Hepatitis B Vaccination Coverage among Foreign-born Canadians: Data from the Community Health Measures Survey

by

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Abstract

Hepatitis B (HB) is vaccine-preventable but remains a leading cause of liver disease worldwide. Since the 1980s, Canadians have received HB vaccination through publicly-funded programs in childhood however 20-25% of Canadians are foreign-born (FB) and may experience barriers to vaccine uptake. This study assesses differences in HB vaccine coverage between FB and Canadian-born (CB) individuals using Statistics Canada's Canadian Health Measures Survey data. The three-year (2007-2011) vaccination coverage among FB Canadians was estimated at 38%, which was significantly lower than the estimate rate for CB sub-population (49%). After adjustment for covariates, immigration status remained a significant predictor of vaccination. Furthermore, the effect of immigration status on vaccination status was modified by birth era such that the relative difference in vaccination coverage was greater among those born in the era of childhood HB vaccination programs (1980s and after) compared to older Canadians. Opportunities for education on the availability of HB vaccination may benefit new Canadians.

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List of Abbreviations

CB	Canadian-born
CCIRH	Collaboration for Immigrant and Refugee Health
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
CNDSS	Canadian Notifiable Disease Surveillance System
DNA	Deoxyribonucleic acid
EHSS	Enhanced Hepatitis Surveillance System
ELISA	Enzyme-linked immunosorbent assay
FB	Foreign-born
HB	Hepatitis B
IU	International units
MEC	Mobile Examination Clinic
NICS	National Immunization Coverage Survey
OR	Odds Ratio
RDC	Research Data Centre
SSHRC	Social Sciences and Humanities Research Council
STI	Sexually transmitted infection
WHO	World Health Organization

Chapter One: **Introduction**

1.1 Study rationale

Infection with the Hepatitis B (HB) virus is a leading cause of liver-disease and related mortality worldwide.(Fauci & Morens, 2012; Sharma, Carballo, Feld, & Janssen, 2015) In Canada, effective public health measures and vaccination programs for children have maintained low HB prevalence overall.(PHAC, 2014; "Reported Cases of Disease in Canada," 2012) However, a greater burden of HB-related disease has been noted in foreign-born (FB) Canadians compared to the Canadian-born (CB) population.(Greenaway, Narasiah, Plourde, Ueffing, & Deschenes, 2011; Pottie et al., 2011; Redditt, Janakiram, Graziano, & Rashid, 2015; Rossi et al., 2012; Rotermann, Langlois, Andonov, & Trubnikov, 2013) In fact, a study conducted by the Canadian Collaboration for Immigrant and Refugee Health (CCIRH) estimates that mortality from viral hepatitis is 1.8–3.8 times higher and mortality from hepatocellular carcinoma is 2.2–4.9 times higher in immigrants compared to non-immigrant Canadians. This disparity represents a significant public health concern because approximately 20-25% of Canadians are born outside Canada.(Chui, Flanders, & Anderson, 2011; Vang, Sigouin, Flenon, & Gagnon, 2015)

Since the HB virus is more prevalent in other parts of the world,(Organization, 2002; Ott, Stevens, Groeger, & Wiersma, 2012) a greater risk of exposure prior to arrival in Canada is thought to be the main reason for this disparity in HB prevalence.(Rossi et al., 2012; Sharma et al., 2015) However, even once residing in Canada, FB Canadians may be at increased risk of exposure due to close contact with infected household

members, greater frequency of travel to highly endemic regions, and socio-economic barriers to healthcare access. While infection is prevented by vaccination with the safe and effective HB vaccine, it is not known whether lower HB vaccine coverage among the FB population may also exist and could perhaps be a contributing factor to the disparity in disease prevalence. Until now vaccine coverage comparisons between FB and CB populations have been difficult to conduct since no national immunization registry exists and regional immunization records do not track immigration status.(Wilson, Deeks, Hatchette, & Crowcroft, 2012)

The main rationale driving this research project is that lower HB vaccination coverage among immigrant Canadians may be a contributing factor to higher HB prevalence in this sub-group of the population. This study rationale is visualized in Figure 1. While this underlying rationale is the driver of the research, the study presented here does not aim to prove the causal mechanism of the rationale but rather aims to use epidemiological evidence to answer the question whether lower vaccination coverage is likely to exist among the FB population compared to the CB population in Canada. However, finding evidence of lower vaccination coverage only supports the rationale but does not prove it.

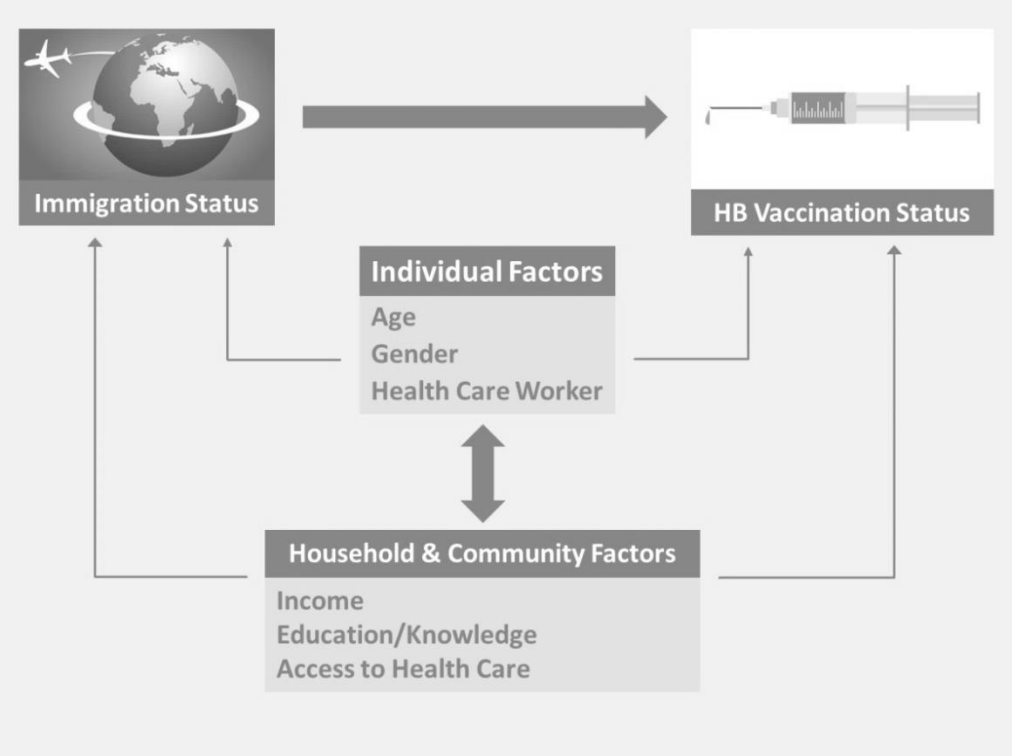

Figure 1: Simplified model representing the rationale driving the study.

1.2 Study objectives and hypotheses

The main aim of this study is to compare HB vaccination coverage between FB and CB populations in Canada using data on self-reported vaccination history and serological evidence of HB immunity from the CHMS to determine if there is a statistically significant difference between the two study populations. The specific objectives of the research are:

1.2.1 Objective 1

To determine whether there is a statistically significant difference in the prevalence of HB vaccination coverage between FB and CB populations in Canada based on: self-reported vaccination status, serological evidence of immunity against HB infection and a binary composite measure based on both self-report and serological evidence:

- Hypothesis 1.1: A lower proportion of FB individuals will self-report HB vaccination compared to CB individuals.
- Hypothesis 1.2: A lower proportion of FB individuals will test sero-positive for HB immunity compared to CB individuals.
- Hypothesis 1.3: A lower proportion of FB individuals will indicate any evidence of HB vaccination compared to CB individuals.

1.2.2 Objective 2

To determine whether concordance between self-report of vaccination status and serological testing for immunity is similar in FB and CB populations.

- Hypothesis 2: The concordance between self-report and serological evidence will be the same for both populations.

1.2.3 Objective 3

To determine if there is an independent effect of immigration status on HB vaccination:

- Hypothesis 3: There is an inverse association between immigrant status and HB vaccination after adjusting for covariates such as community, household and individual factors.

Chapter Two: **Literature Review**

This chapter provides a comprehensive review of the literature on the topic of HB vaccination coverage among FB Canadians. It is divided into five sections. The first section describes the epidemiology of HB in Canada. The second section focuses on the burden of HB among FB Canadians specifically. The third section discusses how HB immunization coverage is monitored in Canada. This is followed by a section that describes the Canadian Health Measures Survey (CHMS) as a useful tool for immigrant and HB research. The concluding section in this chapter is a theoretical framework based on the literature review that guides this study, which aims to assess differences in HB vaccination coverage among FB and CB populations in Canada using the CHMS.

2.1 Liver disease caused by Hepatitis B virus

Infection with the Hepatitis B (HB) virus, is a leading cause of liver disease and premature mortality worldwide.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015; Fauci & Morens, 2012; Lozano et al., 2013; Sharma et al., 2015) The HB virus is an enveloped, double-stranded DNA virus belonging to the *Hepadnaviridae* family. It is one of the smallest known DNA viruses and replicates quickly and exclusively in the hepatocytes (liver cells) of humans and other primates. The main 4 components of the HB virus are illustrated in Figure 2 and include: 1) an abundant surface antigen lipoprotein on the viral envelope (HBsAg), 2) the core antigen which is a protein of the nucleocapsid core (HBcAg), 3) a partially double-stranded genome of 3200 base pairs and 4) a DNA polymerase protein to initiate replication.

Initial infection with the HB virus may lead to acute illness but can turn into chronic long-term disease especially among those that are infected early in life (less than 5 years of age). Chronic HB may develop into liver cirrhosis and liver cancer in up to 20-30% of chronically infected people sometimes leading to premature death since no cure exists for HB. Globally, an estimated 240 million people are chronically infected with HB virus and more than 780 000 people die every year due to complications of HB-related disease.(Lozano et al., 2013; Organization, 2015) While HB is more prevalent in developing countries, it remains a leading cause of rising liver cancer rates in developed countries such as Canada.("Canadian Cancer Statistics: Predictions of the future burden of cancer in Canada ", 2015; De, Dryer, Otterstatter, & Semenciw, 2013)

The HB virus is highly infectious and transmission occurs via direct blood-to-blood or trans-mucosal contact with infected blood and bodily fluids.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015) In developing countries the primary routes of transmission are vertical (from mother-to-newborn) or via exposure to infected close family contacts whereas in developed countries, sexual transmission and sharing of injection drug equipment lead to most new cases.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015) Often people with chronic infection are asymptomatic, and therefore go undetected and untreated until they present with severe liver disease or cancer decades after initial infection.(Greenaway et al., 2011) In addition, some undiagnosed asymptomatic individuals remain infectious to others acting as carriers.

Fortunately, HB is vaccine-preventable.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015; Rossi et al., 2012) The HB vaccine is a

recombinant subunit vaccine which has been proven both safe and highly effective with greater than 90% effectiveness in healthy people who receive a complete vaccine series.(Gilca et al., 2013; Lozano et al., 2013; "National advisory committee on immunization (NACI). Statement on hepatitis B vaccine," 1993; Zanetti et al., 2005) Vaccination has been the most effective public health measure for preventing HB transmission and disease since widespread use in 1982.(Organization, 2002) As such, the World Health Organization recommends universal immunization of children to control the spread of HB worldwide, including in countries of low endemicity.(Mackie, Buxton, Tadwalkar, & Patrick, 2009; Organization, 2002)

2.2 Epidemiology of Hepatitis B in Canada

Canada is a country of low HB endemicity.(Rotermann et al., 2013) A serological survey of HB biomarkers in a nationally representative sample conducted as part of the Canadian Health Measures Survey (CHMS) found the sero-prevalence of present HB infection to be 0.4% (representing 111,800 individuals) among Canadians aged 14 to 79 years with an additional 4.2% of Canadians having evidence of a previous infection (2007–2011). The prevalence rates in Canada are similar to that of other developed countries such as the US, UK and Australia (<2%) but significantly lower than those in developing regions such as Southeast Asia or Sub-Saharan Africa with high prevalence (>8%) or Central Asia and the Middle East with intermediate prevalence (2% to 7%).

One major factor that maintains low prevalence of HB in Canada is publically-funded childhood immunization programs.("Canadian Hepatitis B Immunization Programs By Risk Group," 2015; Mackie et al., 2009; "Vaccine Coverage in Canadian

Children: Results from the 2011 Childhood National Immunization Coverage Survey," 2015) Several formulations of the recombinant surface antigen vaccine against HB are available in Canada (Table 1) and a full series of vaccinations are usually provided in 3 doses given at 1 to 6 month intervals.(Lozano et al., 2013; "National advisory committee on immunization (NACI). Statement on hepatitis B vaccine," 1993) All Canadian provinces and territories introduced routine childhood vaccination against HB in the early 1990s with most people born after 1980 being eligible as summarized in Table 2. All of these programs initially targeted adolescents (school-aged children), but 4 provinces (British Columbia, Quebec, New Brunswick, Prince Edward Island) and the 3 territories (Northwest Territories, Yukon, and Nunavut) later added infant programs.

Policies surrounding screening and immunization of adults at high risk of infection such as injection drug users, those at risk of sexually transmitted infections (STIs), or those with co-morbidities vary widely between provinces and territories("Canadian Hepatitis B Immunization Programs By Risk Group," 2015) and are generally not publically-funded with the exception of healthcare workers that receive employer-funded HB screening and vaccination in most provinces and territories (Table 3).

Furthermore, the Canadian Immunization Guide recommends that all pregnant women be routinely tested for HB. While no studies have reported the level of adherence to this national guideline, the additional opportunity for screening amongst pregnant women may translate into greater opportunity for catch up vaccination thereby potentially leading to higher rates of HB vaccination coverage among women compared to men.[29]

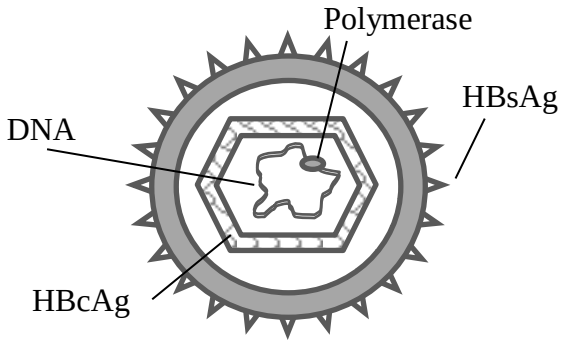

Figure 2: Schematic diagram of Hepatitis B virus.

Table 1: Hepatitis B-protective vaccine preparations authorized for use in Canada.

Name	Type Vaccine	Company
Engerix B	Recombinant hepatitis B vaccine (HB)	GlaxoSmithKline Inc.
Recombivax HB	Recombinant hepatitis B vaccine (HB)	Merck Canada Inc.
TwinRix (Adult)	Combined hepatitis A and hepatitis B vaccine (HAHB)	GlaxoSmithKline Inc.
TwinRix Junior (Pediatric)	Combined hepatitis A and hepatitis B vaccine (HAHB)	GlaxoSmithKline Inc.
Recombivax HB (Pediatric)	Adsorbed vaccine containing diphtheria and tetanus toxoids, acellular pertussis, recombinant hepatitis B, inactivated poliomyelitis and conjugated Haemophilus influenzae type b vaccine (DTaP-HB-IPV-Hib)	Merck Canada Inc.

Table 2: Summary of Canada's Provincial and Territorial routine vaccination programs for infants and children as of July 2015.[27]

Province	Vaccine	Age Group	Doses	Schedule	HB vaccine funded for those born in the childhood vaccine era (1980 or after)
BC	combination vaccine (DTaP-HB-IPV-Hib)	infancy	3	2, 4 and 6 months of age	Yes, for those born on or after Jan 1, 1980
AB	HB	school aged	3	Grade 5	Yes, for those born on or after Jan 1, 1984
SK	HB	school aged	2	Grade 6	Yes, for those born on or after Jan 1, 1984
MB	HB	school aged	2	Grade 4	Yes, for those born on or after Jan. 1, 1989
ON	HB	school aged	2	Grade 7	No, as per routine childhood schedule only
QC	combination vaccine (DTaP-HB-IPV-Hib)	infancy	3	2, 4 and 6 months of age	Yes, for those born in or after 1993
NB	HB	infancy	3	At birth, 2, and 6 months	Yes, for those born in or after 1986
NS	HB	school aged	2	Grade 7	No, as per routine childhood schedule only
PE	combination vaccine (DTaP-HB-IPV-Hib)	infancy	3	2, 4 and 6 months of age	Yes, for those born in or after 1986
NL	HB	school aged	2	Grade 6	Yes, for those born in or after 1986
YT	combination vaccine (DTaP-HB-IPV-Hib)	infancy	3	2, 4 and 6 months of age	Yes for those born on or after Jan 1, 1984
NT	HB	infancy	3	At birth, 1, and 6 months	No, as per routine childhood schedule and those at high risk only
NU	HB	infancy	3	At birth, 1, and 9 months	Yes, for those born in or after 1995

Note: BC = British Columbia, AB = Alberta, SK = Saskatchewan, MB = Manitoba, ON = Ontario, QC = Quebec, NB = New Brunswick, NS = Nova Scotia, PE = Prince Edward Island, NL = Newfoundland, YT = Yukon Territory, NT = Northwest Territories, NU = Nunavut

Table 3: Summary of Canadian Hepatitis B immunization programs by risk group in all provinces and territories as of March 2015.[29]

HB Risk Groups	Provinces and Territories where HB immunization is publicly funded for risk group
Health care workers	BC, AB, SK, PE, NT, YT, NU
Residents and/or staff of institutions for the develop-mentally disabled	All except ON and NS
Occupational or accidental per-cutaneous or per-mucosal exposure to HbsAg-positive blood	All except NB
Staff in childcare settings where there is an HBV-infected child	BC, QC, and YT only
Hepatitis C-positive individuals	All
HIV-positive individuals	All
Heterosexual males and females with multiple sexual partners or recent history of an STD	All except ON
Homosexual and bisexual males	All except ON
Sexual assault victims	All except ON, NB, NL, NT
Household and sexual contacts of acute HBV cases and HBV carriers	All
Inmates of long term correctional facilities	BC, AB, MB, QC, PE, NL, YT, NU
Injection drug users	All
Hemodialysis patients	All
Pre dialysis, peritoneal and hemo dialysis	All
Transplant recipients	All
Hemophiliacs and others receiving multiple infusions of blood or blood products	All
Children under 7 years whose family has immigrated to Canada from high HBV prevalence areas	All
Children under 7 who live with at-risk adults	All except NS and NL
Children in childcare settings where there is an HBV-infected child	All except SK, ON, NB, and NL
Travellers to moderately or highly endemic areas	NT only
Household contacts of internationally adopted children from moderately or highly endemic country of origin	BC, QC, PE, YT and NU only
Foreign-born Canadians from moderately or highly endemic country of origin	None

Despite routine vaccination of children and many cases of HB going unreported due to the asymptomatic nature of initial infection, more infections caused by HB virus are reported each year to the Canadian Notifiable Disease Surveillance System (CNDSS) than any other disease prevented through childhood vaccination programs . ("Reported Cases of Disease in Canada," 2012) In 2011, 0.6 acute cases and 11.4 chronic cases of HB were reported per 100,000 Canadians.(PHAC, 2014)

2.3 Greater burden of Hepatitis B among foreign-born Canadians

Along with the CNDSS, additional data from the Enhanced Hepatitis Strain Surveillance System (EHSSS) is collected from a few sites across Canada to monitor transmission trends.(PHAC, 2014) For surveillance purposes, HB cases are differentiated as acute or chronic and data on chronic infections help determine the burden of disease while acute cases help determine transmission trends. EHSSS data from 2011 indicate that even rates of newly acquired (acute) HB are higher among persons born outside of Canada compared to CB individuals at 0.6 and 0.3 per 100,000, respectively.(PHAC, 2014) Data from the CHMS HB sero-survey also found significantly higher proportions of present and past infections among FB compared to CB individuals.(Rotermann et al., 2013)

Based on a review of evidence pertaining to HB conducted by the Canadian Collaboration for Immigrant and Refugee Health (CCIRH) in 2011, it was confirmed that the mortality from chronic viral hepatitis and liver cancer is significantly higher among the FB than the CB population.(Greenaway et al., 2011; Pottie et al., 2011) The review estimates that mortality from viral hepatitis is 1.8–3.8 times higher and mortality from

hepatocellular carcinoma is 2.2–4.9 times higher in immigrants than non-immigrants. As a result, the CCIRH recommended that all new immigrants from areas of intermediate or high (greater than 2%) HB prevalence are screened for HB and those found susceptible be provided with the vaccine.

The greater burden of HB among foreign-born individuals in Canada is a major public health concern because over 20% of Canada's population is comprised of immigrants.(Chui et al., 2011; Pottie et al., 2011) Also, the majority of recent immigrants come from regions of intermediate and high endemicity, including 59.6% from Asia and the Middle East and 12.5% from Africa.(Chui et al., 2011; Rossi et al., 2012) Regions where high or intermediate HB endemicity exist raise concerns about the effectiveness of national healthcare policies and programs surrounding HB prevention such as vaccination, in those regions. Furthermore, risk of chronic HB increases when infected in early childhood putting those born elsewhere at risk of exposure during the stage of life where they are least likely to recover from an infection.

However, while the evidence suggesting a disparity in HB disease between FB and CB populations is abundant,(Mackie et al., 2009; Pottie et al., 2011; Rossi et al., 2012; Rotermann et al., 2013; Zanetti et al., 2005) no studies have attempted to measure whether low vaccination coverage among new Canadians may exist. Studies in the United States based on data from the National Health And Nutrition Survey (NHANES) conducted routinely by the Centers for Disease Control (CDC) have shown lower vaccination coverage among the foreign-born based on self-reported vaccination status but these results cannot be extrapolated to Canada due to differing immigrant composition and healthcare policies.(Elgar & Stewart, 2008; Wilson et al., 2012)

Several factors may exist for why lower HB vaccine coverage might exist among FB Canadians. For example, it may occur if access to healthcare and childhood vaccinations in other regions is not as universal and comprehensive as in Canada. Also, since most adults will need to pay for HB vaccination in Canada, lower income rates among immigrant households may translate into lower vaccination rates relative to non-immigrant Canadians.(Picot & Hou, 2014; Zhao, Xue, & Gilkinson, 2010) In addition, Canada's publically-funded routine childhood immunization programs may fail to reach immigrants that arrive in Canada at ages older than when childhood vaccination programs are implemented, leaving those not vaccinated in their country of birth, susceptible to infection.(Greenaway et al., 2011; Rossi et al., 2012)

Several reasons exist for why low HB vaccination coverage among immigrants living in Canada may be a public health concern. For instance, immigrants are more likely to be exposed to HB virus through contact with infected individuals in their households and possibly more likely to travel to countries where HB is prevalent.(Lozano et al., 2013; Pottie et al., 2011) In addition, endemic transmission of HB in Canada is limited by a high proportion of people vaccinated in younger age groups however this only benefits communities where the mixing of immune and susceptible individuals is homogenous. Since, FB Canadians often settle in densely populated urban centres(Chui et al., 2011) among high proportions of FB the likelihood of HB transmission through greater likelihood of social mixing within these communities may be increased. Potentially, pockets of under-vaccinated communities could exist that are not as well protected as the overall population of Canadians. Similarly we know that under-immunized pockets have been demonstrated for measles resulting in recent measles

outbreaks.(De Serres et al., 2013; Region, 2014; Services, 2014) Unlike measles however, HB is often asymptomatic and may go undetected for years making it more difficult to treat cases and manage close contacts to mitigate transmission.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015)

2.4 Monitoring Hepatitis B immunization coverage in Canada

Along with surveillance of incident cases, the national public health strategy for monitoring HB includes monitoring immunization coverage.(Picot & Hou, 2014) National immunization coverage estimates are also needed for reporting to international organizations, monitoring progress towards coverage targets, developing targeted public education strategies and estimating population immunity to vaccine-preventable diseases.("Canadian Hepatitis B Immunization Programs By Risk Group," 2015; Picot & Hou, 2014; "Vaccine coverage amongst adult Canadians: Results from the 2012 adult National Immunization Coverage (aNIC) survey," 2014) Although provider medical records are considered the most reliable method of determining vaccination coverage,(Grimaldi-Bensouda et al., 2013) they cannot be used for national estimates in Canada because healthcare services are delivered regionally and no nationwide immunization registry exits. In addition, regional medical records databases are maintained according to differing platforms and methodologies such that linking registries across jurisdictions is not yet feasible. In the absence of consistent provider records, public health authorities rely on self-reports to determine immunization history.

Currently, cross-sectional surveys of self-reported vaccine receipt are used to derive national immunization coverage estimates for Canadians such as the National

Immunization Coverage Surveys (NICS) for adults and children.("Canadian Hepatitis B Immunization Programs By Risk Group," 2015; "Vaccine coverage amongst adult Canadians: Results from the 2012 adult National Immunization Coverage (aNIC) survey," 2014) These surveys indicate that HB immunization coverage varies across population groups. In a 2011 national survey of immunization coverage among Canadian children, it was found that 74.8% of participating parents of 17-year-olds reported immunization of their children against HB (two or more doses).("Canadian Hepatitis B Immunization Programs By Risk Group," 2015) In 2012, a similar survey conducted among adult Canadians (18 years and older) found that 39.7% of all participants reported having been vaccinated against HB.("Vaccine coverage amongst adult Canadians: Results from the 2012 adult National Immunization Coverage (aNIC) survey," 2014) HB immunization coverage was found to be significantly more likely among adults with higher levels of education and healthcare workers, while having an underlying health condition was not a significant predictor of vaccination.("Vaccine coverage amongst adult Canadians: Results from the 2012 adult National Immunization Coverage (aNIC) survey," 2014) For children however, a caregiver reporting that their child had never been immunized was more likely to report having attended post-secondary education.("Canadian Hepatitis B Immunization Programs By Risk Group," 2015) In general, vaccination coverage was negatively associated with age and varied across jurisdictions in both surveys.("Canadian Hepatitis B Immunization Programs By Risk Group," 2015; "Vaccine coverage amongst adult Canadians: Results from the 2012 adult National Immunization Coverage (aNIC) survey," 2014) Several limitations exists with the NICS including low response rate (<15%) possibly due to the questionnaire being

conducted over the telephone and small sample size (approximately 3000 or less) relative to the overall population thereby lacking the power to detect differences between groups such as FB and CB populations.

A limitation of immunization coverage estimates based on self-reports is that reports are subject to recall errors that may be dependent on characteristics of the surveyed person. As such, trends in self-report bias often contribute to overestimation more often than underestimation as evidenced in other studies.(Elgar & Stewart, 2008; Jimenez-Garcia et al., 2014; M. Thompson, 2014; Rolnick et al., 2013) Studies have shown that self-reported receipt of medical services in general is subject to recall errors.(Jimenez-Garcia et al., 2014; Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004; Rolnick et al., 2013) Among CHMS respondents, self-reported measures such as height and weight have been demonstrated as needing adjustment based on demographic characteristics to ensure accuracy.(Elgar & Stewart, 2008) However, little data exists on the differential self-reporting of immunizations between immigrant and non-immigrant populations.

To minimize errors associated with self-report, testing for serum antibody levels can be an alternative source of information about vaccination history.(Denniston et al., 2013; Rossi et al., 2012; Rotermann et al., 2013; Trevisan et al., 2007; Wilson et al., 2012) In cross-sectional sero-prevalence surveys, immunity is determined according to the detection of antibodies in blood sera using serological testing assays.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015; Huzly, Schenk, Jilg, & Neumann-Haefelin, 2008; Krajden, McNabb, & Petric, 2005) For HB, several biomarkers are used to assess immunity, susceptibility and infection in surveyed individuals and are

able to differentiate vaccine-induced immunity from immunity acquired through previous infection.(Wilson et al., 2012) In these assays, viral proteins called the HB surface antigen (HBsAg) and the HB core antigen (HBcAg) are markers of current HB infection. Typically, antibody to HBsAg (anti-HBs) appears after an HB infection has resolved and confers long-term immunity. Vaccine-induced immunity occurs when the HB vaccine promotes anti-HBs production in a vaccinated individual who has not been infected with the HB virus previously. As a result both those infected with the virus and vaccinated persons carry anti-HBsAb. However, antibody to HB core antigen (anti-HBc) will appear only in those who have been infected by the virus which allows those with vaccine-induced immunity to be differentiated from those with previous infection. Those with present or previous infections may also be anti-HBc positive. Those positive for anti-HBcAb and anti-HBsAb are classified as resolved (if negative for HBsAg), while those positive for anti-HBs are only classified as having vaccine-induced immunity. Table 4 summarizes the interpretation of HB serology testing. Anti-HBs titers greater than or equal to 10 IU/litre are considered protective against infection.(Huzly et al., 2008; Krajden et al., 2005)

While cross-sectional studies of HB antibody sero-prevalence are able to provide more objective estimates of population-level immunity compared to self-reports, antibody sero-prevalence can only act as a relative measure of population-level immunity (ie. to examine trends over time or for comparison of groups) and should not be relied upon to act as an absolute measure alone.("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015; Mackie et al., 2009) This is because up to 60% of vaccinated people lose detectable antibody but not necessarily protection 10 to 15 years after

vaccination("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015) and studies have shown antibody titres wane among people within the first few years after vaccination such that about one-third of children vaccinated as infants will have titres below 10 IU/litres by 15 years of age.(Gilca et al., 2013; Zanetti et al., 2005) Therefore, serum antibody levels can confirm the initial response to vaccination but are not an appropriate indicator of long-term immunity (which can only be confirmed by the anamnestic immune response indicated by a rise in anti-HBs to at least 10 IU/L after receiving a booster dose). As a result it is difficult to interpret a negative anti-HBs serologic response as it is not possible to determine if individuals testing negative were never vaccinated, were primary vaccine failures or were tested years after vaccination and have anti-HBs titres that has waned to below the detectable level. A positive anti-HBs serologic response in the absence of any other HB infection markers however is a reliable indicator that vaccine-induced immunity to HB is confirmed.

Although Canada is a country of low HB endemicity, the estimated 2 billion people infected with HB worldwide remain an ongoing source of infection and several generations of targeted vaccination will be needed to eliminate endemic HB transmission in Canada.(Krajden et al., 2005) FB Canadians experience a disproportionate burden of HB disease and may be a group that would benefit from publically funded HB immunization programs as recommended by CCIRH. Thus far, no immigrant screening or targeted catch-up vaccination programs have addressed the CCIRH guidelines. Cost-benefit analyses conducted by Rossi et al. found that the costs of screening and immunizing unvaccinated FB Canadians would be greater than the costs of treating the symptoms of healthy individuals that went on to acquire the disease.(Rossi,

Schwartzman, Oxlade, Klein, & Greenaway, 2013) In other words, prevention through public health intervention was deemed less cost effective than providing medical treatment to those that became diseased. However cost-benefit analyses did not assess the implications on quality of life of those impacted by HB disease.

Table 4: Interpretation of hepatitis B serological testing results.

Tests for Sero-prevalence of IgG Antibodies	Interpretation
HBsAg (-) Anti-HBc (-) Anti-HBs (-)	Susceptible (including waning antibodies to vaccination)
HBsAg (-) Anti-HBc (+) Anti-HBs (+)	Immune due to natural infection
HBsAg (-) Anti-HBc (-) Anti-HBs (+)	Immune due to vaccination
HBsAg (+) Anti-HBc (+) Anti-HBs (-)	Infected: acutely (IgM positive) or chronically (IgM negative)
HBsAg (-) Anti-HBc (+) Anti-HBs (-)	Resolved infection, low-level chronic infection, or resolving acute infection

2.5 The Canadian Health Measures Survey as a source of data on Hepatitis B vaccination

Fortunately, data collected by the CHMS, which is a nationally representative survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada, provides us with the unique opportunity to explore both self-reported vaccination and serological evidence of HB immunity in a nationally representative sample of Canadians which includes a representative proportion of FB Canadians.(Ng, 2015) Using both of these measures of vaccination coverage will allow us to assess consistency of our findings. Furthermore, by assessing the concordance of self-reports and serological evidence in the sub-populations of interest we can determine whether the extent of vaccination status misclassification differs between FB and CB groups. In addition, information form the CHMS household questionnaire will allow us to assess whether the effect of immigration status on vaccine uptake is confounded by individual, household and community factors.

2.6 Theoretical framework

As described in Chapter Two, while the HB vaccine may be available worldwide, a difference in vaccination coverage between FB and CB populations may arise due to differing vaccination policies and programs in foreign jurisdictions compared to Canadian jurisdictions. While this is the community-level exposure that this study aims to assess, it is important to note that several other factors at the community-level, household-level and individual-level could systematically vary between the two sub-groups of the population being compared and could lead to a difference in estimated vaccination coverage. Several measureable indicators of these factors are illustrated in the theoretical framework shown in Figure 3. These factors must be accounted for when conducting data analysis in order to determine whether a difference in vaccination coverage is independent of other covariates.

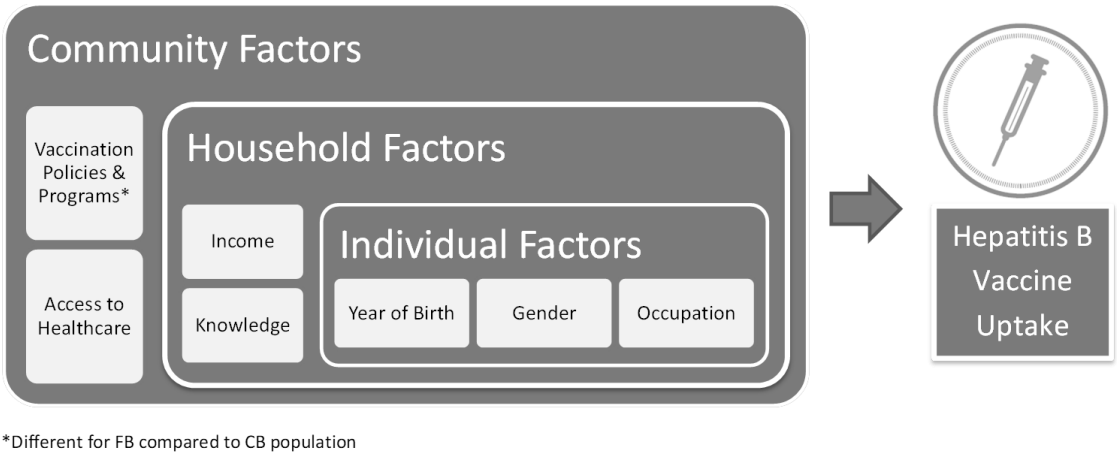

Figure 3: Theoretical framework describing indicators of community-level, household-level and individual-level factors that impact vaccination uptake.

Chapter Three: **Methods**

3.1 Data source: Canadian Health Measures Survey

Data for this study was collected as part of the CHMS which is an ongoing cross-sectional health survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada. The CHMS includes two parts: 1) an in-home interview to gather health, demographic, socio-economic, and lifestyle information, followed by 2) a visit to a mobile examination center (MEC) for direct health measures and biospecimen collection. The data used in this study were obtained from the CHMS Cycle 1 (2007-2009) and Cycle 2 (2009-2011) master files containing de-identified person-level data maintained at the Statistics Canada Research Data Centre (RDC) in Winnipeg, Manitoba.

3.2 Study sample and target population

The CHMS is a multistage cluster, stratified sampling survey.(Giroux, 2006) Through stratification, sampling in the CHMS is divided into five mutually exclusive and exhaustive geographic regions and independent samples are selected from each. Stratified sampling in the CHMS allows for all regions to be represented in national estimates. The five regions in the CHMS are based on Statistics Canada's standard regional boundaries (SRB) and include: British Columbia, the Prairies (Alberta, Manitoba and Saskatchewan), Ontario, Quebec and the Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia and New Brunswick).

Multistage cluster sampling involves first sampling sites, then sampling households, and then sampling individuals within households. For the CHMS primary sampling units for the multi-province cluster sampling strategy were designated as "collection sites" which were identified using the Labour Force Survey (LFS) as an area sampling frame. For the secondary sampling stage, household units within the sites were identified using the 2006 census. Households were selected by simple random sampling such that one individual between age 12 and 79 years would be sampled from each selected dwelling.

In addition, oversampling from certain sub-groups was used to ensure that a sufficient number of respondents were selected from these groups so that robust national estimates and comparisons can be made across sub-groups. For the CHMS oversampling allowed the final sample to be representative of seven age groups (12 to 19-year-olds, 20 to 29-year-olds, 30 to 39-year-olds, 40 to 49-year-olds, 50 to 59-year-olds, 60 to 69-year-olds, and 70 to 79-year-olds) and both sexes.

The CHMS target population is the average Canadian household population living in the ten provinces. The CHMS excludes people living on reserves and other Aboriginal settlements, full-time members of the Canadian Forces, the institutionalized population, and residents of some remote regions.

Thus far, data has been released in its entirety for two cycles of the CHMS. Data for Cycle 1 was collected between March 2007 and February 2009 from 5,604 respondents aged 6 to 79 living in households within 15 sites across Canada. Data for Cycle 2 was collected between August 2009 and November 2011 from 6,395 respondents aged 3 to 79 living in households within 18 sites across Canada. The overall response rate

was 53.5% with a total of 11,385 respondents in the combined cycles. In total, 18.2% of respondents were FB Canadians.

Approximately the same subset of the CHMS respondents used in the HB sero-prevalence study conducted by Rotermann et al. (Rotermann et al., 2013) will be used in this analysis of HB vaccination uptake. This subset includes about 8,400 respondents aged 14 to 79, who completed the MEC component along with the household questionnaire.

3.3 Measures of Hepatitis B vaccination

HB vaccination status is the main outcome variable used in this study. Self-reported HB vaccination status was determined by the survey question worded as follows: “Hepatitis B vaccinations usually come in a 2 or 3 dose series. Have you received a complete series of hepatitis B vaccines? Examples of hepatitis B vaccines include Engerix-B, Recombivax HB, and Twinrix.” Respondents were given the option of answering either “yes”, “no” or “don’t know” to the question.

In addition, serological evidence of immunity to HB was determined for each eligible survey respondent based on sero-positivity for anti-HBsAg (antibody titers ≥10 IU/litre) and sero-negativity for anti-HBcAg (antibody titers <10 IU/litre). A composite binary measure of vaccination status was derived from both these measures as described in Figure 4. The two groups were: likely vaccinated individuals (those with confirmed immunity based on serological evidence of HB antibodies and those that do not have serological evidence of vaccination but self-reported vaccine receipt) versus likely not

vaccinated individuals (those that had no serological evidence of HB antibodies and did not self-report vaccination).

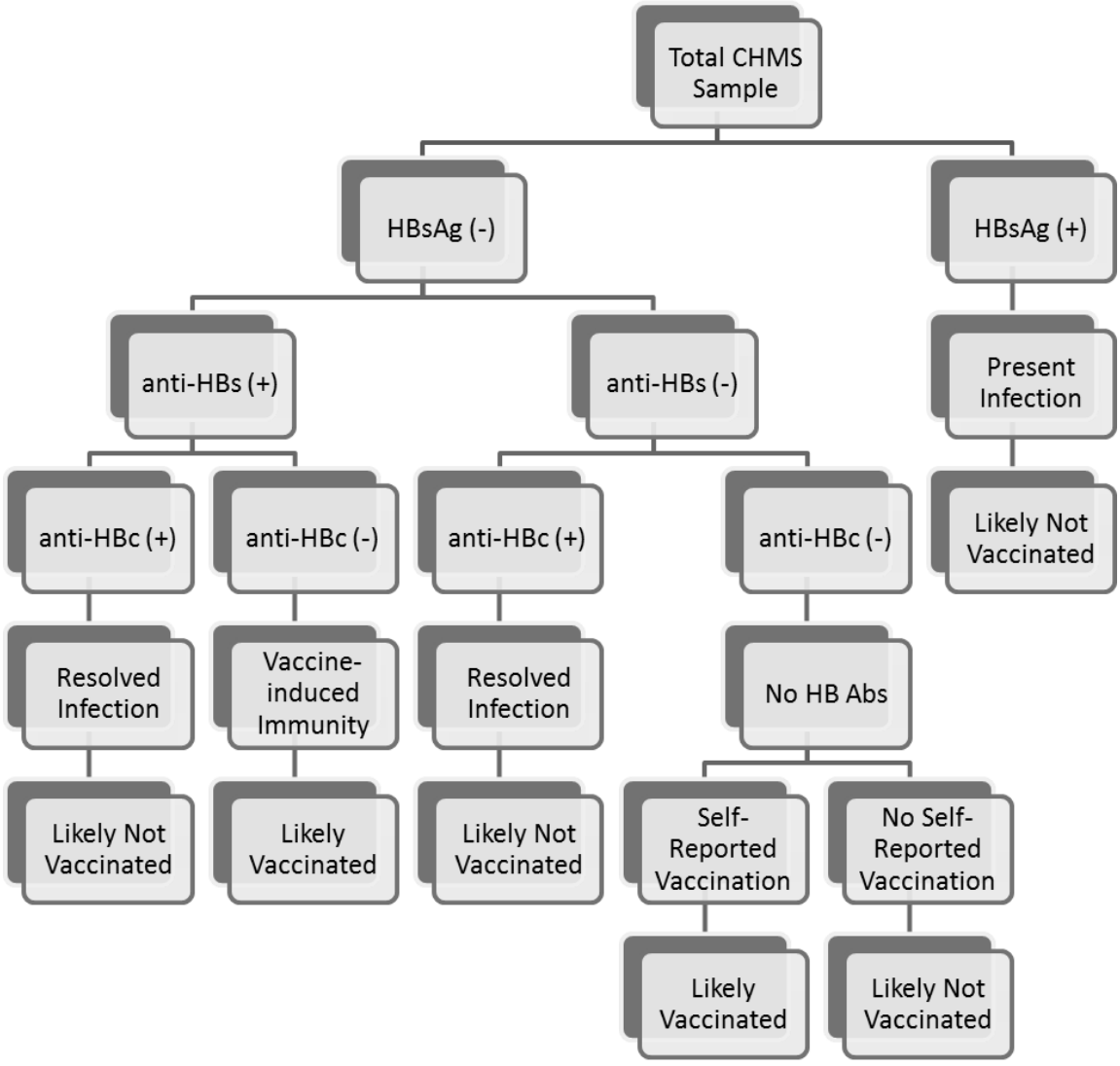

Figure 4: Categories of vaccination status determined based on self-reported vaccination and on serological testing of Hepatitis B (HB) biomarkers.

3.4 Community, household, and individual covariates

Variables indicating the community, household, and individual level covariates described in Figure 3 were accounted for in the analysis. A complete list of CHMS variables used in this study can be found with details and descriptions in Table 5. (Canada, 2011, 2012; Giroux, 2006) Some variables were re-grouped for analysis such that categories correspond with those used in other CHMS studies of HB and immigration.(Ng, 2015; Rotermann et al., 2013) The socio-demographic covariates considered in the analysis include: place of birth, age, sex, occupation, income, education and access to healthcare.

Immigration status is the main exposure of interest and data on country of birth was used to classify the survey respondents into one of the following two groups: 1) those born outside Canada (FB) and 2) those born in Canada (CB).

For descriptive statistics, age groups were based on survey participants' age at blood draw and were grouped according to the 7 representative age groups designated in the CHMS. However, for bivariate and multivariate analyses associating with immigration and vaccination factors, birth years were dichotomized into two birth eras such that participants born before 1980 (before the HB childhood vaccination era) were categorized separately from participants born in or after 1980 (during the vaccination era).

Survey respondents were classified into one of two groups based on their total annual household income, after adjustment for household size: 1) those with higher annual household income and 2) those with lower annual household income. Households were considered to be lower income if their total earnings in the past year were less than

$30,000 (one or two household members), less than $40,000 (three or four members), or less than $60,000 (five or more members). These cutoffs were chosen to be consistent with income categories used in similar studies conducted with Statistics Canada data.(Canada, 2011, 2012; Giroux, 2006)

The education variable was used as an indicator of knowledge and was based on the highest education level achieved by the selected member of the household and dichotomized into two groups: post-secondary graduates versus other.

CHMS survey participants self-reported occupation responses were assigned occupational codes by Statistics Canada according to the National Occupational Classification for Statistics (NOC-S) 2001. Those assigned codes under occupational Category D of the NOC-S were categorized as healthcare workers for this study and the remaining were considered non-healthcare workers to create a dichotomous occupation variable.(Canada, 2011, 2012; Giroux, 2006)

Access to healthcare was based on whether survey respondents answered “yes” or “no” to the question: “do you have a regular medical doctor?”

3.5 Data analyses

The analytical methods used for examining objectives in this study are summarized in Table 6. For Objective 1, vaccine coverage proportions among immigrant and non-immigrant Canadians were compared overall and by sample characteristics including sex, age group, highest household education, household income level and region of residence. Significance of differences in vaccine coverage between groups were

determined using the Pearson's chi-squared test for independence and assessed at the $p < 0.05$ level.

Table 5: A complete list of Canadian Health Measures Survey (CHMS) variables used in the data analysis.

CHMS Variable	Description	Levels
DHH_PRN	Province of residence of respondent (re-grouped into 5 regions)	BC, Prairies, ON, QB, Atlantic
SITE	Site of data collection primary sampling unit	18 different sites sampled from in CHMS Cycles 1 and 2
LAB_HBS	NML - Serum tests: anti-HBs (antibody titre ≥ 10 IU/L, 2 groups)	No, Yes
LAB_HBC	NML - Serum tests: anti-HBc (antibody titre ≥ 10 IU/L, 2 groups)	No, Yes
HEP_12	Ever received complete series of hepatitis B vaccines (Self-reported vaccination, 2 groups)	No/Don't Know, Yes
CLC_AGE	Age of respondent at blood draw (re-grouped into 7 age groups)	**14-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years**
CLC_SEX	Biological sex of respondent (2 groups)	Female, Male
SDC_11	Country of birth (re-grouped into 2 groups)	Canadian-born, Foreign-born
EDUDH04	Highest level of education - Household (4 levels, derived – re-grouped into 2 levels)	Post-Secondary Graduate, Less than Post-Secondary
INCDDIA2	Income adequacy – Household (2 levels, derived from income and household size)	Higher or medium income, Lower income
LBF_SOC	Healthcare Worker Occupational Classification (2 levels, derived based on NOC-S Group D vs. Other Groups)	Healthcare Worker, Not a Healthcare Worker
GEN_20	Having a regular medical doctor as an indicator of access to healthcare	No, Yes

For Objective 2, a concordance analysis was conducted to assess how similarly self-reported vaccination status agrees with serological evidence of vaccine-induced immunity in immigrants compared to non-immigrants. Self-report is subject to recall error and could vary according to socio-demographic characteristics leading to differential misclassification between immigrants and non-immigrants. However, serological evidence of HB immunity is an objective biological measure, although it can be only used relatively due to waning detectable antibodies over time. Therefore checking if the level of agreement between the two measures is similar for immigrants as for non-immigrants, will help assess differential misclassification arising from self-report. Several measures were reported for assessing agreement including the percentage agreement, percentage discordant and Cohen's Kappa coefficient for inter-rater agreement (which accounts for agreement due to chance). If concordance is similar for sub-groups, the composite measure of vaccination based on both self-report and serological evidence was considered valid for use in Objective 3.

For Objective 3, the association of immigration status on HB vaccination after adjusting for related covariates was assessed using multivariate logistic regression models for each outcome. The outcome measure for the final models was vaccination status categorized into according to the flowchart in Figure 4 (likely vaccinated versus ikely not vaccinated). Univariate analysis was performed on covariates followed by multivariate analysis including all covariates. Unadjusted and adjusted odds ratios were reported with corresponding 95% confidence intervals.

Table 6: Analytical methods proposed for the evaluation of objectives in this study

Objective	Analysis	Statistical Method
Objective 1: To determine whether there is a significant difference in the prevalence of HB vaccination coverage between FB and CB populations in Canada based on CHMS measures	Bivariate Analyses	Pearson's Chi-squared Test for significance
Objective 2: To determine whether concordance between self-report and serological measures of vaccination status is similar in FB and CB populations	Concordance Analysis	Cohen's Kappa, Percentage Agreement, Percentage Discordant
Objective 3: To examine whether there is an independent effect of immigration status on vaccination status	Multivariate Analyses	Multivariate regression models based on three different outcomes: 1) outcome: serology 2) outcome: self-report 3) outcome: binary composite measure

3.6 Survey data analysis techniques

Since the CHMS employs a complex sampling design in selecting survey participants, these design characteristics must be accounted for when performing survey data analysis in order to avoid biased estimates and incorrect variances. Separately from the complex sampling design, survey response rates can bias proportion estimates if certain kinds of people systematically refuse to or are not available to participate. All estimated vaccine coverage proportions and odds ratios from regression analysis were obtained using the full sample weights for the combined Cycle 1 and 2 data produced by Statistics Canada to make the sample be representative of the study population and adjust for non-response. Sampling probability weights adjust for unequal probability of selection introduced to the sample by stratification, oversampling, and response rates. The sampling weight is applied to each observation when estimating prevalence in descriptive data analysis.

Cluster-sampling exclusively effects variance estimates because people from the same community are often more similar in some way than those from other communities. Therefore variance within a cluster and variance across clusters needs to be accounted for to avoid the risk of type 1 error (finding differences among subgroups that are not real). Therefore coefficients of variation (CVs) and 95% confidence intervals (CIs) were estimated using the bootstrap method which accounts for survey design effects. The corrected variance for proportion estimates were obtained using 500 bootstrap weights provided by Statistics Canada.

All data analyses for this research were performed using Stata Version 14 (Stata Corp, College Station, TX, USA) as recommended by the RDC network.(Gagné, Roberts,

& Keown, 2011) In Stata, using the addition of the prefix "svy" to several commands adapts them to working with the survey design that is specified under the "svyset" program statement. (Gagné et al., 2011) Specifically the statement was coded as: "**svyset [pweight = wgt_full],strata(region) psu(site) bsrweight(bsw1-bsw500) vce(bootstrap**" in Stata.

In accordance with the Statistics Canada CHMS data user guides,(Canada, 2011, 2012) estimates with CVs less than 16.6% were considered reliable but CVs between 16.6% and 33.3% were interpreted with caution as it indicates the estimate has a high sampling variability. CVs greater than 33.3% were noted as unacceptable quality and not recommended for drawing valid conclusions. In order to meet Statistics Canada's confidentiality and vetting requirements for releasing estimates, response options were re-grouped as needed to meet a minimum of 30 cases per cell (weighted).(Canada, 2011, 2012)

3.7 Ethics and consent

Ethics approval for conducting the CHMS was granted to Statistics Canada by Health Canada's Research Ethics Board. CHMS data are protected by the confidentiality provisions of the federal Statistics Act.

Prior to participation in the MEC component CHMS respondents were asked to review a comprehensive consent booklet that was provided during the at home interview outlining the terms of data use and bio-specimen testing, storage and data usage. Hepatitis testing was only performed if Statistics Canada has been authorized by respondent to provide information regarding Hepatitis B and C to the appropriate provincial authority.

Permission to access CHMS data was sought through the local Research Data Centre (RDC). The RDCs are part of an initiative by Statistics Canada, the Social Sciences and Humanities Research Council (SSHRC) and the university consortia to support Canada's research capacity. RDCs provide students and researchers with access to de-identified microdata from population and household surveys in a secure setting. All data are vetted by Statistics Canada staff before release to ensure disclosure of identifiable variables. All data analyses for this research were conducted at the Manitoba Research Data Centre (MBRDC) at The University of Manitoba in Winnipeg, Canada. This study is a secondary analysis of CHMS data and as such no further ethical approval is formally required.

Chapter Four: **Results**

4.1 Descriptive statistics

The characteristics of the Canadian household population aged 14 to 79 years based on the combined CHMS Cycle 1 and Cycle 2 sample are summarized in Table 7. The combined sample represents approximately 26.1 million Canadians of which 25% (95% CI: 19.7-31.1%) were foreign-born. About 74% (95% CI: 71.2-76.8) of the population were from households with post-secondary degrees and 20% (95% CI: 17.9-23.2) were from families with lower income. The majority (84%; 95% CI: 81.8-86.4) reported having a regular medical doctor and only 5% (95% CI: 3.9-5.9) were employed as healthcare workers. In total, 26% (95% CI: 25.2-26.9) of the population were born in the era of HB vaccination (1980 and after). Overall, Table 8 shows that 30% (95% CI: 27.6-31.4) of the population had serological evidence of immunity to HB while 42% (95% CI: 40.3-44.5) reported receiving a full series of HB immunizations.

Differences in characteristics by immigration status are shown in Table 9. Household size, income and age distribution were significantly different between FB and CB populations ($p<0.01$) with FB Canadians tending to have larger families, be in the medium to higher income household category and have a greater proportion in the 30 to 39 years and 40 to 49 years age groups. However, there was no significant difference between FB and CB populations in terms of proportion of households with post-secondary degrees, proportion in a healthcare occupation as well as gender distribution ($p>0.1$).

As shown in Table 10, the proportion of FB Canadians with serological evidence of HB immunity at 26% (95% CI: 21.0-30.1) was lower, but not statistically significantly different than the estimated proportion of 31% (95% CI: 28.9 - 32.8) among the CB sub-population (X^2 = 21.29, df: 24, p=0.62). The proportion of Canadians that reported receiving a full series of HB immunizations was significantly different between the FB [34% (95% CI: 30.2-38.4)] and CB [45% (95% CI: 42.8-47.5)] sub-populations (X^2 = 77.40, df: 24, p<0.01).

Some study participants did not report household socio-economic status characteristics, income and education, in the CHMS household questionnaire. While only less than 5% did not report highest level of education earned, 25% of the population did not directly report household income. Due to the large proportion of missing values for income, these values were imputed by Statistics Canada based on responses to other income-related questions in the CHMS household questionnaire. Notably, the proportions of missing values for household socio-economic status were consistent and similar among FB and CB populations.

Table 7: Self-reported demographic and socio-economic characteristics of the average Canadian household population aged 14 to79 years, CHMS Cycle 1 (2007-2009) and Cycle 2 (2009-2011).

Characteristics	%	95% confidence interval	
		from	to
Gender			
Male	50.0	49.6	50.3
Female	50.0	49.7	50.4
Age group			
14-19	8.9	8.6	9.3
20-29	17.5	16.5	18.6
30-39	16.7	15.7	17.7
40-49	20.1	19.0	21.3
50-59	17.2	16.1	18.4
60-69	13.0	12.3	13.8
70-79	6.5	5.8	7.2
Occupation			
Healthcare worker	4.8	3.9	5.9
Other occupation	95.2	94.1	96.1
Household Size			
Small	47.5	44.9	50.0
Medium	39.5	37.8	41.4
Large	13.0	11.6	14.5
Household Income			
Lower household income	79.6	76.8	82.1
Medium or higher income	20.4	17.9	23.2
Missing Values: Income			
Not Reported (Imputed)	25.1	23.4	26.9
Reported (Not Imputed)	74.9	73.1	76.6
Household Education			
Post-sec grad in household	74.1	71.2	76.8
Other	25.9	23.2	28.8
Missing Values: Education			
Not Stated	3.8	3.2	4.4
Stated	96.3	95.6	96.8
Access to Healthcare			
Has a regular medical doctor	84.3	81.8	86.4
Does not have a regular doctor	15.7	13.6	18.2

Table 8: Measures of Hepatitis B vaccination coverage in the average Canadian household population aged 14 to 79 years, CHMS Cycle 1 (2007-2009) and Cycle 2 (2009-2011).

Characteristics	%	95% confidence interval	
		from	to
Serology Testing			
Immune	29.5	27.6	31.4
Other	70.5	68.6	72.4
Self-reported Vaccination			
Yes	42.4	40.3	44.5
Other	57.6	55.5	59.7
Composite Measure			
Some evidence of vaccination	46.1	44.0	48.2
No evidence of vaccination	53.9	51.8	56.0

Table 9: Self-reported demographic and socio-economic characteristics of the average Canadian household population aged 14 to 79 years, CHMS Cycle 1 (2007-2009) and Cycle 2 (2009-2011).

Characteristics	Canadian-born			Foreign-born		
		95% confidence interval			95% confidence interval	
	%	from	to	%	from	to
Gender						
Male	49.4	48.2	50.7	51.5	47.8	55.3
Female	50.6	49.3	51.8	48.5	44.7	52.2
Age group*						
14-19	10.7	10.1	11.3	3.7	2.8	5.0
20-29	18.7	17.5	20.0	14	11.5	16.9
30-39	15.4	14.5	16.4	20.5	17.3	24.2
40-49	19.1	17.4	20.9	23.2	19.1	28.0
50-59	17.4	16.3	18.7	16.7	13.5	20.4
60-69	12.8	11.8	13.8	13.9	11.8	16.2
70-79	5.9	5.1	6.9	8	6.4	10.0
Occupation						
Healthcare worker	4.9	3.9	6.2	4.6	2.9	7.2
Other occupation	95.1	93.9	96.1	95.4	92.8	97.1
Household Size*						
Small	49.8	47.1	52.5	40.5	34.6	46.7
Medium	38.8	36.5	41.1	41.8	37.8	45.9
Large	11.4	10.3	12.6	17.7	14.0	22.1
Household Income*						
Lower household income	81.8	78.9	84.4	73	68.0	77.4
Medium or higher income	18.2	15.6	21.1	27.1	22.6	32.1
Household Education						
Post-sec grad in household	73.3	70.4	76.1	76.4	70.8	81.3
Other	26.7	23.9	29.6	23.6	18.7	29.2
Access to Healthcare						
Has a regular medical doctor	84.4	81.9	86.6	83.9	79.4	87.6
Does not have a regular doctor	15.6	13.4	18.1	16.1	12.4	20.6

* this category was significantly different between CB and FB.

Note: All estimates had CV < 16.6%

Table 10: Measures of Hepatitis B vaccination coverage by immigration status in the average Canadian household population aged 14 to 79 years, CHMS Cycle 1 (2007-2009) and Cycle 2 (2009-2011).

Characteristics	Canadian-born			Foreign-born		
		95% confidence interval			95% confidence interval	
	%	from	to	%	from	to
Serology Testing						
Immune	30.8	28.9	32.8	25.5	21.0	30.7
Other	69.2	67.2	71.1	74.5	69.3	79.0
Self-reported Vaccination*						
Yes	45.1	42.8	47.5	34.2	30.2	38.4
Other	54.9	52.5	57.2	65.8	61.6	69.8
Composite Measure*						
Some evidence of vaccination	48.9	46.5	51.3	37.7	32.3	43.2
No evidence of vaccination	51.1	48.7	53.5	62.3	56.7	67.6

* this category was significantly different between CB and FB.

4.2 Bivariate analyses

Based on the flowchart in Figure 4, a binary composite measure of HB vaccination was used to categorize survey participants into one of two groups: likely vaccinated versus likely not vaccinated. The likely vaccinated category includes those with any indicator of vaccination (self-report and/or indicator of immunity in serology testing) and the likely not vaccinated category includes those that had no indicator of vaccination (did not recall being vaccinated and had no indicator of immunity in serology testing).

Nearly an equal number of CB Canadians were in the likely vaccinated category as in the likely not vaccinated category while more FB Canadians tended to be in the likely not vaccinated category. Similarly, those born in the vaccination era, healthcare workers, those in higher income households and those in households with a post-secondary graduate were more likely to be vaccinated, while those born before 1980, those not in healthcare occupations, those in lower income households and those in households without a post-secondary graduate were more likely not vaccinated. However, males tended to be in the likely not vaccinated category, while females were evenly distributed between the two categories. Notably, those having a regular medical doctor tended to be in the likely not vaccinated category while those without a regular medical doctor were more evenly distributed, however the association between vaccination and having a regular medical doctor was not statistically significant. These distributions are summarized in Table 11.

As shown in Table 8 and Table 10 and illustrated in Figure 5, according to the binary composite measure of vaccination, 46% (95%CI: 44.0-48.2) of Canadians were

likely vaccinated in the overall population. This proportion was lower within the FB population (38%; 95% CI: 32.4-43.3) compared to the CB population (49%; 95% CI: 46.5-51.3) and the difference was statistically significant (chi-square statistic: 79.59, df: 24, p<0.001).

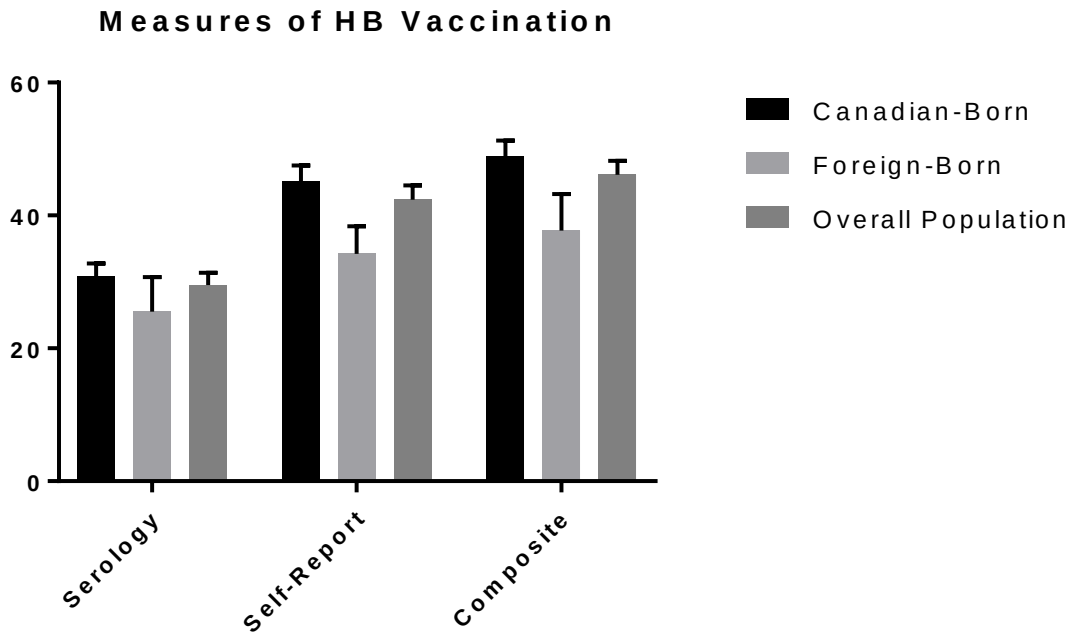

Figure 5: Comparison of vaccination coverage based on the three measures of hepatitis B vaccination among Canadian-born, Foreign-born, and the overall population, Canadians aged 14-65 years.

Table 11. Bivariate associations of demographic, social, and economic by binary composite measure of hepatitis B immunization status, CHMS (2007-2011).

Characteristics	likely vaccinated			likely not vaccinated		
		95% confidence interval			95% confidence interval	
	%	from	to	%	from	to
Place of Birth*						
Foreign-born	37.7	32.3	43.2	62.3	56.67	67.57
Canadian-born	48.9	46.5	51.3	51.1	48.74	53.46
Year of Birth*						
Born in 1980 or after	83.4	79.9	86.9	16.6	13.39	20.46
Born before 1980	33.0	30.7	35.3	67	64.66	69.22
Gender*						
Male	44.0	41.3	46.7	56	53.27	58.75
Female	48.2	45.5	50.9	51.8	49.03	54.47
Occupation*						
Healthcare worker	78.7	71.6	85.8	21.3*	15.04	29.24
Other occupation	44.4	42.2	46.6	55.5	53.36	57.7
Household Income*						
Lower household income	37.3	33.3	41.3	62.7	58.57	66.6
Medium or higher income	48.4	45.9	50.9	51.6	49.17	54.11
Household Education*						
Post-sec grad in household	50.0	47.5	52.5	50	47.49	52.42
Other: no grad or not reporte	34.9	31.4	38.4	65.2	61.6	68.53
Access to Healthcare						
Has regular medical doctor	45.4	43.1	47.7	54.6	52.31	56.86
Does not have regular doctor	49.9	44.6	55.2	50.1	44.83	55.41

* this characteristic was significantly different between category 1 and category 2

4.3 Concordance analyses

Table 12 describes the level of agreement between serology testing results for HB vaccine-induced immunity biomarkers and self-reporting for HB immunization in the Canadian population overall and among FB and CB sub-populations.

The percentage agreement was similar and high within both FB and CB groups at 77%. However, positive agreement (self-reported and seropositive) was lower in the FB group at 18% (95% CI: 16.2% - 20.8%) compared to 26% (95% CI: 24.8% - 28.2%) in the CB group. Negative agreement (did not report and seronegative) was higher in the FB group at 59% (95% CI: 52.8% - 64.4%) compared to 51% (95% CI: 48.1% - 53.0%) in the CB group.

The overall level of agreement as measured by the Cohen's Kappa Coefficient was 0.46 (95% CI: 0.44 - 0.48) in the FB population and 0.52 (95% CI: 0.51 - 0.54) in the CB population. The Cohen's Kappa Coefficient for both populations similarly fall into the 0.4 to 0.6 range which can be interpreted as moderate agreement (cite the reference).

Table 12: Agreement statistics and 95% confidence intervals for Hepatitis B vaccination measures by immigration status in the CHMS (2007-2011).

Category	Foreign-born Population		Canadian-born Population	
	Agreement Statistics (95% CI)	CV	Agreement Statistics (95% CI)	CV
Reported and sero-positive	18.43% (16.24% - 20.84%)	6.37	26.49% (24.81% - 28.23%)	3.29
Reported and sero-negative	15.76% (12.98% - 19.01%)	9.75	18.63% (17.10% - 20.27%)	4.34
Did not report and seropositive	7.10% (4.45% - 11.15%)	23.47	4.33% (3.60% - 5.21%)	9.43
Did not report and sero-negative	58.71% (52.76% - 64.42%)	5.09	50.55% (48.14% - 52.96%)	2.43
Observed agreement	77.14% (69.00% - 85.26%)	-	77.01% (72.95% - 81.19%)	-
Expected disagreement	57.74% (43.66% - 75.80%)	-	51.87% (45.66% - 58.82%)	-
Cohen's Kappa Coefficient	0.46 (0.44 - 0.48)	-	0.52 (0.51 - 0.54)	-

4.4 Multivariate analyses

Table 13 shows the unadjusted and adjusted odds ratios describing the associations between immigration and other covariates with the sero-prevalence of vaccine-induced immunity antibodies in logistic regression models. All characteristics were significantly ($p<0.1$) associated in univariate analyses. In the multivariate model being born in 1980 or after (OR: 10.60; 95% CI: 8.94-12.56; $p<0.01$), being a healthcare worker (OR: 4.9; 3.45-7.00; $p<0.01$), and living in a household with a post-secondary graduate (OR: 1.78; 95% CI: 1.33-2.39; $p<0.01$) were associated with a greater odds of being vaccinated against HB. Being male (OR: 0.68; 95% CI: 0.58-0.81; $p<0.01$) and from a household with a lower income (OR: 0.67; 95% CI: 0.51-0.87; $p<0.01$) were associated with increased risk of not being vaccinated against HB. Odds ratios for all covariates were statistically significant except for being a FB Canadian (OR: 1.04; 95% CI: 0.79-1.36); $p=0.785$) and having access to healthcare through a regular medical doctor (OR: 1.07; 95% CI: 0.79-1.45; $p=0.66$).

Table 14 shows the unadjusted and adjusted odds ratios describing the associations between immigration and other covariates with self-reported HB vaccination in logistic regression models. All factors were significantly associated ($p<0.1$) in univariate analyses except having access to healthcare through a regular medical doctor ($p=0.608$). In a multivariate model, after adjusting for all covariates, having access to healthcare through a regular medical doctor became statistically significantly associated with a greater odds of self-reported HB vaccination (OR: 1.40; 95% CI: 1.09-1.79; $p<0.01$) along with being born in 1980 or after (OR: 6.40; 95% CI: 5.25-7.81; $p<0.01$), being a healthcare worker (OR: 5.29; 95% CI: 3.35-8.35; $p<0.01$), and living in a

household with a post-secondary graduate (OR: 1.78; 95% CI: 1.45-2.23; p<0.01). Being from a household with a lower income (OR: 0.74; 95% CI: 0.59-0.93; p<0.01) was associated with decreased odds of self-reported vaccination as well as being a FB Canadian (OR: 0.74; 95% CI: 0.61-0.89; p<0.01). Notably, being male was not significantly associated with self-reported HB vaccination (OR: 0.91; 0.78-1.07; p=0.246).

Table 15 shows the unadjusted and adjusted odds ratios describing the associations between immigration and other covariates with the binary composite measure of HB vaccination from simple and multivariate logistic regression models. All characteristics were significantly (p<0.001) associated except for access to healthcare (as measured by having a regular medical doctor) which was non-significantly associated (p=0.125). As such, all characteristics were included in the final multivariate model.

According to the final adjusted model, Canadians born in the era of vaccination (OR: 11.57; 95% CI: 8.79-15.22), those who were healthcare workers (OR: 5.41; 95% CI: 3.52-8.30) and those living in households with a post-secondary graduate (OR: 1.87; 95% CI: 1.45-2.40) were significantly (p<0.01) more likely to be vaccinated against HB, whereas males (OR: 0.86; 95% CI: 0.74-0.99) those having a low household income (OR: 0.64; 95% CI: 0.50-0.82) were significantly (p<0.05) less likely to be vaccinated against HB. Having a regular medical doctor was not associated with being vaccinated in the final model (OR: 1.12; 95% CI: 0.83-1.51; p=0.44).

In the final multivariate model using the composite measure of vaccination, immigration status was a significant predictor of vaccination coverage (p<0.05).

Compared to CB Canadians, FB Canadians were an estimated 24% less likely to be vaccinated against HB (OR: 0.76; 95% CI: 0.60-0.98).

Table 13: Unadjusted and adjusted logistic regression models of associations between immigration and other covariates with Hepatitis B vaccination uptake according to serology testing, CHMS (2007-2011).

Variable	Univariate		Model: Vaccinated	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Place of Birth Born outside Canada	0.77 (0.60,0.99)	0.04	1.04 (0.79,1.36)	0.79
Year of Birth Born in 1980 or after	8.93 (7.82,10.20)	0.00	10.60 (8.94,12.56)	0.00
Gender Male	0.71 (0.61,0.81)	0.00	0.68 (0.58,0.81)	0.00
Occupation Healthcare worker	3.95 (2.73,5.71)	0.00	4.92 (3.45,7.00)	0.00
Household Income Lower household income	0.70 (0.54,0.90)	0.01	0.67 (0.51,0.88)	0.00
Household Education Post-sec grad in household	1.83 (1.49,2.24)	0.00	1.78 (1.33,2.39)	0.00
Access to Healthcare Has regular medical doctor	0.82 (0.65,1.03)	0.09	1.07 (0.79,1.45)	0.66

Table 14: Unadjusted and adjusted logistic regression models of associations between immigration and other covariates with Hepatitis B vaccination uptake according to self-report, CHMS (2007-2011).

Variable	Univariate		Model: Self-Report	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Place of Birth Born outside Canada	0.63 (0.53,0.76)	0.00	0.74 (0.61,0.89)	0.00
Year of Birth Born in 1980 or after	5.70 (4.64,7.00)	0.00	6.40 (5.25,7.81)	0.00
Gender Male	0.85 (0.73,0.98)	0.02	0.91 (0.77,1.07)	0.25
Occupation Healthcare worker	4.77 (2.95,7.70)	0.00	5.29 (3.35,8.35)	0.00
Household Income Lower household income	0.670 (0.54,0.83)	0.00	0.74 (0.59,0.93)	0.01
Household Education Post-sec grad in household	1.85 (1.53,2.24)	0.00	1.80 (1.45,2.23)	0.00
Access to Healthcare Has a regular medical doctor	1.06 (0.85,1.31)	0.61	1.40 (1.09,1.79)	0.01

Table 15: Unadjusted and adjusted logistic regression models of associations between immigration and other covariates with Hepatitis B vaccination uptake according to binary composite measure based on both serology testing and self-repot, CHMS (2007-2011).

Variable	Univariate		Model: Composite	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Place of Birth				
Born outside Canada	0.63 (0.50,0.80)	0.00	0.76 (0.60,0.98)	0.03
Year of Birth				
Born in 1980 or after	10.17 (7.79,13.29)	0.00	11.57 (8.79,15.22)	0.00
Gender				
Male	0.84 (0.73,0.97)	0.02	0.860 (0.74,0.99)	0.04
Occupation				
Healthcare worker	4.62 (2.97,7.19)	0.00	5.41 (3.52,8.30)	0.00
Household Income				
Lower household income	0.64 (0.52,0.78)	0.00	0.64 (0.50,0.82)	0.00
Household Education				
Post-sec graduate in household	1.87 (1.55,2.27)	0.00	1.87 (1.45,2.40)	0.00
Access to Healthcare				
Has a regular medical doctor	0.84 (0.66,1.05)	0.13	1.12 (0.83,1.51)	0.44

4.5 Effect modification

Table 16 presents the proportions of Canadians likely vaccinated against HB according to the composite measure of vaccination among FB and CB sub-populations in the overall Canadian population and the corresponding crude odds ratio. An odds ratio of 0.63 (0.60 – 0.67) suggests that the odds of being vaccinated is 37% less likely among FB Canadians compared to the CB population.

Table 17 presents the proportions of Canadians likely vaccinated against HB according to the composite measure of vaccination among FB and CB sub-populations stratified by birth era (either before or after eligibility for routine HB vaccination in childhood) and the corresponding stratified odds ratios. Among those born before 1980, the odds of being vaccinated is 13% less likely among FB Canadians compared to the CB population. However, among those born in the 1980s and after, the odds of being vaccinated is 62% less likely among FB Canadians compared to the CB population.

Table 18 presents the unadjusted and adjusted odds ratios in logistic regression models of the association between vaccination status and immigration status after including an interaction term between immigration status and birth era. The interaction terms between birth era (before or after childhood vaccination) and immigrant status were negative and statistically significant ($p<0.01$) in the logistic regression models. Since the interaction term was significant, ideally data would need to be presented in two separate multivariate logistic regression models stratified by birth era however, in accordance with the Statistics Canada CHMS data user guidelines, this detailed analyses were not released by the MBRDC as the cross-tabulation of immigration status and vaccination status

stratified by birth era yielded estimates with CVs greater than 16.6% indicating high sampling variability such that data must be interpreted with caution.

Table 16: Hepatitis B vaccination by immigration status.

Category	Overall Population	
	Proportion (95% CI)	**CV**
Canadian-Born, likely not vaccinated	38.3% (33.6% - 42.9%)	2.36
Canadian-Born, likely vaccinated	36.7% (32.0% - 41.2%)	2.46
Foreign-Born, likely not vaccinated	15.6% (11.2% - 21.0%)	4.48
Foreign-Born, likely vaccinated	9.4% (6.4% - 13.5%)	7.40
Odds Ratio	0.63 (0.60 - 0.67)	-

Note: Given there is the overall crude odds ratio representing the odds of vaccination among FB Canadians compared to the odds of vaccination among CB Canadians in all age groups.

Table 17: Hepatitis B vaccination by immigration status stratified by birth years.

Category	Those Born Before 1980		Those Born in 1980 and After	
	Proportion (95% CI)	CV	Proportion (95% CI)	CV
Canadian-Born, likely not vaccinated	35.6% (32.1% - 38.8%)	4.81	34.7% (30.4% - 38.5%)	5.92
Canadian-Born, likely vaccinated	37.1% (33.3% - 40.2%)	4.80	42.9% (39.9% - 45.0%)	3.00
Foreign-Born, likely not vaccinated	14.4% (11.3% - 17.9%)	11.92	15.3% (11.6% - 19.6%)	13.47
Foreign-Born, likely vaccinated	12.9% (9.8% - 16.7%)	13.72	7.2% (5.0% - 10.1%)	17.98
Odds Ratio	0.87 (0.84 - 0.90)	-	0.38 (0.33 - 0.44)	-

Table 18: Unadjusted and adjusted logistic regression models of associations between immigration and other covariates including interaction term with hepatitis B vaccination uptake according to binary composite measure based on both serology testing and self-repot, CHMS (2007-2011).

Variable	Unadjusted		Adjusted	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Place of Birth				
Born outside Canada	0.87 [0.069,1.08]	0.21	0.87 [0.71,1.07]	0.20
Year of Birth				
Born in 1980 or after	12.07 [9.06,16.06]	0.00	13.87 [10.3,18.68]	0.00
Interaction: Place of Birth by Year of Birth				
Born outside Canada*Born in 1980 or after	0.44 [0.26,0.73]	0.00	0.46 [0.27,0.77]	0.00
Gender				
Male	-	-	0.85 [0.73,0.99]	0.03
Occupation				
Healthcare worker	-	-	5.36 [3.5,8.22]	0.00
Household Income				
Lower household income	-	-	0.65 [0.51,0.82]	0.00
Household Education				
Post-sec grad in household	-	-	1.87 [1.45,2.41]	0.00
Access to Healthcare				
Has a regular medical doctor	-		1.11 [0.82,1.51]	0.49
Constant				
Constant	0.51 [0.46,0.57]	0.00	0.31 [0.22,0.43]	0.00

Chapter Five: **Discussion**

5.1 Summary of key findings

This analysis using data from the CHMS (2007-2011) indicate that an estimated 46% (95%CI: 44.0-48.2) of Canadians aged 14 to 79 years in the average household population are likely vaccinated against HB virus (2007-2011). This proportion was 38% (95% CI: 32.4-43.3) among FB Canadians and 49% (95% CI: 46.5-51.3) among the CB population. The 11% lower vaccination coverage among FB Canadians was statistically significant ($p<0.01$). Concordance analysis did not show evidence of differential reporting of vaccination status between FB and CB populations in the CHMS data. In multivariate analyses, after adjustment for birth era, gender, occupation, household socio-economic status (education and income), and having regular access to healthcare: immigration status was a significant independent predictor of vaccination coverage ($p<0.05$). In a main effects model, FB Canadians were an estimated 24% less likely to be vaccinated against HB (OR: 0.76; 95% CI: 0.60-0.98) compared to the CB population. Furthermore, the effect of immigration status on likelihood of vaccination was modified by birth era such that the crude odds of being vaccinated among non-immigrants compared to immigrants (OR: 0.87; 95% CI: 0.84-0.90) was significantly greater among those born in the era of childhood HB vaccination (1980s) compared to the odds ratio in older Canadians (OR: 0.38; 95% CI: 0.33-0.44), both of which were significantly different from the overall crude odds ratio (OR: 0.63; 95% CI: 0.60-0.67).

5.2 Interpretation of findings

The overall 46% estimate of HB vaccination coverage in the average Canadian population aged 14-79 years in 2007-2011 based on this analysis aligns with recent national estimates. The results of the 2012 NICS for HB immunization coverage were 39.7% in the general adult population 18 years and older. It makes sense that the estimate for the 14-79 population would be higher than the adult only population due to routine immunization of children in Canada. Approximately 9% of the population in this study was 14 to 17-years-of-age and in the 2011 childhood NICS HB immunization coverage for at least two doses of the HB vaccine by the 17th birthday was 74.8%. In addition, the overall 38% estimate of HB vaccination coverage in the overall FB Canadian sub-population aged 14-79 years in 2007-2011 based on this analysis aligns with a meta-analysis published in 2012, which reviewed 110 studies representing more than 209,000 immigrants to North America showed a prevalence of prior immunity from any cause in 39.7 %.(Rossi et al., 2012)

In this study the proportion of Canadians with serological evidence of vaccine-induced immunity to HB is an estimated 26% in the FB population and 31% in the CB population. While the estimated proportion is 5% lower in FB Canadians this difference was not statistically significant. However, the proportion of Canadians that reported receiving a full series of HB immunizations was 34% in the FB and 45% in the CB, which was a statistically significant difference of 11%. Although there was inconsistency in the magnitude and significance of the vaccination coverage difference as measured by serology versus self-report, both measures indicated lower coverage among FB. If this occurred due to an underestimation in vaccine coverage based on serology among CB

compared to FB, several potential scenarios may explain this finding. First, vaccinated people may lose detectable antibody more readily when their immunity is not challenged. Since FB Canadians are more likely to be exposed to the HB virus, it makes sense that more FB Canadians could retain detectable antibodies for longer due to more frequent challenging of the immune response compared to CB Canadians. Second, a small proportion (<5%)("Epidemiology and Prevention of Vaccine-Preventable Diseases," 2015) of people with previous HB infection may lose only anti-HBc and retain anti-HBs appearing to have immunity to HB without infection and become misclassified here as having vaccine-induced immunity. This too may be more likely to occur among FB Canadians that have known higher prevalence of HB infection. Essentially, both scenarios lead to an overestimation of vaccine-induced immunity among those sero-positive for anti-HBs in the FB population compared to the CB population. Alternatively, if this occurred due to an underestimation of vaccination coverage among FB based on self-report a potential explanation is that FB are less likely to report vaccination due to loss of records compared to CB. However, the observed effect is consistent with the finding that being FB was not significantly associated with being sero-negative for biomarkers of immunity after adjusting for age and other factors but was a risk factor associated with lack of self-reported vaccination according to multivariate models.

The main finding of this study indicates that a disparity in HB vaccination coverage likely exists between the FB and CB populations in Canada and that vaccine coverage is lower among the FB. The composite binary measure of HB vaccination coverage used here to group individuals as likely vaccinated or likely not vaccinated and

to calculate this difference was selected to be as conservative as possible in order to avoid a type 1 error (finding differences among subgroups that are not real).

In addition, in logistic regression analyses, consistent findings were observed between univariate and multivariate models when the binary composite measure was the outcome. Notably, the two inconsistent factors were having access to healthcare through a regular medical doctor and being male. The analyses here showed that while males were equally likely to report being vaccinated as females, they were less likely to be sero-positive for vaccine-induced immunity biomarkers. This effect could be due to differential reporting among males and females. However it is more likely that this is the effect of many women receiving HB screening and re-vaccination with a booster during pregnancy in order to reduce the risk of vertical transmission during childbirth. Also, the final model indicated that having access to healthcare through having a regular medical doctor was not a good predictor of vaccination. This may be because those with chronic conditions are more likely to have a regular doctor than those that are healthy.

The concordance analysis conducted here did not show evidence of differential reporting was observed between FB and CB population as the overall level of agreement between serology results and self-report were the same for FB and CB populations. Furthermore, similar patterns of reporting and non-reporting were observed for income and education variables for FB and CB populations.

In the final model using the binary composite measure indicates that after adjustment for birth era, gender, occupation, household socio-economic status (education and income), and having regular access to healthcare, immigration status was a significant predictor of

vaccination coverage ($p<0.05$). Compared to CB Canadians, FB Canadians were less likely to be vaccinated against HB (OR: 0.76; 95% CI: 0.60-0.98).

There are instances when a variable is identified as a confounder in the conceptual framework but may in fact also be an effect modifier. An effect modifier is present when the measure of association between exposure and outcome varies across a third variable. Understanding the presence of effect modification is of interest because it provides a more detailed description of the true association between exposure and outcome. In the follow up analysis conducted here, effect modification of birth era on the association between vaccination status and immigration status is explored. Stratification is used to quantify the effect modification and including a statistical interaction term in logistic regression is used to determine the statistical significance of the effect modification. Comparison of the crude overall odds ratio of vaccination status in FB and CB with crude odds ratios of the data stratified by birth era suggest that the association between vaccination status and immigration status is stronger among people who born in the 1980s or after compared to those born before 1980.

The findings here show that the modifying effect of birth era is such that the association of being born in the 1980s or after and being born outside Canada combined decreases the likelihood of being vaccinated more than you would expect given the effect of each factor on likelihood of vaccination individually. Effect modification like this may work on an additive or multiplicative scale. Since, vaccination is a public health intervention rather than a biological phenomenon, we can reasonably interpret the effect modification of birth era on likelihood of vaccination to work on the additive scale.

5.3 Policy implications

Public health interventions, including three decades of HB control with vaccination, have been highly successful in reducing the disease burden in Canada. Continued and broadened use of childhood vaccination programs could eventually lead to total elimination of endemic transmission of the virus which should be the ultimate goal.(Meireles, Marinho, & Van Damme, 2015)

As recommended by the CCIRH, FB Canadians experience a disproportionate burden of HB disease and may benefit from publically funded HB immunization programs.(Greenaway et al., 2011) However since publication of this recommendation in 2011, no national immigrant vaccination programs have been implemented. The findings from this study suggest that lower vaccination coverage among FB Canadians may exist even independently of other individual, household and community level factors and therefore provides more evidence to support the CCIRH recommendation.

Analyses conducted by Rossi *et al.* found that screening and immunization of immigrant Canadians would not be as cost-effective as treating the symptoms of those with disease.(Rossi et al., 2013) However, the cost of HB vaccines alone is no longer an issue because economies of scale, local production of vaccines, competition among vaccine manufacturers, and other factors have decreased the price of monovalent HB vaccine from $3.00 (US) per dose in 1990 to $0.30 per dose by 2001 (US).(Meireles et al., 2015) While screening via serology testing remains costly, this cost may be avoided by providing vaccination to all immigrant Canadian that do not report being vaccinated as this study showed that the proportion of Canadians that have immunity markers despite

not recalling and reporting vaccination is a very low proportion around 7% therefore costs of screening could be avoided by using self-report instead of serological screening.

It is hoped that this study may help generate awareness of the issue among healthcare providers and lead to greater opportunities for education of new Canadians on HB and the availability of vaccination programs in Canada.

5.4 Study strengths

Using data from the CHMS to address the objectives of this research, grants this study numerous strengths. Most notably with over 8,400 Canadians participating in the household questionnaire and MEC components of the CHMS to provide the data used here, a major strength of this study is the large sample size which helps ensure adequate statistical power to detect differences and relatively precise estimates to be calculated separately for each of the FB and CB sub-populations. Along with large sample size, the representativeness and generalizability of this sample to the average household population is achieved by to the complex sampling design described earlier and adds external validity to this analysis.

In addition, confounding of the association between immigrant status and vaccination coverage by other individual, household or community-level covariates as shown in Figure 3 was reduced by the use of multiple logistic regression analysis. As the determinants of vaccine uptake tend to be diverse, controlling for as many potential confounders as possible was attempted in this analysis to reduce confounding bias. This was made possible by the comprehensive and detailed design of the CHMS which

provides a wide range of important covariates including two separate measures that could be used to estimate HB vaccination uptake is a major strength of the dataset.

Furthermore, since the CHMS was designed and carried out by experts at Statistics Canada, it benefits from the standardization of both the household interview and clinical assessment portion of the survey adding additional internal validity to the study. Through the use of trained Statistics Canada personnel the inter-rater bias of having multiple individuals carry out these interviews and clinical assessments is minimized and consistency is maintained in the questions asked and how they were asked, the equipment available and technique used. Furthermore, thanks to the design of the CHMS, there was no missing information with variables such as income, which had lower reporting, as they were imputed as needed. This helped to simplify the analysis and minimized the effect of non-response bias although it should be noted that assumptions are made to conduct the imputations.

5.5 Study limitations

This study is a secondary analysis of previously collected CHMS data therefore variables to be used were selected based on their availability. Since the CHMS data was not primarily collected for examining HB vaccination coverage among the immigrant and non-immigrant Canadian sub-groups, some limitations to the dataset do exist in turn limiting the conclusions that can be made from the results of this study. For example, the sampling probability weights provided do not adjust for the survey's low-response rate without additional assumptions and the use of probability weights relies on the untestable assumption that the probability of non-response is independent of the exposure and

outcome of this specific analysis. Potential limitations regarding reliability of absolute coverage estimates based on serological data and reporting bias based self-report have been discussed earlier. These limitations were already addressed in the analysis.

Although the CHMS was designed to produce national estimates and not estimates for the immigrant sub-group, the validity of the pooled CHMS Cycle 1 and 2 data has previously been assessed and confirmed for immigrant health research (Ng, 2015). A 2015 study published in Statistics Canada's Health Reports evaluated the representativeness of the pooled CHMS immigrant sample by comparing demographic and socio-economic distributions with the 2006 Census and the 2011 National Household Survey (NHS). This study found the CHMS immigrant sample to be similar to the 2006 Census and 2011 NHS samples, with only slight overestimation of recent immigrants (those arriving after 1995), 30- to 49-year-olds, and immigrants from South/Central America. This study also found that results from the CHMS on five self-reported health outcomes (overall health, mental health, blood pressure, smoking, and obesity) were similar with the immigrant sample in the 2009-2010 Canadian Community Health Survey (CCHS).

Furthermore, the Rotermann et al. study of HB sero-prevalence (Rotermann et al., 2013), based on the same sample used here, also found that the foreign-born group was adequately represented in the subset of respondents that provided samples for hepatitis testing with 23.5% (95% CI: 17.8-29.2) of this group being foreign-born. As well, this study determined that representation of the foreign-born from areas with high levels of HB infection such as China, Africa and some South American countries, were comparable to 2006 Census estimates. Inclusion of areas with high foreign-born

concentrations such as Vancouver, Toronto and Montreal among the collection sites in both cycles is cited as a factor that contributed to good representation from the immigrant subgroup.

Furthermore, the CHMS did not gather information about when those self-reporting vaccination completed their immunization series, so age at vaccination cannot be discerned. This may be important because studies have shown an elevated risk of immune non-response to vaccination in adults compared to children due to age-associated changes in immune function(Fisman, Agrawal, & Leder, 2002; Mackie et al., 2009). This was partially addressed by comparing differences in vaccine coverage proportions stratified by age group and controlling for age in regression modelling. Since HB vaccination only became widely used around 1980, it is fair to assume that all respondents (immigrant and non-immigrant) in older age groups (30 years and greater in 2007-2011 CHMS data) were exclusively vaccinated as adults regardless of place of birth.

Lack of information on vaccination timing means temporality is a limitation in this study. Therefore among vaccinated immigrants, we don't know if immigration occurred before vaccination or vice versa. However, controlling for period of immigration to Canada in Objective 6 will help us determine whether vaccination uptake varies with time spent in Canada.

CHMS responses on self-reported vaccination status were not validated against provider medical records. As a result, misclassification due to recall error could occur such that some classified as vaccinated based on self-report may actually be unvaccinated (incorrectly recalled vaccination) while some in the not vaccinated group may actually be

vaccinated individuals (did not recall vaccination). Such misclassification will only impact the aim of the study (ie to determine if a difference in HB vaccination coverage exists between immigrants and non-immigrants) if misclassification is differential between FB and CB populations. As noted earlier, a concordance analysis between self-report and serology testing was conducted to assess whether the misclassification is differential. This assessment is only valid under the assumption that serology results are non-differential among vaccinated immigrants and non-immigrants despite differences in vaccine products and vaccination practices. While the HB vaccine is known to be very effective (evidence shows that even one dose is over 85% effective and booster doses are not recommended even decades after vaccination in healthy people), population vaccine effectiveness depends on quality of the public health programs as well. Furthermore, it is unlikely that the prevalence of immune competence would be lower among immigrants as studies have shown that immigrants generally have better health than the average Canadian as indicated by the well documented healthy immigrant effect. (Vang et al., 2015)

In addition, the CHMS dataset lacks data on immigrant type since FB Canadians can be further classified into four groups dependent on reason for immigration into Canada, including: immigrants (subgroups: economic and family class), refugees, asylum seekers, and adopted children. Studies have found higher HB sero-prevalence among refugees and asylum seekers compared immigrants and adopted children (Rossi et al., 2012). Unfortunately, this limitation of the CHMS is difficult to address here and all FB Canadians were grouped into one category. Since self-selected economic-class and family-class immigrants represent the highest proportion of immigrants in Canada

(generally economic or family class immigrants represent 80% or more of the newcomers in any given year) the results of this analysis should be considered to apply to that group only(Chui et al., 2011; Pottie et al., 2011) with the assumption that no difference in response rate exists between these two subgroups although this cannot be ruled out.

Similarly, another limitation of the dataset was that immigration specific variables such as age at immigration, year of immigration and region of birth could not be accounted for due to small sample size. As such there was an inability to stratify the analysis by country and/or region of origin, and time since migrations along with immigrant type. This is an issue because it is unlikely the FB population is homogenous with respect to HB risk and vaccine uptake. In fact, it possible that immigrants from certain countries may have much lower vaccine uptake than reported here whereas others have rates comparable to or even higher than those among CB Canadians. Using additional cycles of the CHMS may be needed to explore these variables.

The representativeness of the CHMS data in general should be interpreted with caution as data are based on a sample which excludes hard-to-reach populations (e.g. institutionalized and homeless persons, First Nations living on reserves). Also, the generalizability of the survey may be impacted by non-response bias as it is not known whether non-responders were significantly different compared to responders. It is likely though that those from immigrant communities who do not speak an official language were not included and certain that the CB comparison group did not include First Nations people living on reserves, inmates, and the homeless. In general, findings based on the 2007-2009 and 2009-2011 CHMS can be applied to the overall household population aged 14 to 79 years only.

In addition, it should be noted that the conceptual model driving the study objectives is simplified to make the analysis possible. The adjustment for all covariates implies that they are all considered confounders rather than mediators, colliders, or effect modifiers (with the exception of birth era in the follow up analysis). Also, it is assumed that community, household and individual factors like income remain the same before and after immigration. The impact of factors preceding immigration compared to after immigration is not differentiated. Furthermore, the conceptual model does not consider effectiveness of HB vaccine programs. In reality, while effective and safe vaccine products are available in the market that does not mean that worldwide HB vaccination program are equally accessible or effective. In particular, program effectiveness is a function of many factors (not just vaccine efficacy) including uptake, compliance, vaccine delivery (e.g. maintenance of cold chain), host factors and herd immunity which were not considered here. In most cases the operation of these factors will result in less effective programs in low-resource settings. The potential consequences of these factors on the interpretation of this study's results are unknown.

Chapter Six: **Conclusion and Future Directions**

6.1 Conclusion

The results of this study indicate that a disparity in HB vaccination coverage exist between the FB and CB populations in Canada. The findings of this study are important because information on vaccination coverage is useful for developing targeted public health strategies to address health inequities and for managing potential outbreak scenarios.

6.2 Future directions

It is hoped that the results of this study may demonstrate the utility of the CHMS for evaluating vaccination coverage among Canadians as well as for the study of health-related outcomes in immigrant populations. Since the CHMS is planned to run for a total of seven cycles, the results of this study based on the first two cycles (2009-2011) may represent the baseline difference between vaccination coverage before the evidence-based clinical recommendations regarding HB for immigrants and refugees were developed by the CCIRH and published in the CMAJ in 2011. Data from future cycles could be used to evaluate the impact of these guidelines and the extent to which they were implemented by provinces. In addition, the utility of the results determined here could help support plans to add more vaccine-related questions to the CHMS and for more sero-prevalence studies to be conducted with CHMS biological specimens in future studies.

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