that are not entirely well

understood.[20] Without information on the gender composition of the studied population, we are unsure if our pooled seroprevalence estimates may have over or underestimated the proportion of migrants who are truly infected. In addition, some cases of acute HBV may have been misclassified as chronic HBV in our analysis, as HBsAg is also present in the serology of acutely infected individuals. However, this is unlikely to have had a large impact on our findings, because as discussed, most HBV infections in foreign-born populations originate early in life and progress to a chronic infection.

In immigrant-receiving countries, international migrants from intermediate and high HBV-endemic countries are a very important group at risk for chronic hepatitis B. On July 28th, 2011, the world celebrated the first World Hepatitis Day sponsored by the WHO. The objective of this awareness day was to focus attention on the global health threat of hepatitis and to promote actions to confront it.[120] This represented a global call to action that will not only benefit those living in intermediate and high HBV-endemic countries but also serves as a reminder for low HBV-endemic countries of the presence of large numbers of undetected persons living with chronic HBV. Our study highlights the fact that migrants living in high-income, low hepatitis B endemic countries remain an important group at risk for chronic HBV and if the infections are identified early, transmission of HBV to susceptible household members and individual morbidity and mortality from liver disease could potentially be decreased, through existing screening and vaccination interventions.

Tables:

Table 1: Systematic Review Search Strategy

1	exp Hepatitis B/
2	(hepatitis b or hepatitis b virus or chronic hepatitis b or hbv or chb).tw.
3	1 or 2
4	exp "Emigration and Immigration"/
5	(resettlement or re-settlement or border crossing or newcomer or naturalized citizen or nonnative or settler or new arrival or displaced person or in-migration or migration or migrant or immigrant or immigration or emigrant or emigration).tw.
6	4 or 5
7	exp Refugees/
8	(asylum seeker or refugee or displaced person or alien).tw.
9	7 or 8
10	3 and (6 or 9)

Table 2: Characteristics of Included Studies Reporting Chronic Hepatitis B Infection

	Number of Studies (%)	**Total Sample Size (%)**
Total	110	209,822
Immigrant Status		
Immigrants	44 (40.0)	70,204 (33.5)
Adopted Children	6 (5.5)	2,306 (1.1)
Refugees	56 (50.9)	127,418 (60.7)
Asylum Seekers	1 (0.9)	7,000 (3.3)
Mixed	3 (2.7)	2,894 (1.4)
Age Group		
Immigrants		
Immigrant Adults	25 (22.7)	22,849 (10.9)
Immigrant Children	4 (3.6)	812 (0.4)
Adopted Children	6 (5.5)	2,306 (1.1)
No Age Reported	15 (13.6)	46,543 (22.2)
Refugees and Asylum Seekers		
Refugee Adults	27 (24.5)	23,181 (11.0)
Refugee Children	5 (4.5)	1,032 (0.5)
No Age Reported	25 (22.7)	110,205 (52.5)
Mixed Adults	3 (2.7)	2,894 (1.4)
Exclusive Region of Origin		
Latin America	2 (1.8)	374 (0.2)
Eastern Europe	15 (13.6)	7,865 (3.7)
Middle East & North Africa	1 (0.9)	414 (0.2)
Sub-Saharan Africa	14 (12.7)	8,579 (4.1)
South Asia	2 (1.8)	282 (0.1)
East Asia & The Pacific	26 (23.6)	26,957 (12.8)
Mixed	50 (45.5)	165,351 (78.8)
Country of Landing		
Australia	7 (6.4)	9,952 (4.7)
Canada	4 (3.6)	14,715 (7.0)
Denmark	4 (3.6)	2,251 (1.1)
France	4 (3.6)	7,440 (3.5)
Greece	9 (8.2)	14,812 (7.1)
Ireland	1 (0.9)	919 (0.4)
Israel	8 (7.3)	8,270 (3.9)
Italy	18 (16.3)	8,600 (4.1)
Netherlands	2 (1.8)	31,142 (14.8)
Norway	1 (0.9)	206 (0.1)
Spain	8 (7.3)	5,717 (2.7)
Sweden	1 (0.9)	133 (0.1)

Switzerland	1 (0.9)	1,299 (0.6)
United Kingdom	2 (1.8)	949 (0.5)
United States	40 (36.4)	103,417 (49.3)
Participant Selection Method		
Clinic/Hospital-Based Screening	34 (30.9)	13,704 (6.5)
Screening Upon Reception/Arrival	42 (38.2)	131,856 (62.8)
Pregnant Women	18 (16.4)	55,546 (26.5)
Invited for Screening	8 (7.3)	6,329 (3.0)
Other	8 (7.3)	2,387 (1.1)
Decade of Publication		
Before 1980	1 (0.9)	414 (0.2)
1980-1989	23 (20.9)	21,287 (10.1)
1990-1999	26 (23.6)	59,168 (28.2)
2000-present	60 (54.5)	129,013 (61.5)

Table 3: Pooled Seroprevalence of Chronic Hepatitis B Infection Stratified by Immigrant Class and Region of Origin among 110 studies

	Number of Studies	**Number of Subjects***	**Pooled HBsAg Seroprevalence Percent (95% CI) †**	I^2 **(%)**
Overall Seroprevalence	110	209,822	7.2 (6.3 – 8.2)	98.1
Immigrants	50	72,510	5.1 (4.0 – 6.4)	97.0
Refugees	57	134,418	9.6 (8.2 – 11.1)	98.1
Mixed	3	2,894	7.7 (6.7 – 8.7)	0
East Asia & The Pacific	40	62,258	11.3 (10.3 – 12.4)	89.1
Immigrants	16	8,550	8.6 (6.7 – 10.9)	89.2
Refugees	23	53,381	13.2 (12.0 – 14.4)	85.8
Mixed	1	327	8.6 (6.0 – 12.1)	0
Sub-Saharan Africa	33	22,219	10.3 (9.1 – 11.8)	86.2
Immigrants	12	4,581	9.9 (7.1 – 13.7)	90.3
Refugees	19	16,022	10.5 (9.0 – 12.2)	84.3
Mixed	2	1,616	10.7 (8.1 – 13.9)	65.5
Eastern Europe & Central Asia	37	31,549	5.8 (4.3 – 7.9)	96.8
Immigrants	13	14,301	5.9 (4.1 – 8.5)	93.4
Refugees	22	17,169	5.9 (3.7 – 9.1)	97.5
Mixed	2	79	6.6 (0.8 – 37.2)	63.5
South Asia	11	1,567	4.6 (2.6 – 7.8)	71.5
Immigrants	4	441	2.4 (0.3 – 15.4)	73.3
Refugees	5	845	6.5 (3.8 – 11.1)	71.9
Mixed	2	281	2.0 (0.9 – 4.5)	0
Middle East & North Africa	17	19,127	2.0 (1.6 – 2.9)	79.0
Immigrants	8	12,541	1.8 (1.3 – 2.7)	79.8
Refugees	7	6,470	2.6 (1.3 – 4.9)	84.7
Mixed	2	116	3.6 (1.4 – 9.2)	0
Latin America & Caribbean	18	29,554	1.7 (1.1 – 2.7)	86.1
Immigrants	9	9,539	1.4 (0.8 – 2.7)	77.2
Refugees	7	19,580	3.1 (0.8 – 11.6)	92.3
Mixed	2	435	0.6 (0.2 – 2.0)	0

* The total number of subjects for each specific region exceeds those reported in Table 2 because they include available data from studies that included mixed populations in terms of region of origin.

† Proportions were logit transformed prior to pooling.

Table 4: Multivariate Random-Effects Logistic Regression of Chronic Hepatitis B Infection among 89 studies*

Variable	**Number of Studies**	**Unadjusted OR (95% CI)**	***P* Value**	**Adjusted OR (95% CI)**	***P* Value**
Immigrant Status					
Immigrant	36	Reference		Reference	
Refugee	53	1.71 (1.18 – 2.49)	0.005	1.42 (1.01 – 1.99)	0.042
Region of Origin†					
Latin America	16	Reference		Reference	
Eastern Europe	35	2.32 (1.99 – 2.69)	<0.001	2.29 (1.97 – 2.67)	<0.001
Middle East	15	1.34 (1.14 – 1.58)	<0.001	1.34 (1.14 – 1.58)	<0.001
Sub-Saharan Africa	31	6.71 (5.84 – 7.71)	<0.001	6.68 (5.81 – 7.68)	<0.001
South Asia	9	3.72 (2.72 – 5.10)	<0.001	3.76 (2.75 – 5.15)	<0.001
East Asia	39	10.8 (9.45 – 12.3)	<0.001	10.8 (9.44 – 12.3)	<0.001
Decade of Study					
1980s	29	Reference		Reference	
1990s	24	0.81 (0.50 – 1.32)	0.40	1.58 (1.03 – 2.43)	0.035
2000s	36	0.59 (0.38 – 0.92)	0.02	1.17 (0.80 – 1.74)	0.41

* Three studies of the 110 total studies were dropped because they did not report separate estimates for refugees and immigrants, and a further 18 studies were dropped because they did not report separate estimates for the different region of origins within that study.

† The sum of the total number of studies for each origin is greater than 89 because several studies reported more than one origin.

CI = Confidence Interval
OR = Odds Ratio

Table 5: Characteristics of Included Studies Reporting Hepatitis B Immunity

	Number of Studies (%)	**Total Sample Size (%)**
Total	39	40 330
Immigrant Status		
Immigrants	12 (30.8)	5,318 (13.2)
Adopted Children	4 (10.3)	1,889 (4.7)
Refugees	22 (56.4)	32,796 (81.3)
Asylum Seekers	0	0
Mixed	1 (2.6)	327 (0.8)
Age Group		
Immigrants		
Immigrant Adults	7 (17.9)	2,621 (6.5)
Immigrant Children	2 (5.1)	579 (1.4)
Adopted Children	4 (10.3)	1,889 (4.7)
No Age Reported	3 (7.7)	2,118 (5.3)
Refugees and Asylum Seekers		
Refugee Adults	13 (33.3)	16,555 (41.0)
Refugee Children	1 (2.6)	81 (0.2)
No Age Reported	8 (20.5)	16,160 (40.0)
Mixed Adults	1 (2.6)	327 (0.8)
Exclusive Region of Origin		
Latin America	0	0
Eastern Europe	9 (23.1)	6,164 (15.3)
Middle East & North Africa	1 (2.6)	121 (0.3)
Sub-Saharan Africa	6 (15.4)	1,055 (2.6)
South Asia	1 (2.6)	206 (0.5)
East Asia & The Pacific	12 (30.8)	19,146 (47.5)
Mixed	10 (25.6)	13,638 (33.8)
Country of Landing		
Australia	2 (5.1)	435 (1.1)
Canada	2 (5.1)	14,411 (35.7)
Denmark	0	0
France	1 (2.6)	481 (1.2)
Greece	3 (7.7)	2,025 (5.0)
Ireland	0	0
Israel	6 (15.4)	2,095 (5.2)
Italy	7 (17.9)	2,254 (5.6)
Netherlands	0	0
Norway	1 (2.6)	206 (0.5)
Spain	1 (2.6)	75 (0.2)
Sweden	0	0

Switzerland	1 (2.6)	1,299 (3.2)
United Kingdom	0	0
United States	15 (38.5)	17,049 (42.3)
Participant Selection Method		
Clinic/Hospital-Based Screening	11 (28.2)	3,646 (9.0)
Screening Upon Reception/Arrival	18 (46.2)	31,797 (78.8)
Pregnant Women	2 (5.1)	706 (1.8)
Invited for Screening	4 (10.3)	2,577 (6.4)
Other	4 (10.3)	1,604 (4.0)
Decade of Publication		
Before 1980	1 (2.6)	121 (0.3)
1980-1989	7 (17.9)	16,074 (39.9)
1990-1999	14 (35.9)	6,483 (16.1)
2000-present	17 (43.6)	17,652 (43.8)

Table 6: Pooled Seroprevalence of Hepatitis B Immunity Stratified by Region of Origin and Immigrant Class among 39 studies

	Number of Studies	**Number of Subjects***	**Pooled anti-HBs Seroprevalence Percent (95% CI) †**	I^2 **(%)**
Overall Seroprevalence	39	40,330	39.7 (35.7 – 43.9)	98.1
Immigrants	16	7,207	33.7 (25.1 – 43.5)	98.3
Refugees	22	32,796	41.5 (37.1 – 46.0)	97.9
Mixed	1	327	76.5 (71.5 – 81.0)	0
East Asia & The Pacific	14	19,204	50.2 (45.8 – 54.6)	92.3
Sub-Saharan Africa	7	1,120	41.7 (37.6 – 45.9)	45.3
Eastern Europe & Central Asia	12	8,207	30.1 (21.8 – 39.9)	98.6
South Asia	2	364	10.6 (5.9 – 18.3)	71.7
Middle East & North Africa	2	131	24.3 (10.7 – 46.2)	31.7
Latin America & Caribbean	2	29	33.0 (5.8 – 79.8)	55.4

* The total number of subjects for each specific region exceeds those reported in Table 5 because they include available data from studies that included mixed populations in terms of region of origin.

† Proportions were logit transformed prior to pooling. Separate rates for immigrants and refugees within each region were not calculated because there were too few studies.

anti-HBs = Hepatitis B Surface Antibody
CI = Confidence Interval

Table 7: Regional Estimates of the Burden of Chronic Hepatitis B Infection in Immigrants and Refugees

	Number of Immigrants*	Estimated Number of Infected Immigrants	Percent of Immigrants with Chronic HBV
North America			
Canada	4 271 500	285 000	6.7
United States	35 500 500	1 607 000	4.5
Europe			
Austria	993 000	58 000	5.8
Belgium	411 000	22 500	5.5
Czech Republic	390 000	26 500	6.8
Denmark	286 000	16 500	5.8
Finland	181 000	11 500	6.4
France	2 348 000	113 500	4.8
Germany	4 784 000	284 000	5.9
Greece	684 000	39 000	5.7
Israel	1 148 000	54 000	4.7
Italy	3 684 500	201 500	5.5
Netherlands	1 395 000	73 500	5.3
Norway	395 000	25 500	6.5
Portugal	385 500	22 500	5.8
Republic of Ireland	247 000	17 000	6.9
Spain	3 487 000	128 500	3.7
Sweden	965 500	52 500	5.4
Switzerland	691 000	41 000	5.9
United Kingdom	3 002 000	193 500	6.4
Oceania			
Australia	2 141 000	176 000	8.2
New Zealand	491 500	47 500	9.7

*The number of immigrants was obtained from recent census data from all immigrant-receiving countries and then rounded (See Supplementary Appendix Table S1).

Figures:

Figure 1: Flowchart of the Identification, Screening, and Inclusion/Exclusion of Studies

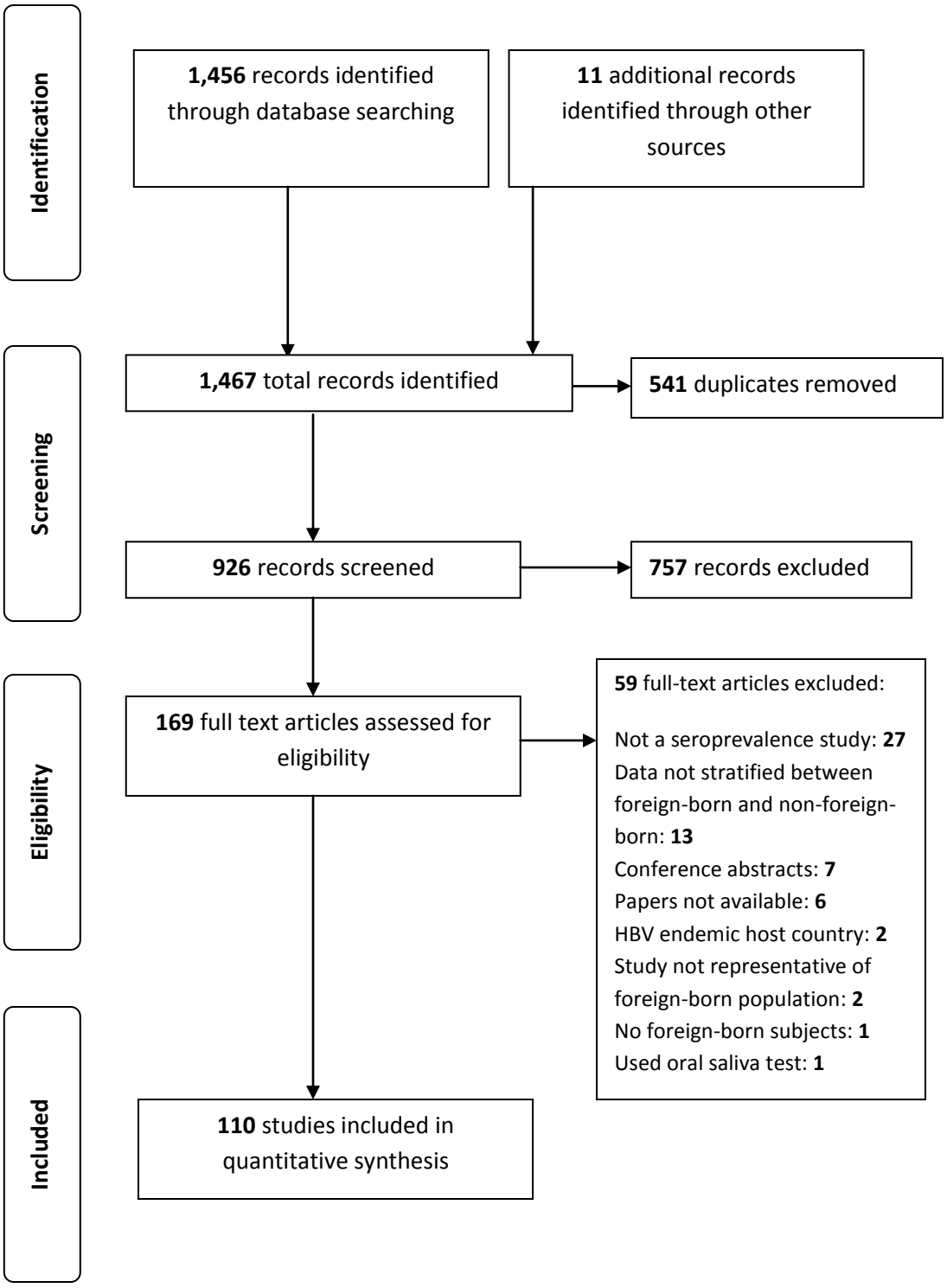


Figure 2: Seroprevalence of Chronic Hepatitis B by Region of Origin: Global Classification and Estimates in the Migrant Population

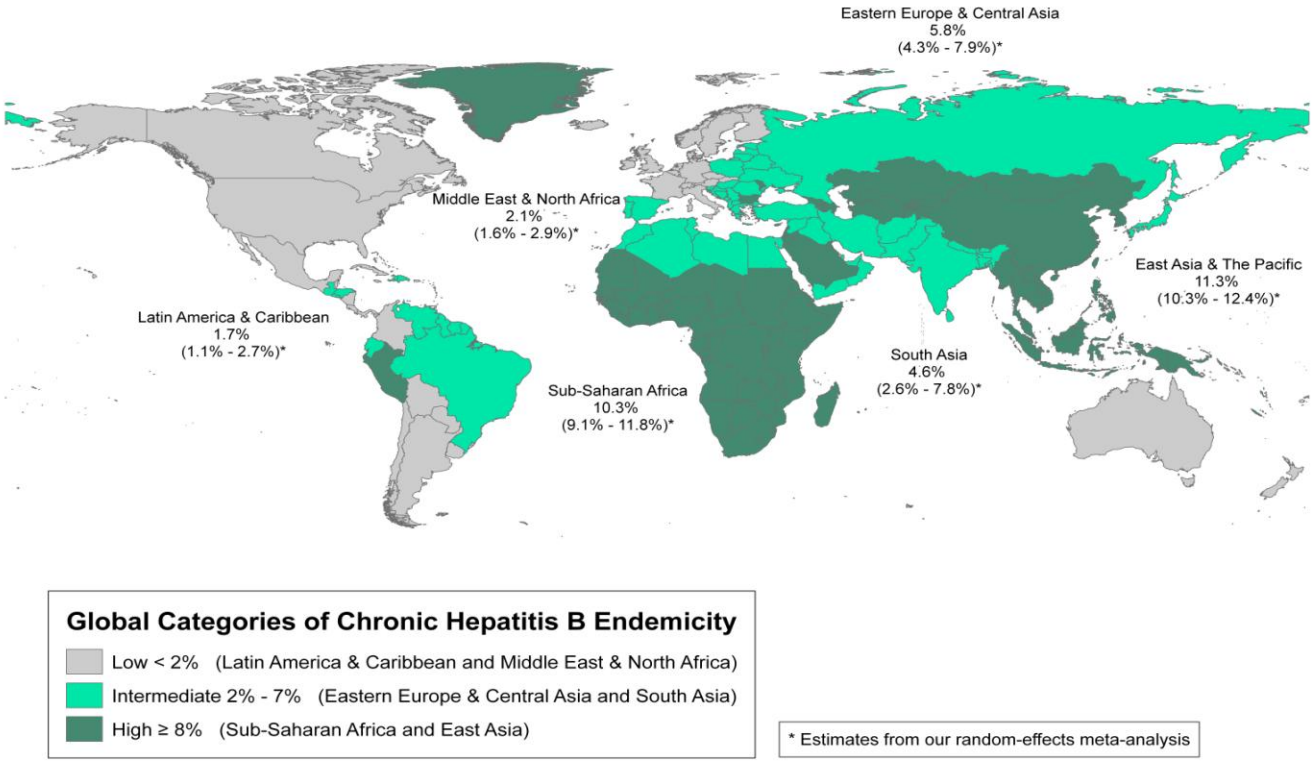


Figure 3: Estimated Number of Migrants with Chronic Hepatitis B Infection Living in North America and Oceania

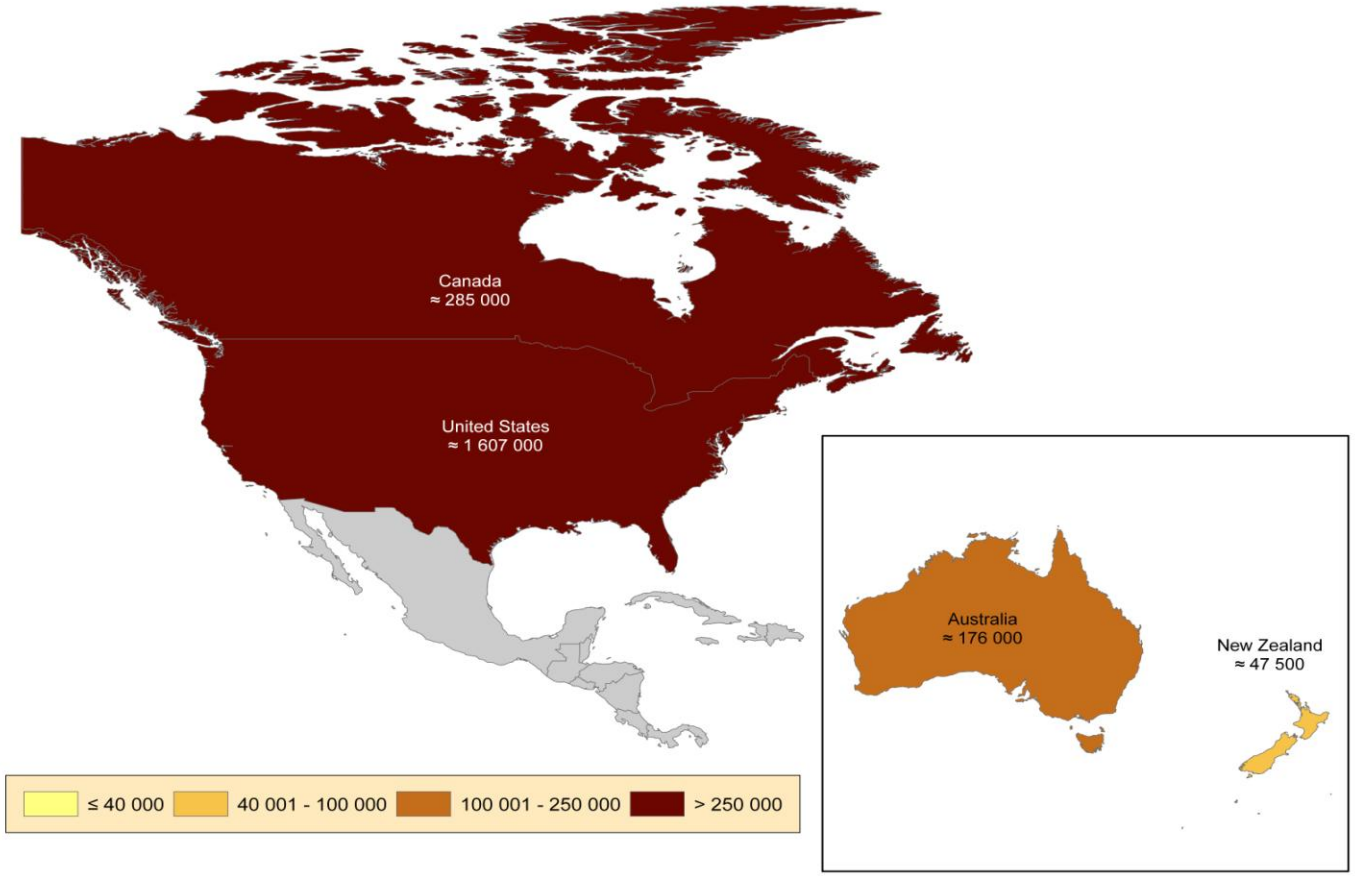
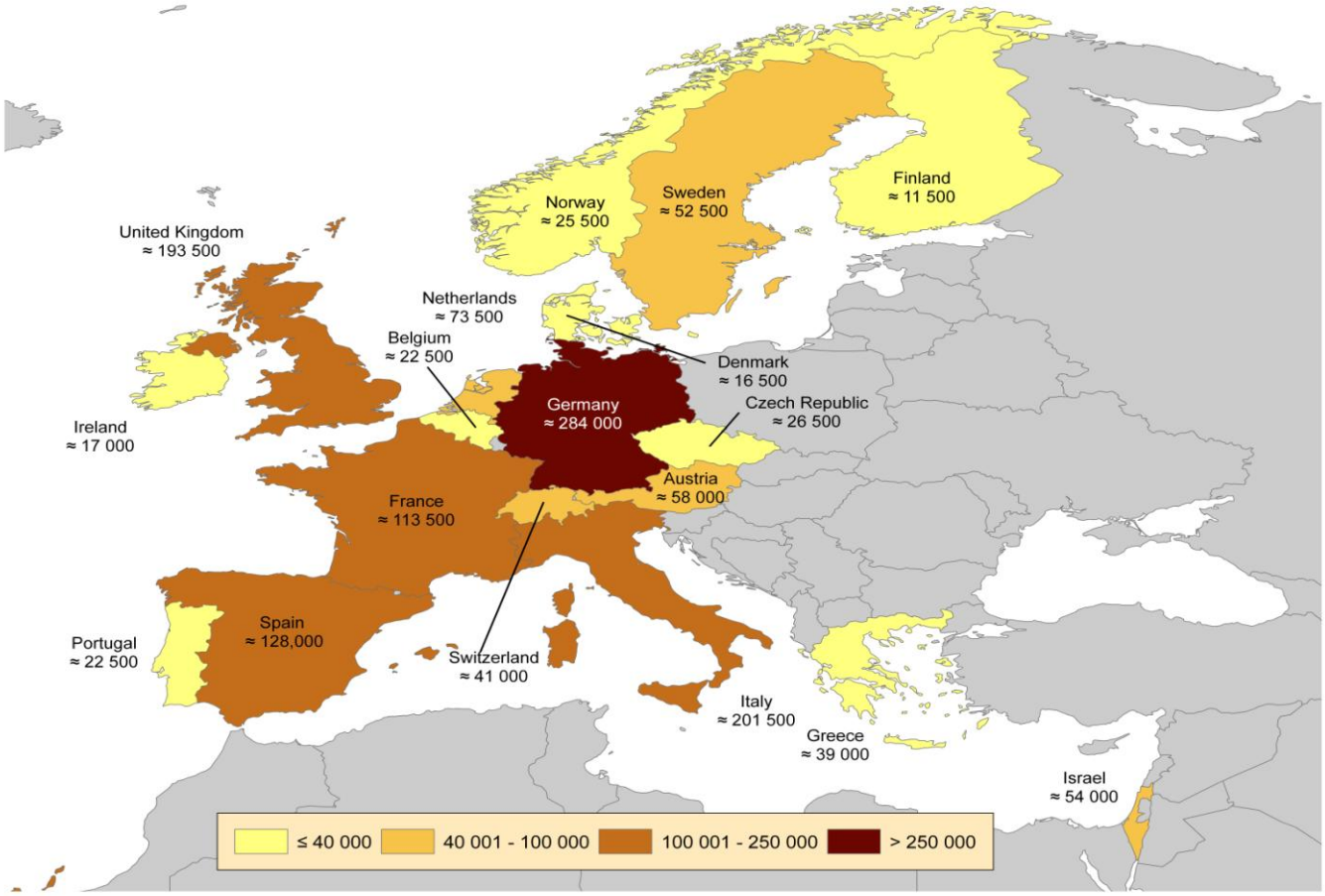


Figure 4: Estimated Number of Migrants with Chronic Hepatitis B Infection Living in Western Europe



CHAPTER 4: Cost-Effectiveness Analysis of Interventions for Hepatitis B in Canadian Immigrants

4.1 Introduction

The second objective of this thesis was to determine the cost-effectiveness of several screening, treatment, and vaccination strategies that can potentially be implemented to reduce morbidity and mortality from HBV in adult Canadian immigrants and refugees. In the first manuscript, we found that international migrants have a higher prevalence of chronic hepatitis B infection than the native-born population of immigrant-receiving countries and this prevalence can exceed 10% in migrants from HBV-endemic areas, such as East Asia and Sub-Saharan Africa. Furthermore, at least 50% of migrants had no serologic evidence of immunity and are thus susceptible to acquiring an infection. These findings suggested that immigrants and refugees in low hepatitis B endemic countries would benefit from screening and vaccination programs because a relatively large proportion of migrants are chronically infected and susceptible. However, few studies have examined how beneficial screening and vaccination programs are at reducing morbidity and mortality from HBV in adult migrants from an economic perspective. In the study that follows, we considered the costs associated with performing screening and providing antiviral therapy or immunization, along with the costs associated with treating acute and chronic HBV infections and liver disease sequelae, to assess the cost-effectiveness of instituting screening and vaccination programs for new Canadian immigrants.

To perform a cost-effectiveness analysis examining interventions for hepatitis B, a decision-analytical model was developed, which included decision

trees and multiple Markov processes. Decision trees are the simplest modeling tool for cost-effectiveness studies, and consist of a series of linear pathways, termed "branches", representing options for a series of logically-ordered alternative events.[81] In the following manuscript, decision trees were used to model the infection status of immigrants upon arrival (i.e.: chronically infected, immune or susceptible), and their acceptance of the interventions being offered. The intervention (i.e. screening and/or vaccination) was modeled at the beginning of the time horizon. Markov models, which are used to model more complex pathways and outcomes that can reoccur over time, were used to model the natural history of HBV infection and liver disease sequelae after the interventions have been offered.

In this model, we assumed that adult immigrants could arrive to Canada in one of these mutually exclusive health states: immune, susceptible, or chronically infected with HBV. To determine the proportion of new arrivals to Canada who are chronically infected or immune, results from the meta-analysis in Manuscript #1 were used. Using a systematic review to help inform parameter estimates in cost-effectiveness studies is recommended, though is not always feasible because of the large number of parameters that can be modeled in a cost-effectiveness analysis.

In the manuscript that follows, the term "immigrant" is used in a more encompassing sense to refer to any permanent resident that decides to settle within Canada, including government-assisted refugees or asylum seekers.

4.2 Manuscript #2 – "Screening and Vaccination Strategies for Preventing Hepatitis B Related Morbidity and Mortality in Immigrants: A Cost-Effectiveness Analysis"

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Abstract:

Background: During the last four decades, immigration to Canada has increased from areas where hepatitis B virus (HBV) is endemic. Most chronic HBV infections in immigrants are asymptomatic and many are unaware of their infection. As a result, immigrants are at greater risk of developing liver disease, compared to the Canadian-born population.

Objectives: We conducted a cost-effectiveness analysis of four HBV screening and immunization strategies designed to identify susceptible or chronically infected adult immigrants, in order to provide vaccination or antiviral therapy to reduce the HBV burden in immigrant communities.

Methods: A cost-effectiveness analysis was performed using a decision-analysis model involving a Markov process to model chronic HBV sequelae. Seroprevalence estimates were obtained from a systematic review. Transition probabilities, intervention and medical costs, and utilities were obtained from the published literature. Interventions were compared by calculating incremental cost-effectiveness ratios, defined as the additional health benefit of a strategy, measured in quality-adjusted life years (QALY) gained, with the next least costly, undominated strategy. One-way, two-way and probabilistic sensitivity analyses were performed to address uncertainty in parameter estimates. Costs and outcomes were modeled over a 45-year period and discounted at a rate of 3% per annum.

Results: The “Screen and Treat” strategy was found to be the most cost-effective strategy with a cost of $37,675/QALY gained, relative to the status quo of no screening or vaccination. The “Screen, Treat and Vaccinate” strategy was found to provide little added benefit, as it was expected to cost $698,844/QALY gained, relative to the Screen and Treat strategy. The “Universal Vaccination” and “Screen and Vaccinate” strategies were dominated by the Screen and Treat strategy, as they generated fewer QALYs than the former strategy. The Screen and Treat strategy remained the most cost-effective intervention after varying model parameters in one-way, two-way and probabilistic sensitivity analyses.

Conclusion: Screening immigrants for chronic HBV was found to be cost-effective and can contribute to reducing HBV-associated morbidity and mortality.

Background

Despite the availability of an effective vaccine and the recent introduction of antiviral therapy, hepatitis B virus (HBV) infection remains one of the world's most prevalent viral infections and a significant cause of global morbidity and mortality. Globally, it is estimated that over 350 million people are chronically infected with HBV and nearly one in three individuals have evidence of previous exposure to HBV.[38] People who are chronically infected with HBV carry a 15% to 25% risk of mortality from cirrhosis or hepatocellular carcinoma (HCC), over the course of their lives. In areas of the world where HBV is endemic, primary liver cancer is one of the leading causes of cancer mortality in otherwise healthy adults.[22] Every year, between 500,000 and 1.2 million deaths are attributed to complications from HBV or liver disease-related sequelae.[16]

In Canada, rates of new acute HBV infections have declined considerably in children and young adults, primarily as a result of universal vaccination, and through interventions that have reduced exposure to blood and blood products contaminated with HBV.[78,79] However, high rates of chronic HBV infection still persist, particularly among foreign-born populations, who have developed a chronic infection in their country of origin. In HBV-endemic areas, where many new arrivals to Canada originate from, the seroprevalence of the hepatitis B surface antigen (HBsAg) can exceed 2% in the general population, and in areas of high endemicity, the seroprevalence of HBsAg is greater than 8%.[38,50] As a result of their greater risk of chronic carriage and the asymptomatic nature of chronic HBV, immigrants carry a disproportionate share of the liver disease burden in many immigrant-receiving countries. Recent cohort studies using administrative

databases in Canada have found that both male and female immigrants have a significantly higher age-adjusted standardized mortality ratio for liver cancer, compared to the Canadian-born population.[56] Furthermore, immigrants and refugees from East Asia were found to have between a two- and six-fold, age-adjusted, greater risk of being diagnosed with liver cancer.[57]

Despite the greater risk of chronic liver disease and the large HBV-related disease burden in foreign-born populations, there are currently no targeted vaccination or screening programs for HBV in Canada. Recently, the Canadian Collaboration for Immigrant and Refugee Health (CCIRH) has recommended that all newly arriving immigrants from areas where HBsAg seroprevalence $\geq 2\%$ be screened for chronic HBV to identify immigrants who would benefit from appropriately timed antiviral treatment to reduce the risk of liver disease progression.[63] Those found to be susceptible are recommended to receive the three-dose vaccination series. These health interventions are designed to identify susceptible and chronically infected adult immigrants, in order to provide vaccination or antiviral therapy to reduce morbidity and mortality from HBV.

In this study, we evaluated the cost-effectiveness of four incremental vaccination and screening programs offered to adult immigrants during their first year in Canada.

Methods:

Intervention Strategies

A decision-analysis tree, which incorporated Markov processes to represent the natural history of HBV disease, was developed using TreeAge Pro 2011 (TreeAge Inc., Williamstown, MA) to evaluate the cost-effectiveness of four screening and vaccination strategies in a cohort of newly-arriving immigrants who were all assumed to be unaware of their HBV infection status and asymptomatic, if chronically infected. These strategies were compared to the status quo of no targeted screening or vaccination for new Canadian immigrants.

The four strategies evaluated in this analysis were:

a) Universal Vaccination:

For this strategy, immigrants are offered the three-dose vaccine series for HBV, without any serologic testing to determine who is already infected or immune, during their first year, after arrival in Canada. Those who are already infected and comply with the intervention will not receive any benefit from immunization and would proceed normally through the natural history of HBV disease. Those who are susceptible will generate protective antibodies according to their compliance with receiving one, two or three doses of the vaccine (See Appendix 3: Figure S1).

b) Hepatitis B Surface Antibody (anti-HBs) Screening and Vaccination:

In this strategy, immigrants are invited for serologic testing for anti-HBs to determine who has prior immunity to HBV, after arrival to Canada. Those found to have no serologic evidence of immunity are offered the three-dose vaccine series for HBV, as in the Universal Vaccination strategy. Those who decline serologic

testing and those found to be immune are not offered to be immunized. Similarly, those who are already chronically infected and accept the vaccine will receive no benefit from immunization (See Appendix Figure S2).

c) HBsAg Screening and Treatment:

In this strategy, immigrants are offered serologic testing for HBsAg to determine who is chronically infected, again during their first year in Canada. Those found to be positive for HBsAg will be referred to visit a liver specialist for further investigations and to determine the need for antiviral therapy. If treatment is indicated, then immigrants will be offered treatment with a first-line nucleoside analogue.[121] Those immigrants who are found not to require antiviral therapy will be followed up annually to determine if treatment is needed in subsequent years (See Appendix Figure S3).

d) Anti-HBs and HBsAg Screening, Treatment or Vaccination:

For this strategy, immigrants are offered serologic testing for both anti-HBs and HBsAg, during their first year in Canada. Those found to be chronically infected are referred to a liver specialist, as in the HBsAg Screening and Treatment strategy. Those found to be susceptible are offered the three-dose vaccination series. Those who decline initial serologic testing are not offered vaccination and are not referred to a liver specialist (See Appendix Figure S4).

Model Structure

In this model, the immigrant population of interest is a hypothetical cohort of 100,000 individuals who are all assumed to be 30 years of age, which is the average age of new arrivals to Canada during the last five years.[11] The time horizon used in the Markov model was 45 years. This length of follow up was chosen because it allowed sufficient time for distant health outcomes, such as HCC, to develop, and allowed us to investigate costs and outcomes over the entire lifetime of the cohort.

At the onset, all immigrants are assumed to be in one of four mutually-exclusive underlying HBV health states: susceptible, immune, stable chronic infection or active chronic infection. For simplicity, we assumed that immigrants were otherwise healthy and did not arrive with cirrhosis or HCC.[83] After accepting or declining the intervention being offered during their first year, immigrants enter the Markov model based on the outcome of the intervention. For example, those who initially arrive susceptible and accept to be vaccinated would enter the Markov model in the immunized state, if they developed an immune response to the vaccine. In the Markov model, subjects can proceed to develop compensated cirrhosis, decompensated cirrhosis, HCC, receive a liver transplant or hepatectomy, or die from these illnesses or die from other non HBV-related causes (Figure 1). The annual probabilities of transitioning between states in the model were obtained from cohort studies and from other cost-effectiveness analyses and systematic reviews (Table 1). The age-specific risk of death from other causes was obtained from Statistics Canada.[122]

Immigrants who have a *stable chronic* infection are assumed not to be candidates for antiviral treatment, as we considered them to have normal levels of

liver enzymes, low levels of circulating HBV DNA (viral load), and were HBeAg negative.[121] Immigrants who have an *active chronic* infection are assumed to be candidates for antiviral therapy as we considered them to have elevated liver enzymes, high levels of circulating HBV DNA, and were HBeAg positive, indicating active viral replication.[123] This dichotomous classification for chronic HBV infection was used to simplify the different combinations of clinical characteristics, such as viral load and HBeAg status, which guide clinical practice for managing patients with chronic HBV.[121] Based on the relatively young age that immigrants develop chronic infections in HBV endemic countries and the fact that most of these perinatally acquired chronic infections can remain in an immune-tolerant phase for over twenty years[21], we assumed that 50% of chronically infected immigrants would have stable chronic infection and 50% would have active chronic infection upon arrival to Canada.[89] This assumption was varied in a sensitivity analysis to determine how it would affect our results.

Susceptible individuals can become chronically infected, after landing in Canada, if they acquire an acute infection and fail to clear the virus. We assumed that the annual risk of infection in susceptible adults was 4.8 per 100,000 people among 30 to 39 year-olds, and 3.1 per 100,000 people among those $\geq$ 40 years.[32] We utilized rates from the general Canadian population, as incidence rates of acute HBV infection were unavailable for Canadian immigrants. The rates in the Canadian population approximated rates in the U.S. foreign-born population, after accounting for under-reporting due to the often asymptomatic nature of acute HBV infections in adults, which were estimated at 5.0 per 100,000 people.[117]

We estimated that 5% of adult immigrants who acquire an acute HBV infection will develop chronic hepatitis B.[13,23] All new cases of chronic HBV acquired in adult immigrants were assumed to be active chronic infections because most acquired cases in adults are associated with elevated levels of liver enzymes and circulating viral DNA.[21]

Seroprevalence Estimates

To determine the initial proportions of Canadian immigrants who arrived chronically infected or with prior immunity, data from a systematic review and meta-analysis that reported region of origin-specific HBsAg and anti-HBs seroprevalence estimates in immigrants and refugees were used (See Manuscript #1). These seroprevalence estimates were weighted by the proportion of Canadian immigrants, arriving between 2001 and 2006, from each of the same world regions to determine an overall average HBsAg and anti-HBs seroprevalence estimate for newly-arriving immigrants in the model (Appendix Figure S5).[124]

Model Assumptions

For each of the strategies that utilized serologic testing, we assumed that 70% of the population would accept to be screened. Since no estimate exists for compliance with serologic testing in this population, we included a wide range for this model parameter, as well as for all other compliance estimates (Table 1). Similarly, we assumed that 70% would accept the first dose of the HBV vaccine, if offered, and of these 85% and then 90% would receive second and third doses, respectively, given that they received the previous dose. Vaccine immunogenicity following each of the three doses was 42.5%, 75% and 90%, respectively, and was

assumed to provide lifelong immunity.[25] We assumed that this population was not concurrently infected with either HCV or HIV, and therefore would not influence rates of immunogenicity from the vaccine. Furthermore, we assumed that acceptance of serologic testing or immunization was independent of an individual's initial infection status. Since chronic HBV is often asymptomatic in adults and we assumed immigrants were unaware of whether they were susceptible, immune or infected, this assumption of independence is valid and is not expected to influence the generalizability of our model.

For those found to be chronically infected after serologic testing, we assumed that 60% would agree to visit a liver specialist to determine if they need treatment (Table 1).[88] If treatment is indicated because an immigrant is found to have an active chronic infection, we assumed that 75% would immediately initiate antiviral therapy. We assumed that being on antiviral therapy would reduce the risk of progressing from active chronic infection to compensated cirrhosis, HCC or death, by 50%.[61]

Direct and Indirect Cost Estimates

All direct and indirect costs were calculated in Canadian dollars for the year 2011 and summarized in Table 2 and Table 3, respectively. Published costs from previous years were converted into 2011 dollars using the Consumer Price Index for health care goods and services.[125] Our primary economic evaluation was performed from a health-care system perspective and included all direct medical costs attributed to acute and chronic HBV infections and their sequelae. A secondary analysis was performed from a societal perspective and also considered

indirect costs. Indirect costs included out-of-pocket costs to patients and their families plus lost income due to death or disability.

Program costs related to serologic testing and visits to liver specialists were obtained from medical payment schedules from the Quebec and British Columbia Ministry of Health (Table 2).[126,127] Vaccine costs were obtained from the CDC vaccine price list, as Canadian costs for the vaccine were not available publically. These costs approximated vaccine costs obtained through personal correspondence from the Montreal Public Health Department, which were $10 per dose.[128] Direct and indirect medical costs associated with an acute HBV episode, including time lost from work were incorporated into the model.[129] We estimated that the average daily gross wage for an adult immigrant was $142.50 ($19/hr for 7.5 hours), and that symptomatic acute infections would require a short time off from work (Table 3).[130]

Direct health-care costs for chronic HBV and liver disease sequelae were obtained from a Canadian study that calculated the expected cost of care for patients with chronic HBV and resulting complications (Table 2).[131] Antiviral treatment was assumed to cost $8,089 per year, which is the average between the annual cost of Tenofovir and Entecavir, the two first line antiviral medications for chronic HBV.[132] We assumed that one year's worth of work would be lost following a liver transplant and four months of work would be lost following a hepatectomy. It was assumed that all immigrants were employed until age 65.

Health-State Utilities

Chronic HBV infections and the long-term liver diseases that result from infection have a substantial impact on an individual's quality of life. We used utility estimates for chronic HBV-related health states elicited from uninfected Canadian respondents to calculate quality-adjusted life years (QALYs) in the cost-effectiveness analysis (Table 4).[133] All future costs and outcomes were discounted at an annual rate of 3%, as recommended by the Panel of Cost-Effectiveness in Health and Medicine.[87]

Cost-Effectiveness Analyses

In our base-case analysis, we calculated the number of HBV-related deaths prevented for each of the four interventions relative to the status quo strategy. Strategies were compared by calculating their incremental cost-effectiveness ratios (ICER), defined as the additional health benefit of an intervention, measured in QALYs gained, with the next least costly undominated strategy.[81] One-way and two-way sensitivity analyses were performed to determine how key assumptions regarding compliance estimates and cost parameters would influence base-case results. A probabilistic sensitivity analysis (PSA), using 10,000 Monte Carlo simulations, was conducted to simultaneously assess uncertainty around all key parameters used.[134,135] All variables were assumed to be uniformly distributed throughout their ranges for the PSA. Results from the PSA were assessed with a cost-effectiveness acceptability curve where different threshold values for cost per QALY gained were considered. The probability that the cost per QALY gained lies below each threshold was then estimated.

Results:

Base Case: Health-Care Perspective

Under base-case assumptions, the status quo strategy of no immigrant screening or vaccination was both the least costly and least effective strategy (Table 5). The model estimated that, under the status quo, 3,029 HBV-related deaths would occur over a 45-year period in a cohort of 100,000 new Canadian immigrants. The Universal Vaccination and Screen and Vaccinate strategies were found to prevent only one and two additional HBV-related deaths, respectively, compared to the status quo. Both strategies cost more than the status quo and generated more QALYs, but were excluded in the decision-analysis by extended dominance, as their ICERs were found to be higher than the Screen and Treat strategy, which was the next more effective alternative.

The Screen and Treat and Screen, Treat and Vaccinate strategies were not dominated by any others (Table 5 and Figure 2). The Screen and Treat strategy was found to be the most cost-effective, as the model predicted that it would prevent 11% of HBV-related deaths (332 deaths) and would cost $37,675/QALY gained, compared to the status quo. The Screen, Treat and Vaccinate strategy was shown to provide little added benefit beyond the Screen and Treat strategy, as the model estimated that this strategy would prevent only one additional HBV-related death and would cost $698,844 per additional QALY gained, compared to the Screen and Treat strategy.

Sensitivity Analysis: Health-Care Perspective

One-way sensitivity analyses were performed for variables with uncertain parameters. In all cases, the status quo remained the least costly and least effective

strategy. Furthermore, the ranking of interventions, in terms of their cost-effectiveness ratios, remained unchanged. The Screen and Treat strategy was always the most cost-effective and the Screen and Vaccinate and Universal Vaccination strategies were always dominated.

The results from the model were most sensitive to active HBV treatment efficacy. The ICER for the Screen and Treat strategy increased from $28,050/QALY gained to $58,878/QALY gained, when the treatment efficacy for HBV was reduced from 75% to 25%. In a two-way sensitivity analysis, that included treatment efficacy and treatment costs, the ICER for the Screen and Treat strategy increased as antiviral treatment became more costly, and increased more quickly as treatment efficacy declined (Figure 3).

ICERs were not sensitive to the proportion of immigrants complying with the various components of the interventions, such as accepting serologic testing, visiting a liver specialist, or accepting antiviral treatment and were also insensitive to changes in annual direct medical costs for HBV-related sequelae (Figure 4). The choice of the discount rate did not have a marked effect on the ICER of the Screen and Treat strategy, as it ranged between $31,647/QALY gained and $42,257/QALY gained, when costs and outcomes were discounted at a rate between 0% and 5% per annum.

The cost-effectiveness of the Screen and Treat strategy remained relatively consistent as the proportion of immigrants who were chronically infected at arrival was varied (Figure 5). The ICER for this strategy was $50,270/QALY gained, relative to no screening or vaccination, at a HBsAg seroprevalence of 0.2%, and decreased to $40,000/QALY gained at a seroprevalence of 1.0%. At 13%, the ICER

declined only marginally from the base-case estimate of $37,675/QALY gained (6.52% HBsAg seroprevalence), to $37,475/QALY gained.

Results from the PSA showed that the Screen and Treat strategy had a 62% chance of costing under $40,000/QALY gained and an 84% chance of costing under $50,000/QALY gained, relative to no screening or vaccination, when all uncertain model parameters were varied simultaneously (Figure 6 and Appendix Figure S6). The 95% confidence interval for the ICER of the Screen and Treat strategy ranged between $29,602/QALY gained and $38,743/QALY gained.

Societal Perspective

When societal costs were included in the model, the status quo strategy remained the least costly and least effective, and the Screen and Vaccinate and Universal Vaccination strategies were absolutely dominated by the Screen and Treat strategy (Table 6). Indirect costs contributed to approximately 8% of the total costs associated with the health interventions. The Screen and Treat strategy was markedly more cost-effective from a societal perspective, as its ICER, relative to no screening or vaccination, decreased by 82%. This strategy would cost $6,478/QALY gained, compared to the status quo, and would be very cost-effective. The Screen, Treat and Vaccinate strategy, which also was undominated, would cost $671,551 per additional QALY gained relative to the Screen and Treat strategy.

Discussion:

In order to determine the most cost-effective intervention to reduce morbidity and mortality from HBV in newly arriving adult Canadian immigrants, we evaluated four vaccination and screening strategies. Our results suggest that targeted screening of immigrants for chronic HBV, followed by offering antiviral treatment to those whom it is indicated, would prevent 11% of HBV-related deaths and is the most cost-effective option to reduce morbidity and mortality from HBV. From a health-care perspective, it would cost $37,675 to increase one QALY in a cohort of immigrants who are offered serologic testing and treatment for chronic HBV. When societal costs are considered, screening and treating adult immigrants would cost $6,478/QALY gained, relative to no intervention. In North America, investigators have considered a willingness-to-pay threshold of $50,000/QALY gained as being cost-effective, although this threshold is arbitrary, and the relative cost-effectiveness of any intervention needs to be considered along with the availability of resources and the budgets of health planners.[136]

The Screen and Treat strategy was found to be most cost-effective because this intervention identifies those immigrants who arrive with an asymptomatic chronic HBV infection. Without any screening, these chronically infected immigrants are at an elevated risk of progression to HBV-related sequelae, such as cirrhosis and HCC, over the course of their lifetime. With the timely identification of infected individuals and proper use of antiviral treatment, the risk of developing sequelae can be reduced.[123] In our base-case analysis, we assumed that 6.5% of new Canadian immigrants were chronically infected, and these individuals had between a 0.34% to 2.4% annual risk of progressing to compensated cirrhosis or HCC. Compensated cirrhosis and HCC cost the Canadian health-care system more than

$9,000 and $15,000, per person every year, respectively. A relatively inexpensive screening program would then reduce the long-term costs associated with chronic HBV sequelae and be cost-effective.

The interventions that involved immunization, such as the Universal Vaccination and Screen and Vaccinate strategies, were found to be dominated by the strategies that included screening for chronic HBV. This can be explained by the large costs associated with vaccinating an entire cohort against new HBV infections, relative to the small decrease in morbidity and mortality that would occur from preventing sequelae from a small number of new infections. Immunizing adult immigrants is not an attractive option because the risk of acquiring a new acute infection within the community is low, as it occurs in about 5 per every 100,000 adult immigrants, and only about 5% of adults develop a chronic infection after an acute episode. Furthermore, vaccination interventions that do not also screen for chronic HBV will have no effect on reducing morbidity and mortality from the large proportion of immigrants who arrive with a chronic infection.

Through one-way and multivariate sensitivity analyses, we demonstrated that our results were robust across a range of parameters. The ICER for screening and providing antiviral therapy for chronic HBV, relative to the status quo, did not change appreciably, as it ranged between $37,095 and $40,117 per QALY gained when compliance estimates with the interventions were varied between 40% and 100%. Furthermore, the model was also robust to a range of health care costs associated with HBV sequelae. A PSA, which allowed all model parameters to vary simultaneously, including utilities and transition probabilities, found that this

intervention had an 84% chance of costing less than $50,000 per QALY gained, relative to no screening or vaccination.

The cost-effectiveness of screening for chronic HBV remained relatively unchanged as the proportion of immigrants who entered Canada with a chronic infection varied. Using data from a systematic review on the seroprevalence of HBsAg in international migrants and standardizing it to the proportion of immigrants who recently settled in Canada, we estimated that 6.52% were chronically infected. When this parameter was varied between 0.2% and 13%, the ICER remained below $50,000 per QALY gained, suggesting that this strategy can be applied to immigrants from areas of low HBV endemicity, such as Latin America or the Middle East, as well as to immigrants from areas where HBV is endemic, such as East Asia and Sub-Saharan Africa.[38,50]

The results of our analysis were sensitive, however, to the cost of antiviral medications and their treatment efficacy. During the last few years, several new antiviral treatments have become available for patients with chronic HBV. The costs for each of these antiviral drugs vary considerably and can range between $5,000 and $15,000 per year, for low-cost oral nucleotide agents and more expensive peg-interferon α-2 therapy.[137,138] In addition, various drugs have different treatment efficacies and resistance profiles.[61] Even at high antiviral costs, the intervention was cost-effective when treatment reduced the risk of disease progression by more than 50%.

In this study, health outcomes were measured in terms of QALYs, rather than life-years gained or number of cases of chronic HBV prevented. This outcome measure was chosen because it would best represent the effectiveness of the

screening and vaccination strategies being evaluated for a disease that has several different sequelae that can occur as a result of a HBV infection. Using QALYs allowed us to capture both the increase quantity and quality of life of the cohort that could experience various health states such as cirrhosis, liver cancer and liver transplant or hepatectomy, which each have their own impact on an individual's quality of life.

Several studies have addressed the cost-effectiveness of HBV interventions in immigrant communities and the findings of our analysis are consistent with the results from these studies.[83,89] Hutton et al. found that a targeted screening program for chronic HBV, as well as a screening program that also included vaccination of close contacts would be cost-effective among Asian and Pacific Islander populations in the United States. From a health-care perspective, both interventions were expected to cost approximately $40,000/QALY gained and would prevent 20% of HBV-related deaths.[83] In a Canadian study, Wong et al. reported that screening and treating immigrants would be moderately cost-effective, though this study used a more elaborate disease progression model and included smaller transition probabilities than in other HBV cost-effectiveness studies.[89]

Our analysis has several limitations that should be considered. First, we used a simplified model of the natural history of HBV which did not take into account HBeAg status, HBV DNA viral load, or alanine aminotransferase (ALT) levels. Instead, we modeled chronic infection with stable and active chronic HBV states. The results of our analysis, however, were of similar magnitude to the results of a previous cost-effectiveness analysis that incorporated HBeAg, HBV DNA, and ALT variables.[89] Secondly, we made several assumptions regarding compliance

with screening, vaccine uptake, specialist visits, and treatment adherence, as there were no epidemiologic studies that reported estimates for these parameters in immigrant populations. Nonetheless, our estimates were similar to compliance parameters used in other cost-effectiveness studies in similar populations and when these estimates were varied in sensitivity analyses, they were found not to have a significant impact on our results.[88] Finally, the Markov model that we used in our study was a static disease model that only followed a single cohort from arrival until death. The model did not include entry of future cohorts of immigrants arriving in Canada, who may have reduced seroprevalences of chronic HBV because perinatal HBV vaccination is increasingly being administered in many HBV endemic countries. Other models, such as stochastic disease transmission models, which account for new cohort entry, do not incorporate economic elements, such as state costs or discounting, and are of limited used for economic evaluations.[139]

Results from this study show that screening for chronic HBV in adult immigrants after arrival is likely to be cost-effective, regardless of their origin. Public health officials and clinicians who work with populations of new arrivals to Canada are encouraged to offer serologic testing and raise awareness about HBV in immigrant communities. Targeted screening of immigrants can substantially reduce chronic HBV and liver disease health disparities between new immigrants and the general population of Canada.

Tables:

Table 1: Seroprevalence Estimates, Intervention Compliance and Transition Probabilities for Hepatitis B Screening and Vaccination Strategies

Variable	Base-case estimate	Range for sensitivity analysis	Source
Hepatitis B Prevalence			
Chronic HBV Infection	6.52%		Calculated
Prior HBV Immunity	32.35%		Calculated
Compliance with Interventions			
Serologic Testing	70%	40% - 100%	[83]
1st Dose of vaccine	70%	40% - 100%	Assumed
2nd Dose of vaccine, given 1st dose	85%	50% - 100%	Assumed
3rd Dose of vaccine, given 2nd dose	90%	50% - 100%	Assumed
Visit Liver Specialist, if chronically infected	60%	40% - 100%	[88]
Accept antiviral treatment, if indicated	75%	50% - 100%	Assumed
Intervention Characteristics			
HBsAg testing sensitivity	99.5%		[140]
HBsAg testing specificity	99.5%		[140]
anti-HBs testing sensitivity	100%		[141]
anti-HBs testing specificity	97.9%		[141]
Vaccine Immunogenicity, one dose	42.5%	30% - 55%	[25]
Vaccine Immunogenicity, two doses	75%	62.5% - 87.5%	[25]
Vaccine Immunogenicity, three doses	90%	80% - 100%	[25]
Antiviral Treatment Efficacy	50%	25% - 75%	[61]
Annual Acute Hepatitis B Transitions			
Risk of Infection			
30-39 Year Olds	0.0048%		[32]
≥ 40 Year Olds	0.0031%		[32]
Symptomatic Infection	40%	30% - 50%	[32]
Hospitalization, given symptomatic infection	40%	12% - 50%	[83,117]
Fulminant Hepatitis	1.5%	1% - 5%	[28,83]

Mortality from Fulminant Hepatitis	85%	53% - 100%	[28,142]
Chronic Infection	5%	1% - 10%	[13,23]
Annual Chronic Hepatitis B Transitions			
Risk of Death from other causes	Age Specific		[122]
Probability of HBsAg seroconversion	0.5%	0% - 1%	[143]
Probability That a Chronic HBV Infection is Stable	50%	30% - 70%	[21,24,89]
Stable Chronic Infection			
To Active Chronic Infection	1.8%	0.84% - 2.7%	[144]
To Hepatocellular Carcinoma	0.34%	0.11% - 0.5%	[83,144,145]
To Death	0.72%	0.38% - 0.93%	[144,146]
Active Chronic Infection			
To Compensated Cirrhosis	2.4%	0.7% - 3.8%	[83,147,148]
To Hepatocellular Carcinoma	1.1%	0.27% - 2.77%	[144,145,149]
To Death	1.0%	0.25% - 1.5%	[144,146]
To Antiviral Treatment	50%	25% - 75%	Assumed
Active Chronic Infection Treatment			
To Defaulting Treatment	10%	0% - 20%	Assumed
To Compensated Cirrhosis	1.2%	0.6% - 2.8%	Assumed 50% treatment efficacy
To Hepatocellular Carcinoma	0.55%	0.28% - 0.83%	Assumed 50% treatment efficacy
To Death	0.5%	0.25% - 0.75%	Assumed 50% treatment efficacy
Compensated Cirrhosis			
To Decompensated Cirrhosis	5.0%	3.24% - 7.0%	[83,150]
To Hepatocellular Carcinoma	5.0%	3.0% - 6.6%	[144,145,151]
To Death	3.0%	1.3% - 4.8%	[83,150,152]

Decompensated Cirrhosis			
To Hepatocellular Carcinoma	6.3%	3.0% - 7.0%	[83,145,153]
To Liver Transplant	10%	0% - 40%	Assumed
To Death	22.5%	9.9% - 31.4%	[83,144,150]
Hepatocellular Carcinoma			
To Liver Transplant	5.9%	5% - 40%	[154,155]
To Hepatectomy	24.5%	15% - 45%	[154,155]
To Death	35%	8.1% - 54.5%	[121,144,156]
Liver Transplant 1st Year			
To Death	9.2%	5% - 20%	[157]
Post Liver Transplant			
To Death	5%	1% - 15%	[157]
Hepatectomy 1st Year			
To Death	6%	0% - 8%	[158]
Post Hepatectomy			
To Death	12%	9% - 17%	[158]

Table 2: Program Costs and Utilities for Hepatitis B Prevention and Treatment Strategies *

Variable	Base-case estimate	Range for sensitivity analysis	Source
Discount rate, costs and utilities	3%	0% – 5%	[87]
Program costs			
Vaccine price per dose	$28.15		[128]
Vaccine administration per dose	$15		[83]
Cost of Hepatitis B Surface Antigen test	$10.40		[127]
Cost of Hepatitis B Surface antibody test	$11.08		[127]
Laboratory administration	$45		Assumed
Liver Specialist Visit	$176.30		[126]
Liver Specialist Testing and administration	$136.58		[127]
Direct medical costs – Acute Infection			
Symptomatic acute infection, no hospitalization	$375	$188 – $647	[159]
Symptomatic acute infection, hospitalization	$4,515	$2,372 – $11,148	[129]
Fulminant Hepatitis	$18,044		[159]
Direct annual medical costs – Chronic Disease			
Active Chronic Infection related costs	$1,001	$911 – $1,166	[131]
Chronic Hepatitis B Treatment	$8,089	$7,057 – $9,196	[131,132]
Compensated cirrhosis costs	$9,279	$7,759 – $11,628	[131]
Decompensated cirrhosis costs	$13,137	$9,722 – $19,174	[131]
Hepatocellular carcinoma costs	$15,620	$12,411 – $20,109	[131]
1st Year Liver Transplant costs	$115,907	$110,364 – $124,995	[131]
Post Liver Transplant costs	$44,734	$39,117 – $53,992	[131]
1st Year Hepatectomy costs	$80,397	$57,722 – $105,170	[160]
Post Hepatectomy costs	$17,886	$8,943 – $26,829	[160]

* All costs are in 2011 Canadian Dollars.

Table 3: Indirect Costs for Hepatitis B Prevention and Treatment Strategies *

Variable	Base-case estimate	Range for sensitivity analysis	Source
Indirect costs – Acute Infection			
Symptomatic acute infection, no hospitalization, time lost from work (three days)	$427.50	$0 - $712.50	Assumed
Symptomatic acute infection, hospitalization, time lost from work (eight days)	$1,140	$660 - $1,800	Calculated from [129]
Fulminant hepatitis, time lost from work (five days)	$712.50	$285 - $998	Assumed
Indirect costs – Chronic Disease			
Average annual health care expenditures	$5,811		[161]
Forgone income due to premature death or liver transplant (until age 65)	$37,050	$21,450 - $58,500	Calculated from [130]
Forgone income due to hepatectomy	$12,350	$7,150 - $19,500	Calculated from [130]
Palliative Care for HCC-related death	$3,095	$0 - $5,000	[162]

* All costs are in 2011 Canadian Dollars.

Table 4: Health-State Utilities for Markov Model

Utilities	Base-case estimate	Range for sensitivity analysis	Source
Susceptible	0.99	0.95 - 1.0	Assumed
Immune	0.99	0.95 - 1.0	Assumed
Stable Chronic Infection	0.95	0.9 - 1.0	Assumed
Active Chronic Infection	0.85		[133]
Hepatitis B Treatment	0.90	0.85 - 0.95	Assumed
Compensated Cirrhosis	0.83		[133]
Decompensated Cirrhosis	0.45		[133]
Hepatocellular Carcinoma	0.47		[133]
Liver Transplant (1st Year)	0.71		[133]
Post Liver Transplant	0.80		[133]
Hepatectomy (1st Year)	0.75	0.70 - 0.80	Assumed
Post Hepatectomy	0.85	0.80 - 0.90	Assumed

Table 5: Direct Costs and Health Outcomes of Screening and Vaccination Strategies in a Cohort of 100,000 Immigrants

Strategy [a]	**Average Cost per person**	**Hepatitis B-related deaths**	**Deaths Prevented**	**Average Effectiveness (QALY)**	**Incremental Cost per QALY gained, compared to Status Quo**	**Incremental Cost per QALY gained, compared to next least costly strategy**
Status Quo	$148,799	3,029.126	…	24.68629	…	…
Screen for Immunity and Vaccinate	$152,399	3,027.273	1.853	24.78067	$38,139	Excluded by Extended Dominance
Universal Vaccination	$152,401	3,028.509	0.617	24.78070	$38,157	Excluded by Extended Dominance
HBsAg Screen and Treat	$152,527	2,697.034	332.092	24.78524	$37,675	$37,675 [b]
Screen for both, Treat and Vaccinate	$152,566	2,695.881	333.245	24.78530	$38,051	$698,844 [c]

[a] Ranked from least costly to most costly.

[b] Compared with Status Quo (No Screening or Vaccination) strategy.

[c] Compared with HBsAg Screen and Treat strategy.

Table 6: Direct and Indirect Costs and Health Outcomes from a Societal Perspective for Hepatitis B Health Interventions

Strategy [a]	**Average Societal Costs per person**	**Average Total Cost per person**	**Average Effectiveness (QALY)**	**Incremental Cost per QALY gained, compared to Status Quo**	**Incremental Cost per QALY gained, compared to next least costly strategy**
Status Quo	$16,374	$165,173	24.68629	…	…
HBsAg Screen and Treat	$13,287	$165,814	24.78067	$6,478	$6,478 [b]
Screen for Immunity and Vaccinate	$13,437	$165,836	24.78070	$7,028	Dominated
Universal Vaccination	$13,438	$165,839	24.78524	$6,727	Dominated
Screen for both, Treat and Vaccinate	$13,286	$165,852	24.78530	$6,858	$671,551 [c]

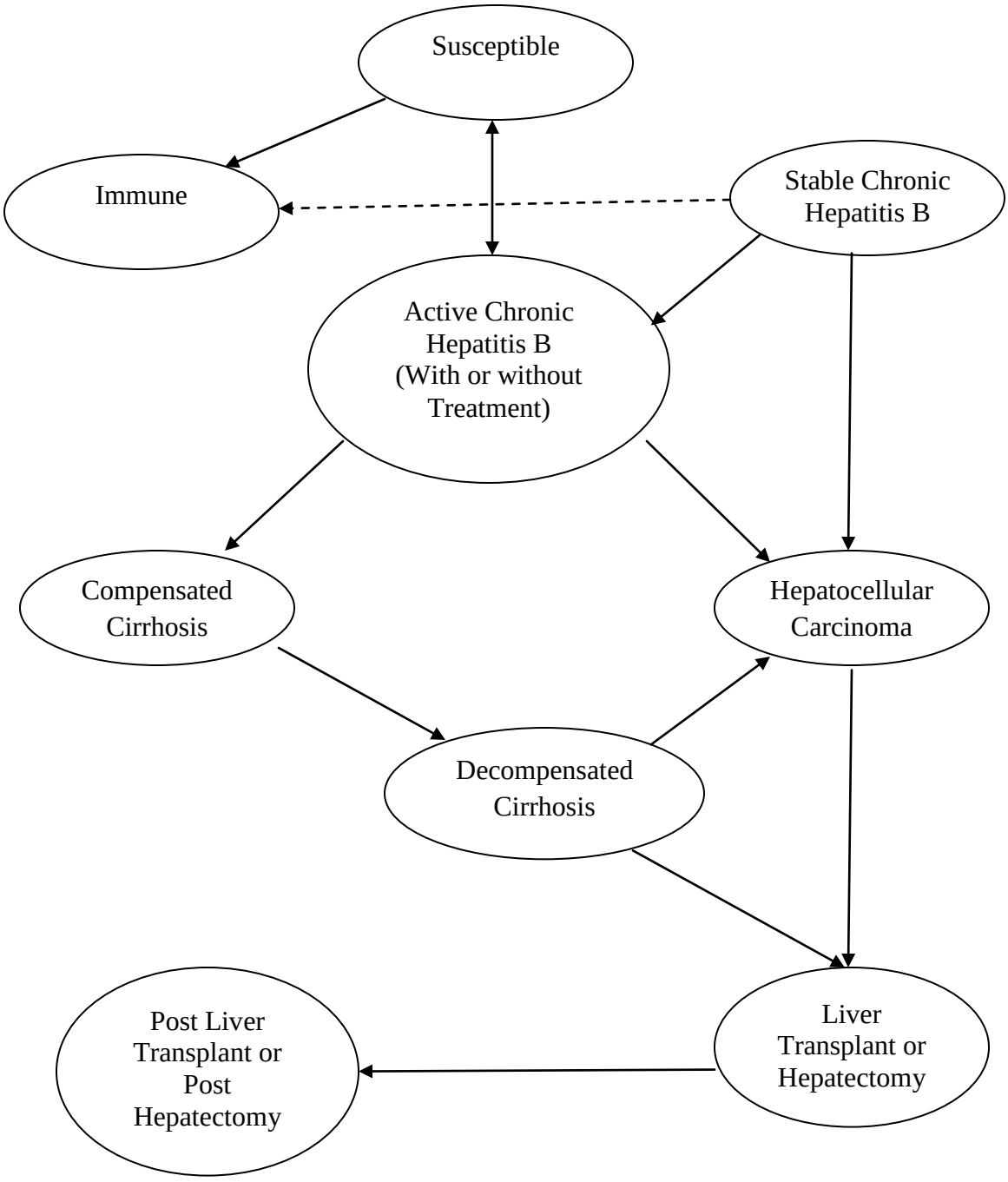
[a] Ranked from least costly to most costly.

[b] Compared with Status Quo (No Screening or Vaccination) strategy.

[c] Compared with HBsAg Screen and Treat strategy.

Figures:

Figure 1: Markov Model Representing the Natural History of Hepatitis B*



* All states can transition to the death state

Figure 2: Cost-Effectiveness Plane for all the Screening and/or Vaccination Strategies

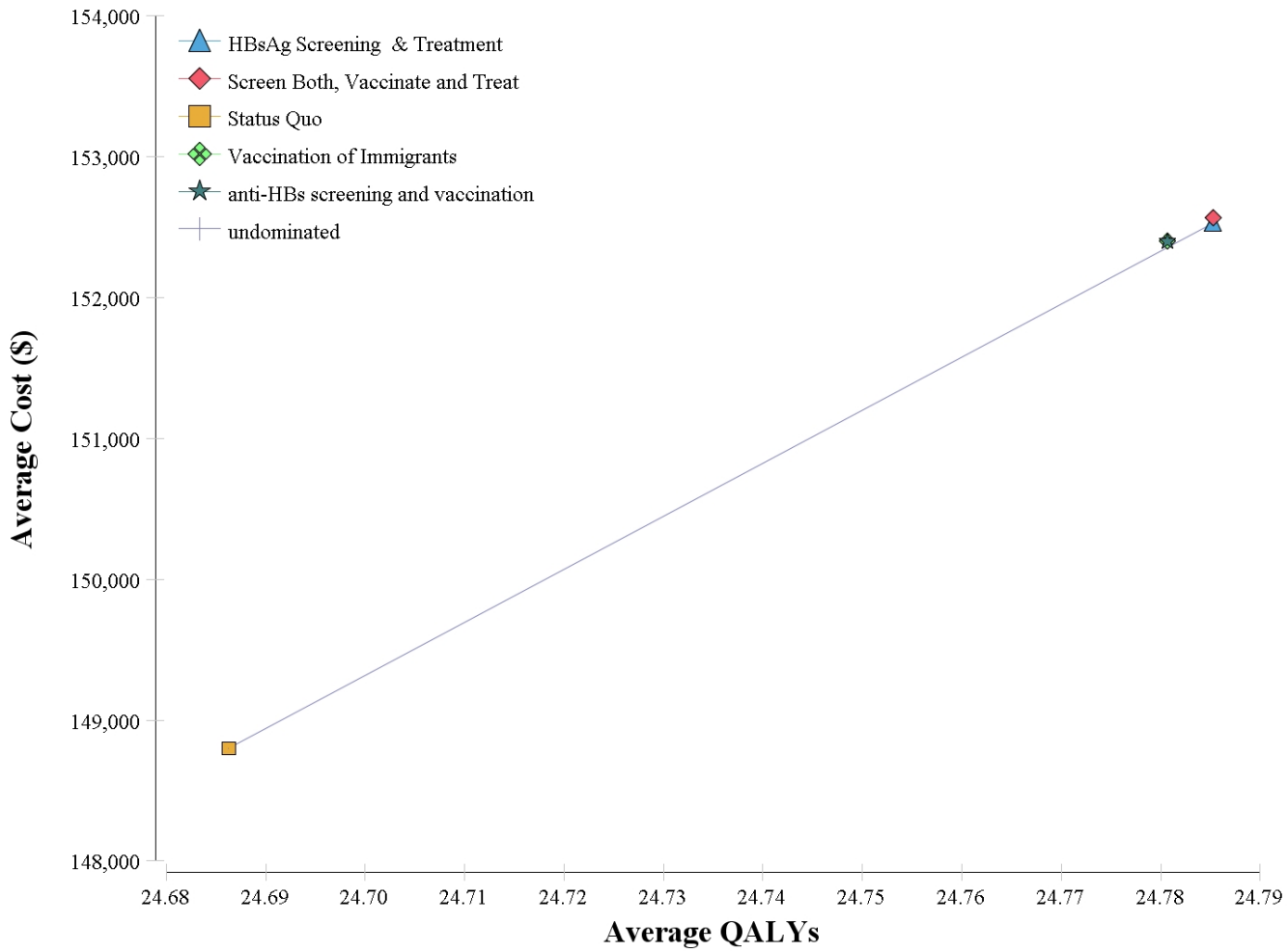


Figure 3: Two-Way Sensitivity Analyses for HBV Treatment Efficacy and Treatment Costs on the Screen and Treat Strategy, compared to the Status Quo

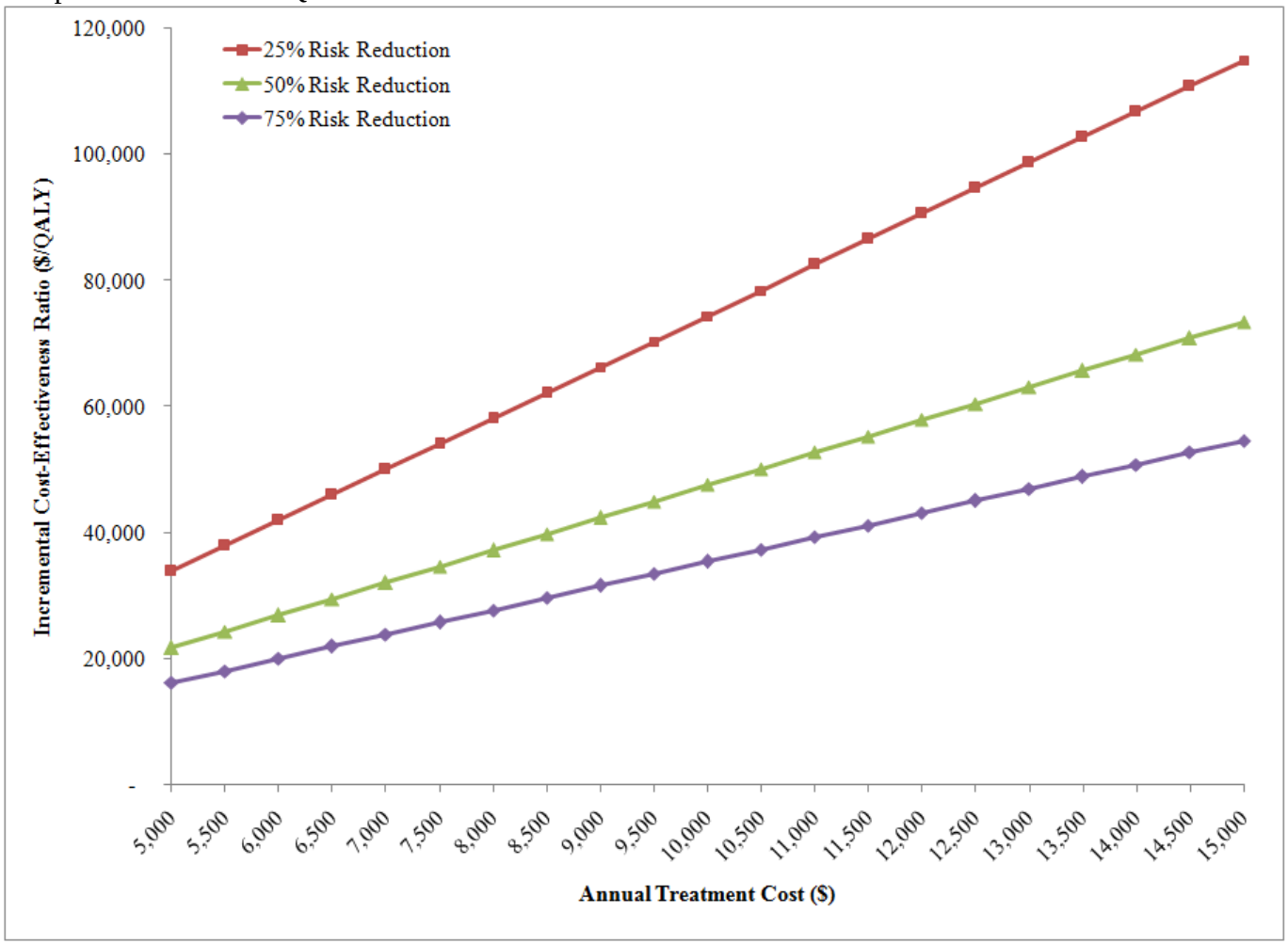


Figure 4: Tornado Diagram for One-Way Sensitivity Analyses for the Screen and Treat Strategy

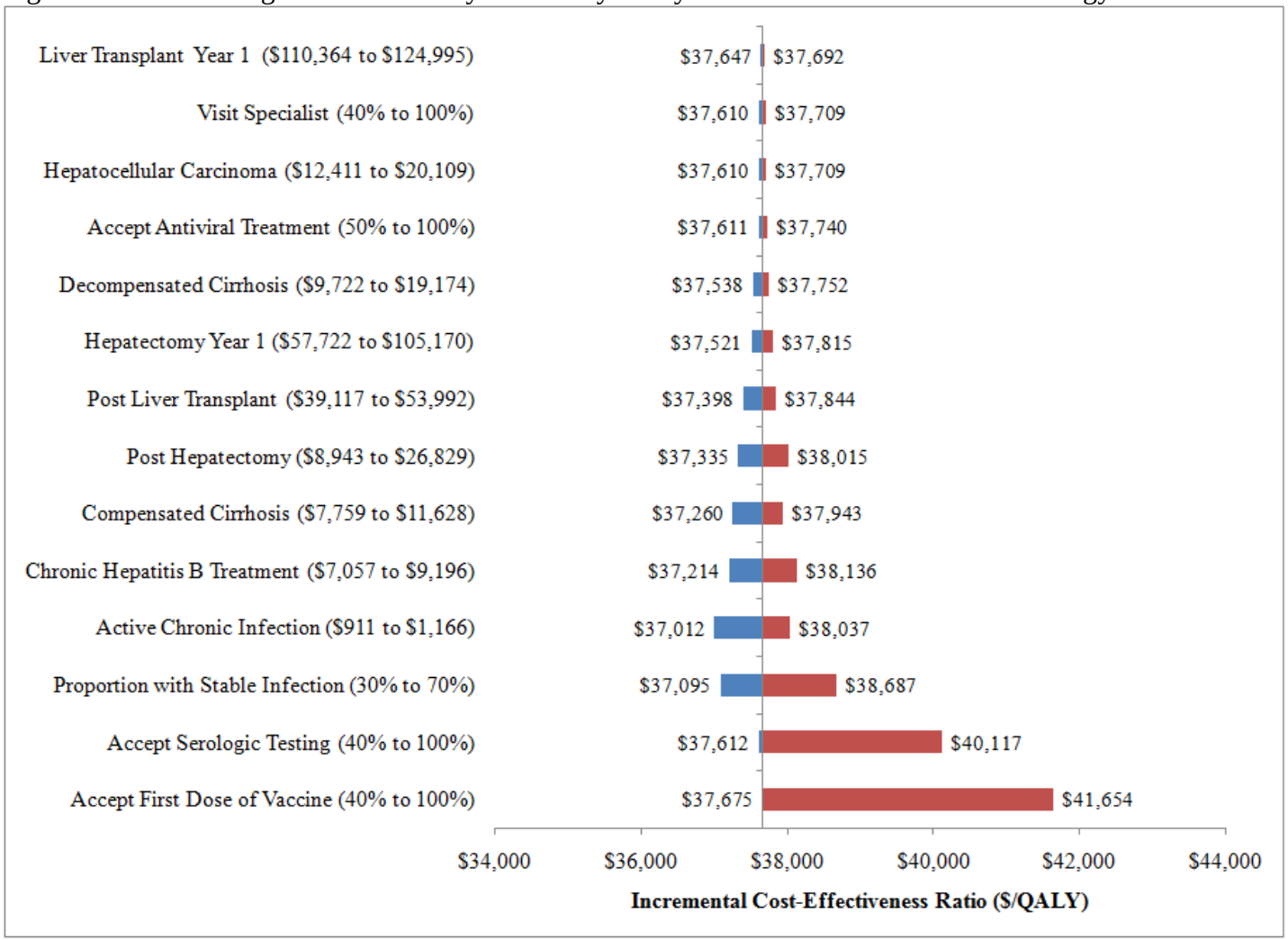
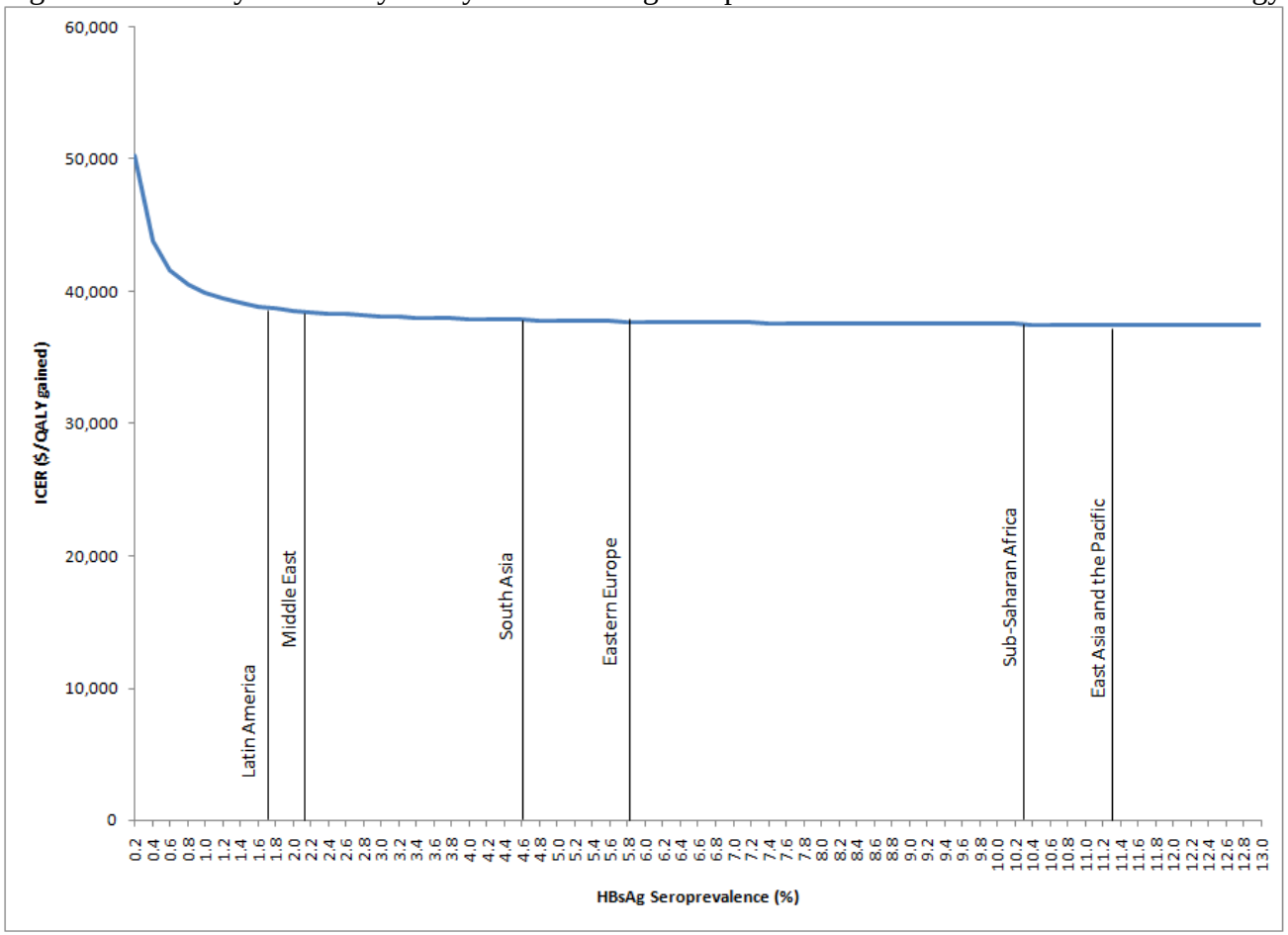
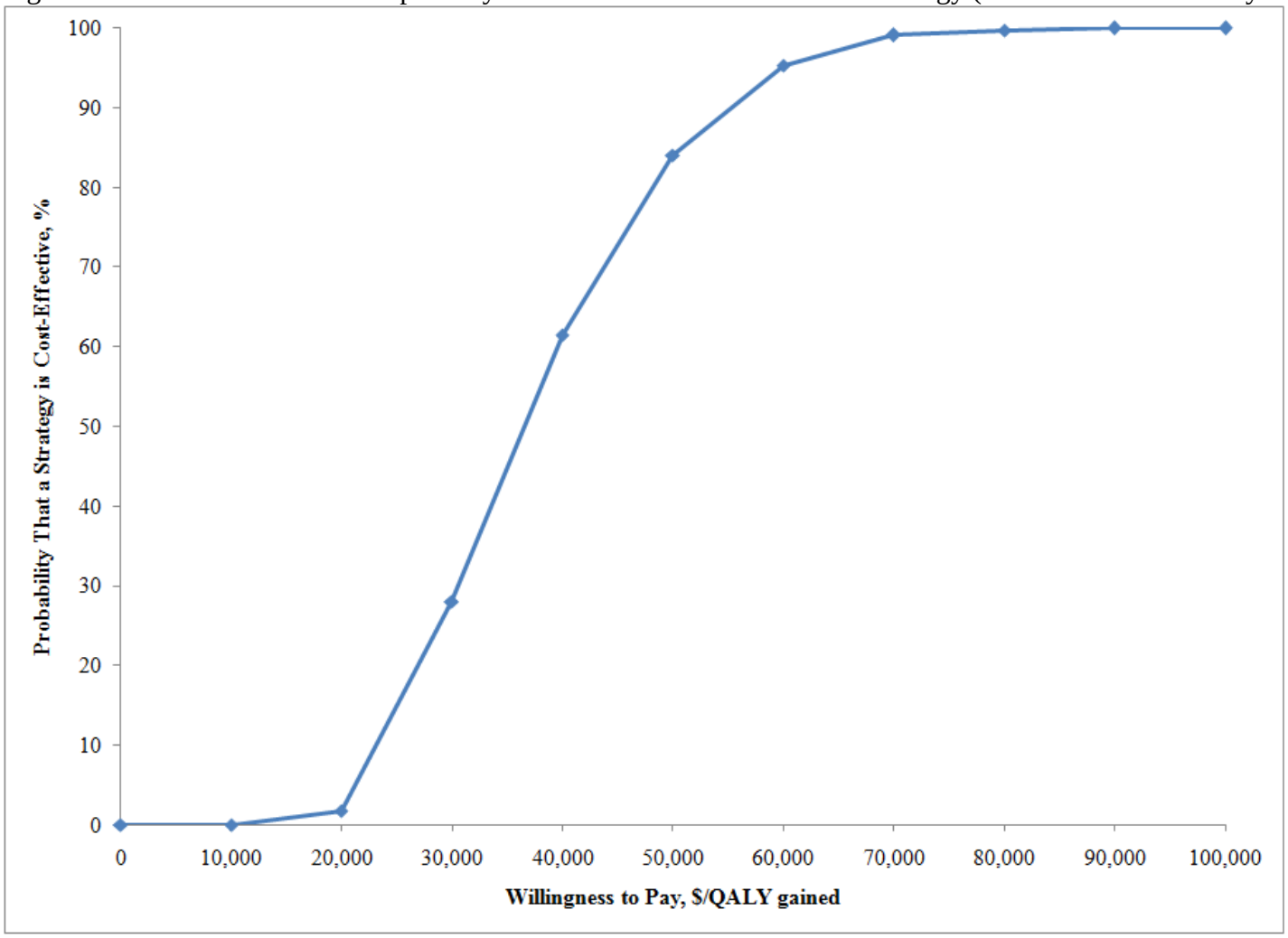


Figure 5: One-Way Sensitivity Analysis for HBsAg Seroprevalence on the Screen and Treat Strategy



* Vertical bars denote the estimated HBsAg seroprevalence in immigrants from noted regions (Source: Manuscript #1 – Table 3)

Figure 6: Cost-Effectiveness Acceptability Curve for the Screen and Treat Strategy (Probabilistic Sensitivity Analysis)



CHAPTER 5: Discussion

5.1 Summary of Results

In order to address the first objective of determining the burden of HBV infection among immigrants and refugees, a systematic review was performed to identify seroprevalence surveys reporting the proportion of migrants who were positive for serologic markers of infection and immunity. The seroprevalence of HBV infection in international migrants was found to parallel the estimated seroprevalence in the migrants' region of origin. The seroprevalence of immunity was highest in those regions where the prevalence of infection was high, namely East Asia and Sub-Saharan Africa. Using a random-effects logistic model, we found that region of origin was the strongest predictor of infection, after adjusting for immigrant status and decade of study. Furthermore, refugees were found to have a significantly greater risk of infection, compared to immigrants, in the adjusted regression model. After incorporating national census data from immigrant-receiving countries, it was estimated that nearly 3.5 million immigrants and refugees are chronically infected with HBV.

To determine how cost-effective several interventions involving screening and/or vaccination would be in reducing morbidity and mortality from HBV, a decision-analysis tree, with a Markov model to simulate liver disease progression, was developed. The decision-analysis model estimated that screening for chronic HBV infection in adult immigrants would reduce mortality from liver disease by 11% and would be cost-effective, relative to no targeted intervention in this population. Universal vaccination or screening for prior immunity before

vaccination would not be cost-effective in this population because the cost associated with preventing a small number of new infections in adults was outweighed by the cost of immunizing a large population and the cost of existing untreated chronic HBV infections. The strategy of screening for chronic HBV remained cost-effective in populations that had both low and high risk of chronic infection, suggesting that the strategy can be applied to new arrivals from many different regions of origin.

5.2 Public Health Implications

The research presented in this thesis was performed at a time when policy makers and public health officials are beginning a new era for hepatitis control.[120] Preventative tools to control transmission, such as vaccination, and antiviral therapy that can reduce progression to chronic liver disease, are available and can contribute to reducing morbidity and mortality from HBV. Unfortunately, however, inadequate capacity to deliver these interventions has prevented the realization of hepatitis disease control, even in developed countries.

There are three major barriers related to increasing the number of immigrants who receive serologic testing and immunization for HBV. First, there exists a need to improve knowledge and awareness related to HBV among primary-care practitioners. In a Canadian survey among family medicine trainees, only 54% of respondents indicated that they would recommend vaccination to susceptible individuals and 27% indicated that they believed immigrants from HBV-endemic countries do not require screening.[118] These knowledge gaps in primary prevention practices may contribute to an under-diagnosis of chronic HBV and decrease the

uptake of immunization within this high-risk population. The development of accessible and simplified guidelines and electronic resources for management of high-risk patients for HBV may be useful to increase awareness among practitioners who work with foreign-born patients in Canada.

Second, surveys of immigrant populations have shown less than optimal levels of awareness and knowledge regarding HBV, its modes of transmissions, and the interventions available to prevent the acquisition of the infection and the availability of treatment to prevent liver disease from developing.[68,69,163] As a result, only a small proportion of immigrants have reported ever being screened for the infection and an even smaller proportion has reported receiving at least one dose of the vaccine after arriving in Canada or the United States. Studies of East Asian immigrants residing in North America have suggested that there exist both social and structural barriers that prevent receiving screening and vaccination and access to health care for chronic HBV.[84,164] These barriers include stigmatization, fear of a positive result, inability to communicate with service providers, and the failure to recognize the need to be tested, if they are feeling well. To improve access to screening and vaccination in this community, awareness about the infection needs to be increased and barriers have to be overcome to reduce fear and stigmatization and improve patient-provider communication.

Lastly, there are no existing targeted screening programs or formal policies in place that can identify immigrants and refugees and provide them access to the available health interventions for HBV. In Canada, as part of the Immigration Medical Examination, immigrants and refugees are screened for TB, syphilis, and

HIV, prior to arrival. Although initially mandated to identify migrants who would place excessive strain on the Canadian health care system, this formal medical assessment of migrants provides an opportunity to offer health promotion and preventative activities, such as contact with health officials after arrival for treatment, follow-up or vaccination. These types of activities are already being provided to HIV-positive migrants who after screening are referred to medical officials for treatment and counseling.[165] A health policy review found that Canadian immigrants who were identified to be HIV-positive through the IME had treatment adherence rates comparable to Canadian-born HIV patients and demonstrated the success of health promotion activities for persons diagnosed with HIV during the IME.[6]

Recently, the National Collaborating Centre for Methods and Tools released a background paper highlighting evidence-based guidelines to inform decision makers with regards to public health policy and program delivery.[166] These guidelines promote the use of systematic reviews to identify, appraise and synthesize available information to answer a research question. Furthermore, the guidelines also promote the use of economic evaluations, as they bring together information from different areas, such as health economics and epidemiology, and incorporate various public health and epidemiological concepts, such as intervention compliance, natural history of diseases, and health-care system and societal costs. The research presented in this thesis followed this evidence-based and multidisciplinary approach to public health research, as we used a systematic review to synthesize available information on HBV infection and immunity and

incorporated this information into a cost-effectiveness model that examined the public health impacts of screening and vaccination interventions in a population of newly-arriving immigrants to Canada.

The IME provides an opportunity for serologic testing for HBV in an entire cohort of newly arriving immigrants and refugees. Every year, nearly 250,000 new permanent residents are admitted into Canada, and at least 6% are estimated to be chronically infected with HBV. Screening migrants for HBV during the immigration process can inform migrants about their infection status and immigration officials can direct immigrants to resources where they can receive the necessary treatment, care and counseling for their chronic hepatitis B infection. Targeted screening may also improve awareness within the community, minimize transmission to susceptible individuals and reduce barriers to care.[64]

5.3 Directions for Future Research

The public health interventions for HBV examined in this thesis focused solely on adult migrants. Future economic evaluations of HBV interventions may wish to consider immunization strategies for immigrant children who have still not reached the age for the school-based universal immunization program. In addition, cost-effectiveness studies can also be considered for vaccinating infants at birth, who were born to foreign-born parents from HBV-endemic countries. The epidemiology of HBV is different in children, because unlike adults, acute infections in infants are more likely to progress to chronic infection and infants are also at an elevated risk of being exposed to the virus if family members or close contacts are chronically infected.

Future research may also examine the cost-effectiveness of population-based screening for HCC in the general immigrant population, or among those immigrants who are known to be chronically infected, with alpha-fetoprotein or liver ultrasound. Screening can be performed at different ages, as liver cancer in immigrants may occur as much as two decades earlier than in native-born liver cancer patients.[17] Conducting further modeling on specific health interventions can help inform policy makers about which strategies are cost-effective and worth promoting to reduce morbidity and mortality from chronic HBV infection.

CHAPTER 6: Conclusion

The prevalence of chronic HBV infection is notably higher among foreign-born migrants residing in traditional immigrant-receiving countries, than among the native-born population. HBsAg seroprevalence was highest among immigrant and refugees from East Asia and Sub-Saharan Africa, where the seroprevalence of infection exceeded 10%. Nearly half of all migrants lacked protective antibodies to HBV. These findings suggest that interventions such as screening and vaccination can be effective in reducing morbidity and mortality because they would be able to identify a large number of chronically infected migrants and immunize an even greater number of susceptible migrants.

When the cost-effectiveness of these interventions was explored among adult immigrants in Canada, the Screen and Treat strategy was found to be the most cost-effective, while the vaccination interventions were either dominated or prohibitively expensive. Screening immigrants for chronic HBV infection has been recommended by both the CCIRH and the CDC, as this intervention can reduce morbidity and mortality by identifying chronically infected individuals and providing them with effective antiviral therapy. We would recommend that public health agencies and medical associations in Canada promote screening for chronic HBV infections in all new immigrants and promote activities designed to increase awareness of chronic HBV and liver disease among both the general immigrant community and public health and health-care professionals.

Immigrants are becoming an increasingly important component of Canadian society. Interventions designed to indentify immigrants and refugees with chronic

HBV will help reduce the burden of infection in immigrant communities, improve their quality of life, and eliminate health disparities between Canadian-born and foreign-born populations.

Appendices

Appendix 1: Data Extraction Form

Part 1: COVERSHEET

1) Study number: _____

2) Data extracted by: _____

3) Date extraction completed:
YYYY/MM/DD

4) Article title: _____

5) First author (Last Name): _____

6) Journal name: _____

7) Publication year: _____

8) a) Author contacted ☐ Yes ☐ No
b) If Yes. Date contacted:
YYYY/MM/DD
c) If Yes: Author e-mail:

9) a) Final status ☐ Included ☐ Excluded
b) Reason for exclusion:

10) Notes: _____

Part 2: STUDY POPULATION CHARACTERISTICS

11a) Type of publication:
☐ Peer-reviewed paper
☐ Unpublished report
☐ Other

11b) If "Other publication type" then other is: _____

12a) Start date of study: _____
YYYY/MM/DD

12b) End date of study: _____
YYYY/MM/DD

13a) Country of Study: _____

13b) City (if applicable):_____

14a) Study design:
☐ Ecologic
☐ Cross-sectional
☐ Case-control

☐ Prospective cohort
☐ Retrospective cohort
☐ Case-Series
☐ Other

14b) If "Other study design" then other is:_____

15a) What gender is being studied?
☐ Male
☐ Female
☐ Both
☐ Not mentioned

15b) What proportion of the study population is male? _____
15c) Are pregnant females included? ☐ Yes ☐ No ☐ Not specified
15d) If yes, then what proportion of females are pregnant?_____

16a) Exclusive category of Immigration status of study participants:
☐ Immigrant ☐ Refugee
☐ Asylum Seeker ☐ Foreign born
☐ Mixed ☐ Other
☐ Adopted children ☐ Not Mentioned

16b) If "Other exclusive category of immigration status" then other is:_____

16c) If immigration status is mixed then the included categories are:

c1)	Immigrant	☐ Yes	☐ No
c2)	Refugee	☐ Yes	☐ No
c3)	Asylum Seeker	☐ Yes	☐ No
c4)	Foreign born	☐ Yes	☐ No
c5)	Other	☐ Yes	☐ No

16d) If "Other mixed category of immigration status" then other is:_____

17a) Age (years) of the screened population:
a1) Mean _____
a2) Median _____
a3) Range low: __
a4) Range high: _

17b) Is the outcome data stratified by age? ☐ Yes ☐ No ☐ Not specified

18a) Is the outcome data stratified by country of origin? ☐ Yes ☐ No

18b) Exclusive Country of Origin:
☐ Not mentioned
☐ Mixed
☐ Latin America and Caribbean
☐ Eastern Europe and Central Asia
☐ Middle East & North Africa
☐ Sub-Saharan Africa
☐ South Asia
☐ East Asia & Pacific
☐ Non-World Bank Region
☐ Other

18c) If "Other Exclusive Country of Origin", then other is:_____

19a) If Mixed Country of Origin the regions of origin are included?

a1)	Latin America and Caribbean	☐ Yes	☐ No
a2)	Eastern Europe and Central Asia	☐ Yes	☐ No
a3)	Middle East & North Africa	☐ Yes	☐ No
a4)	Sub-Saharan Africa	☐ Yes	☐ No
a5)	South Asia	☐ Yes	☐ No
a6)	East Asia & Pacific	☐ Yes	☐ No
a7)	Other/Unknown	☐ Yes	☐ No

19b) If "Other Mixed Country of Origin" then other is___

20) Does the underlying population have co morbidities or confounders?
☐ Yes ☐ No ☐ Not specified

21a) If yes, what Comorbidities/Confounders are present?

a1)	Tuberculosis	☐ Yes	☐ No
a2)	Intestinal Parasites	☐ Yes	☐ No
a3)	Malaria	☐ Yes	☐ No
a4)	Other Viral Hepatitis Infections	☐ Yes	☐ No
a5)	Other	☐ Yes	☐ No

21b) If "Other Comorbidities/ Confounders" then other is:_____

Part 3: Risk of Bias/Quality Assessment

A: SELECTION BIAS		
22. How was the recruitment of study participants carried out?	☐ Clinic or Hospital Based Screening ☐ Screening Upon Arrival or at a Receiving Centre ☐ Pregnant Women Screening ☐ Invited for Screening ☐ Other	
23. What was the non-response rate or drop-out rate?		
B: INFORMATION BIAS		
24. What was the testing method?	☐ ELISA or EIA ☐ Reverse passive hemagglutination (RPHA) ☐ Radioimmunoassay (RIA) ☐ Other ☐ Not specified	
25. Was testing done the same way in the entire study population?	☐ Yes ☐ No ☐ Unable to tell	
C: CONFOUDERS		
26. List the major confounders (HIV status, IV Drug use, Homelessness, MSM) adjusted in the analysis or design (i.e. by matching)?	*Confounder*	Analysis or Match
27. MOST IMPORTANT DESIGN FLAWS:		

PART 4: SEROPREVALENCE DATA

A) Hepatitis B Surface Antigen (HBsAg)

28) Number of participants screened_____
29) Number of participants positive _____

30) HBsAg Total Seroprevalence (29/28):_____

IF Mixed Country of Origin has stratified outcomes:

31) Latin America and Caribbean ☐ Yes ☐ No
- a1) Number of participants screened:_____
- a2) Number of participants positive: _____
- a3) HBsAg Seroprevalence: _____

32) Eastern Europe and Central Asia ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) HBsAg Seroprevalence: _____

33) Middle East & North Africa ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) HBsAg Seroprevalence: _____

34) Sub-Saharan Africa ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) HBsAg Seroprevalence: _____

35) South Asia ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) HBsAg Seroprevalence: _____

36) East Asia & Pacific ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) HBsAg Seroprevalence: _____

B) Immunity

39a) Study reports the seroprevalence of immunity ☐ Yes ☐ No
Defined as either the presence of Anti-HBs or the presence of both Anti-HBs and Anti-HBc

39b) Which type of immunity is being reported?
☐ Anti-HBs alone (vaccinated)
☐ Anti-HBs and Anti-HBc (Resolved infection)
☐ Any immunity
☐ Not specified

40) Number of participants screened_____

41) Number of participants immune _____

42) Total Seroprevalence of immunity (41/40):_____

IF Mixed Country of Origin has stratified outcomes:

43) Latin America and Caribbean ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) Seroprevalence of immunity: _____

44) Eastern Europe and Central Asia ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) Seroprevalence of immunity: _____

45) Middle East & North Africa ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) Seroprevalence of immunity: _____

46) Sub-Saharan Africa ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) Seroprevalence of immunity: _____

47) South Asia ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) Seroprevalence of immunity: _____

48) East Asia & Pacific ☐ Yes ☐ No
- a1) Number of participants screened: _____
- a2) Number of participants positive: _____
- a3) Seroprevalence of immunity: _____

Appendix 2: Supplemental Material for Manuscript #1

Table S1: Foreign-born Population by Region of Origin in Major Immigrant-Receiving Countries

	Report Year	Latin America and Caribbean	Eastern Europe and Central Asia	Middle East and North Africa	Sub-Saharan Africa	South Asia	East Asia and the Pacific	Total
North America								
Canada	2006[167]	698,935	712,825	413,450	252,645	755,445	1,438,045	**4,271,345**
United States	2009[168]	20,455,547	2,944,186	893,333	1,492,785	2,713,675	7,000,964	**35,500,490**
Europe								
Austria	2010[169]	18,017	839,271	45,691	21,222	26,972	41,955	**993,128**
Belgium	2011[170]	16,061	189,294	109,964	60,163	15,913	19,789	**411,184**
Czech Republic	2010[171]	1,793	304,057	4,843	2,028	2,037	75,356	**390,114**
Denmark	2009[172]	8,886	123,509	59,549	23,315	33,916	36,762	**285,937**
Finland	2011[173]	4,833	106,488	17,486	18,601	11,084	22,621	**181,113**
France	2006[174]	166,961	421,999	1,131,726	425,009	60,329	141,709	**2,347,733**
Germany	2010[175]	104,193	3,706,019	330,191	154,627	163,751	325,441	**4,784,222**
Greece	2001[176]	859	621,945	23,708	4,377	24,392	8,595	**683,876**
Israel	2008[177]	65,940	555,640	398,480	91,000	20,710	15,850	**1,147,620**
Italy	2010[178]	229,092	2,014,922	642,720	165,645	320,030	311,936	**3,684,345**
Netherlands	2011[179]	319,995	407,683	274,286	114,479	67,195	211,347	**1,394,985**
Norway	2011[180]	23,628	156,668	51,018	50,398	47,067	65,795	**394,574**
Portugal	2010[181]	125,161	123,261	3,040	106,161	9,700	17,953	**385,276**
Republic of Ireland	2006[182]	7,951	143,287	7,789	38,547	18,129	31,172	**246,875**
Spain	2007[183]	1,569,837	896,697	642,240	173,949	69,881	134,138	**3,486,742**
Sweden	2011[184]	74,709	377,986	261,144	95,757	55,601	100,373	**965,570**

Switzerland	2010[185]	48,501	455,968	40,642	52,818	51,115	42,179	**691,223**
United Kingdom	2001[186]	339,979	293,989	218,186	759,137	1,030,483	359,990	**3,001,764**
Oceania								
Australia	2006[187]	86,385	374,825	193,216	210,934	259,662	1,016,118	**2,141,140**
New Zealand	2006[188]	7,638	22,422	16,533	59,118	56,391	329,289	**491,391**

Tables S2: 110 Included Studies in Systematic Review

Source	Year of Study	Country of Landing	Region of Origin	Age range, y	Immigrant Status	Population Screened	HBsAg Seroprevalence (%)	anti-HBs Seroprevalence (%)
Adair et al, 1999[189]	1997	United States	Sub-Saharan		Immigrant	73	13.7	
Almog et al, 1999[190]	1992-1993	Israel	Eastern Europe	17-49	Immigrant	599	4.8	19.2
Arevalo et al, 1989[191]	1983-1987	United States	Mixed	(Median: 26)	Immigrant	277	8.3	
Aubert et al, 2010[192]	2007-2008	France	Mixed	18-88 (Mean: 40)	Immigrant	481	9.4	64.7
Aweis et al, 2001[193]	2000	United Kingdom	Sub-Saharan	1-80	Immigrant	317	7.3	
Baldo et al, 2000[194]	1996	Italy	Mixed	18-43 (Mean: 28)	Immigrant	255	3.1	
Barry et al, 1983[195]	1979-1980	United States	East Asia & Pacific		Refugee	83	15.7	56.6
Beggio et al, 2007[196]		Italy	Mixed		Immigrant	199	4.0	32.2
Ben-Porath et al, 1986[197]		Israel	Sub-Saharan		Refugee	357	12.6	44.8
Bjerke et al, 2011[198]	2009	Norway	South Asia	18-44 (Mean: 27.3)	Immigrant	206	0.5	7.8
Bonura et al, 2005[199]	2001-2003	Italy	Mixed	18-44 (Mean: 30)	Immigrant	310	4.2	
Bottecchia et al, 2011[200]	2007-2008	Spain	Mixed	(Median: 51.5)	Immigrant	1,718	7.0	
Caruana et al, 2005[201]		Australia	East Asia & Pacific	15-92 (Median: 44)	Mixed	327	8.6	76.5
Catanzaro et al, 1982[202]	1980-1981	United States	East Asia &Pacific		Refugee	301	14.0	
CDC, 2006[203]	2005	United States	Mixed	20-83 (Median: 45)	Immigrant	915	11.7	
CDC, 1991[204]	1979-1991	United States	Mixed		Refugee	36,812	15.0	

Chadwick et al, 1982[205]		United Kingdom	East Asia & Pacific		Refugee	632	15.0	
Chaudhary et al, 1981[48]	1979-1980	Canada	East Asia & Pacific		Refugee	14,347	11.6	48.9
Chaves et al, 2009[206]	2004-2008	Australia	East Asia & Pacific	16-86 (Median: 30)	Refugee	141	14.2	
Chemtob et al, 1991[207]	1987	Israel	Sub-Saharan	2-67 (Mean: 23)	Refugee	144	18.8	41.7
Chiaramonte et al, 1998[208]	1989-1995	Italy	Mixed	0-76 (Mean: 28.5)	Immigrant	1,683	8.9	
Chironna et al, 2003[209]	2000	Italy	Mixed	1-55 (Mean: 24)	Refugee	1,005	3.9	
Chironna et al, 2000[210]		Italy	Eastern Europe	2-72 (Mean: 25)	Refugee	670	13.6	47.6
Chironna et al, 2001[211]	1999	Italy	Eastern Europe	2-72 (Mean: 13)	Refugee	526	2.9	12.0
Christenson et al, 1997[212]		Sweden	Mixed		Immigrant	133	1.5	
Dalekos et al, 1995[91]		Greece	Eastern Europe	0-81	Refugee	1,025	22.1	40.5
Denburg et al, 2007[213]	2006	Canada	East Asia & Pacific		Refugee	64	14.1	43.8
Denis et al, 1994[214]	1992-1993	France	Mixed		Immigrant	5,125	2.5	
Elefsiniotis et al, 2007[215]	2003-2005	Greece	Mixed	16-45	Immigrant	8,698	3.5	
Engebretsen et al, 1984[216]	1981-1983	United States	East Asia &Pacific		Refugee	552	11.8	
Entzel et al, 2003[217]	1999-2000	United States	Latin America	0-6 (Mean: 3.5)	Refugee (Children)	244	0.4	
Fabris et al, 2008[218]		Italy	Mixed	(Mean: 27.7)	Immigrant	47	6.4	
Faustini et al, 1994[219]	1991	Italy	Mixed	1-67 (Mean: 24)	Immigrant	138	5.1	27.8
Fitzpatrick et al,	1981-1985	United States	East Asia &	11-19 (Mean:	Refugee	74	13.5	

1987[220]			Pacific	14.7)	(Children)			
Flatau et al, 1993[221]	1991	Israel	Sub-Saharan	1-76 (Mean: 29)	Refugee	200	11.5	47.1
Franco-Paredes et al, 2007[222]	2005-2006	United States	Sub-Saharan	(Mean: 25)	Refugee	31	32.3	
Friedman et al, 1998[223]	1984-1985	United States	Mixed	14-44 (Mean: 26)	Immigrant	288	5.9	
Garcia-Samaniego et al, 1994[224]	1992-1993	Spain	Sub-Saharan	16-53 (Mean: 31.4)	Immigrant	435	20.7	
Germinario et al, 2000[225]		Italy	Eastern Europe	0-10	Refugee (Children)	415	0.5	
Gish et al, 2011[226]		United States	East Asia & Pacific		Immigrant	1,798	6.0	54.0
Gjerdingen et al, 1997[227]	1994-1995	United States	East Asia & Pacific	(Mean: 27.7)	Refugee	429	17.9	42.2
Gjorup et al, 2003[228]	1994-1995	Denmark	Mixed	5-19	Immigrant (Children)	144	2.1	
Glikberg et al, 1997[229]		Israel	Eastern Europe		Immigrant	102	15.7	
Goldenring et al, 1983[230]	1979-1982	United States	East Asia & Pacific	(Mean: 19.5)	Immigrant (Children)	89	16.9	
Goodman et al, 1984[231]	1980-1981	United States	East Asia & Pacific		Refugee	849	11.7	55.5
Hayes et al, 1998[232]	1994	United States	Mixed		Refugee	124	4.0	21.1
Hill et al, 1991[233]		United States	East Asia & Pacific		Refugee	679	17.4	
Hornstein et al, 1991[234]	1985-1988	Israel	Sub-Saharan		Refugee	224	16.5	47.2
Huerga et al, 2002[235]	1989-2001	Spain	Sub-Saharan	0-13 (Mean: 7)	Immigrant (Children)	75	6.7	32.0
Hurie et al, 1995[236]	1990-1993	United States	Eastern Europe		Refugee	496	0.4	
Hurie et al, 1992[237]	1984-1989	United States	East Asia &	0-75 (Mean:	Refugee	754	18.7	45.1

			Pacific	22.6)				
Jenista et al, 1987[238]		United States	Mixed		Adopted Children	68	5.9	
Jensen et al, 2003[239]	2000-2001	Denmark	Mixed		Immigrant	1,010	1.7	
Judson et al, 1984[240]	1981-1982	United States	East Asia & Pacific		Refugee	516	14.7	
King et al, 2001[241]	2000-2001	Australia	Mixed		Asylum Seeker	7,000	2.5	
Kulstrunk et al, 1992[242]		Switzerland	Eastern Europe	0-53	Refugee	1,299	9.1	46.8
Lange et al, 1987[243]	1985-1986	United States	East Asia & Pacific	0.2-12	Adopted Children	360	2.8	3.4
Levinne et al, 1980[244]	1979	Canada	East Asia & Pacific		Refugee	192	10.9	
Levy et al, 2010[245]		United States	Mixed	(Median: 24)	Immigrant	701	0.6	
Lifson et al, 2002[90]	1999	United States	Mixed	(Mean: 23)	Refugee	2,353	7.4	36.7
Lin et al, 2007[65]	2001-2006	United States	East Asia & Pacific	18-101 (Median: 53)	Immigrant	2,386	10.7	
Lopez-Velez et al, 2003[246]	1989-1999	Spain	Mixed	0-82 (Median: 28)	Mixed	662	7.1	
Majori et al, 2008[247]	2004-2005	Italy	Sub-Saharan	0-60 (Mean: 31.7)	Illegal Immigrant	182	9.3	39.6
Malamitsi-Puchner et al, 1996[248]		Greece	Eastern Europe	14-42 (Mean: 25.1)	Refugee	500	13.4	53.0
Manzardo et al, 2008[249]	2001-2004	Spain	Mixed	0-80 (Mean: 29.5)	Mixed	1,905	7.7	
Martin et al, 2006[250]	2003-2004	Australia	Mixed	0-89	Refugee	1,974	5.4	
Meints et al, 2010[251]	2003-2006	United States	Mixed		Immigrant	1,685	3.1	
Meropol, 1995[252]	1991-1993	United States	Mixed	1-18 (Median: 8.2)	Refugee (Children)	81	7.4	43.2
Milionis, 2010[253]	2000-2009	Greece	Eastern Europe	10-23 (Mean:	Immigrant	504	11.7	35.1

				15.6)	(Children)			
Museru et al, 2010[254]	2003-2007	United States	Mixed		Refugee	6,347	10.7	
Museru et al, 2009[255]	2005-2008	United States	Sub-Saharan	16-48 (Mean: 28)	Refugee	74	23.0	
Nahmias et al, 1993[256]	1978-1991	Israel	Sub-Saharan		Refugee	6,230	11.5	
Nelson et al, 1997[257]	1994-1995	United States	East Asia & Pacific	19-71 (Median: 34)	Immigrant	96	13.5	49.0
Ooi et al, 2006[258]	1999-2002	United States	Mixed	(Mean: 39)	Immigrant	209	1.9	20.0
Palumbo et al, 2007(a)[259]	2005	Italy	Mixed	15-47 (Mean: 22.6)	Refugee	556	10.8	
Palumbo et al, 2007(b)[260]	2005-2006	Italy	Latin America	15-43 (Mean: 21.3)	Refugee	130	10.8	
Palumbo et al, 2008[261]	2003-2004	Italy	Mixed	15-39 (Mean: 24)	Refugee	890	9.3	
Panagopoulouset al, 2004[262]	1994-2002	Greece	Mixed		Immigrant	3,017	4.7	
Papaevangelou et al, 2006[263]	2003	Greece	Mixed		Immigrant	596	8.2	
Parenti et al, 1987[264]	1980-1984	United States	Sub-Saharan	0-55	Refugee	53	9.4	
Patel et al, 2002[265]	1991-1999	United States	East Asia & Pacific		Immigrant	743	13.9	
Perez-Molina et al, 2011[266]	1989-2008	Spain	Mixed	(Mean: 31.5)	Immigrant	322	10.6	
Pottie et al, 2007[49]	2004-2005	Canada	Mixed		Refugee	112	5.4	
Ranger et al, 1990[267]	1984-1988	France	Mixed	13-47 (Mean: 28)	Immigrant	1,206	2.6	
Rein et al, 2010[268]	2006-2008	United States	Mixed		Refugee	31,980	2.8	
Roberts et al, 1985[269]	1980-1982	United States	East Asia & Pacific	16-51 (Mean: 25.3)	Refugee	97	5.2	
Roudot-Thoraval et		France	Mixed	16-44 (Mean:	Immigrant	628	3.0	

al, 1989[270]				26)				
Roussos et al, 2003[271]		Greece	Mixed	18-69 (Mean: 31.7)	Refugee	130	15.4	
Saiman et al, 2001[272]	1997-1998	United States	Mixed	0-12 (Mean: 1.6)	Adopted Children	499	2.8	35.1
Salleras et al, 2009[273]	2004	Spain	Mixed		Immigrant	114	0.9	
Sandler et al, 1977[274]		Israel	Middle East		Immigrant	414	1.2	28.9
Santantonio et al, 1993[275]	1991	Italy	Eastern Europe	1-46 (Mean: 20)	Refugee	393	19.1	37.2
Sheikh et al, 2009[276]	2005-2006	Australia	Mixed	1-17	Refugee (Children)	218	3.2	
Skinhoj et al, 1981[277]	1979	Denmark	East Asia &Pacific		Refugee	564	10.5	
Skinhoj et al, 1983[278]	1979-1980	Denmark	East Asia & Pacific		Refugee	533	10.3	
Skliros et al, 2001[279]		Greece	Eastern Europe	(Mean: 31.6)	Refugee	154	7.1	
Skliros et al, 1999[280]		Greece	Eastern Europe	1-75	Refugee	188	9.0	
Smith et al, 2000[281]	1999	Ireland	Eastern Europe		Refugee	919	2.8	
Smith et al, 1984[282]		Australia	East Asia & Pacific		Refugee	108	13.0	46.3
Smith-Garcia et al, 1989[283]	1978-1987	United States	South Asia	0-20	Adopted Children	76	6.6	
Stadler et al, 2008[284]	1999-2006	United States	Mixed	0-16 (Mean: 2.2)	Adopted Children	1,228	1.1	67.2
Stroffolini et al, 2003[285]		Italy	Mixed		Immigrant	597	5.9	
Tafuri et al, 2010[286]	2008	Italy	Mixed	7-52 (Mean: 23.9)	Refugee	529	8.3	
Tiong et al, 2006[287]	2005-2006	Australia	Sub-Saharan		Refugee	184	8.2	
Tong et al, 1984[288]	1982	United States	East Asia & Pacific	(Mean: 52)	Immigrant	243	13.6	56.4

Toro et al, 2006[289]	2002-2003	Spain	Mixed	0-89 (Median: 29.5)	Immigrant	486	5.3	
Ugwu et al, 2008[290]	1998-2001	United States	Mixed	(Median: 19)	Refugee	8,754	7.1	31.1
van Steenbergen et al, 2001[291]	1993-1998	Netherlands	Mixed		Immigrant	30,937	2.2	
Veldhuijzen et al, 2008[292]	2004	Netherlands	Mixed	18-65	Immigrant	205	1.0	
Viviano et al, 2006[293]	2002-2005	Italy	Eastern Europe	1-12 (Mean: 6.3)	Adopted Children	75	4.0	41.3

Table S3: Random-Effects Logistic Regression Models with Interaction Terms

Model	Coefficient	SE	95% CI	Odds Ratio	95% CI
INTERACTION BETWEEN IMMIGRANT STATUS AND REGION OF ORIGIN					
Intercept	-4.0208	0.16986	(-4.35, -3.69)		
Refugee	0.04260	0.21668	(-0.38, 0.47)	1.04	(0.68, 1.60)
Eastern Europe	1.10305	0.11377	(0.88, 1.32)	3.01	(2.41, 3.77)
Middle East	0.25069	0.11764	(0.02, 0.48)	1.28	(1.02, 1.62)
Sub-Saharan Afr.	1.81121	0.11679	(1.58, 2.04)	6.12	(4.87, 7.69)
South Asia	-0.08776	0.66958	(-1.40, 1.22)	0.92	(0.25, 3.40)
East Asia	1.78579	0.13355	(1.52, 2.05)	5.96	(4.59, 7.72)
Ref:East Europe	-0.45038	0.15464	(-0.75, -0.15)	0.64	(0.47, 0.86)
Ref: Middle Eas	0.01833	0.17389	(-0.32, 0.36)	1.02	(0.72, 1.43)
Ref: Sub-Sahar	0.13887	0.14810	(-0.15, 0.43)	1.15	(0.86, 1.54)
Ref:South Asia	1.57331	0.69037	(0.22, 2.93)	4.82	(1.25, 18.9)
Ref:East Asia	0.67054	0.15800	(0.36, 0.98)	1.96	(1.43, 2.67)
INTERACTION BETWEEN IMMIGRANT STATUS AND DECADE					
Intercept	-2.9758	0.2809	(-3.53, -2.43)		
Refugee	1.0254	0.3349	(0.37, 1.68)	2.79	(1.45, 5.38)
Year 1990s	0.4798	0.3746	(-0.25, 1.21)	1.62	(0.78, 3.37)
Year 2000s	-0.0188	0.3652	(-0.73, 0.70)	0.98	(0.48, 2.01)
Ref:Year1990s	-0.9583	0.4743	(-1.89, -0.03)	0.38	(0.15, 0.97)
Ref:Year2000s	-0.6209	0.4491	(-1.50, 0.26)	0.54	(0.22, 1.30)
INTERACTION BETWEEN DECADE AND REGION OF ORIGIN					
Intercept	-3.54279	0.45113	(-4.43, -2.66)		
Eastern Europe	-0.56751	0.45804	(-1.47, 0.33)	0.57	(0.23, 1.39)
Middle East	-0.27897	0.50667	(-1.27, 0.71)	0.76	(0.28, 2.04)
Sub-Saharan Afr.	1.22159	0.45598	(0.33, 2.12)	3.39	(1.39, 8.29)
South Asia	0.30121	0.50435	(-0.69, 1.29)	1.35	(0.50, 3.63)
East Asia	1.62126	0.44832	(0.74, 2.50)	5.06	(2.10, 12.2)
Year 1990s	-0.21335	0.48542	(-1.16, 0.74)	0.81	(0.31, 2.09)
Year 2000s	-0.76333	0.47605	(-1.70, 0.17)	0.47	(0.18, 1.18)
1990s:East Euro	1.63177	0.47241	(0.71, 2.56)	5.11	(2.03, 12.9)
1990s:Mid East	0.48603	0.52116	(-0.54, 1.51)	1.63	(0.59, 4.52)
1990s:Sub-Saha	0.52232	0.47134	(-0.40, 1.45)	1.69	(0.67, 4.25)
1990s:South As	-4.41758	87.98	(-176, 168)	0.01	(0, 10000)
1990s:East As	0.07901	0.47001	(-0.84, 1.00)	1.08	(0.43, 2.72)
2000s:East Euro	1.93829	0.47895	(1.00, 2.88)	6.95	(2.72, 17.8)
2000s:Mide East	0.61403	0.52240	(-0.41, 1.64)	1.85	(0.66, 5.14)
2000s:Sub-Saha	0.81029	0.46570	(-0.10, 1.72)	2.25	(0.90, 5.60)
2000s:South As	1.43081	0.54588	(0.36, 2.50)	4.18	(1.43, 12.2)
2000s:East As	0.76052	0.45687	(-0.13, 1.66)	2.14	(0.87, 5.24)

Appendix 3: Supplemental Material for Manuscript #2

Figure S1: Decision Tree for Universal Vaccination

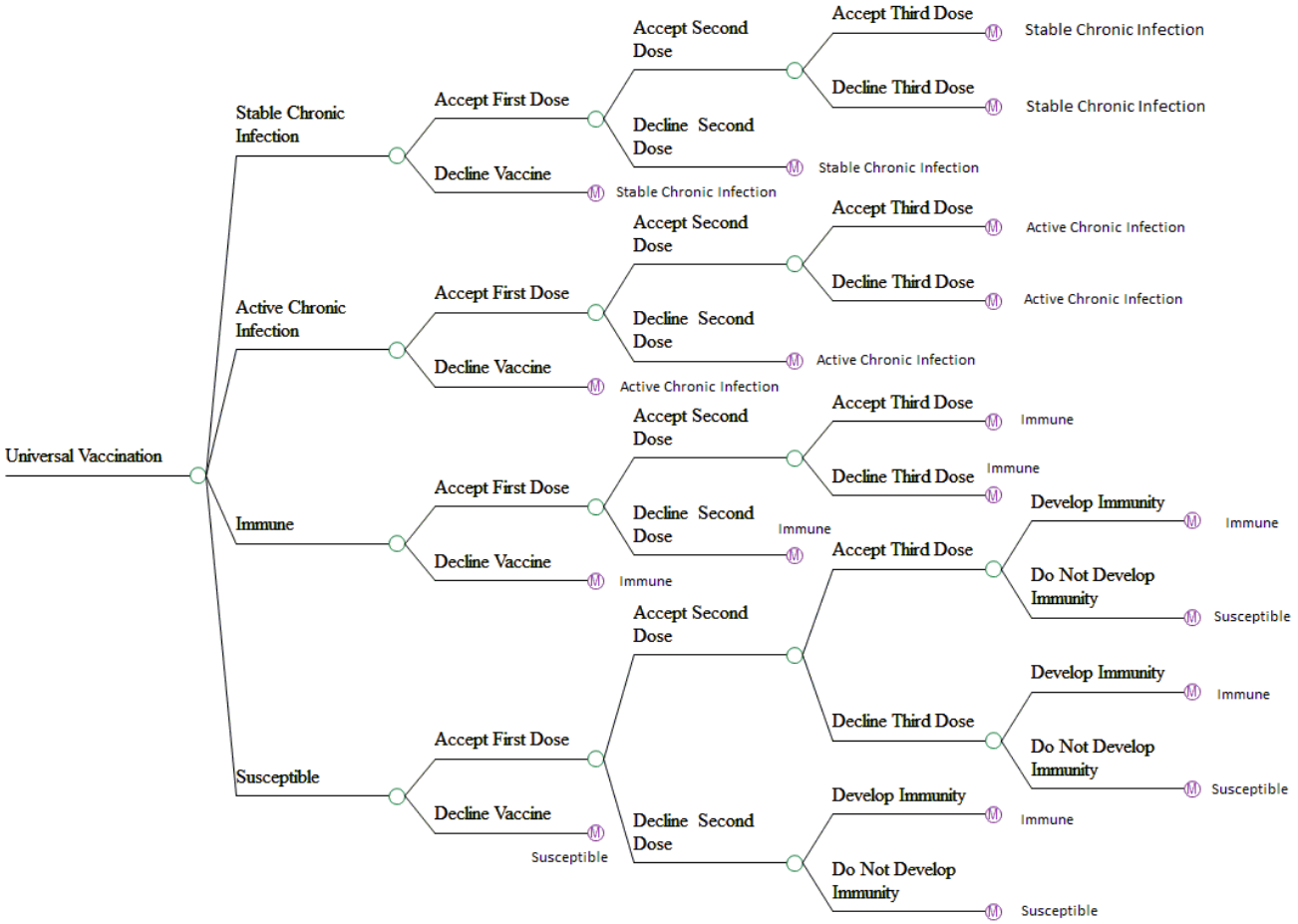


Figure S2: Decision Tree for anti-HBs Screening and Vaccination

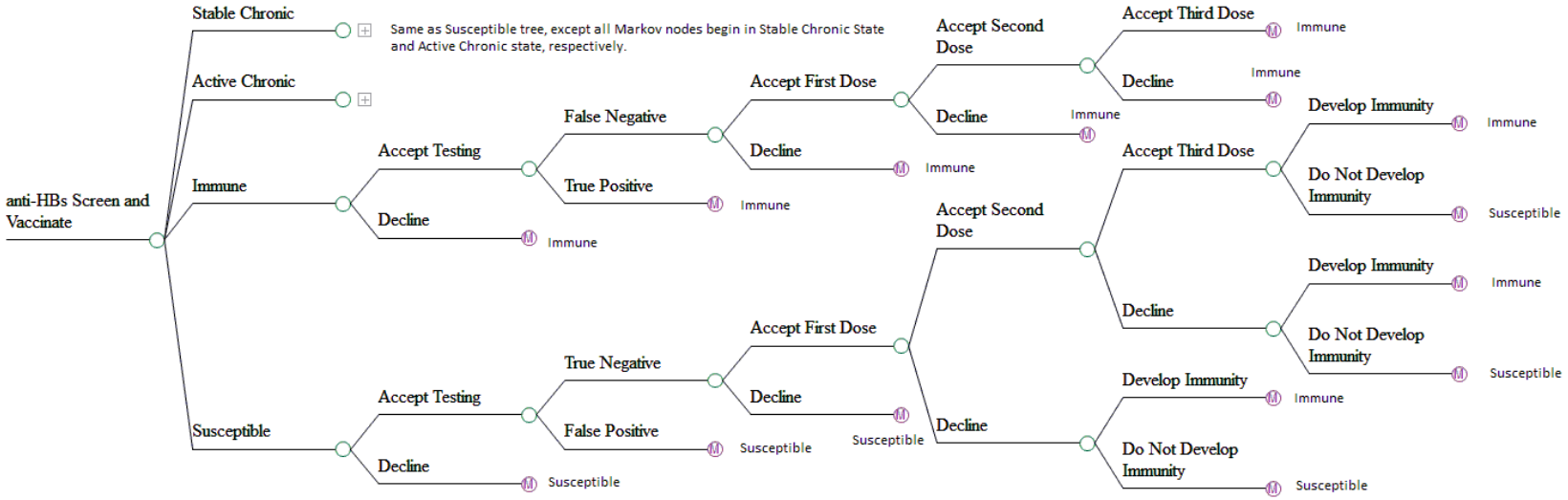


Figure S3: Decision Tree for HBsAg Screening and Treatment

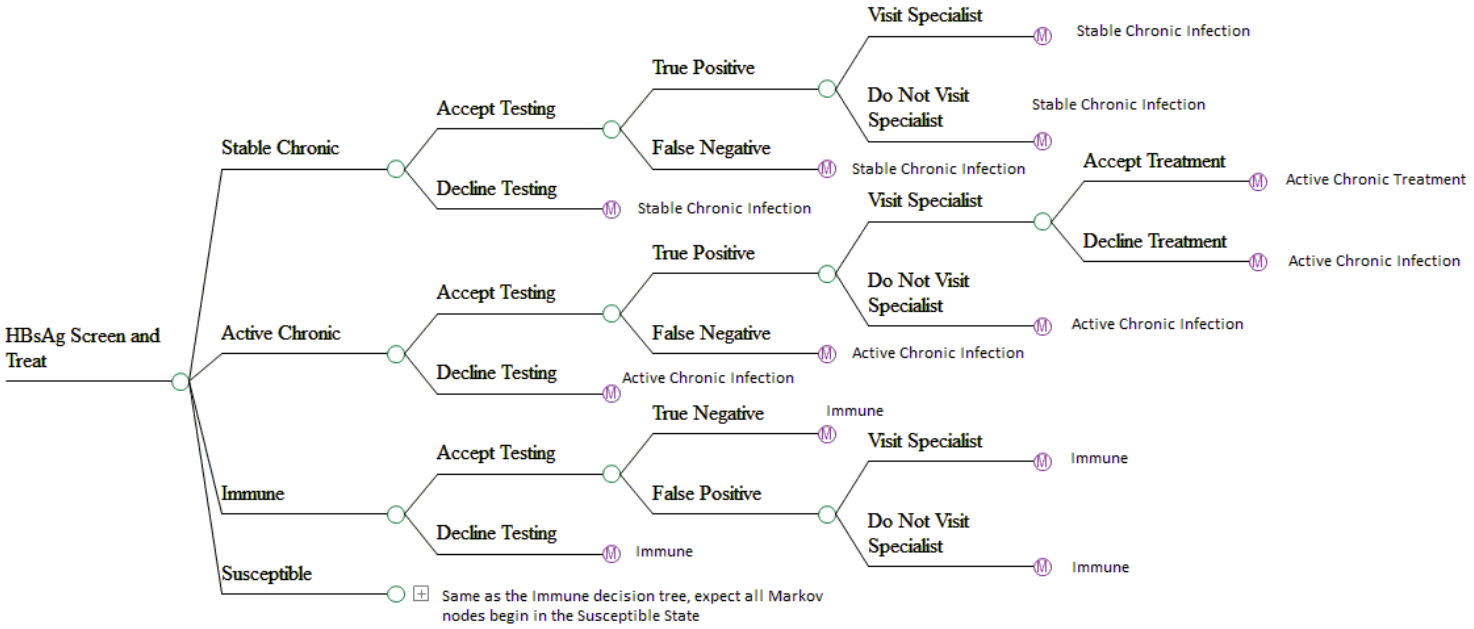


Figure S4: Decision Tree for anti-HBs and HBsAg Screening, Vaccination or Treatment

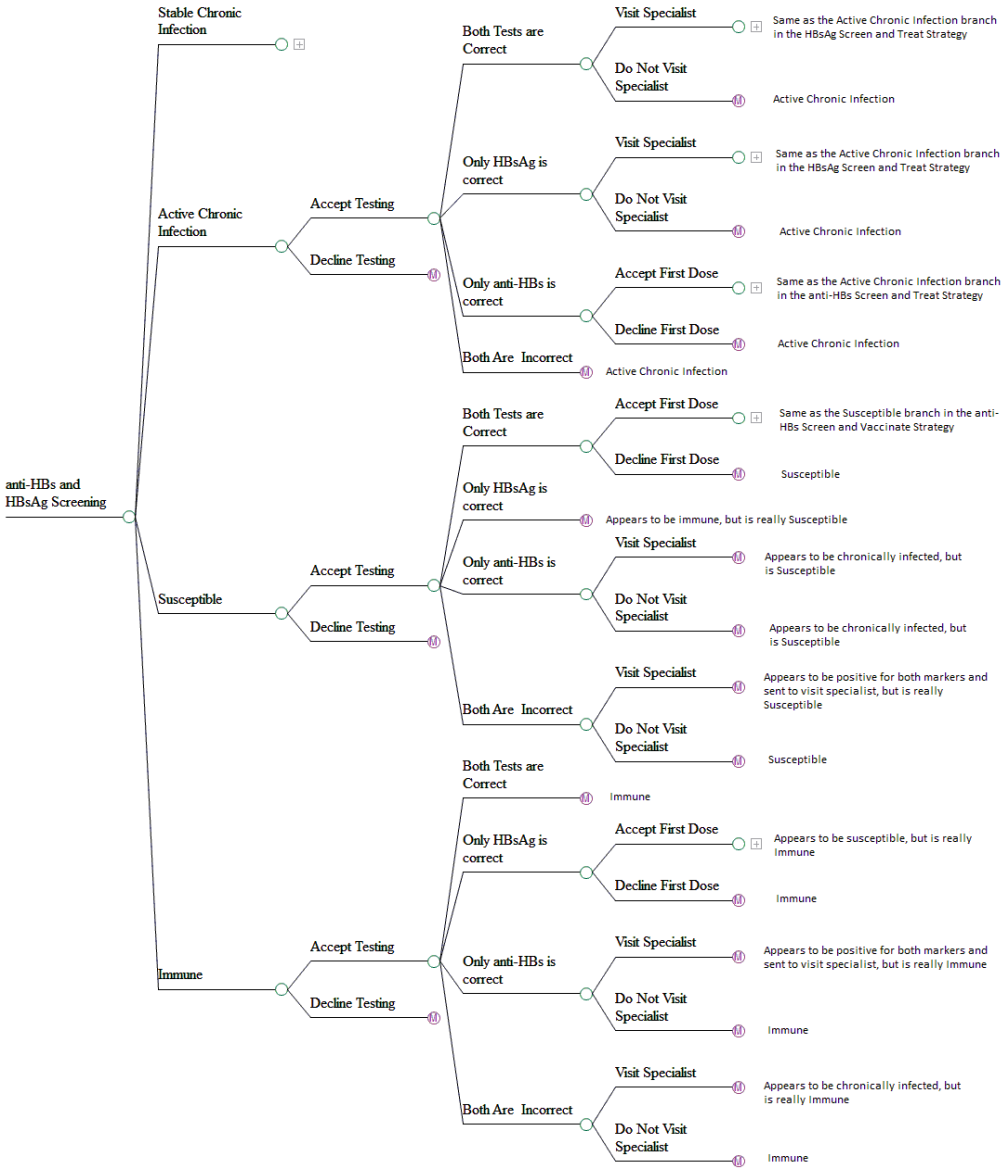


Figure S5: Calculations to Estimate the Seroprevalence of Infection and Immunity in Canadian Immigrants

Region	**Pooled HBsAg Seroprevalence**	**Pooled anti-HBs Seroprevalence**	**Number of Immigrants, 2001-2006**	**Percentage**
Latin America & Caribbean	1.7%	33.0%	119,585	12.24%
Eastern Europe & Central Asia	5.8%	30.1%	92,545	9.48%
Middle East & North Africa	2.1%	24.3%	155,715	15.95%
Sub-Saharan Africa	10.3%	41.7%	68,360	7.00%
South Asia	4.6%	10.6%	224,850	23.02%
East Asia & The Pacific	11.3%	50.2%	315,515	32.31%
Total			976,570	100%

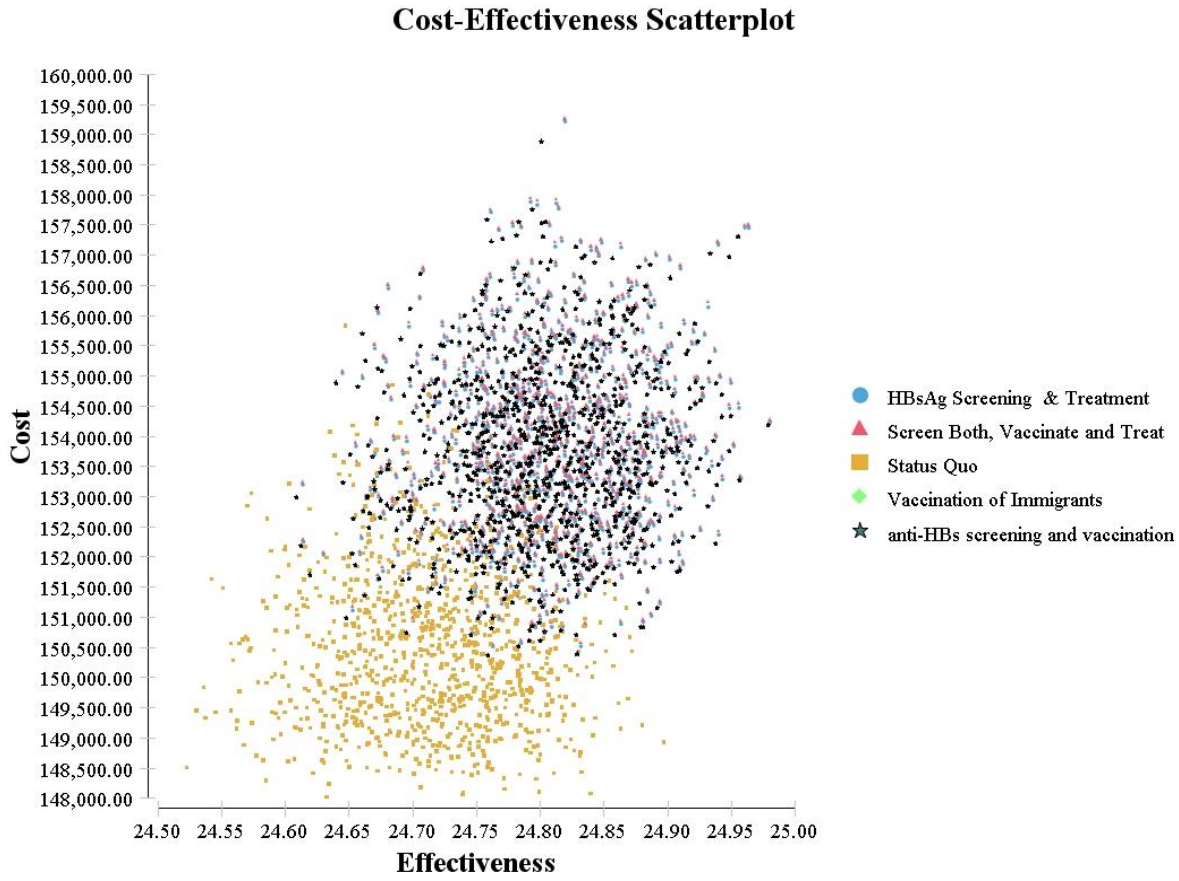
Calculating a Weighted Average for Base-Case HBsAg Seroprevalence

Point Estimate:
(0.1224*1.7) + (0.0948*5.8) + (0.1595* 2.1) + (0.0700*10.3) + (0.2302*4.6) + (0.3231*11.3) = 6.52%

Calculating a Weighted Average for Base-Case anti-HBs Seroprevalence

Point Estimate:
(0.1224*33.0) + (0.0948*30.1) + (0.1595* 24.3) + (0.0700*41.7) + (0.2302*10.6) + (0.3231*50.2) = 32.35%

Figure S6: Results of the Monte Carlo Simulation used to derive the Cost-Effectiveness Acceptability Curve for Screen and Treat Strategy



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