Estimating and Comparing the Burden of Chronic Hepatitis C in the Immigrant and the Non-Immigrant Population in Québec

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June 2012

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Masters of Science in Epidemiology

Abstract

Background: Immigrants have higher mortality from chronic viral hepatitis and hepatocellular carcinoma as compared to those born in Canada. Approximately 20% of this burden is likely due to hepatitis C (HCV). Despite this disparity there are no screening programs to detect chronic HCV in immigrants after arrival in Canada. This is partly due to a lack of population-based data describing the burden of chronic HCV in immigrants.

Methods: To fill this gap, we created a case series of all cases of chronic hepatitis C reported from 1991-2008 in Québec through linking the MADO (Québec Reportable Disease) database to 5 other Québec administrative databases; the MICC (Québec Landed Immigrants), the RAMQ (Québec provincial health insurance and physician billing) and the hospitalization databases. Reported rates were estimated using the reported number of cases in immigrants and non-immigrants during the study period. Québec census data from 1991, 1996, 2001, and 2006 (stratified by immigrant and non-immigrant status) was used for the denominator. Rates, rate ratios, and 95% CIS were calculated using the Poisson distribution. Proportions of cases with chronic hepatitis C associated complications were calculated and compared in immigrants and non-immigrants.

Results: A total of 20,459 cases of chronic hepatitis C (1,980 immigrants and 18,479 non-immigrants) were reported between 1998-2007. Cases from 1991-1997 were excluded due to incomplete laboratory reporting during this period. Immigrant cases were older (mean age 47.1 vs. 43.1 years, $p < 0.0001$) and were less likely to be male (53.1% vs. 68.2%, $p < 0.0001$). The overall rate of chronic hepatitis C was similar for immigrants and non-immigrants [rates/100,000 (95%CI) were 25.2 (24.1-26.4) vs. 27.8 (27.4-28.2), rate ratio= 0.91]. Immigrants from several world regions however had higher rates of chronic hepatitis C as compared to the non-immigrant population; Eastern Europe/Central Asia [77.6 (68.2-87.0) rate ratio = 2.8], Sub-Saharan Africa [60.2 (51.5-68.8), rate ratio = 2.2], South Asia [48.1 (41.5-54.7), rate ratio = 1.7]. Immigrants had a higher proportion of compensated cirrhosis (15.1% vs. 12.9%, p= 0.007) and hepatocellular carcinoma (1.2% vs. 0.6%, p= 0.005) compared to non-immigrants

Conclusions: Immigrants from several world regions are at increased risk for chronic hepatitis C, have a higher proportion of hepatitis C related complications and are diagnosed a mean of > 8 years after arrival in Canada. Many immigrants would therefore benefit from early screening and appropriately timed treatment for chronic hepatitis C to decrease associated morbidity and mortality.

Résumé

Introduction : Les immigrants ont un plus haut taux de mortalité causée par l'hépatite virale chronique et le carcinome hépatocellulaire comparativement aux individus nés au Canada. Approximativement 20% de ce fardeau serait dû au virus de l'hépatite C (VHC). En dépit de cette disparité, il n'existe aucun programme de dépistage du VHC chez les immigrants à leur arrivée au Canada. Ceci est en partie dû au manque de données basées sur des populations décrivant le fardeau du VHC chronique chez les immigrants.

Méthodes : Afin de pourvoir à ce manque, nous avons créé une série de cas de tous les cas d'hépatite C chronique rapportés entre 1991-2008 au Québec en reliant la base de données MADO (Maladies à Déclaration Obligatoire du Québec) à cinq autres bases de données administratives québécoises; le MICC (immigrants arrivés au Québec), la RAMQ (assurance maladie provinciale du Québec et facturation des médecins) et les bases de données d'hospitalisation. Les taux rapportés ont été estimés en utilisant le nombre de cas rapportés chez les immigrants et les non immigrants durant la période d'étude. Les données de recensements de 1991, 1996, 2001 et 2006 (stratifiées en statut d'immigrant ou non immigrant) ont été utilisées comme dénominateur. Les taux d'incidences (TI), TI relatifs et les IC 95% ont été calculés avec la distribution de Poisson. La proportion de cas avec complications associées à l'hépatite C chronique a été calculée et comparée chez les immigrants et non immigrants.

Résultats : Un total de 20 459 cas d'hépatite C chronique (1 980 immigrants et 18 479 non immigrants) ont été rapportés entre 1998-2007. Les cas datant de 1991 à 1997 ont été exclus dû au manque d'information complète de méthodes de laboratoire durant cette période. Les cas d'immigrants étaient plus âgés (âge moyen de 47.1 vs 43.1 années, p<0.0001) et moins probables chez les hommes (53.1% vs 68.2%, p <0.0001). Le TI d'hépatite C chronique était similaire entre immigrants et non immigrants [TI/100 000 (IC 95%) étaient de 25.1 (24.1-26.4) vs 27.8 (27.4-28.2), TI relatif = 0.91]. Les immigrants de plusieurs régions du monde, cependant, avaient un TI plus élevé d'hépatite C chronique comparativement aux non immigrants : l'Europe de l'Est/l'Asie centrale [77.6 (68.2-87.0), TI relatif = 1.7], l'Afrique subsaharienne [60.2 (51.5-68.8), TI relatif = 2.2], l'Asie du Sud [48.1 (41.5-54.7), TI relatif = 1.7]. Les immigrants avaient une proportion plus élevée de cirrhose compensée (15.1% vs 12.9%, p = 0.007) et de carcinome hépatocellulaire (1.2% vs 0.6%, p = 0.005) comparativement aux non immigrants.

Conclusions : Les immigrants de plusieurs régions du monde sont à un risque plus élevé d'hépatite C chronique, ont une proportion plus élevée de complications liées à l'hépatite C et reçoivent un diagnostic en moyenne >8 ans après leur arrivée au Canada. Beaucoup d'immigrants bénéficieraient donc du dépistage et du traitement précoces pour l'hépatite C afin de diminuer la morbidité et la mortalité qui y sont associées.

Acknowledgments

I would firstly like to sincerely thank my primary supervisor, Dr. Christina Greenaway for giving me the opportunity to be a part of this great project and providing me with immense guidance and support throughout my research experience. I have learnt a great deal about the process of conducting research, and its many obstacles. I am also very grateful to my co-supervisor, Dr. Jean-Francois Boivin, who provided great insight and feedback on my project. I would also like to thank Dr. Gillian Bartlett for her input and guidance with the study design.

I would especially like to acknowledge the assistance of Sonya Cnossen, who kindly offered her help through the entire research project. Her help is greatly appreciated.

Finally, I would like to thank my parents and my brothers, Ahmed and Omer for their endless love, support and encouragement.

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Abbreviations

HCV Hepatitis C Virus

HCC Hepatocellular carcinoma

EIA Enzyme Immunoassay

ELISA Enzyme-linked immunosorbant assay

RIBA Recombinant immunoblot assay

RT PCR Reverse transcription polymerase chain reaction

WHO World Health Organization

DSP Directions de santé publique

IDU Intravenous drug use

IDUs Intravenous drug users

SVR Sustained virologic response

INF Interferon

IRPA Immigration and Refugee Protection Act

HIV Human immunodeficiency virus

MADO Maladies à déclaration obligatoire

MICC Ministère de l'Immigration et des Communautés Culturelles

RAMQ Régie de l'assurance-maladie du Québec

FIPA Fichier d'inscription des personnes assurées

Med-Echo Maintenance et exploitation des données pour l'étude de la clientèle hospitalière

LSPQ Laboratoire de Santé Publique du Québec

CAI Commission d'accès à l'information du Québec

ICD-9 International Classification of Diseases, edition 9

DIN Drug identification number

Chapter 1: Introduction

1.1 Burden of hepatitis C

Hepatitis C (HCV) is an important cause of morbidity and mortality worldwide with approximately 2-3% of the world's population (170 million people) chronically infected with HCV (**1, 2**). The majority of acutely infected individuals with HCV (85%) develop chronic HCV, which leads to significant morbidity and mortality. Twenty to thirty percent of individuals with chronic HCV develop cirrhosis and liver failure (**1, 3-6**). Of those with chronic HCV, 1-5% of individuals develop hepatocellular carcinoma (HCC). HCV-related HCC cases occur almost exclusively in individuals with cirrhosis (**1, 7**). HCV is responsible for 20-30% of the approximately 550,000 annual deaths due to HCC globally (**2**). HCC has a poor long-term prognosis with a 5-year survival rate of less than 5% (**8**). Overall, several different factors can influence the rate of progression of chronic hepatitis C to cirrhosis and HCC, including alcohol, age, time of infection, co-infection with hepatitis B and severity of liver histology (**5**). Individuals with chronic hepatitis C are largely asymptomatic before developing cirrhosis or HCC. Therefore early screening and appropriately timed treatment for hepatitis C is essential to potentially prevent the progression of the disease. If initiated in the

early asymptomatic stages, treatment can decrease HCV associated morbidity and mortality, highlighting the need for screening in those at risk for HCV.

In Canada, immigrants have a 2-4 fold increased mortality due to HCC likely due to undetected and untreated viral hepatitis (**9**). Twenty to thirty percent of this is likely attributable to chronic hepatitis C infection extrapolated from its contribution to the global burden of HCC (**10, 11**). Immigrants are a high-risk group for hepatitis C because the majority originate from countries with a higher seroprevalence of hepatitis C as compared to that in Canada (**9, 12, 13**). There are several small seroprevalence studies of hepatitis C in the Canadian immigrant population suggesting that the seroprevalence of chronic hepatitis C in the immigrant population mirrors that in their countries of origin (**14, 15**).

1.2 Rationale for the study

Over the past 40 years the majority of new immigrants to Canada have originated from countries with a higher seroprevalence of hepatitis C than that in Canada (**13**). The immigrant population in Canada has an increased morality from viral hepatitis; however the epidemiology of hepatitis B and C are poorly described in this population. This study will provide the first population-based data on the burden of chronic hepatitis C including rates of chronic hepatitis C and hepatitis C associated complications in immigrants as compared to non-immigrants. The results of this study will help to inform policy makers of the importance of chronic hepatitis C in the immigrant population in Canada and to

identify high-risk groups who may benefit from HCV screening. Screening and appropriately timed treatment can decrease excess morbidity and mortality due to hepatitis C.

1.3 Thesis objectives

The primary objective of this thesis was to estimate and compare the burden of chronic hepatitis C in the immigrant and non-immigrant population in Québec between 1991 and 2008. Specific objectives included firstly, calculating and comparing overall rates of chronic hepatitis C in the immigrant and non-immigrant populations during this time period and stratifying them by important variables such as age, sex and country of origin. Secondly, to determine the proportion of chronic cases of hepatitis C in immigrants and non-immigrants who ever had drug dependence during the study period. Finally, to calculate and compare rates of hepatitis C related complications, hospitalization rates and death rates in immigrants as compared to non-immigrants

Chapter 2: Literature Review

2.1 Biology of hepatitis C

Hepatitis C is caused by the hepatitis C virus, an enveloped single stranded, positive sense RNA virus that belongs to the family flaviviridae (**1, 16**). Identified in 1989, the pathogenesis and the body's immune reaction to HCV are incompletely understood. The first stage of HCV infection is acute hepatitis C; however, it is infrequently diagnosed because it is usually asymptomatic or presents with mild non-specific symptoms (**17**). A distinguishing characteristic of HCV is the high rate (75-85%) with which it progresses from acute to chronic infection (**1**). In addition to the silent onset of acute HCV to chronic HCV, it is normally characterized by a long asymptomatic latency period prior to presenting with chronic sequelae (**4**).

HCV is characterized by a large degree of genetic variability, being classified into at least 6 major genotypes (1-6) and many subtypes (a,b,c etc.) (**6**). The different HCV genotypes are distributed differentially worldwide. Genotypes 1-3 are distributed worldwide e.g. Europe, North America and Japan. More than 70% of chronic HCV infections in North America are due to genotype 1. Genotype 4 is found primarily in the Middle East, Egypt and Central Africa. Genotype 5 is found in South Africa and genotype 6 is found primarily in Asia (**1, 5**). Knowledge of HCV genotypes is pertinent with regards to the treatment regimen, duration

and predicting response to treatment. Genotype 1 is relatively resistant to interferon therapy and therefore requires longer duration of treatment, compared to genotypes 2 and 3 which are more sensitive to treatment (**1**).

2.2 Methods of diagnosis

The diagnosis of hepatitis C is made by detecting serum antibodies and viral RNA. The diagnostic test of choice for screening for HCV is the detection of antibodies (anti-HCV) with an enzyme immunoassay (EIA) (**1**). EIAs are generally easy to implement in most laboratories, have good performance characteristics and are relatively inexpensive (**18**). Three different EIA generations have been developed for the detection of HCV antibodies, with each generation having improved sensitivity and specificity. In 1990, the first generation of EIA (EIA 1) became available for clinical labs but it was poorly sensitive and specific. The sensitivity of the EIA 1 ranged from 70-80% and many false positive reactions occurred. In addition the time to detection of antibodies after infection (time to seroconversion) was approximately 16 weeks (**19**). In 1992, a second generation EIA (EIA 2) became available and had improved sensitivity and specificity with 92-95% of patients' HCV being detected. In addition, the EIA 2 decreased the window period for HCV seroconversion to 10 weeks (**18, 19**). Finally in 1993, a third generation EIA (EIA 3) became available and had a sensitivity of 97%, and specificity of 99.3-100% and with the time to detection or seroconversion of HCV decreasing to 7-8 weeks (**20, 21**).

Confirmatory HCV tests were developed to distinguish true from false positive EIA results. A commonly used test is the recombinant immunoblot assay (RIBA), in which HCV proteins are run on a nitrocellulose strip and specific HCV proteins can be identified. If an individual is a true positive, antibodies against HCV antigens in their serum react with HCV specific protein bands on the nitrocellulose strip. A positive result requires the appearance of at least two reactive bands. RIBA is used to distinguish false positive EIA results due to non-specific binding from true positive EIA results (**19**).

The presence of HCV RNA in an individual's blood provides evidence of active HCV infection. Detection of HCV RNA through the highly sensitive method of reverse transcription polymerase chain reaction (RT PCR) is currently the gold standard for confirming the diagnosis of active hepatitis C (**19**). The sensitivity of RT PCR for detecting HCV RNA is 100 molecules/ml of serum (**18, 19, 22**) and its specificity is 97-99% (**21**). RT PCR allows detection of HCV RNA 1-3 weeks after exposure (**23**).

Table 2.1 Interpretation of diagnostic test results for HCV

Diagnostic Test*			Interpretation
Anti-HCV (EIA or CIA)	**Anti-HCV (RIBA or LIA)**	**HCV RNA (PCR)**	
Positive	Positive	Positive	Active HCV infection, acute or chronic.
Positive	Positive	Negative	Resolved HCV infection; acute HCV during a low-level viremia period.
Negative	Negative	Positive	Early acute HCV infection; chronic HCV in the immunosuppressed; chronic HCV with seroreversion (rare); rarely false positive HCV RNA test.
Positive	Negative	Negative	False positive anti-HCV EIA test.
Negative	Negative	Negative	No HCV infection; HCV infection during window period during very early infection.

* EIA = enzyme imuunoassay; CIA = enhanced chemiluminescence immunoassay; RIBA = recombinant immunoblot assay; LIA = line immunoassay; PCR= polymerase chain reaction.

Currently in Canada, the Canadian Blood Services screens all blood donations for the presence of HCV using two tests. An EIA test has been used since 1990 to detect HCV antibodies and RT PCR was added in 1999 to detect the presence of the hepatitis C virus. Only blood that is negative for both tests can be distributed (**24**).

2.3 Epidemiology of hepatitis C

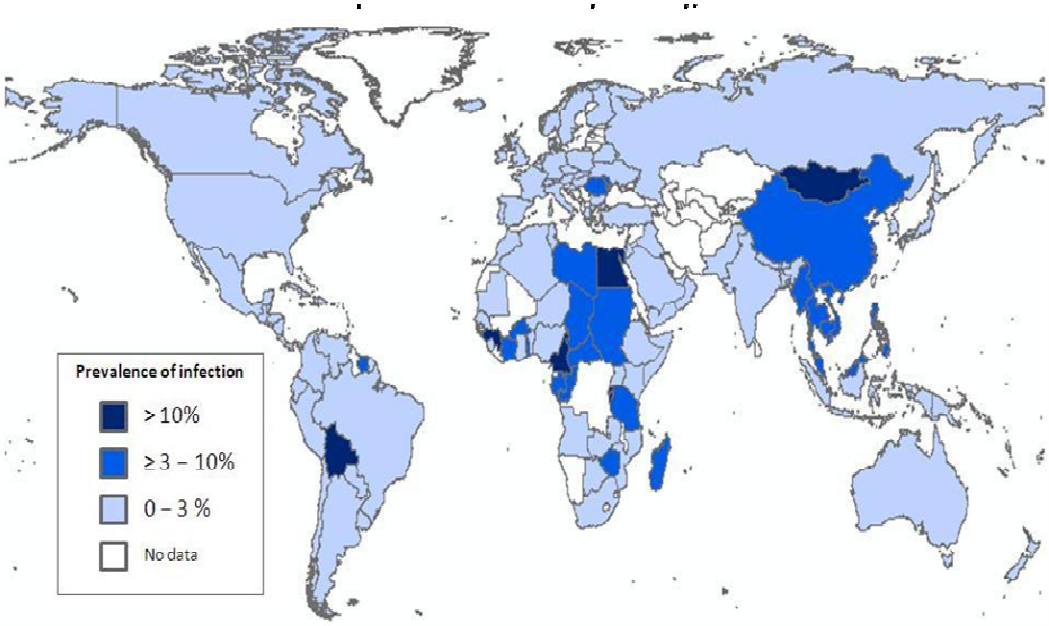
2.3.1 *Hepatitis prevalence worldwide*

The prevalence of HCV varies based on global region of origin, as shown in Figure 2.1. In 1999 the World Health Organization (WHO) estimated that approximately 170 million people worldwide were infected with chronic HCV with a global seroprevalence of about 2-3% (**5**). There are few population-based seroprevalence studies of HCV. Most seroprevalence studies have been performed in specific populations such as blood donors or drug users, both of which are not representative of the general population (**25, 26**). The estimated global prevalence of HCV is shown in Table 2.2. The seroprevalence of HCV is lowest in Europe (1.0%) and highest in Africa with an estimated prevalence of 5.3% (**27**). Approximately 20-30% of individuals with chronic hepatitis C develop cirrhosis (**6**), while 1-5% develop HCC (**1**). HCC is the fifth most common cancer worldwide, with 20% of all HCC cases being attributable to chronic HCV (**10**).

Table 2.2 Estimated worldwide infected population and prevalence rate of hepatitis C, by WHO region (1999) (27)

Region	Infected population (millions)	Prevalence rate, %
Europe	8.9	1.0
Americas	13.1	1.7
Southeast Asia	32.2	2.2
Western Pacific	62.2	3.9
Eastern Mediterranean	21.3	4.6
Africa	31.9	5.3

Figure 2.1 Estimated hepatitis C prevalence by country/area in 1999 (28)



Source: Greenaway C, Wong D, Assayag D et al. Evidence-based clinical guidelines for immigrants and refugees. CMAJ 2011.

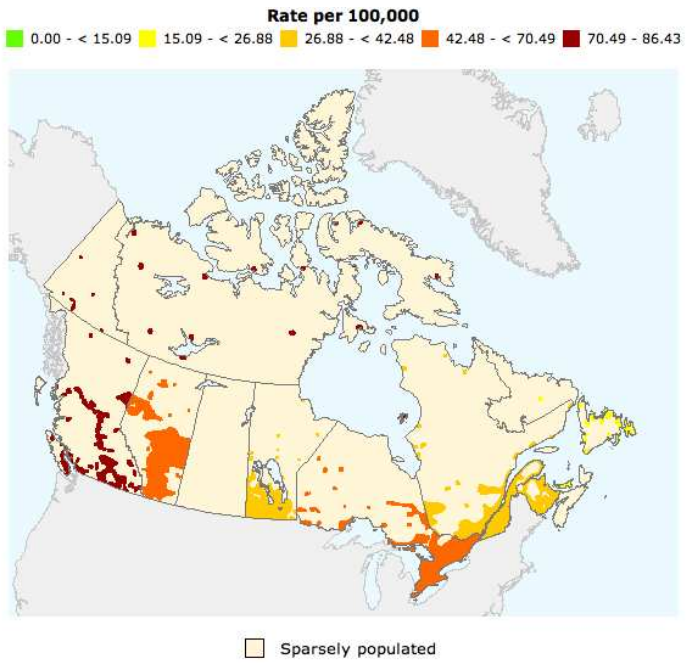
2.3.2 Hepatitis prevalence in Canada

In Canada, hepatitis C first became reportable in British Columbia in 1991, and became reportable in most Canadian provinces and territories by January 1999 (**3, 29**). Hepatitis C only became reportable in Québec in April 2002. In 2002, it was estimated that 251,000 individuals in Canada were infected with HCV, a prevalence of 0.8% (0.68-0.94%) and approximately 5,000 new cases of HCV infection occur in Canada each year. Moreover, 9,400 Canadians had cirrhosis and 3,200 had liver failure (**13**). With the increasing prevalence of HCV

in Canada, it has become a significant health concern; however due to the largely asymptomatic nature of the disease, its burden is not well documented (**12**).

The prevalence of HCV varies across provinces and territories (Figure 2.2) (**30**). In 2004, the highest rates of HCV were in the Yukon Territories, followed by the Northwest Territories and British Columbia (**30**). However, this may be due to differential reporting, as HCV was first reportable in British Columbia followed by other provinces in later years. Hepatitis C cases are first reported to the provinces and territories and data is then sent to and collated at the Public Health Agency of Canada.

Figure 2.2 Rate of hepatitis C per 100,000 in Canada, 2004 (**30**)

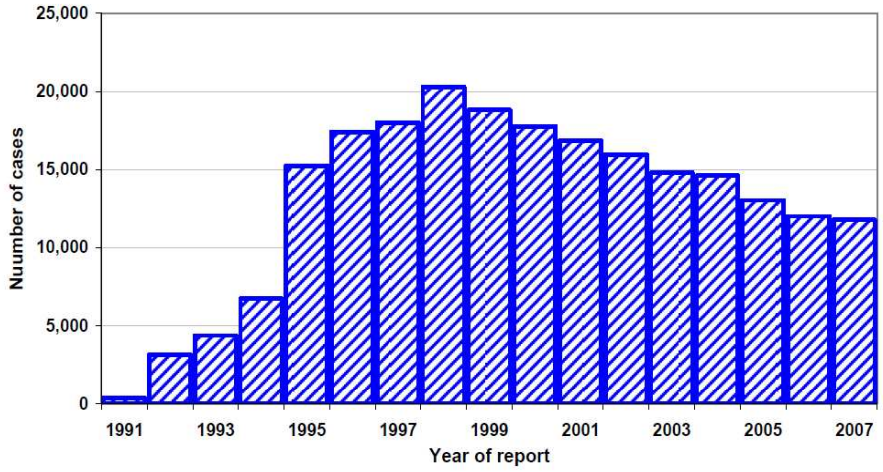


Source: Notifiable Diseases Online [cited Oct, 10, 2011]; Available from: http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/m_prov-eng.phtml?minx=-2565558&miny=-866267&maxx=3392873&maxy=4008812&CAUSE=173&YEAR=04&SEX=3&AGEGROUP=0&reClassifyMap=Update+Map&DATATYPE=r&ecumenes=on

The Public Health Agency of Canada recently updated the hepatitis C prevalence estimates developed in 2002 by incorporating new data on HCV progression and reported HCV cases in order to characterize the epidemiology of hepatitis C in Canada in 2007 (**31**). In 2007, it was estimated that there were 242,521 (0.78%) people in Canada infected with HCV. Approximately 7,900 of these individuals had become newly infected in 2007, primarily due to injection drug use. The impact of hepatitis C related sequelae on health appeared to be considerable in Canada, with 15,800 individuals living with cirrhosis and 5,500 with liver failure in 2007.

A total of 212,782 hepatitis C cases were reported between 1991 and 2007. The number of annual reported HCV cases increased between 1991-1998 and peaked in 1998 with 20,280 reported cases of HCV. The number of annually reported HCV cases has steadily decreased since 1998 (**31**). Figure 2.3 illustrates the adjusted number of hepatitis C cases reported in Canada from 1991-2007, adjusting for the missing number of cases in the early years likely due to delayed reporting of cases to the Public Health Agency of Canada. The number of reported HCV cases is most likely an underestimate of the true HCV prevalence in Canada, due to the asymptomatic nature of the disease leading to a large number of undiagnosed cases.

Figure 2.3 Adjusted number of reported cases of HCV in Canada, 1991-2007 (31)



Source: Remis R. Modelling the incidence and prevelence of hepatitis C and its sequelae. *Public Health Agency of Canada* 2007

2.3.3 Hepatitis prevalence in Québec

Hepatitis C officially became reportable in Québec in April 2002; therefore the Maladies à déclaration obligatoire (MADO) database is incomplete for HCV cases detected prior to this date. Clinical laboratories however, began to report HCV cases in the early 1990's. Between 1997 and 1999, most of the 18 regional Directions de santé publique (DSP) in Québec were receiving confirmed HCV laboratory case reports comparable in number to those received after 2000. The dramatic increase seen in the number of HCV case reports between 1997 and 2002 is most likely due to increased testing and reporting (**32**).

Due to the late date at which HCV became officially reportable in Québec, the number of cases before 2002 likely underestimates that true burden of

hepatitis C in the population (**32**). In addition, the nature of HCV infection also likely contributes to underreporting as many people who are newly infected do not exhibit symptoms and may not be tested for HCV (**33**).

2.3.4 Passive surveillance of hepatitis C in Canada

Prior to the implementation of routing blood screening for hepatitis C in 1990, hepatitis C posed a considerable threat to the Canadian blood supply. Therefore, an investigation of the Canadian blood system was commissioned to identify patients who had received blood or blood products between 1978 and 1990, before HCV screening was introduced (**34**). There are two types of programs, referred to as look-backs. A targeted look-back involves notifying recipients of blood from donors who were found to be HCV positive and advising them to undergo testing. A general look-back involves identifying all individuals who received blood before routine HCV blood screening was implemented and advising them to undergo testing (**35**).

In Canada, collection of data on viral hepatitis is done through a national surveillance system. Between 1992 and 1998, there was a great increase in the number of reported hepatitis C cases in Canada, due to increased reporting by provinces and territories. This was most likely attributable to increased awareness and testing. In addition, federal compensation was given to cover the cost of look-back studies (**36**).

In 1998 an enhanced sentinel site surveillance system for acute and chronic hepatitis B and C was established to obtain a more accurate picture of cases. It contributes to the collection of information on chronic hepatitis B and C infection, hepatitis related risk factors, and viral hepatitis genotype (**37**) .

Hepatitis C surveillance at the DSP involves two methods of data collection. Firstly, in cases that are reported to the DSP (from laboratories or physicians), epidemiological information is collected through case investigations, obtained from questionnaires distributed to physicians requesting information about reported HCV cases. Secondly, enhanced surveillance is information obtained through telephone interviews, of these newly detected cases. Enhanced Surveillance was developed to expand the data captured through routine surveillance, and to evaluate its accuracy (**32**).

Passive public health surveillance data underestimates the true total number of cases due to low detection of asymptomatic cases. Whether an individual exhibits symptoms due to hepatitis is dependent on the type of hepatitis, stage of disease (acute vs. chronic), and the age of the individual. The majority of acute hepatitis C cases are asymptomatic, and all chronic hepatitis C cases are asymptomatic unless they develop cirrhosis or hepatocellular carcinoma.

Hepatitis C will be typically detected in one of three ways in a passive surveillance system. Firstly, testing may be done due to the presence of symptoms

consistent with the diagnosis such as cirrhosis or hepatocellular carcinoma. Secondly, cases can be screened due the presence of perceived risk factors for viral hepatitis such as HIV, and intravenous drug use (IDU). Lastly, screening can take place during work up for other conditions that cause increased liver enzymes such as heart failure etc.

HCV case investigations as part of enhanced surveillance began in September 2003 in Québec to obtain information beyond the basic demographic data through a questionnaire sent to the physician whom ordered the positive HCV test. There was a reporting delay in 25% of cases, in which reported cases were found to be diagnosed more than 12 months before the date of the positive HCV test that led to the case report. Several factors may account for this time discrepancy between the date of HCV diagnosis and date of detection. For example, cases detected before HCV became officially reportable in 2002, cases detected under research protocols where not reporting to the DSP was approved, and cases detected and reported anonymously then reported nominally at a later date (**32**). Delayed reporting of hepatitis C cases to the DSP may have affected the rates of hepatitis C calculated in this study. If the reporting delay occurred at the start of the study period our rates of hepatitis C would be an overestimate, as individuals diagnosed before the start of the study period would be included. However, if the reporting delay occurred towards the

end of the study period, individuals diagnosed during the study period would be missed, resulting in an underestimation of the true rates.

2.3.5 Risk factors and mode of transmission

HCV is transmitted through the exchange of blood or bodily fluid contaminated with HCV. The most efficient mode of transmission is through direct percutaneous exposures such as transfusion of blood or blood products, transplantation of organs or tissues from infectious donors, sharing of contaminated needles among intravenous drug users (IDUs) or contaminated medical instruments (**38**). Tattooing and body piercing are other potential methods of transmission if performed using contaminated instruments (**3**). Vertical transmission of HCV, from an infected mother to child may also occur (**39, 40**). A review of 77 prospective cohort studies between 1990 and 2000 found the rate of mother to infant HCV transmission to be 4-7% per pregnancy in women with HCV. Co-infection with HIV in the mother increases the rate of HCV transmission 4 to 5 fold (**41**). HCV can also be transmitted through sexual contact, however the efficacy of transmission is low (**42**). For individuals with chronic HCV, the approximate risk of sexual transmission of HCV for those in monogamous partnerships is 0-0.6% per year, as compared to the risk of 1% per year in those with multiple sexual partners (**43**). Co-infection with HIV-1 seems to increase the risk of sexual transmission of HCV (**44, 45**). A case control study that controlled for other risk factors of HCV: IDU and blood transfusion, found that

anti-HCV positivity was observed in 18.7% of individuals whose partner was HIV positive compared to 1.6% of those who did not have HIV (**46**).

Much of the global variability in prevalence of HCV can be explained by differences in the frequency and extent to which different risk factors have contributed to the transmission of community acquired HCV infection (**25**). Methods of HCV transmission vary between high income and low income countries. In most high income countries, the transmission of HCV through blood transfusions and organ transplants has been virtually eliminated due to the practice of routine screening of the blood supply and organ donors for HCV since 1990 (**25, 26**). Currently in high income countries, the group at highest risk for HCV transmission are previous and current IDUs. Over the past 30 years in the United States and Australia, IDUs have accounted for 60% and 80% of prevalent HCV infections, respectively. Each country has an overall HCV seroprevalence of 1.8% (**47**) and 2.3% (**25, 48**) in the general population.

In contrast, in low income countries the major mode of transmission of HCV is through unscreened contaminated blood products, or is acquired through unsafe injections or medical procedures (**5, 25, 26**). The devastating consequences of these practices are currently evident in Egypt as a result of a mass programme using parenteral therapy (repeated intramuscular injections with contaminated, reused needles) to treat schistosomiasis (an intestinal parasite infection). The widespread use of parenternal antichistosomal therapy

(PAT) in Egypt began in the 1920's and was finally discontinued in the 1980's after the development of the first effective oral medication. As a result of the mass PAT campaign the current national HCV prevalence in Egypt is approximately 15-20% (**26**). A study conducted in Egypt from 1961-1986 to analyze the role of PAT in the spread of HCV found a significant association between HCV and exposure to PAT (RR=1.31 95%CI (1.08-1.59)). In addition, a cohort effect was observed where HCV prevalence was higher in older cohorts compared to younger cohorts coinciding with the gradual introduction of oral antischistosomal medication (**49**). Egypt is one example of how unsafe injections lead to HCV infections; in 2000 the WHO estimated that up to 40% of chronic HCV infections globally were acquired through unsafe injections or medical procedures (**50, 51**).

In Canada the mode of transmission of hepatitis C is similar to other high-income countries. Prior to the introduction of routine blood supply screening for HCV in 1990, having received a blood transfusion was the second most common method of transmission following IDU. However, the risk has markedly decreased to being virtually nonexistent today due to appropriate blood screening (**52**). Currently, the primary mode transmission of HCV in Canada is through IDU, and accounts for at least 60% of all HCV transmissions (**3, 53**). A study in Vancouver found that the prevalence of chronic HCV was 81.6% among a cohort of 1,345 IDUs (**54**). A cohort of IDUs in Montreal demonstrated an HCV

prevalence of 70% (**55**), while a cohort of untreated illicit opiate users self-reported a 56% HCV prevalence rate (**56**).

2.4 Clinical manifestations of hepatitis C

2.4.1 Asymptomatic stage

Chronic hepatitis C is defined by the persistence of HCV RNA for at least 6 months (**57**). The majority of individuals who develop chronic hepatitis C are asymptomatic until they develop advanced stage of cirrhosis or liver cancer (**1**). Although the chronic stage of hepatitis C is characterized by a prolonged period at the start of infection in which there are no symptoms, some individuals experience mild nonspecific symptoms (Table 2.3) (**4**). The most frequently reported symptom is fatigue; however, anorexia, nausea, right upper quadrant discomfort, dark urine, and itching may also occur (**58**). In addition, tests for levels of liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are also used as markers of disease severity in both acute and chronic HCV.

Table 2.3 Differences between acute and chronic HCV infection (58)

	Acute HCV infection	**Chronic HCV infection**
Clinical manifestations	Asymptomatic or jaundice, dark urine, light stool, malaise, anorexia, asthenia	Asymptomatic or asthenia, malaise, aching muscles/joints, hepatomegaly, hepatic encephalopathy, ascites
Liver function tests (ALT, AST)	Elevated (usually 5-10 X normal)	Normal or elevated (2-3 X normal)

2.4.2 Complications (cirrhosis and hepatocellular carcinoma)

Chronic hepatitis C leads to several long term sequelae, primarily cirrhosis, HCC and liver failure. It is estimated that 20-30% of chronically infected individuals will develop cirrhosis, which takes about 20-30 years to develop (**6**). Furthermore, HCV associated cirrhosis results in liver failure and death in 20-25% of patients (**1**). The risk of developing HCC in individuals with chronic HCV is 1-5%, usually occurring 25-30 years after HCV infection (**1, 7**). HCV-related HCC cases occur almost exclusively in individuals with cirrhosis (**7**). HCC is the fifth most common cancer worldwide, with 20% of all HCC cases being attributable to chronic HCV (**10**). HCC has a poor long-term prognosis with a 5-year survival rate of less than 5% (**8**). Overall, several different factors can influence the rate of progression of cirrhosis and HCC including: alcohol, age, time of infection and severity of liver histology (**5**).

2.4.3 Extra hepatic manifestations

Hepatitis C is associated with the development of a wide range of extra hepatic manifestations including mixed cryoglobulinemia, membranoproliferative glomerulonephritis, non-Hodgkin's lymphoma, Sjogren syndrome, porphyria cutaneous tarda, lichen planus, leukocytoplasic vasculitis, and various endocrine and neurologic manifestations (**59, 60**). A study assessing the prevalence of extra hepatic manifestations in hepatitis C patients found at

least one clinical manifestation in 38% of patients (**61**), while another study found up to 74% of hepatitis C patients had at least one extra hepatic manifestation (**62**).

Most extra hepatic manifestations of HCV are associated with autoimmune or lymphoproliferative states, which may be due to HCV's ability to replicate in lymphoid cells (**17**). Studies have shown that cryoglobulinemia, a systematic vasculatic disease characterized by the presence of abnormal proteins in the blood which precipitate in cool serum is found in approximately 40% of patients with hepatitis C (**60, 62, 63**). A study found that rheumatoid factor was present in 70% of hepatitis C patients (**63**).

Several studies have demonstrated a link between Type II diabetes mellitus and chronic hepatitis C (**64-66**). Alison et al. reported an increased rate of diabetes mellitus (50%) among 34 patients with HCV related-cirrhosis compared to a rate of just 9% in patients with cirrhosis unrelated to hepatitis C (**64**). A study conducted in the USA found the prevalence of diabetes mellitus to be significantly higher in patients with hepatitis C compared to patients with hepatitis B. In addition, an association between diabetes mellitus and HCV genotype 2 was observed (**65**). The mechanism and direction by which the two diseases are linked is still yet to be fully understood; however these studies present interesting findings.

2.5 Treatment

There is currently no vaccine available for the prevention of hepatitis C. There are however, several effective medications that will successfully eradicate HCV infection and decrease the progression to cirrhosis, liver failure or HCC (**67, 68**). The efficacy of HCV treatment is assessed by measuring HCV RNA viral load in the serum. Hepatitis C is considered eradicated if a sustained virologic response (SVR) is achieved and is defined as the absence of hepatitis C RNA 6 months after completion of treatment (**69, 70**).

The first treatments for hepatitis C were introduced in 1986 but were poorly effective. In 1986, interferon alfa-2b was the first therapy used in the treatment of non A, non B hepatitis, 3 years before the hepatitis C virus was identified. The response to treatment as measure by SVR was low (~10%). In 1998, the addition of the nucleoside analog ribavirin to the interferon treatment regimen was associated with an increase in SVR to about 30% (**71**). A further advance in HCV treatment was the development of pegylated interferon in 2002. This involved covalently attaching a polyethylene glycol to the interferon molecule enhancing its biological activity and increasing its half-life, thus improving response rates (**71**). A total of 48 weeks of standard interferon with ribavirin achieved sustained response rates of as high as 43% (**72**), whereas 2 large randomized controlled trials demonstrated that 48 weeks of pegylated interferon with ribavirin increased the SVR to 54-56% (**73, 74**).

Given the success of combination treatment, the standard of care for treatment of hepatitis C since 2002 has been weekly subcutaneous injections of pegylated interferon alpha in combination with daily oral ribavirin administered over 24-48 weeks depending on the individuals HCV genotype (**75**).The response rate to treatment, medication dosage and duration of treatment are dependent on the individual's HCV genotype (**28**). For individuals with genotype 1, HCV treatment is administered over 48 weeks and SVR ranges from 42-46%. Response rates in those with genotype 2 or 3 are higher at 76-82% and treatment duration is shorter compared to genotype 1 (24 weeks) (**76-81**).Treatment of HCV results in several adverse events (**76**). Registration trials of pegylated interferon alpha and ribavirin indicate that 10-14% of patients discontinue therapy due to adverse events, limiting the treatment's success. The most common side effects experienced in the trials were flu-like symptoms including fatigue, headache, fever and rigors experienced by more than 50% of patients. In addition, psychiatric side effects such as depression, irritability and insomnia occurred in 22-31% of patients (**73, 74**). The need for better treatment for HCV has prompted further research and recent development of new drugs with improved sustained response rates.

Recent licensure of new potent protease inhibitors have been an important advance in the treatment of hepatitis C. The two newly developed therapies boceprevir and telaprevir act as HCV serine protease NS3/4A

inhibitors, which is essential in HCV viral replication and assembly (**82**). Both boceprevir and telaprevir are only effective against HCV genotype 1; they don't have clinically significant activity against other HCV genotypes (**83**). Among HCV genotype 1 patients, addition of boceprevir or telaprevir to standard therapy with ribavirin and pegylated Interfereon results in higher rates of SVR, and shorter duration of therapy (**84**). An SVR of 70-80% is observed when either boceprevir or telaprevir is used with pegylated interferon and ribavirin in treatment naïve individuals. Despite their similar SVR rates, each protease inhibitor has a unique side effect profile (**85**).

Phase 3 trials demonstrated that side effects were significantly more frequent in patients treated with protease inhibitors compared to those treated solely with pegylated interferon and ribavirin (**86**). Two phase 3 clinical trials (**87, 88**) led to the approval of boceprevir as an effective treatment (with pegylated interferon and ribavirin) for HCV genotype 1. The most common side effects in patients receiving boceprevir-based triple therapy compared to the controls (pegylated interferon and ribavirin) were anaemia and dysgeusia (**87, 88**). Anaemia was reported in 49% of boceprevir recipients compared to 29% in controls and dysgeusia occurred more than twice as often in boceprevir recipients compared to controls (**87**). Three phase 3 clinical trials led to the approval of telaprevir as an effective treatment (with pegylated interferon and ribavirin) for HCV genotype 1 (**89-91**). The most common side effects associated

with telaprevir based triple therapy compared to the control (pegylated interferon and ribavirin) were anaemia, nausea, diarrhoea, anal or rectal discomfort, rash and pruritus. The incidence of these side effects was at least 10% higher in the telaprevir recipients compared to the controls (**90**).

In addition to the higher frequency of side effects associated with protease inhibitors, the cost of treatment compared to pegylated interferon and ribavirin in higher. Treatment with pegylated interferon and ribavirin can cost up to $30,000 per course of treatment (**36**). 12 weeks of treatment with telaprevir is about $50,000 and boceprevir costs $26,400, $35,200, or $48,400 for 24, 32 and 44 weeks of treatment respectively (**86**). The treatment regimen with protease inhibitors is considerably more costly as they must be taken along with pegylated interferon and ribavirin. Despite these drawback, protease inhibitors represent a major advance in the ability to treat HCV infection in genotype 1 individuals, with a marked increase in SVR (**90**).

Both boceprevir and telaprevir were approved for use in Canada by Health Canada in August, 2011 for treatment of chronic hepatitis C genotype 1 in combination with current standard therapy, pegylated interferon alpha and ribavirin. This was based on the result of recently published phase 2 and phase 3 trials.

2.6 Immigration in Canada

2.6.1 Canada's immigration policy

Immigration is an essential part of Canada's identity as immigrants make an important contribution to Canada's social, cultural and economic development. According to the World Bank in 2010, Canada was home to the fifth largest immigrant population worldwide, with approximately 7.2 million immigrants making up ~20% of the Canadian population (**92**). This high rate of immigration has led to a change in the epidemiology of several infectious diseases in Canada. With respect to hepatitis C, the majority of Canadian immigrants originate from countries with a higher seroprevalence of hepatitis C risk as compared to those born in Canada (**93**).

In 1967, a points system as a means to evaluate newly applying immigrants was introduced in the Canadian immigration process with the purpose of eliminating prejudice in the selection of immigrants. Immigrants were assigned points based on several qualities such as, knowledge of English or French, age, education and training and employment opportunities in Canada. If they attained a certain number of points, they were permitted to immigrate to Canada. Subsequently, the Immigration Act, was passed in 1976 and implemented in 1978 and is the foundation of current immigration policy. This Act outlined that the main objectives of Canada's immigration policy were the promotion of Canada's demographic, economic, cultural and social goals, family

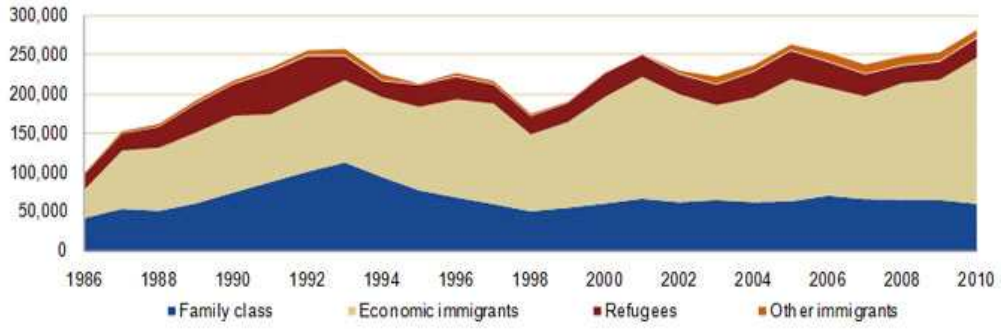
reunification and the protection of refugees (**94**). In 2002, the Immigration Act was revised and replaced by the Immigration and Refugee Protection Act (IRPA), which is the basis of Canada's current immigration practices (**95**).

The foreign-born population in Canada falls under two main categories: permanent and temporary residents. The IRPA outlines three main categories for the selection of permanent residents: family class, economic class and humanitarian class, reflecting the three main objectives of Canada's immigration program. The three main objectives are firstly, to support the development of a successful Canadian economy. Secondly, to reunite family members of immigrants residing in Canada. Lastly, to carry out Canada's humanitarian duty to protect refugees and vulnerable populations (**96**). Conversely, temporary residents are individuals who plan to stay in Canada for a limited period of time and include workers, international students and visitors. Temporary residents participate in the development of the Canadian economy by contributing to the labour market, and purchasing goods and services however they are required to leave Canada upon completing their work or schooling (**97**).

In 2010, 69.3% of the permanent residents admitted to Canada were accepted under the economic class (Figure 2.4). Over the past 25 years, the greatest proportion of permanent residents in Canada have been of the economic class (Table 2.4). There are several categories of economic immigrants, including, skilled workers who enter the labour market and business immigrants

who plan on being self-employed. All of whom are selected on the basis of their ability to contribute to the Canadian economy. Over the past 20 years the proportion of economic immigrants settling in Canada has close to doubled. In 2010, 18.2% of permanent residents were in the family class, having been sponsored by relatives living in Canada. A minority of permanent residents (9.2%) were in the refugee classification and include government-assisted refugees, privately sponsored refugees, and refugee claimants who are accepted as refugees after arriving in Canada. Finally, 3.3% of permanent residents were classified as 'other immigrants' which include live-in-caregivers (who care for children, sick or elderly people), humanitarian classifications, etc.

Figure 2.4 Number of permanent residents in Canada by category, 1986-2010 (98)



Source: Immigration overview: Permanent and temporary residents [cited Nov, 11, 2011]; Available from: www.cic.gc.ca/english/resources/statistics/facts2010/permanent/01.asp#category

Table 2.4 Mean number and proportion of permanent residents in Canada by category over a 25 year period, 1986-2010 (98)

Permanent resident category	Mean (percentage)
Family Class	67,961 (30.87)
Economic Immigrants	117,432 (53.35)
Refugees	29,498 (13.40)
Other Immigrants	5,3235 (2.38)
Total	220,125 (100)

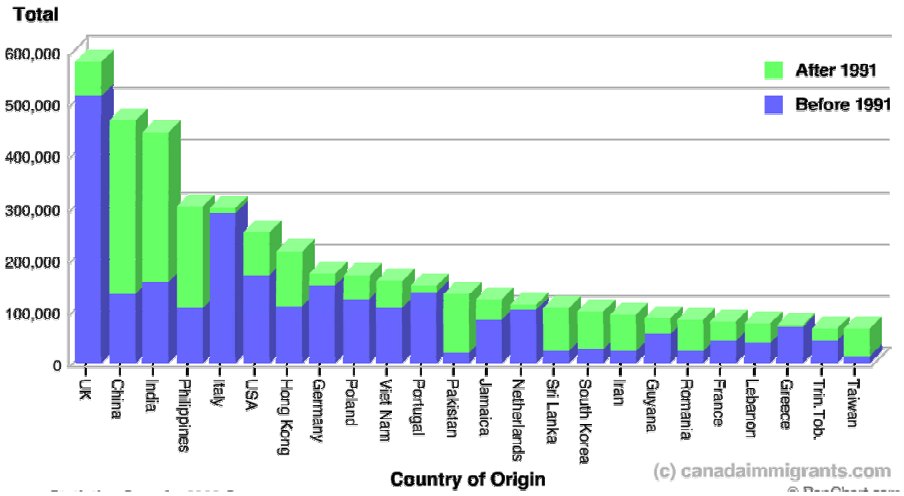
According to Canada's immigration policy all individuals wishing to gain permanent residency status must undergo a medical examination. The medical examination includes a physical exam, chest x-ray, urinalysis and syphilis and human immunodeficiency virus (HIV) serology. In 2001, it was recommended by Health Canada that HIV antibody testing be added to the examination (**99**). Mandatory HIV testing was subsequently added to the immigrant medical examination in 2002 in order to decrease the burden to the health care system and to decrease transmission of HIV in Canada. The main purpose of the medical examination is to assess inadmissibility of applicants to Canada based on medical factors such as possible danger to public health and excessive demand on health services (**99**). The medical examination does not currently test Canadian immigrants for the presence of hepatitis C infection.

2.6.2 Canada immigrant profile

Immigration plays an important role in shaping Canada's demographic make-up and contributes to an increasing level of diversity. Canada has a high annual influx of approximately 250,000 permanent residents. Over the past 75 years the foreign born population in Canada has steadily increased. Between the years of 2001 and 2006, the Canadian foreign-born population grew by 13.6%, which was four times faster than the 3.3% growth rate of the Canadian-born population (**93**).

The pattern of source countries of immigrants has changed dramatically over time. In 1971, the majority (61.6%) of new immigrants originated from Europe and during the late 1960's only 12.1% of immigrants were from Asia (including the Middle East). Over the past 4 decades there has been a major shift in this distribution. The number of European immigrants has decreased steadily over the years and accounted for only 16.1% of recent immigrants in 2006 (Figure 2.5). In contrast, the proportion of new immigrants from Asia continued to increase reaching 50.9% in the late 1980's, as recorded in the 1991 census. Due to Canada's changing immigration profile, for the first time in 2006, there was a greater proportion of foreign born individuals from Asia and the middle East (40.8%) compared to those from Europe (36.8%) (**93**).

Figure 2.5 Distribution of immigrants by top countries of origin in 2006 by period of arrival (before/after 1991) (100)



Source: Canadian Immigration Statistics (Statistics Canada, 2006) [cited Dec, 10, 2011]; Available from: http://www.canadaimmigrants.com/statistics.asp

In recent years, immigrants arriving in Canada are more likely to seek residence in a metropolitan area compared to previously. A total of 97.2% of immigrants landing in Canada between 2001 and 2006 resided in either a census metropolitan area or a census agglomeration (urban community). Toronto, Montreal and Vancouver were home to 3,891,800 foreign-born individuals in 2006, accounting for 62.9% of Canada's total foreign-born population. These immigrants represented 45.7% of Toronto's population, 39.6% of Vancouver's population and 20.6% of Montreal's population (**93**).

The variation in the different source countries of immigrants arriving in Montreal, Toronto and Vancouver is shown Table 2.5. In 2006, Montreal was home to 12% of Canada's total foreign-born population, behind only Toronto

(37.5%) and Vancouver (13.4%). Montreal welcomes immigrants from all over the world, however most immigrants originate from French speaking countries. In 2006, Montreal was home to 60% of all recent immigrants to Canada whose first language was French. In addition, four out of the ten primary countries of origin of new immigrants to Montreal are French speaking (**93**).

Table 2.5 Top 10 countries of birth for immigrants in Montreal, Toronto and Vancouver that immigrated from 1996-2001 (based on the 2001 Census) (101)

Rank	Montreal	Toronto	Vancouver
1	Algeria	China, People's Republic of	China, People's Republic of
2	China, People's Republic of	India	Taiwan
3	France	Pakistan	India
4	Haiti	Philippines	Hong Kong
5	Morocco	Sri Lanka	Philippines
6	India	Honk Kong	Korea, South
7	Romania	Iran	Iran
8	Sri Lanka	Russian Federation	United States
9	Philippines	Korea, South	United Kingdom
10	Russian Federation	Jamaica	South Africa, Republic of

2.6.3 The health of immigrants

The health of the immigrant population is influenced by a variety of different factors, including the environments of their original and new countries and by the process of migration itself. The effect of migration on a particular health outcome is dependent on who is migrating, where they migrate from, where they migrate to and what health outcome is being measured (**102**). The

complex process of migration is further complicated by the fact that it is not a random process and therefore the selection of immigrants may influence health and disease risk (**102**). It has been shown that recent Canadian immigrants are generally healthier than the non-immigrant population (**103**). In addition, a study conducted in the United States, showed that recent immigrants are generally healthier than the US born population and had a lower all-cause mortality (**104**). This phenomenon of the immigrant population being healthier than the native population is known as the "healthy immigrant effect." Several factors contribute to the immigrant populations' better health. Firstly, people in poor health tend not to migrate to another country. In addition, Canada has a very selective immigration policy which includes a medical exam and is partially based on employability which requires good health (**103**).

However, several studies show that immigrants who reside in Canada for long periods of time no longer exhibit this health advantage, and certain subgroups exhibit poor health outcomes similar to the non-immigrant population (**105**). This suggests that the health benefit associated with the healthy immigrant effect in new immigrants wanes over time.

Despite the health advantage enjoyed by recent immigrants, studies have shown that immigrants carry a disproportionate burden from viral hepatitis (**9**).

2.7 Epidemiology of hepatitis C in the immigrant population

2.7.1 Prevalence of hepatitis C in the immigrant population globally

The global seroprevalence of hepatitis C is estimated to be ~2-3%; however this varies between and within countries. With the increasing level of globalization due to travel and migration, health trends in one area have both local and global implications. There has been increasing data demonstrating an increase in the burden of migration-related chronic viral hepatitis in Western Countries (**106**).

2.7.2 Prevalence of hepatitis C in the Canadian immigrant population

The prevalence of hepatitis C in the immigrant population has been estimated in several different studies. Our team is conducting a systematic review and meta-analysis of these studies to determine the seroprevalence of hepatitis C in the immigrant population. In preliminary analysis of 62 studies, representing 67,724 immigrants and refugees the overall pooled seroprevalence of chronic hepatitis C was 2.0% and ranged from 0.9%-4% for immigrant groups from different World regions (**107**). This suggests that that burden of hepatitis C in the immigrant population is similar to the seroprevalence in their countries of origin and is higher than the mean HCV seroprevalence in Canada, of 0.8% (**13**). In 2002, it was estimated that 241,000 Canadians were infected with HCV,

202,000 of whom were born in Canada and 49,000 of whom were born elsewhere (**13**). The mode of transmission of HCV infection in the non-immigrant and immigrant populations is likely to be quite different. In the non-immigrant population, 63% of HCV infections were attributed to IDU whereas only 33% of HCV infections in the immigrant population were related to IDU (**13**). In general, immigrants are more likely to become infected with HCV due to contaminated injections or medical equipment, unscreened blood transfusions, or organ transplants in their countries or origin (**27**).

Over the past 40 years most new immigrants to Canada have originated from regions (Asia, Africa, Central/South America) that have high seroprevalence rates of hepatitis C (**13**), leading to an increase in the seroprevalence of hepatitis C infection in Canada. Studies have shown that viral hepatitis related mortality rates are greater in refugees and immigrants as compared to the non-immigrant population (**9, 11, 108**). A recent study found immigrants to have a 1.8-3.8 fold increased mortality from viral hepatitis and 2.2-4.9 fold increased mortality from HCC as compared to the Canadian population (**11**). Based on the global contribution of hepatitis C to the burden of HCC, about 20-30% of HCC mortality is attributable to chronic hepatitis C (**28**). Hepatitis C is an important public health concern among the Canadian immigrant population that requires further investigation to better define the burden and groups at highest risk that would benefit from screening.

Chapter 3: Study Objectives

3.1 Objectives

3.1.1 Overall objective

To determine and compare the burden of chronic hepatitis C in immigrants as compared to the non-immigrant population between 1998-2007.

3.1.2 Specific objectives

1. To estimate rates of reported cases of chronic hepatitis C in immigrants and non-immigrants overall, by age and sex, region of origin, and by calendar year of diagnosis.
2. To compare rates of reported chronic hepatitis C between immigrants and non-immigrants.
3. To calculate and compare the proportion of complications from cirrhosis, HCC, hospitalizations and death in immigrants and non-immigrants with chronic hepatitis C.
4. To calculate and compare the proportion of drug dependence among immigrants and non-immigrants with chronic hepatitis C.

3.2 Hypothesis

We hypothesized that the rates of newly detected chronic hepatitis C and its long-term sequelae (cirrhosis and HCC) would be higher in the immigrant population as compared to the non-immigrant population.

Chapter 4: Methods

4.1 Study design

This was a retrospective study of all reported cases of chronic hepatitis C reported in Québec from January 1, 1991- June 30, 2008. Six Québec population databases (described below) were linked through common unique identifiers to create a case series of all reported cases of chronic hepatitis C in immigrants and non-immigrants. The denominator used to calculate rates in immigrants and non-immigrants was obtained from the census data collected by Statistics Canada in 1991, 1996, 2001 and 2006.

4.2 Sources of Québec administrative data

All confirmed cases of viral hepatitis (A, B, C, D and E) present in the public health reportable disease database, the Maladies à Déclaration Obligatoire database (MADO) from 1991-2008 were linked to the Régie de l'Assurance Maladie du Québec (RAMQ) databases [Fichier d'inscription des personnes assurées- FIPA (sociodemographic data), Fichier de services médicaux (physician billing claims for visits/procedures), Fichier de services pharmaceutiques (medication dispensed)], the hospital discharge database entitled the Maintenance et Exploitations des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo) and the landed immigrant database of the

Ministère de l'Immigration et des Communautés Culturelles (MICC). Once our research team created a final linked database with all cases of viral hepatitis, cases of chronic hepatitis C were extracted into a separate database and used for this study.

4.2.1 Maladies à Déclaration Obligatoire database (MADO)

This is a provincial public health mandatory reportable infectious disease passive surveillance system. In 1991, mandatory reporting of HCV infection started in British Columbia. Gradually other provinces followed suit, and since January 1st 1999 most physicians and laboratories throughout Canada have been required by law to report all cases of viral hepatitis C, both acute and chronic (**3**). Although hepatitis C only became a reportable disease in Québec in 2002 it has been consistently reported from most laboratories since 1998. All cases of HCV are serologically proven and reported to the Public Health Region they were diagnosed in (see Appendix 9.1). This data is sent from the 18 Québec Public Health Regions to Laboratoire de Santé Publique du Québec (LSPQ), and collated into a single provincial MADO database.

A significant proportion of HCV cases in the MADO database are non-nominal. This is because some clinics in Montreal, which cater to a large number of gay men, and IDUs, do not provide nominal data on HCV cases. The cases that were missing a name and or RAMQ number led to a lower linkage than was initially anticipated. It is also possible that these cases could have been counted

more than once in the MADO database particularly if these individuals presented to a different clinic where testing for HCV was done either nominally or non-nominally (**32**).

4.2.2 Régie de l'Assurance Maladie du Québec database (RAMQ)

RAMQ is the provincial public health insurance program provider in Québec. Medical service coverage is universal to all residents of Québec including immigrants who have been granted permission to live in Canada. The RAMQ database is made up of 3 different databases (see Appendix 9.2). Firstly, the Fichier d'inscription des personnes assurées (FIPA) contains demographic information on all Québec residents who are eligible for health care and registered with RAMQ. This database includes a unique RAMQ health number for each individual in addition there is a unique visa number for all immigrants.

Secondly, the Fichier de services médicaux database contains all physician billing information for inpatient and ambulatory medical services provided to Québec residents including: physician visits, surgical procedures, and diagnostic procedures. Diagnoses are coded using the International Classification of Diseases, edition 9 (ICD-9). Lastly, the Fichier de services pharmaceutiques database contains information on medication dispensed to Québec residents eligible for this insurance, which is approximately 50% of all residents.

4.2.3 Maintenance et Exploitations des Données pour l'Étude de la Clientèle Hospitalière database (Med-Echo)

This is the Québec hospital discharge database, containing information on all Québec hospital admissions since the year 1967 (see Appendix 9.2). Several variables are present in the database, including: primary and secondary discharge diagnoses (ICD-9), admission and discharge dates, length of stay and ICU admission.

4.2.4 Ministère de l'Immigration et des Communautés Culturelles database (MICC)

The MICC landed immigrant database consists of demographic information on all immigrants that have been granted permission to reside In Québec (see Appendix 9.2). Approximately 90% of newly arrived immigrants each year are "landed" (have permission to live in Canada) immigrants (**96**), and are therefore entered into the MICC database and are eligible to receive health care through RAMQ. The other 10% of new immigrants fall in the refugee class (**96**). Within this class, sponsored refugees, individuals who have been forced to flee their country because of war persecution or violence have RAMQ health coverage upon arrival. Asylum seekers, individuals seeking protection as refugees and are waiting for their claim to be assessed are covered under a federal government program and are not entered into the MICC database unless they

become accepted as a refugee. The MICC database includes several variables including: RAMQ number, sex, immigrant category, date of admission, date of entry, date of birth and country of birth. This linkage will allow for the stratification of rates of chronic hepatitis C by immigrant category, and country of origin, which are all likely important determinants of chronic hepatitis C.

4.2.5 Database linkages

The administrative databases used in the study were linked deterministically through unique identifiers. The FIPA database was linked to the MADO database as well as the other RAMQ databases through a unique RAMQ number present for each individual. The MICC database was linked to the FIPA through the presence of a unique visa number present for each immigrant. For the purposes of this study the MADO and MICC databases were sent to RAMQ where the linkages were performed. Each of these databases contained a scrambled unique identifier for each person and was transmitted back to the research team allowing for linkage into a non-nominal database. Individuals with a visa number, who did not link with the MICC database were also flagged as immigrants. In the linked database, immigrants with hepatitis were classified as case series 1, non-immigrants with hepatitis were classified as case series 3 and finally immigrants identified by a visa number but did not link to MICC were classified as case series 2 (see appendix 9.3). The final linked database had demographic, health service and immigration variables (see appendix 9.2) available for analysis.

4.3 Study population

4.3.1 Case series of chronic hepatitis C

All newly reported cases of chronic hepatitis C identified in the MADO database between January 1, 1991 – June 30, 2008 and registered in the FIPA database were defined as a case. Given the fact that laboratories only began routinely reporting hepatitis C in 1998 and that hepatitis C only became a reportable disease in Québec in 2002, there are very few reported cases of hepatitis C prior to 1998 (Figure 5.1). In addition, reported chronic hepatitis C data was only available for the first half of 2008. For this reason only cases reported between January 1, 1998 to December 31, 2007 that linked to the FIPA database were included in the final linked database. Linking the MICC database to the RAMQ and MADO database allowed for the calculation of disease specific rates and predictors of viral hepatitis in the immigrant population and the non-immigrant population separately. Individuals present in the FIPA database (with a visa number) and the MADO databases but not in the MICC database (case series 2) were added to the study case series and analyzed as immigrant cases, as they possessed all necessary variables except for region of origin (see Appendix 9.3).

4.4 Variables of interest

4.4.1 Explanatory variables

The predictors of chronic hepatitis C analyzed in this study were the demographic variables: age, sex, immigrant/non-immigrant status and when available, region of origin for immigrants. In addition, drug dependence as defined in Table 4.1 (a surrogate for intravenous drug use (IDU)) was analyzed, as it is a known risk factor in the transmission of HCV.

Age is a known predictor of hepatitis C. Age at episode was the variable used and calculated as the time between date of birth and date of episode. Age was used as both a continuous and categorical variable divided into ages <15, 15-49 and >49. Sex was also analyzed as a possible predictor of chronic hepatitis C.

Immigration status (defined as immigrant or non-immigrant) was analyzed in order to demonstrate the difference in chronic hepatitis C between immigrants and non-immigrants. Prevalence of hepatitis C is known to differ by region of origin and is therefore an important predictor of chronic hepatitis C in the immigrant population. A region of origin variable was therefore created for immigrants and defined according to the immigrant's country of birth. Countries were classified into 11 world regions as defined by the World Bank: East Asia and Pacific, Latin America and Caribbean, Middle East and North Africa, South Asia, Sub-Saharan Africa, Western Europe, Eastern Europe and Central Asia, Australia and New Zealand, United States, Other and Canada (see Appendix 9.4).

Drug dependence, an important predictor of chronic hepatitis C was analyzed in immigrants vs. non-immigrants. A variable was created identifying if an individual ever had a code for drug dependence or use of methadone any time during the study period. Methadone was used as a marker of drug dependence as it is primarily used as maintenance anti-addictive in patients with an opioid dependency such as heroin and morphine. Drug dependence in this study was defined as the presence of ICD-9 codes of drug dependence in the Fichier de services médicaux (physician billing database) or a drug identification number (DIN) for methadone in the Fichier de services pharmaceutiques database (Table 4.1). A DIN, is a unique number assigned to each medication in the Fichier de services pharmaceutiques database. Individuals with any ICD-9 codes for drug dependence or a DIN for use of methadone were used as a surrogate for IDUs; however, not all those with drug dependence would have taken drugs intravenously. The proportion of those with drug dependence out of all chronic hepatitis C cases was calculated over the entire study period (1998-2007), and by time period. 95% CIs were calculated to compare the proportion of those with drug dependence between immigrants and non-immigrants.

Table 4.1 ICD-9 Codes and DIN used to define drug dependence in immigrant and non-immigrant chronic hepatitis C cases

Fichier de services médicaux	
Description	**ICD 9 Code**
Opioid type dependence, unspecified	3040
Sedative, hypnotic or anxiolytic dependence	3041
Cocaine dependence, unspecified	3042
Cannabis dependence, unspecified	3043
Amphetamine and other psychostimulant dependence	3044
Hallucinogen dependence, unspecified	3045
Other specified drug dependence, unspecified	3046
Combinations of opioid type drug with any other	3047
Combinations of drug dependence excluding opioid type drug	3048
Unspecified drug dependence	3049
Opioid abuse	3055
Cocaine abuse	3056
Amphetamine or related acting sympathomimetic abuse	3057
Fichier de services pharmaceutiques	
Drug	**DIN**
Methadone	02247698, 02247698, 02247700, 02247701, 02247694, 02241377

4.4.2 Outcomes variables

The main objective of the study was to estimate the rates of reported cases of chronic hepatitis C in the immigrant and non-immigrant population. Therefore, the main dependent variable for each individual in the study was the presence of chronic hepatitis C. Individuals were identified as a case if they were

a newly reported case in MADO during the study period and linked with the FIPA database.

Another objective of the study was to estimate and compare the proportion of immigrant and non-immigrant chronic hepatitis C cases with four hepatitis C related complications, hospitalizations and deaths. The four hepatitis C related complications considered were: compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. These were all defined by the presence of ICD-9 codes in the RAMQ Fichier de services médicaux or Med-Echo Hospitalization database (Table 4.2). If an individual with chronic hepatitis C was diagnosed at any time during the study with these ICD-9 codes, they were classified as having one of the four HCV related complications. Each of these variables was created as a binary variable (had complication/didn't have complication). For example, if cases were diagnosed at one time with "cirrhosis of liver without mention of alcohol" they were classified as having compensated cirrhosis. The ICD 9 code, cirrhosis of liver "without mention of alcohol" was chosen to define compensated cirrhosis to better capture individuals that developed cirrhosis as a result of hepatitis C rather than alcohol consumption. If an individual was diagnosed more than once with a certain complication, the first diagnostic code was counted as the presence of the complication.

The proportion of immigrants and non-immigrants with chronic hepatitis C who were admitted to hospital was calculated in the database created through the linkage of the MADO and FIPA databases with the Med-Echo database. The proportion of cases admitted for any reason as well as for any of the four hepatitis C related complications were also calculated. Complications were identified with ICD-9 codes as shown in Table 4.2.

The proportion of chronic hepatitis C cases that died during the study period was identified. These individuals were identified as either having a date of death from the variable for death present in the FIPA database or an ICD-9 code representing death in the Med-Echo hospitalization database (Table 4.2).

Table 4.2 ICD-9 codes for hepatitis C associated complications in immigrant and non-immigrant chronic hepatitis C cases

Complication Description	**ICD 9 Code***
Compensated cirrhosis	
Cirrhosis of liver without mention of alcohol	571.5
Decompensated cirrhosis	
Viral hepatitis B with hepatic coma	70.2
Hepatic encephalopathy	572.2
Portal hypertension	572.3
Hepatorenal syndrome	572.4
Esophageal varices with bleeding	456.0
Esophageal varices without mention of bleeding	456.1
Esophageal varices in diseases classified elsewhere	456.2

Complication Description	ICD 9 Code*
Hepatocellular Carcinoma	
Malignant neoplasm of liver, primary	155.0
Malignant neoplasm of intrahepatic bile ducts	155.1
Liver transplant	
Liver transplant	51.5
Death	798.0

*ICD-9 codes were obtained from the Fichier de services médicaux and the Med-Echo Hospitalization databases.

4.5 Data management and cleaning

4.5.1 Database characteristics

Six Québec administrative population-based databases including MADO, RAMQ (FIPA, the Fichier de services médicaux, and the Fichier de services pharmaceutiques), Med- Echo and MICC were linked deterministically from January 1, 1991 to June 30, 2008 for the purposes of the study. This was the database used to calculate rates of chronic hepatitis C and determine predictors of hepatitis C and associated complications. There were a total of 20,459 cases of chronic hepatitis C in this final linked database (see Appendix 9.3).

A major limitation of this study is that 20.1% (n=5,142) of all reported cases of chronic hepatitis C in the MADO database could not be linked to the FIPA database and therefore other administrative databases. This was due to absence of nominal data or a RAMQ number for a large proportion of chronic hepatitis C cases particularly from certain clinics in Montreal. These individuals

were included in the overall chronic hepatitis C rate calculations in the entire MADO database; however, they could not be included in the analyses stratified as immigrant or non-immigrants, nor could they be included in the calculation of complication rates as these records did not link to the physician billing database (see Appendix 9.3).

A total of 20,459 cases of chronic hepatitis C reported between 1998-2007 were successfully linked with the FIPA database as well as the physician billing and Med-Echo databases. This linkage resulted in 1,980 immigrant cases (case series 1 and 2) and 18,479 non-immigrant cases (case series 3). Of the immigrant chronic hepatitis C cases, 1,533 (case series 1) were present in the MICC database; however, 447 (case series 2) were not found in the MICC database. Cases in case series 3 were identified as immigrant cases due to the presence of a visa number in the FIPA database.

For construction of the databases it was requested that linkage of individuals in the MICC and FIPA databases begin in January 1986. The MICC database includes individuals who arrived in Québec that particular year. Therefore, individuals in case series 2 may have been immigrants who arrived prior to 1986. As although they had a visa number in the FIPA database they would not have been present in the MICC database because it only included immigrants who arrived after 1986. In addition, immigrants who move to Québec from another province are not present in the MICC database. A visa

number for these individuals is present in the FIPA database however, because their visa number (given by another province) is recorded in the RAMQ database when they request RAMQ health coverage. Immigrants in case series 2 include those who arrived prior to 1986, arrived from another province or due to data entry errors of the visa number in either database. Therefore, persons in case series 2 are missing the information present in the MICC database such as region or origin, date of entry, and date of arrival given they did not link to the MICC database. These 447 cases were still classified as immigrant cases and were included in the chronic hepatitis C rate calculations for all immigrants; however, they were not included in the rates stratified by region of origin.

4.5.2 Database cleaning

Before the analysis stage, the databases were cleaned and several issues were addressed. Firstly duplicate observations were removed from each individual database. The databases were then linked through the use of unique identifiers.

4.6 Statistical analysis

4.6.1 Descriptive analyses

Descriptive analyses were conducted for both the MADO database (all reported cases of chronic hepatitis C) and the chronic hepatitis C linked database (cases of chronic hepatitis C that were linked) to characterize the study

population's defining characteristics. For the linked chronic hepatitis C database all analyses were conducted separately in immigrant and non-immigrants in order to allow for comparisons.

Mean, median, inter quartile range and range of ages were calculated for both the MADO and linked databases. Proportions with 95% CIs for age distributions of age groups: <15, 15-49 and >49, sex and Québec Public Health regions of chronic hepatitis C diagnoses were also calculated for the MADO and linked databases. Region of origin was described for immigrants in the chronic hepatitis C linked database. For the linked database, age and sex values were compared in immigrants and non-immigrants. For the continuous variable, age, difference between immigrants and non-immigrants was calculated using a t-test. For the categorical variable, sex, difference between immigrants and non-immigrants was calculated using a chi square test. The formula used to calculate the 95% CIs for drug dependence was: proportion +/- (1.96 * ((sqrt(proportion(1-proportion)/total number of cases))).

4.6.2 Rates and rate ratios of chronic hepatitis C

Rates of newly reported chronic hepatitis C/100, 000 persons per year and 95% CIs were estimated using the MADO database from 1991-2008 (numerator). The denominator for these rates was obtained from census data. Annual, age stratified and sex stratified rates were calculated.

Rates for the entire study period, annual rates and period rates (1998-2000, 2001-2004, 2005-2007) of newly reported chronic hepatitis C/100, 000 and 95% CIs were calculated using the Poisson distribution in the linked database between 1998-2007 in immigrants and the non-immigrants. Overall rates of chronic hepatitis C and all subsequent rates calculated in the linked database were restricted to the years 1998-2007 due to the low number of cases observed prior to 1998. The number of chronic hepatitis C cases (numerator) was derived from the chronic hepatitis C linked study database. The denominator for the rates in the immigrant population was obtained from the census in 1996, 2001 and 2006 and only included immigrants living in Québec during the study period. The denominator for the rates of chronic hepatitis C in the non-immigrant population was estimated using census data for the Québec population (with immigrants removed) in 1996, 2001 and 2006. The numbers for intercensal years were calculated using linear interpolation.

Annual rates of newly detected chronic hepatitis C and 95% CIs were calculated for immigrants and non-immigrants separately. Overall rates as well as those stratified by age and sex were calculated for immigrants and non-immigrants. In addition, rates of chronic hepatitis C and 95% CIs were stratified by region or origin, for the immigrant population. Finally, rate ratios and 95% CIs of the rates of newly detected chronic hepatitis C in immigrants as compared to non-immigrants overall and stratified by age, sex and region of origin were

calculated. All confidence intervals were calculated using a Poisson distribution. The formula used to calculate the 95% CIs for rates was: rate +/- (1.96 * ((sqrt (number of cases) /denominator) * 100,000)), while the formula used to calculate the 95% CIs for rate ratios was: Rate ratio ± exp [ln (IRR) +/- (1.96* sqrt((1/immigrant cases) + (1/non-immigrant cases))].

As this calculation is an approximation, when negative values were obtained for the lower limit of confidence intervals, the value was set to zero.

The proportion of drug dependent individuals was calculated in immigrant and non-immigrant chronic hepatitis C cases. A chi square test was conducted to determine if there was a significant difference between the proportion of drug dependence in immigrant and non-immigrant cases.

The mean (± SD) and median age at episode were calculated for drug dependent and non-drug dependent chronic hepatitis C cases by time period, for immigrants and non-immigrants. Chi square tests were conducted to see if there were significant differences between the mean age at episode in drug dependent and non-drug dependent cases, for each time period in immigrants and non-immigrants.

4.6.3 Proportions of hepatitis C associated complications and hospitalizations

The proportions of long-term complications associated with hepatitis C, including compensated and decompensated cirrhosis, hepatocellular carcinoma

and death were calculated in immigrant and non-immigrant chronic hepatitis C cases. All cause and liver associated hospitalizations were also calculated. The proportions and 95% CIs of complications and hospitalizations occurring in chronic hepatitis C cases were calculated and compared between immigrants and non-immigrants. The formula used to calculate 95% CIs was: proportion +/- (1.96 * ((sqrt(proportion(1-proportion)/total number of cases))). Chi square tests were used to determine if there were significant differences between the proportions of complications in immigrants and non-immigrants.

SAS version 9.2 (SAS Institute, Cary, North Carolina) was used to conduct all analyses in this study.

4.7 Ethics approval

4.7.1 Ethics approval to access all 6 databases

Letters of support were obtained for permission to gain access to each of the administrative databases including MADO, MICC, the RAMQ databases (the FIPA, the Fichier de services médicaux, the Fichier de services pharmaceutiques) and Med-Echo. To obtain access to the MADO database, letters of support were received from each of the 18 Public Health Departments in Québec who gave permission to access the MADO data from each of their respective Public Health Departments. The MADO database is housed at the Laboratoire de Santé Public du Québec (LSPQ) and written permission was also received from Dr. Anne-

Marie Bourgault, Scientific Director at the LSPQ, so that the provincial MADO database (including data from all 18 Québec Public Health Departments) could be sent to RAMQ for linkage. This permission was conditional on receiving ethics approval from la Commission d'accès à l'information du Québec (CAI) and the ethics committee at the Jewish General Hospital (JGH). A letter of permission to access the MICC database was obtained from Mme. Maire-Josée Lemay, the Director of Research at MICC and was conditional upon receiving CAI and JGH ethics approval.

Letters of approval were received from CAI, the JGH Ethnics committee and the Montreal Public Health Department ethics committee. All letters of support mentioned above are found in Appendix 9.10.

Chapter 5: Results

5.3 MADO database analysis (unlinked)

5.3.1 Characteristics of chronic hepatitis C cases

The MADO database (unlinked database) contained a total of 29,460 reported cases of chronic hepatitis C reported from January 1, 1991 to June 30, 2008. Descriptions of population characteristics are shown in Table 5.1. Details of the linked database are described in section 5.4. The mean age (±SD) of cases was 42.7±13.9 years, and 75% of the cases were < 50 years old. The majority of chronic hepatitis C cases were male (66.2%) and almost half (42.8%) of all cases were diagnosed in Montreal, while all other regions except Montérégie had less than 10% of the population each.

Table 5.1 Demographic characteristics of individuals in the MADO database (cases of hepatitis C) (1991-2008)

Characteristic	**Cases N (%)**
Total N*	29,460
Age†	
Mean (±SD)	42.67±13.9
Median	41.00
Range	0-99
IQR (25%-75%)	34-49
Age categories	
<15	388 (1.3)
15-49	21,953 (74.5)
>49	7,119 (24.2)
Sex	
Male	19,512 (66.2)
Female	9776 (33.2)
Québec Public Health Region	
Abitibi-Témiscamingue	475 (1.6)
Bas-Saint-Laurent	236 (0.8)
Capitale-Nationale	2,672 (9.1)
Chaudière-Appalaches	643 (2.2)
Côte-Nord	223 (0.8)
Estrie	963 (3.3)
Gaspésie-îles de la Madeleine	134 (0.5)
Lanaudière	1114 (3.8)
Laurentides	2361 (8.0)
Laval	1223 (4.2)
Mauricie et Centre du Québec	1432 (4.9)
Montréal	12599 (42.8)
Montérégie	3527 (12.0)
Nord-du-Québec	31 (0.1)
Nunavik	21 (0.1)
Outaouais	1428 (4.9)
Saguenay – Lac- Saint Jean	342 (1.2)
Terres Cries de la Baie James	24 (0.1)
Ne sais pas	12 (0.0)

5.3.2 Rates of chronic hepatitis C

The total number of reported cases of chronic hepatitis C cases in the MADO database between 1991-2008 varied by year, as presented in Figures 5.1 and 5.2. The number of cases was low between 1991-1996, with fewer than 500 cases reported per year. The number of cases began to increase in 1997 (1707 cases) and increased each year peaking in 2000 (3091 cases) and then steadily decreased between 2001-2007 (see Appendix 9.5). Due to the low reported rates from 1991-1997 the analysis for the linked study was restricted to 1998-2007. As, data was only available for half of 2008 it was also excluded from the study period, and only full years were included.

Figure 5.1 Total number of chronic hepatitis C cases per year, in the MADO database (1991-2008)

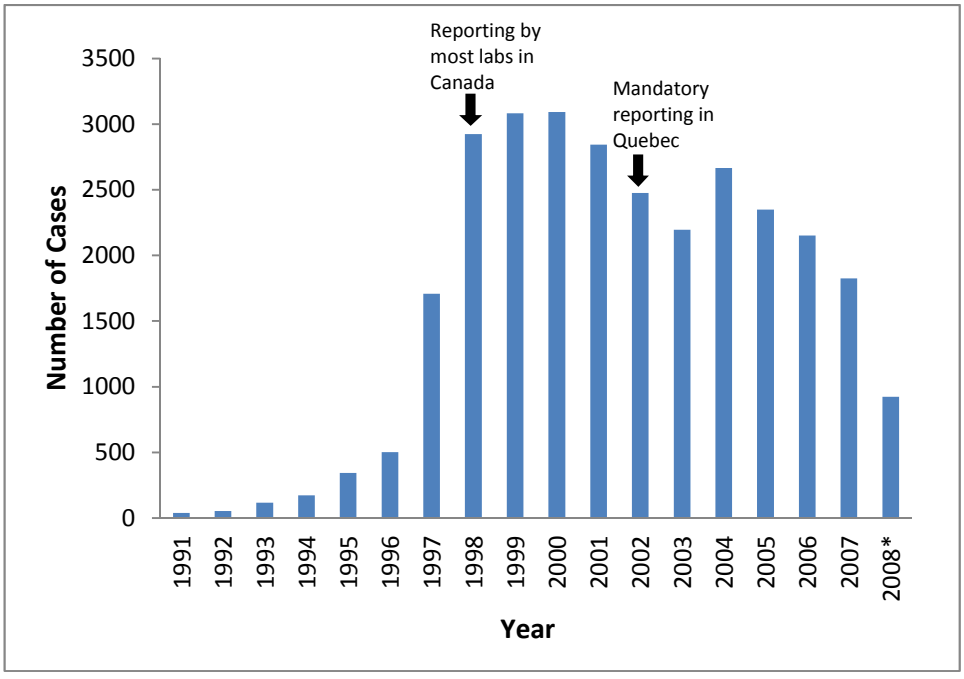
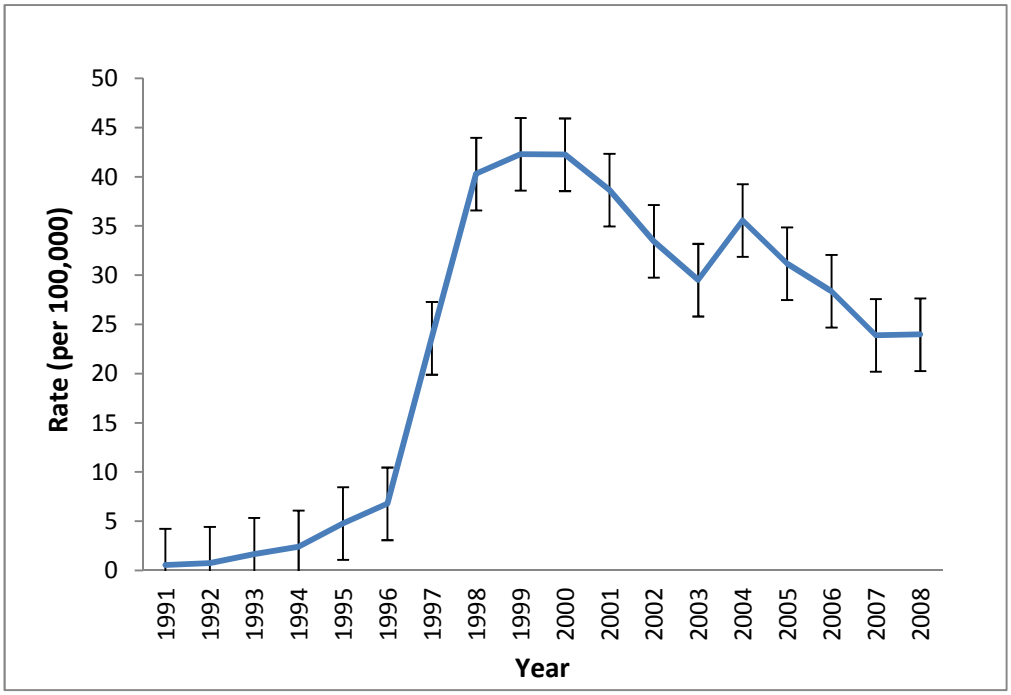


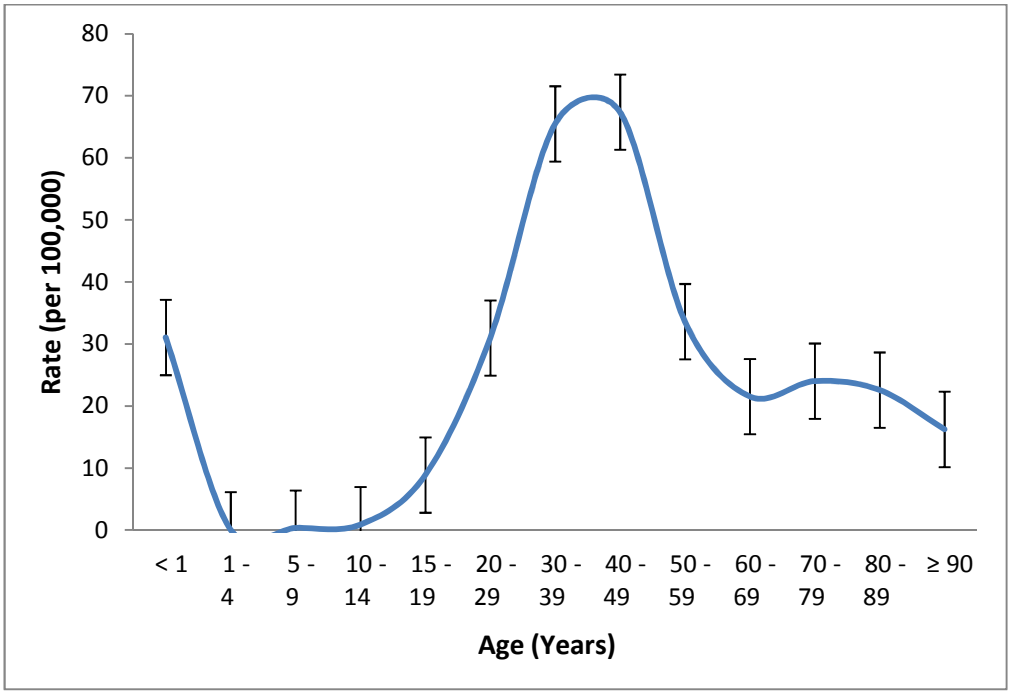
Figure 5.2 Annual rates of chronic hepatitis C in the MADO database (1991-2008)*



*The rate of chronic hepatitis C was adjusted for the year 2008, due to chronic HCV case data only being available for half of the year.

The reported rates of chronic hepatitis C reported in the MADO database appeared to vary considerably by age group as shown in Figure 5.3. The reported rate of chronic hepatitis C was 31.1 cases/100,000 for those under 1 year of age. It was very low (under 1 case/100,000) for individuals aged 1-14 years and increased for those aged 15 to 49. The highest rate of chronic hepatitis C was found in individuals aged 40-49 (67.4 cases/100,000). Rates were lower for individuals aged 50 to 89, with rates ranging between 21.5-33.6 cases/100,000.

Figure 5.3 Rates of chronic hepatitis C stratified by age group, in the MADO database (1998-2007)



5.4 Linked database analysis

5.4.1 Characteristics of chronic hepatitis C cases

The final linked database contained 20,459 reported cases of chronic hepatitis C cases from January 1, 1998 to December 31, 2007 (Table 5.2). The database consisted of both immigrant (9.7%) and non-immigrant (90.3%) chronic hepatitis C cases. The overall mean age (±SD) of cases was 43.5±13.6 years; however, immigrants were older than non-immigrants with a mean age of 47.1±

15.1 years as compared to 43.1±13.4 years ($p < 0.0001$). Overall, 73.7% of the entire case series was between the ages of 15 and 49.

The immigrant population had a lower proportion of males compared to the non-immigrant population, 53.1% vs. 61.6% ($p < 0.0001$). The majority of immigrant cases were diagnosed in Montreal (78.8%), with all other regions having less than 10% of the immigrant cases. In comparison, a considerably lower number of non-immigrant cases (37.6%) were diagnosed in Montreal. The second highest region of diagnosed chronic hepatitis C cases for non-immigrants was Montérégie, in which 14.1% of the non-immigrant chronic hepatitis C cases were diagnosed.

The mean estimated time between arrival to Canada and date of reporting chronic hepatitis C episode in immigrants was 8.4 $\pm$6.9 years over the entire study period. This mean time since arrival was longer towards the end of the study period as compared to the beginning of the study period. In 1998-2000 the mean time between arrival and date of chronic hepatitis C episode in immigrants was 7.8 $\pm$ 8.0 years, and increased to 8.0 $\pm$ 5.8 years in 2000-2004 and 9.3 $\pm$ 7.0 years in 2005-2007.

Table 5.2 Demographic characteristics of individuals in the linked database (cases of chronic hepatitis C) (1998-2007)

Characteristic	Total N (%)	Immigrants N (%)	Non-Immigrants N (%)	P value
Total N	20,459			
Immigrants	1,980 (9.7)			
Non-Immigrants	18,479 (90.3)			
Age				
Mean	43.5± 13.6	47.1 ± 15.1	43.1 ± 13.4	<0.0001
Median	42.0	45.0	42.0	
Range	0-96	0-95	0-96	
IQR (25%-75%)	35-50	36.5-56	35-49	
Age categories				
<15	116 (0.6)	12 (0.6)	104 (0.6)	
15-49	15,073 (73.7)	1243 (62.8)	13830 (74.8)	
>49	5,270 (25.8)	725 (36.6)	4545 (24.6)	
Sex				
Male	13,650 (66.7)	1052 (53.1)	12,598 (61.6)	<0.0001
Female	6,807 (33.3)	926 (46.8)	5881 (31.8)	<0.0001
Public Health Region				
Abitibi-Témiscamingue	390	3 (0.2)	387 (2.1)	
Bas-Saint-Laurent	175	1 (0.1)	174 (0.9)	
Capitale-Nationale	1717	48 (2.4)	1669 (9.0)	
Chaudière-Appalaches	455	5 (0.3)	450 (2.4)	
Côte-Nord	132	1 (0.1)	131 (0.7)	
Estrie	692	25 (1.3)	667 (3.6)	
Gaspésie-îles de la Madeleine	83	0 (0.0)	83 (0.5)	
Laurentides	790	11 (0.6)	779 (4.2)	
Laval	1576	24 (1.2)	1552 (8.4)	
Estrie	830	104 (5.3)	726 (4.2)	
Mauricie et Centre du Québec	1110	7 (0.4)	1103 (6.0)	
Montréal	8511	1560 (78.8)	6951 (37.6)	
Montérégie	2756	154 (7.8)	2602 (14.1)	
Nord-du-Québec	27	0 (0.0)	27 (0.2)	
Nunavik	12	0 (0.0)	12 (0.1)	
Outaouais	927	33 (1.7)	894 (4.8)	
Saguenay – Lac- Saint Jean	255	4 (0.2)	251 (1.4)	
Terres Cries de la Baie James	15	0 (0.0)	15 (0.1)	
Ne sais pas	6	0 (0.0)	6 (0.0)	
Region of Origin			NA	
East Asia & Pacific		303 (19.8)		

Characteristic	Total N (%)	Immigrants N (%)	Non-Immigrants N (%)	P value
Latin American & Caribbean		161 (10.5)		
Middle East & North Africa		225 (14.7)		
South Asia		205 (13.4)		
Sub-Saharan Africa		186 (12.1)		
Western Europe		273 (17.8)		
Eastern Europe & Central Asia		158 (10.3)		
United States		20 (1.3)		

5.4.2 Rates of chronic hepatitis C

The annual rates of reported chronic hepatitis C (see Appendix 9.6) have fluctuated considerably for both immigrants and non-immigrants over the study period of 1998 to 2007 as shown in Figure 5.4. The rate of chronic hepatitis C was significantly higher in the non-immigrant population compared to the immigrant population (rate/100,000 (95%CI): 33.2 (32.4-34.0) vs. 23.5 (21.4-25.5), respectively) at the beginning of the study (1998-2000). There was no significant difference however, between the rates of chronic hepatitis C of immigrants and non-immigrants for the 2001-2004 period. Although the rate of chronic hepatitis C was higher in the immigrant population compared to the non-immigrant population from 2005-2007 [24.7 (22.8-26.7) vs. 22.6 (22.0-23.3)], respectively, the difference in rates was not significant. There was a significant decrease in the rate of chronic hepatitis C in the non-immigrant population from the start to the end of the study period [33.2 (32.4-34.0) vs. 24.6 (24.0-25.2)]

(Figure 5.5). However, the increased rate in the immigrant population over the study period has been non-significant [23.5 (21.4-25.5) vs. 26.2 (24.5-27.9)].

Figure 5.4 Annual reported rates of chronic hepatitis C in immigrants and non-immigrants (1998-2007)

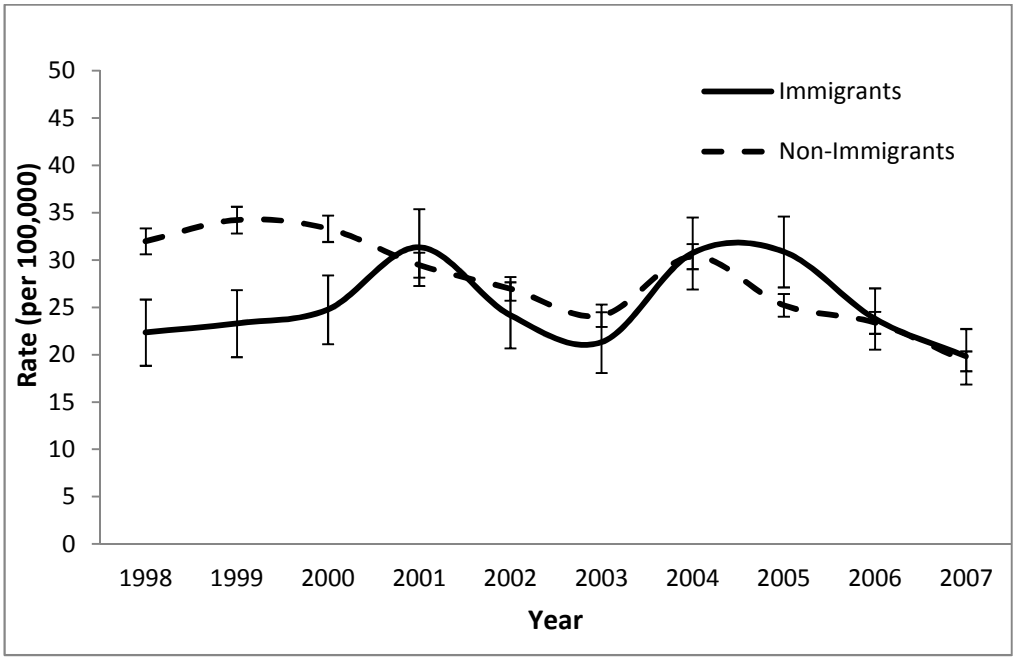
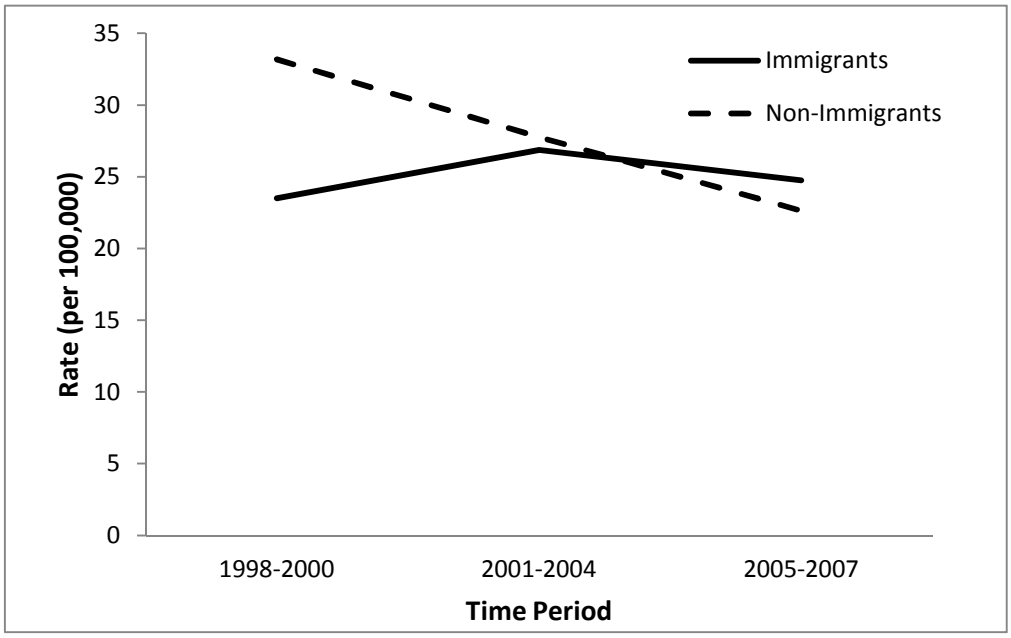


Figure 5.5 Reported rates of chronic hepatitis C in immigrants and non-immigrants by time period (1998-2007)

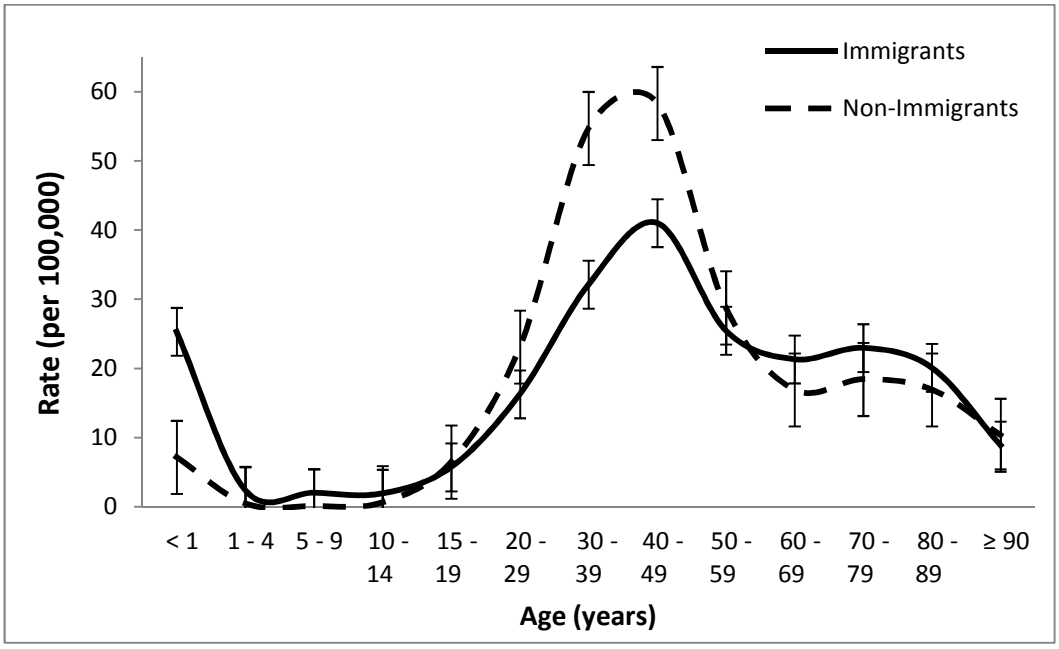


5.4.3 Rates of chronic hepatitis C by age and sex

Patterns of age-stratified rates of newly reported cases of chronic hepatitis C were similar for immigrants and non-immigrants as shown in Figure 5.6. The rate of chronic hepatitis C in the <1 year age category was greater in immigrants compared to non-immigrants (rate/100,000 (95% CI): 25.3 (0-75.0) vs. 7.2 (5.3-9.1), respectively); however the difference was not significant due to a very low number of cases in the immigrant population. The highest rate of chronic hepatitis C for both immigrants and non-immigrants was in cases aged 40-49; however, the rate was significantly higher for non-immigrants [41.0 (37.7-44.3) vs. 58.3 (56.9-59.7)]. For ages over 60, the rate of chronic hepatitis C appeared to be greater in immigrants compared to non-immigrants. However,

this difference in rate was only significant in cases aged 60-69 [21.3 (18.4-24.3) vs. 16.9 (15.9-18.0)].

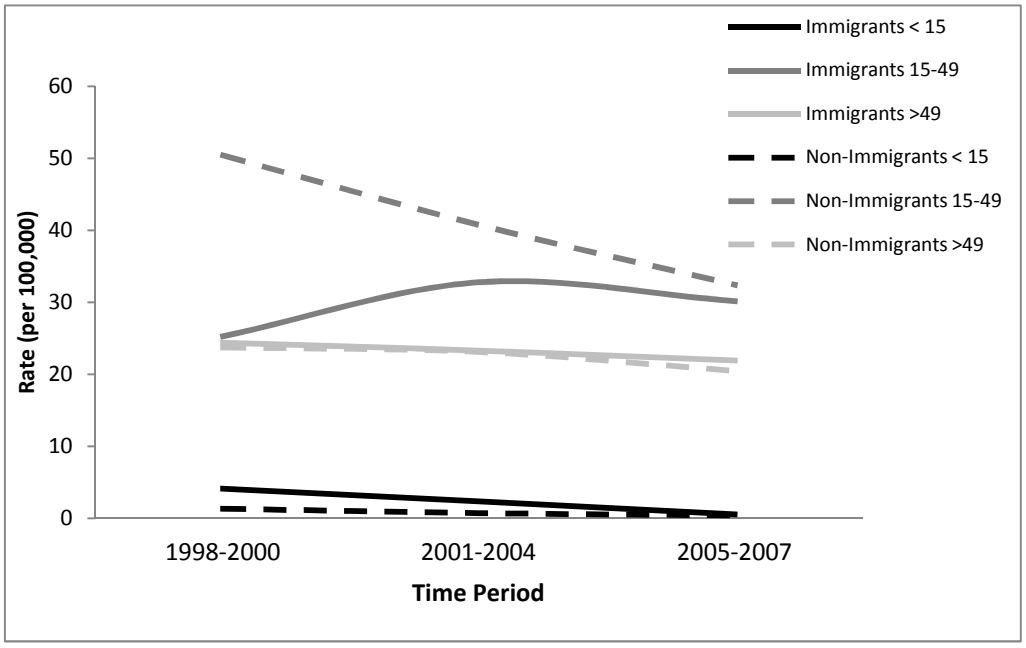
Figure 5.6 Reported rates of chronic hepatitis C in immigrants and non-immigrants by age group (1998-2007)



There was no significant difference in rate of chronic hepatitis C between immigrants and non-immigrants for cases under 15 [2.2 (1.0-3.5) vs. 0.8 (0.7-1.0)] or over 49 [23.1 (21.4-24.8) vs. 22.4 (21.8-23.1)] during the study period. However, the reported rate of newly detected chronic hepatitis C cases for those aged 15-49 was higher in non-immigrants as compared to immigrants over the study period [41.3 (40.6-42.0) vs.29.9 (28.2-31.5)]. The rate of chronic hepatitis C for individuals in this age group decreased significantly in the non-immigrant

population over the study period, from 50.4 (49.0-51.8) in 1998-2000 to 32.5 (31.3-33.6) in 2005-2007 (Figure 5.7). In contrast, the rates of chronic hepatitis C increased in the immigrant population over the study period from, 25.3 (22.4-28.2) in 1998-2000 to 30.2 (27.3-33.1) in 2005-2007; however, this increase was not significant.

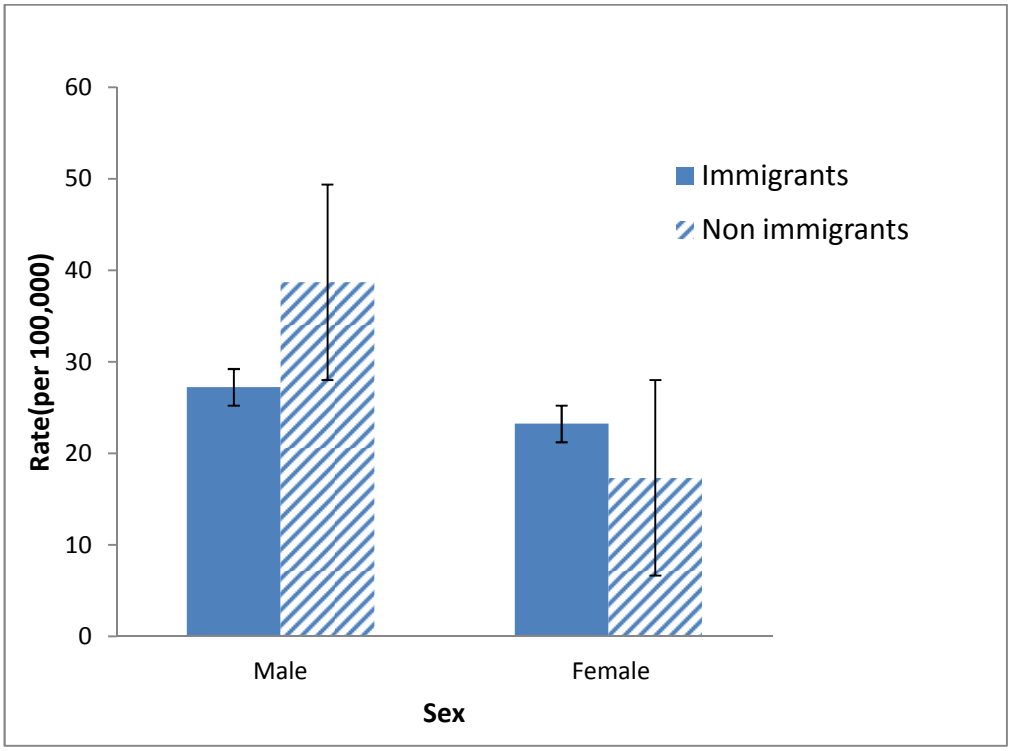
Figure 5.7 Age specific reported rates of chronic hepatitis C by time period in immigrants and non-immigrants (1998-2007)



The rate of chronic hepatitis C was significantly greater in males for both immigrants and non-immigrants as shown in Figure 5.8. For immigrants the rate of chronic hepatitis C cases in males compared to females was 27.2 (25.6-289) vs. 23.2 (21.7-24.7), respectively. For non-immigrants the rate of chronic hepatitis C

in males compared to females was 38.7 (38.0-39.4) vs. 17.3 (16.9-17.7), respectively.

Figure 5.8 Sex specific reported rates of chronic hepatitis C in immigrants and non-immigrants (1998-2007)

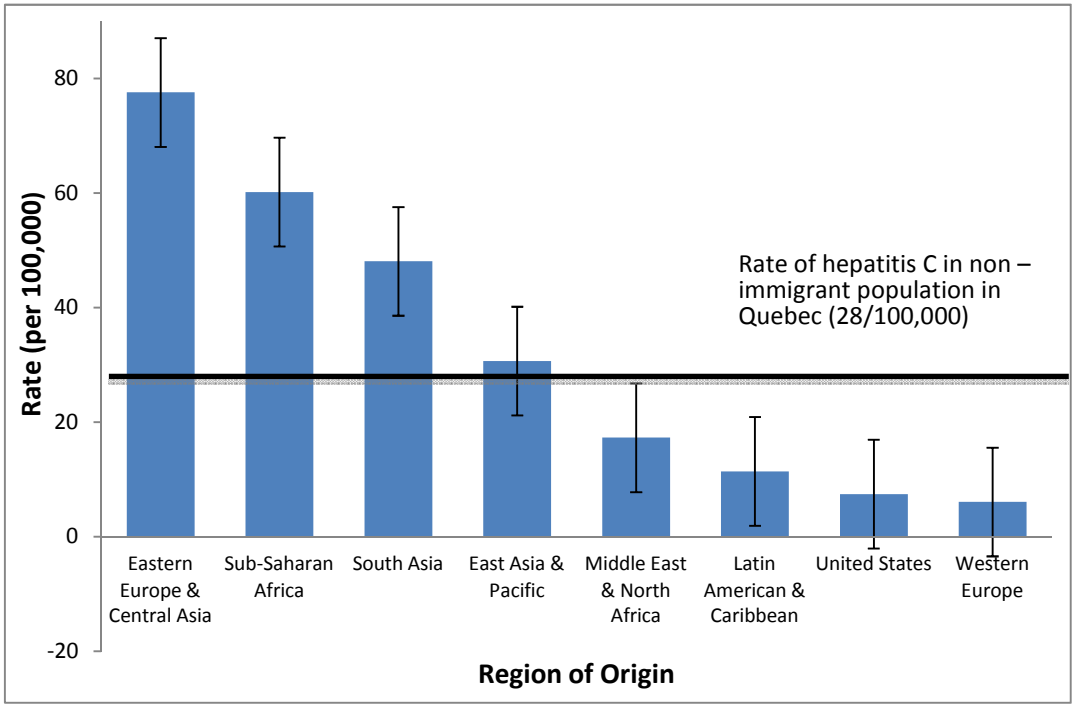


5.4.4 Rates of chronic hepatitis C by region of origin

Rates of chronic hepatitis C in the immigrant population varied by region of origin (Figure 5.9). Immigrants from Eastern Europe and Central Asia had the highest rate of chronic hepatitis C, followed by Sub-Saharan Africa and South Asia. The rates/100,000 (95%CI) for these regions were: 77.6 (68.2-87.0), 60.2

(51.5-68.8) and 48.1 (41.5-54.7), respectively. The rate ratio comparing the rate of chronic hepatitis C in immigrants compared to non-immigrants was 2.8 (2.5-3.2) for immigrants from Eastern Europe and Central Africa, 2.2 (1.9-2.4) for immigrants from Sub-Saharan Africa, 1.7 (1.5-2.0) for South Asia and 1.1 (1.0-1.2) for immigrants from East Asia and Pacific. The rate ratios comparing immigrants and non-immigrants for all other regions of origin: Middle east and North Africa, Latin America and Caribbean, Western Europe and the United States were under 1 (see Appendix 9.6).

Figure 5.9 Rates of hepatitis C in the immigrant population by region of origin



A large portion of immigrants from Eastern Europe and Central Asia came from Romania (39.7%), Russia (14.9%), and the USSR (13.0%) (see Appendix 9.7). The USSR had a strikingly high rate of chronic hepatitis C compared to other countries in the region, 631 (419-843) (see Appendix 9.8). 40% of Sub-Saharan African immigrants came from the Democratic Republic of Congo, which had the highest rate of chronic hepatitis C in the region, 210 (161-259). Immigrants from South Asia were mainly from Pakistan (71.6%), whose rate of chronic hepatitis C was 189 (158-219), the highest in the region. A total of 48.5% of East Asian and Pacific Immigrants originated from Viet Nam and 24.1% were from Cambodia. The rate of chronic hepatitis C in these two countries was 60.5 (50.8-70.3) and 86.1 (66.4-105.9), respectively. The top 3 countries (70%) for immigrants from the Middle East and North Africa were: Morocco, Egypt and Algeria, with Egypt having the highest rate of chronic hepatitis C 33.3 (24.4-42.3). 52% of immigrants from Latin America and the Caribbean were Haitian who had a chronic hepatitis C rate of 15.9 (12.5-19.3). Finally, 64.6% of immigrants from Western Europe were from France and Italy.

5.4.4 Drug dependence in chronic hepatitis C cases

The proportion of drug dependence was significantly greater in non-immigrant chronic hepatitis C cases compared to immigrant chronic hepatitis cases over the entire study period, 34.6% vs. 4.9% ($p < 0.0001$), respectively. The proportion of drug dependence in non-immigrant chronic hepatitis C cases

decreased significantly over the study period, while the proportion of drug dependence in immigrant chronic hepatitis C cases did not change significantly (Table 5.3).

Table 5.3 Proportion of drug dependence (overall and by time period) in immigrant and non-immigrant chronic hepatitis C cases

	Drug dependent	Number of cases	Percent	95% CI	P value
Overall					
Immigrants	97	1980	4.9	3.9-5.8	<0.0001
Non Immigrants	6396	18479	34.6	33.9-35.3	
1998-2000					
Immigrants	30	502	6.0	3.9-8.0	<0.0001
Non-immigrants	2648	6542	40.5	39.3-41.7	
2001-2004					
Immigrants	37	833	4.4	3.0-5.8	<0.0001
Non-immigrants	2411	7376	32.7	31.6-33.8	
2005-2007					
Immigrants	30	645	4.7	3.0-6.3	<0.0001
Non-immigrants	1337	4561	29.3	28.0-30.6	

The mean age at episode of chronic hepatitis C was significantly higher in the drug dependent cases compared to the non-drug dependent cases in both immigrants and non-immigrants over the entire study period as shown in Table 5.4.

Table 5.4 Age at episode of those who were drug dependent and non-drug dependent by time period in immigrant and non-immigrant chronic hepatitis C cases

	Median	Mean	SD	P value
Immigrants				
1998-2000				
drug dependent	35.5	36.7	10.1	<0.0001
Non-drug dependent	46.0	49.0	16.2	
2001-2004				
drug dependent	40.0	38.9	11.9	0.0016
Non-drug dependent	45.0	46.7	14.9	
2005-2007				
drug dependent	31.5	33.7	11.4	<0.0001
Non-drug dependent	46.0	47.8	14.2	
Non-Immigrants				
1998-2000				
drug dependent	36.0	35.8	8.4	<0.0001
Non-drug dependent	43.0	45.4	15.1	
2001-2004				
drug dependent	38.0	37.5	9.0	<0.0001
Non-drug dependent	45.0	46.8	14.1	
2005-2007				
drug dependent	39.0	38.3	9.8	<0.0001
Non-drug dependent	46.0	47.0	12.8	

5.5 Complications

The proportion of cases with hepatitis C related complications (cirrhosis and HCC) differed significantly between immigrants and non-immigrants (Table 5.5). Proportions of all complications (compensated cirrhosis, decompensated cirrhosis, HCC and liver transplant) appeared higher in the immigrant population compared to the non-immigrant population; however, they were only

significantly different for compensated cirrhosis and HCC. The proportion of deaths (from any cause) was significantly greater in the non-immigrant population compared to the immigrant population, 13.6% vs. 8.3% ($p < 0.0001$), respectively. Attributable mortality was not verified but will be part of future analyses of this database.

In the hospitalization database, several reasons for hospitalization were analyzed. The proportion of cases hospitalized for any condition during the study period was significantly greater for non-immigrants compared to immigrants. The proportion of cases ever hospitalized for a liver related condition during the study period was not significantly different in the immigrant population compared to the non-immigrant population ($p=0.475$). A significantly higher proportion of immigrants were hospitalized for HCC compared to non-immigrants ($p =0.001$). The proportion of cases hospitalized for compensated cirrhosis was almost significantly higher in immigrants compared to non-immigrants ($p=0.055$).

Table 5.5 Hepatitis C related complications from the physician billing and hospitalization databases in immigrant and non-immigrant chronic hepatitis C cases (Appendix 9.9)

Immigrants (N=1,980)			**Non-Immigrants (N=18,479)**		
Complications (Physician Billings Database)					
	Percent	**95% CI**	**Percent**	**95% CI**	**P-value**
Compensated Cirrhosis	15.1	13.5-16.7	12.9	12.4-13.4	0.007
Decompensated Cirrhosis	2.4	1.7-3.0	1.8	1.6-2.0	0.087
HCC	1.2	0.7-1.6	0.6	0.5-0.7	0.005
Liver Transplant	0.1	0.0-0.1	0.0	0.0-0.01	0.973
Death	8.3	7.1-9.5	13.6	13.1-14.1	< 0.0001
Hospitalizations (Med-Echo Database)					
For any condition	43.6	41.4-45.8	60.0	59.3-60.7	<0.0001
For any liver related condition	6.6	5.5-7.7	6.2	5.8-6.5	0.475
Specific liver conditions:					
Compensated Cirrhosis	5.5	4.5-6.5	4.6	4.3-4.9	0.055
Decompensated Cirrhosis	3.1	2.4-3.9	3.5	3.2-3.7	0.433
HCC	1.8	1.2-2.4	1.0	0.9-1.2	0.001

Chapter 6: Discussion

In this study, the overall reported rate of chronic hepatitis C was similar for immigrants and non-immigrants [rates/100,000 (95%CI) 25.2 (24.1-26.4) vs. 27.8 (27.4-28.2), rate ratio= 0.91]. Immigrants from several world regions, however, had higher rates of chronic hepatitis C as compared to the non-immigrant population; Eastern Europe/Central Asia [77.6 (68.2-87.0) rate ratio = 2.8], Sub-Saharan Africa [60.2 (51.5-68.8), rate ratio = 2.2], South Asia [48.1 (41.5-54.7), rate ratio = 1.7]. There was an important delay in diagnosis for immigrants with a mean of 8.3 $\pm$ 6.9 years after arrival to Canada before the diagnosis was made. A higher proportion of Immigrant cases had hepatitis C related complications compared to non-immigrant cases. In addition, immigrant cases were less likely to be drug dependent as compared to non-immigrant cases (4.9% vs. 34.6%) and therefore do not demonstrate the classical risk factor associated with hepatitis C most commonly found in Canada. These findings highlight that immigrants from several world regions were at an increased risk for chronic hepatitis C and could therefore benefit from early screening.

6.1 Main findings

The reported rate of chronic hepatitis C cases significantly decreased in non-immigrants over the study period. However, there was not a similar decrease in the chronic HCV rate in the immigrant population. Higher estimated rates of chronic HCV in the non-immigrant population at the beginning of the study period may have been due to look back studies conducted throughout Canada. These studies were aimed at detecting recipients of blood from donors who donated blood and were later tested as being HCV positive, and individuals who received blood before routine HCV screening was implemented in order to advise them to undergo HCV testing (**35, 109-112**). These retrospectively detected cases of hepatitis C in the non-immigrant population may have contributed to the higher rate of reported hepatitis C at the start of the study period.

Rates of reported chronic hepatitis C were found to be significantly higher in immigrants from certain regions of origin as compared to non-immigrants. The following four regions of origin had the highest rates of chronic hepatitis C: Eastern Europe/Central Asia [rates/100,000 (95% CI) = 77.6 (68.2-87.0) rate ratio = 2.8], Sub-Saharan Africa [60.2 (51.5-68.8), rate ratio = 2.2], South Asia [48.1 (41.5-54.7), rate ratio = 1.7, East Asia and Pacific [30.7 (27.2-34.1), rate ratio=1.1]. Region of origin is an important predictor of hepatitis C in the

immigrant population as the prevalence of hepatitis C varies in different global regions (**27**). Most reported hepatitis C seroprevalence studies are performed in select populations such as blood donors, and not the general population. These select populations may either have increased or decreased risk of hepatitis C and their results may therefore not be representative of the general population (**113**). The WHO reported the highest prevalence rates of HCV in Africa and the Eastern Mediterranean (Table 2.2) (**27**), consistent with the high reported rates of HCV found in this study.

Country specific rates of reported chronic hepatitis C demonstrated the variation of hepatitis C risk within regions of origin (see Appendix 9.8). Immigrants from the USSR, Democratic Republic of Congo, Rwanda and Pakistan were found to have the highest rates of chronic hepatitis C over the study period. High HCV rates in these immigrant populations are due to the high prevalence rates of HCV in their countries of origin. The mode of HCV transmission is a major cause of the disparity in HCV prevalence between developed and developing countries. In developed countries, the main source of HCV infections is IDU, while in developing countries the main modes of transmission are unsafe therapeutic injections and blood transfusions (**113**). Overall, reported rates of chronic HCV stratified by immigrants' region of origin and country illustrate important groups of immigrants at greater risk for chronic hepatitis C.

Immigrant cases of chronic hepatitis C were found to be significantly older compared to non-immigrants upon diagnosis, with a mean age (±SD) of 47.1 ± 15.1 years compared to 43.1 ±13.4 years ($p < 0.0001$). In addition, the age specific rates of chronic hepatitis C in immigrants aged 60-66 and 70-79 were significantly higher compared to non-immigrants (see Appendix 9.6). The higher rate of chronic hepatitis C in older immigrants compared to non-immigrants suggests the presence of a delay in the detection of HCV infection in the immigrant population. Analysis of the mean time between arrival to Canada and diagnosis of chronic hepatitis C shows that there is indeed a delay period. The mean time between arrival and diagnosis of chronic hepatitis C in immigrants was 8.3 ± 6.9 years over the study period.

Hepatitis C related complications; cirrhosis and HCC are known to develop in the late stages of the disease, many years after onset of infection. Cirrhosis usually develops 20 years after onset of infection, while HCC develops after 30-50 years (**1, 17**). It has been shown that older age (>55 years) is an independent factor associated with the development of HCC among patients with HCV-related cirrhosis (**114**). In addition, a study illustrated that incidence rates of HCC increase with age reaching a maximum in 75-85 year olds (**8**). The immigrant population in the study was older in comparison to non-immigrants and a greater proportion of immigrant chronic hepatitis C cases were diagnosed with liver associated complications during the study period compared to non-

immigrant cases. This supports the hypothesis that there was a delay in the diagnosis of chronic hepatitis C in the immigrant population compared to the non-immigrant population, leading them to be diagnosed later in life, and therefore have a higher proportion of hepatitis related complications. In contrast, the higher risk of hospitalization for HCC among immigrant cases could have been due to a higher proportion of individuals who were co-infected with hepatitis B compared to non-immigrant cases.

The delayed detection of hepatitis C in immigrants compared to non-immigrants is likely due to recognition that many immigrants are at risk for hepatitis C but lack the classical risk factor of IDU. Chronic hepatitis C is an asymptomatic disease, until its later stages. Individuals are therefore unlikely to know if they are infected unless they interact with the health care system or if a health care worker thinks of screening for the disease. IDU is a recognized risk factor for chronic hepatitis C. Therefore, IDUs may be diagnosed with hepatitis C either during the asymptomatic stage because their health care providers screen for the illness or if they present with symptoms of hepatitis C related complications. On the other hand, most immigrants will only be detected when they are symptomatic with complications of hepatitis C. Immigrants may also encounter several barriers when attempting to access health care, not experienced by the non-immigrant population, which may contribute to the delay in diagnosis. These barriers include language, location, community

awareness and cultural sensitivity. A study conducted in Toronto found that the three main barriers to health care access cited by immigrants were geographic, economic and socio-cultural in nature (**115**). In addition, the delay in diagnosis of chronic hepatitis C in immigrants may be due to the delayed health seeking behavior among immigrants who have been previously diagnosed, but are unaware of treatment options available to them in Canada. Immigrants may also be diagnosed when they become symptomatic many years after having been infected in their countries of origin.

A significantly greater proportion of non-immigrant chronic hepatitis C cases died during the study period in comparison to immigrant cases, 13.6% (13.1%-14.1%) vs. 8.3% (7.1%-9.5%), respectively. However, as these were deaths from any cause they may not be attributable to chronic hepatitis C. Further analysis is needed to look at the cause of death and other co-morbidities. This difference in deaths between immigrant and non-immigrant chronic hepatitis C cases could be in part due to life style risk factors associated with chronic hepatitis C, such as IDU or other associated co-morbidities such as HIV, and hepatitis B. A total of 4.9% (3.9%-5.8%) of immigrant chronic hepatitis C cases were drug dependent, while a significantly higher proportion of non-immigrant cases were drug dependent 34.6% (33.9%-35.3%). This large difference between immigrants and non-immigrants was expected, as IDU is known to be the main mode of HCV transmission in Canada while the primarily

mode of HCV transmission in immigrant source countries is unsafe injections or medical procedures such as surgery or blood transfusions. In order to attribute the chronic hepatitis C in non-immigrants to drug dependence, it would have been ideal to have a control population of non-immigrants without chronic hepatitis C in order to compare the two groups. A control population was not available for this analysis; however, using the prevalence of IDU in Montreal as a surrogate, only 0.66% of individuals living in Montreal were IDUs in a study conducted in 1996 (**116**). There are no similar data on IDUs in the immigrant population. However, we would not expect this prevalence to be substantially higher than that in the general population in Montreal or Canada. The large difference in the proportion of drug dependence between immigrants and non-immigrants found in this study is an important difference between the two groups.

6.2 Study strengths and limitations

6.2.1 Population based databases and generalizability

A major strength of this study is that it is the first ever population-based study of chronic hepatitis C in immigrants in Canada. The use of the RAMQ health administrative data provided a population-based sample, as >99% of all persons living in Québec and >90% of all immigrants were present in this database. This is due to health care coverage being provided free to all

permanent residents of Québec. All cases of chronic hepatitis C were obtained from the MADO database, a complete and accurate database of reported cases of viral hepatitis in Québec. The MICC database contained >90% of all immigrants (permanent residents) arriving in Québec. The RAMQ databases provided information regarding demographic data, medical services provided and dispensed medication, while the Med-Echo database contained information on all hospital admissions for the cases. Linkage with the MICC database provided a unique opportunity to describe rates by immigration status (immigrant vs. non-immigrant) and country of origin, an important predictor of hepatitis C, as these variables are not present in reportable infectious disease surveillance data in Canada or Québec. The use of Québec census data ensured the inclusion of the entire Québec population. Conducting a population-based study provided large sample sizes in addition to generalizable results to the entire Québec population.

Another strength of this study is the accuracy of the diagnosis of hepatitis C, since all cases of chronic hepatitis C reported in the MADO database are serologically confirmed. The ten-year study duration provided a large sample size of chronic hepatitis C cases, a long enough time frame to detect hepatitis C related complications and to examine the trend of chronic hepatitis C over time.

The results of this study are representative of all the Québec immigrant population and are likely generalizable to other immigrant populations in Canada

or other countries given rates were stratified by age, sex and region and country of origin. However, it is possible that immigrants from the same region of origin but who settle in different provinces in Canada or other world regions may have different characteristics or hepatitis C risk factors, other screening policies or access to health care.

6.2.2 Limitations due to passive HCV surveillance

The major limitation of this study is the method of hepatitis C detection in cases reported in the MADO database. Viral hepatitis cases are detected through a passive public health surveillance system, therefore newly reported rates do not reflect the true incidence of chronic hepatitis C in the population. Due to the absence of a systematic screening program for viral hepatitis, the passive surveillance system depends on physician testing or screening for hepatitis C. Physician screening will be influenced by perceived risk factors associated with hepatitis C or a symptomatic disease resulting to an under detection of cases. Cases in the MADO database are therefore likely detected either because an individual presents with symptoms consistent with hepatitis C, or is asymptomatic but undergoes screening due to the presence of risk factors for viral hepatitis (e.g. IDU, HIV) or is screened during the work up for another condition that causes increased liver enzymes.

Passive surveillance leads to an underestimation of rates of chronic hepatitis C due to underreporting of the asymptomatic disease. The reported

rates of chronic hepatitis C in our study are therefore underestimates of the true incidence of the disease. Passive surveillance will most likely sufficiently detect the long-term sequelae of hepatitis C due to their symptomatic nature and need for medical attention.

6.2.3 Limitations due to non-linkage and missing data

A large proportion (20%) of chronic hepatitis C cases (N=5,142) identified In the MADO database over the study period did not link to the FIPA database (see Appendix 9.3). These individuals were not part of the linked analysis and therefore could not be classified as immigrant or non-immigrant cases. Although overall rates in the MADO database were calculated and presented these unlinked cases lead to further underestimation of the true rates of chronic hepatitis C and associated complications in immigrants and non-immigrants. It is also unclear if among these unlinked cases the proportions of immigrant and non-immigrant cases are the same as those in the linked cases.

Almost 23% of chronic hepatitis C cases (N=447) (case series 2) were found in the MADO and RAMQ databases but could not be linked to the MICC database (see Appendix 9.3). Due to non-linkage with the MICC database rates of chronic hepatitis C by region of origin were further underestimated.

The variable used to estimate the proportion of drug dependence in the immigrant and non-immigrant chronic hepatitis C cases has not been validated and is a surrogate of intravenous drug use. Therefore, the resulting proportions

may either be an over or underestimate of the true proportion of IDUs in chronic hepatitis C cases.

6.3 Future and additional planned analyses

In order to better understand the health condition of the case series, the role of co-infection with HIV and hepatitis B will be analyzed for immigrant and non-immigrant cases of chronic hepatitis C. In addition further analyses to determine attributable mortality are planned by examining other diagnostic codes in the Med-Echo hospitalization database reported at the time of death of each case. Immigrant class (immigrant vs. refugee), a potentially important predictor of hepatitis C will also be included in future analyses.

To address the limitation of unlinked cases, a multiple imputation model is planned to determine what proportion of the unlinked chronic hepatitis C cases (cases in MADO that did not link to FIPA) occurred in immigrants vs. non-immigrants. We also plan to perform a survival analysis and describe predictors of hepatitis C in immigrants including immigrant class (refugee vs. immigrant) and adjust this by region of origin, age and sex in a Cox Regression using this case series of chronic hepatitis C cases in immigrants and the cohort of immigrants who arrived in Québec during the study period.

6.4 Policy implications

Immigrants are an important and growing segment of the Canadian population who have increased mortality from viral hepatitis and hepatocellular carcinoma as compared to the Canadian born population. Despite this disparity the epidemiology of viral hepatitis is poorly described in this population. The finding that immigrants from several regions of origin have greater reported rates of chronic hepatitis C, higher rates of associated complications as compared to the non-immigrant population and a long delay in time to diagnosis after arrival (>8 years) highlights the need for implementation of hepatitis C screening programs for the immigrant population as soon as possible after arrival in Canada.

There are currently no programs in Canada that screen for viral hepatitis in the immigrant population either before or after arrival to Canada. The older age at detection and the higher rate of complication suggests that there is a delay in diagnosis of hepatitis C in immigrants. This study shows that immigrants would benefit from early screening for hepatitis C so that progression to long term complications such as cirrhosis and HCC with their associated morbidity and mortality can be avoided.

A recent study by Coffin et al. on the cost-effectiveness of general population screening for hepatitis C stated that general population screening was cost-effective as long as HCV seropositivity in the tested population was

over 0.5% (**117**). As the HCV seroprevalence in the immigrant population is approximately 2% (**107**) most immigrant groups would benefit from screening for hepatitis C, furthermore society as a whole would benefit.

Chapter 7: Conclusion and Summary

Immigrants are an important and growing part of the Canadian population. The majority of newly arrived immigrants over the past 40 years have originated from countries with higher rates of chronic hepatitis C as compared to Canada (approximately 2% vs. 0.8%). Although, immigrants have been shown to have higher mortality from viral hepatitis (20% of which is likely due to chronic hepatitis C) and hepatocellular carcinoma compared to those born in Canada there are currently no screening programs to detect chronic hepatitis C in immigrants after arrival.

This study analyzed and compared reported rates of chronic hepatitis C in the immigrant and non-immigrant population between 1998-2007. Rates of chronic hepatitis C decreased in non-immigrants over the study period; however, rates did not significantly change in the immigrant population. Immigrants from several world regions had higher rates of chronic hepatitis C as compared to the non-immigrant population: Eastern Europe/Central Asia [rates/100,000 (95%CI) =77.6 (68.2-87.0) rate ratio = 2.8], Sub-Saharan Africa [0.2 (51.5-68.8), rate ratio = 2.2], South Asia [48.1 (41.5-54.7), rate ratio = 1.7]. In addition, immigrant chronic hepatitis C cases had higher proportions of hepatitis C associated complications compared to non-immigrant cases: compensated cirrhosis (15.1% vs.12.9, p= 0.007) and hepatocellular carcinoma (1.2% vs. 0.6%, = 0.005).

The older age of immigrants at diagnosis of chronic hepatitis C and the higher proportion of hepatitis C related complications compared to the non-immigrant population suggests that there is an important delay in the detection of hepatitis C in immigrants. Due to the largely asymptomatic nature of hepatitis C, the main reasons for detection are the presence of risk factors or complications associated with hepatitis C. Immigrants, arriving largely from developing countries, contract hepatitis C through different modes compared to the non-immigrant population and thus the majority do not exhibit characteristic risk factors of hepatitis C, e.g. IDU. The data in our study clearly showed that drug dependence is much less common in immigrants who are diagnosed with chronic hepatitis C as compared to non-immigrant cases (4.9% vs. 34.6%). Therefore, it is important to inform Canadian health care providers that immigrants are an important group of individuals at risk for hepatitis C, even in the absence of IDU, who would benefit from screening. Further analysis of this database will provide additional information as to the attributable morality in immigrants and non-immigrants, the role of co-infection with HIV and hepatitis B and describe the magnitude of contributing risk from different predictors of hepatitis C in this population such as immigrant class, age, sex and region of origin.

The results of this study confirm that immigrants are an important group at risk for chronic hepatitis C and its associated complications. However, the

diagnosis of chronic hepatitis C in immigrants is often delayed and the disease is under-diagnosed in this population. The availability of new effective therapies for hepatitis C have made early screening and appropriately timed therapy an important strategy in decreasing hepatitis C associated morbidity and mortality. A large portion of immigrants could therefore benefit from screening as soon as possible after arrival in Canada to ensure that those infected with chronic hepatitis C can be detected early and associated complications prevented.

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Chapter 9: Appendices

Appendix 9.1 Case definitions of viral hepatitis in Maladies à Déclaration Obligatoire (MADO) (118)

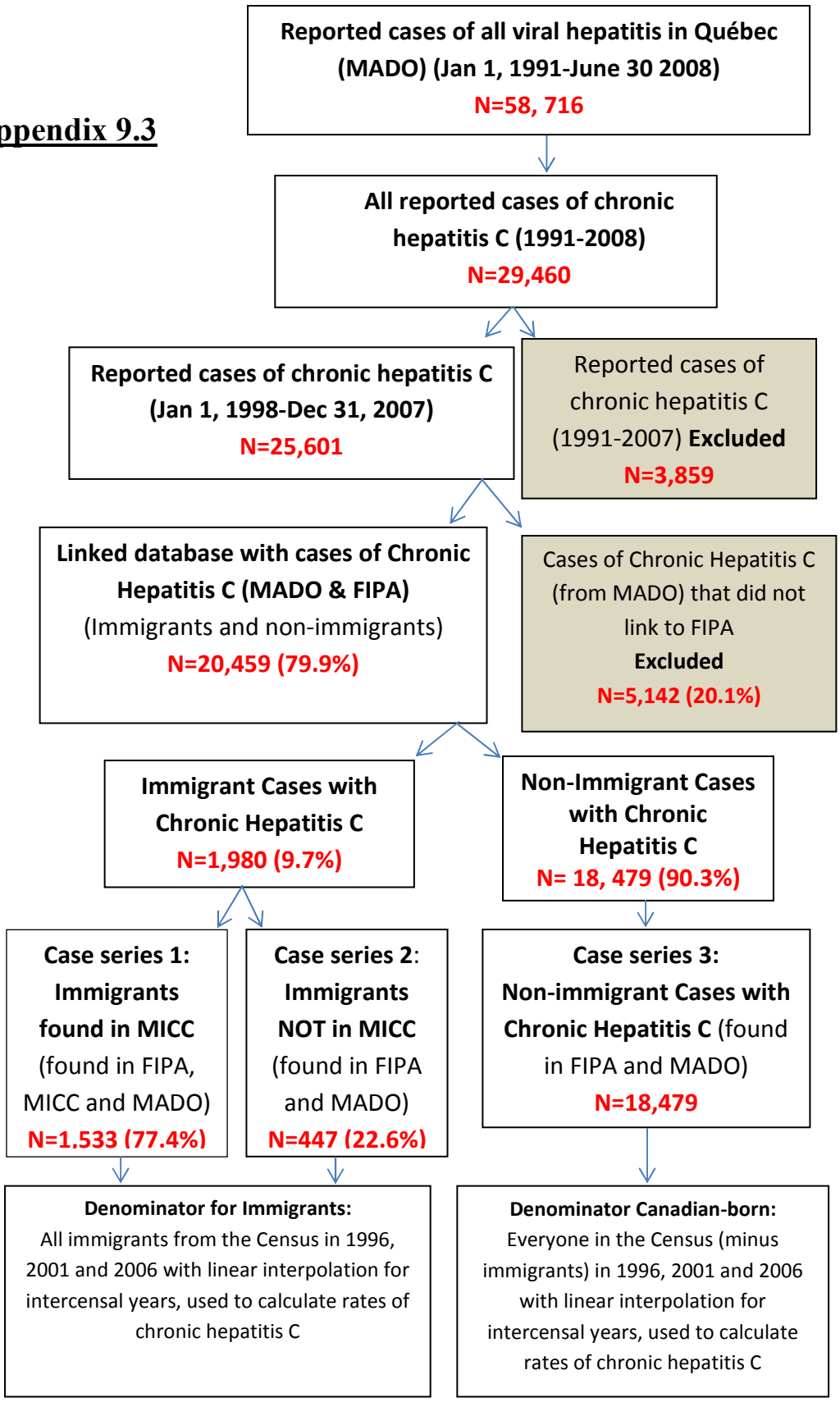
All cases are confirmed by serologic markers and are definite cases of hepatitis C. The category of confirmed vs. probable refers to stage of disease (acute, chronic or indeterminate) based on availability of clinical information

HEPTATITIS C	
ACUTE HEPATITIS C	
Confirmed case	In an individual > 1 year of age with the following 7 conditions: 1. Clinical picture consistent with acute hepatitis (ie. jaundice, dark urine) or increase in hepatitis enzymes AST or ALT AND 2. Increase in hepatic enzymes AST or ALT more than 2.5 times the upper limit of normal AND 3. Serologic detection of anti-Hepatitis C IgG and confirmed with a second test such as another EIA or a RIBA or detection of Hepatitis C DNA by PCR 4. Hepatitis A IgM negative 5. Anti-HBc IgM negative and HBsAg negative 6. Exposure in the previous 6 months of a specific source of transmission* 7. No other apparent cause for hepatitis OR Seroconversion from hepatitis C Ab negative to hepatitis C Ab positive within 6 months of a known exposure OR In a newborn less than 1 year of age, detection of hepatitis C DNA by PCR * Intravenous drug use, receipt of blood products, sexual contact with a know hepatitis C positive individual
UNDETERMINATED STAGE OF HEPATITIS C	
Confirmed Case	In a person > 1 year of age an there is not sufficient information as outlined above to classify as an acute case of hepatitis C, are required to have the two following conditions: 1. Serologic detection of anti-Hepatitis C confirmed either by another EIA or by a RIBA OR 2. Detection of hepatitis C DNA by PCR

Appendix 9.2 Variables in the databases used in the study

Database	Primary Use in this study	Data Variables to be used
MADO Database (« Maladies à déclaration obligatoire » ie Mandatory Reportable Infectious Disease Database of Québec)	Case Ascertainment	RAMQ# (75%), age, gender, date of birth, ***Disease classification:*** 1) acute hepatitis A, 2) acute, chronic or indeterminate hepatitis B 3) acute, chronic or indeterminate hepatitis C Date disease reported, Public health jurisdiction reported in
MICC Database (Landed Immigrant Database of the Ministère de l'Immigration et des Communautés Culturelles)	Classify cases as immigrant or Canadian-born Provide denominator data for the immigrant population	VISA# , date of landing , date of arrival date of birth, gender , country of birth , immigration class [immigrants (economic, family reunification or other) or refugees], intended occupation, level of education
Fichier d inscription des personnes assurées (FIPA) Database (RAMQ)	Demographics of the population Link to MADO, and other RAMQ (by RAMQ#) and to MICC (by VISA #).	RAMQ# , VISA# , age, gender, postal code (first three digits), income/education indicators from postal code area, date of death, date coverage terminated
Fichier des Services Médicaux Database (RAMQ)	Health care utilization and cost data for out and in patients	RAMQ # , date of claim, location of service (hospital, ER, outpatient), type of service (visit, procedure with surgical and diagnostic procedures coded according the Canadian classification of diagnostic, therapeutic and surgical procedures), diagnosis of conditions coded with ICD-9-CM diagnostic code as provided by a physician, date of service, specialty of MD, reimbursement for the claim.
Fichier de services pharmaceutiques Database (RAMQ)	Medication utilization	Drug name, drug identification number (DIN#), drug form, duration prescribed, quantity of drug dispensed, date prescribed
Med-Echo Database *(Maintenance et Exploitations des Données pour l'Étude de la Clientèle Hospitalière ie Hospital Services Database)*	Health care utilization and cost data for inpatients	RAMQ# , date of admission, place of admission (ward/ICU/ER),admission diagnosis (ICD-9-CM codes), in-hospital procedures (eg surgery, liver biopsy etc), speciality of MD, primary and secondary discharge diagnoses (ICD-9-CM codes), date of discharge, reimbursement for the claim.

Appendix 9.3


Reported cases of all viral hepatitis in Québec (MADO) (Jan 1, 1991-June 30 2008)
N=58, 716
All reported cases of chronic hepatitis C (1991-2008)
N=29,460
Reported cases of chronic hepatitis C (Jan 1, 1998-Dec 31, 2007)
N=25,601
Reported cases of chronic hepatitis C (1991-2007) Excluded
N=3,859
Linked database with cases of Chronic Hepatitis C (MADO & FIPA)
(Immigrants and non-immigrants)
N=20,459 (79.9%)
Cases of Chronic Hepatitis C (from MADO) that did not link to FIPA
Excluded
N=5,142 (20.1%)
Immigrant Cases with Chronic Hepatitis C
N=1,980 (9.7%)
Non-Immigrant Cases with Chronic Hepatitis C
N= 18, 479 (90.3%)
Case series 1: Immigrants found in MICC (found in FIPA, MICC and MADO)
N=1.533 (77.4%)
Case series 2: Immigrants NOT in MICC (found in FIPA and MADO)
N=447 (22.6%)
Case series 3: Non-immigrant Cases with Chronic Hepatitis C (found in FIPA and MADO)
N=18,479
Denominator for Immigrants:
All immigrants from the Census in 1996, 2001 and 2006 with linear interpolation for intercensal years, used to calculate rates of chronic hepatitis C
Denominator Canadian-born:
Everyone in the Census (minus immigrants) in 1996, 2001 and 2006 with linear interpolation for intercensal years, used to calculate rates of chronic hepatitis C

Appendix 9.4 World Bank regions

East Asia/ Pacific (1):
American Samoa, Belau, Brunei, China, Cook Islands, Fiji, French Polynesia, Guam, Hong Kong, Indonesia, Japan, Kampuchea, Kiribati, Laos, Macao, Malaysia, Marshall Islands, Micronesia, Mongolia, Myanmar, Nauru, New Caledonia, North Korea, Philippines, Pitcairn Island, Singapore, Solomon Islands, South Korea, Taiwan, Thailand, Tonga, Tuvalu, US Pacific Trust Territories, Vanuatu, Vietnam, Wallis and Fatuna, Western Samoa

Latin America/ Caribbean (2):
Anguilla, Antigua, Argentina, Aruba, Bahamas, Barbados, Belize, Bermuda, Bolivia, Brazil, Cayman Islands, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Falkland Islands, French Guyana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Netherlands Antilles, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, St. Christopher and Nevis, St. Lucia, St. Vincent and the Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands, Uruguay, Venezuela, Virgin Islands (US), Virgin Islands (British)

Middle East/ North Africa (3):
Algeria, Djibouti, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates, Western Sahara, Yemen

South Asia (4):
Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka

Sub-Saharan Africa (5):
Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde Islands, Central African Republic, Chad, Comoros, Congo, Cote D'Ivoire, Equitorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mayotte, Mozambique, Namibia, Niger, Nigeria, Réunion, Rwanda, Sao Tomé and Principe, Senegal, Seychelles, Sierra Leone, Somali, South Africa, St. Helena and Ascension, Sudan, Swaziland, Tanzania, Togo, Uganda, Zaire, Zambia, Zimbabwe

Western Europe (6):
Andorra, Austria, Belgium, Cyprus, Czech and Slovak Republic, Denmark, Finland, France, Germany, Gibraltar, Greece, Hungary, Iceland, Ireland, Italy, Leichtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, San Marino, Spain, Sweden, Switzerland, United Kingdom, Vatican City State, Yugoslavia

Eastern Europe/ Central Asia (7):
Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia, Moldova, Russian Federation, Romania, Tajikistan, Turkey, Turkmenistan, Ukraine, USSR, Uzbekistan

Australia/ New Zealand (8):
Australia, New Zealand

Unites States (9):
Unites States of America

Other (10):
Greenland, St. Pierre and Miquelon, Other

Canada (11):
Newfoundland, PEI, Nova Scotia, New Brunswick, Québec, Ontario, Manitoba, Saskatchewan, Alberta, British Columbia, Yukon Territories, Northwest Territories

Appendix 9.5. Rates of chronic hepatitis C in the MADO database

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL
1991	39	7021766	0.56	0.38	0.73
1992	54	7064926	0.76	0.56	0.97
1993	118	7111985	1.66	1.36	1.96
1994	173	7148460	2.42	2.06	2.78
1995	343	7175946	4.78	4.27	5.29
1996	502	7204295	6.97	6.36	7.58
1997	1707	7232193	23.60	22.48	24.72
1998	2923	7253733	40.30	38.84	41.76
1999	3081	7281240	42.31	40.82	43.81
2000	3091	7315099	42.26	40.77	43.74
2001	2843	7354609	38.66	37.24	40.08
2002	2475	7397706	33.46	32.14	34.77
2003	2196	7440804	29.51	28.28	30.75
2004	2665	7489181	35.58	34.23	36.94
2005	2349	7533457	31.18	29.92	32.44
2006	2152	7581350	28.39	27.19	29.58
2007	1826	7636022	23.91	22.82	25.01
2008**	923	3849333	23.98	22.43	25.53
Age Group[+]					
< 1 year	239	769592	31.06	27.12	34.99
1 - 4 years	19	3186036	0.60	0.33	0.86
5 - 9 years	15	4461371	0.34	0.17	0.51
10 - 14 years	42	4789248	0.88	0.61	1.14
15 - 19 years	428	4818297	8.88	8.04	9.72

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL
20 - 29 years	2950	9520790	30.98	29.87	32.10
30 - 39 years	7039	10746911	65.50	63.97	67.03
40 - 49 years	8470	12568983	67.39	65.95	68.82
50 - 59 years	3438	10225832	33.62	32.50	34.74
60 - 69 years	1461	6787052	21.53	20.42	22.63
70 - 79 years	1093	4550230	24.02	22.60	25.44
80 - 89 years	378	1674089	22.58	20.30	24.86
≥ 90 years	29	178419	16.25	10.34	22.17
Sex					
Male	19512	36400254	53.60	52.85	54.36
Female	9776	37883098	25.81	25.29	26.32
Total					

**2008 is half a year therefore the census denominator was divided by 2

[+]rates stratified by age were calculated for the years 1998-2007, due to the low detection rates before this period.

Appendix 9.6. Rates of chronic hepatitis C in immigrants and non-immigrants (linked database) (1998-2007)

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
1998								
Immigrants	157	702440	22.4	18.9	25.8	0.7	0.6	0.8
Non-Immigrants	2096	6551293	32.0	30.6	33.4			
1999								
Immigrants	166	712239	23.3	19.8	26.9	0.7	0.6	0.8
Non-Immigrants	2249	6569001	34.2	32.8	35.7			
2000								
Immigrants	179	722718	24.8	21.1	28.4	0.7	0.6	0.9
Non-Immigrants	2197	6592381	33.3	31.9	34.7			
2001								
Immigrants	230	733828	31.3	27.3	35.4	1.1	0.9	1.2
Non-Immigrants	1952	6620781	29.5	28.2	30.8			
2002								
Immigrants	184	761044	24.2	20.7	27.7	0.9	0.8	1.0
Non-Immigrants	1791	6636662	27.0	25.7	28.2			
2003								

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Immigrants	168	788536	21.3	18.1	24.5	0.9	0.8	1.0
Non-Immigrants	1606	6652268	24.1	23.0	25.3			
2004								
Immigrants	251	816880	30.7	26.9	34.5	1.0	0.9	1.2
Non-Immigrants	2027	6672301	30.4	29.1	31.7			
2005								
Immigrants	261	845072	30.9	27.1	34.6	1.2	1.1	1.4
Non-Immigrants	1688	6688384	25.2	24.0	26.4			
2006								
Immigrants	208	873965	23.8	20.6	27.0	1.0	0.9	1.2
Non-Immigrants	1569	6707384	23.4	22.2	24.5			
2007								
Immigrants	176	888445	19.8	16.9	22.7	1.0	0.9	1.2
Non-Immigrants	1304	6747577	19.3	18.3	20.4			
Overall								
Immigrants	1980	7845168	25.2	24.1	26.4	0.9	0.9	1.0
Non-Immigrants	18479	66438033	27.8	27.4	28.2			
1998-2000								
Immigrants	502	2137397	23.5	21.4	25.5	0.7	0.6	0.8

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Non-Immigrants	6542	19712674	33.2	32.4	34.0			
2001-2004								
Immigrants	833	3100288	26.9	25.0	28.7	1.0	0.9	1.0
Non-Immigrants	7376	26582013	27.7	27.1	28.4			
2005-2007								
Immigrants	645	2607483	24.7	22.8	26.6	1.1	1.0	1.2
Non-Immigrants	4561	20143346	22.6	22.0	23.3			
Immigrants								
1998-2000								
<15	6	145040	4.1	0.8	7.4		-	-
15-49	290	1147774	25.3	22.4	28.2			
>49	206	844561	24.4	21.1	27.7			
2001-2004								
<15	5	212892	2.3	0.3	4.4			
15-49	537	1637597	32.8	30.0	35.6			
>49	291	1249773	23.3	20.6	26.0			
2005-2007							-	-
<15	1	186006	0.5	0	1.6			
15-49	416	1378514	30.2	27.3	33.1			
>49	228	1039940	21.9	19.1	24.8			

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Non-Immigrants								
1998-2000								
<15	52	3941578	1.3	1.0	1.7			
15-49	5192	10302753	50.4	49.0	51.8			
>49	1298	5468336	23.7	22.4	25.0			
2001-2004								
<15	37	5065225	0.7	0.5	1.0			
15-49	5467	13417428	40.7	39.7	41.8			
>49	1872	8099360	23.1	22.1	24.2			
2005-2007								
<15	15	3655507	0.4	0.2	0.6			
15-49	3171	9770915	32.5	31.3	33.6			
>49	1375	6713653	20.5	19.4	21.6			
Age								
< 1 year								
Immigrants	1	3948	25.3	0	75.0	3.5	0.5	25.5
Non-Immigrants	55	765644	7.2	5.3	9.1			
1 - 4 years								

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Immigrants	2	84009	2.4	0	5.7	4.9	1.1	21.5
Non-Immigrants	15	3102027	0.5	0.2	0.7			
5 - 9 years								
Immigrants	4	197309	2.0	0.0	4.0	17.3	4.6	64.4
Non-Immigrants	5	4264062	0.1	0.0	0.2			
10 - 14 years								
Immigrants	5	258672	1.9	0.2	3.6	3.0	1.2	7.8
Non-Immigrants	29	4530576	0.6	0.4	0.9			
15 - 19 years								
Immigrants	18	313822	5.7	3.1	8.4	0.9	0.5	1.4
Non-Immigrants	293	4504475	6.5	5.8	7.2			
20 - 29 years								
Immigrants	146	895731	16.3	13.7	18.9	0.7	0.6	0.8
Non-Immigrants	1994	8625059	23.1	22.1	24.1			
30 - 39 years								
Immigrants	483	1502263	32.2	29.3	35.0	0.6	0.5	0.6
Non-Immigrants	5059	9244648	54.7	53.2	56.2			
40 - 49 years								
Immigrants	596	1452069	41.0	37.7	44.3	0.7	0.6	0.8
Non-Immigrants	6484	11116914	58.3	56.9	59.7			
50 - 59 years								

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Immigrants	323	1267267	25.5	22.7	28.3	0.9	0.8	1.0
Non-Immigrants	2579	8958565	28.8	27.7	29.9			
60 - 69 years								
Immigrants	199	932743	21.3	18.4	24.3	1.3	1.1	1.5
Non-Immigrants	991	5854309	16.9	15.9	18.0			
70 - 79 years								
Immigrants	152	661852	23.0	19.3	26.6	1.2	1.0	1.5
Non-Immigrants	717	3888378	18.4	17.1	19.8			
80 - 89 years								
Immigrants	48	238695	20.1	14.4	25.8	1.2	0.9	1.6
Non-Immigrants	243	1435394	16.9	14.8	19.1			
≥ 90 years								
Immigrants	3	33716	8.9	0	19.0	0.9	0.2	3.0
Non-Immigrants	15	144703	10.4	5.1	15.6			
Age groups								
<15								
Immigrants	12	543938	2.2	1.0	3.5	2.7	0.8	9.5
Non-Immigrants	104	12662309	0.8	0.7	1.0			
15-49								
Immigrants	1243	4163885	29.9	28.2	31.5	0.7	0.1	4.4

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Non-Immigrants	13830	33491096	41.3	40.6	42.0			
>49								
Immigrants	725	3134273	23.1	21.4	24.8	1.0	0.2	6.3
Non-Immigrants	4545	20281349	22.4	21.8	23.1			
World Region								
East Asia & Pacific	303	988056	30.7	27.2	34.1	1.1	1.0	1.2
Latin American & Caribbean	161	1412661	11.4	9.6	13.2	0.4	0.4	0.5
Middle East & North Africa	225	1301523	17.3	15.0	19.5	0.6	0.5	0.7
South Asia	204	424316	48.1	41.5	54.7	1.7	1.5	2.0
Sub-Saharan Africa	187	310781	60.2	51.5	68.8	2.2	1.9	2.4
Western Europe	169	2785889	6.1	5.2	7.0	0.2	0.2	0.3
Eastern Europe & Central Asia	262	337740	77.6	68.2	87.0	2.8	2.5	3.2
United States	20	269177	7.4	4.2	10.7	0.3	0.2	0.4
Canada	1	8811	11.3	0	33.6	0.4	0.06	2.9
SEX								
Male								
Immigrants	1052	3861402	27.2	25.6	28.9	0.7	0.7	0.8
Non-Immigrants	12598	32538852	38.7	38.0	39.4			
Female								

Year	Number of Cases	Census Denominator	Reported rate (per 100,000)	Lower 95% CL	Upper 95% CL	Rate Ratio (IRR)	Lower 95% CL	Upper 95% CL
Immigrants	926	3983952	23.2	21.7	24.7	1.4	1.3	1.5
Non-Immigrants	5881	33899146	17.3	16.9	17.8			

Note: Age Calculated as age at time of chronic hepatitis episode

Appendix 9.7 Countries of birth for each region of origin for cases of chronic hepatitis C (1998-2007)

	Country of Birth	Frequency	Percentage
East Asia & Pacific	Viet Nam	147	48.51
	Cambodge	73	24.09
	Chine	33	10.89
	Philippines	14	4.62
	Laos	10	3.30
	Taïwan	9	2.97
	Hong Kong	5	1.65
	Japon	5	1.65
	Thaïlande	3	0.99
	Corée du Sud	2	0.66
	Malaisie	1	0.33
	Myanmar	1	0.33
	Total	**303**	**100**
Latin American & Caribbean	Haïti	84	52.17
	Mexique	13	8.07
	Pérou	9	5.59
	Rép. dominicaine	7	4.35
	Guatemala	6	3.73
	Brésil	6	3.73
	Argentine	6	3.73
	Colombie	5	3.11
	Venezuela	4	2.48
	El Salvador	4	2.48
	Cuba	3	1.86
	Uruguay	2	1.24
	Honduras	2	1.24
	Chili	2	1.24
	Trinité-et-Tobago	1	0.62
	Porto Rico	1	0.62
	Paraguay	1	0.62
	Nicaragua	1	0.62
	Jamaïque	1	0.62
	Guyana	1	0.62

	Country of Birth	Frequency	Percentage
	Costa Rica	1	0.62
	Bolivie	1	0.62
	Total	**161**	**100**
Middle East & North Africa	Maroc	78	34.67
	Égypte	53	23.56
	Algérie	25	11.11
	Iran	24	10.67
	Liban	21	9.33
	Tunisie	6	2.67
	Israël	6	2.67
	Syrie	6	2.67
	Iraq	4	1.78
	Palestine	1	0.44
	Arabie saoudite	1	0.44
	Total	**225**	**100**
South Asia	Pakistan	146	71.57
	Inde	27	13.24
	Afghanistan	15	7.35
	Bangladesh	11	5.39
	Sri Lanka	5	2.45
	Total	**204**	**100**
Sub-Saharan Africa	Rép. dém. du Congo	71	37.97
	Burundi	33	17.65
	Rwanda	27	14.44
	Cameroun	20	10.70
	Éthiopie	5	2.67
	Madagascar	4	2.14
	Tchad	3	1.60
	Guinée	3	1.60
	Kenya	2	1.07
	Congo	2	1.07
	Ghana	2	1.07
	Somalie	2	1.07
	Maurice	2	1.07
	Zimbabwe	1	0.53
	Tanzanie	1	0.53
	Angola	1	0.53
	Bénin	1	0.53
	Gabon	1	0.53

	Country of Birth	Frequency	Percentage
	Côte d'Ivoire	1	0.53
	Mali	1	0.53
	Mauritanie	1	0.53
	Nigéria	1	0.53
	Burkina Faso	1	0.53
	Soudan	1	0.53
	Total	**187**	**100**
Western Europe	France	84	49.70
	Italie	25	14.79
	Pologne	12	7.10
	Yougoslavie	8	4.73
	Portugal	7	4.14
	Espagne	7	4.14
	Allemagne	5	2.96
	Suisse	5	2.96
	Royaume-Uni	4	2.37
	Belgique	3	1.78
	Tchécoslovaquie	2	1.18
	Grèce	2	1.18
	Hongrie	2	1.18
	Estonie	1	0.59
	Suède	1	0.59
	Slovénie	1	0.59
	Total	**169**	**100**
Eastern Europe & Central Asia	Roumanie	104	39.69
	Russie	39	14.89
	Union soviétique	34	12.98
	Ukraine	28	10.69
	Rép. de Moldavie	14	5.34
	Kazakhstan	10	3.82
	Bulgarie	6	2.29
	Ouzbékistan	5	1.91
	Arménie	4	1.53
	Géorgie	4	1.53
	Turquie	3	1.15
	Kirghizistan	3	1.15
	Bosnie-Herzégovine	2	0.76
	Bélarus	2	0.76

	Country of Birth	Frequency	Percentage
	Tadjikistan	2	0.76
	Lettonie	1	0.38
	Azerbaïdjan	1	0.38
	Total	**262**	**100**
United States	États-Unis	20	100
	Total	**20**	**100**

Appendix 9.8 Rates of chronic hepatitis C reported in Québec for selected countries of birth (1998-2007)

Country	Number of Cases	Census denominator	Reported rate/ 100,000	Lower 95% CL	Upper 95% CL
Cambodia	73	84773	86.1	66.4	105.9
Vietnam	147	242819	60.5	50.8	70.3
Taiwan	9	30945	29.1	10.1	48.1
China	33	304005	10.9	7.2	14.6
Philippines	14	147670	9.5	4.5	14.4
Hong Kong	5	58636	8.5	1.1	16.0
South Korea	2	33128	6.0	-2.3	14.4
Dominican Republic	7	31412	22.3	5.8	38.8
Mexico	13	61896	21.0	9.6	32.4
Haiti	84	527461	15.9	12.5	19.3
Peru	9	80239	11.2	3.9	18.5
Colombia	5	81620	6.1	0.8	11.5
Egypt	53	159014	33.3	24.4	42.3
Morocco	78	259374	30.1	23.4	36.7
Iran	24	80825	29.7	17.8	41.6
Tunisia	6	48592	12.3	2.5	22.2
Algeria	25	212251	11.8	7.2	16.4
Syria	6	90401	6.6	1.3	11.9
Lebanon	21	321894	6.5	3.7	9.3
Pakistan	146	77157	189.2	158.5	219.9
Afghanistan	15	33011	45.4	22.4	68.4
Bangladesh	11	61606	17.9	7.3	28.4
India	27	156302	17.3	10.8	23.8
Democratic Rep. Of Congo	71	33770	210.2	161.3	259.1

Country	Number of Cases	Census denominator	Reported rate/ 100,000	Lower 95% CL	Upper 95% CL
Rwanda	27	13297	203.0	126.5	279.6
Burundi	33	16787	196.6	129.5	263.7
Cameroon	20	15949	125.4	70.4	180.4
Guinea	3	9487	31.6	-4.2	67.4
Somalia	2	6561	30.5	-11.8	72.7
Ghana	2	18719	10.7	-4.1	25.5
Senegal	0	13957	0.0	0.0	0.0
France	84	549450	15.3	12.0	18.6
Italy	25	707614	3.5	2.1	4.9
USSR	34	5385	631.4	419.2	843.7
Ukraine	28	47570	58.9	37.1	80.7
Romania	104	198036	52.5	42.4	62.6
Russia	39	78499	49.7	34.1	65.3
Turkey	3	59206	5.1	-0.7	10.8

Appendix 9.9 Proportions of complications and hospitalizations in chronic hepatitis C cases (1998-2007)

Immigrants (N=1,980)					Non Immigrants (N=18,479)					
MOD database	**cases**	**proportion**	**L-CI**	**U-CI**	**MOD database**	**cases**	**proportion**	**L-CI**	**U-CI**	**P value**
Compensated Cirrhosis	299	0.151	0.135	0.167	Compensated Cirrhosis	2390	0.129	0.124	0.134	**0.0067**
Decompensated Cirrhosis	47	0.024	0.017	0.030	Decompensated Cirrhosis	337	0.018	0.016	0.020	**0.0865**
HCC	23	0.012	0.007	0.016	HCC	114	0.006	0.005	0.007	**0.0047**
Liver Transplant	1	0.001	0.000	0.001	Liver Transplant	9	0.000	0.000	0.001	**0.9725**
Death	164	0.083	0.071	0.095	Death	2509	0.136	0.131	0.141	**< 0.0001**
Hospitalization database					**Hospitalization database**					
For any condition	863	0.436	0.414	0.458	**For any condition**	11085	0.600	0.593	0.607	**<0.0001**
For any liver related condition	130	0.066	0.055	0.077	**For any liver related condition**	1138	0.062	0.058	0.065	**0.475**
Specific liver conditions:					**Specific liver conditions:**					
Compensated Cirrhosis	109	0.055	0.045	0.065	Compensated Cirrhosis	841	0.046	0.043	0.049	**0.0552**
Decompensated Cirrhosis	62	0.031	0.024	0.039	Decompensated Cirrhosis	641	0.035	0.032	0.037	**0.4333**
HCC	36	0.018	0.012	0.024	HCC	186	0.010	0.009	0.012	**0.0009**