Rates of reported cases of Acute and Chronic Hepatitis B infection in the Immigrant and Non-Immigrant Populations in Quebec from 1991-2008

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Abstract

Background

Early screening and appropriately timed treatment for chronic hepatitis B (HBV) can prevent the development of cirrhosis, end stage liver disease or liver cancer. New infections can be prevented through vaccination. Immigrants have increased mortality from viral hepatitis and liver cancer, most of which is likely due to undetected chronic HBV, as they are not routinely screened before or after arrival in Canada. The aim of this study was to estimate and compare the rates of newly reported cases of acute and chronic HBV among immigrant and Canadian-born populations.

Methods

A population-based cohort study of all reported cases of acute and chronic hepatitis B identified in the Quebec reportable disease database (MADO) from 1991-2008 were deterministically linked to the Quebec immigration database (MIDI). Annual cumulative incidence of reported cases of acute and chronic HBV were estimated and stratified by age, sex, and region of origin. Comparative rate ratios in immigrants vs. non-immigrants were calculated. Numerators were derived from the linked database and denominators were estimated from census data. Poisson regression was used to model and compare the trends in change of disease-specific rates over the study period.

Results

From 1991 to 2008, a total of 2,750 acute HBV and 14,633 chronic HBV reported cases were identified and linked. Immigrants accounted for only 5.5% (N=151) of acute HBV infections and they were younger than non-immigrants (30.2 vs. 37.7 years, $p < .01$). Crude annual cumulative incidence rates of reported cases of acute HBV decreased by 12.7% per year in non-immigrants,

but only by 4.2% per year in immigrants over the study period. Immigrants accounted for 43% (N=6,306) of chronic HBV reported cases and they were younger and less likely to be male compared to non-immigrants. Immigrants from South East Asia, Sub-Saharan Africa and Eastern Europe/Central Asia had the highest rates of chronic HBV [191.4/100,000 population; 95% CI (189.2, 201.9), 170 (156.8, 181.2) and 44.9 (40.7, 49.2) respectively] with rates ratios ranging from 6.2 (5.6, 6.9) to 26.9 (25.9, 28.1) compared to non-immigrants. Over the study period, crude annual cumulative incidence rates of reported cases of chronic HBV decreased by 7.2% annually in non-immigrants whereas they increased by 1.9% per year in immigrants.

Conclusions

Increasing cumulative incidence rates of reported cases of chronic HBV over the study period in immigrants and very high cumulative incidence rates in certain sub-groups suggest that many immigrants groups could benefit from targeted HBV screening programs.

Résumé

Introduction

Le dépistage précoce et le traitement approprié de l'hépatite B chronique peuvent prévenir le développement d'une cirrhose du foie, de l'insuffisance hépatique en phase terminale ou du cancer du foie. Les nouvelles infections peuvent être prévenues grâce à la vaccination. Les immigrants ont un taux de mortalité plus élevé associée à l'hépatite virale B et au cancer du foie, probablement dû au fait que ces maladies n'ont pas été détectées à temps et les infections ne sont pas systématiquement dépistées avant ou après l'arrivée au Canada. L'objectif de cette étude était d'estimer et de comparer les taux de nouveaux cas déclarés d'hépatite B aiguë et chronique chez les immigrants et les natifs du Canada.

Méthodes

Une cohorte de tous les cas déclarés d'hépatite virale B aiguë et chronique identifiés dans la banque de données des Maladies à déclaration obligatoire du Québec (MADO) entre 1991 et 2008 qui ont été reliés aux banques de données du Ministère de l'Immigration, de la Diversité et de l'Inclusion du Québec (MIDI), de la Régie de l'assurance maladie du Québec (RAMQ) et des hospitalisations (MED-ÉCHO). Les taux d'incidence annuelle ont été estimés et stratifiés selon l'âge, le sexe et la région d'origine. Les taux d'incidence relatifs ainsi que les intervalles de confiance à 95% chez les immigrants et les non-immigrants ont été calculés. Les numérateurs ont été calculés à partir de la banque de données reliées et les dénominateurs ont été estimés à partir des données des recensements canadiens. La régression de Poisson a été utilisée pour modéliser et comparer les tendances relatives des variations des taux de chaque infection au cours de la période de l'étude.

Résultats

De 1991 à 2008, un total de 2,750 cas déclarés d'hépatite virale B aiguë et 14, 633 cas d'hépatite B chronique ont été identifiés et reliés. Les immigrants représentaient seulement 5,5% (N=151) des cas d'hépatite B aiguë et ils étaient plus jeunes que les non-immigrants (30,2 vs 37,7 ans, p <0,01). L'incidence annuelle des cas déclarés d'hépatite B aiguë a diminué de 12,7% par an chez les non-immigrants et de seulement 4,2% par an chez les immigrants au cours de la période de l'étude. Les immigrants représentaient 43% (N = 6306) des cas déclarés d'hépatite B chronique et ils étaient plus jeunes avec moins de sex masculin par rapport aux non-immigrants. Les immigrants en provenance d'Asie du Sud-Est, de l'Afrique subsaharienne et de l'Europe de l'Estet d'Asie centrale avaient les taux les plus élevés de cas déclarés d'hépatite B chronique [191,4/100,000 population ; $IC_{95\%}$ (189,2-201,9), 170 (156,8-181,2) et 44,9 (40.7-49.2) respectivement] avec des ratios allant de 6,2 (5,6-6,9) à 26,9 (25,9-28,1) par rapport aux non-immigrants. Au cours de la période de l'étude, l'incidence des cas déclarés d'hépatite B chronique a diminué de 7,2% par an chez les non-immigrants et a augmenté de 1,9% par an chez les immigrants.

Conclusion

L'augmentation des taux d'hépatite virale B chronique au cours de la période de l'étude chez les immigrants et les taux très élevés chez certains sous-groupes suggèrent que de nombreux groupes d'immigrants pourraient étre ciblés par des programmes spécifiques de dépistage.

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Table of Contents

List of tables

List of figures

List of appendices

Abbreviations

CDC: Centers for Disease Control and Prevention

CCIRH: Canadian Collaboration for Immigrant and Refugee Health

CNDSS: Canadian Notifiable Disease Surveillance System

DIN: Drug Identification Number

DMP: Designed Medical Practitioner

EHSS: Enhanced Hepatitis Strain Surveillance System

ETOH: Ethyl alcohol

FIPA: Fichier d'inscription des personnes assurées

FSM: Fichier de services médicaux

FSP: Fichier de services pharmaceutiques

FSA: Forward Sortation Areas

GAVI: Global Alliance for Vaccination and Immunization

GFCV: Global Fund for Children's vaccination

HBIG: Hepatitis B Immune Globulin

HBcAg: Hepatitis B core Antigen

HBeAg: Hepatitis B e Antigen

HBsAg: Hepatitis B surface Antigen

HBV: Hepatitis B Virus

HCC: Hepatocellular Carcinoma

HIV: Human Immunodeficiency Virus

ICD: International Classification of Diseases

IDU: Intravenous Drug use

IME: Immigration Medical Exam

IRPA: Immigration and Refugee Protection Act

LSPQ: Laboratoire de santé publique du Québec

MADO: Maladies à déclaration obligatoire

MED-ÉCHO: Maintenance et exploitation des données pour l'étude de la clientèle hospitalière

MIDI: Ministère de l'Immigration, de la Diversité et de l'Inclusion

PCR: Polymerase Chain Reaction

PEP: Post Exposure Prophylaxis

RAMQ: Régie de l'assurance maladie du Québec

TB: Tuberculosis

WHO: World Health Organization

1 Introduction

1.1 Context

Hepatitis B virus (HBV) infection represents a serious global health threat as it is estimated that approximately one third of world's population has serological evidence of past or present infection and that more than 350 million individuals are chronic carriers.[1] A large proportion of these individuals live in Asia and Africa.[1] HBV ranks among the world's top ten causes of infectious disease-related mortality and results in approximately 1 million deaths each year due to cirrhosis and hepatocellular carcinoma (HCC).[2]

In Canada, the overall prevalence of chronic HBV infection in the general population is low, around 0.5-1%.[3] Modeling studies have suggested that the incidence and mortality from HBV-associated HCC will increase by more than 50% by 2020.[4] Furthermore, a recent Ontario Burden of Infectious Disease Study found that chronic HBV was the 5th leading infectious cause of significant years of life lost due to premature mortality.[5] This is because more than half (55%) of individuals living in Canada with chronic HBV are asymptomatic, unaware of their infection and remain undiagnosed.[6] Inexpensive diagnostic tests, effective treatments and vaccination to prevent transmission are widely available.[7] It is therefore important to detect those at risk for viral hepatitis so that HBV transmission can be prevented through vaccination, and cirrhosis and HCC due to chronic HBV can be prevented through early detection and appropriately time treatment.

1.2 Rationale

Immigrants constitute a growing part of the Canadian population. Based on the 2011 National Household Survey, nearly one in five Canadians (20.6%) was foreign-born.[8] In addition, forcasts

estimate that at least one-quarter (25% to 28%) of the Canadian population will be foreign-born by 2031.[9] Immigrants are a risk group for chronic HBV infection in Canada. The majority of immigrants who have arrived in Canada over the past four decades have originated from countries with a high prevalence of HBV (>2% HBsAg postive). As a consequence the overall seroprevalence of chronic HBV in Canadian immigrants ~12 fold higher than the Canadian-born population (6% vs 0.5%).[10] This has resulted in a 2-4 fold increased mortality due to viral hepatitis and HCC compared to the Canadian population.[11] This is primarily due to the large pool of asymptomatic, undetected and untreated HBV infection in the immigrant population.[7] Despite the increased prevalence and increased risk of death from viral hepatitis and HCC, there are no population-based data on the groups of immigrants at highest risk for acute and chronic HBV. Our study was designed to address this gap. Futhermore, despite the existence of an effective vaccine to prevent transmission of infection, readily available screening and effective treatments that reduce the development of chronic liver disease, Canada has no systematic screening programs to detect chronic HBV infection in the immigrant population, nor is HBV vaccination verified or updated. There are also no targeted HBV vaccination programs for new immigrants.[7] Therefore, identifying and treating infected persons and vaccinating those found susceptible, will benefit both the individual and society.

1.3 Objectives

The overall objective of this study was to measure the rates of reported cases of acute and chronic HBV in the immigrant and Canadian-born populations and identify subgroups at risk who may benefit from screening and vaccination.This thesis had three specific objectives. The first was to estimate and compare the annual cumulative incidence of reported cases of acute and chronic HBV in immigrants as compared to the Canadian-born population from 1991-2008,

stratified by important predictors such as age, sex, region of origin and immigrant status. The second objective was to model and compare the trend in change of rates of reported cases of acute and chronic HBV in immigrants and non-immigrants over the study period. The third objective was to describe and compare the pattern of underlying co-morbidities that may have led to the detection of reported cases of chronic HBV in immigrants and non-immigrants.

2 Literature review

2.1 Hepatitis B Virus

2.1.1 Composition and biology of HBV

HBV is a small DNA virus belonging to the *Hepadnaviridae* family of viruses and humans are the only known natural host.[12] The virus particle (virion) is 42-47 nm in diameter and is composed of an outer envelope and an icosahedral protein nucleocapsid core. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity. The outer envelope contains embedded proteins that are involved in viral binding and entry into susceptible cells. The hepatitis B virion, also known as the Dane particle, is the infectious particle present in an infected individual. In addition to the Dane particles, filamentous and spherical non-infectious bodies lacking a core can be found in the serum of infected individuals. The most abundant protein found in the envelope of the HBV virion and in self-assembling, noninfectious spherical or tubular particles is the 24-kD S protein known as the Hepatitis B surface antigen (HBsAg) and is encoded by the preS–S (presurface-surface) region of the genome. The inner core of the virus is made of the hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg), a partially double-stranded DNA molecule, and DNA polymerase with reverse transcriptase activity.[13] The HBcAg and HBeAg are encoded by the preC-C (precore-core) region of the genome, while the viral polymerase, a multifunctional enzyme involved in DNA synthesis and RNA encapsulation, is encoded by the P coding region.[12] The majority of infected persons clear the virus, i.e., clear HBsAg, HBeAg and develop antibodies to HBsAg (anti-HBsAg). The persistence or clearance of HBeAg determines the course in those who are HBsAg positive.[13] Due to substitutions within the coding region for HBsAg, mutants has been found in chronic carriers and those with these mutations may be missed with testing using HBsAg.[14]

There are at least eight HBV genotypes (A-H) based upon an inter-group divergence of ≥ 8% in the complete nucleotide sequence.[15] Increasing evidence suggested that HBV genotypes impact on clinical outcomes, HBeAg seroconversion rates, mutational patterns in the precore and core promoter regions, and response to antiviral therapy.[16,17] In addition, each HBV genotype follows certain geographical and ethnic distribution: genotype A is most frequent in North America, North-Western Europe, Sub-Saharan Africa, India, and some regions of South America; genotypes B and C occur primarily in Asia; genotype D is most common in the Mediteranean region and Eastern Europe, although it has a worldwide distribution; genotype E occurs mainly in west Africa; genotype F in Central and South America; genotype G has been reported in the USA, France, Germany, United Kingdon, and Italy; and genotype H is found only in Central America (Table 2-1).[18-23]

2.1.2 Natural history

The natural history of HBV infection is determined by a dynamic and complex interplay between the virus and the host immune response factors.[24] Following exposure to HBV, two thirds of patients are asymptomatic and have subclinical infection and one third have acute hepatitis with jaundice, of whom a minority (< 1%) develop fulminant hepatitis.[25] The outcome of acute infection is mostly dependent on age at exposure: up to 95% of individuals who acquire HBV infection as infant progress to chronic infection compared to 25% of those infected during childhood, and 5% of those infected as adults.[26] In people who progess to chronic HBV infection, HBeAg is positive and HBV DNA are initially high and remain so for a variable period of time (a few years to several decades). A large proportion of patients eventually lose HBeAg and produce antibody to HBeAg (anti-HBe). The observed rate of clearance of HBeAg in persons with or without elevated serum alanine aminotransferase (ALT) levels ranges between

8% and 12% per year.[27,28] HBV genotype determines the rate of seroconversion of HBeAg to anti-HBe. Individuals infected with genotype C remain HBeAg positive for many years longer as compared to those infected with genotypes A, B, D, or F.[29]

Table 2-1. Geographic distribution, prevalence, and clinical significance of HBV genotypes

Genotype	Geographic Distribution	Clinical Significance
A	Sub-Saharan Africa*, Northern Europe (28.3%), Western Europe (38.5%), East Europe (30.5%) and North America (25.1%)	Better response to interferon and peginterferon vs. all other genotypes
B	Japan (12%), China (41%), Hong Kong (33%), Thailand (12%), Vietnam (12%), Taiwan (71%), Philippines (22%), Greenland (90%), Alaska (4%), Northern Canada (75%)	Lower disease activity, younger age at HBeAg seroconversion, lower risk of HCC, and better response to peginterferon therapy compared with genotype C
C	Korea (100%), China (53%), Taiwan (22%), Japan (85%), Pacific islands (57.7%), Australia (31.8%), Philippines (27%), Vietnam (30%)	More severe disease and worse clinical outcome, including a higher risk of HCC
D	Middle East (94.8%), Northern Africa (79.2), Southern Asia (58.7%), Central Asia (88%)	Associated with precore mutation
E	West Africa (59.2%), Central Africa (49.2%)	Unknown
F	Central (36%) and South America (35.9%)	Unknown
G	Central America (3.6%), North America (0.9%), Europe (France, Germany) (0.7%)	Unknown
H	Central America (35.1%)	Unknown

* Eastern Africa (93.0%), South Africa (74.3%), Central Africa (31.0%),Western Africa (11.3%)

Chronic HBV infection, which is common after neonatal or childhood infection, may be broadly divided into four phases: 1) Immune tolerance; 2) immune clearance; 3) low replicative or inactive; and 4) reactivation phase residual.[30]

The first phase, which can last for 20-40 years, is characterized by positive HBeAg, very high viremia and normal ALT concentrations, and minimum histological activity.[31,32] For people acquiring infection during adolescence or adulthood, mostly in low endemic countries, there is no first phase (immune tolerance). Rather, there is a direct progression to the second phase (immune clearance), which is of short duration.

The second phase or immune clearance is the consequence of the loss of immune tolerance. Falling serum HBV DNA, rising ALT concentrations, and active liver disease are characteristics of this phase.[33,34] The mechanisms behind the loss of immune tolerance are not well understood. However, this sequence of events reflects the fact that early in the natural history of chronic HBV infection, the immunologic tolerance is relatively higher, whereas, later in the course of the infection the tolerance is lower, resulting in symptomatic episodes of acute hepatitis.[32,35-37] A characteristic feature of this phase is an increase in aminotransferases, which are thought to be consequences of immune-mediated lysis of infected hepatocytes following increased T cell responses to HBV core antigen (HBcAg) and HBeAg.[38,39] Evidence suggests that the duration of this phase, and the frequency and severity of the flares, increase the risk of cirrhosis and HCC.[40,41] In addition, recurrent flares occur more frequently in men, which is why HBV-related long-term complications including cirrhosis and HCC are more frequent in men compared to women.[42] Seroconversion of HBeAg to anti-HBe is one of the main outcomes of this phase and several factors predict higher rates of spontaneous HBeAg seroconversion including older age

(as patients get older they have more time to seroconvert)[40], high levels of aminotransferases[43], and HBV genotype[44].

During the third phase, HBeAg is no longer detectable (HBeAg seroconversion) despite the persistence of HBsAg and this usually leads to clinical remission and life-long inactive liver disease. The presence of anti-HBe, low or undetectable serum HBV DNA, and normal levels of aminotransferase also characterize this phase.

The fourth phase is characterized by recurrence of HBV viremia despite HBeAg negativity and moderate or increased hepatic necroinflammation. The spontaneous seroconversion in the course of chronic HBV infection that occurs in roughly 10-20% of patients usually signals a better outcome.[28,45,46] On the other hand, persistent or recurrent rises in serum ALT and a failure of immune clearance predict a poor clinical outcome with increased risks of cirrhosis and HCC.[47,48]

2.1.3 Pathogenesis

HBV is not directly cytopathogenic. Thus, the cascade of events leading to liver injuries and viral suppression appears to be mostly immune-mediated and involves a complex host-pathogen interaction.[49-52] The main mechanism believed to be responsible for liver damage and viral suppression involves the recognition of infected hepatocytes by virus-specific CD8+ cytotoxic T lymphocytes, via class I human lymphocyte antigen (HLA-I)-presenting HBV peptide fragments. Thus, the T-cell immune response not only plays a key role in viral suppression and recovery, but also contributes to liver injury in acute and chronic infection. Furthermore, the role played by several cytokines, such as interferon gamma and tumor necrosis factor (TNF), has been recognized as contributing to the host immune response by inhibiting viral replication, reducing proliferation of viruses, and modulating the immune response.[53-55] During the acute phase of the infection, clinical signs become apparent after an incubation period ranging from 45 to 180 days

(average of 60 to 90 days) and some evidence suggests that this variation correlates with the amount of virus in the inoculum, the mode of transmission and host factors.[56] Antiviral cytokines produced by cells of both the innate and adaptive immune responses are responsible for the clearance of HBV DNA.[57,58]

In patients with chronic HBV infection, the weak and insufficient HBV-specific T cell responses can lead to persistent inflammatory response and failure to clear HBV.[12,59-61] It is now well established that HBV replicates throughout the course of chronic HBV infection, that the immune response plays a key role in liver insult, and that the balance between immune response and viral replication is a dynamic process.[37,62] Also, it has been shown that HBV genotypes play a role in natural history, clinical outcomes, and response to therapy in the disease profiles (Table 2-1). For instance, individuals with genotype A are highly likely to clear HBV DNA and HBeAg and have sustained HBeAg remission following seroconversion as compared to those with genotype D. Asians with genotype B experience HBeAg seroconversion at a younger age, have less severe liver disease, and a better response to treatment compared to patients with genotype C.[63,64] Genotype C has lower cumulative rates of spontaneous HBeAg seroconversion at 1, 3, and 5 years compared to genotype B (0% vs. 6%, 18% vs. 24%, and 34% vs. 46%).[63]

2.1.4 Transmission

HBV spreads through direct contact with blood or body fluids from an infected person.[1] Principal routes of HBV transmission include vertical transmission or perinatal from mother to child, unprotected sexual contact with an infected person, sharing infected injection-drug use equipment, accidental needlestick, injuries with contaminated sharp materials and blood products.[1] Modes of transmission have distinct distributions based on prevalence of HBsAg and HBeAg (Table 2-2). Perinatal, early childhood, and infected blood (unscreened blood products)

transmission occur in high-prevalence regions. Nearly 90% of HBeAg seropositive mothers vertically transmit HBV to their offspring compared to 10-20% of HBeAg seronegative mothers.[65] Vertical transmission appears to be more common in Asia than in Africa, where horizontal transmission prevails, mainly because of the higher prevalence of HBeAg in Asia.[66,67] In areas of intermediate prevalence, mixed patterns of transmission have been observed. In low-prevalence regions, however, unprotected sexual intercourse, needle-sharing among IV drug users, and exposure to contaminated materials constitute the main routes of infection mostly among young adults and adolescents.[30]

2.1.5 Epidemiology of HBV infection

2.1.5.1 Global seroprevalence and risk factors

Globally, over 350 million persons are chronically infected with HBV leading to more than 786,000 deaths per year due to liver failure and HCC.[1] Worldwide, 50% of primary liver cancer are due to HBV and is the sixth most common cancer and the second most common cause of death from cancer globally: HBV ranks as the second leading carcinogen after tobacco.[68,69] The vast majority of HBV deaths occur in resource-poor countries, where the prevalence of HBsAg carriage varies from 2% to 20% in the general population.[32] Nearly 45% of the world's population live in areas of high endemicity (China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon basin), where the prevalence of chronic HBV infection is ≥8%, and the lifetime risk of contracting HBV infection is more than 60% (Table 2-2 and Figure 2-1). An additional 43% live in areas of intermediate endemicity (Southwest Asia, Eastern and Southern Europe, Russia, and Central and South America), where the HBsAg seroprevalence is 2%-7% and the lifetime risk of infection is 20%-60%. The remaining 12% live

in areas of low endemicity (North America, Western Europe, Australia, and Japan) where the HBsAg seroprevalence is less than 2% and the lifetime risk of infection is less than 20%.[70]

HBV risk factors include: unprotected sexual intercourse with multiple partners, needle-sharing among IV drug users, being born to an infected mother, transfusion of unscreened blood products, tattooing or body piercings using poorly or unsterilized equipments, working or residing in a health-care setting, living in prison, being a patient or employee in a haemodialysis center, and settings involving nonsexual interpersonal contact over a long period (household contacts of an infected person).[71,72]

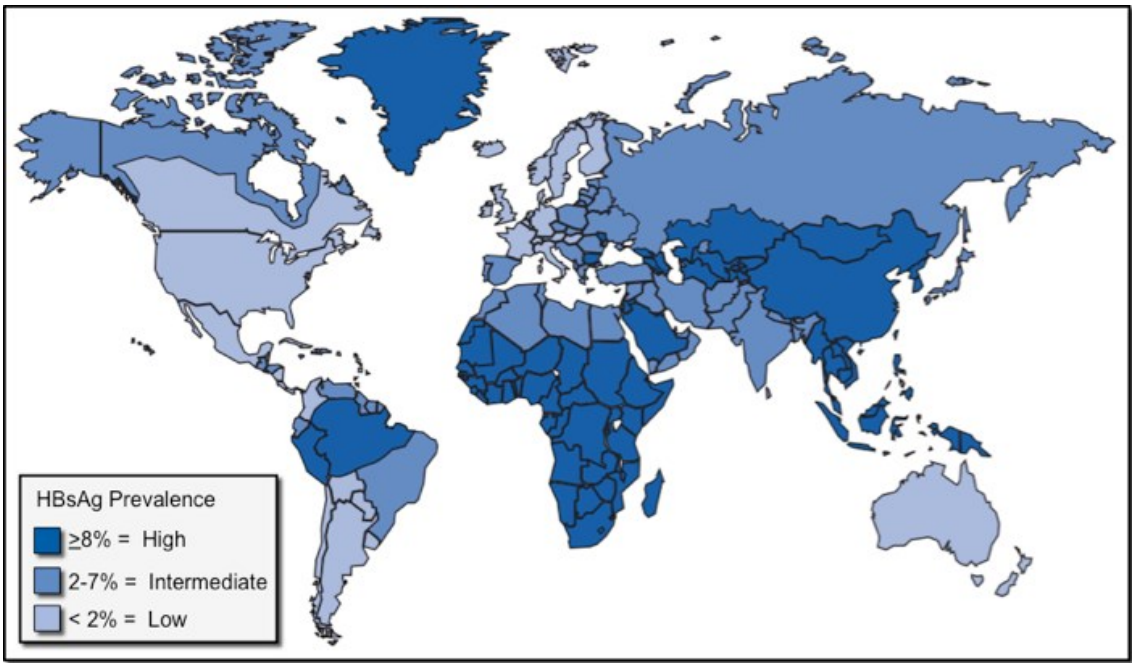


Figure 2-1. Geographic distribution of chronic hepatitis B virus (HBV) infection

Source: Source: CDC. Travelers' health; yellow book. Atlanta, GA: US Department of Health and Human Services, CDC; 2008.

Table 2-2. HBV transmission patterns

HBsAg prevalence	Countries	Transmission routes	Risk groups	Life time risk Infection
High prevalence **HBsAg ≥8%** 45% of global population	China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon basin	Perinatal, household transmission, blood, percutaneous, sexual, early childhood common	General population, contacts of infected people, MSM, IDU	> 60%
Intermediate prevalence **HBsAg 2-7%** 43% of the global population	Southwest Asia, eastern and southern Europe, Russia, and Central and South America	Vertical and horizontal, sexual, percutaneous, medical care	All age-groups	20-60%
Low prevalence HBsAg **< 2%** 12% of the global population	North America, Western and Northern Europe, Australia, and parts of South America.	Sexual, secretions, percutaneous	Mostly adult risk groups: Homosexuals (MSM), IDU, immigrants from endemic countries, health care workers (HCWs), multiple sexual partners	< 20%

2.1.5.2 Seroprevalence and Incidence in Canada

HBV infection has been reportable since 1969 to the National Notifiable Disease Reporting System (NNDR) and is the responsibility of Health Canada, the Division of Disease Surveillance, since 1988. Seroprevalence is based on laboratory data and national routine and enhanced surveillance,[73] serosurveys of selected subpopulations such as blood donors,[74] and modeled estimates.[75] The only routine HBV surveillance in Canada is for acute HBV and there is enhanced surveillance with some estimate of chronic HBV.[76] The overall prevalence of HBsAg in Canada ranges from 0.5 to 1%: as low as 0.1% in the Canadian-born popuation, and 6.9% and 7.4% in the Inuit population and immigrants from high endemic regions respectively.[3,77]

Recent data from both the Canadian Notifiable Disease Surveillance System (CNDSS) and the Enhanced Hepatitis Strain Surveillance System (EHSSS) showed that between 2009 and 2011, the rate of reported cases of chronic HBV decreased by 19.1% (from 14.1 to 11.4 per 100,000). In 2011, the highest rate was observed in British Columbia (22.4 per 100,000), followed by Alberta, Yukon, Saskatchewan, and Quebec (15.0, 14.1, 6.9, and 6.1 per 100,000, respectively). In British Columbia, the majority of chronic HBV infections cases were in immigrants from countries where HBV is endemic.[78] Chronic HBV infection in Canada is therefore primarily a disease of immigrants from endemic countries. Data from the childhood HBV surveillance study clearly showed that non-Canadian-born children had a risk ratio 12 fold higher compared to Canadian-born children.[79] A recent systematic review and meta-analysis also showed that the seroprevalence of chronic HBV was approximately 12 fold higher in migrants (0.5% vs 6.3%).[10] The highest prevalence was found in migrants from East Asia and the Pacific (11.3%), Sub-Saharan Africa (10.3%), and Eastern Europe and Central Asia (5.8%).[10] Other high-risk groups in Canada include Aboriginals and homeless individuals.[77]

The majority of migrants arriving in Canada originate from intermediate or high HBV prevalence countries.[10] This means that the HBV prevalence in Canada will continue to rise if the source countries and the numbers of migrants from these countries remain constant. Consequently, chronic HBV-related complications and deaths among immigrants would be expected to rise in the upcoming years resulting in important clinical and economic burden, unless appropriate actions are taken. In a Canadian popuation-based study, immigrants were found to have a 2-4 fold higher mortaltiy from viral hepatitis and HCC as compared to the Canadian population. This is likely largely due to undetected HBV infection in the migrant population.[11]

Recent Canadian cost-effectiveness studies have shown that it is at least moderately cost-effective to screen for chronic HBV infection and that this decreases HBV-related morbidity and mortality.[80,81] Compared to no intervention, screening for chronic HBV infection, and providing treatment if indicated, was the most cost-effective intervention at a cost of $40,880 per additional QALY gained.[80] This benefit held for immigrants <55 years of age and if the HBV seroprevalence in the country of orign was 3% or greater.[80] Another Canadian study found that HBV screening and treatment were also cost-effective, compared to no systematic intervention, but to a lesser degree than the study by Rossi et al.[81] Immigration has a considerable impact on the prevalence of chronic HBV infection in high-income countries and may place a heavy burden on the health-care system because of the high costs of HBV-related long-term complications. There is a growing body of evidence reporting a disproportionate increase of chronic viral hepatitis burden among the foreign-born populations in the United States and Europe.[82,83] In the US, 63% of the 27.9 million new immigrants who arrived between 1974 and 2008 were born in countries of intermediate or high chronic HBV infection prevalence.[84] Approximately 1.3 million

new cases of chronic HBV infection were imported to the United States during 1974-2008, giving an overall estimate prevalence of 4.6% among all new immigrants.[84]

With regard to acute HBV, recent data from the CNDSS showed that incidence rates of reported cases of acute HBV have decreased steadily from 1.0 to 0.6 per 100,000, corresponding to a 35.9% decrease between 2005 and 2011.[78] In 2011, data from the EHSSS suggested that rates of reported cases of acute HBV were higher among aboriginal persons as well as persons born outside of Canada.[78] Since 1971, the NNDR has reported that the number of notified cases of acute and chronic HBV in Canada has increased markedly, peaking in 1989, fluctuating from 1990 to 1995 and decreasing dramatically thereafter.[3] The increasing number of reported cases between 1971 and 1989 had been attributed to better reporting and testing for HBV, a rise in ID use and an increased number of immigrants from intermediate or high endemic regions.[3] However only a few provinces have been reporting chronic hepatitis B.[78] Due to limitations of the NNDR data, HBV incidence rates in Canada could not have been calculated directly from the reported number of HBV cases. Thus, after the removal of non-acute cases, the estimated rates of acute HBV infection decreased from 5.0 to 3.5 per 100,000 population between 1992 and 1995.[3]

2.1.6 Clinical manifestation and complications

2.1.6.1 Acute HBV

The clinical spectrum of disease in acute HBV infection in adults range in severity from minimal symptoms to fulminant hepatitis.[85] Acute HBV is rarely symptomatic and its symptoms are often nonspecific and last one to six months: nearly 70% of patients with acute HBV exhibit subclinical or anicteric hepatitis, whereas only 30% have icteric hepatitis.[85] Manifestations may include insidious onset of fever, fatigue, nausea, malaise, abdominal discomfort and anorexia

with jaundice or high serum ALT levels.[85] Less than 1% of patients develop fulminant hepatis B characterized by marked liver damage and liver failure.[85] Massive immune-mediated lysis of infected hepatocytes is believed to be the physiopathologic mechanism involved in fulminant hepatitis, which is why many patients with fulminant hepatitis B have no evidence of virus replication at presentation.[86] Coinfection with other hepatitis viruses or the presence of underlying liver disease contribute to the severity of the disease.[87]

2.1.6.2 Chronic HBV

Chronic HBV infection is defined as the detection of HBsAg in the serum for more than 6 months.[1] Most individuals with chronic HBV infection remain symptoms free for decades until development of long-term sequelae including end-stage clinical symptoms from decompensated cirrhosis or HCC.[88] Prior to diagnosis, asymptomatic individuals with chronic HBV can unknowingly spread the virus to other people through unprotected sexual intercourse, mother to infant transmission or other modes where blood or contaminated secretions are shared. In the dynamic natural course of the infection, periodic activation of the host immune response against infected hepatocytes leads to acute flares and accelerates the progression to cirrhosis.[46,48,88] (Figure 2-2).

About 15%–25% of people with chronic HBV develop serious liver conditions, such as cirrhosis after infection.[41,89] During chronic HBV infection, HBeAg-negative individuals progress to cirrhosis more slowly as compared to those who are HBeAg positive with an annual incidence of 2% to 6% and 8% to 10% respectively. The 5-year cumulative incidence to develop cirrhosis ranges from 8 to 20% in HBeAg-positive individuals.[46] Cofactors that increase the risk of cirrhosis include alcohol, viral hepatitis C (HCV) or HIV coinfection, high HBV DNA levels,

and HBV genotype C.[41,46] Approximately 6% of patients with compensated cirrhosis develop decompensated cirrhosis each year.[71,90] Decompensated cirrhosis is associated with a poor prognosis and only 14-28% of patients survive for 5 years.[46] Patients with cirrhosis and long-term high viremia are at increased risk to develop HCC or liver failure (decompensation). Genotype C HBV infection has a higher risk of HCC because seroconversion from HBeAg occurs decades later than in other genotypes.[29,91] HCC develops approximately 25 to 30 years following chronic infection and re-generation of hepatocytes damaged by the immune system is believed to be play a key role in increasing eventual mutations.[85] In patients with cirrhosis, the 5-year cumulative risk of progression to HCC is estimated to range between 5% and 30%.[92] Factors associated with increased risk of HCC include male gender, older age, a family history of HCC, HBV genotype C, and HCV coinfection.[35] Nonetheless, 30% to 50% of HBV-associated HCC occurs in the absence of cirrhosis.[35]

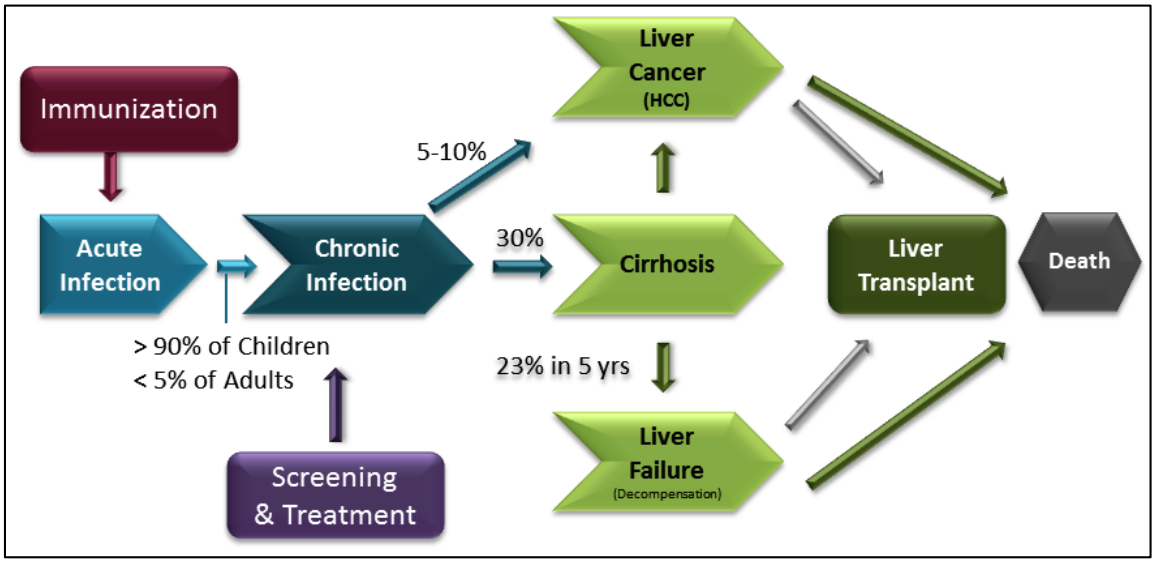


Figure 2-2. HBV disease progression
Adapted from (source): http://www.medscape.org/viewarticle/471116

2.1.6.3 Extrahepatic manifestations

Although hepatocytes consitute the main target of HBV, there is a spectrum of extrahepatic manifestations associated with both acute and chronic HBV infections.[93] The two main extrahepatic complications of chronic HBV are polyarteritis nodosa, a systemic inflammation of small- or medium-sized muscular arteries, and renal disease. Other manifestations include diseases related to the immune system such as serum sickness–like syndrome, cryoglobulinemia, Guillain-Barré Syndrome, and dermatologic conditions.[94,95] Circulating immune complex reactions that occur in the skin, joints, muscles, and kidneys might play a role in the pathophysiology of these associated symptoms.[95]

2.1.7 Diagnostic tests

Serologic markers associated with HBV infection include HBV surface antigen (HBsAg) and antibody to HBsAg (anti-HBs); HBV core antigen (HBcAg) and antibody to HBcAg (anti-HBc IgM and IgG); and HBV e antigen (HBeAg) and antibody to HBeAg (anti-HBe) (Table 2-3). HBsAg is widely used as the hallmark of infection and its persistence for at least 6 months signals chronic HBV infection. In addition, HBc IgG persists during chronic and during acute flares of chronic HBV infection, and HBc IgM has also been observed, but at lower titer.[31] Anti-HBs signals immunity to HBV infection and represents the only marker that appears as the immune response following hepatitis B vaccination. HBV DNA measures the viral load and reflects the replication activity of the virus. During the acute phase of infection, the surface antigen (HBsAg) becomes detectable in the serum after an incubation period ranging from 4 to 10 weeks, followed shortly by the appearance of IgM antibody against the hepatitis B core antigen in the early phase (Figure 2-3).[96]

Table 2-3. Interpretation of HBV serologic test results

HBsAg **anti-HBc** **anti-HBs**	Negative Negative Negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	Negative Positive Positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	Negative Negative Positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	Positive Positive Positive Negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	Positive Positive Negative Negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	Negative Positive Negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs** **HBeAg**	Positive Positive Negative Negative Negative	Chronically infected in association with precore or core promoter mutations (increased aminotransferase and high HBV DNA levels)

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005; 54(No. RR-16)

A challenge in the diagnosis of hepatitis B is the rare identification of cases in which viral mutations change the antigens such that they become undetectable.

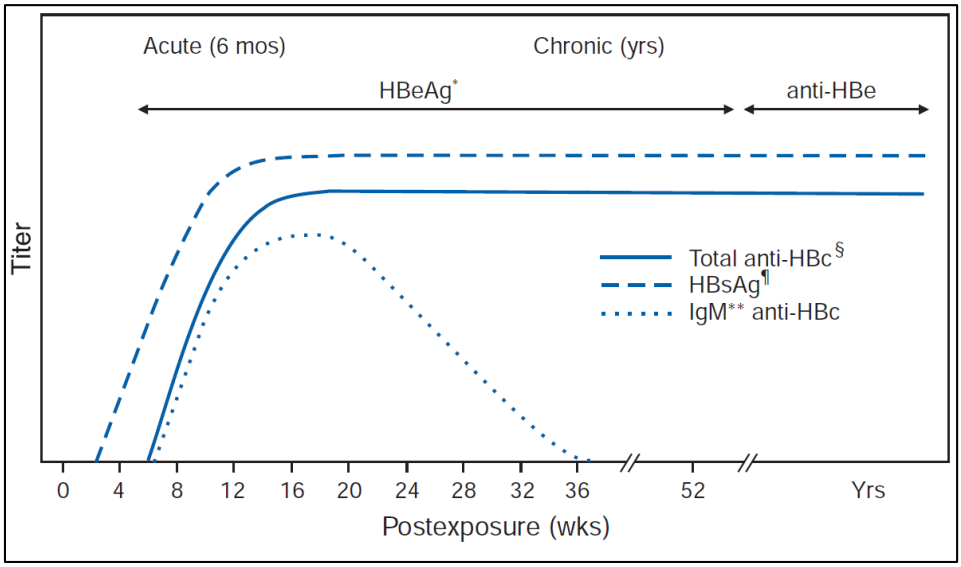


Figure 2-3. Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection
Source: Morbidity and Mortality Weekly Report, available at www.cdc.gov/mmwr

2.1.8 Vaccination, early detection and treatment

2.1.8.1 Vaccine and postexposure prophylaxis

Transmission of HBV can be prevented through HBV vaccination. A safe, reliable and highly effective vaccine to prevent HBV has been available since 1982.[1] Vaccine efficacy studies have demonstrated that 95% (90% to 100%) of immunized persons develop protective antibody response following a series of 3 doses.[97] Adults over 40 years of age, particularly males and those with chronic diseases, are less likely to develop protective antibody response.[98] Approximately 90% of recipients 40 years old or greater respond to a three-dose series, and by 60 years, only 75% of recipients develop protective antibody response.[99] The highest risk of exposure to chronic HBV occurs in high endemic regions, most commonly perinatal and early

childhood infections, making universal infant immunization the most effective and cost-effective preventive measure against HBV infection and its consequences in these countries.[100]

HBV vaccine is the first cancer-preventing vaccine for humans. Since 1982, the WHO has recommanded that "all infants receive the hepatitis B vaccine as soon as possible after birth, preferably within 24 hours of delivery."[1] A recent mathematical modelling study predicted that routine infant HBV vaccination would prevent up to 75% of HBV-related deaths globally; "If 100% of vaccination coverage with 3 doses was achieved and if 100% of infants received a dose of vaccine at birth, up to 95% of all HBV-related deaths could be prevented".[101]

As of 2013, infant Hepatitis B vaccination programs had been introduced in 183 countries. An estimated 81% of all newborns globally were estimated to have been covered with 3 doses of hepatitis B vaccine.[102] There continue to be, however, regional and local disparities due to limited financial resources, competing health priorities, poor management of health systems, and inadequate monitoring and supervision. Nonetheless, a growing number of international partners such as the Global Alliance for Vaccines and Immunizations (GAVI) or the Global Fund for Children's Vaccines (GFCV) are striving to promote health and immunisation mostly in some of the world's poorest countries.[103] These efforts are expected to improve vaccination coverage with the ultimate goal of controlling HBV worldwide.

Both Hepatits B immune globulin (HBIG) and HBV vaccine are recommended for HBV post-exposure prophylaxis. Given in the perinatal period, this combination is highly effective. A recent Cochrane review showed that vaccine plus hepatitis B immunoglobulin given the pernatal period reduced hepatitis B transmission by nearly 99.9% (RR 0.08, 95% CI 0.03 to 0.17).[104] To prevent vertical transmission, all pregnant women are required to undergo HBsAg testing during prenatal visits or at the time of delivery. If the mother is positive, the newborn should receive the

initial dose of HBV vaccine within 12 h of birth and a course of two doses 1 month and 6 months after the first dose.[105] For post-exposure prophylaxis of sexual contacts, a dose of HBIG should also be provided within 14 days of the last sexual intercourse with the HBV-infected person. Similarly, sexual abuse victims should receive both vaccine and HBIG, if the perpetrator is infected with HBV or if the HBV status cannot be assessed.[105] Hepatitis B prevention also includes universal immunization of children and post-exposure intervention for those exposed to HBV, particularly infants born to HBV-infected mothers.[105]

In 1991, the Canadian Hepatitis B Working Group recommanded a universal HBV vaccination program for preadolescents. Some Canadian provinces, including Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia and Newfoundland and Labrador, offer universal vaccination of adolescents or preadolescents instead of infants; in 2001, BC introduced an infant vaccination prorgram becoming the only province to offer universal vaccination to both infants and adolescents. Other provinces and territories have implemented a universal school-based HBV vaccination program targeting preadolescents 9 to 13 years old.[106] In 1983, vaccination programs that targeted high risk groups such as those who receive multiple blood products, hemodialysis patients, infants born to mothers with chronic HBV infection, health care workers, homosexual males, IDUs and sexual and households contacts of those chronically infected with HBV, were recommended.[107] In 1989, routine testing of all pregnant women for chronic HBV infection and the administration of immunoprophylaxis to the infants of positive mothers began in Quebec.[108] In 1994, Quebec introduced a school-based pre-adolescent HBV vaccination program in which 3 doses of HBV vaccine were given to grade 4 pupils (age 9 years).[108] This program has resulted in a decreaed rates of reported cases of acute HBV in Quebec.[109,110]

2.1.8.2 Early detection and management

Early case identification and medical management of chronically infected people can delay disease progression, reduce HBV-related complications and prevent HBV-related deaths.[7,111] In addition, screening and knowing HBV status allow for HCC surveillance in those at increased risk even if they do not undergo treatment. Furthermore, since persons with chronic HBV infection represent the reservoir for new HBV infections, early identification of these persons complements vaccination strategies and decrease the risk of disease transmission.[84] Screening also allows for primary prevention of HBV through counselling persons with chronic infection to adopt appropriate behaviors that could reduce the risk of transmission to others. It also provides an opportunity to screen close contacts for chronic HBV infection and to provide vaccination to those who are non-immune.

Screening for chronic HBV infection meets the generally accepted public health screening criteria: 1) It is a serious health condition that can be diagnosed during the prolonged assympomatic period ; 2) Highly sensitive, specific, commercially available and minimally invasive screening tests are widely available; 3) Chronically infected patients have years of life to gain if medical management is initiated early, prior to the development of liver sequelae; and 4) It is cost-effective.[112] In 2007, the Centers for Disease Control and Prevention (CDC) issued recommendations to screen for chronic HBV those born in geographic regions where the HBsAg prevalence $\geq$2% (includes much of Eastern Europe, Asia, Africa, the Middle East, and the Pacific Islands). This includes almost all groups of immigrants, refugees, asylum seekers, and internationally adopted children born in these regions, regardless of vaccination status in their country of origin.[111] They also recommended screening high risk groups including persons with behaviors that increase exposure to HBV (MSM and IV drug users), persons receiving cytotoxic

or immunosuppressive therapy, and persons with liver disease of unknown etiology. Screening certain indigenous populations was also recommended. In Canada, the Canadian Collaboration for Immigrant and Refugee Health (CCIRH), a national advocacy group including specialists, primary care practitioners, researchers, policymakers, and immigrant community leaders dedicated to improving the health of immigrants and refugees have made similar recommendations for HBV screening and HBV vaccination.[7]

Despite availibility of good screening tests and effective therapies there are systemic barriers to screening as well as barriers at the level of individual patients, practitioners as well as the health care system. In a recent Canadian survey, almost 55% of HBV infected individuals were unaware of their infection prior to screening.[6] Similarly, studies conducted in the United States have shown that 40%-60% of immigrants have relatively little knowledge about HBV transmission and its complications.[113] As a consequence, less than 50% of at-risk immigrants have ever been screened for Hepatitis B.[113] There are also large gaps in healthcare provider knowledge about HBV, particularly among primary care or family physicians who represent the point of entry into the healthcare system. In one study, 21% of primary care physicians didn't know how to manage a patient who had been found to be HBsAg positive during screening.[114] Finally, there are no routine HBV screening programs for immigrants from intermediate or high prevalence countries.

2.1.9 Treatment

In more than 95% of immunocompetent adults, acute HBV infection spontaneously resolves and episodes usually only require supportive measures.[1] Main indications for treatment of chronic HBV include active liver inflammation, high HBV DNA levels, advanced fibrosis, and cirrhosis.

Since the clearance of hepatitis B virus (HBV) infection is rarely, if ever, achievable, the aim of pharmaceutical therapy is to achieve a sustained suppression of viral load, thereby minimizing or delaying progression to cirrhosis and HCC.[115] Markers to assess treatment are biochemical (normalization of ALT), virologic (suppression of HBV DNA to undetectable levels), serologic (loss of HBeAg or HBsAg and seroconversion to anti-HBe or anti-HBs), and histologic (decreased inflammation on liver biopsies with no worsening of fibrosis).[73,116,117] Currently, seven antiretroviral drugs are approved by the FDA including two formulations of subcutaneously injected interferons (standard or interferon alfa-2b and pegylated interferon alfa-2a) and five orally administered nucleos(t)ide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir).[78,117] These approved treatments have been associated with positive outcomes including improvements in biomarkers (HBV DNA, HBeAg loss or seroconversion, decrease in ALT levels) and improvements in liver histology.[118] In addition, newer therapies can dramaticly decrease viraemia. Furthermore, following 6 months of treatment with PEG-IFN, HBsAg clearance can be achieved in 3 to 6% of patients. Likewise, the loss of HBsAg can also be achieved using nucleos(t)ide analogues.[118] In Canada, there are eight approved hepatitis B drugs (emtricitabine plus the seven aforementioned drugs).[119] These antiviral agents vary in their usage, effectiveness, resistance profiles, and side effects.

2.2 Immigrant populations in Canada and Quebec

Global migration has reached unprecedented levels over the past four decades. It is now estimated that more than 232 million international migrants live outside their countries of origin.[120] Canada hosts nearly 7.3 million migrants constituting 20% of the Canadian population according to the 2011 census.[8] Since 1990, Canada has admitted approximately 230,000 immigrants per year equal to about 0.7% of the Canadian population.[120-122] Quebec has received

approximately 42,000 immigrants per year since 1990, the vast majority (>85%) of whom resided in Montreal.[123] In the 2011 Census, a total of 4,945,060 people were aged 65 and older in Canada, an increase of more than 14.1% between 2006 and 2011. This rate of growth was higher than that of children aged 14 and under (0.5%) and people aged 15 to 64 (5.7%).[124] Consequently, the number of seniors aged 65 and over has continued to catch up with the number of children from 2006 to 2011.[124] To tackle this demographic challenge, immigration has been proposed as one of the key factors that could help slow the pace at which the population is expected to age.[125]

2.3 Canadian immigration policy

Immigration in Canada is guided by the Immigration and Refugee Protection Act (IRPA), which is the legal federal framework for immigration.[126] Citizenship and Immigration Canada (CIC) has the responsibility to apply this law and to set the overall target level of immigration for Canada as well as the number of immigrants accepted in each specific category.[127] Immigrants are classified into four main categories under which they are admitted into the country as permanent residents: 1) Economic Class (skilled workers, business immigrants, provincial and territorial nominees, the Canadian Experience Class, and live-in caregivers, as well as their spouses or partners and their dependents); 2) Family Class (spouses or partners, dependent children, parents, grandparents and other close relatives sponsored by Canadian citizens and permanent residents); 3) Protected Persons (government-assisted refugees, privately sponsored refugees and persons who received protected person status in Canada as a result of a positive asylum claim); and 4) Other. The IRPA gives CIC the authority to grant permanent resident status to individuals and families who would not otherwise qualify in any category, e.g., in cases where there are strong humanitarian and compassionate considerations, or for public policy

reasons.[11] Since 2008, the proportion of Economic Class immigrants has exceeded 60%. The Family Class is currently the second largest category of immigrants, accounting for slightly more than one in five immigrants (20%-25%). Data for 2011 showed that Protected Persons accounted for 11.2% of all immigrants admitted that year and the Other category nearly 3%.[128]

2.4 The Immigration Medical Exam (IME)

The influx of new immigrants to Canada has important implications for the health-care system and the health of individuals. Consequently, following Canadian legislation, all applicants for permanent residence are required to undergo an Immigration Medical Examination (IME) conducted by a CIC-designated medical practitioner. The IME includes a complete medical exam and the following laboratory tests: chest X-ray (age 11 or older) to detect active tuberculosis, blood tests for syphilis and HIV (age 15 or older), and a urinalysis (age 5 or older). Once the exam has been completed, the results are sent to CIC.[129] The purpose of this exam is to assess inadmissibility to Canada with an overall objective to prevent transmission of communicable diseases to the Canadian population and to prevent the entry of individuals who will place excessive demands on the Canadian health care system.[130]

2.5 Demography of immigration to Canada

Before 1970, the vast majority of immigrants (>70%) originated from Europe and the United States (~15%). During this time, Asia accounted for <10% , and Africa, the Middle East and the Caribbean accounted for <5% of all immigrants.[130] Post-1970 figures show a striking reversal. Nationwide, by 2002, so-called traditional sources of immigration had been outpaced by Asia and the Pacific (52%), and Africa and the Middle East (20%). Europe and the UK contributed to only 17% of immigrant flows, the US only 2%, and South and Central America 9%.[131] A large

proportion of immigrants originate from developing and resource-constrained countries where health conditions and the prevalence of many infectious diseases is higher than in Canada. The source countries of the majority of Canadian immigrants have intermediate or high prevalence of chronic HBV infection (Figure 2-4). Countries of origin of immigrants in Quebec are quite different from those in Canada. In 2006, the major source countries of origin of Canadian immigrants were China (13%), India (13%). and the Philippines (13%), whereas in Quebec, the top 3 countries of origin were Algeria (11%), France (8%), and Morocco (6%) (Table 2-4).

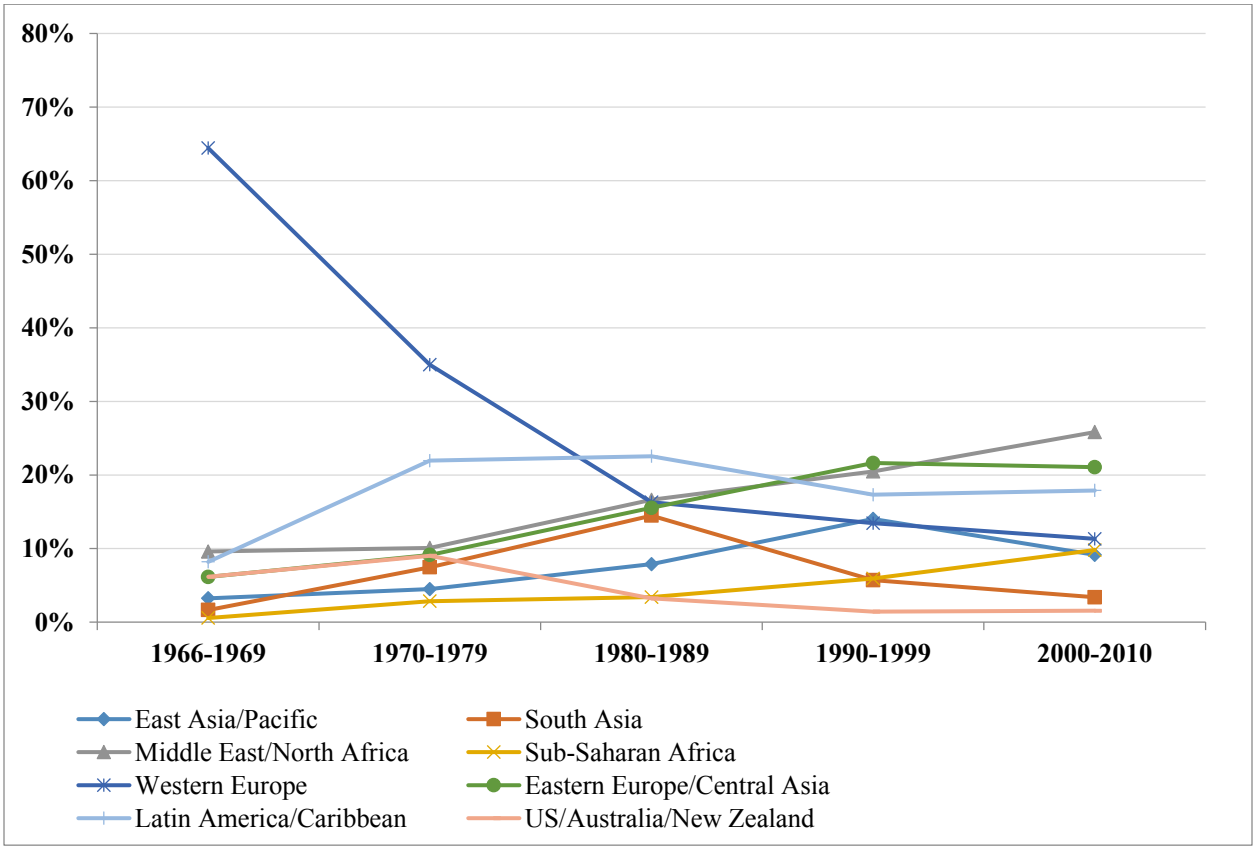


Figure 2-4. Region of Origin of immigrants arriving in Canada from 1966-2010

(Source: http://www.cic.gc.ca/english/resources/statistics/facts2010/permanent/10.asp).

Table 2-4. Top ten countries of birth, Canada vs. Quebec, 2006

Rank	Canada	%	Quebec	%
1	China	13	Algeria	11
2	India	13	France	8
3	Philippines	7	Morocco	6
4	Pakistan	5	Columbia	5
5	USA	4	China	5
6	UK	3	Lebanon	4
7	Iran	3	Romania	4
8	Columbia	3	India	3
9	Korea	2	Haiti	3
10	Algeria	2	Tunisia	3

Sources: 1) Immigration, Diversité et Inclusion Québec (http://www.midi.gouv.qc.ca/fr/recherches-statistiques/stats-immigration-recente.html); 2) Citizenship and Immigration Canada (http://www.cic.gc.ca/english/resources/statistics/facts2013/permanent/10.asp)

2.6 Summary

Globally, it is estimated that over 2 billion of people are infected with HBV, of whom nearly over 350 million persons are chronic carriers at risk of HBV-related liver disease. Chronic HBV is a public health priority for the following reasons: i) Undetected chronically infected individuals are at high risk to develop cirrhosis, liver failure, or HCC and they serve as a reservoir for virus transmission; ii) HBV transmission can be prevented through immunizing susceptible individuals; and iii) progression to HBV-associated long-term sequelae can be prevented through early screening and appropriately time therapy.

Migration, as an important component of globalization and is an ever growing phenomenon. The majority of immigrants to Canada over the past 4 decades originate from intermediate and high HBV prevalent countires. They have higher mortality from chronic viral hepatitis and from HCC than the Canadian-born population, likely because half of the cases are not detected. Despite this and unlike HIV and TB, there are no systematic screening programs for immigrants during the

immigration exam or after arrival. Moreover, there are no population based data on the incidence of chronic HBV. This study will fill this gap and will help with decisions regarding health care resource allocation.

3 Study objectives and hypothesis

3.1 Objectives

3.1.1 Overall objectives

Measure the annual cummulative incidence rates of reported cases of acute and chronic HBV in the immigrant and Canadian-born populations in a cohort of all the reported cases of hepatitis B in Quebec from 1991-2008 and identify the subgroups at highest risk.

3.1.2 Specific objectives

1) Estimate and compare the annual cumulative incidence of reported cases of acute and chronic HBV in immigrants as compared to the Canadian-born population from 1991-2008, stratified by important predictors such as age, sex, and region of origin.

2) Model and compare the trend in change of incidence rates of reported cases of acute and chronic HBV in immigrants and non-immigrants over the study period.

3) Describe and compare the pattern of underlying conditions or co-morbidities that may have led to the detection of chronic HBV in immigrants and non-immigrants.

3.2 Hypothesis

We hypothesized that immigrants would have higher reported rates due to acute and chronic hepatitis B as compared to non-immigrants.

4 Methods

4.1 Study design

A retrospective cohort of all notified and laboratory-confirmed acute and chronic HBV cases in Quebec between 1991 and 2008.

4.2 Data sources

4.2.1 Overview

To meet our objectives, six Quebec population-based databases were linked through common unique identifiers. All cases of acute and chronic HBV (all are laboratory confirmed) identified in the *Maladies à déclaration obligatoire* database (**MADO**) the public health reporting database. These cases were linked to the *Régie de l'assurance maladie du Québec* (**RAMQ**) databases which include: 1) The *Fichier d'inscription des personnes assurées* (**FIPA**) containing sociodemographic data, 2) The *Ficher de services médicaux* rémunérés à l'acte (**FSM**) database containing physician billing claims for visits/procedures), 3) *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (**MED-ÉCHO**) containing the hospital discharge data, 4) The *Fichier de services pharmaceutiques* (**FSP**) containing medications dispensed and 5) the *Ministère de l'Immigration,de la Diversité et de l'Inclusion* (**MIDI**) database including variables on the landed immigrants (i.e., have permission to live in Canada).

4.2.2 Description of the administrative database

4.2.2.1 Maladies à déclaration obligatoire (MADO)

The MADO database is the provincial public health mandatory reportable infectious disease passive surveillance system. It is the most complete and accurate database of reported cases of viral hepatitis in Quebec because all physicians and laboratories are required by law to report all

cases of acute and chronic hepatitis B with standard case definitions that have been used since 1991 (Appendix 1). All the cases are serologically confirmed and the clinical information classifies then into the different stages of the disease, i.e., for hepatitis B cases are classified as confirmed or probable acute, confirmed or probable chronic or indeterminate hepatitis B, depending how much clinical information is available (Appendices 1 & 2).[132] Data on cases (including nominal information) of acute and chronic hepatitis B are collected in each of the 18 Quebec Public Health regions and sent to a central repository at the *Laboratorie de Santé Publique du Québec* (LSPQ). As reporting is nominal, duplicate cases (may occur if an individual travels or moves within the province) reported within more than one Public Health Region are removed by the LSPQ.

4.2.2.2 Régie de l'assurance maladie du Québec (RAMQ)

RAMQ is the provincial organization that administers public health-care insurance programs and prescription drug insurance plan in the province of Quebec. Coverage for medical services is universal and all landed immigrants that have been given permission to live in Canada are eligible for coverage. The database comprises information on medical and pharmaceutical services and patients' demographic characteristics in three sources of data: FIPA, FSM, and FSP. The FIPA database contains demographic information, and a unique RAMQ health number for all Quebec residents registered with RAMQ. In immigrants files, there is also a visa number. The RAMQ number provides a deterministic link bewteen all RAMQ databases, MED-ÉCHO and the MADO database. The visa number provides a determistic linkage with the MIDI permanent immigrant database. The FSM database includes all physician reimbursement claims for inpatient and ambulatory medical services (physician visits, surgical procedures, and diagnostic procedures) provided to Québec residents. All diagnoses are coded with the International

Classification of Diseases, Ninth Revision and Tenth, clinical modification (ICD-9-CM/ICD-10).[133] The FSP database contains data on all dispensed medication (including medications that require special permission to access, such as methadone and interferon). Approximately 50% of the population are covered by the provincial prescription plan (FSP) and for whom specific information on medication utilization is available. Details of variables in each of the databases that will be used in this study are listed in the appendix 3.

4.2.2.3 Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO) (Quebec Hospital Discharge Data)

This database contains information on all hospital admissions for the province of Quebec since 1987. Each record contains identifying demographic information along with the primary diagnosis on admission and total number of 15 possible secondary diagnoses (ICD-9-CM), and admission and discharge dates, and location of admission.

4.2.2.4 The Landed Immigrant Database of the Ministère de l'Immigration, de la Diversité et de l'Inclusion (MIDI) of Quebec

The Landed Immigrant Database of MIDI contains demographic information on all immigrants who have been given permission to live in Quebec. Quebec receives ~40,000 new immigrants per year and 95% are in the "landed" class, are registered in the MIDI database and are eligible for RAMQ health coverage.[134,135] The remaining 5% were refugee claimants or "other class" and were excluded because they receive health care coverage from organizations other than RAMQ. Approximately 85% of all landed immigrants per year registered in the MIDI database actually settle in the province and are eligible for and register with RAMQ for health coverage. The other 15% arrive in Canada (are registered in the MIDI database) but take up residence in a province other than Quebec and are not eligible for RAMQ coverage.[136] These individuals were identified

and excluded as they were not present in the FIPA database as they never landed in Quebec or stayed very briefly and never applied for health insurance. Of the immigrants that take up residence in Quebec, only ~5% leave Quebec each year to move to another province or outside of Canada.[136] We accounted for this as there is a variable in the RAMQ database that determines if an individual has left the province and the date that they moved. Cases of hepatitis that occur in immigrants that arrived in another province and then moved to Quebec during the study period could potentially be misclassified. In a study by CIC, only 6% of all immigrants living in Quebec between 1980-1995 and that submitted income tax in 1995 had moved to Quebec from another province.[137] Immigrants who arrived prior to 1985 may be misclassified as non-immigrants as linkage to the MIDI database only began in 1985. In 2000 a 3 month waiting period prior to eligibility for health insurance (and registration with FIPA) was instituted. Therefore between 2008-2008, immigrants who developed symptomatic acute or chronic hepatitis B in the first 3 months after arrival would have been excluded from the analysis as they would not be registered with FIPA.

4.3 Study population

4.3.1 Construction of the study cohort

All initially reported cases of acute and chronic HBV in the MADO database occurring in individuals registered in the FIPA database between January 1, 1991 and June 30, 2008 were eligible for study entry. Individuals were censored from the cohort: 1) on emigration from the province; 2) on the date of death; or 3) at the end of the study period, whichever occured first.

4.3.2 Ascertainment of cases of acute and chronic HBV

All cases of initially reported acute and chronic HBV identified in the MADO database between January 1, 1991- June 30, 2008 and registered in the FIPA database at the time of detection were included as a case.[138] The major limitation of passive public health surveillance data is underdetection of asymptomatic cases and thus underestimation of the actual total number of cases (detection bias). Despite this, these data are usually satisfactory for monitoring trends of disease.[139] Approximately 70% of cases of acute HBV are asymptomatic.[140] Cases of acute or chronic HBV reported in a passive surveillance database were detected either because health care workers screened for these infection due to presence of symptoms consistent with the diagnosis, perceived epidemiologic risk factors for viral hepatitis or during work up for other conditions.

4.4 Data gathering

4.4.1 Outcome variables

Outcomes of interest for the study objectives are newly reported cases of acute and chronic HBV. Acute and chronic HBV were identified using the MADO database and were laboratory-diagnosed (Appendix 3).

4.4.2 Exposure

The exposure was the immigration status assigned through linkage with the MIDI Landed Immigrant Database.

4.4.3 Covariates

Covariates such as age, sex, and region of origin (for immigrants) are important risk factors for acute and chronic HBV, thus reported incidence rates were stratified by these variables. These covariates were identified in the RAMQ, FIPA and MIDI databases. As per RAMQ data, age

was classifed into 9 categories: 0-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-59, 60-69, and ≥70 years. Regions of origin were classified based on the World Bank country classification into six 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.[141] When the database was created only viral hepatitis A, B, C, D and E were requested from the MADO database. Although HIV is present in the MADO database this was not available in the study database and therefore HIV specific diagnostic codes and HIV specific medications were used to indentify HIV.

4.4.4 Conditions leading to chronic HBV detection

There are no routine HBV screening programs in Quebec except for pregant women, Chronic HBV may be diagnosed through 1) pre-natal screening, 2) chronic sequelae of HBV ie compensated, decompensated cirrhosis or HCC, 3) other liver associated conditions that will precipiate HBV screening (alcoholic liver disease, other liver disease, congestive heart failure), 4) co-morbidities that put the person at risk for HBV such as HIV or HCV infection, 5) TB because the presence of chronic HBV may increase the risk of INH hepatotoxity, 6) Cancers or rheumatologic conditions because of concern about virus reactivation due to chemotherapy or other immunosuppresive therapy.

The MED-ÉCHO and Physician Billing databases with ICD 9/10 codes were used to identify these conditions.[133,142] Details of ICD 9/10 codes used to identify co-morbidities are outlined in Appendix 4. Deliveries were identified in the 9 months after the diagnosis through the universal presence of a delivery procedure code (code 6903: vaginal, code 6912: caesarean, and code 6913: caesarean plus hysterectomy) in the RAMQ physician billing database. This should capture 99% of all pregnancies in this cohort since almost all deliveries (>99%) in Quebec occur

in the hospital and this code is required for the physician to be paid for the delivery. For other conditions we identified diagnostic codes 1, 2 or 3 months before or after the diagnosis. Data from FSP was to identify certain conditions such as diabetes and HIV that have disease specific medications. In addition to diagnostic codes, methadone prescriptions was used to identify drug abuse (Appendix 5).

4.5 Statistical analysis

4.5.1 Descriptive analysis

All analyses were performed in SAS software (SAS version 9.4, SAS Institute, Cary, North Carolina, USA). Descriptive statistics were performed on the cohort of all reported cases of acute and chronic HBV during the study period (1991-2008). Continuous variables such as age and time since arrival were reported with mean, median, and range of values. Means for immigrants and non-immigrants were compared using Student's *t* tests. Categorical variables including age, sex, region of origin, immigration class, and medical co-morbidities were reported as frequencies and percents, and groups were compared using χ^2 tests.

4.5.2 Cumulative incidence of reported acute and chronic HBV

Annual cumulative incidence of reported acute and chronic HBV rates/100,000 population and 95% confidence intervals (CI) were calculated for immigrants and non-immigrants between 1991-2008. Numerators of the annual number of cases were derived from the created linked hepatitis database. The denominators of the total population of immigrants and non-immigrants living in Quebec each year during the study period were calculated from census data in 1991, 1996, 2001, and 2006 with linear extrapolation for the intercensal years. Since data for 2008 was available only until June 30, the half of the population in 2008 was used. This was possible as

census data is stratified by immigrant status (immigrant vs. non-immigrant) and the country of origin of the immigrants. Stage-specific cumulative incidence rates of reported cases in the immigrant population were stratified by age, gender, region of origin, and immigration class and for the Canadian-born, stratified by age and gender. Rate ratios and 95% CI of overall and stratum-specific disease incidence in immigrants compared to the Canadian-born population were calculated.

4.5.3 Percent change per year

The percent change per year of cumulative incidence rates of reported acute and chronic HBV in immigrants and non-immigrants over the study period was estimated with Poisson regression adjusting for age and sex. For either immigrants or non-immigrants, the model included rates as the outcome and year of diagnosis (calendar year) as the main covariate, adjusting for age and sex. The percentage change per year was computed as follows: $100*(e^{ß}-1)$, where ß represents the coefficient of the time variable (year) in the model.

4.5.4 Medical co-morbidities

We described the pattern of underlying conditions or co-morbidities that may have led to the detection of chronic HBV in immigrants and non-immigrants. Proportions of deliveries or pregnancy-related events including miscarriage and stillbirth that occurred in the 9 months after the diagnosis or all co-morbid or high-risk conditions (HIV, HCV, TB, liver diseases, compensated and decompensated cirrhosis, HCC, ETOH abuse, IDU, cancers, and rheumatologic conditions) that occurred one month prior to and one month after the diagnosis were estimated.

4.5.5 Inverse probability weighting

We assessed the impact of unlinked cases on the estimated acute and chronic HBV cumulative incidence rates using the inverse probability weighting (IPW) method. This approach adjusts for missing data using the weighting scheme. The idea underlying IPW for missing data is to perform a complete case (CC) analysis and weight the CC by the inverse of their probability of having data observed, i.e., not being missing. Observed outcomes were up-weighted by one divided by the probability of being measured to compensate for those similar subjects who were missing.[115,116] The predictive value of the Forward Sortation Areas (FSA), i.e., the three first digit of the postal code used as a proxy for residence area, age, and sex were used to predict immigrant status for unlinked cases. The first three digits of the postal code with hepatitis type is a good proxy for immigrant status because immigrants tend to live in certain areas in Quebec. First, using complete cases characteristics, FSA was modeled as the dependent variable in a multiple logistic regression including age, sex, and HBV year of diagnosis as predictors. The intercept and the regression coefficients for the model were used to calculate predictive probabilities. These predictive probabilities were used to generate weights that were applied into the dataset. From this model, the predictive value of FSA to be observed was computed and an inverse proportional weight was assigned. The distribution of weights was similar for immigrants and non-immigrants. Thus, a second model was computed with immigration status as dependent variable (observed/not observed) and adjusted for age, sex, FSA, and year of HBV diagnosis. Similarly, a weight (the inverse probability of immigration status being observed) was assigned to observed cases. A final weight was assigned as the product of weights from the two models. Weighted and unweighted incidence rates were calculated. Rate ratios with 95% CI between

immigrants and non-immigrants for unweighted and weighted cumulative incidence rates were estimated and compared.

5 Results

5.1 Cohort of reported hepatitis cases from MADO database

The construction of the cohort for acute HBV with exclusions at different steps is presented in Figure 5-1 and for Chronic HBV in Figure 5-2. From 1991 to 2008, a total of 3460 cases of acute HBV, 17,721 cases of chronic HBV and 3417 cases of indeterminate HBV that were reclassified as chronic HBV were reported.

Of the 3460 acute HBV cases that were identified, 2 (0.06%) were excluded because of duplicates and 671 (19.4%) were unlinked. Of the remaining 2787 cases, 170 (6.1%) occurred in immigrants and 2617 (93.9%) occurred in non-immigrants. An additional of 19 (11.2%) acute HBV cases in immigrants were excluded because the episode occurred before permanent resident status in Quebec or the episode occurred after the person became non-eligible for RAMQ. Only 18 (0.7%) acute HBV cases were excluded in non-immigrants, primarily because they became non-eligible for RAMQ. (Figure 5-1).

A total of 21,001 cases of chronic HBV were identified but 5,623 (26.8%) were excluded because they did not link to the RAMQ databases. A total of 6907 (44.9%) of cases occurred in immigrants and 8327 (56.9%) occurred in non-immigrants. An additional 601 (8.7%) of chronic HBV cases in immigrant were excluded because the episode occurred before being granted permanent residence in Quebec or because the episode was diagnosed after the individual became ineligible for RAMQ. Only 144 (1.7%) chronic HBV cases were excluded in non-immigrants, primarily because they became non-eligible for RAMQ. (Figure 5-2)

Figure 5-1. Flow chart of cohorts' creation- Acute HBV

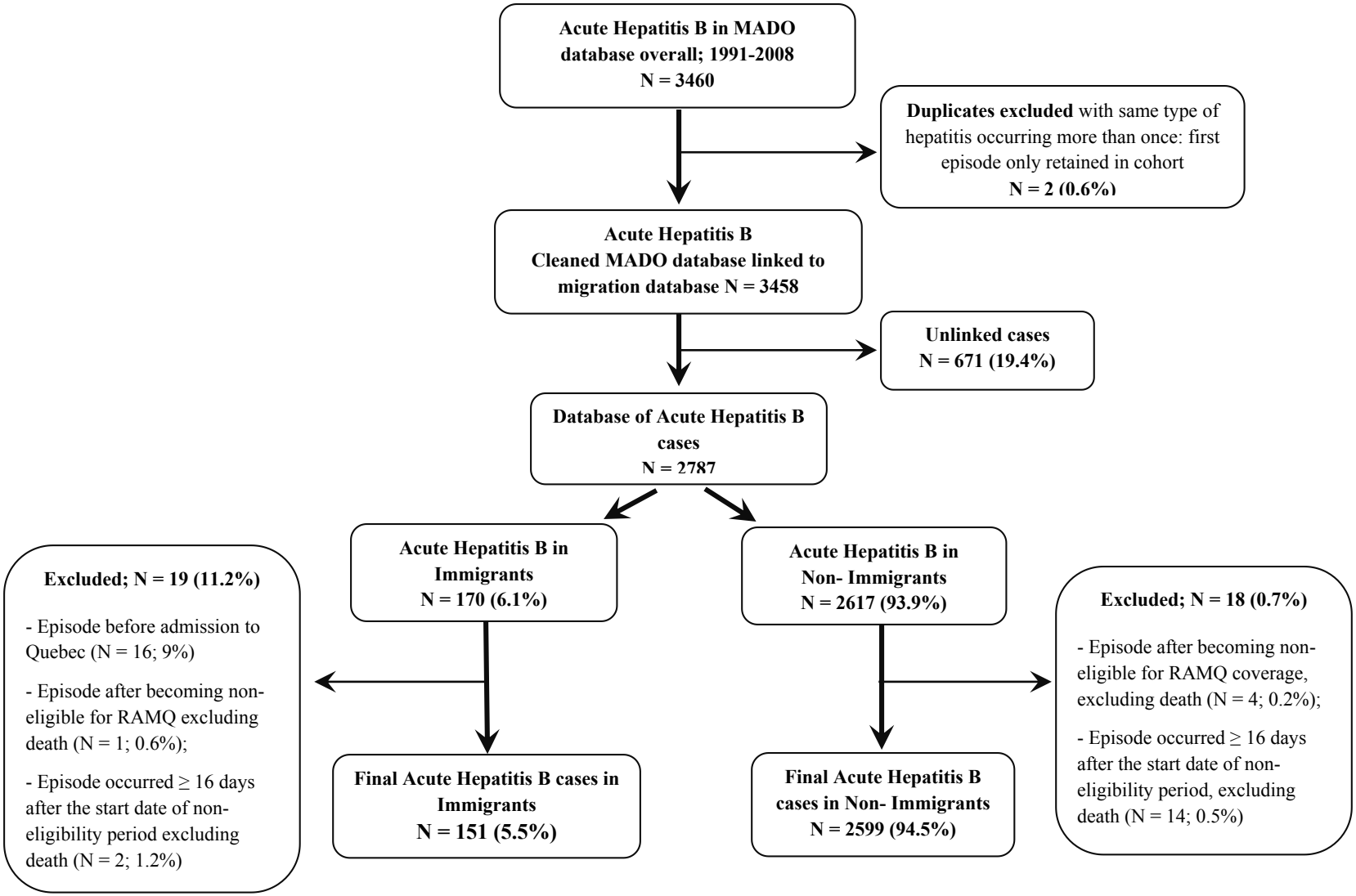
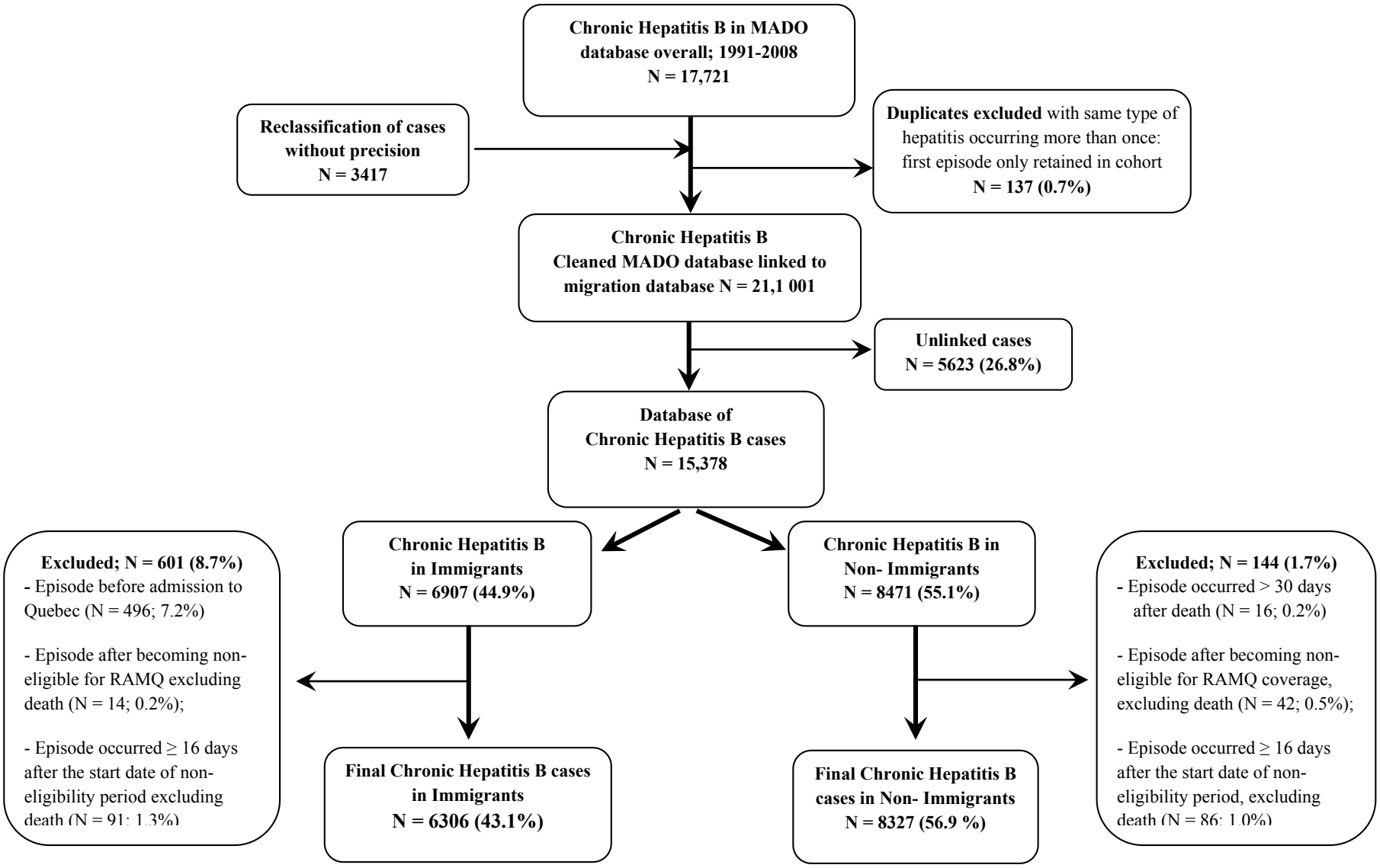


Figure 5-2. Flow chart of cohorts' creation- Chronic HBV



5.2 Characteristics of reported rates of acute HBV cases

Population characteristics are shown in table 5-1. Immigrants accounted for 5.5% (n=151) of reported acute HBV cases. Immigrants were younger than non-immigrants (mean age 30.2 vs. 37.7 years; p<.001). The age distribution in immigrants was bimodal with a peak in those <5 years of age and a second peak in those 30-39 years of age (Figure 5-3). The majority of cases (71%) occurred in males both immigrants and non-immigrants. The largest proportion of immigrants originated from East Asia and the Pacific (26%), Latin America and the Caribbean (22%), and the Middle East and North Africa (13%). Most of migrants were in economy and family class (immigrants; 66%).

Table 5-1. Demographic characteristics of reported Acute HBV cases

Characteristics	Immigrants N=151 (5.5)	Non-immigrants N=2599 (94.5)	P value
Age (years)			
Mean ± SD	30.2 ± 15.2	37.7 ± 13.8	<.0001
Sex			
Female	44 (29.1)	760 (29.2)	0.97
Male	107 (70.9)	1839 (70.8)	
Immigration category			
Refugees	44 (29.1)		
Other immigrants†	99 (65.6)		
Regions of origin			
East Asia and the Pacific	39 (25.8)		
Latin America and the Caribbean	33 (21.8)		
South Asia	10 (6.6)		
Western Europe	18 (11.9)		
Middle East and North Africa	20 (13.3)		
Sub-Saharan Africa	11 (7.3)		
Eastern Europe and Central Asia	11 (7.3)		
US, Australia, and New Zealand	1 (0.7)		
Time between arrival and diagnosis (years)			
Mean ± SD	6.7 ± 5.9		
Min-Max	2 days- 27.5		

Results are presented as n (%).† Included permanent residents who were workers, spouses, children, and students.

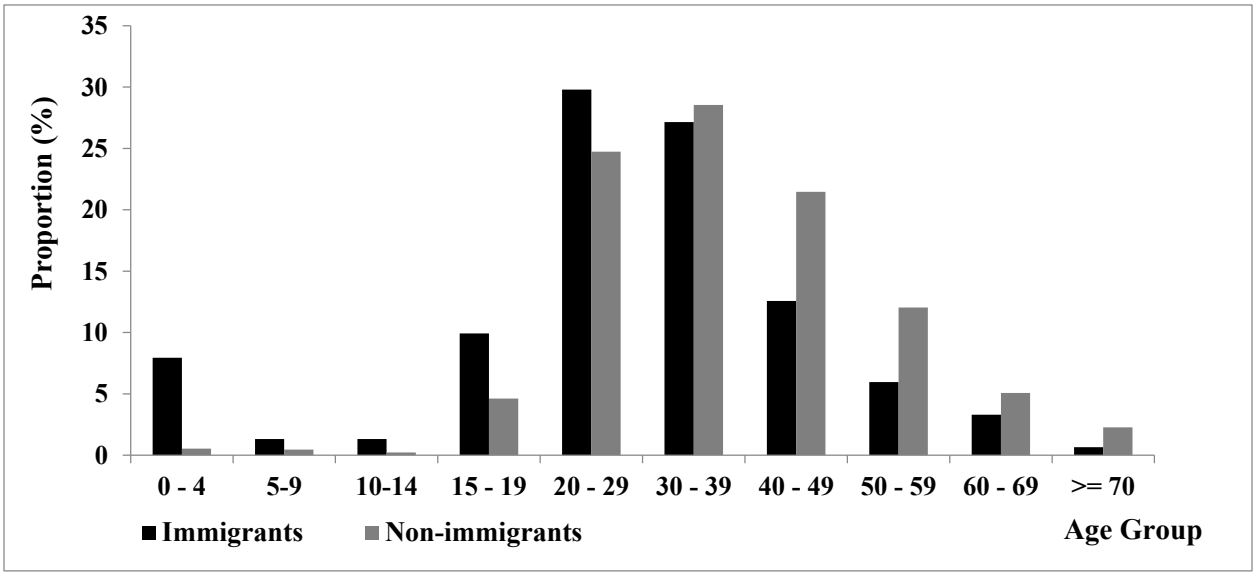
Overall, the mean time to diagnosis after arrival to Quebec increased with age and those less than 5 years of age had the shortest mean time to diagnosis (Table 5-2).

Table 5-2. Time (years) to Acute HBV diagnosis in immigrants since time of arrival

Age group	Immigrants	Non-immigrants	Time to diagnosis in immigrants		
			N	Min- Max	Mean ± SD
0 - 4	12 (7.9)	14 (0.5)	12	0.03-0.2	0.09 ± 0.06
5 - 9	2 (1.3)	12 (0.5)	2	0.23-0.9	0.58 ± 0.49
10 - 14	2 (1.3)	6 (0.2)	2	0.66-9.6	5.15 ± 6.35
15 - 19	15 (9.9)	120 (4.6)	14	1.27-10.7	5.38 ± 2.97
20 - 29	45 (29.8)	643 (24.7)	44	0.18-16.9	5.67 ± 4.39
30 - 39	41 (27.2)	742 (28.6)	39	0.49-19.9	7.1 ± 5.71
40 - 49	19 (12.6)	558 (21.5)	16	0.01-27.5	12.38 ± 7.45
50 - 59	9 (6.0)	313 (12.0)	9	6.05-23.2	12.35 ± 6.16
60 - 69	5 (3.3)	132 (5.1)	5	0.07-17.5	7.04 ± 6.58
≥ 70	1 (0.7)	59 (2.3)	0	-	-

Results are presented as n (%)

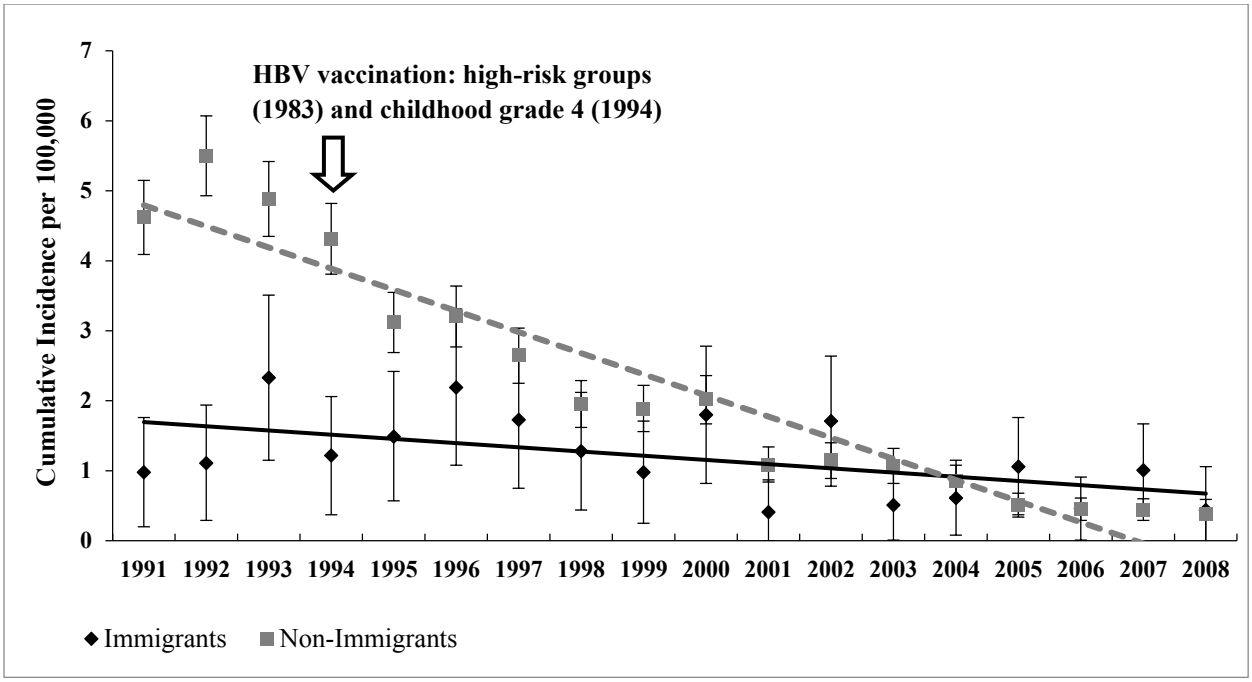
Figure 5-3. Age at Acute HBV diagnosis of reported cases by immigration status



5.3 Annual cumulative incidence of reported rates of acute hepatitis B infections in immigrants as compared to the Canadian-born population

Over the study period as a whole, the reported cumulative incidence rate was higher in non-immigrants vs. immigrants (2.3/100,000 vs. 1.2/100,000) with a rate ratio of 0.5 (95% CI=0.4-0.6) (Table 1, Appendix 6). Cumulative incidence rates of acute HBV decreased in non-immigrants by 12.7% per year and only by 4.2% per year in immigrants (Figure 5-4).

Figure 5-4. Trend in cumulative incidence rates of reported cases of Acute HBV



HBV incidence rates decreased annually by 12.7 % per year in non-immigrants, and decreased by 4.2 % per year in immigrants over the study period. Annual change in rates were estimated with Poisson regression and adjusted for age and sex.

Cumulative incidence stratified by age group are shown in Table 2, Appendix 6. In summary, in non-immigrants, rates were highest in the 15-39 year old group, slightly lower in the ≥40 years old group and lowest in those <15 years old [3.7/100,000 vs. 2.1 vs 0.14] (Table 5-3). In immigrants, rates were highest in the 15-39 years age group (2.2/100,000). Immigrant children <

15 years of age had lower rates, however they had a 12.9 fold higher rate compared to non-immigrants [1.81/100,000 vs 0.14] (Table 5-3).

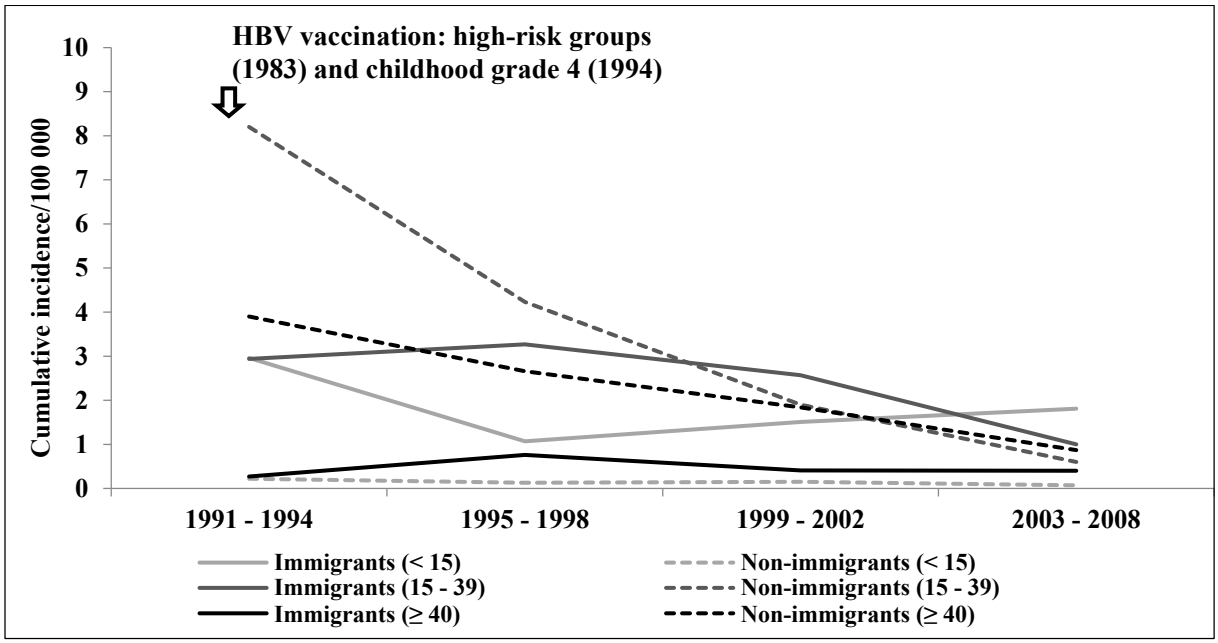
Table 5-3. Cumulative incidence rates of reported case of Acute HBV by age group

Age Group	Immigrants Rate (95% CI)	Non-Immigrants Rate (95% CI)	Rate Ratio
Overall	1.17 (1.0-1.37)	2.26 (2.17-2.34)	0.52 (0.44-0.61)
<15 years	1.81 (0.92-2.7)	0.14 (0.09-0.19)	12.9 (7.1-23.5)
15-39 years	2.24 (1.80-2.67)	3.66 (3.48-3.84)	0.61 (0.50-0.75)
≥40 years	0.45 (0.30-0.61)	2.07 (1.95-2.20)	0.22 (0.16-0.31)

Overall, the reported rates of acute HBV infection cases declined in almost all age-group during the study period (Figure 5-4). In non-immigrants, rates decreased in all age groups, mainly in 15-39 years old by 14.6% /year, and by 9.6% per year in those older than 40 years of age and by 4%/ year in those <15 years ($p < 0.001$). In immigrants, rates decreased by 4.9% /year only in 15-39 year olds, and no significant change was observed in the younger <15 years ($p=0.29$) and those older than 40 years of age ($p=0.12$) (Figure 5-5).

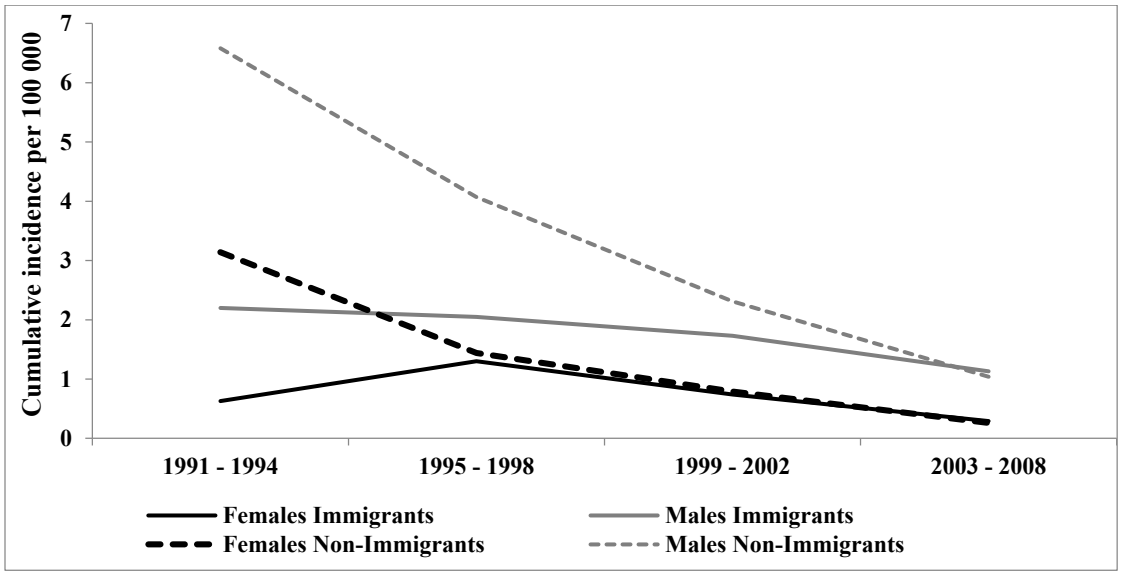
Cumulative incidences stratified by sex are shown in Table 3, Appendix 6. In summary, cumulative incidence rates were lower in females as compared to males for both immigrants (0.7 vs 1.7/100,000) and non-immigrants (1.3 vs. 3.3/100,000), with rates ratios of 0.4. Rates were higher however in non-immigrants males and females as compared to their immigrant counterparts. Rates decreased more dramatically in non-immigrants females and males (15.2% and 11% per year) as compared to non-immigrant females and males (3% per year) (Figure 5-6).

Figure 5-5. Trend in cumulative incidence rates of reported cases of Acute HBV stratified by age group



In non-immigrants rates decreased by 4%/ year in those <15 years, by 14.6% /year in 15-39 year olds, and by 9.6% per year in those older than 40 years of age. In immigrants rates only decreased in 15-39 year olds by 4.9% /year. Annual change in rates were estimated with Poisson regression and adjusted for sex and year at diagnosis.

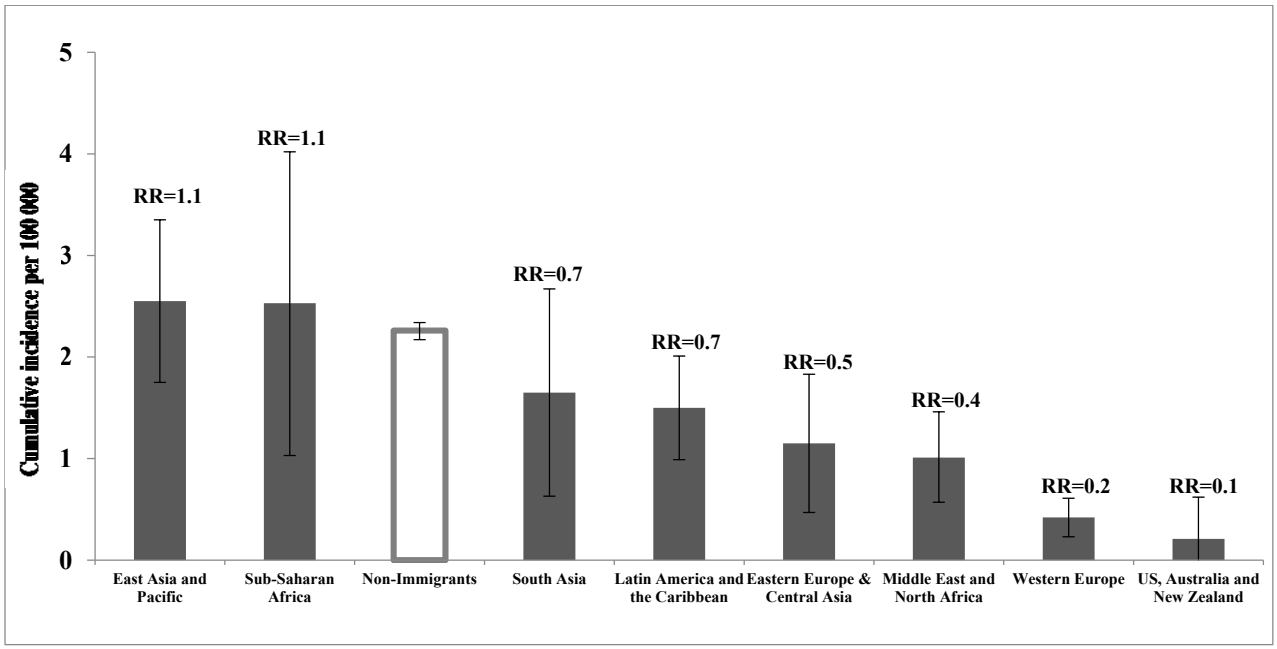
Figure 5-6. Trend in cumulative incidence rates of reported cases of Acute HBV stratified by sex



In non-immigrants, incidence rates decreased by 15% per year in females and 11.7% per year in males over the study period. Rates decreased less dramatically in immigrants compared to non-immigrants, but only in males decrease by 3% per year. Annual change in rates were estimated with Poisson regression and adjusted for age and year at diagnosis.

Cumulative incidence rates of reported cases of acute HBV were similar in immigrants from East Asia and Sub-Saharan Africa compared to non-immigrants. All other regions of origin had lower cumulative incidence compared to the non-immigrant population. (Figure 5-7; Table 4, Appendix 6).

Figure 5-7. Cumulative incidence rates of reported Acute HBV cases stratified by the region of origin



RR : Rate ratio comparing rates in immigrant vs. Non-immigrants

5.4 Characteristics of reported cases of chronic HBV

Population characteristics are shown in table 5-4. Immigrants accounted for 43.1% (N=6306) of chronic HBV cases. Immigrants were younger (34.6 vs. 43.7 years, p<.001) and were less likely to be males (53.2% vs. 68.7%) compared to non-immigrants. The peak age groups for immigrants was 30-39 years whereas for non-immigrants was 40-49 years (Figure 5-8). Almost half of cases in immigrants originated from East Asia and the Pacific (47.2%) and 11.7% originated from Sub-Saharan Africa (Table 5-4). Overall, the mean time to diagnosis after admission was 6.3 years (range 0-28.4) and increased with age where those less than 5 years of age had the shortest

Table 5-4. Demographic characteristics of reported Chronic HBV cases

Characteristics	Immigrants N=6306 (43.1)	Non-immigrants N=8327 (56.9)	P value
Age (years)			
Mean ± SD	34.6 ± 13.1	43.7 ± 14.8	<.0001
Sex			
Female	2952 (46.8)	2608 (31.3)	<.0001
Male	3354 (53.2)	5719 (68.7)	
Immigration categories			
Refugees	1340 (21.3)		
Other immigrants†	4212 (66.8)		
Regions of origin			
East Asia and the Pacific	2979 (47.2)		
Sub-Saharan Africa	735 (11.7)		
Latin America/ and the Caribbean	582 (9.2)		
Middle East and North Africa	512 (8.1)		
Eastern Europe and Central Asia	431 (6.8)		
South Asia	196 (3.1)		
Western Europe	98 (1.6)		
US, Australia, and New Zealand	5 (0.1)		
Time between arrival and diagnosis (years)			
Mean ± SD	6.3 ± 6.1		
Min-Max	0- 28.4		

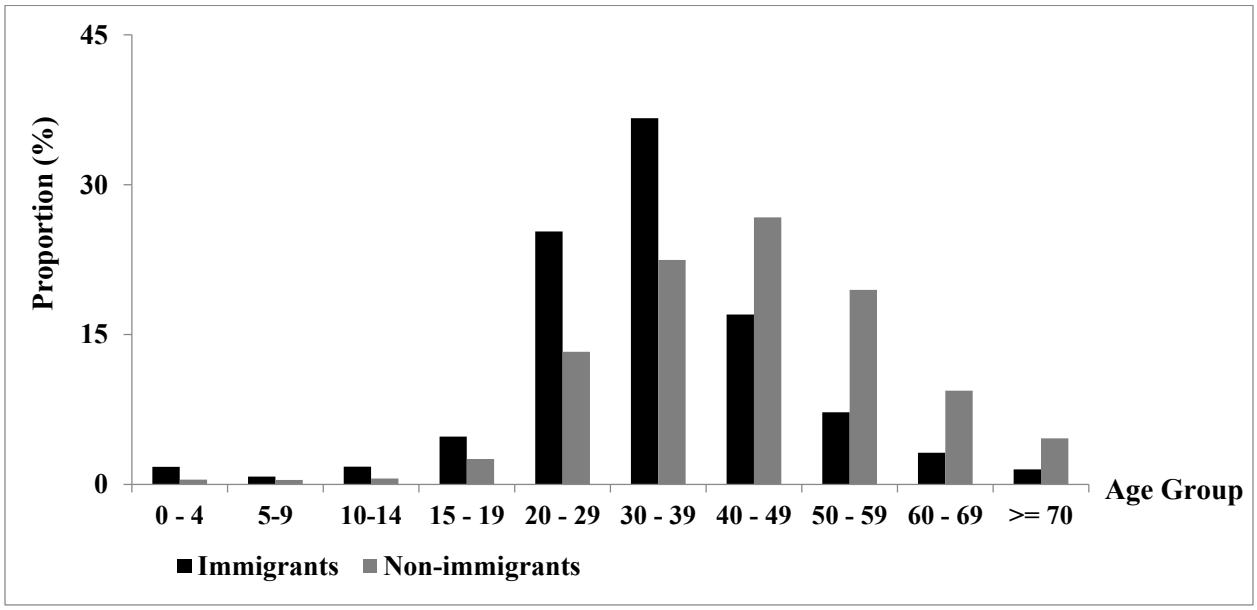
Results are presented as n (%)

† Included permanent residents who were workers, spouses, children, and students.

Table 5-5. Time from admission to Chronic HBV notification stratified by age group

Age group	Immigrants	Non-immigrants	Time to diagnosis in immigrants (years)		
			N	Min- max	Mean ± SD
0 - 4	111 (1.8)	40 (0.5)	110	0-13.3	0.33± 0.53
5 - 9	50 (0.8)	38 (0.5)	48	0-46.7	1.48± 1.81
10 - 14	112 (1.8)	49 (0.6)	105	0-14.4	4.17± 4.19
15 - 19	302 (4.8)	212 (2.6)	283	0-18.7	6.05± 4.75
20 - 29	1596 (25.3)	1105 (13.3)	1457	0-26.6	5.31± 5.54
30 - 39	2312 (36.7)	1870 (22.5)	1937	0-28.4	5.26± 5.52
40 - 49	1072 (17.0)	2225 (26.7)	927	0-28	8.18± 6.34
50 - 59	456 (7.2)	1622 (19.5)	414	0-427.4	10.13± 7.14
60 - 69	200 (3.2)	781 (9.4)	186	0-26.6	10.32± 6.88
≥70	95 (1.5)	385 (4.6)	85	0.26-27.3	11.75± 6.97

Figure 5-8. Age at Chronic HBV diagnosis by immigration status



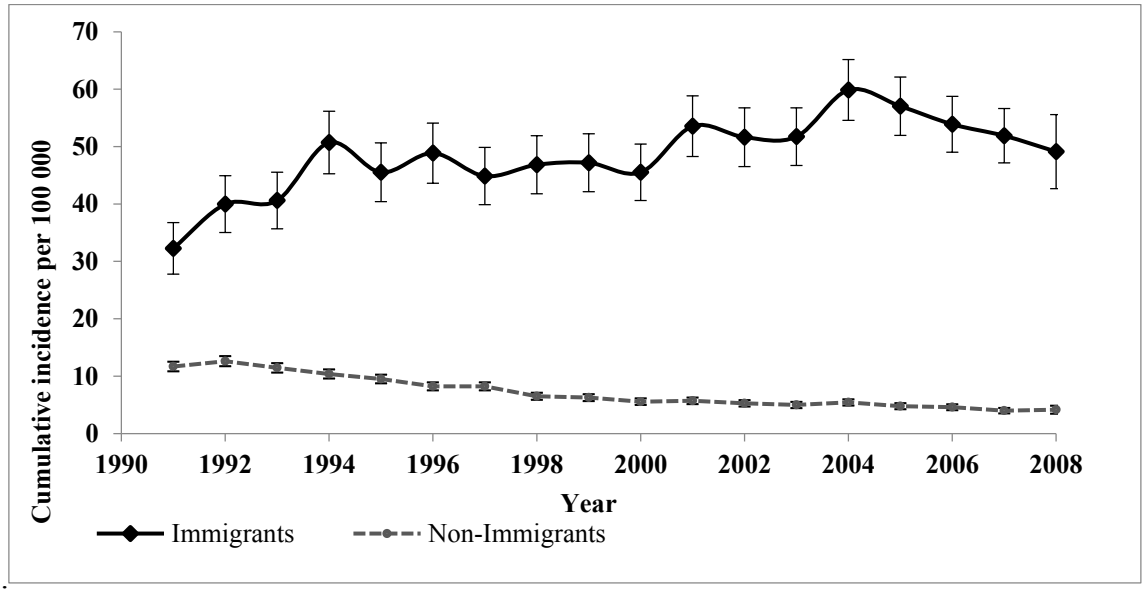
5.5 Annual cumulative incidence rates of reported cases of chronic HBV infections in immigrants as compared to the Canadian-born population

Over the study period, the overall cumulative incidence rates of reported cases was 6.8/100,000 (95% CI=6.6-7.0) and was higher in immigrants compared to non-immigrants (48.9/100,000 vs. 7.23) (Table 5, Appendix 7). Incidence rates decreased by 7.2% annually in non-immigrants, whereas it increased by 1.9% per year in immigrants (Figure 5-9). Cumulative incidences stratified by age group are show in Table 6, Appendix 7. Immigrants 15-39 years of age had the highest cumulative incidence (93.3/100,000) and this decreased dramatically in those >40 years of age (24.4/100,000). Immigrant children < 15 years of age had a 55.4 fold higher incidence as compared to their non-immigrant counterparts (30.8/100,000 vs. 0.56) (Table 5-6). In non-immigrants rates decreased in all age groups over the study period, by 11.9%/ year in those <15 years, by 11.6% /year in 15-39 year olds, and by 5.4% per year in those older than 40 years of age. In contrast, in immigrants rates decreased only in those <15 years of age (6.5% per year) whereas rates increased in other age groups. In those 15-39 years old, rates increased by 2.1% per year and in those >40 years of age by 3.4% per year (Figure 5-10).

Table 5-6. Cumulative incidence rates of reported case of Chronic HBV by age group

Age Group	Immigrants Rate (95% CI)	Non-Immigrants Rate (95% CI)	Rate Ratio
Overall	48.9 (47.8-50.2)	7.2 (7.1-7.4)	6.8 (6.6-7.0)
<15 years	30.8 (27.2-34.5)	0.6 (0.5-0.6)	55.4 (44.9-68.4)
15-39 years	90.3 (90.5-96.1)	7.7 (7.5-8.0)	12.0 (11.5-12.6)
≥40 years	24.4 (23.3-25.5)	9.8 (9.5-10.1)	2.5 (3.4-2.6)

Figure 5-9. Trend in cumulative incidence rates of reported cases of Chronic HBV



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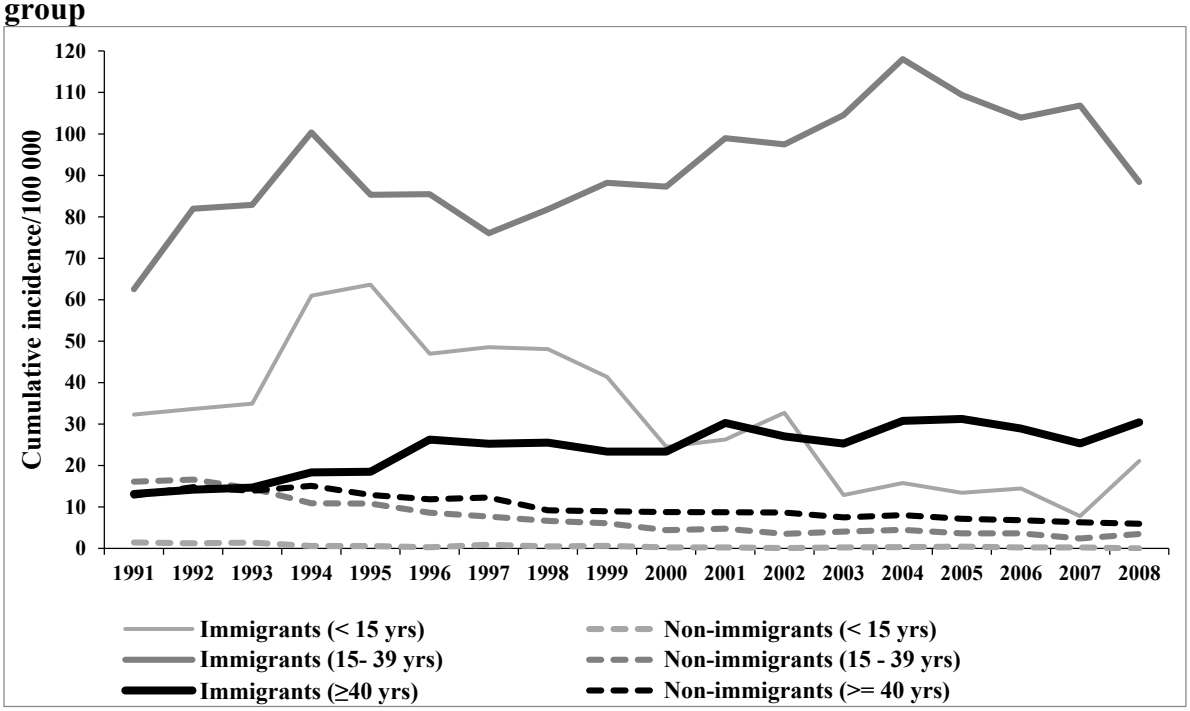
HBV incidence decreased annually by 7.2% in non-immigrants, and increased by 1.9% in and immigrants respectively. Annual change in rates were estimated with Poisson regression and adjusted for age and sex.

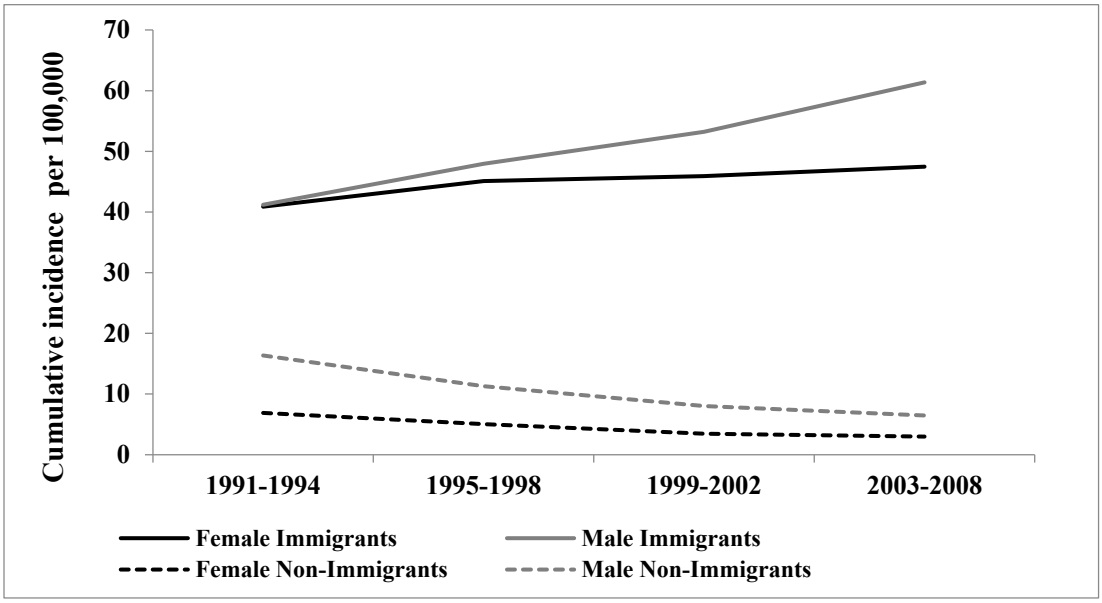
Figure 5-10. Annual incidence rates of reported cases of Chronic HBV stratified by age group



In non-immigrants rates decreased by 11.9%/ year in those <15 years, by 11.6% /year in 15-39 year olds, and by 5.4% per year in those older than 40 years of age. In immigrants rates decreased only in those <15 years of age and decreased by 6.5% per year. Rates increased in other age groups and by 2.1% per year in those 15-39 years old and by 3.4% per year in those >40 years of age. Annual change in rates were estimated with Poisson regression and adjusted for sex and year at diagnosis.

Rates were higher in males for both immigrants and non-immigrants (Table 9, Appendix 7). In non-immigrants, incidence rates in both females and males at a similar rate over the study period, 6.9 % and 7.3% respectively. Rates increased in both female and male immigrants, but increased at a lower rate in females as compared to males (0.9% and 2.8% per year) (Figure 5-11). The highest cumulative incidence occurred in immigrants from East Asia and the Pacific (191.4/100,000), Sub Saharan Africa (162.2/100,000) and Eastern Europe and Central Asia (31.5). (Figure 5-12). Rate ratios for different regions of origin ranged from 3.7 to 26.7 (Table 11, Appendix 7).

Figure 5-11. Annual incidence rates of reported Chronic Hepatitis B cases stratified by sex

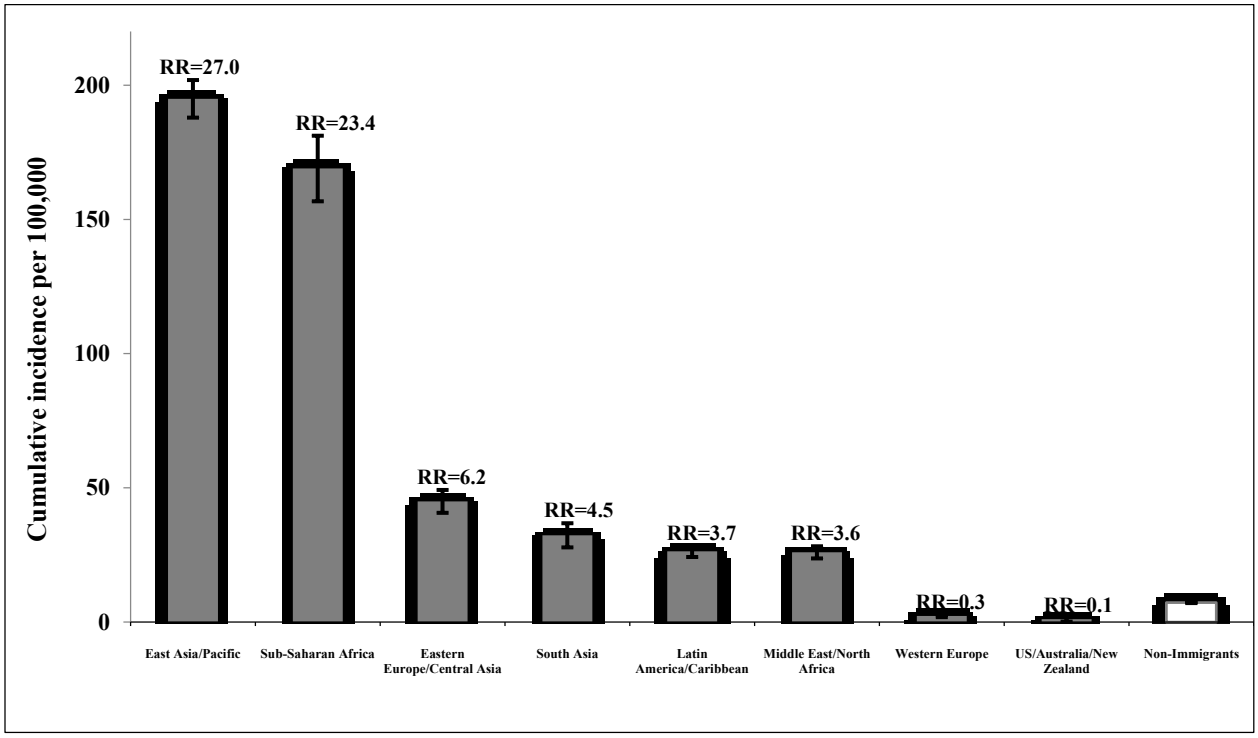


In non-immigrants, incidence rates decreased by 6.9 % per year in females and 7.3% per year in males over the study period. In contrast rates increased in immigrant males increased by 2.8% per year and by 0.9% per year in immigrant females. Annual change in rates were estimated with Poisson regression and adjusted for age and year at diagnosis.

Table 5-7. Cumulative incidence rates (95% CI) of reported case of Chronic HBV stratified by sex and age group

Age group	Immigrants		Non-Immigrants	
	Female	Male	Female	Male
Overall	45.3	52.6	4.4	10.1
	(43.7-47.0)	(50.8-54.4)	(4.3-4.6)	(9.9-10.4)
<15 years	31.8	29.8	0.6	0.6
	(26.6-36.9)	(24.6-35.0)	(0.4-0.7)	(0.4-0.7)
15-39 years	94.3	92.0	5.3	10.2
	(90.3-98.3)	(88.0-95.9)	(4.9-5.6)	(9.8-10.7)
≥40 years	17.5	31.4	5.4	14.7
	(16.2-18.9)	(29.5-33.2)	(5.1-5.7)	(14.2-15.2)

Figure 5-12. Cumulative incidence of reported Chronic HBV cases stratified by region of origin



RR : Rate ratio comparing rates in immigrant vs. non-immigrants

5.6 Pattern of underlying co-morbidities that may have led to the detection of chronic hepatitis B in immigrants and non-immigrants

Overall, pregnancy was the most prevalent condition that led to the detection of chronic HBV in immigrants as compared to non-immigrants (14.8% vs. 3.5%), followed by cancer (2.5% vs. 5.6%), diabetes mellitus (2.4% vs. 2.9%), co-infections (HIV, Tuberculosis) (2% vs. 2.6%), and liver complications (compensated cirrhosis, decompensated cirrhosis, and HCC) (1.9% vs. 5.6%). Restricting analysis only among women of childbearing age, pregnancy represented 42.5% in immigrant compared to 26% in non-immigrants (Tables 5-8 and 5-9). Comparing immigrants and non-immigrants 40 years old or greater, cancer (8.4% vs. 13.7%), diabetes mellitus (8.2% vs. 9%), liver complications (4.3% vs. 8.3%), and co-infections (3.2% vs. 3.3%) were the most prevalent conditions led to the detection of chronic HBV (Table 12, Appendix 7).

Table 5-8. Prevalent medical conditions 1 month before and 1 month after Chronic HBV diagnosis

Medical condition	Immigrants		Non-immigrants		Total	
	1 month before	1 month after	1 month before	1 month after	Immigrants	Non-immigrants
Compensated cirrhosis	41	37	223	191	64 (1.01)	313 (3.76)
Decompensated cirrhosis	16	9	90	37	22 (0.35)	114 (1.37)
Hepatocellular carcinoma	24	12	31	23	33 (0.52)	43 (0.52)
HIV	28	34	99	152	47 (0.75)	199 (2.39)
Tuberculosis	45	42	11	11	76 (1.21)	18 (0.22)
Alcohol abuse	23	14	196	101	31 (0.49)	268 (3.22)
Drug abuse	10	3	75	26	12 (0.19)	98 (1.18)
Diabetes mellitus	68	94	90	177	148 (2.35)	242 (2.91)
Congestive heart failure	9	5	61	44	13 (0.21)	94 (1.13)
Pregnancy (delivery)	45	891	27	268	935 (14.83)	295 (3.54)
Pregnancy related	2	1	8	7	3 (0.05)	14 (0.17)
Cancer	88	112	240	329	155 (2.46)	464 (5.57)
Solid neoplasms	49	59	151	196	82 (1.30)	272 (3.27)
Hematopoietic conditions	12	18	36	73	21 (0.33)	87 (1.04)
Rheumatologic conditions	4	7	30	18	8 (0.13)	41 (0.49)
Miscellaneous	10	14	35	29	21 (0.33)	54 (0.65)

Results are presented as n (%)

Table 5-9. Prevalence of medical conditions 1 month before and 1 month after Chronic HBV diagnosis among women of childbearing age (15-39 years)

Medical condition	Immigrant Females		Non-immigrant Females		Total Females	
	1 month before	1 month after	1 month before	1 month after	Immigrants	Non-immigrants
Compensated cirrhosis	1	1	5	7	1 (0.05)	9 (0.84)
Decompensated cirrhosis	1	0	2	0	1 (0.05)	2 (0.19)
Hepatocellular carcinoma	0	0	0	1	0 (0.00)	1 (0.09)
HIV	3	5	5	5	7 (0.33)	9 (0.84)
Tuberculosis	12	12	0	1	21 (0.98)	1 (0.09)
Alcohol abuse	2	6	9	2	6 (0.28)	11 (1.02)
Drug abuse	2	1	7	4	2 (0.09)	10 (0.93)
Diabetes mellitus	9	20	4	6	27 (1.26)	8 (0.74)
Congestive heart failure	0	0	1	0	0 (0.00)	1 (0.09)
Pregnancy (delivery)	42	869	26	254	910 (42.5)	280 (26.02)
Pregnancy related	0	0	1	1	0	1 (0.09)
Cancer	9	15	9	15	22 (1.03)	20 (1.86)
Solid neoplasms	2	1	3	3	3 (0.14)	5 (0.46)
Hematopoietic conditions	1	1	1	0	2 (0.09)	1 (0.09)
Rheumatologic conditions	1	1	1	1	1 (0.05)	2 (0.19)
Miscellaneous	0	1	3	4	1 (0.05)	4 (0.37)

Results are presented as n (%)

5.7 Inverse probability weighting

Results of the inverse probability weighting are summarized in tables 5-10 and 5-11. More details are shown in appendices 6 and 7, Tables 5 & 13. For cumulative incidence rates of reported cases of acute HBV, unweighted and weighted rate ratios (0.5 [0.4-0.6], and 0.5 [0.47-0.6]) of immigrants vs. non-immigrants were similar. Likewise, the unweighted and weighted rate ratios (6.8 [6.6-7.0] and 7.0 [6.8-7.2]) of immigrants vs. non-immigrants for the cumulative incidence rates of reported cases of chronic HBV overlapped.

Table 5-10. Unweighted vs. weighted cumulative incidence rates of reported Acute HBV cases

	Cumulative incidence rates		Rate ratio
	Immigrants	Non-immigrants	
Unweighted	1.17 (0.98-1.36)	2.26 (2.17-2.34)	0.52 (0.44-0.61)
Weighted	1.62 (1.40-1.84)	3.01 (2.91-3.11)	0.54 (0.47-0.62)

Table 5-11. Unweighted vs. weighted cumulative incidence rates of reported Chronic HBV cases

	Cumulative incidence rates		Rate ratio
	Immigrants	Non-immigrants	
Unweighted	48.94 (47.73-50.15)	7.23 (7.07-7.38)	6.77 (6.55-7.00)
Weighted	66.62 (65.21-68.03)	9.53 (9.36-9.71)	6.99 (6.79-7.19)

6 Discussion

6.1 Summary of main findings

6.1.1 Acute HBV

From 1991 through 2008, a total of 2750 acute HBV cases were identified and successfully linked to healthcare and immigration databases. Immigrants accounted for only 5.5% (N=151) and were younger than non-immigrants. Time to diagnosis since arrival to Quebec was shorter in the youngest age group. In both immigrants and non-immigrants, the majority of cases occurred in males. Over the study period, the overall cumulative incidence of reported cases decreased in both immigrants and non-immigrants and in both sexes. The decline in rates was more marked in non-immigrants as compared to immigrants over the study period. In immigrants, rates also declined in those aged 15-39 years and non-significant change has been observed in other age groups.

The pattern of decreasing reported rates of acute HBV cases observed in this study is similar to results obtained in surveillance data from Canada[78,110,117] and elsewhere (USA, Australia, England, and EU)[119,143-145]. A recent report from the surveillance conducted by the Public Health Agency of Canada showed a declining trend from 1.0 to 0.6 per 100,000 observed between 2005 and 2011.[78] Also, between 1992 and 2001, rates of acute HBV infection decreased dramatically from 5.0/100,000 to 0.6/100,000 population.[3] In Manitoba, acute HBV infection has decreased dramatically from 6.5 per 100,000 person-years to 0.86 per 100,000 person-years, between 1996 and 2003.[146] In the United States, the rate declined from 8.4 to 2.6 per 100,000 between 1980 and 2003.[147] The decreasing rate of acute HBV in Canada is likely due to several factors including: implementation of universal childhood vaccination programs, targeted vaccination programs for

groups at risk, such as health care workers, MSM, IDUs, and change in high risk behaviors in certain settings.[105]

Regarding vaccination, in 1991, all provinces and territories have implemented a universal school-based HBV vaccination program targeting preadolescents 9 to 13 years old.[106] In 1994, Quebec introduced a school-based pre-adolescent HBV vaccination program targeting children in grade 4 (age 9 years).[108] Thus, the successful implementation of the universal school-based program has contributed to decreased reported cases of acute HBV.[110,117,146] In the pre-vaccination period, the incidence of HBV among health care workers (HCWs) was as high as 50 to 120/100,000 populations [148] and the risk of infection following an HBV-positive needle stick or sharps injury was estimated to be 2% to 40%, in the absence of vaccination.[149] However, following the implementation of HBV immunization of HCWs and improvement of infection prevention and control among health care workers, the risk has decreased dramatically over the past 20 years.[3]

The only moderately decreased trend of acute HBV over the study period among immigrants suggests a differential impact of the aforementioned programs on this sub-group. The overly long mean time to diagnosis of acute HBV of 6.7±5.9 years suggests that most of these cases were acquired after arrival in Canada. It is therefore likely that exposure occurred in household or sexual contacts of an undetected carrier, due to the presence of other risk factors or through exposure during travel in HBV endemic countries. In fact, it has been shown that young children during the first decade of life, living in a household with a chronically infected person, develop new infection at a rate of 1% to 2% per year.[150,151] In a study in Quebec, rates of acute HBV decreased across all age groups except in those 10 years or younger, among whom 53% were foreign-born.[117] This highlights the need to provide catch-up vaccination to susceptible

immigrants upon their arrival to prevent HBV transmission from undetected chronic HBV infected individuals. In immigrant children <5 years old, the mean time to diagnosis after arrival was 33 days suggesting that some of these cases were imported from their countries of origin. Travel to HBV endemic countries is also an important risk factor for acquisition of HBV. Immigrants travelling to their countries of origin have a 2.8 fold higher risk of developing HBV as compared to their host population.[152] Transmission during travel in endemic areas occurs due to risky behaviours such as piercing, tattooing, casual sex or through medical procedures (blood exposure, invasive procedures, or injections).[152,153] Therefore, advice and vaccination of non-immune travellers should be provided prior to travel. Nonetheless, further investigations are needed to explore reasons for the differential and to devise effective measures to reduce the gap.

The gender-specific trends paralleled the overall downward trends in immigrants and non-immigrants. Rates were consistently higher in males. Previous reports also indicated that incidence rates for acute HBV were higher in males than females.[78,146] Consistently higher acute HBV rates in males compared to females in both immigrants and non-immigrants could be attributable, in part, to the higher propensity for males to engage in risky behaviors such as unprotected sex with multiple partners especially during travel in high endemic countries or to engage in intravenous drug use.[154] One study from the Netherlands showed that 67% (18/27) of acute HBV cases were acquired while traveling to hepatitis B endemic countries.[155] Most of cases were infected through sexual contact, through unsafe medical practice (circumcision and injections) and though inadvertent percutaneous or mucosal contact with blood or infectious fluid.[155] Another study found that males constituted a larger proportion of IDUs among people with acute HBV.[154]

In summary, our findings showed that there has been a differential impact of the vaccination and other HBV preventive programs resulting in dramatic decrease rates of reported cases of acute HBV in all age groups. The impact, however, has been much more modest in immigrants suggesting that HBV vaccination and hepatitis education programs targeting this population could be beneficial, although they represent only 5.5% of reported acute cases.

6.1.2 Chronic HBV

During the study period, a total of 14,633 reported cases of chronic HBV were identified and successfully linked to healthcare and immigration databases. Immigrants accounted for 43% of all chronic HBV cases and they were less likely to be male and were younger compared to non-immigrants. Over the study period, incidence rates of reported cases of chronic HBV decreased across all age groups in non-immigrants, whereas it increased in immigrants, especially among the 15-39 years age group. Similarly, rates decreased in both males and females among non-immigrants whereas it increased on both sexes among immigrants. The South-East Asia, Sub-Saharan Africa, and Eastern Europe and Central Asia regions had the highest rates of chronic HBV infection.

We found that immigrants have disproportionately higher rates of chronic HBV compared to non-immigrants, consistent with data reported from most developed countries. This is likely due to the fact that in the past four decades more than 70% of immigrants who arrived in Canada have originated from countries with intermediate or high rates of endemic hepatitis B had the highest rates of chronic HBV infections.[7] A study of the epidemiology of HBV in North-Western European countries study showed that, despite the very low incidence of Hepatitis B in Northern and North-Western European countries, international migration had an obvious impact on the

Hepatitis B prevalence in the investigated countries.[156] For instance, in the Netherlands 70% of the chronic HBV patients were born abroad.[156] In Sweden, among chronic HBV infections, 87.7% of notified cases were of foreign origin. In Denmark, 72% of chronic HBV cases were mother-to-child transmission and 99% of these cases were from immigrant children.[156] In the United Kingdom, 60% of cases of chronic HBV infection occurred in those born outside of the UK.[157] In the United States, almost 95% of new chronic HBV cases were imported and surveillance data from CDC suggests that among all reported cases of chronic HBV infections for whom place of birth was known, those born outside the United States accounted for about 30% vs. 3% of US born.[84,158]

Over the study period, we found that the incidence rate of reported cases of chronic HBV in non-immigrants decreased by 7.2% per year, whereas it increased by 1.9% per year in immigrants. Similar findings have been reported in the United States from 1974 through 2008, during which period the estimated number of imported chronic HBV increased nearly 17 times compared to domestic cases.[84] However, one key difference with the present study is that the number of cases imported to the United States during 1974–2008 was estimated by multiplying country-specific HBsAg prevalence by the annual number of immigrants from each country, assuming that these prevalence rates remained constant over the study period, while in reality, country-specific prevalence data may have been changing. In addition, the data used were from a variety of sources and, some represented expert consensus rather than actual serologic prevalence in the case of countries with limited epidemiologic data. More recently, data from the CNDSS showed that between 2009 and 2011, the rate of reported cases of chronic HBV decreased by 19.1%, from 14.1 to 11.4 per 100,000.[78] The CNDSS data, however, were restricted to age, sex, year of diagnosis, and reporting province/territory, and did not stratify by region of origin of immigrants.

Our findings provide more robust epidemiological information on HBV since we used well-known databases deterministically linked, including additional details about countries of origin of immigrants, and all cases were serologically confirmed.

The downward trend observed among the Canadian-born could reflect the efficiency of comprehensive preventive programs such as screening of all pregnant women since 1989 and immunization.[159] A similar trend has been observed in the USA where the estimated number of cases among U.S.-born declined from nearly 30,000 to 3,700 between 1988 and 2006.[84] In Europe, the incidence of reported HBV cases has declined from 6.7 cases per 100,000 population in 1995 to 1.5 cases per 100,000 population in 2005. [160] However, the category of case definition used and the source of reporting varied greatly between the surveillance systems in Europe. In contrast, a recent report from the European Centre for Disease Prevention and Control (ECDC) showed that the rate of reported chronic infections has increased from 5.7 per 100 000 in 2006 to 7.4 in 2013.[161] Differences may partly be due to the fact that their surveillance numbers were not stratified by immigrant status.

Increasing rates in immigrants may be due to pre-natal detection, increased detection due to increased awareness by practitioners, attention to aging immigrants presenting with underlying immunosuppressive illnesses or chronic liver conditions, or just a cohort effect of a larger pool of immigrants who have arrived since 1970s. A large proportion of reported cases (43%) in childbearing female immigrants were being detected during pregnancy, thus reflecting the efficiency of screening pregnant women, which helped identify HBV-infected female immigrants who otherwise would not have been detected. Similar findings have been reported in a recent study conducted in the US where a significantly larger percentage of HBV cases was found in foreign-born pregnant women compared with US-born.[162] This may partially explain

the increasing trend of detected chronic HBV observed in immigrant females within the age group of 15-39 years. This success story should be highlighted. Although women are being picked up in pre-natal screening, the large reservoir of chronic HBV in at-risk immigrants is being detected many years after their arrival, with the main underlying conditions that may have led to detection among older immigrants (40 years or greater) including cancer, diabetes mellitus, liver complications, and co-infections (HIV, TB). Thus increasing detection may reflect a combination of newly imported chronic infection and old imported infection in immigrants who have arrived since the 1970, 80s and 90s. In addition, the increase over the last four decades in the immigrant population from intermediate and high endemic countries comprising nearly 70% of those aged 35 years or under may also contribute to the increasing trend observed in immigrants, especially among those aged 15-39 years.[163,164]

Furthermore, the increasing percent per year (2.1%) and the higher rates of HBV in the 15-39 year age range compared to the older age group could be attributed not only to newly detected newer immigrants but also to spontaneous clearance in the older age group. This is supported by findings that older age is one of the most important factors for HBsAg seroclearance and that the probability of HBsAg seroclearance increases along with the duration of infection, which is longer in infected persons from settings where HBV infection occurs predominantly during the perinatal period or early childhood.[165]

There is also sex differential for both immigrants and non-immigrants. HBV is higher in males compared to females, in part due to increased exposure but also due to decreased clearance[166] and hormonal factors.[167] It has been suggested that estrogen and androgen might play a role in this gender disparity.[168,169] Sex hormones are important immunomodulators and exogenous pathogens may bind to hormone receptors expressed in immune cells lines, which might explain

the higher incidence of autoimmune diseases in females.[170,171] The immune clearance of HBV antigens is achieved faster in women, as well as the control of progression in HBV-related complications.[169]

A recent systematic review and meta-analysis on seroprevalence of chronic HBV infection in immigrants and refugees found a higher prevalence rates in migrants from most world regions, mostly in those from East Asia (11.3%), Sub-Saharan Africa (10.3%), and Eastern Europe (5.8%).[10] Our findings that the highest cumulative incidence of reported cases of chronic HBV occurred in immigrants from East Asia and the Pacific, Sub-Saharan Africa, and Eastern Europe are consistent with the aforementioned study, suggesting that region of origin is an important predictor of HBV. This pattern reflects the global epidemiology of the distribution of HBV and highlights the impact that the recent change in immigration trends has on the epidemiology of chronic HBV infection in Canada. In addition, this pattern provides external validity to our results.

The mean time to diagnosis since admission of nearly 6 years is a concern and represents a missed opportunity for testing since prompt screening and identification of chronic infection with HBV is key not only to ensure that infected persons benefit from appropriate care that could prevent or delay long-term complications, but also help to prevent transmission to others. This delay can be explained at least partially by the lack of systematic screening programs to detect chronic HBV infection in the immigrant population.[7]

It is therefore important to implement a routine screening of these populations for the following reasons. First, to detect and vaccinate those found to be susceptible to HBV. This is supported by a recent systematic review and meta-analysis by Rossi et al. that showed more than 50% of

immigrants from high/intermediate regions were non-immune to HBV and would therefore benefit from vaccination.[10] Furthermore, this will be in line with recommendations from the CDC and the CCIRH that all immigrants from countries with a HBV seroprevalence of 2% or greater should be screened for chronic HBV infection and prior immunity to HBV and susceptible individuals should be vaccinated.[7,172] Second, early identification of people with chronic HBV can lead to the reduction of the risk of end stage liver disease, HCC and HBV-related mortality through appropriately timed treatment. It is well documented that newer treatments can result in rapid suppression of HBV replication, normalization of serum transaminases, and restoration of liver function, ultimately increasing in survival by preventing or delaying onset of liver disease.[173,174] This would benefit not only the patient, but also the healthcare system in saving money from expensive treatment for long-term consequences of chronic HBV infection. Third, prevention of further spread of infection by vaccinating non-immune sexual and household contacts. Indeed, early identification of infected persons opens the window for primary prevention by counseling infected persons to adopt safe and responsible behaviors that reduce the risk of transmission to others and by allowing identification of close contacts who need testing and vaccination if found susceptible. Further reasons for screening include the reliability and the inexpensive cost of HBV testing, and its cost-effectiveness.[80,81] Hence, immigrants from intermediate and high endemic countries should be offered adequate education regarding HBV key facts and benefits of testing since HBV infection can be prevented, treated, and even eliminated.

The implementation of a successful screening program would require tremendous education and outreach efforts involving a number of stakeholders including media and policy-makers with the goal to have a large proportion of at-risk immigrants tested. Indeed, despite the aforementioned

recommendations, it has been observed that only a low proportion of immigrants are actually being screened given that screening occurs primarily on an ad hoc basis in the primary care setting.[175,176] Thus, to meet these challenges, two key recommendations have been made by the US Institute of Medicine.[177] First, it is very important "*to work with key stakeholders (other federal agencies, state and local governments, professional organizations, health care organizations, educational institutions and cultural centers) to develop hepatitis B programs for health care and social service providers*".[177] Given that family physicians are at the forefront of the health care system, it is important to raise their awareness about Hepatitis B. Second, "*work with key stakeholders to develop, coordinate, and evaluate new and effective outreach and education programs to target at-risk populations and to raise awareness in the general population about hepatitis B*".[177]

In summary, our findings showed a decrease in rates of reported cases of chronic HBV in non-immigrants and an increase in immigrants especially those aged 15-39 years. Therefore, targeted screening and if needed, vaccination of this population would be essential for the control of HBV infection.

6.2 Strengths and Limitations of the study

6.2.1 Strengths

To our knowledge, this is the first population-based study in Canada to estimate and compare rates of reported cases of acute and chronic HBV infection among immigrants from all world regions and among non-immigrants. The use of administrative databases covering the entire Quebec population provided a number of advantages: 1) Population-based data with numbers large enough to be stratified by important predictors of HBV, i.e., age, sex and country of origin.

Such stratified data may be generalizable outside of Quebec; 2) The presence of a visa number in both the RAMQ database and the MIDI database provided a unique opportunity to reliably link these databases and to accurately assign immigration status and country of origin; 3) Use of MADO database distinguished acute from chronic HBV based on laboratory diagnoses; and 4) The universal health care system provides access to all health care utilization and thus can detect health conditions that may have led to HBV diagnoses.

6.2.2 Limitations

This study had several limitations. First, like any other passive public health surveillance, there is underestimation of reported cases due to underreporting of asymptomatic cases. Indeed, most of HBV cases are asymptomatic and a large proportion of infected individuals are unaware until symptoms of disease-related complications develop several years after infection.[6] In addition, screening of HBV is not systematic, thus reported cases depended on the physician's decision to test. Hence, most reported cases are likely to be selective and to include: 1) Patients tested because of HBV-related symptoms; 2) patients in the high-risk groups including IDUs and MSM; 3); and 3) patients tested because of other conditions involving the liver directly or indirectly (treatment-induced liver toxicity). This is likely to introduce a detection bias. Moreover, the fact that 23% of unlinked cases were excluded in our analysis contributed to further underestimate the incidence rates of HBV. Second, unlinking these cases meant that we could not have their information regarding the immigration status, raising the possibility of misclassification. To address this situation, we used the inverse probability weighting (IPW) as a sensitivity analysis.[115] The results of this method did not show evidence of statistical differences between weighted and unweighted rate ratios suggesting non-differential misclassification. Thus it is unlikely that unlinked cases biased our estimates. In 2000 a 3 month waiting period prior to

eligibility for health insurance (and registration with FIPA) was instituted. Therefore between 2008-2008, immigrants who developed symptomatic acute or chronic hepatitis B in the first 3 months after arrival would have been excluded from the analysis as they would not be registered with FIPA. Furthmore, immigrants who arrived prior to 1985 may be misclassified as non-immigrants and is a limitation of the database. Despite the above mentioned limitations, results of this study present important findings of epidemiological and public health interest.

6.3 Implications for practice

Despite the overall declining rates of acute HBV over the study period, the impact of measures put in place since the early 1990s showed some differential between immigrants and non-immigrants. It is therefore appropriate to take this differential into account and improve immunization coverage in immigrants. Continued education of the population, especially those at risk should be considered.

With respect to chronic HBV, our data suggest that immigrants are affected disproportionately. At this stage of the disease, only early screening and management could be beneficial for immigrants and their families. Thus, from a public health perspective, this situation should heighten awareness of policy makers and health care professionals mostly family medicine practitioners so that immigrants from intermediate and high endemic countries, primarily those in the age group of 15-39 years, be considered as a population at high risk and routinely screened. They should be provided with information regarding the disease and the importance of testing. Susceptible individuals should be immunized and chronically infected people closely monitored and treated.

6.4 Future analyses

To fully understand the burden of chronic HBV, further analyses are ongoing to estimate and compare the rates of associated complications (cirrhosis and HCC), hospitalizations, and death in immigrants as compared to the Canadian-born population.

7 Conclusions

Increasing rates of chronic HBV over the study period in immigrants and very high HBV rates in certain sub-groups suggest that many immigrant groups might benefit from targeted HBV screening programs. Effective implementation of these measures might not only reduce HBV morbidity and mortality, but also prevent transmission in Canada. Translating these suggestions into practice would require substantial advocacy and political and financial commitment.

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9 Appendices

Appendix 1. Case Definitions of Viral Hepatitis in the Maladies à déclaration obligatoire (MADO) [133]

*All cases were confirmed by serologic markers and are definite cases of hepatitis B. The category of confirmed vs probable refers to stage of disease (acute, chronic or indeterminate) based on availability of clinical information.

Acute Hepatitis B	
Confirmed case	Detection of anti-HBc IgM and HBSAg or Presence of the 3 following conditions: - Clinical picture consistent with acute hepatitis (i.e, jaundice, dark urine) or increase in hepatitis enzymes AST or ALT AND - Presence of HBSAg but a negative anti-HBc IgM AND - No other apparent explanation for hepatitis OR - Newborn infant with positive serology for HBSAg and born to a mother that is also HBSAg positive
Probable Case	Presence of the following 3 conditions: - Clinical picture consistent with acute hepatitis (i.e, jaundice, dark urine) OR increase in hepatitis enzymes AST or ALT AND - Presence of HBSAg but serology for anti-HBc IgM not requested or not available AND - No other apparent explanation for hepatitis *In those recently vaccinated for hepatitis A, in addition to having the presence of hepatitis A IgM there must also be an epidemiologic link with a confirmed case of hepatitis A.
Chronic Hepatitis B Carrier	
Confirmed case	Detection of HBsAg in blood on two separate occasions at least 6 months apart
Probable case	Presence of one of the following 3 conditions: - Serologic detection of HBsAg and reported to be a "carrier", "chronic carrier" by a physician OR -Serologic detection of HBsAg in an asymptomatic person - Serologic detection of Hepatitis B DNA (by PCR) in an asymptomatic person
Undeterminated stage of Hepatitis B	
Serologic detection of HBsAg in a person but without any information allowing classifying as either an acute or chronic case of hepatitis B.	

Appendix 2. Changes to the definition from 1991-2008 the Maladies à déclaration obligatoire (MADO) [177]

Periods	Acute HBV	Chronic HBV
Changes in 2008 to the 2006 version	None	None
Changes in 2006 to the 2005 version	None	None
Changes in 2005 to the 2004 version	None	Added a third condition for probable cases of chronic HBV: Serologic detection of Hepatitis B DNA (by PCR) in an asymptomatic person
Changes in 2004 to the 2001 version	None	None
Changes in 2001 to the 1997 version	Suppression of the criterion requiring more than 2.5 times the upper limit of normal for liver enzymes.	
Changes in 1997 to the 1991 version	Adding of a new category: "confirmed case" (cas confirmé) and precisions.	

Appendix 3. Details of the Databases used in this study

Database	Primary Use in the study	Data Variables to be used
MADO Database Mandatory Reportable Infectious Disease Database of Quebec)	Case Ascertainment	RAMQ# , age, gender, date of birth. **Disease classification:** Acute and chronic hepatitis B
Fichier de services médicaux Database	Provide diagnostic codes for inpatients and outpatients	Diagnostic codes classified by ICD9/10-CM
MIDI Database (Landed Immigrant Database of the Ministere of Immigration, Diversity et Integration)	Classify cases as immigrant or Canadian-born Provide denominator data for the immigrant population	VISA#, date of landing , date of arrival date of birth, gender , country of birth
Fichier de services pharmaceutiques Database	Medication utilization	Drug name, drug identification number (DIN#), date prescribed
MED-ÉCHO Database		RAMQ#, date of admission, place of admission (ward/ICU/ER), admission diagnosis (ICD9/10-CM codes, primary and secondary discharge diagnoses (ICD9/10-CM codes)

Appendix 4. Details of ICD codes used in the study

ICD-9		ICD-10	
Chronic cirrhosis			
571.5	without mention of alcohol	K74.0 K74.1 K74.2 K74.60 K74.69	Hepatic fibrosis Hepatic sclerosis Hepatic fibrosis with hepatic sclerosis Unspecified cirrhosis of liver Other cirrhosis of liver
Decompensated cirrhosis			
070.6	Unspecified viral hepatitis with hepatic coma	B19.0	Unspecified viral hepatitis with hepatic coma
572.2	Hepatic encephalopathy	I85.01	Esophageal varices with bleeding
572.3	Portal hypertension	I85.9	Esophageal varices without bleeding
572.4	Hepatorenal syndrome	I85.11	Secondary esophageal varices with bleeding
572.8	Other sequelae of chronic liver diseases	K76.6	Portal hypertension
456.0	Esophageal varices with bleeding	K76.7	Hepatorenal syndrome
456.1	Esophageal varices without mention of bleeding		
456.20	Esophageal varices in diseases classified elsewhere with bleeding		
Hepatocellular carcinoma (HCC)			
155.0	Malignant neoplasm of liver (primary)	C22.0	Liver cell carcinoma
155.1	Malignant neoplasm of intrahepatic bile ducts	C22.1	Intrahepatic bile duct carcinoma
		C22.8	Malignant neoplasm of liver, primary, unspecified as to type
HIV			
042	Human immunodeficiency virus [HIV] disease	B20-B24	Human immunodeficiency virus [HIV] disease
V08	Asymptomatic Human Immunodeficiency Virus [HIV] Infection	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Tuberculosis			
010-018	All stages- pulmonary and extrapulmonary	A15-A19	Tuberculosis

Alcohol use/abuse

305.0	Alcohol abuse	F10.951	Alcohol use, unspecified with alcohol-induced psychotic disorder with hallucinations
291.3	Alcohol-induced psychotic disorder with hallucinations	F1Ø.99	Alcohol use, unspecified with unspecified alcohol-induced disorder
303.0	Alcohol dependence syndrome		
291.9	Unspecified alcohol-induced mental disorders		
291.81	Alcohol withdrawal	F1Ø.239	Alcohol dependence with withdrawal, unspecified
291.0	Alcohol withdrawal delirium	F1Ø.231	Alcohol dependence with withdrawal delirium
303.9	Other and unspecified alcohol dependence		
291.1	Alcohol-induced persisting amnestic disorder	F1Ø.96	Alcohol use, unspecified with alcohol-induced persisting amnestic disorder
357.5	Alcoholic polyneuropathy		
425.5	Alcoholic cardiomyopathy	I42.6	Alcoholic cardiomyopathy
535.3	Alcoholic gastritis	K29.2	Alcoholic gastritis
291.2	Alcohol-induced persisting dementia	F1Ø.27	Alcohol dependence with alcohol-induced persisting dementia
571.0	Alcoholic fatty liver	K7Ø.Ø	Alcoholic fatty liver
571.3	Alcoholic liver damage, unspecified	K7Ø.9	Alcoholic liver disease, unspecified
571.1	Acute alcoholic hepatitis	K7Ø.1Ø	Alcoholic hepatitis without ascites
571.2	Alcoholic cirrhosis of liver	K7Ø.3Ø	Alcoholic cirrhosis of liver without ascites
790.3	Excessive blood level of alcohol	R78.0	Excessive blood level of alcohol
980.x	Toxic effect of alcohol	T51	Toxic effect of alcohol
V11.3	Personal history of alcohol abuse	Z71.4	Counselling for Alcohol Abuse
		Z72.1	Counselling for Alcohol use

Drug use

292.x	Drug-induced mental disorders	F11-F16, F18, F19	Mental and behavioural disorders due to psychoactive substance use (excluding

			alcohol, nicotine)
304.x	Drug-dependence (by type)	R78.1-R78.5	Finding of opiate, cocaine, hallucinogen, and other psychotropic drug in blood
305	Nondependent abuse of drugs	Z71.5	Drug abuse counseling and surveillance
305.9	Other, mixed, or unspecified drug abuse	Z72.2	Drug use counselling
305.5	Opioid abuse		
305.6	Cocaine abuse		
Diabetes Mellitus			
250.0	Diabetes mellitus without mention of complication	E10-E14	Diabetes mellitus
250.1-250.9	Diabetes mellitus without mention of complication or manifestation		
362.53	Cystoid macular degeneration		
Congestive heart failure			
428	Heart failure	I50	Heart failure
428.9	Heart failure, unspecified	I5Ø.9	Heart failure, unspecified
428.0	Congestive heart failure, unspecified	I50.0	Congestive heart failure
428.1	Left heart failure	I5Ø.1	Left ventricular failure
428.2	Systolic heart failure		
428.3	Diastolic heart failure		
428.4	Combined systolic and diastolic heart failure		
398.91	Rheumatic heart failure (congestive)	IØ9.81	Rheumatic heart failure
402	Hypertensive heart disease	I11.0	Hypertensive heart disease with (congestive) heart failure
Delivery			
6903	Vaginal	080-084	Delivery
6912	caesarean		
Pregnancy-related			
634-639	Pregnancy with abortive outcome (miscarriage, etc.)	000-008	Pregnancy with abortive outcome
779.9	Congenital debility NOS, Stillbirth	P95	Fetal death of unspecified cause
761.8	Spontaneous abortion		
Cancers			
140-239	neoplasms	C00-C97	Malignant neoplasms

Solid neoplasm			
140-195	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue	C00-C75	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue
140-149	Malignant neoplasms of lip, oral cavity and pharynx	C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
150-159	Malignant neoplasms of digestive organs	C15-C26	Malignant neoplasms of digestive organs
160-165	Malignant neoplasms of respiratory and intrathoracic organs	C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
170-176	Malignant neoplasms of bone, skin, connective tissue and breasts	C40-C41	Malignant neoplasms of bone and articular cartilage
		C43-C44	Melanoma and other malignant neoplasms of skin
		C45-C49	Malignant neoplasms of mesothelial and soft tissue
		C50-C50	Malignant neoplasm of breast
		C51-C58	Malignant neoplasms of female genital organs
179-189	Malignant neoplasms of genitourinary organs	C60-C63	Malignant neoplasms of male genital organs
		C64-C68	Malignant neoplasms of urinary tract
190-199	Malignant neoplasms of other and unspecified sites	C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
		C73-C75	Malignant neoplasms of thyroid and other endocrine glands
		C76-C80	Malignant neoplasms of ill-defined, secondary and unspecified sites
Haematopoietic neoplasm			
200-208	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue
Miscellaneous neoplasms			
235-238	Neoplasms of uncertain behavior	C97-C97	Malignant neoplasms of independent (primary)

239	Neoplasms of unspecified nature		multiple sites
Rheumatologic disorders			
710	Diffuse diseases of connective tissue	M30-M36	Systemic connective tissue disorders
714	Rheumatoid arthritis and other inflammatory polyarthropathies	M05-M14	Inflammatory polyarthropathies
725	Polymyalgia rheumatica	M35.3	Polymyalgia rheumatica

Appendix 5. Medications

Methadone (Drug use)	**HIV**
Diabetes	
Acétohexamide	Abacavir (sulfate d')
Chlorpropamide	Abacavir (sulfate d') / lamivudine / zidovudine
Gliclazide	Abacavir (sulfate d') 46564 *
Gliclazide 46056 *	Abacavir (sulfate d')/lamivudine
Glimépiride	Adéfovir dipivoxil
Glyburide	Amprénavir
Insulin lispro / insulin lispro protamine suspension	Amprenavir 46743 *
Insuline aspart	Atazanavir (sulfate d')
Insuline aspart/ insuline aspart protamine	Darunavir
Insuline détémir	Darunavir (ethanolate)
Insuline glargine	Delaverdine (mésylate de) 46461 *
Insuline glulisine	Delavirdine (mésylate de)
Insuline injectable (humaine)	Didanosine
Insuline isophane (boeuf et porc)	Didanosine 46581 *
Insuline isophane (boeuf et porc) 46537 *	Éfavirenz
Insuline isophane (humaine)	Efavirenz 46544 *
Insuline isophane (porc)	Éfavirenz/ emtricitabine/ ténofovir disoproxil (fumarate de)
Insuline isophane bio-synthétique de séquence humaine	Emtricitabine/ ténofovir disoproxil (fumarate de)
Insuline isophane semi-synthétique de séquence humaine	Enfuvirtide
Insuline isophane(humaine)/ insuline injectable(humaine)	Étravirine
Insuline lente (boeuf et porc)	Fosamprénavir calcique
Insuline lente (boeuf et porc) 46538 *	Indinavir (sulfate d')
Insuline lente (porc)	Lamivudine
Insuline lente bio-synthétique de séquence humaine	Lamivudine 46514 *
Insuline lente semi-synthétique de séquence humaine	Lamivudine/ zidovudine
Insuline lispro	Lopinavir/ ritonavir
Insuline lispro 46322 *	Lopinavir/ritonavir 46714 *
Insuline lispro/ insuline lispro protamine	Maraviroc
Insuline lispro/insuline isophane (humaine) 46607 *	Nelfinavir (mésylate de)
Insuline protamine zinc (boeuf et porc)	Nelfinavir 46475 *
Insuline semilente (boeuf et porc)	Névirapine
Insuline sulfatée	Névirapine 46505 *
Insuline ultralente (boeuf et porc)	Raltégravir
Insuline ultralente bio-synthétique de séquence humaine	Ritonavir
Insuline ultralente semi-synthétique de séquence humaine	
Insuline zinc cristalline (boeuf et porc)	
Insuline zinc cristalline (boeuf et porc) 46536 *	

Insuline zinc cristalline (porc)	Saquinavir
Insuline zinc cristalline (porc)/ insuline isophane (porc)	Saquinavir (mésylate de)
Insuline zinc cristalline bio-synthétique de séquence humaine	Saquinavir 46519 *
Insuline zinc cristalline semi-synthétique de séquence humaine	Stavudine
	Stavudine 46311 *
Insulines isophane et zinc cristalline bio-synthétique de séquence humaine	Tipranavir
	Zalcitabine
Insulines isophane et zinc cristalline semi-synthétiques de séquence humaine	Zidovudine
Insulines zinc cristalline et isophane bio-synthétiques de séquence humaine	
Insulines zinc cristalline et isophane semi-synthétiques de séquence humaine	
Metformine (chlorhydrate de)	
Pioglitazone (chlorhydrate de)	
Pioglitazone (chlorhydrate de) 46678 *	
Répaglinide	
Repaglinide 46568 *	
Rosiglitazone (maléate de)	
Rosiglitazone (maléate de) 46642 *	
Rosiglitazone (maléate de)/ metformine (chlorhydrate de)	
Tolbutamide	

Appendix 6. Supplemental Results- Acute HBV

Supplemental table 1. Cumulative incidence rates of reported cases of acute HBV

Year	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
1991	6	0.98 (0.20-1.76)	296	4.62 (4.09-5.15)	0.21 (0.09-0.48)
1992	7	1.11 (0.29-1.94)	354	5.50 (4.93-6.07)	0.20 (0.10-0.43)
1993	15	2.33 (1.15-3.51)	316	4.88 (4.35-5.42)	0.48 (0.28-0.80)
1994	8	1.22 (0.37-2.06)	280	4.31 (3.81-4.82)	0.28 (0.14-0.57)
1995	10	1.49 (0.57-2.42)	203	3.12 (2.69-3.55)	0.48 (0.25-0.90)
1996	15	2.19 (1.08-3.31)	209	3.21 (2.77-3.64)	0.68 (0.41-1.16)
1997	12	1.73 (0.75-2.71)	173	2.65 (2.25-3.04)	0.65 (0.36-1.17)
1998	9	1.28 (0.44-2.12)	128	1.95 (1.62-2.29)	0.66 (0.33-1.29)
1999	7	0.98 (0.25-1.71)	124	1.89 (1.56-2.22)	0.52 (0.24-1.11)
2000	13	1.80 (0.82-2.78)	133	2.02 (1.67-2.36)	0.89 (0.50-1.58)
2001	3	0.41 (-0.05-0.87)	72	1.09 (0.84-1.34)	0.38 (0.12-1.19)
2002	13	1.71 (0.78-2.64)	76	1.15 (0.89-1.40)	1.49 (0.83-2.69)
2003	4	0.51 (0.01-1.00)	71	1.07 (0.82-1.32)	0.48 (0.17-1.30)
2004	5	0.61 (0.08-1.15)	57	0.85 (0.63-1.08)	0.72 (0.29-1.79)
2005	9	1.06 (0.37-1.76)	34	0.51 (0.34-0.68)	2.10 (1.00-4.37)
2006	4	0.46 (0.01-0.91)	30	0.45 (0.29-0.61)	1.02 (0.36-2.90)
2007	9	1.01 (0.35-1.67)	30	0.44 (0.29-0.60)	2.28 (1.08-4.80)
2008	2	0.44 (-0.17-1.06)	13	0.38 (0.17-0.59)	1.16 (0.26-5.12)
Overall	151	1.17 (0.98-1.36)	2599	2.26 (2.17-2.34)	0.52 (0.44-0.61)

Supplemental table 2. Cumulative incidence rates of reported cases of Acute HBV stratified by age group

Period	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
< 15 years					
1991- 1994	5	2.96 (0.37-5.55)	12	0.22 (0.09-0.34)	13.57 (4.78-38.52)
1995- 1998	2	1.07 (-0.41-2.54)	7	0.13 (0.03-0.23)	8.21 (1.71-39.53)
1999- 2002	3	1.51 (-0.20-3.22)	8	0.15 (0.05-0.26)	9.77 (2.59-36.82)
2003- 2008	6	1.81 (0.36-3.27)	5	0.07 (0.01-0.14)	24.54 (7.49-80.41)
Overall	16	1.81 (0.92-2.69)	32	0.14 (0.09-0.19)	12.89 (7.07-23.49)
15- 39 years					
1991- 1994	27	2.94 (1.83-4.05)	843	8.20 (7.65-8.75)	0.36 (0.24-0.53)
1995- 1998	32	3.27 (2.14-4.41)	416	4.23 (3.82-4.64)	0.77 (0.54-1.11)
1999- 2002	26	2.57 (1.58-3.56)	175	1.90 (1.62-2.19)	1.35 (0.89-2.04)
2003- 2008	16	1.00 (0.51-1.48)	71	0.60 (0.46-0.74)	1.66 (0.96-2.85)
Overall	101	2.24 (1.80-2.67)	1505	3.66 (3.48-3.84)	0.61 (0.50-0.75)
≥ 40 years					
1991- 1994	4	0.27 (0.01-0.54)	391	3.90 (3.52-4.29)	0.07 (0.03-0.19)
1995- 1998	12	0.76 (0.33-1.19)	290	2.66 (2.36-2.97)	0.28 (0.16-0.51)
1999- 2002	7	0.41 (0.11-0.71)	222	1.84 (1.60-2.08)	0.22 (0.10-0.47)
2003- 2008	11	0.40 (0.17-0.64)	159	0.87 (0.73-1.00)	0.46 (0.25-0.86)
Overall	34	0.45 (0.30-0.61)	1062	2.07 (1.95-2.20)	0.22 (0.16-0.31)

Supplemental table 3. Cumulative incidence rates of reported cases of Acute HBV stratified by sex

Year	Immigrants					Non-immigrants				
	Female		Male		Ratio (Immigrants)	Female		Male		Ratio (Non-immigrants)
	N	rates per 100,000	N	rates per 100,000		N	rates 100,000	N	rates per 100,000	
1991 - 1994	8	0.63 (0.19-1.07)	28	2.20 (1.38-3.01)	0.29 (0.13-0.63)	414	3.14 (2.84-3.45)	832	6.58 (6.14-7.03)	0.48 (0.42-0.54)
1995 - 1998	18	1.30 (0.70-1.90)	28	2.05 (1.29-2.81)	0.63 (0.35-1.14)	192	1.44 (1.24-1.64)	521	4.07 (3.72-4.42)	0.35 (0.30-0.42)
1999 - 2002	11	0.74 (0.30-1.18)	25	1.73 (1.05-2.41)	0.43 (0.21-0.87)	106	0.79 (0.64-0.94)	299	2.31 (2.05-2.57)	0.34 (0.27-0.42)
2003 - 2008	7	0.29 (0.08-0.51)	26	1.13 (0.70-1.57)	0.26 (0.11-0.60)	48	0.26 (0.18-0.33)	187	1.04 (0.89-1.18)	0.25 (0.18-0.34)
Overall	44	0.68 (0.48-0.88)	107	1.68 (1.36-2.00)	0.40 (0.28-0.57)	760	1.29 (1.20-1.38)	1839	3.26 (3.11-3.41)	0.40 (0.36-0.43)

Supplemental table 4. Cumulative incidence rates of reported cases of Acute HBV stratified by regions of origins

Region of origin	Immigrants		Non-immigrants (N=2599)		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
East Asia/Pacific	39	2.55 (1.75-3.35)			1.13 (0.82-1.55)
South Asia	10	1.65 (0.63-2.67)			0.73 (0.39-1.36)
Middle East/North Africa	20	1.01 (0.57-1.46)			0.45 (0.29-0.70)
Sub-Saharan Africa	11	2.53 (1.03-4.02)			1.12 (0.62-2.03)
Western Europe	18	0.42 (0.23-0.61)	2599	2.26 (2.17-2.34)	0.19 (0.12-0.30)
Eastern Europe/Central Asia	11	1.15 (0.47-1.83)			0.51 (0.28-0.92)
Latin America/Caribbean	33	1.50 (0.99-2.01)			0.66 (0.47-0.93)
US/Australia/New Zealand	1	0.21 (-0.20-0.62)			0.09 (0.01-0.66)
Overall	151	1.17 (0.99-1.36)			0.52 (0.44-0.61)

Supplemental table 5. Unweighted vs. Weighted Cumulative incidence rates of reported Acute Hepatitis B cases per year

	Immigrants		Non-immigrants			
Year	**Unweighted Rate**	**Weighted Rate**	**Unweighted Rate**	**Weighted Rate**	**Unweighted Rate Ratio**	**Weighted Rate Ratio**
1991	0.98 (0.45-2.13)	1.63 (0.89-3.00)	4.62 (4.12-5.18)	6.53 (5.93-7.18)	0.21 (0.09-0.48)	0.25 (0.13-0.47)
1992	1.11 (0.54-2.30)	1.62 (0.88-2.97)	5.50 (4.96-6.10)	7.76 (7.11-8.47)	0.20 (0.10-0.43)	0.21 (0.11-0.39)
1993	2.33 (1.41-3.85)	3.55 (2.36-5.33)	4.88 (4.37-5.45)	6.77 (6.16-7.43)	0.48 (0.28-0.80)	0.52 (0.34-0.80)
1994	1.22 (0.62-2.40)	1.64 (0.91-2.95)	4.31 (3.84-4.85)	5.98 (5.41-6.60)	0.28 (0.14-0.57)	0.27 (0.15-0.50)
1995	1.49 (0.81-2.75)	2.25 (1.37-3.71)	3.12 (2.72-3.58)	4.24 (3.77-4.77)	0.48 (0.25-0.90)	0.53 (0.32-0.89)
1996	2.19 (1.33-3.62)	3.10 (2.03-4.73)	3.21 (2.80-3.67)	4.25 (3.78-4.78)	0.68 (0.41-1.16)	0.73 (0.47-1.14)
1997	1.73 (0.99-3.03)	2.42 (1.50-3.89)	2.65 (2.28-3.07)	3.41 (2.99-3.89)	0.65 (0.36-1.17)	0.71 (0.43-1.16)
1998	1.28 (0.67-2.44)	1.77 (1.02-3.06)	1.95 (1.64-2.32)	2.50 (2.14-2.91)	0.66 (0.33-1.29)	0.71 (0.40-1.26)
1999	0.98 (0.48-2.03)	1.36 (0.73-2.53)	1.89 (1.58-2.25)	2.41 (2.07-2.82)	0.52 (0.24-1.11)	0.56 (0.29-1.08)
2000	1.80 (1.05-3.08)	2.50 (1.59-3.95)	2.02 (1.70-2.39)	2.54 (2.18-2.95)	0.89 (0.50-1.58)	0.99 (0.61-1.60)
2001	0.41 (0.14-1.20)	0.55 (0.22-1.41)	1.09 (0.86-1.37)	1.37 (1.11-1.68)	0.38 (0.12-1.19)	0.40 (0.15-1.09)
2002	1.71 (1.00-2.92)	2.21 (1.38-3.55)	1.15 (0.92-1.43)	1.41 (1.15-1.72)	1.49 (0.83-2.69)	1.57 (0.94-2.64)
2003	0.51 (0.20-1.30)	0.63 (0.27-1.48)	1.07 (0.85-1.35)	1.28 (1.04-1.59)	0.48 (0.17-1.30)	0.49 (0.20-1.21)
2004	0.61 (0.26-1.43)	0.77 (0.36-1.66)	0.85 (0.66-1.11)	1.02 (0.80-1.29)	0.72 (0.29-1.79)	0.76 (0.34-1.72)
2005	1.06 (0.56-2.02)	1.30 (0.73-2.33)	0.51 (0.36-0.71)	0.60 (0.44-0.82)	2.10 (1.00-4.37)	2.16 (1.11-4.20)
2006	0.46 (0.18-1.18)	0.58 (0.25-1.35)	0.45 (0.31-0.64)	0.54 (0.39-0.74)	1.02 (0.36-2.90)	1.08 (0.42-2.73)
2007	1.01 (0.53-1.93)	1.25 (0.70-2.24)	0.44 (0.31-0.63)	0.51 (0.37-0.71)	2.28 (1.08-4.80)	2.44 (1.24-4.80)
2008	0.44 (0.12-1.61)	0.55 (0.17-1.78)	0.38 (0.22-0.65)	0.46 (0.28-0.75)	1.16 (0.26-5.12)	1.21 (0.32-4.60)
Overall	1.17 (1.00-1.37)	1.62 (1.42-1.86)	2.26 (2.17-2.34)	3.01 (2.92-3.12)	0.52 (0.44-0.61)	0.54 (0.47-0.62)

Appendix 7. Supplemental Results- chronic HBV

Supplemental table 5. Cumulative incidence rates of reported cases of chronic Hepatitis B

Year	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
1991	198	32.27 (27.78-36.77)	748	11.67 (10.84-12.51)	2.76 (2.36-3.23)
1992	251	39.97 (35.03-44.92)	812	12.61 (11.75-13.48)	3.17 (2.75-3.65)
1993	261	40.61 (35.68-45.53)	741	11.45 (10.63-12.28)	3.55 (3.08-4.08)
1994	333	50.70 (45.26-56.15)	674	10.38 (9.60-11.17)	4.88 (4.28-5.57)
1995	305	45.52 (40.41-50.63)	618	9.50 (8.75-10.25)	4.79 (4.18-5.50)
1996	334	48.86 (43.62-54.10)	536	8.22 (7.52-8.92)	5.94 (5.19-6.81)
1997	311	44.86 (39.87-49.85)	538	8.23 (7.53-8.92)	5.45 (4.74-6.27)
1998	329	46.84 (41.78-51.90)	425	6.49 (5.87-7.10)	7.22 (6.25-8.34)
1999	336	47.18 (42.13-52.22)	411	6.26 (5.65-6.86)	7.54 (6.53-8.71)
2000	329	45.52 (40.60-50.44)	366	5.55 (4.98-6.12)	8.20 (7.07-9.52)
2001	393	53.55 (48.26-58.85)	378	5.71 (5.13-6.28)	9.38 (8.15-10.80)
2002	393	51.64 (46.53-56.75)	350	5.27 (4.72-5.83)	9.79 (8.48-11.31)
2003	408	51.74 (46.72-56.76)	331	4.98 (4.44-5.51)	10.40 (9.00-12.02)
2004	489	59.86 (54.56-65.17)	362	5.43 (4.87-5.98)	11.03 (9.63-12.64)
2005	482	57.04 (51.94-62.13)	319	4.77 (4.25-5.29)	11.96 (10.38-13.78)
2006	471	53.89 (49.03-58.76)	308	4.59 (4.08-5.10)	11.74 (10.17-13.55)
2007	461	51.89 (47.15-56.63)	269	3.99 (3.51-4.46)	13.02 (11.20-15.13)
2008	222	49.12 (42.66-55.58)	141	4.15 (3.47-4.84)	11.83 (9.58-14.62)
Overall	6306	48.94 (47.73-50.15)	8327	7.23 (7.07-7.38)	6.77 (6.55-7.00)

Supplemental table 6. Cumulative incidence rates of reported cases of Chronic Hepatitis B stratified by age group (Age <15 years)

Year	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
1991	13	32.29 (14.74-49.84)	20	1.45 (0.81-2.08)	22.32 (11.10 44.87)
1992	14	33.66 (16.03-51.29)	17	1.23 (0.65-1.82)	27.30 (13.46-55.38)
1993	15	34.91 (17.24-52.58)	19	1.38 (0.76-2.00)	25.28 (12.85-49.75)
1994	27	60.96 (37.97-83.96)	8	0.58 (0.18-0.99)	104.47 (47.46-229.95)
1995	29	63.64 (40.48-86.81)	8	0.59 (0.18-0.99)	108.52 (49.61-237.38)
1996	22	46.95 (27.33-66.57)	4	0.29 (0.01-0.58)	159.32 (54.90-462.34)
1997	23	48.56 (28.72-68.41)	12	0.89 (0.39-1.40)	54.36 (27.05-109.25)
1998	23	48.09 (28.44-67.75)	6	0.45 (0.09-0.81)	106.44 (43.34-261.40)
1999	20	41.38 (23.24-59.52)	8	0.61 (0.19-1.03)	67.94 (29.93-154.25)
2000	12	24.55 (10.66-38.44)	3	0.23 (-0.03-0.49)	106.39 (30.02-377.01)
2001	13	26.28 (11.99-40.56)	3	0.23 (-0.03-0.50)	112.77 (32.14-395.74)
2002	17	32.72 (17.17-48.28)	1	0.08 (-0.08-0.23)	416.71 (55.46-3131.35)
2003	7	12.86 (3.33-22.38)	3	0.24 (-0.03-0.51)	53.95 (13.95-208.64)
2004	9	15.79 (5.47-26.10)	4	0.32 (0.01-0.64)	49.14 (15.13-159.57)
2005	8	13.43 (4.12-22.73)	5	0.41 (0.05-0.76)	33.04 (10.81-101.01)
2006	9	14.47 (5.02-23.92)	3	0.25 (-0.03-0.53)	58.65 (15.88-216.65)
2007	5	7.78 (0.96-14.61)	3	0.25 (-0.03-0.53)	31.37 (7.50-131.28)
2008	7	21.10 (5.47-36.73)	0	-	-
Overall	273	30.81 (27.16-34.47)	127	0.56 (0.46-0.65)	55.41 (44.89-68.39)

Supplemental table 7. Cumulative incidence rates of reported cases of Chronic Hepatitis B stratified by age group (Age 15-39 years)

Year	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
1991	139	62.52 (52.12-72.91)	419	16.10 (14.56-17.65)	3.88 (3.20-4.70)
1992	186	81.96 (70.18-93.74)	429	16.62 (15.05-18.19)	4.93 (4.15-5.86)
1993	192	82.87 (71.15-94.59)	370	14.45 (12.97-15.92)	5.74 (4.82-6.83)
1994	237	100.36 (87.59-113.14)	276	10.88 (9.59-12.16)	9.23 (7.76-10.98)
1995	205	85.30 (73.63-96.98)	271	10.80 (9.51-12.08)	7.90 (6.59-9.47)
1996	209	85.46 (73.87-97.05)	214	8.62 (7.47-9.78)	9.91 (8.19-11.99)
1997	187	76.06 (65.15-86.96)	188	7.70 (6.60-8.80)	9.88 (8.07-12.09)
1998	202	81.79 (70.51-93.07)	159	6.63 (5.60-7.66)	12.33 (10.02-15.18)
1999	219	88.21 (76.52-99.89)	143	6.07 (5.08-7.06)	14.53 (11.77-17.94)
2000	218	87.27 (75.68-98.85)	102	4.40 (3.55-5.26)	19.81 (15.66-25.06)
2001	249	98.99 (86.70-111.29)	108	4.74 (3.85-5.64)	20.87 (16.65-26.15)
2002	255	97.49 (85.52-109.46)	79	3.52 (2.74-4.29)	27.73 (21.54-35.69)
2003	284	104.53 (92.37-116.69)	90	4.06 (3.22-4.90)	25.75 (20.31-32.64)
2004	333	118.03 (105.35-130.71)	98	4.48 (3.59-5.37)	26.35 (21.03-33.01)
2005	320	109.40 (97.41-121.38)	78	3.62 (2.81-4.42)	30.25 (23.62-38.74)
2006	315	103.91 (92.43-115.38)	77	3.62 (2.81-4.43)	28.69 (22.37-36.81)
2007	325	106.85 (95.24-118.47)	50	2.39 (1.73-3.05)	44.74 (33.22-60.26)
2008	135	88.39 (73.48-103.30)	36	3.49 (2.35-4.63)	25.32 (17.53-36.57)
Overall	4210	93.30 (90.48-96.12)	3187	7.75 (7.48-8.02)	12.04 (11.50-12.60)

Supplemental table 8. Cumulative incidence rates of reported cases of chronic HBV stratified by age group (Age ≥ 40 years)

Year	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
1991	46	13.11 (9.32-16.90)	309	12.75 (11.33-14.17)	1.03 (0.75-1.40)
1992	51	14.19 (10.30-18.09)	366	14.77 (13.26-16.29)	0.96 (0.72-1.29)
1993	54	14.67 (10.76-18.58)	352	13.90 (12.45-15.35)	1.06 (0.79-1.41)
1994	69	18.33 (14.01-22.66)	390	15.10 (13.60-16.59)	1.21 (0.94-1.57)
1995	71	18.48 (14.18-22.78)	339	12.88 (11.51-14.25)	1.43 (1.11-1.85)
1996	103	26.27 (21.20-31.34)	318	11.86 (10.56-13.16)	2.21 (1.77-2.77)
1997	101	25.25 (20.32-30.17)	338	12.27 (10.96-13.58)	2.06 (1.65-2.57)
1998	104	25.51 (20.61-30.42)	260	9.20 (8.08-10.32)	2.77 (2.21-3.48)
1999	97	23.34 (18.69-27.98)	260	8.97 (7.88-10.06)	2.60 (2.06-3.29)
2000	99	23.35 (18.75-27.95)	261	8.77 (7.70-9.83)	2.66 (2.11-3.36)
2001	131	30.27 (25.08-35.45)	267	8.74 (7.69-9.78)	3.46 (2.81-4.27)
2002	121	27.04 (22.22-31.86)	270	8.66 (7.63-9.70)	3.12 (2.52-3.87)
2003	117	25.30 (20.72-29.89)	238	7.49 (6.54-8.44)	3.38 (2.71-4.21)
2004	147	30.77 (25.80-35.74)	260	8.03 (7.05-9.00)	3.83 (3.13-4.69)
2005	154	31.24 (26.31-36.17)	236	7.15 (6.24-8.06)	4.37 (3.57-5.35)
2006	147	28.90 (24.23-33.57)	228	6.78 (5.90-7.66)	4.27 (3.47-5.25)
2007	131	25.34 (21.00-29.67)	216	6.28 (5.44-7.11)	4.04 (3.25-5.02)
2008	80	30.41 (23.75-37.07)	105	5.96 (4.82-7.10)	5.10 (3.81-6.82)
Overall	1823	24.37 (23.25-25.49)	5013	9.78 (9.51-10.05)	2.49 (2.36-2.63)

Supplemental table 9. Cumulative incidence rates of reported cases of Chronic HBV stratified by sex

Year	Immigrants					Non-immigrants				
	Female		Male			Female		Male		
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	Ratio (Immigrants)	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	Ratio (Non-immigrants)
1991-1994	518	40.88 (37.36-44.40)	525	41.21 (37.69-44.74)	0.99 (0.88-1.12)	907	6.89 (6.44-7.34)	2068	16.36 (15.66-17.07)	0.42 (0.39-0.46)
1995-1998	625	45.11 (41.58-48.65)	654	47.95 (44.28-51.63)	0.94 (0.84-1.05)	673	5.05 (4.67-5.43)	1444	11.29 (10.70-11.87)	0.45 (0.41-0.49)
1999-2002	682	45.92 (42.47-49.37)	769	53.23 (49.47-57.00)	0.86 (0.78-0.96)	467	3.46 (3.15-3.78)	1038	8.03 (7.54-8.51)	0.43 (0.39-0.48)
2003-2008	1127	47.47 (44.70-50.24)	1406	61.37 (58.16-64.58)	0.77 (0.72-0.84)	561	2.98 (2.74-3.23)	1169	6.47 (6.10-6.84)	0.46 (0.42-0.51)
Overall	2952	45.33 (43.70-46.97)	3354	52.63 (50.84-54.41)	0.86 (0.82-0.91)	2608	4.44 (4.27-4.61)	5719	10.14 (9.87-10.40)	0.44 (0.42-0.46)

Supplemental table 10. Cumulative incidence rates of reported cases of chronic HBV cases in immigrants stratified by sex and age group

Year	Cumulative incidence rates per 100,000- Females						Cumulative incidence rates per 100,000- Males					
	N	< 15	N	15 - 39	N	≥40	N	< 15	N	15 - 39	N	≥40
1991-1994	27	32.54 (20.26-44.81)	407	90.02 (81.27-98.76)	84	11.48 (9.02-13.93)	42	48.77 (34.02-63.52)	347	74.63 (66.78-82.48)	136	18.82 (15.65-21.98)
1995-1998	68	71.27 (54.33-88.22)	421	86.09 (77.87-94.32)	136	16.98 (14.13-19.83)	29	31.46 (20.01-42.90)	382	78.16 (70.33-86.00)	243	31.04 (27.13-34.94)
1999-2002	31	29.81 (19.31-40.30)	469	91.97 (83.65-100.30)	182	20.89 (17.85-23.92)	31	32.76 (21.23-44.29)	472	94.17 (85.67-102.66)	266	31.34 (27.58-35.11)
2003-2008	20	11.27 (6.33-16.22)	846	102.88 (95.95-109.82)	261	18.93 (16.64-21.23)	25	16.34 (9.94-22.75)	866	109.25 (101.98-116.53)	515	38.27 (34.97-41.58)
Overall	146	31.76 (26.60-36.91)	2143	94.27 (90.27-98.26)	663	17.53 (16.19-18.86)	127	29.82 (24.63-35.00)	2067	91.97 (88.00-95.93)	1160	31.35 (29.55-33.16)

Supplemental table 11. Cumulative incidence rates of reported cases of chronic HBV stratified by region of origin

Region of origin	Immigrants		Non-immigrants		Ratio
	N	Cumulative incidence rates per 100,000	N	Cumulative incidence rates per 100,000	
East Asia and Pacific	2979	194.92 (187.92-201.92)			26.97 (25.86-28.12)
South Asia	196	32.31 (27.79-36.84)			4.47 (3.88-5.15)
Middle East and North Africa	512	25.97 (23.72-28.22)			3.59 (3.29-3.93)
Sub-Saharan Africa	735	168.98 (156.76-181.20)			23.38 (21.68-25.21)
Western Europe	98	2.29 (1.84-2.74)	8327	7.23 (7.07-7.38)	0.32 (0.26-0.39)
Eastern Europe and Central Asia	431	44.95 (40.71-49.19)			6.22 (5.65-6.85)
Latin America and the Caribbean	582	26.38 (24.24-28.53)			3.65 (3.36-3.97)
US, Australia, and New Zealand	5	1.05 (0.13-1.96)			0.14 (0.06-0.35)
Overall	6306	48.96 (47.76-50.17)			6.77 (6.56-7.00)

Supplemental table 12. Prevalence of medical conditions in 1 year prior to diagnosis for Chronic Hepatitis B cases stratified by age group

	Immigrants			Non-immigrants		
Medical condition	**< 15**	**15-39**	**≥40**	**< 15**	**15-39**	**≥40**
Compensated cirrhosis		13 (0.31)	41 (2.25)		48 (1.51)	291 (5.80)
Decompensated cirrhosis		8 (0.19)	14 (0.77)		18 (0.56)	95 (1.89)
Hepatocellular carcinoma		4 (0.10)	23 (1.26)		5 (0.16)	31 (0.62)
HIV		26 (0.62)	22 (1.21)	1 (0.79)	166 (5.21)	139 (2.77)
Tuberculosis	8 (2.93)	74 (1.76)	36 (1.97)	1 (0.79)	10 (0.31)	24 (0.48)
Alcohol abuse		17 (0.40)	18 (0.99)		149 (4.68)	311 (6.20)
Drug abuse		14 (0.33)	10 (0.55)		104 (3.26)	155 (3.09)
Diabetes mellitus	1 (0.37)	50 (1.19)	149 (8.17)		35 (1.10)	452 (9.01)
Congestive heart failure		7 (0.17)	18 (0.99)		8 (0.25)	163 (3.25)
Pregnancy (delivery)		70 (1.66)	3 (0.16)		55 (1.73)	1 (0.02)
Pregnancy related			1 (0.05)		1 (0.03)	4 (0.08)
Cancer	1 (0.37)	141 (3.35)	153 (8.39)	4 (3.15)	152 (4.77)	689 (13.74)
Solid		35 (0.83)	75 (4.11)	2 (1.57)	47 (1.47)	362 (7.22)
Hematopoietic neoplasm	1 (0.37)	10 (0.24)	19 (1.04)	2 (1.57)	15 (0.47)	103 (2.05)
Rheumatologic neoplasms		5 (0.12)	11 (0.60)		13 (0.41)	78 (1.56)
Miscellaneous neoplasm		15 (0.36)	22 (1.21)		21 (0.66)	97 (1.93)

Supplemental table 13. Unweighted vs. Weighted Cumulative incidence rates of reported Chronic Hepatitis B cases per year

Year	Immigrants		Non-Immigrants			
	Unweighted Rates	Weighted Rates	Unweighted Rates	Weighted Rates	Unweighted Rate Ratios	Weighted Rate Ratios
1991	32.27 (27.78-36.77)	51.00 (45.35-56.65)	11.67 (10.84-12.51)	17.24 (16.22-18.26)	2.76 (2.36-3.23)	2.96 (2.61-3.35)
1992	39.97 (35.03-44.92)	62.08 (55.92-68.25)	12.61 (11.75-13.48)	18.08 (17.04-19.12)	3.17 (2.75-3.65)	3.43 (3.06-3.85)
1993	40.61 (35.68-45.53)	61.69 (55.62-67.76)	11.45 (10.63-12.28)	16.04 (15.06-17.02)	3.55 (3.08-4.08)	3.85 (3.43-4.32)
1994	50.70 (45.26-56.15)	77.39 (70.66-84.11)	10.38 (9.60-11.17)	14.25 (13.33-15.17)	4.88 (4.28-5.57)	5.43 (4.87-6.05)
1995	45.52 (40.41-50.63)	66.72 (60.53-72.90)	9.50 (8.75-10.25)	12.81 (11.94-13.68)	4.79 (4.18-5.50)	5.21 (4.64-5.84)
1996	48.86 (43.62-54.10)	70.05 (63.77-76.32)	8.22 (7.52-8.92)	10.96 (10.16-11.77)	5.94 (5.19-6.81)	6.39 (5.69-7.17)
1997	44.86 (39.87-49.85)	63.57 (57.64-69.51)	8.23 (7.53-8.92)	10.71 (9.92-11.50)	5.45 (4.74-6.27)	5.94 (5.27-6.69)
1998	46.84 (41.78-51.90)	64.88 (58.92-70.83)	6.49 (5.87-7.10)	8.47 (7.76-9.17)	7.22 (6.25-8.34)	7.66 (6.77-8.67)
1999	47.18 (42.13-52.22)	65.27 (59.33-71.20)	6.26 (5.65-6.86)	7.98 (7.29-8.66)	7.54 (6.53-8.71)	8.18 (7.22-9.27)
2000	45.52 (40.60-50.44)	61.80 (56.07-67.53)	5.55 (4.98-6.12)	6.95 (6.31-7.59)	8.20 (7.07-9.52)	8.89 (7.81-10.13)
2001	53.55 (48.26-58.85)	71.90 (65.77-78.04)	5.71 (5.13-6.28)	7.09 (6.45-7.73)	9.38 (8.15-10.80)	10.14 (8.96-11.49)
2002	51.64 (46.53-56.75)	67.06 (61.24-72.88)	5.27 (4.72-5.83)	6.40 (5.79-7.01)	9.79 (8.48-11.31)	10.47 (9.21-11.91)
2003	51.74 (46.72-56.76)	67.36 (61.63-73.08)	4.98 (4.44-5.51)	6.07 (5.48-6.67)	10.40 (9.00-12.02)	11.09 (9.74-12.62)
2004	59.86 (54.56-65.17)	76.82 (70.81-82.83)	5.43 (4.87-5.98)	6.57 (5.95-7.18)	11.03 (9.63-12.64)	11.70 (10.35-13.22)
2005	57.04 (51.94-62.13)	72.42 (66.69-78.16)	4.77 (4.25-5.29)	5.73 (5.15-6.30)	11.96 (10.38-13.78)	12.64 (11.13-14.36)
2006	53.89 (49.03-58.76)	67.53 (62.09-72.98)	4.59 (4.08-5.10)	5.44 (4.88-6.00)	11.74 (10.17-13.55)	12.42 (10.90-14.15)
2007	51.89 (47.15-56.63)	64.18 (58.91-69.45)	3.99 (3.51-4.46)	4.71 (4.19-5.23)	13.02 (11.20-15.13)	13.62 (11.88-15.63)
2008	49.12 (42.66-55.58)	60.62 (53.44-67.79)	4.15 (3.47-4.84)	4.84 (4.10-5.58)	11.83 (9.58-14.62)	12.52 (10.32-15.20)
Overall	48.94 (47.73-50.15)	66.62 (65.21-68.03)	7.23 (7.07-7.38)	9.53 (9.36-9.71)	6.77 (6.55-7.00)	6.99 (6.79-7.19)