Application of the Health Care System to First Nations and Non-First Nations Patients with Chronic Hepatitis C

by

Julia Uhanova

A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfilment of the requirements of the degree of

Doctor of Philosophy

Department of Community Health Science

University of Manitoba

Winnipeg, Manitoba, Canada

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DEDICATION

To the most important people in my life: my parents, my husband and my daughter

with my deepest love and devotion

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ABSTRACT

Approximately 240,000–300,000 persons are infected with hepatitis C virus (HCV) in Canada. However, there are no data on hepatitis C incidence, clinical features and management in Canadian First Nations (FN). The present study examines the incidence and demographics of HCV in FN and non-First Nations (non-FN) persons and evaluates how HCV-infected Manitobans in these two subpopulations use the health care.

Objectives:

1. To describe the incidence of hepatitis C (HC) by comparing rates and demographics of HCV infection in FN and non-FN populations.
2. To compare the clinical features between HCV-infected FN and non-FN individuals.
3. To compare health care resources utilization (1) between FN and non-FN individuals with hepatitis C and (2) between hepatitis C cohort and the general population.

Methods: Multiple administrative and public health databases were linked to develop a comprehensive Hepatitis C Research Database. Between 1/1/1991 and 31/12/2002, 5018 HCV-positive Manitoba residents were identified. The demographically-matched population control cohort was drawn from the Population Registry. Demographic and clinical information, hospital separations, physician office visits, prescription drugs use, etc. were compared between FN and non-FN persons with HC as well as between HCV and non-HCV cohorts.

Results: FN persons with HC were more often female and younger than non-FN HCV-infected persons. While risk factors for the progression of HC to cirrhosis were doubled

in the FN group, decompensated disease and mortality were the same in both groups. FN persons with HC had higher rates of health care use overall (hospital and ambulatory care), but lower rates of liver disease-related health care use compared to non-FN persons with HC. Finally, FN patients received antiviral treatment less often than non-FN patients.

Conclusions: The results of this study confirm that the rates of HC are higher among FN compared to non-FN persons yet liver disease-related care was less frequent among this group despite similarities in clinical features. Persons with HC used more health care compared to non-infected Manitobans. The created database facilitates designing subsequent projects to further examine HCV in Manitoba, to forecast the future burden of the disease, and to formulate specific health programmes of prevention and care.

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GLOSSARY

AFN	Assembly of the First Nations
AI/AN	American Indians/Alaska Natives
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
anti-HCV	Antibodies to hepatitis C virus
AOR	Adjusted odds ratio
ASMR	Age-standardized mortality rate
AST	Aspartame aminotransferase
CAID	Community Acquired Infections Division
CDC	Communicable Disease Control
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CIDPC	Centre for Infectious Disease and Prevention Control
CIHR	Canadian Institutes of Health Research
CLD	Chronic liver disease
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CSC	Correctional Services Canada
DIN	Drug Identification Number
Dx	Diagnosis
EBV	Epstein-Barr virus
EHSSS	Enhanced Hepatitis Strain Surveillance System

EIA	Enzyme-linked immunoassay
ESLD	End-stage liver disease
EtOH	Alcohol
FN	First Nations
FNIHB	First Nations and Inuit Health Branch
FSA	Forward Sortation Area
HCC	Hepatocellular carcinoma
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HRS	Hepatorenal syndrome
ICD-9-CM	International classification of diseases, 9^{th} edition, clinical modifications
IDU	Injection Drug Use or User
IFN	Interferon
IFN-γ	Interferon Gamma
IL	Interleukin
INAC	Indian and Northern Affairs Canada
LCDC	Laboratory Centre for Disease Control
MCHP	Manitoba Centre for Health Policy
MHHL	Manitoba Health and Healthy Living
MHSC	Manitoba Health Registration Number

NAFLD	Non-alcoholic fatty liver disease
NANB	Hepatitis non-A non-B
NASH	Non-alcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NNDRS	National Notifiable Disease Reporting System
Non-FN	not a First Nation
OLT	Orthotopic liver transplant
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
PHIN	Personal Health Identification Number
PHN	Public Health Nurse
PPHB	Population and Public Health Branch
RIBA	Recombinant immunoblot assay
SBP	Spontaneous bacterial peritonitis
STD	Sexually transmitted disease
STI	Sexually transmitted infection
SVR	Sustained virological response
SVS	Status Verification System
TB	Tuberculosis
Tx	Treatment
VHIU	Viral Hepatitis Investigative Unit
VHSD	Viral Hepatitis Surveillance Database

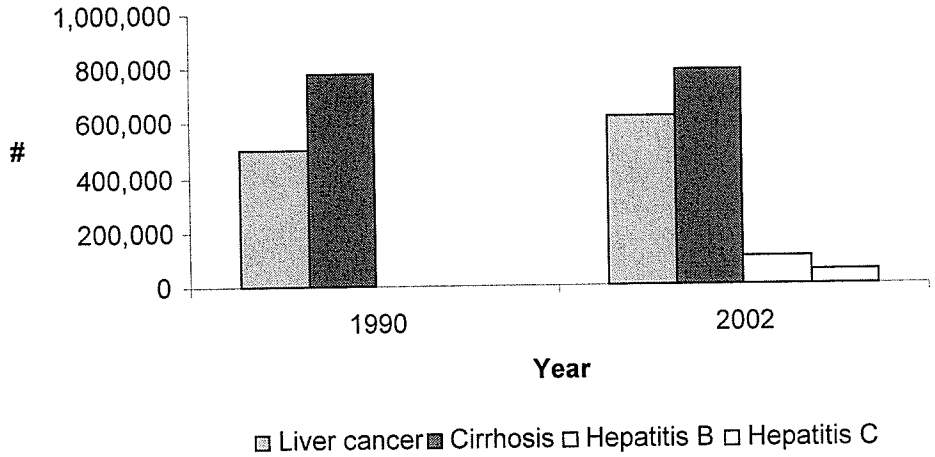
CHAPTER ONE BACKGROUND

1.1 VIRAL HEPATITIS

Viral hepatitis (VH) is a broad term for an inflammation of the liver caused by a viral agent. The resulting infection can be acute or chronic. The disease can be asymptomatic or it can manifest itself in a range from mild to fulminant form. Overall, viral hepatitis is one of major causes of hepatic morbidity and mortality. There are eight hepatotropic viruses recognized and described to date, and 5 of them are the viral hepatitis viruses – A, B, C, D, and E. Of these, hepatitis A, B, and C viruses are the most important, both in terms of the magnitude of spread and the severity of the diseases they cause. Many millions of people are affected by viral hepatitis each year. The World Health Organization (WHO) estimates that nearly 1.4 million cases of hepatitis A occur in the world yearly[1]. It is estimated that 350 million people are chronically infected with hepatitis B virus (HBV) worldwide, and another 180 million people are chronically infected with hepatitis C virus (HCV)[2,3]. There are 4 million acute clinical hepatitis B cases worldwide and an estimated three to four million people become newly infected with HCV each year[3,4,5]. The significant numbers of chronic viral hepatitis B and C infections contribute greatly to the overall disease burden. Liver diseases rank twelfth overall as the cause of death in the USA and 11th in Canada[6-7]. Moreover, according to a Global Burden of Disease study, almost 1.3 million deaths in the world are attributed to cirrhosis of the liver (779,000, ranked 13th) and liver cancer (501,000, ranked 22nd) in 1990. Almost two thirds of these deaths (820,000) were due to chronic hepatitis B and C viral infections[8-9]. By 2002, the number of deaths from liver cancer increased by almost 25% to 618,790. Deaths from liver cirrhosis numbered 786,433, and another 156,265

deaths were directly attributed to hepatitis B and C (103,051 and 53,214 respectively)[10] (Figure 1.1). However, there are great regional variations in the deaths from hepatitis B and C (viral hepatitis-related cirrhotic deaths excluded). In Africa, South-East Asia, and the Western Pacific regions, deaths from hepatitis B outnumbered deaths from hepatitis C. In Europe, the numbers were similar with slightly more deaths directly attributable to hepatitis C than hepatitis B (4,467 and 4,601 respectively). In the Americas, there were 25% more deaths from hepatitis C (7,237) than from hepatitis B (5,702)[10]. Moreover, HCV is responsible for 50–76% of all liver cancer cases and two thirds of all liver transplants in the developed world[3].

Figure 1.1 Global Burden of Disease: Deaths, Year 1990 vs. 2002



Source: *Murray CJL and Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease study, 1997 and WHO, Revised GBD 2002 Estimates for Countries.*

1.2 VIRAL HEPATITIS C

Viral hepatitis C is an inflammation of the liver caused by the hepatitis C virus, which is transmitted through direct contact with infected blood. People who received contaminated blood and blood products (effective testing of the blood supply was instituted in 1990), and those who use illicit drugs and share injecting equipment are at a particularly high risk for contracting hepatitis C. Infected blood may also enter the bloodstream through skin cuts, punctures, or tears (e.g. tattooing or body piercing, sharing snorting equipment and some household items such as razors or toothbrushes, etc.), and this too may lead to infection with the hepatitis C virus. Vertical (mother to child) transmission and, to some degree, sexual transmission also occur. The onset of the disease is, for the most part, asymptomatic; but once established, chronic infection can cause persistent inflammation of the liver, called chronic hepatitis C. It is characterized by the continuous presence of the hepatitis C virus in blood, which can be detected by the test for viral RNA. The disease can eventually, albeit slowly, progress to various degrees of hepatic fibrosis (which interferes with normal liver function) and to advanced liver disease (such as cirrhosis). In some cases, those with cirrhosis will progress and develop various complications of cirrhosis, liver failure, or hepatocellular carcinoma (HCC), sometimes referred to as liver cancer. The severity of the disease, though, varies greatly from person to person[11], and there are no reliable predictors as to who will progress to end-stage liver disease and who would have only a mild condition or no clinical disease at all.

For years, up until its relatively recent discovery (hepatitis C virus was identified only in 1989[12]), the disease caused by this virus was known as "non-A, non-B hepatitis" (NANB) or sometimes referred to as "post-transfusion hepatitis". As the "old" name suggests, it was a form of hepatitis occurring in transfusion recipients, and it was different from other known forms of viral hepatitis (hepatitis A or hepatitis B)[9]. With the discovery of HCV it was shown that at least 90% of the NANB hepatitis was, in fact, hepatitis C.

In the past two decades, chronic hepatitis C virus infection is rapidly becoming a major health problem in the world, and Canada is no exception. Thus, the Expert Panel on Hepatitis C Epidemiology in its 1998 report recognized the significant burden hepatitis C imposes on our health care system, and more importantly, outlined the potential of this disease to considerably increase its burden in the near future[13]. The Panel provided predictions of the hepatitis C burden in Canada from 1999 up to 2008 (Table 1.1). While noting that only 30% of infected Canadians are aware of their infection, the model predicted the increase in incidence of cirrhosis and prevalence of end-stage liver disease, which would double in 10 years, while deaths from liver failure and liver cancer (HCC) would increased by 140% and 70% respectively *(Ibid)*.

Table 1.1 Predictions of HCV Burden in Canada (1999 – 2008)

CONDITION	P/I^	1999	2003	2008
MILD HEPATITIS	P*	164,278	135,926	106,556
	I**	-	-	-
CIRRHOSIS	P	20,223	29,130	39,312
	I	2,974	3,771	4,120
END-STAGE LIVER DISEASE	P	2,366	3,575	5,555
	I	-	-	-
HEPATOCELLULAR CARCINOMA	P	-	-	-
	I	313	393	534
LIVER TRANSPLANTS	P	-	-	-
	I	217	316	610
LIVER DEATHS	P	-	-	-
	I	629	904	1,522

^*P- prevalence, I-incidence*

**Annual prevalent cases, ** Annual incident cases*

Source: Division of Blood-borne Pathogens, Health Canada: Report on the Meeting of the Expert Panel on Hepatitis C Epidemiology, June 17-18, 1998.

The same Expert Panel acknowledged the difficulties in obtaining relevant epidemiologic information, since very little of it was published or readily accessible to investigators. This is even more evident in relation to Canada's Aboriginal populations. There have been some research data suggesting that Inuit and First Nations Peoples may have the highest prevalence of HCV infection of all the various ethnic populations of Canada but lower rates of treatment of their chronic infection. Compared to Caucasians, Canadian First Nations people may have higher rates of spontaneous clearance of hepatitis C virus following initial infection. While a few Canadian studies explore the question of the prevalence of HCV infection in Canadian First Nations, much less is known and

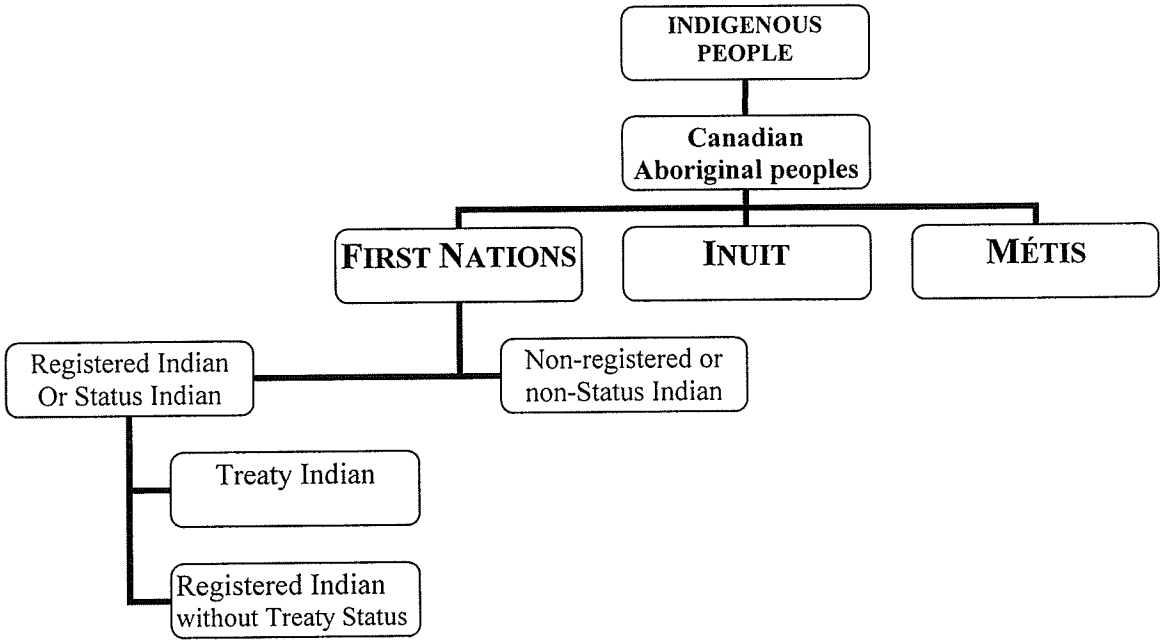
published about the natural history of the disease in this segment of the Canadian population.

1.3 Aboriginal and First Nations populatuons

While there is no single definition of what it means to be indigenous, two general characteristics stand out: a population with 'an ancient relationship with a defined territory' and with an ethnic distinctiveness from the surrounding populations and dominant culture of the country[14]. The term "Indigenous people" can be applied to Aboriginal people internationally as well as to the Aboriginal people of Canada. It is estimated that indigenous populations account for at least 5000 distinct peoples in over 72 countries but they represent fewer than 6% of the world population[15]. On the international level, the size of indigenous populations varies. For example, the Maori account for 14% of New Zealand's total population, while Canadian Aboriginal peoples comprise 3.3% of the country's population. In 2001, Aboriginal peoples accounted for 2.2% of Australia's population and for 1.5% of the population of the United States[16]. There are many similarities which between indigenous people and indigenous societies despite their differences in both culture and geographic location.

"Aboriginal people" is a collective name for the original peoples of North America and their descendants. Aboriginal peoples have occupied the territory now called Canada for thousands of years. The Canadian Constitution recognizes three groups of Aboriginal people - Indians, Métis and Inuit (Figure 1.2). These are three separate peoples with unique heritages, languages, cultural practices and spiritual beliefs[17,18].

Figure 1.2 Canadian Aboriginal Peoples



First Nations (or First Nations peoples) refers to the Indian peoples in Canada. The term "Indian" (as used in the *Indian Act*), collectively describes all the Indigenous people in Canada who are not Inuit or Métis. There are three categories of Indians (or First Nations) in Canada: Status Indians, Non-Status Indians and Treaty Indians[17].

- Status Indians are Indian (First Nations) persons who are registered under the 1876 *Indian Act*. The Act sets out the requirements for determining who is a Status Indian. Individuals who are Status Indians may also be Treaty Indians.

- Treaty Indians are Status Indians who belongs to a First Nation that signed a treaty with the Crown.

- Non-Status Indians are people who consider themselves Indians or members of a First Nation but whom the Government of Canada does not recognize as Indians

under the *Indian Act*, either because they are unable to prove their status or have lost their status rights. This may be because their ancestors were never registered, or because they lost their Indian status through discriminatory practices in the past.

The Inuit are the Aboriginal people of Arctic Canada. They have traditionally lived above the tree-line, primarily in Nunavut, the Northwest Territories and the northern parts of Labrador and Quebec.

The Métis are the third distinct group of people recognized as Aboriginal in Canada. They are people with mixed First Nations and European ancestry who identify themselves as a separate group from the Indians, the Inuit and non-Aboriginal people. The Métis have a unique culture that draws on their multiple ancestral origins, such as Scottish, French, Ojibway and Cree.

According to the Assembly of First Nations (AFN), there are 633 First Nations bands, representing 52 nations or cultural groups and more than 50 languages within the group collectively known as "First Nations" or "Indians". Each nation has its own spirituality, traditional political structure, and history[18]. Merging indigenous peoples into one group ignores the vast amounts of diversity among them and at the same time imposes a uniform identity on them, which may not be historically accurate. However, there is some practicality in being able to consider them as equals when it comes to making use of research. As shown repeatedly, indigenous people have troubling similarities in the

patterns of health and social status[19]. Indigenous people in any given country suffer from inferior health and social status compared to those of the dominant population; a generally lower life expectancy than non-indigenous populations and a higher incidence of many diseases including diabetes, tuberculosis, HIV/AIDS, as well as addictions, suicides, and other mental health problems[14,18,19]. All this fully applies to the Canadian First Nations. Consequently, First Nations living conditions / quality of life ranks 63rd which places Canadian First Nations amongst Third World conditions[20]. Despite improvements achieved in the past few decades, (such as the increase in life expectancy of FN males and females in 1980-2000 from 60.9 yrs. to 66.9 yrs. and from 68 yrs. to 76.6 yrs. respectively[20]), much remains to be done to bring the health of FN population to the overall Canadian standards.

1.4 Race and Ethnicity in Medical Research

Studies of epidemiology and the natural history of diseases as they pertain to different races and ethnic populations has become a regular subject in medical research. They are based on the assumption that an individual's racial background is associated with a certain genetic distinctiveness, which, in turn, could be significant in determining patterns of disease, responses to treatments, and outcomes of various conditions in different populations.

It has to be noted, however, that there is a degree of confusion in the literature as to what constitutes a "racial group" and an "ethnic background"[21]. While race is a biological entity (of which there are only four), ethnicity is a social construct which pertains to specific systems of beliefs and values, ways of behaving according to role prescriptions

and cultural practices, among other things. Many authors refer to "ethnicity", while, in fact, they study underlying racial differences, which, regardless of how small they are biologically, should in principle be minute differences in genetic structure.

Genetic causes have been extensively investigated for many diseases, such as diabetes, alcohol related disorders, heart diseases, obesity, some cancers, psychiatric disorders, and others. However, they are generally regarded as less significant than socioeconomic disadvantages, which are often central to the contemporary aboriginal experience. Some geographically or culturally isolated populations can be studied for genetic influences on physiological phenomena or diseases, such as the Pima Indians of Arizona who have extremely high prevalence of type 2 diabetes mellitus (non-insulin-dependent DM)[22]. Another example of such relationships is the studies revealing that certain mutations predispose Jewish Ashkenazi women to breast cancer[23]. Also known are studies of various medical problems, such as diabetes, obesity and high blood pressure among members of Amish communities in Pennsylvania. Shuldiner and his colleagues found that although the Amish and Caucasians had the same levels of obesity, the incidence of Type 2 diabetes in the Amish was about half that of the U.S. Caucasian population. Similarly, with a diet higher in fat and cholesterol, the Amish had lower cholesterol levels[24]. But even these cases are complex, since non-genetic factors also influence the outcome (such as lifestyle factors vs. genetic factors in the Amish or Pima studies). Both genetic and environmental factors (socioeconomic conditions, education, opportunities, lifestyle choices, etc.) seem to shape the patterns of health and disease among different populations.

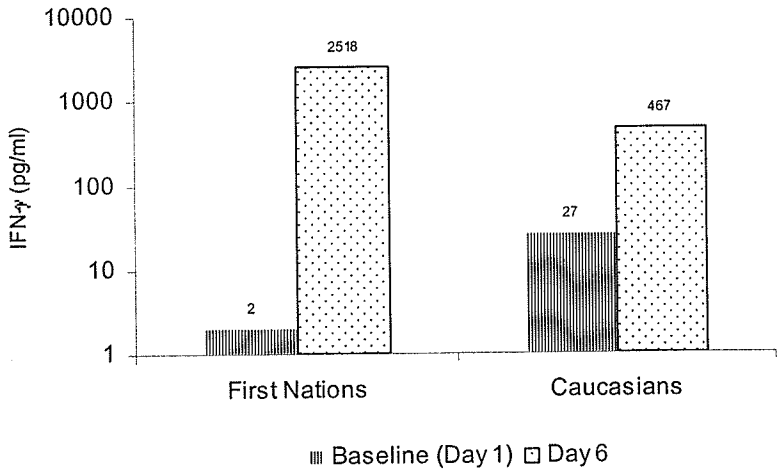
Likewise, there have been a number of studies evaluating the impact of ethnicity on immunity at the genetic level in various populations, including North American indigenous peoples[25-30]. With the development of treatment for hepatitis C, a number of studies examined various antiviral therapies for hepatitis C and predictors of the response to such therapy[31-45]. It is now well established that the outcome of treatment for chronic hepatitis C is dependent on both viral (e.g. genotype, viral load, etc.) and an array of host factors (e.g. age, gender, presence of cirrhosis, etc.)[31-37]. There is an ever-growing body of evidence suggesting that an individual's racial background may also play an important role. For example, a number of studies report significantly lower responses to interferon monotherapy[32,38-40] or combination therapy (interferon and ribavirin)[34-37,41,46] among African-American as compared to Caucasian patients. Current research points towards possible immunologic differences at baseline and in response to antiviral therapy being determined by one's racial background[42,46]. Specifically, Kimball et al. demonstrated a significant difference in baseline cytokine production between African American and Caucasian individuals infected with HCV[42]. The same authors suggest that understanding the influence of race on the balance between cytokine activities may be important in understanding mechanisms of resistance and sensitivity to interferon-based therapy. These data, as well as those of Sugimoto et al. suggest certain racial differences in immunologic requirements for HCV clearance[43]. There are also data pointing to enhanced response to antiviral therapy among South East Asian patients[44-45].

Furthermore, certain ethnic variations in the incidence and prevalence of HCV infection, whether due to the influence of genetic or environmental factors, are repeatedly observed;

African Americans have a higher prevalence of chronic HCV infection than Caucasians[47-48]. Canadian First Nations and American Indian/Alaskan Natives have been reported to have a higher incidence of acute HCV infection[49], but also seem to have a lower rate of chronicity than other populations[49-52]. This could be because indigenous populations – such as Alaskan Natives- have been reported to have rates of spontaneous clearance as a high as 56%, as compared to 35% in Caucasians[52]. Similarly, in a large community-based cohort of illicit drug users in Vancouver, HCV clearance occurred more frequently in individuals of Aboriginal ancestry as compared with Caucasians[53].

In tune with the above data, information is currently emerging that certain genetic or immunologic characteristics pertaining to Canadian First Nations ancestry may play a role in HCV infection[25,30]. Aborsangaya et al. showed that the ability of peripheral blood mononuclear cells (PBMC) to produce interferon gamma (IFN-γ) is significantly enhanced in First Nations versus Caucasian PBMC. Specifically, the production of IFN-γ by First Nations PBMC 6 days after IFN-α stimulation increased 1,260-fold versus 17-fold by Caucasian PBMC (Figure 1.3). Also, a genetic tendency — and corresponding capacity — of First Nations peoples to produce less interleukin-10 (IL-10) could contribute to an ethnically distinct disease outcome, including more efficient clearance of acute HCV infection.

Figure 1.3 IFN-γ production by PBMC in response to IFN-ά stimulation



Source: The above data was supplied by Dr. J.Rempel via personal communications

Yet others argue that it is not race-specific characteristics that underlie apparent differences in the rates of certain conditions and treatment responses, but rather broad and complex socioeconomic constants coupled with cultural practices and beliefs that impact the host's immune system and antiviral properties[21,54-55]. These authors contend that what controversially appears to be a racial difference may also be a product of a combination of factors such as socioeconomic position, education, family structure and community networks, which are overlooked as the real reasons for race distinctions when it comes to individual diseases. It seems reasonable to take seriously both genetics and the environment (which includes not only socioeconomic conditions and education, but also such factors as opportunities, lifestyle choices, etc.) when it comes to shaping the patterns of health and disease among different populations. And hepatitis C, being as much a social problem as it is medical one, needs to be addressed from various perspectives, accounting for the potential heterogeneity of intrinsic host factors. With this in mind, I

will examine various aspects of hepatitis C epidemiology and health care use in Manitoba and compare the results between First Nations and non-First Nations populations.

1.5 Study Questions

The aforementioned Expert Panel on Hepatitis C Epidemiology outlined areas of research which needed to be intensified in order to improve our understanding of hepatitis C in Canada. Research in the area of natural history and epidemiology of HCV infection was named as one part of the emerging themes. Since then, a significant body of knowledge has been accumulated regarding many aspects of HCV infection. Yet, there is scarcity of published data on the prevalence of hepatitis C and its clinical features and management in the Canadian First Nations. The present study is designed to fill these gaps in our knowledge. It will focus on the incidence of diagnosis and demographics of HCV infection in the First Nations and non-First Nations populations and examine clinical features and health care resource utilization of HCV infected Manitobans in these two subpopulations. Then health care utilization by Manitoba residents with hepatitis C will be compared with a randomly selected population-based matched cohort of controls. Selection of the controls is based on sex, 5-year age group, First Nation status, and geographic location (regional health authority within Manitoba).

The three major ***Specific Objectives*** of this study are as follows:

1. To provide detailed information on the reported incidence of HCV infection in Manitoba's First Nations and non-First Nations populations. This will involve

describing and comparing crude and adjusted rates of hepatitis C in the two subpopulations and in different geographic regions within the province, and demographic characteristics of infected populations.

2. To examine, describe and compare natural history and clinical outcomes in First Nations and non-First Nations populations. This will include rates of hospitalization, comorbidity and complications, re-admissions, mortality, etc.

3. To assess health care utilization between (1) HCV-infected First Nations and non-First Nations individuals and (2) to evaluate the overall trends in the utilization of health care resources in the HCV-infected cohort and in the general population.

Null Hypotheses to be tested:

- The incidence of HCV infection is similar in First Nations and non-First Nations cohorts.
- Patterns in health resource utilization and standards of care are similar after adjustments are made for co-morbidity.
- Overall health care resource utilization is similar between cohorts of HCV-infected patients and the general population.

The results of this study are essential (a) for understanding the disease features in First Nation and non-First Nation populations and (b) for predicting future resource utilization for HCV-infected individuals. These results will provide information on the overall as

well as diagnostic and treatment-related health care used by First Nations and non-First Nations patients and will also identify areas requiring additional resources and/or improvement. Finally, the results obtained in this study will lead to designing specific health programs of hepatitis C prevention and care.

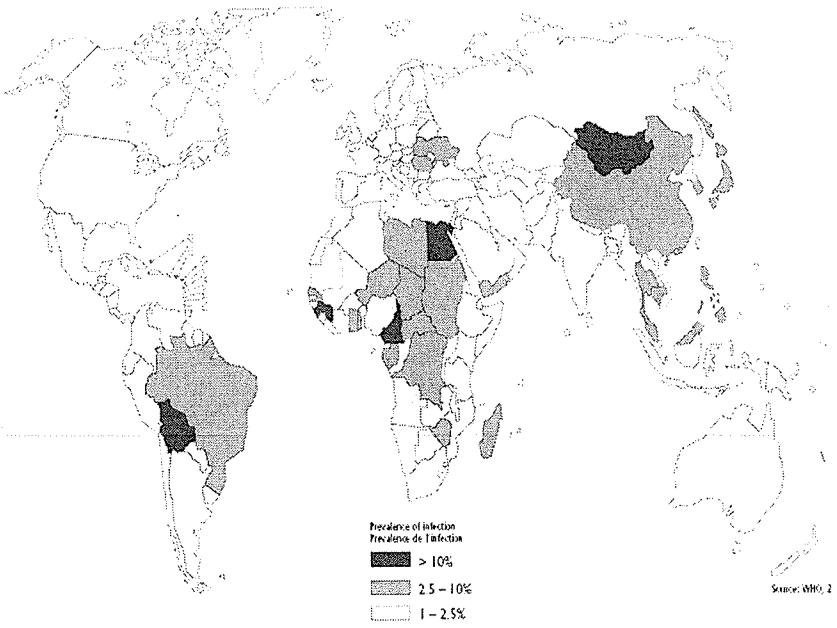
CHAPTER TWO LITERATURE REVIEW

2.1 Global Burden of Hepatitis C

2.1.1 Prevalence of chronic HCV infection

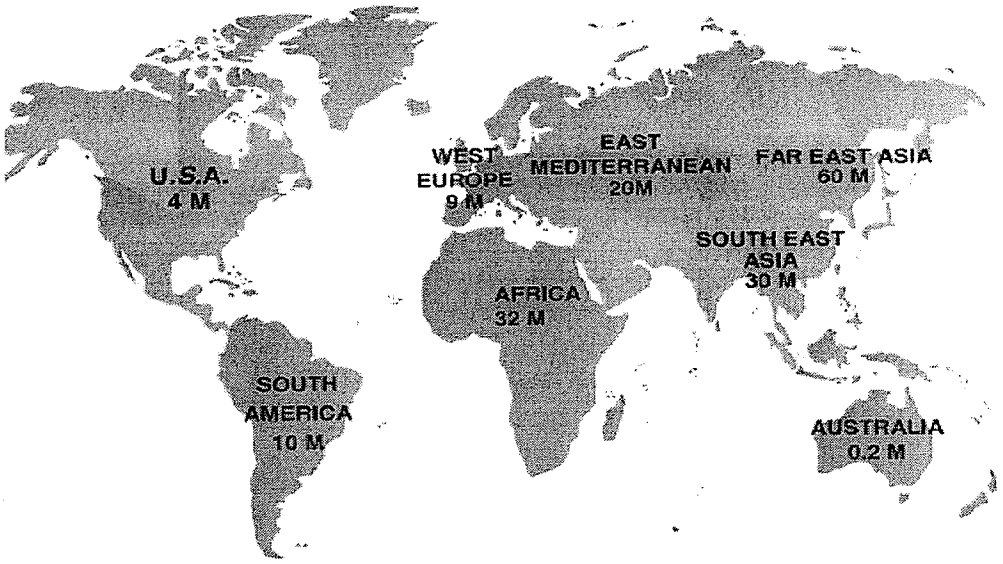
Although recognized since 1970 as a form of viral hepatitis (then called "post-transfusion hepatitis" or "hepatitis non-A-non-B"), hepatitis C generated particularly intensive scientific, clinical, and public interest during the past two decades. Hepatitis C infection has become a global health problem with an estimated 170 to 180 million people infected around the world[3,11,13,56], reaching pandemic proportions in all industrialized countries (Figure 2.1 and 2.2). The prevalence of infection varies greatly, from 1% in Western Europe and 1.7% on the American continent to 5.3% in Africa (Table 2.1), and approximately 3% worldwide[57].

Figure 2.1 Global prevalence of hepatitis C



Source: Weekly epidemiological record ***No. 6, 2002****, 77, 41–48*

Figure 2.2 Estimated worldwide prevalence of hepatitis C infection



Source: Brown and Gaglio, Liver Transpl 2003[56]

But there is a great deal of variation in prevalence within the regions as well. While the African continent seems to have the highest overall prevalence, it is driven mostly by the high prevalence of infection in Central Africa (6%), while the estimated prevalence of infection in West Africa and Southern and East Africa is 2.4% and 1.6% respectively[58].

The region with the lowest overall prevalence (Europe) has the largest variations in prevalence of hepatitis C infection among all WHO regions (WHO regions do not strictly correspond with geographic regions). Many Western European and Scandinavian countries have HCV prevalence around 1%. The prevalence of HCV infection reported in the United Kingdom is 0.4-1.0%, 0.9% in Belgium, and 1.05% in France[59-60]. Countries such as Italy, Eastern European nations and some Middle-Eastern countries have a much higher prevalence of HCV infection. For example, several studies showed that the

prevalence of antibodies to HCV in various regions of Italy vary from 3.6% in Northern Italy to 8.4%-22.4% in Central and Southern regions[61]. In the republic of Georgia, the prevalence of hepatitis C infection was found to be 6.7%[62]. In Russia, regional variations are between 0.7% and 3.8%[61, 63].

High prevalence of HCV infection in the Eastern Mediterranean region is mostly driven by an extremely high prevalence of hepatitis C infection in Egypt – 25%[56,64], while its close neighbors Saudi Arabia and Yemen have an HCV prevalence of 1.8% and 2.1% respectively[61] (for WHO regions and countries see Appendix 1). Similarly, while the estimated prevalence of hepatitis C in the Western Pacific is 3.9%, variations between countries are significant: from 1% in Japan to 3.2-5.6% in Thailand to 16-17% in Mongolia[51,65]. A 1996-1998 nationwide serosurvey in Australia revealed age-standardized prevalence of antibodies to HCV to be 2.3% (95% CI 1.8% - 2.9%)[66]. HCV prevalence derived from this serosurvey was 3 times the number of HCV infections reported to the National Notifiable Disease Surveillance System during 1991-1998, hence confirming that only approximately 1/4 to 1/3 of infected individuals are aware of their infection[66].

The first true population study of the prevalence of HCV infection was conducted in the United States in 1988-1994 within National Health and Nutrition Examination Survey (NHANES) III. The directly measured prevalence of hepatitis C infection was found to be 3.9 million persons or 1.8% of the US population[67]. Furthermore, 2.7 million of those HCV-infected individuals or 1.3% of the US population had evidence of chronic hepatitis

C infection *(Ibid)*. Within the more recent 1999-2002 NHANES study, more than fifteen thousand people were tested for antibodies to HCV and for HCV-RNA[68]. The results clearly showed that there is no decline in the prevalence of chronic hepatitis as of yet, despite the observed tendency toward a decreasing number of acute cases. For instance, the overall prevalence of HCV infection was found to be 1.6%, which translates into 4.1 million individuals who have ever been infected with the HCV. Likewise, the prevalence of chronic hepatitis C was found to be 1.3%, or an estimated 3.2 million. These results represent an increasing burden of chronic hepatitis in the United States compared to the results obtained a decade earlier[68].

Table 2.1 Estimated prevalence of hepatitis C and the numbers of infected individuals by WHO Region

WHO Region	Total Population (Millions)	Hepatitis C prevalence Rate %	Infected Population (Millions)	Countries by WHO Region where data are not available (N)
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	7
Europe	858	1.03	8.9	19
South-East Asia	1 500	2.15	32.3	3
Western Pacific	1 600	3.9	62.2	11
Total	**5 811**	**3.1**	**169.7**	**57**

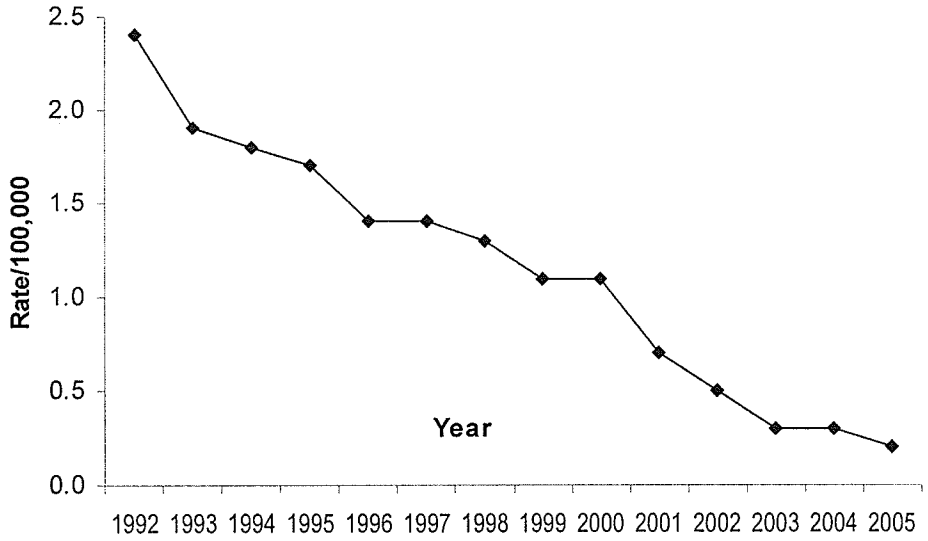
Source: Weekly Epidemiological Record. N° 49, 10 December 1999, WHO

2.1.2 Incidence of acute HCV infection

The incidence of HCV infection is difficult, if not impossible, to determine due to the very nature of the disease. While many countries collect data on hepatitis C, routine reporting includes mostly newly recognized chronic cases of HCV infection, since there is no distinction between acute and chronic cases of hepatitis C based on laboratory testing. Furthermore, because most of the cases of acute HCV infection are asymptomatic (estimated 70-80%), only a small minority of acute clinical cases or documented instances of seroconversion are diagnosed as acute hepatitis C. Thus, the surveillance based on routine or even enhanced reporting of acute hepatitis C grossly underestimates the real incidence of infection. Despite these limitations, there is evidence that the incidence of acute hepatitis C had changed over time, and much like with the prevalence of chronic hepatitis C, there are geographic variations in the incidence of acute HCV infection[69].

In the United States, the incidence of confirmed acute hepatitis C decreased from 2.4 per 100,000 population in 1982 to 0.2 per 100,000 in 2005 (Figure 2.3). Accounting for asymptomatic infection and underreporting, it was estimated that as many as 20,000 new HCV infections occurred in 2005[70]. Using current seroprevalence data and sentinel surveillance as a background, mathematical models were developed to estimate past incidence of hepatitis C in the United States. The annual incidence has declined more than six times from the estimated 180,000 cases in 1984 to 28,000 in 1995 (Figure 2.4). This decline is presumed to be associated with a decrease in acute cases associated with injection drug use rather than to the decline of transfusion-associated acute hepatitis C[71].

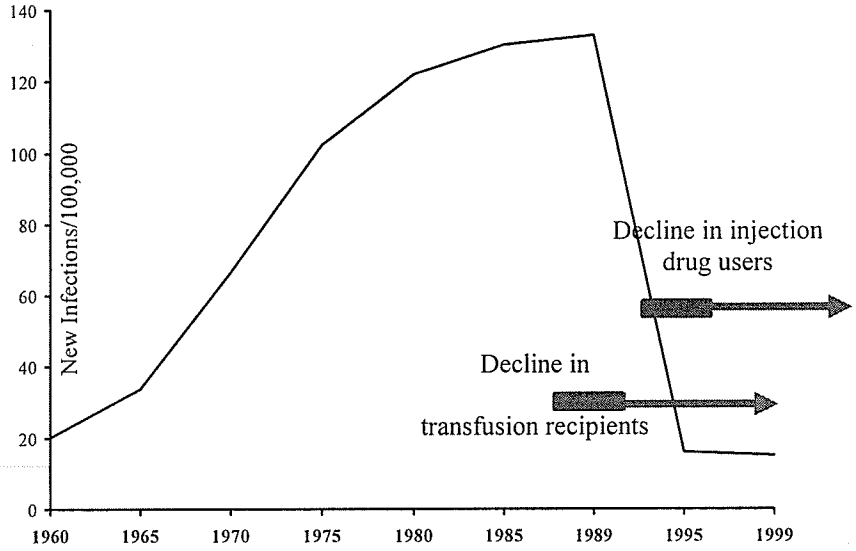
Figure 2.3 Incidence of Acute Hepatitis C*, USA, 1992-2005



**Acute hepatitis C was reported as hepatitis NANB up until 1995*

Source: Wasley et al. MMWR 2007;56(3):1-24[68]

Figure 2.4 Estimated Incidence of Acute HCV Infection, USA, 1960-1999



Adapted from Centers for Disease Control and Prevention, Division of Viral Hepatitis, slide sets, http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/index.htm[72]

The role of HCV in the etiology of acute viral hepatitis in USA had also changed over time. While in 1982-1993 HCV (or NANB hepatitis) accounted for 16% of all acute viral hepatitis, in the later years of 1996-2006 it decreased to 8-9%[72-73].

Data from Italian surveillance showed that the incidence of acute HCV infection decreased from 5 per 100,000 in 1985 to 1 per 100,000 in 1991, while the rest of Europe reports much lower incidence[3,69].

In Australia, the average annual incidence, derived from 1997-2000 surveillance for newly acquired HCV infection results, was approximately 0.6 cases per 100,000 population. New HCV infections came to only 2.8% of total reported cases of HCV infections during that time[74].

The highest incidence rates of acute hepatitis C are still observed in Egypt, ranging from 0.8 to 6.8 per 1,000 person-years, which amounts to 31% of acute viral hepatitis cases in Egypt[75].

2.1.3 Temporal Variations in the Incidence of HCV infection

As noted above, there are not only geographic but also temporal variations in the global incidence of HCV infection. So far, three distinct patterns have been described, based on the observed age-specific prevalence of HCV infection. The first pattern is characterized by the highest prevalence of hepatitis C among 30-49 yr. olds, with very low prevalence among those younger than 20 and older than 60 yrs of age. Such prevalence is observed in the USA, Canada, Australia and in Western European countries, pointing towards the peak of transmission in the recent past, some 10-30 years ago[69,76].

In Mediterranean countries such as Italy, Spain, Greece, and also in Japan, the age-specific prevalence is low among both children and younger adults but high among older adults, and is greatest among those 50 yr. of age and older[69,76-77]. That indicates that the greatest risk of infection appeared to be 30-50 years ago, or sometime between 1945 - 1975. Egypt has a somewhat unique pattern, in that the rates are high in all age groups, which is indicative of both past and ongoing risk of HCV acquisition[69,77].

2.2. Incidence and Prevalence of Hepatitis C in Canada

Hepatitis C is a reportable communicable disease in Canada, and it was introduced into the national surveillance program in 1991. Prior to that, hepatitis Non-A Non-B was reportable for the period from 1983 to 1999 and it was removed from national surveillance in 2000[78] (Table 2.2).

Table 2.2 Annual numbers of newly reported cases, hepatitis non-A non-B (NANB) and hepatitis C, Canada, 1990-2004

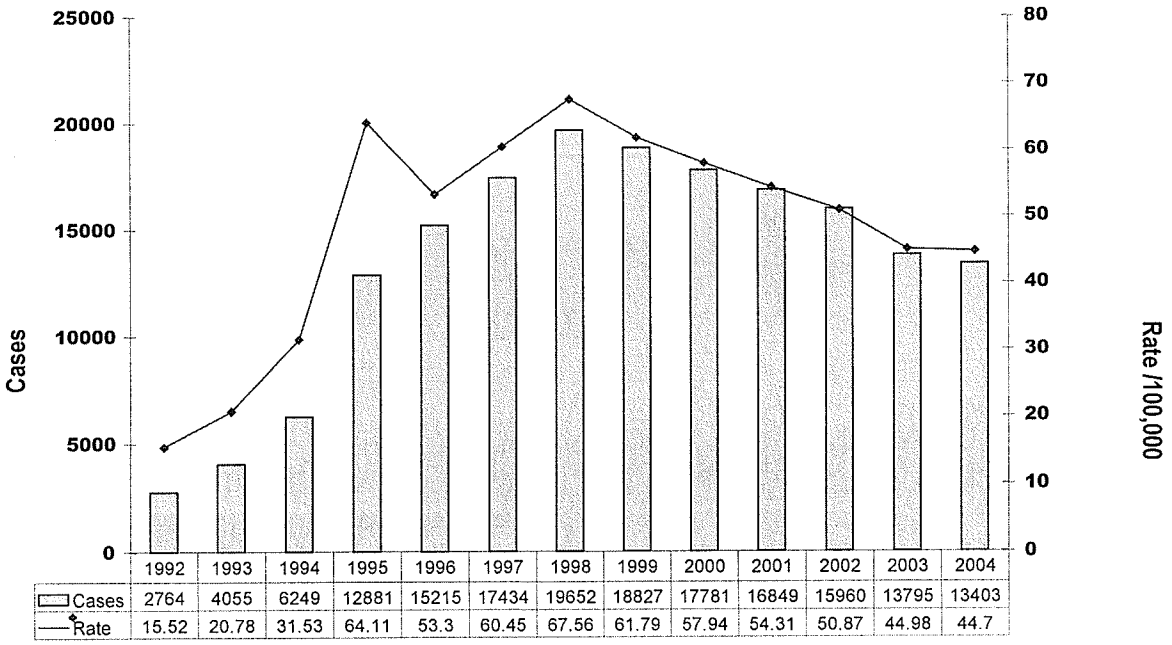
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Hepatitis NANB	256	143	0	0	0	0	1	0	0	0					
Hepatitis C			2764	4055	6249	12881	15215	17434	19652	18827	17781	16849	15960	13795	13403

Source: Public Health Agency of Canada (PHAC), Disease Surveillance, Notifiable Diseases On-Line[78]

The first five Canadian provinces to join national reporting in 1992 were Prince Edward Island, Ontario, Saskatchewan, Alberta, and British Columbia. Manitoba was the last of

the provinces to join national surveillance in 1999. The number of reported cases steadily increased since 1992, reaching the highest number of newly diagnosed hepatitis C cases (19,652) and the highest incidence of 67.6 per 100,000 population in 1998. That rise was mainly due to the recognition of previously acquired infection. Since 1999, the rate of newly reported hepatitis C decreased 1/3 to 44.7 per 100,000 in 2004 (Figure 2.5). It is believed that approximately 65% of estimated cases of chronic hepatitis C infection in Canada have been identified[78].

Figure 2.5 Incidence of newly reported cases, hepatitis C, Canada, 1991-2004



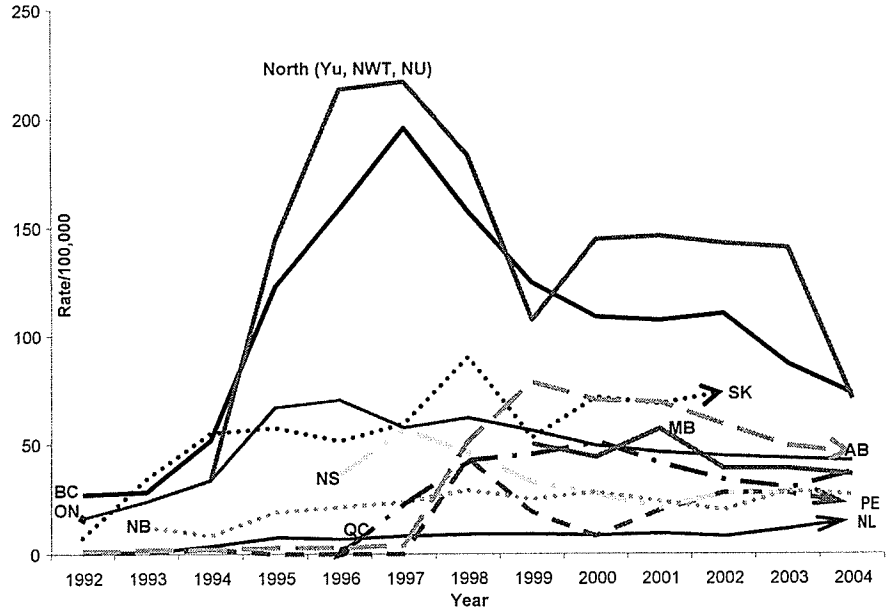
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Cases	2764	4055	6249	12881	15215	17434	19652	18827	17781	16849	15960	13795	13403
Rate	15.52	20.78	31.53	64.11	53.3	60.45	67.56	61.79	57.94	54.31	50.87	44.98	44.7

Source: PHAC, Disease Surveillance, Notifiable Diseases On-Line[78]

The majority of all cases in Canada come from British Columbia, Alberta, and Ontario. Reported rates of hepatitis C are persistently highest in British Columbia and in the

Canadian North, while the lowest rate is found in Newfoundland and Labrador (Figure 2.6).

Figure 2.6 Incidence of Newly Reported Cases, Hepatitis C, Canada, Provinces and Territories, 1991-2004



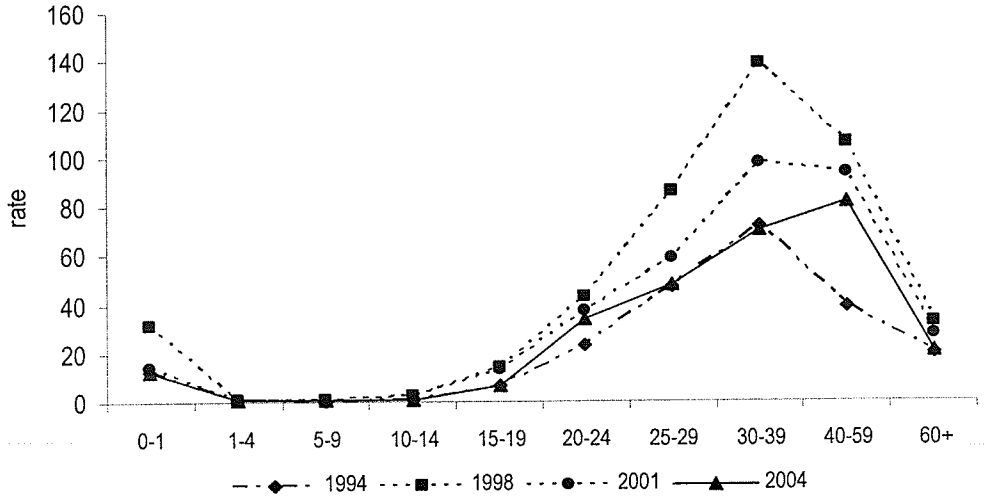
Source: PHAC, Disease Surveillance, Notifiable Diseases On-Line[78]

The true prevalence of HCV infection in Canada is not known. The estimate of the current national prevalence of HCV infection lies in the plausible range between 210,000 and 300,000 persons[2,13,77,79]. This estimate confirms the view that HCV infection is, indeed, an epidemic and is a major public health concern in Canada. The estimated prevalence of HCV infection varies among the provinces, with British Columbia having the highest (1.4%), and Newfoundland the lowest (0.1%)[80] prevalence. Within provinces, prevalence figures vary considerably and depend on the population studied. Amongst

blood donors, prevalence is approximately 0.2%, while among pregnant, otherwise healthy women, the prevalence is reported to be 0.9%[81-82]. The highest prevalence reported to date in Canada is among populations of injection drug users (65% - 80%) and prison inmates (25% - 40%)[83]. Among the cohorts of injection drug users in Vancouver and Montreal, the prevalence of HCV was reported as 85% and 70% respectively, and the annual incidence was reported as 26% and 27% respectively[84].

The highest age-specific incidence of newly reported hepatitis C was consistently found among adults in the 30-39 age group, but since 2002 there has been a slight shift towards the highest incidence among individuals 40-59 years of age (Figure 2.7 and 2.8). Such a trend persisted in 2002, 2003, and 2004[78].

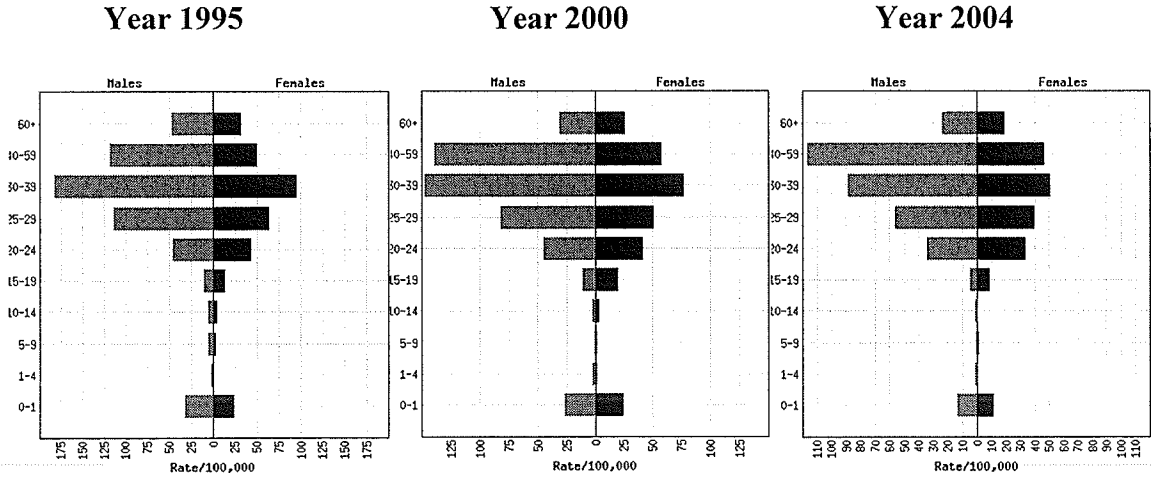
Figure 2.7 Age-specific rates of hepatitis C, Canada, 1994, 1998, 2001 and 2004



Source: PHAC, Disease Surveillance, Notifiable Diseases On-Line[78]

As evident from the National Surveillance, the rates of newly reported hepatitis C are driven mostly by the rates among males, which are almost twice the rates among females in any year since the beginning of reporting (Figure 2.8). In all age groups rates among males are higher than the rates among females, except for the age category of 15-19 yrs, in which females have rates higher than males. Figure 2.8 also illustrates the already mentioned change in age-specific incidence. The highest rates of newly reported hepatitis C cases in 1995 were clearly among individuals from the 30-39 yr. age group for both sexes. By the year 2000, while still the highest; these rates were very close to the rates among those of 40-59 yr. olds. In 2004, the rates of newly reported hepatitis C were the highest among 40-59 yr. old males, while the rates among 30-39 yr. old females and those among 40-59 yr. old females were very similar (figure 2.8).

Figure 2.8 Rates of hepatitis C by age and sex, 1995, 2000, and 2004, Canada

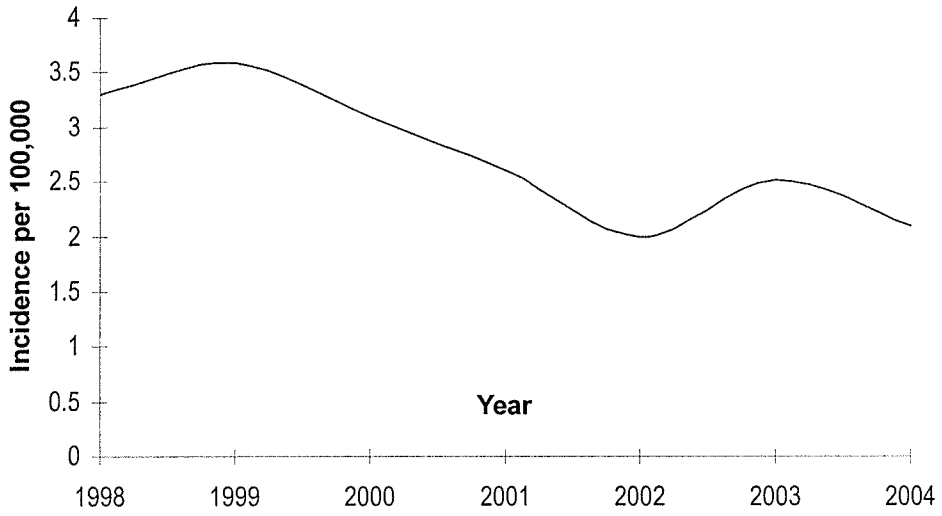


Source: PHAC, Disease Surveillance, Notifiable Diseases on Line[78]

For reasons already mentioned above, there is no reliable data on the incidence of HCV infection in Canada. An Enhanced Surveillance System for acute hepatitis B and C augmented the routine national reporting of notifiable diseases and provided some data on the incidence of acute hepatitis C. The data obtained from four sentinel health regions in Canada during 1998/1999 yielded 102 cases of acute hepatitis C for an incidence of 2.9 per 100,000[85]. Based on the 1999-2000 data collected by the enhanced surveillance system, it was estimated that approximately 1,000 clinically recognized acute HCV infections occur annually in Canada. Furthermore, assuming that 75% to 80% of acute HCV infections are asymptomatic, it is estimated that there will be approximately 4,500 new HCV infections annually[86]. In his report, Remis estimated the incidence of HCV infection in Canada to be 16.3 per 100,000 population[87].

An analysis of seven years of surveillance within the aforementioned Enhanced Hepatitis Strain Surveillance System (EHSSS) revealed that the incidence rate of newly acquired HCV infection declined by about 1/3 from 3.3/100,000 in 1998 to 2.1/100,000 in 2004 (Figure 2.9). The incidence rate among males was 1.3 times higher than the incidence among females. Also, the highest age-specific incidence across the whole study period was among 30-39 yr. olds, followed by the incidence among 15-29 yr. olds[88].

Figure 2.9 Incidence of Newly Acquired Hepatitis C, Canada, 1998-2004



Source: Wu H-X et al. Scand J Inf Dis 2006; 38(6): 482 — 489[88]

Despite the slight decrease in the incidence of newly acquired HCV infections, the consequences of such a decrease would not immediately translate into the decline in the prevalence of chronic hepatitis C, which remains an important medical and societal issue for reasons discussed below.

2.3. SOCIETAL AND ECONOMIC BURDEN OF HCV DISEASE

In Canada, according to various estimations, there are approximately 240,000 – 300,000 individuals chronically infected with HCV[2,13,79-81,87]. Having become one of the most common liver diseases, chronic hepatitis C now has multiple medical and social implications. Hepatitis C is characterized by a high rate of chronicity following acute infection (50-70% according to the most recent data), an indolent course towards

cirrhosis in 5-25% of cases and an increased risk of hepatocellular carcinoma (HCC)[83]. As many as 15-30% of those chronically infected over time (usually several decades) will eventually develop cirrhosis and its complications and/or require liver transplants[2, 79-81,87,89].

The annual risk of death in patients with cirrhosis due to hepatitis C is 2.1-3.0%, with an estimated 1,000 deaths occurring in Canada annually due to chronic hepatitis C[91].
Chronic hepatitis C-related end stage liver disease has rapidly become the single major indication for liver transplantation, accounting for 35-40% of all liver transplants in Canada, the United States, Australia and some European countries[92-95]. In Canada, HCV-related liver transplants account for almost 35% of all liver transplantations, twice the number of the next most common diagnosis – alcoholic liver disease[86,93-94].

Since 1991 (after the identification of HCV) the rates of hospitalization for hepatitis non-A non-B (which was, almost exclusively, HCV) increased in Canada (Figure 2.10), while the number of deaths and the age-standardized mortality rate (ASMR) has been increasing steadily since 1994 (Figure 2.11). According to ElSaadany et al., ASMRs among males are higher than among females and were the highest in the 60+ age group. The highest rates are found in British Columbia and the Yukon[86].

Figure 2.10 Hospital Admissions and Age Standardized Hospitalization Rates for Non-A, Non-B Hepatitis by Year, Canada, 1980-1998*

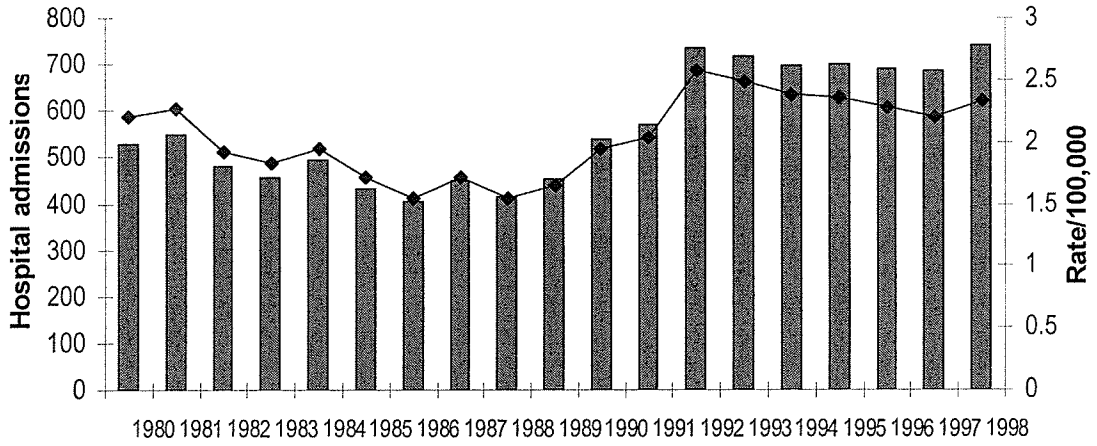
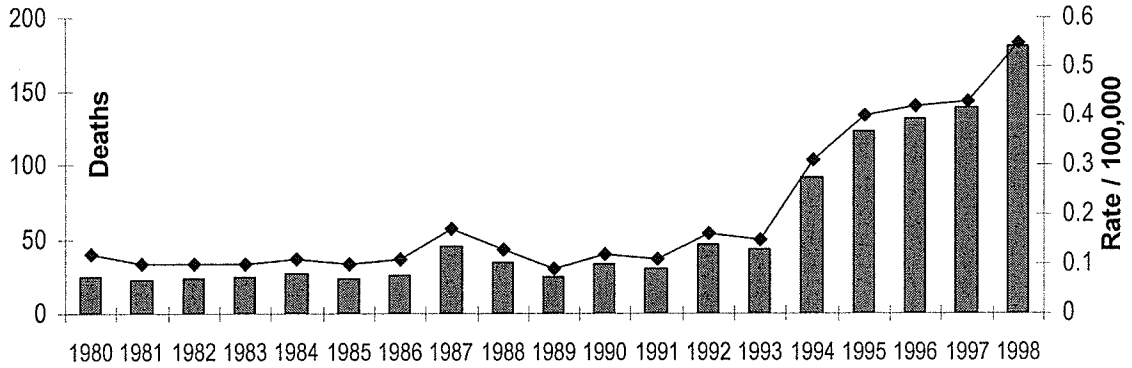


Figure 2.11 Deaths and Age Standardized Mortality Rates for Non-A, Non-B Hepatitis by Year, Canada, 1980-1998*



**From: Blood-borne pathogens routine surveillance system report. Health Canada, 2002*

In the United States, current estimates of medical and work-loss costs of HCV-related acute and chronic liver disease are greater than $600 million annually[96] and are projected to rise substantially. Similarly, the burden of chronic hepatitis C in Canada for the next decade will likely increase as those infected during the peak incidence years of the 1960's - 1980's are reaching the advanced stages of their hepatitis C-related liver disease and are

beginning to enter the health care system. This will certainly increase medical and financial demands on the Canadian health care system even further. Despite recent decreases in the incidence of HCV infection (through such measures as donor blood screening and/or declines in unsafe injection drug use practice), the effects of these decreases in HCV-related liver diseases will not be apparent for several decades to come.

Another important economic consideration is the cost of antiviral therapy. While, when successful, it would prevent the progression of chronic hepatitis C to end-stage liver disease, it also has important consequences for society and for individual patients. As the cost of drug therapies to treat chronic hepatitis C infection is high and continues to increase, there is already concern that for many patients, therapy is prohibitively expensive. For example, a two-week kit of Pegetron therapy (pegylated interferon and ribavirin) costs ~$900 and, for the more common 48-week treatment, this translates into more than $21,000 per patient (CAD). Provincial health care plans carry a heavy financial burden compensating patients for the cost of drugs. Treatments of the not infrequent side effects of therapy can also be expensive (e.g. erythropoietin and granulocyte colony stimulating factor). Not surprisingly, the progression of chronic hepatitis C infection to end-stage liver disease is accompanied by an escalating annual cost of care: from $299 for mild chronic hepatitis C to $1,331 for compensated cirrhosis to $ 8,755 for portal hypertensive bleeding, $10,463 for ascites, and $17,300 for hepatic encephalopathy (all these figures do not include the cost of medications). Finally, the cost of liver transplantation is $78,017 for the first year alone[97]. The recent realization of universal recurrence and rapid progression of hepatitis C after transplant with graft loss 5

years after the initial transplant[98] impose additional burdens on the Canadian health system. Most recently, Nguyen and colleagues showed that the total cost of care per person (the cost of pharmaceuticals was not included) increased from $2630 CAD to $3514 between the pre- and first post-diagnosis year in Alberta, but decreasing to $2694 in the second post-diagnosis year. A significant cost was attributed to the mental-health component of care[99].

Wong and colleagues estimated future hepatitis C costs and mortality in the United States[100]. Their model predicts $10.7 billion in direct medical expenditures due to hepatitis C during the years 2010-2019. While there were approximately 10,000 annual deaths from HCV-related liver disease in 1995-96 in the USA, the model predicts 165,900 deaths from chronic liver disease and 27,200 deaths from HCC. The number of chronic hepatitis C cases and related deaths is higher than the number of chronic hepatitis B infections and HBV- related deaths (table 2.3). The loss of 1.83 million years of life in those younger than 65 years of age will cost $54.2 billion.

Likewise, the health and economic burden of chronic HCV infection in Canada is increasing, while for hepatitis A and B it is either decreasing or not changing significantly (Table 2.4). The steady increase in hepatitis C-related rates of hospitalization and mortality is caused by the progression of chronic hepatitis in those infected during 1960-1980 to clinical and decompensated forms. By 2010, the cost of HCV-related care in Canada is estimated to be $1 billion. These data support predictions

that chronic hepatitis C will lead to a substantial economic and health burden over the next 10-20 years[101].

Table 2.3 Disease Burden from Viral Hepatitis A, B, and C in the United States

	Hepatitis A	Hepatitis B	Hepatitis C
Number of acute clinical cases reported, 1995	31,582	10,805	4,576
Estimated number of acute clinical cases	94,000	64,000	8,000
Estimated annual acute infections, 1984-1995	125,000-200,000	128,000-320,000	28,000-180,000
Number of persons with chronic infection	-	1-1.25 MIL.	3.9 MIL.
Number of deaths attributable to chronic infection each year (estimated)	-	6,000	8,000-10,000
Percent ever infected	33.0%	5.3%	1.8%

From: CDC, Hepatitis Branch, 1997

Table 2.4 Disease Burden from Viral Hepatitis A, B, and C in Canada

		Hepatitis A	Hepatitis B	Hepatitis C*
Number of acute clinical cases reported:				
	- In 1980	1,377	1,164	1,294*
	- In 1998	880	1,273	21,686
Rate (per 100,000):				
	- In 1980	5.62	4.77	8.69*
	- In 1998	3.60	4.18	75.18
Number of Hospital Admissions:				
	- In 1980	556	382	530*
	- In 1998	193	249	741
Age-standardized Rate of Hospitalizations				
	- In 1980	2.21	1.55	2.20*
	- In 1998	0.64	0.79	2.33
Number of deaths:	- 1980/84	38	15	25*
	- 1995/98	22	103	181
Annual ASMR:	- 1980/84	0.006	0.08	0.11*
	- 1995/98	0.004	0.31	0.45

*since 1992

From: Health Canada, CCDR, 2002[86]

2.4 HCV Transmission and Risk Factors For HCV Infection

Hepatitis C is the most frequent bloodborne infection in the world. The contribution of various routes of transmission to the disease burden is unequal. Thus, the most efficient way of transmitting and acquiring hepatitis C virus is by direct contact with infected blood (Table 2.5):

Table 2.5 Routes of HCV Transmission

I.	**Direct contact with blood via:**
	Injection drug use (IDU) Transfusion of blood, clotting factors, etc., and transplant from infected donor Therapeutic, surgical and dental procedures, including hemodialysis (contaminated equipment, unsafe injection practices) Occupational (needle stick) Intranasal cocaine use Other non-therapeutic use of needles (cosmetic services, rituals with scarification, blood letting, etc.) Household (sharing razors, toothbrushes, manicure sets, etc.)
II.	**Vertical (mother-to-child) transmission**
III.	**Sexual transmission**

Injection drug use, blood and/or blood product transfusions, and therapeutic manipulations using contaminated and non-sterilized equipment contributed most significantly to the disease burden worldwide. From all of the above, the highest contribution to the disease spread with 60 to 80% infected is injection drug use. This is by far the most efficient route of HCV transmission. Transfusions of blood and/or blood components were other important transmission mechanisms prior to the introduction of reliable screening for HCV in 1990. Up to 90% of hemophiliacs were infected with HCV prior to 1990, but currently this is not the case. Nowadays, the risk of infection from blood transfusion is minimal, and is estimated to be less than 1 per 100,000 units of transfused blood and/or blood products[102,103]. However rare, it can not be prevented

entirely, as it may occur during the 4-8 wk. window period when the donor is already infected but the production of antibodies has not yet reached detectable levels.

Such routes as occupational (e.g. needle stick injury) exposure, intranasal cocaine use, various non-medical applications of needles (e.g. a variety of beauty and cosmetic services, rituals with scarification, blood letting etc.) as well as household contacts (sharing razors, toothbrushes, etc.) pose intermediate to low risk of HCV transmission.

The rate of vertical (from mother to child) transmission of HCV is believed to be somewhere between 0 to 7%. In certain high risk groups, the risk can be as high as 80%. Mother-to-infant transmission of HCV may be intrauterine, intrapartum, or postnatal. However, most infections seem to occur *in utero* as the result of a high viral load in the mother. Prolonged traumatic labor and internal fetal monitoring may slightly increase the risk of an HCV transmission. A 10-year review of published data by Yeung and colleagues revealed that the prevalence of anti-HCV–positive women among all pregnant women varied from as low as 0.6% in so-called "general" populations to as high as 70-95% in the pregnant intravenous drug users, with viremia present in 65.5%[104]. An overall rate of transmission among almost 6,000 mother-infant pairs was 1.7%, but for viremic women this rate was 4.3% (Table 2.6). The highest risk of HCV transmission (approximately 20%) is repeatedly found among HIV-co-infected mothers[104-106]. Higher viral load and IDU increase the risk, while the mode of delivery and breastfeeding do not appear to influence the rate of HCV transmission (Table 2.6).

Table 2.6 Risk of vertical transmission of HCV

	All AB positive (anti-HCV+)	Viremic only (HCV-RNA+)
NIH (2002)*	2%	4-7%
HIV co-infected	20%	
Yeung (2001)**	1.7%	4.3%
HIV co-infected	19.4%	
IDU	8.6%	
Vaginal delivery	4.3%	
C-section	3.0%	
Breastfed	3.7%	
Not breastfed	3.9%	
Can Paed Soc (1997)^		12.6%
HIV-co-infected	21.0%	

*Sources: *NIH Consensus statement, 2002*[106]
**Yeung et al, Hepatology 2001*[104]
^*Pediatrics &Child Health, 1997*[105]

The role of sexual transmission of HCV is still debatable. While it is not an efficient route of HCV transmission, due to its nature the actual number of infected persons may be substantial. An estimated seroprevalence of HCV among long-term monogamous partners of HCV-infected persons in the United States is 2-3%, but it doubles to 4-6% among individuals involved in high-risk sexual activities (e.g. those with multiple sex partners, sex workers, and men who have sex with men)[106]. However, even in these so-called "high risk" groups the rates of HCV are lower than those of many other sexually transmitted diseases, including HIV and hepatitis B. On the other hand, studies from Egypt demonstrated potential sexual transmission in monogamous couples from 3% to 34%. Moreover, as reported by Kamal et al, 15% of sexual contacts of individuals with acute hepatitis C developed HCV viremia, and the identity of the virus was confirmed by

phylogenetic analysis[107]. Yet another prospective cohort study found no evidence of HCV transmission between spouses after 3 years of follow up[109] (Table 2.7).

Table 2.7 Risk of sexual transmission of HCV

Population	HCV transmission	Reference
Steady monogamy - Overall incidence - High risk (STD, sex workers)	<3% partners infected <0.1% per year 4-6%	*Tetrault N*[108], *Am J Gastro, 2005*
Prospective cohort study of steady monogamous spouses, no other risk - At entry - 3 years of follow-up	 2% (12/600) 0% (0/216)	*Tahan et al.*[109], *Am J Gastro, 2005*
MSM cohort, Montreal - At entry - Annual Incidence	 2.9% (31/1,085) 1 per 2,653 person-years	*Alary et al.*[110], *Am J Pub Health, 2005*
Spouses of health care workers with acute hepatitis C, no other risks	15% (8/52)	*Kamal et al.*[107], *J Virol. 2004*

Some additional factors may increase the risk of contracting hepatitis C virus, such as history of incarceration, with 25-40% of inmates infected due to frequent sharing of sharp instruments, IDU or snorting equipment, and other items. Similarly, residence in the hyperendemic areas, such as Egypt or some regions of Taiwan and Japan, where incidence rates of HCV infection were reported 110 per 10,000 and 28-36 per 10,000 respectively[69], and such a large reservoir of individuals infected with HCV provides a source of transmission to others at risk.

Summarizing various, mostly cross-sectional, studies, the reported prevalence of HCV infection ranges from 0.2% to 90% and depends primarily on the specific groups studied (Table 2.8).

Table 2.8 Estimated prevalence of HCV in different subpopulations (%)

Population	USA	Canada	World
History of IDU	72 - 89	45 - 82	60 - 80
Prison Inmates	30 - 40	25 - 40	20 - 45
Transfusion recipients	5 - 9	1.8 - 3.2	5 – 10
Blood Donors	0.16	0.2	0.7 - 4.9
Organ Donors	2.4	1.0	2.0 - 4.9
Pregnant Women	1.0	0.9	0.9 - 2.4
General Population	1.5 - 2.3	1.2 - 2.0	0.6 - 2.9

2.5. Hepatitis C in Aboriginal Populations of the World

While ethnic variations in the prevalence of other hepatitis viruses (A, B, D, and E) are reported in many parts of the world, with the highest prevalence among aboriginal (often socially and economically disadvantaged) populations, the case is not so clear when it comes to hepatitis C virus. The paucity of published information may play a certain role in this. To date, only studies from South East Asia clearly documented an increased prevalence of hepatitis C in aboriginal inhabitants. A number of studies among Taiwanese Aboriginals have been reported to date. The prevalence of HCV in these populations ranged from 17% to 35%, compared to 1% among adult volunteer blood donors[111-114]. Suggested routes of infection in these populations include the possible contribution of illegal medical services and practices[111], poor antiseptic medical practices

and the use of non-disposable medical instruments due to the insufficiency of medical personnel and facilities in these communities as compared with the other regions in Taiwan at the time[112]. The use of non-disposable needles during mass vaccination campaigns may have been another contributing factor.

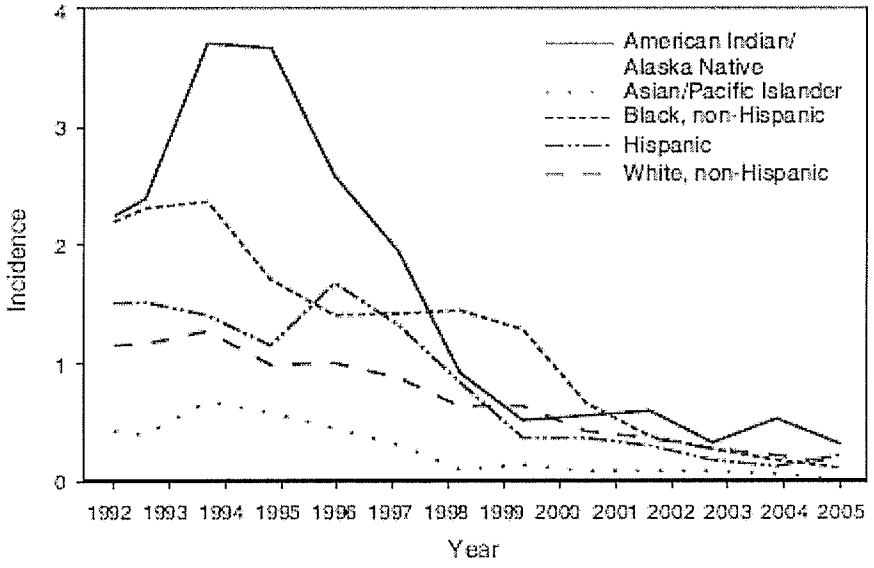
In Mongolian members of nomadic tribes who lived in "gers" (movable houses) around the capital city of Ulaanbaatar, the prevalence of hepatitis C was found to be 17%[65], but it was similar to the prevalence of hepatitis C among the residents of the city (16%). However, this could be a reflection of geographic differences in HCV prevalence, which is known to be extremely high in Southeast Asia.

Published studies of hepatitis C prevalence in Australian Aboriginals report a similar prevalence of anti-HCV among aboriginal and non-aboriginal inmates, but this is most likely the result not of ethnicity but of risk factors such as being incarcerated and/or being an injection drug user[115,116]. In addition, a number of studies of Aboriginal communities found that the involvement in injection drug use is on the rise among Australian Aboriginal people, particularly among females[117].

It is not known how common acute or chronic HCV infection is among American Indian and Alaska Natives. However, chronic liver disease is the 5th leading cause of death among American Indian and Alaska Natives compared to the 12th leading cause in the general United States population[118]. Most certainly, chronic liver disease resulting from infection with HCV contributes to this ranking. Historically, the incidence of hepatitis C among American Indians/Alaska Natives was the highest in the USA (Figure 2.12).

While declining significantly since the mid-90s, it still remains somewhat higher than for the rest of the US population. Thus, the incidence of acute HCV infection in 2005 was 0.36/100,000 among American Indians/Alaska Natives, compared to the lowest incidence of 0.02/100,000 among Asians/Pacific Islanders[70]. According to the US Department of Human Services, in 2006 American Indian/Alaska Natives were 2.7 times more likely to develop a case of hepatitis C, as compared to the Caucasian population. Thus, the incidence of acute hepatitis C in 2006 among American Indians/Alaska Natives was 0.54 per 100,000 population compared to 0.20 per 100,000 among Caucasians[119].

Figure 2.12 Incidence of acute hepatitis C per 100,000 population by race/ethnicity and year, USA, 1992-2005



**Acute hepatitis C was reported as hepatitis NANB up until 1995*

Source: Wasley et al. MMWR 2007;56(3):1-24[70]

A recent published study of the epidemiology of hepatitis C among Alaska Natives[120] suggests the minimum prevalence estimates of 0.82%, which is somewhat lower than the prevalence of 1.8% that is reported in the general US population by Alter[67]. According to other reports, prevalence rates of hepatitis C in the Arctic are <1.4%[121,122.] A high prevalence of both HCV exposure and chronic hepatitis C was reported in urban native-American population in Omaha, Nebraska. Antibodies to HCV were found in 11.5%, while chronic infection was present in 8.6% [123].

Several studies from South America reported either absence or low prevalence of infection with hepatitis C virus among various Latin American indigenous communities and tribes. In Bolivia, no carriers of HCV antibodies were found in indigenous communities of the Andean plateau[124]. A study of an indigenous tribe in Brazil (Parakana tribe) revealed HCV prevalence of 1.4% and 1.6% among two communities[125]. Another study of the Brazilian Amerindian population (Karitiana Indians) revealed antibodies to HCV in 1.7% of subjects[126]. None of the 550 samples taken from Bari Indians, living in different mountain communities in Venezuela, were found to be positive for anti-HCV[127-128].

The reported prevalence of hepatitis C in Siberian natives, whose culture and living conditions resemble those of Canadian Inuit, was 1.4%[129]. Anti-HCV prevalence among aboriginal inhabitants of Northwest Siberia (Nenets) was as low as 0.9%[130]. Similarly, the prevalence of HCV infection among West Greenland Inuit was 1%[131]. Notably, all of the

above studies unanimously reported both very high hepatitis B infection and carrier rates as well as extremely high rates (where tested) of hepatitis A infection.

The reasons for the apparently low rates of hepatitis C infection in Australia, South America, or the Arctic North are not clear. According to the Australian Federation of AIDS Organizations, it is just a matter of time before a substantial increase in HIV (and, therefore, in HCV) rates among indigenous drug users in Australia become evident[132]. Echevarria et al. (1996) suggested the possibility that the marginalization of indigenous populations of South America regarding access to the health care system prevented these populations from being infected with hepatitis C via medical interventions[128]. In the northern and Arctic regions, injection drug use was not common, if practiced at all, and drugs were not readily available. This possibly played a role in keeping Russian Arctic communities relatively clear of the virus. However, a more satisfactory explanation of the observed phenomena is yet to be proposed.

2.6 HEPATITIS C IN CANADIAN ABORIGINAL POPULATIONS

While a wealth of information has been accumulated about various clinical and epidemiologic aspects of hepatitis C, the true extent of infection and its burden among Canadian Aboriginal populations remains largely unknown. Recently, data emerged suggesting that this particular segment of the population might suffer from a higher rate of hepatitis C than Canadian-born non-Aboriginal individuals. This is in resonance with the opinions of both clinicians and individuals who work directly with clients in the area

of hepatitis C support, prevention, and control. However, published data that systematically examine this question are limited. For the most part, information analyzed with regard to ethnicity has concerned population groups already at higher risk for the acquisition of blood borne infections in general (such as prison inmates and injection drug users). As noted by Riben et al., the national surveillance data is not sufficient for determining the number of cases of hepatitis C among Aboriginal populations either, because most provinces do not collect information on ethnicity. The use of computerized provincial databases can assist in identifying cases only among Treaty Status First Nations but it precludes the identification of Inuit or Métis or non-Treaty Indians[133].

The already mentioned large population-based studies conducted within the National Health and Nutrition Examination Survey (NHANES-III and NHANES 1999-2002) revealed that the prevalence of hepatitis C in the United States varied within different ethnic groups, with the highest prevalence of HCV infection found in minority populations[67-68]. Thus, one can not simply assume that the prevalence of hepatitis C infection in Aboriginal populations would be the same as that reported in the general population residing in urban centres (from where the majority of data have been collected to date). Moreover, the diversity of North American populations, both in the United States and in Canada, each with a distinct cultural, historical and genetic heritage provides both a background and a partial explanation for the differences in the epidemiology of many diseases within various ethnic populations. Furthermore, as repeatedly demonstrated for other forms of viral hepatitis as well as for tuberculosis, sexually transmitted diseases, etc., there is a consistently increased prevalence of these

infections among Aboriginal populations as compared to Canadian-born non-aboriginal people[134-136], possibly due to different patterns of risk and various contributing factors.

Reported cases of hepatitis C in the First Nations population in 1999 varied between the provinces and comprised from 0.4% to 29.3% of all reported cases within the province[133]. Rates of reported HCV infection among First Nations in Saskatchewan tripled in the 5-year period from 1994 to 1998[133,135,137]. Similarly, rates of newly reported HCV infection in Alberta during 1998-2001 were 4 times higher for the First Nations compared to the non-First Nations populations: 283.6 vs. 68.4 per 100,000 population respectively[138]. In the same period Manitoba rates were 680.2 vs. 188.1 respectively[139] (Figure 2.13 and Table 2.9).

Figure 2.13 Rates of newly reported HCV infection in Prairie Provinces, First Nations vs. non-First Nations

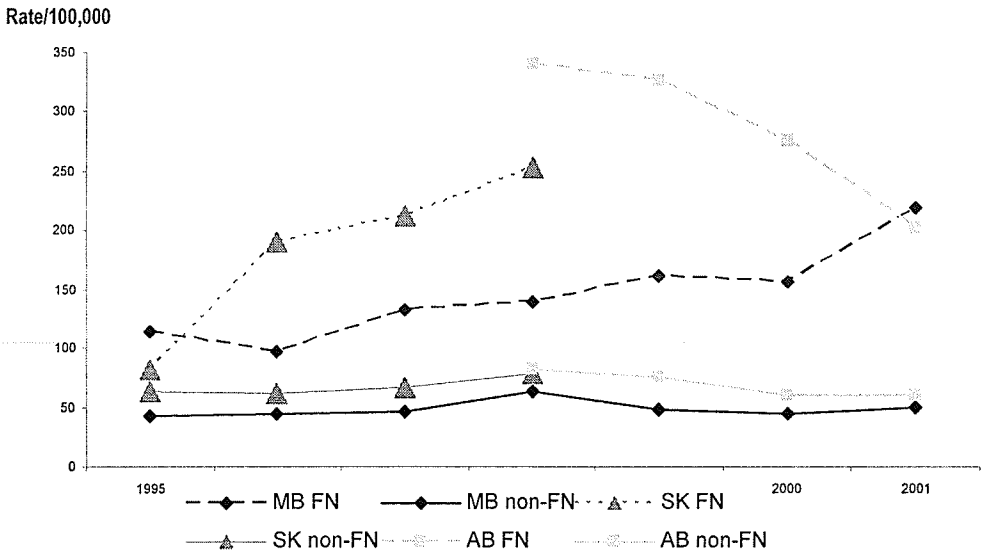
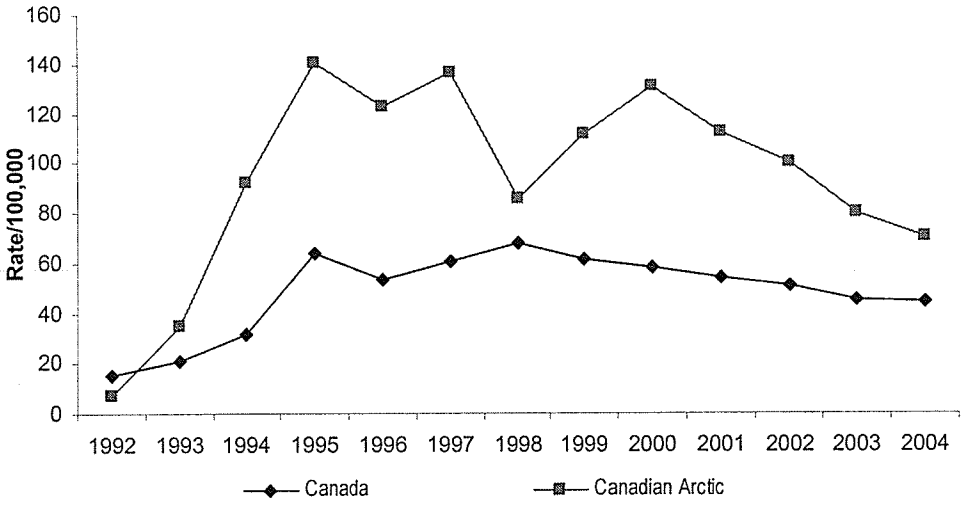


Table 2.9 Rates of newly reported HCV infection in Prairies, FN vs. non-FN

Population	1995	1996	1997	1998	1999	2000	2001
MB FN	113.8	96.9	132.3	140.0	161.5	156.9	218.5
MB non-FN	43.0	44.0	46.3	63.1	47.5	44.4	49.5
SK FN	81.2	191.1	212.6	253.1			
SK non-FN	63.7	61.6	67.0	78.6			
AB FN				339.1	327	275.2	202.3
AB non-FN				81.5	74.2	59.3	59.5

In British Columbia, the prevalence of anti-HCV was 18% amongst attendees of a First Nations alcohol and drug rehabilitation program[140]. The Enhanced Surveillance of Canadian Street Youth study revealed 6% of self-identified Aboriginals in British Columbia to be anti-HCV positive[133]. Rates of hepatitis C in the Canadian North (North West Territories, Yukon, and Nunavut) are among the highest in Canada[78] (Figure 2.14).

Figure 2.14 Rates of newly reported hepatitis C, Canada and the North, 1992-2004



Source: PHAC, Disease Surveillance, Notifiable Diseases On-Line[78]

While they represent only 6% (Manitoba Health registry count) to 10% (statistics Canada 1996 count) of the Manitoba population, 18%-20% of all reported hepatitis C cases in 1999 - 2003 were among self-identified Aboriginal people[139]. Based on these data, the known prevalence of hepatitis C among Manitoba First Nations is 1.5% as compared to approximately 0.5% for the non-aboriginal Manitobans. A recent cross-sectional survey of three rural communities revealed that the evidence of a past hepatitis C infection in the First Nations community in central Manitoba was 2.2%, while in the two Inuit communities it was a disproportionately high 15.2%[49-50]. The only population study describing the prevalence HCV infection in First Nations and non-First Nations populations came from Manitoba. According to the public health laboratory data, 10.3% of all confirmed positive results for antibodies to HCV in the province were from First Nations individuals, who represent approximately 6% of the province's population[141]. This data confirms the excessive burden of HCV infection in Canadian First Nations.

Initiated by Health Canada in 1998, an Enhanced Hepatitis C surveillance system included four health regions (Calgary, Edmonton, Winnipeg, and Ottawa-Carleton) and it accounted for ~11% of the Canadian population. The system provides estimated data on the incidence of acute hepatitis C in these sites. While an overall incidence of acute hepatitis C cases was 3.64 per 100,000 in 1999 and 3.29 per 100,000 in 2000, the rates were 7-8 times higher for aboriginal than for non-aboriginal, non-immigrant Canadians: 18.8 vs. 2.25 per 100,000 in 1999 and 17.5 vs. 2.57 per 100,000 respectively[142].

Published information on the prevalence of hepatitis C among Aboriginal people within the study of "high risk" populations in Canada came from several provinces. The highest prevalence of HCV markers (65% - 90%) reported to date is among populations of injection drug users. A recent study described the prevalence of viral hepatitis A, B and C markers among street involved youth in Winnipeg and found that the anti-HCV prevalence among self-identified Aboriginal youth was 20.1% as compared to 14.4% among those of non-aboriginal ethnicity[143]. When further analyzed, the rates of HCV infection were 22.3% among self-identified Métis and 19.4% among self-identified First Nations participants. Overall, Aboriginal people were over-represented in the cohort of street involved people (62%) and 33% of them reported injection drug use (IDU) compared to 22% of non-aboriginal individuals involved in with IDU *(Ibid)*.

A prevalence of hepatitis C was reported to be 18% among attendees of First Nations alcohol and drug rehabilitation program in British Columbia[133]. A large incidence study of HCV infection among British Columbia injection drug users during an HIV outbreak provided data on hepatitis C incidence and prevalence among the Aboriginal IDU population[140]. The overall prevalence of HCV at enrolment in this study was 81.6%. Forty percent of initially seronegative participants acquired HCV during the 16-month of follow-up. The seroconversion was slightly more frequent among Aboriginal drug users (53%) than among white (43%) and significantly more frequent than among individuals of other ethnic backgrounds (26%)[140].

The second highest prevalence of hepatitis C in Canada is documented among populations of prison inmates (25% - 40%). The results of the Prince Albert Seroprevalence Study, conducted in the community and provincial correctional facilities (Saskatchewan), revealed the prevalence of HCV infection amongst injection drug users to be 49.5%, while that amongst their sexual partners who were not injection drug users was 6.3%. The total prevalence was 40.7%, and 92.0% of the study population were Aboriginal people[144]. According to the Correctional Services of Canada Report (2000), the Edmonton Institution for Women had the highest rates of hepatitis C infection (74.6%) and HIV (11.9%), and over 35% of those infected were Aboriginal[145]. Co-infection with both hepatitis C and HIV poses particular concerns, as HIV may expedite the progression of hepatitis C to severe hepatitis and cirrhosis. There is an alarming over-representation of co-infected individuals of aboriginal heritage. Likewise, the data from the Lethbridge HIV Connection (an organization working with both HIV and HCV programmes) revealed 90% of co-infected people are Aboriginal, although this ethnic group only comprised 7.6% of the total population in the Region[146] (Chinook health Region, Alberta). Even among populations of similar risk, Aboriginal peoples still have a higher prevalence of HCV infection.

2.7 FACTORS CONTRIBUTING TO THE INCREASED PREVALENCE OF HCV INFECTION IN THE CANADIAN ABORIGINAL POPULATIONS

Indigenous peoples of Canada include many geographically diverse groups of people with distinct cultures, languages, and history. Their health, environment, and lifestyle are

unique to each particular group, yet a nearly universal experience of colonization, urbanization, and loss of traditional culture is common by Aboriginal peoples regardless of the geographic area they inhabit. Social disadvantages experienced by people generation after generation, could not but shape the collective and individual coping responses, which are frequently associated with risk taking rather than risk decreasing. Colonial policy towards aboriginal peoples in North America (and similarly in Australia, New Zealand, Russia, and other countries with a colonial past) created not adaptation and assimilation with the dominant culture but social marginalization, loss of cultural identity, and, ultimately, disenfranchisement of aboriginal peoples. The colonial intent of eradicating aboriginal cultures and the simultaneous imposition of the colonizing culture's value system has led to a marginalized socialization response in a lot of individuals of various aboriginal cultures. The product of such a form of socialization is that many individuals tend not to function well either in their own culture or in the dominant majority culture.

The overall poor health status and the unhealthy lifestyle with poor diet and high body mass index, alcohol and drug abuse, as well as high prevalence of mental health problems, chronic diseases such as diabetes, renal diseases, cardiovascular diseases, and other ailments are common in Aboriginal populations[147]. As study after study reveals, poor health and such social issues as poverty, low education level, and high unemployment among Aboriginal people may lead to an early and more regular involvement in high-risk activities[147-153]. Hepatitis C should be viewed as not just a medical problem, but first and foremost a social problem, the medical side of it (the

having of the disease and its consequences) being a consequence of a combination of structural inequalities exhibited in factors such as a socioeconomic status, level of education, and psychological problems. These may be the real reasons which put Aboriginal people at an increased risk for infection with the hepatitis C virus. In tune with the idea of empowerment of individuals and groups, it is important to hear what the Aboriginal people themselves say about why they are at risk for infection with the hepatitis C virus. The Chee Mamuk Aboriginal program identified the following factors responsible for the high rates of hepatitis C in their Hepatitis C teaching toolkit: Nomadic Lifestyle, Residential School Syndrome, Loss of Culture and Spirituality, Language and Literacy Issues, Loss of Traditional Parenting Skills, Breakdown of Family, Unhealthy Foster Care, Sexual Abuse, Low Self-Esteem, Isolation, Lack of Awareness, Alcohol Abuse, Injection Drug Use, Time in Prison, Tattooing, and Poor Access to Health Services[154].

Injection drug use, time in prison, and tattooing are the most obvious immediate factors which place an individual at an increased risk of acquiring hepatitis C infection. Since an effective screening of all blood products was instituted in Canada in 1990, blood transfusions are very safe and they no longer pose an appreciable risk for contracting hepatitis C. At present, injection drug use is the principal and most efficient route of acquiring hepatitis C. High rates of involvement in injection drug use among aboriginal Canadians, and youth in particular, are well-documented[143,148,155-156]. In a study of risk behaviour among Aboriginal youth in seven Canadian cities, 21% of 15-24 year olds reported injecting drugs[155]. Among attendees of *Vancouver's Needle Exchange Program*

the prevalence of HCV was 88%, and 27% of clients were First Nations[156]. In yet another study of injection drug users in Vancouver, the prevalence of hepatitis C among aboriginal drug users was 90%[148]. In both the study of street connected youth in Winnipeg and *Winnipeg Injection Drug Epidemiology* (WIDE) study, a disproportionately high percentage of participants identified themselves as Aboriginal (63% and 64.2% respectively)[143,149]. As many as 40-50% of drug users report sharing needles (both lending and borrowing), thus effectively propagating the infection among the IDU community. It is also suggested that the sharing of needles is more common in a similar shared ethnic context[150]. Thus, Aboriginal drug users share drug injecting/snorting paraphernalia mostly with each other. This may explain why even among the groups of similar risk behaviour, such as IDU, the rates of hepatitis C infection are still higher among drug users of aboriginal ancestry as compared to non-aboriginal drug users[148].

Hepatitis C is also a significant health problem in correctional facilities, with 27-40% of inmates being infected with HCV[156-158]. While the estimated prevalence of hepatitis C infection in Canada is 0.8%, it is 20 times higher among Canadian inmates[159]. Again, the major risk factor is the use of injection drugs either in the past or while incarcerated. For obvious reasons, the sharing of needles is widespread. 82% of those who continued using drugs in prison reported sharing needles[158]. Tattooing is another risk factor prevalent in correctional institutions, with the common practice of re-using equipment due to limited access to sterile instruments. This provides an effective environment for further spread of hepatitis C virus among prison inmates. Furthermore, in contrast with the expected proportion of 2.5%, aboriginal people represent a significant proportion of inmates (17%

of male and 26% of female inmates), and the numbers are even higher on the Prairies (49% in Manitoba and 72% in Saskatchewan provincial institutions 41%)[159,160]. Thus, a significant group of Aboriginal individuals is at risk of acquiring the hepatitis C virus while incarcerated.

The over-representation of people of aboriginal ancestry among injection drug users and prison inmates (both groups with high prevalence of HCV) promotes the continuous transmission of HCV infection among Aboriginal people[131,135-137,148,149,156]. The HCV-infected inmates returning to their home communities provide a continuing source of infection, as the probability of them being treated while incarcerated is extremely low. Similarly, access to quality health care and treatment in particular is a significant problem for those addicted to drugs. An IDU community worker from British Columbia explained: "The biggest challenge people face is treatment. Will they qualify and will they be able to handle the treatments? The criteria in BC [and elsewhere in Canada] are very rigid and a lot of our clients don't meet these criteria so treatment is denied"[161]. An IDU community worker in Kingston resonates: "*Too often doctor [sic] doesn't offer any follow-up after they [injection drug users] test positive for hepatitis C because they are drug users. The doctors are passing judgment that the clients are doing something they shouldn't do*"[162]. Addicted individuals are expected to abstain from drug and/or alcohol use for at least 6 months to be considered for treatment (the reasons for that are risk of re-infection if IDU is continued as well as compliance with the weekly treatments which last for a year). If these individuals continue their at risk behaviour (which happens more

often than not) treatment is not offered and in the meantime they continue to be a reservoir of infection.

As evidenced from the analysis of both NHANES hepatitis C studies, injecting drugs and high-risk sexual activity had the strongest association with the HCV infection among adults 17-59 years of age, but also independently associated were poverty, fewer than 12 years of education, and being divorced / separated[67-68]. The first two (poverty and a low level of education) as well as high rates of unemployment and unstable housing were found to be prevalent among the Winnipeg IDU population[149]. Moreover, a high mobility of Aboriginal people between reserves and inner city centres may introduce HCV infection even in remote (and previously unaffected by HCV) aboriginal communities[148,149,163]. Inmates returning to the communities, street-involved people, the homeless or those with unstable housing can all be a means of introducing hepatitis C to reserves and off-reserve communities. Their limited income may be conducive to sharing personal hygiene items such as razors and toothbrushes, which is also implicated as a possible medium of hepatitis C transmission. More importantly, high mobility of injection drug users living off reserve between urban areas and home communities facilitates sharing injection and snorting equipment. For example, a potential dispersion of HIV and other blood-borne pathogens into rural American Indian / Alaska Native communities already has already been reported, presumably being a consequence of regular migration between rural and urban areas[163,210]. Similarly, high mobility of the Winnipeg IDU population and the increase in the number of HIV cases from the rural communities has been reported[148,149].

An HIV epidemic provided additional insights into distinct patterns of risk and prevalence of infection among aboriginal and non-aboriginal Canadian populations. According to Health Canada, there is no evidence that the HIV epidemic among Aboriginal peoples is fading. The proportion of newly reported HIV cases attributed to Aboriginal people increased from less than 1% prior to 1990 to almost 24% in 1999. Even more important for hepatitis C, the proportion of HIV cases attributed to IDU decreased among Caucasians while steadily increasing among Aboriginal Canadians: from less than 5% before 1990 to 19% in 1991/93 to 34% in 1994/96 to as high as 51% in 1997/99[149,164]. Similarly, in British Columbia the identification of IDU as the primary risk factor for HIV/AIDS was reported to be 50% for Aboriginal women and 19% for Aboriginal men, compared to 7.4% and 3.2% for non-Aboriginal women and men, respectively[156]. This trend has direct implications for the potential for HCV spread amongst Canadian Aboriginals. This is very similar to the findings of the WIDE study which documented that since the mid-1980's the number of [self-identified] Aboriginal people initiating drug injections exceeded the number of non-Aboriginals, while the opposite trend was noted prior to the mid-1980[149].

Another alarming finding of the *WIDE* study was the fact that while almost 80% of participants reported ever having been tested for HIV, only 45% reported having been tested for HCV and 36% for HBV, possibly pointing to a lack of awareness about viral hepatitis B and C in this segment of the population[149]. The same problem was identified by the *Chee Mamook* group[154]. Similar themes are repeatedly found while conducting needs assessment or hepatitis C programmes evaluation. Comments such as "*many of the*

street–involved people and women in the correctional system devote most of their energy to surviving and hepatitis C is a lower priority among many problems" or "*...there is lack of information particularly when compared to the extensive information available on HIV*"[165] are common. There is virtually no access to literature on hepatitis C in Aboriginal languages. Aboriginal educator Nicole Eshkakogan reported in 2003 that "*most Aboriginal youth are unaware that hepatitis C is spread through contact with blood. There is just not much being done to educate or expand awareness about hepatitis among aboriginal youth*"[166]. Even more people are still not aware that sharing drug snorting equipment and participating in traditional rituals with skin cutting, tattooing, and body piercing with shared instruments also poses risk of hepatitis C transmission.

From an Aboriginal prospective, the loss of traditional culture, parenting and teaching correlates with high rates of hepatitis C. Aboriginal patient advocate Carl Orr says: "*if we think about hepatitis C from a different perspective, there is correlation between traditional teachings and hepatitis C. Traditionally, when an animal is caught and skinned, it is very important to be careful with the animal's blood. If any of the animal's blood enters open wounds, that animal's disease may be passed on. The same principle applies for hepatitis C... We must ask ourselves: Why have Aboriginal People lost this traditional teaching along the way? Why has hepatitis C infected aboriginal population in such high numbers?*"[151]. This is an excellent example of both how the suppression of traditional knowledge may have contributed to the spread of high-risk behavior, and how the recovery of traditional teachings can pave the way to effective disease prevention.

2.8 NATURAL HISTORY OF HEPATITIS C

Hepatitis C is caused by a RNA virus, which belongs to the flaviviridae family. The virus is highly variable and is classified into 6 major genotypes from 1 to 6 and more than 100 subtypes[167]. Viral genotype does not influence the clinical picture of the disease, but it does affect treatment outcomes and the duration of therapy, which will be discussed later. After the acquisition of HCV, the average incubation period lasts for 6-7 weeks, but may vary from 2 to 26 weeks (Table 2.10). In more than 80% of infected individuals acute hepatitis C is asymptomatic, and only about 20% may experience various symptoms of malaise, jaundice, and other symptoms of acute hepatitis such as abdominal pain, nausea, have dark urine and pale stool, etc. with the elevation of ALT more than 10 times the normal range. Acute HCV infection has a variable course. Some individuals are able to spontaneously clear the virus, their ALT returns to normal, and HCV-RNA is undetectable after 6 months from infection. However, in the majority of cases the infection becomes chronic, with fluctuating levels of both ALT and HCV-RNA titers.

Table 2.10 Natural history of HCV Infection

	Average	Range
Incubation period	6-7 weeks	2-26 weeks
Acute illness (jaundice)	Mild (≤20%)	
Chronic infection	75%	50% - 85%
Cirrhosis (20 yrs.)	10% - 20%	2% - 30%
- in children and young women	2% - 4%	
- in mid-age transfusion recipients	20% - 30%	
Cirrhosis (40 yrs.)	20% - 40%	10% - 50%
- in those <40 yrs. when infected	10% - 30%	
- in those ≥40 yrs. when infected	30% - 50%	
Mortality from chronic liver disease	1% - 5%	
HCC	1% - 5%	

Unfortunately, there are no reliable predictors of spontaneous resolution of hepatitis C, and the answer to the question of frequency of HCV clearance after initial infection remains elusive. While earlier studies, based primarily on the observation of transfusion recipients, reported very high levels of chronicity – up to 85%, later population cohort studies demonstrated a much lower proportion of chronicity (55%) after documented iatrogenic acquisition of HCV in younger healthy women and children[168-170]. Hoofnagle suggests that between 55% and 85% of infected individuals develop chronic infection[167]. The two aforementioned NHANES studies of HCV infection in the United States, with thousands of participants tested, revealed that the prevalence of chronic hepatitis C among those infected with HCV was 72% in 1988-1994, showing that less than 30% of those who acquired HCV infection successfully cleared the virus. Even smaller was the proportion of viral clearance in the 1999-2002 study cohort, with the prevalence of chronic HCV infection of 81.2% and viral clearance of less than 20% [67-68].

According to the data from Dawood and colleagues, ninety percent of those tested positive for antibodies to the hepatitis C virus in Manitoba also had chronic infection[141]. In a sophisticated study by Kamal, 52 health care workers with documented acute hepatitis C after needle stick injury were followed prospectively. In this cohort, only 17% of the index patients had spontaneous recovery (9/52), while 83% became chronically infected[107].

The course of chronic infection is also characterized by great variability. While some individuals have no or minimal chronic hepatitis and might even be unaware of their

infection, others experience progressive disease with significant morbidity and an increased risk of developing cirrhosis of the liver and liver failure, eventually resulting in death. As with the question of viral clearance, there are various estimates of the proportion of cases which progress to clinical hepatitis, cirrhosis, and its complications (Table 2.11).

Table 2.11 Progression of Chronic Hepatitis C to various clinical stages

Population	F/up (Yr.)	Cirrhosis (%)	HCC (%)	Death (%)
Prospective Studies:[170-173]				
- Acute transfusion-associated hepatitis	8-16 yr.	7.0-15.6	0-1.3	1.3-3.7
Retrospective Studies:[174-175]				
- Chronic hepatitis C	10-29 yr.	16.8-55.0	1.0-23.4	3.7-15.3
Cohort Studies:				
- *Recipients of contaminated Ig[167]	17 yr.	2.0	0	0
- *Pediatric cardiac surgery patients[169]	17 yr.	0.3	0	0
* *HCV-RNA positivity was 55%*				

Thus, the highest rates (%) of progression to cirrhosis were reported by several prospective studies of post-transfusion hepatitis and retrospective reviews of individuals with diagnosed chronic hepatitis C in the tertiary care centers[169-174]. In such cases, after 10-30 years of follow up, 7-55% of those with chronic hepatitis C developed cirrhosis, up to 23% developed hepatocellular carcinoma, and 1.3-15.3% died. However, cohort studies of pediatric patients and younger healthy females revealed a much more benign course of infection, both in terms of rates of chronicity (55%) and in terms of the progression to cirrhosis of only 0.3% and 2% respectively[167,169] (Table 2.11).

Various factors are known to influence the course of chronic hepatitis C. Age at initial infection has long been recognized as playing an important role in hepatitis C outcome. Age 40 and above at the time of HCV acquisition is unfavorable, as is the male gender. Alcohol consumption and co-infection with HIV are also known to promote progression. Some of the other factors, such as iron overload and hepatic steatosis, have been shown to negatively affect the outcomes of the antiviral combination therapy. Fatty liver, often with concurrent obesity, insulin resistance, and diabetes are common in chronic hepatitis C patients. All these related conditions can be associated with both disease severity and poor response to therapy[178-181]. However, the latest research demonstrates that it is not the presence of fatty liver per se but rather insulin resistance, showed evidence of an independent association with lower rates of sustained virological response (SVR) [179-180]. On the other hand, the Italian group demonstrated that the grade of steatosis was negatively associated with SVR[181].

Similarly, elevated liver iron is shown to be a negative prognostic factor for alpha-interferon response in chronic hepatitis C[182-185]. It was also an independent risk factor for liver fibrosis progression in the cohort of thalassemia patients[185]. However, the Trent Hepatitis Study Group in its repeat biopsy study demonstrated, somewhat surprisingly, that such factors as necroinflammation, duration of infection, alcohol consumption, ALT levels, current or past hepatitis B virus infection, ferritin, HCV genotype, and steatosis or iron deposition in the initial biopsy were not independently associated with the progression of hepatic fibrosis[186], while age and the presence of any fibrosis on the initial biopsy were. Some of these surprising findings could be explained by the relatively short

period of observation 2.5 yrs. as compared to the long course of the disease. The same study revealed that fibrosis progressed in less than three years in 33% of untreated hepatitis C patients, including those with persistently normal ALT. However, a few other studies involving assessment of biopsies found the higher necroinflammation score, older age, and alcohol consumption to be independent predictors of fibrosis progression[187-190]. The rates of progression in these studies were similar to that of the Trent group.

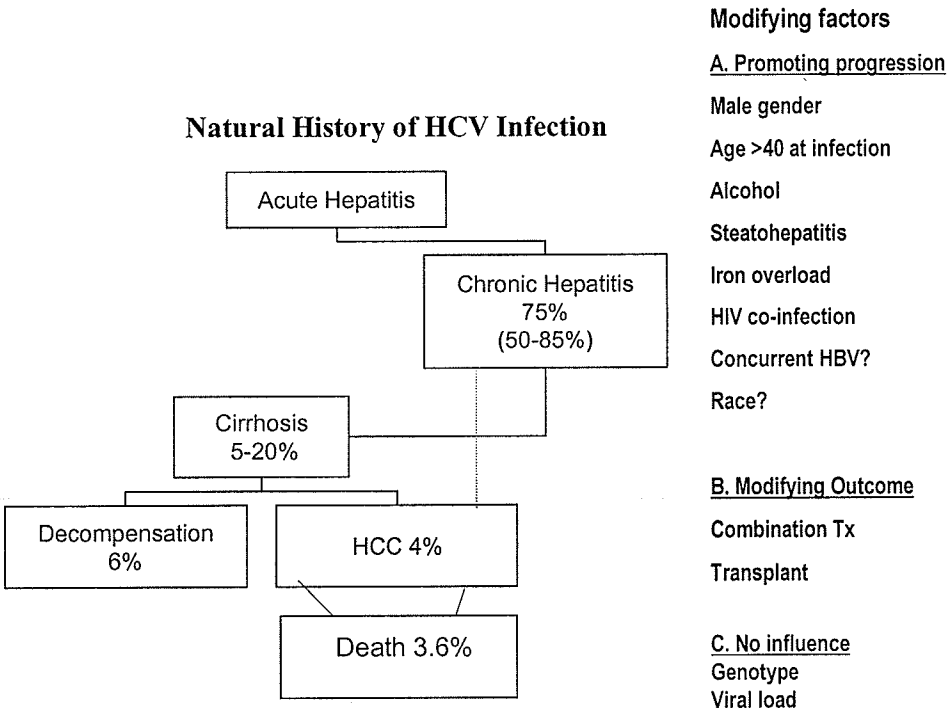
Viral load and viral genotype does not seem to influence the clinical picture of the disease, with the exception of the genotype 3 and its association with hepatic steatosis[191]. However, genotype does affect treatment outcomes and the duration of therapy. For instance, the response to treatment is higher for the infection caused by genotype 2 and 3 virus than genotype 1 or 4 disease, and the duration of treatment is 50% shorter (24 weeks) for the former as opposed to the latter (48 weeks), and the success of treatment is the most significant outcome modifying factor (Figure 2.15).

Chronic hepatitis C has an insidious course. It may (or may not) progress slowly and asymptomatically for the first two decades after infection. Some individuals may develop nonspecific symptoms of mild fatigue and malaise. In those patients whose chronic hepatitis C has a progressive course, clinically significant symptoms may first appear at the time of the development of advanced liver disease. In unfavorable cases, cirrhosis progresses to a decompensated state, which manifests in ascites, esophageal varices with or without bleeding, hepatic encephalopathy, and eventually liver failure. Others may develop hepatocellular carcinoma. Liver transplantation as the therapeutic option is available only to a small minority of individuals with end-stage liver disease. On the

other hand, successful treatment with combination therapy (pegylated interferon and ribavirin) is the most important factor for preventing the progression of chronic hepatitis C to its end stages and decreasing the burden of hepatitis C on the population level.

Freeman and Dore with colleagues developed a Markov model of liver disease progression. Their model estimated that the risk of progression to cirrhosis is 7% after 20 years and 20% after 40 years of infection[192-193]. Corresponding estimates for hepatitis C-related mortality are 1% and 4%. They confirmed that those with a heavy alcohol intake, who are co-infected with HIV or HBV, and those who have already progressed to moderate to severe hepatitis all are at increased risk of advanced liver disease.

Figure 2.15 Natural history of HCV infection and disease-modifying factors



2.9 NATURAL HISTORY OF HEPATITIS C IN FIRST NATIONS

While there is some evidence pointing towards an enhanced immunologic ability of First Nations individuals to effectively resolve HCV infection as compared to Caucasians[49-50], the extent to which this occur remains unclear. Analysis of nine years of data in Manitoba (1995-2003) revealed that while the total proportion of individual with self-limiting (resolved) HCV infection was only 10.3%, this was different when ethnic background was taken into account[141]. Thus, 14.4% of First Nations individuals had evidence of resolved HCV infection (anti-HCV positive and HCV-RNA negative test results) as compared to 9.8% of non-First Nation individuals. The proportion of females with resolved infection was somewhat higher than the proportion of males (16% vs.12%)[140]. Yet in a study of HCV prevalence in urban native population from the Great Plains area, while the prevalence of HCV exposure was 11.5% (8% among females and 18% among males), 25% of them had self-limiting infection[123]. Prevalence of chronic infection was 8.6% overall, 6% among females and 13% among males. Overall, 75% of infected individuals had chronic hepatitis, while 25% had evidence of resolved infection, with males and females having a similar proportion of viral clearance: 27% and 23% respectively[123].

On the other hand, Alaskan Natives have been reported to have rates of spontaneous clearance as a high as 56% as compared to 35% in Caucasians[194]. Similarly, in a large community-based cohort of illicit drug users in Vancouver, HCV clearance occurred in 23% overall, but increased HCV clearance was associated with the Aboriginal race (AOR 3.24)[195].

The course of infection among those who do develop chronic hepatitis C is a cause for concern. Alcohol abuse is a prevalent problem of First Nations people and a significant factor predisposing a person to the development of cirrhosis in HCV infected patients[3, 112,120,196-198]. Similarly, obesity and hepatic steatosis are associated with more rapid fibrogenesis[178-181], and these too are more common in the First Nations populations. Since approximately 50% of diabetics have fatty livers, one would justifiably expect higher rates of progression and/or more complications in HCV-infected diabetic patients. Among American-Indian women, type 2 diabetes was found to be more common in those with than in those without HCV infection[178]. Given that the prevalence of diabetes among First Nations peoples is at least 3 times higher than among their non-First Nations counterparts, one can predict more advanced liver disease and its complications among First Nations patients. Finally, HIV co-infection expedites progression to cirrhosis[152-153,184,199] and HIV/AIDS cases among Aboriginal peoples have increased steadily over the past decade: Aboriginal people, who make up only 5% of the total population in Canada, represent 16% of the new HIV infections[150,152].

These data confirm that chronic hepatitis C poses a significant burden and challenge to the Canadian First Nations populations and needs to be investigated more closely.

CHAPTER THREE METHODS

3.1 RESEARCH OBJECTIVES

The principal focus of the present work was to examine various aspects of viral hepatitis C infection in First Nations and non-First Nations populations of Manitoba. A key point was to determine whether and to what extent differences exist in the application of health services to the two populations. A further major objective was to assess the burden hepatitis C imposes on the health care system by evaluating whether individuals with chronic hepatitis C use health care resources more extensively as compared to non-infected individuals. Guided by these main goals, the project consisted of three distinct parts with three separate main objectives.

The first objective was to provide a descriptive epidemiology of hepatitis C infection in First Nations and non-First Nations Manitobans. This part of the study consisted of the following:

3.1.1 Objective 1: DESCRIPTIVE EPIDEMIOLOGY

ANALYSIS OF INCIDENCE AND DEMOGRAPHICS OF HCV INFECTION IN MANITOBA:

- overall and annual incidence of newly diagnosed HCV infection in Manitoba amongst First Nations and non-First Nations populations;
- incidence of newly diagnosed HCV infection in different demographic groups;
- incidence of newly diagnosed HCV infection in different geographic regions, such as by regional health authority (RHA) and by urban (Winnipeg) vs. South rural vs. Northern rural residence.

The second objective was to examine the natural history of chronic hepatitis C and compare clinical features of the disease between First Nations and non-First Nations populations.

3.1.2 Objective 2: NATURAL HISTORY AND CLINICAL FEATURES OF HEPATITIS C

DETERMINING THE EXTENT OF THE DISEASE BY CALCULATING PERCENTAGE OF INDIVIDUALS WITH:

- Decompensated cirrhosis (by identifying records containing specified procedure or liver disease sequelae-related codes) – see the methodology section below for detailed discussion.
- Conditions characteristic of the natural history of chronic hepatitis C: portal hypertension, hepatocellular carcinoma, ascites, esophageal varices, etc.

DESCRIBING OTHER IMPORTANT CLINICAL FEATURES BY CALCULATING PERCENTAGE OF INDIVIDUALS WITH:

- Concurrent alcohol abuse and alcohol-related liver disease.
- Other hepato-biliary comorbidities, including HBV infection, non-alcoholic fatty liver disease, etc.
- Non-hepatic comorbidities (chronic conditions) with clinical relevance to chronic hepatitis C, e.g. diabetes and HIV infection.
- All-cause mortality.
- In-hospital deaths.

The final objective of this study had two components. One was to determine if chronic hepatitis C infection resulted in an increased use of health care services by infected individuals compared to non-infected persons (by comparing overall health care use between First Nations and non-First Nations individuals with chronic hepatitis C and a demographically matched population control cohort). The second component was to examine and compare the liver disease–related health care utilization between First Nations and non-First Nations persons with chronic hepatitis C. Hence, this part of the study consisted of the following:

3.1.3. Objective 3: ANALYSIS OF HEALTH CARE UTILIZATION OF FIRST NATIONS AND NON-FIRST NATIONS INDIVIDUALS AND COMPARISON WITH MATCHED POPULATION CONTROLS

1. ANALYSIS OF HOSPITALIZATIONS:
    - Overall hospital use (percent of patients who had hospital records)
    - Out-patient hospital use (percent of patients who had outpatient hospital records with the stay of 0 days)
    - Hospitalizations (percent of patients who had inpatient hospital records and the length of stay $\geq$1 day)
    - Rates of hospitalizations per person/years
    - Rates of outpatient visits per person/years
    - Average length of stay (LOS) and percent of long stays (>1 month).

- Proportion of liver disease-related and non-liver hospitalizations (records with the most responsible diagnosis of liver disease)
- In-hospital deaths

2. ANALYSIS OF PHYSICIAN VISITS:
   - Overall physician contacts (percent of patients having at least one record of physician visit)
   - Rates of physician visits per person/years
   - Proportion of liver disease-related and non liver disease-related visits
   - Rates of care by specialists and GPs

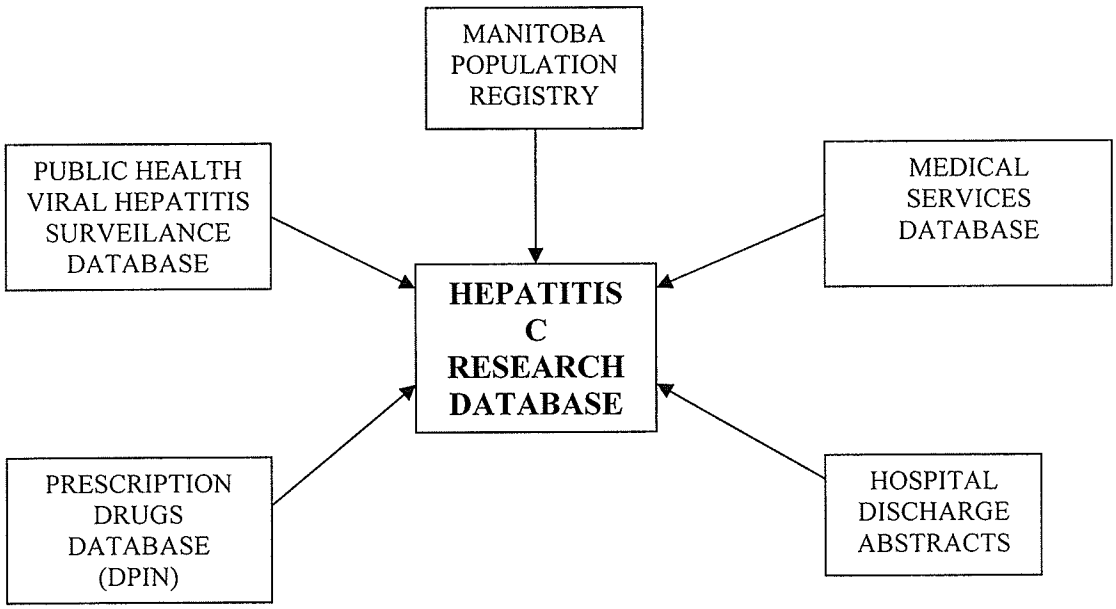
3. PRESCRIPTION MEDICATION USE
   - Overall use of prescription drugs (percent of patients having at least one record of a prescription drug)

4. RESOURCE UTILIZATION FOR HCV-RELATED CARE:
   - Proportion of chronic hepatitis C patients who underwent liver biopsy
   - Frequency and rates of procedures to control complications of advanced liver disease: paracentesis, treatment of esophageal varices, TIPS, etc.
   - Proportion of chronic hepatitis C patients who received liver transplants
   - Percentage of chronic hepatitis C patients who received antiviral therapy

3.2 DATA SOURCES

For the purpose of carrying out this project, the Hepatitis C Research Database was created. The database was developed by linking together the provincial Viral Hepatitis Surveillance Database with the Manitoba Health registry and medical coverage files, hospital separation records, physician reimbursement claims, and prescription drugs data (Drug Program Information Network) (Figure 3.1). All administrative databases except DPIN contain records dating back to 1970. The latter was introduced in 1994.

Figure 3.1 Structure of the Hepatitis C Research Database



The Hepatitis C Research Database is a population-based provincial cohort of individuals with chronic hepatitis C infection and matched controls, consisting of basic demographic data and complete health care utilization data extracted from the above databases. It is comprised of the following segments: 1) the CDC case file for all viral hepatitis reported to Manitoba Health; 2) the Manitoba Health registry and medical coverage file of CDC-

linked hepatitis cases and their matched controls; 3) a case-control file of extracted hospital separation records; 4) a case-control file of physician reimbursement claims; and 5) a case-control file of prescription drug data from the Drug Program Information Network (DPIN). The detailed description of source databases is presented below.

3.2.1. Viral Hepatitis B and C Surveillance Database

The foundation database for this project was the Viral Hepatitis B and C Surveillance Database, maintained by the Communicable Disease Control Unit (CDC) of the Department of Public Health, Manitoba Health. In Manitoba, all surface antigen (HBsAg) positive results for hepatitis B and positive hepatitis C antibody (anti-HCV) test results are reported to the Communicable Disease Control Unit and then referred to the appropriate public health jurisdiction for follow up. Public Health Nurses (PHN) contact newly identified HBsAg-positive and anti-HCV-positive individuals and complete an investigation form for each person. The investigation form includes patient's demographic, epidemiological and clinical data and information regarding their sexual and needle-sharing contacts. The information collected by the PHNs is then entered into a database managed by the CDC Unit. The database is an Access database with detailed demographic information on all individuals who have ever tested positive for hepatitis B and/or C in the province including the patient's name, date of birth, gender, address, regional health authority (RHA) based on the patient's residence at the time of testing, the patient's ethnicity (treaty vs. non-treaty status), Manitoba Health Registration Number (MHSC number) and Manitoba Personal Health Identification Number (PHIN).

The database also contains information on the physician requesting the testing including: the physician's number, facility number, and RHA. Other public health-required data are also captured in the database, such as the presence of clinical symptoms, identification of the person's risk factors such as exposure to blood and blood products, injection drug use or the snorting of drugs, high risk sexual activity, history of incarceration or of living in endemic countries, etc. However, because the patients' contacts with the public health nurses are voluntary, the public health interview information in the database is incomplete, since it is based only on those who agreed to provide such data and moreover on the data whose veracity as well as completeness can not be ascertained.

The records on all hepatitis C patients from this database were requested. After removing personal identifiers (keeping 3 first letters of the first and last names), the data was released in electronic form for use in this project. Through scrambled patients' PHINs, the database was linked to the Manitoba Health Population Registry and other administrative databases.

3.2.2. Manitoba Health Population Registry

The computerized provincial Population Registry has been maintained by Manitoba Health since 1970. The registry contains demographic information such as dates of birth, gender, treaty First Nations status, residential postal code; period of coverage data as beginning and end of coverage and the reason for ending (such as death, moving to another province, becoming subject to federal jurisdiction, etc.); Manitoba Health

Number, and individual PHIN. The Registry is regularly updated with the Office of Vital Statistics and the information on new registrations and deaths is added. Linking this data with the CDC cases enhanced the Research Database with the information on the length of follow-up (in cases of ended or interrupted coverage) and with information on deaths.

To compare the health care utilization of HCV and non-HCV infected individuals, a population control cohort was selected from the registry based on the following matching demographic variables: 5-year age group, gender, residential postal code, and treaty First Nations status. Hepatitis C cases identified in the CDC database were excluded from the population from which the control cohort was drawn. Details of matching process are described in Section 3.4.3.

3.2.3. Medical Services Claims Database

The Provincial Medical Services Database is maintained by Manitoba Health and Healthy Living (MHHL) and provides information on physician-patient encounters in the province. As most physicians in Canada, physicians in Manitoba a paid on a fee-for–service basis and submit their claims to MHHL for reimbursement. Salaried physicians also submit evaluation claims (shadow billing)[200]. All physicians' billing claims in Manitoba are submitted to the Manitoba Health Services Commission, and this information is entered to the database. Information is recorded in the database from physicians' reimbursement claim cards for emergency, ambulatory, hospital outpatient and office care, and therefore includes a record of all physician-patient interactions, including data on diagnostic tests and procedures performed in a physician's office or

laboratory. In the database, physician service records include information on the patient's identity (age, gender, residential area, etc.), date and type of service provided (according to the Manitoba Health tariff codes[201]), and for each service the reason for its provision, namely the most responsible diagnosis, which is coded according to the *International Classification of Diseases, 9-th revision, Clinical Modification* (ICD-9-CM) code. It also contains information on physician identifiers and specialty codes. Each billing record contains a single tariff and a single 3-digit diagnostic code. If more than one service was provided during a visit, then more than one claim for the same service date had to be submitted for payment, and the corresponding number of records added to the database for the same date. Generally, multiple records for the same visit are quite common, which makes this database the largest in terms of the number of records contained in the database.

3.2.4. Hospital Abstracts database

The Provincial Hospital Abstracts database is another source of data for the project. This database captures all hospitalizations, emergency department visits, day surgeries and procedures, etc. It includes all separations for Manitoba residents and non-Manitoba residents hospitalized in acute and chronic care facilities in Manitoba, as well as all separations for all Manitobans admitted to out-of-province facilities[202]. The records include information on the most responsible diagnosis, comorbidities, and complications. All hospital abstracts, whether inpatient or outpatient, use an identical format and are recorded in the same file[200]. This information includes the patient's identification data,

dates of hospital admission and discharge, admission type (emergent, urgent, elective, etc.), transfers, accident code, patient's separation, consult services, the patient's diagnoses and procedures performed in the hospital coded according to ICD-9-CM codes. Diagnosis types are recorded for all diagnoses (primary, secondary, or complication). Procedures are recorded with the date of the procedure, its location, and the specialty of the physician performing the procedure. Up to 16 diagnostic codes and up to 12 procedure codes can be recorded on each hospital abstract.

3.2.5. Prescription Drugs Database

The Drug Program Information Network (DPIN) is a database of pharmaceutical use and is the most recent addition to the administrative databases in Manitoba (since 1994). It is an administrative claims database of prescriptions dispensed for out-of-hospital usage in Manitoba to its resident population. It also includes prescriptions for outpatient use dispensed by hospitals. The DPIN database includes prescription data for Manitoba citizens who are registered with the Pharmacare, Nursing Home, Family Services and Palliative Care Drug programs. DPIN is administered through real-time computer links with every community-based pharmacy in the province and is maintained by the Manitoba Ministry of Health[203]. The claim data include the following information: the DIN (Drug Identification Number), the brand name, the generic name, the strength and the dosage form, the number of days supply, the metric quantity, the number of refills, as well as personal identifiers (PHIN) and physician and pharmacy identifiers, which make the linkage of these data possible.

3.3 Case Definition and Study Population

Case Definition

A case is defined as any individual who is a resident of Manitoba and who has ever tested positive for antibodies to hepatitis C virus (anti-HCV) by enzyme-linked immunoassay (EIA), and confirmed positive by recombinant immunoblot assay (RIBA) or polymerase chain reaction (PCR) for HCV-RNA. All diagnostic and confirmatory testing for HCV in Manitoba is performed by the Cadham Provincial Laboratories.

Study Population

Cases were derived from the Manitoba population of approximately 1,150,000[204-205]. Patients who received care in Manitoba but who were not residents of Manitoba are excluded from the study. The study period includes all available data from January 1, 1991, when diagnostic testing for HCV became available, to December 31, 2002.

The cohort of HCV-infected individuals was further divided into the two groups for subsequent analysis and comparison according to the presence or absence of a treaty status number. Information on treaty status is recorded in the Manitoba Health population registry ("A Code"). According to it, the current count of the Treaty First Nations is ~65,000 (approximately 6% of the Manitoba population)[204]. However, this may underestimate the First Nations population of the province by about 1/3 (see discussion of limitations below). Those identified by the "A" code comprised the "First Nations" group in the analysis. Those who do not have the "A" code in the Registry are labeled "non-

First Nations". That may include First Nations individuals without treaty status, the Métis, Inuit, as well as individuals of any other racial descent.

The non-infected control cohort was drawn from the general population of Manitoba in a ratio of approximately 20:1 (20 non-HCV controls per 1 hepatitis C case). Subjects for this [non-HCV-infected] cohort were randomly selected from the population Registry, excluding those subjects who are identified as the members of hepatitis C case cohort (HCV-infected). The non-HCV cohort was matched to the HCV cohort to control for the potential confounding according to the following variables: year of diagnosis of HCV, 5-year age interval, gender, residence (by the postal code), and Treaty status.

3.4 DATABASE LINKAGE PROCESS

3.4.1. Data preparation

The Manitoba Health Population Registry contained 1,852,466 unique records and included all individuals currently registered with the health coverage plan in Manitoba as well as historical records of those who had been previously registered with the plan; hence the total number of records exceeds the total number of current Manitoba residents by 60% (according to the 2006 Statistics Canada census, the population of Manitoba in 2006 was 1,148,401)[205].

The CDC Viral Hepatitis B and C Surveillance Database file contained a total of 7,578 records. There were 352 duplicate records for 176 PHINs for individuals having both

Hepatitis B and one for Hepatitis C. Such double records were converted into a single record with the information combined (hepatitis B data was added to hepatitis C record). The remaining empty records were eliminated, bringing the number of records to 7,402.

Further review of the eligible records revealed that there were 36 records with 16 unique PHINs containing multiple records with different demographic data. While PHINs were the same, the demographic information was different when records were compared on first and last name, sex, and birth date. A manual review of these records revealed that all of these records seemed to be unique people based on demographics. These records were forwarded to the Manitoba Health programmer in order to allow each record the opportunity to merge with the proper registry entry and to correct the PHINs. Nine PHINS (18 records) had reversed month and day of the birthday, and were corrected to a single record with the date of birth according to the registry. The remaining 27 records with 7 PHINs could not be linked back to the registry and were declared invalid. Eliminating these records created a "clean" copy of the CDC viral hepatitis file to a total of 7,375 unique records, which comprised 97.3% of the original data.

3.4.2. Linkage of CDC viral hepatitis surveillance database and population registry file

The CDC Viral Hepatitis Surveillance Database (CDC VHSD) is maintained and routinely updated by manual entry of the information received by the CDC Unit. As the result, it has missing values and incomplete entries for some of the essential data elements such as PHINs, dates, and some other demographic data. In order to fill in the

missing values and obtain the information on the health coverage for the study population, the population registry file was used. The main matching variable for the linkage of the CDC VHSD and population registry was PHIN. Other matching variables were last name (3 first letters), first name (3 first letters), date of birth, and sex. In the data sets released by Manitoba Health's programmers all original PHINs were scrambled, and last names were truncated after the first 3 letters.

Out of 7,375 records, 91% (6,701 records) linked to the population registry dataset by scrambled PHIN. Of these, 36 records (0.5%) were considered improper matches because their demographic variables did not match across the records. These records were added to the 674 records that had not matched by PHIN, creating a total of 710 records which needed to be linked by probabilistic matching techniques. Thus, the overall success of the deterministic matching was 90.4% (6,665 out of 7,375 records from CDC data file and population registry file matched completely by the selected variables).

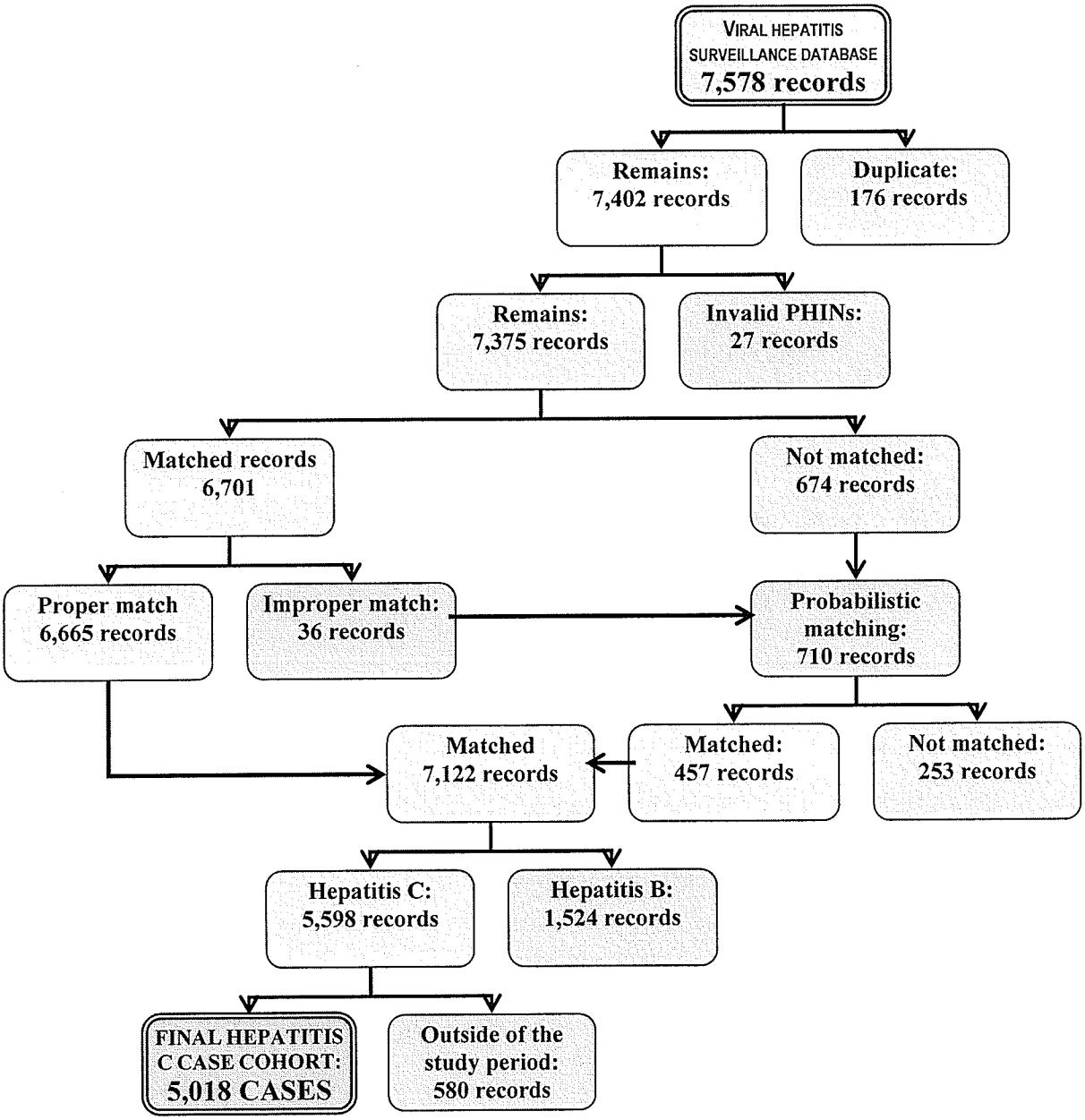
Probabilistic matching of 710 records that did not match in the previous step was done using the following 8 demographic variables: Last Name (first 3 letters), First Name (first 3 letters), sex, day of birth, month of birth, year of birth, Manitoba Health Family Registration Number, and the first three digits of the postal code (known as Forward Sortation Area-FSA). Because women routinely change last names via marriage, all probabilistic matching procedures were conducted separately for males and females. Using SAS Linkage Macro (linkpro)[206], another 457 records from the CDC VHSD were matched to the corresponding records from the population registry. The total matched set

comprised 7,122 records. Of these, 1,524 records were of hepatitis B cases and another 580 records were either prior to January 1, 1991 or after December 31, 2002, and were therefore excluded. The final hepatitis C case cohort contained 5018 records (Figure 3.2).

3.4.3. Selection of controls

Prior to obtaining health services information from administrative sources, a population-based control cohort was selected. The control cohort was drawn from the Manitoba population registry with the exclusion of those who were already identified in previous step as members of the hepatitis C case cohort. A random sample of approximately 100,000 records was selected and classified according to a 5-year age group (e.g. 30-34 yrs., 35-39 yrs., etc.), sex, residence (by FSA), and treaty status (by "A" code) to match the demographic and geographic distribution of the cases. Due to the small number of cases, several age groups were combined into larger age intervals: 0-10 yrs., 11-17 yrs., 18-24 yrs., and 75+ yrs. The control cohort was drawn in a ratio of approximately 20 to 1 (20 non-HCV controls per 1 hepatitis C case). However, not every combination of age, sex, and residence amongst cases had corresponding 20 controls, particularly among the First Nations cohort. Hence, the frequency matching resulted in the selection of 94,282 controls for 5,018 cases (a total of 99,300 study records) with the control-to-case ratio of 18.8. There were 9,802 controls for 671 cases among First Nations (the control-to-case ratio of 14.6) and 84,480 controls for 4,347 non-First Nations cases (the corresponding ratio of 19.4).

Figure 3.2 Stepwise construction of the study's hepatitis C cohort



3.4.4 Merging of the case-control file with the medical services information

The completed case-control file of 99,300 records was merged with the hospital discharge abstracts data, physicians' billing claims data, and pharmacy services data

(DPIN) using the scrambled PHINs as the key merging variable. As the result of merging, the complete data set for the project included the following elements (Table 3.1):

Table 3.1 Hepatitis C research database elements

Source data set	Records N	Variables N	Data elements
Case-control file	99,300	83	Study ID, complete demographic data. Incomplete basic clinical data (reason for testing, symptoms, HBV and HCV laboratory profile), risk factors
Hospital abstracts file	317,564	126	Study ID, patient demo, admission and discharge dates, total days, hospital data, in- or outpatient indicator, transfers, separation. Clinical data: diagnostic category, type, up to 16 diagnostic and 12 procedure's codes, consultations, primary services and specialty codes,
Physician services claims file	13,287,000	15	Study ID, some patient's demographics, Visit information: tariff, primary services, service date, specialty, responsible diagnosis, facility
Prescription drug file (DPIN)	6,553,360	14	Study ID, some patient's demo , claim and service date, drug identification number (DIN), days of supply, dose, therapeutic class, the metric quantity

3.5 Statistical Methodology

The Hepatitis C Research Database contains a wealth of demographic, clinical and utilization information suitable for the study of the epidemiology, natural history, and health care use imposed by chronic hepatitis C, as well as for comparison of all relevant outcomes between First Nations and non-First Nations Manitobans. The three distinct objectives of this research project require different methodological approaches to analyzing such a comprehensive set of data. Therefore, the methodology of this population-based case-control study is divided into 3 components according to the principal objectives and each section is discussed in detail further.

All statistical analysis was performed using SAS 9.1 for Windows statistical software. Categorical variables were evaluated using Chi-square analysis. The $\chi 2$ test of association (or F-test when warranted) was used to examine differences in demographic factors, clinical variables, and resource utilization and intensity. Continuous variables were assessed using Student's t-test or analysis of variance. Statistical significance was considered when a P-value falls below 5% in all analyses. The 95 percent confidence intervals for significant differences were computed. To compare prevalence of HCV infection between populations, both crude and adjusted comparisons were made between the two patient cohorts - First Nations versus non-First Nations. Direct age/sex adjusted rates were obtained for each cohort and the overall study population. The age/sex distribution of the Manitoba population for the corresponding year was used. The bivariate (presence or absence) measure of health care utilization was compared between HCV infected First Nations and non-First Nations cohorts by means of the logistic

regression. Conditional logistic regression for matched sets was performed for the comparison of association between various health risks (e.g. exposure to alcohol, HIV infection, etc) and chronic hepatitis C in FN and non-FN cohorts.

Table 3.2 Summary table of statistical methods used for specific analyses

Analysis	Methods and Tests
Incidence of newly reported HCV infection	Annual number of cases Annual incidence per 100,000 population (crude and adjusted) FN-to-non-FN ratio of adjusted incidence rates
Demographic distribution of cases	Crude and directly age-and-sex standardized rates Age-specific incidence rates for males and females FN-to-non-FN ratio of adjusted incidence rates Female-to-male ratio of adjusted incidence rates
Incidence by RHA; Winnipeg vs. non-Winnipeg; Urban vs. Northern vs. South rural Manitoba	Cumulative incidence Crude and directly age/sex standardized cumulative incidence rates FN-to-non-FN ratio of adjusted incidence rates
Natural history: frequency of decompensated cirrhosis and each of the related conditions; co-infections and other conditions of interest	Frequency statistics (Chi-square test) comparing FN and non-FN cases Adjusted OR comparing cases to controls overall and FN cases and controls vs. non-FN cases and controls
Analysis of all-cause and hospital mortality	Frequency statistics (Chi-square test); SMR; Mortality rates per 1,000 person-years
Length of stay (LOS) Proportion of long stays	T-test for the difference in mean LOS and non-parametric Mann-Whitney U test for the difference in median LOS Frequency statistics (Chi-square test)

Analysis	Methods and Tests
Bivariate assessment of hospitalizations, outpatient, day and ambulatory visits.	Frequency statistics (chi-square test, Fisher exact test)
Number of hospitalizations, outpatient, day, ambulatory visits per patient	Quantitative analysis by t-test for means and non-parametric Mann-Whitney U test for medians
Rates of inpatient and outpatient hospital visits and physician visits	- Annual rates - Rates per year prior to and since hepatitis C diagnosis
Liver -related hospitalizations, outpatient, same day, and ambulatory visits.	Frequency statistics (chi-square test, Fisher exact test)
Number of liver hospitalizations and visits per patient	Quantitative analysis by t-test for means and non-parametric Mann-Whitney U test for medians
Rates of inpatient and outpatient hospital visits and physician visits	- Annual rates - Rates per year prior to and since hepatitis C diagnosis
Liver-related conditions Main reasons for hospitalization, ambulatory, day and physician visit.	Frequency statistics (Chi-square test) comparing FN and non-FN cases Adjusted OR comparing cases to controls overall and FN cases and controls vs. non-FN cases and controls
Liver-related procedures Number of liver-related diagnostic and treatment procedures: overall, while hospitalized, day, outpatient, and ambulatory	Frequency statistics (Chi-square test, Fisher exact test) Quantitative analysis by t-test for means and non-parametric Mann-Whitney U test for medians Cumulative rates of procedures.
Proportion received anti-HCV treatment	Frequency statistics (Chi-square test, Fisher exact test)

3.6 Analysis of the Incidence and demographics of HCV infection in Manitoba

This objective was dedicated to providing the descriptive epidemiology of 5,018 cases of HCV infection diagnosed in Manitoba during 1991-2002. Considering the nature of HCV infection, with very few acute cases and its largely asymptomatic course until later stages when liver disease develops, the true incidence and prevalence of this infection is impossible to determine. However, for the purpose of this study, the term "incidence" is used to stress that the study is concerned with all new cases of hepatitis C diagnosed in Manitoba. Therefore, all newly reported cases are viewed as incident cases, although they not necessarily represent a newly acquired infection, but rather a newly diagnosed infection.

Although testing of blood samples for hepatitis C in Manitoba began in 1991, the confirmation and reporting requirements had changed over time. From 1991 to 1995, the 1st and 2nd generation immunoassays were used to detect antibodies to HCV and there were no RNA assays to confirm chronic infection. Consequently, cases reported from 1991 to 1995 may include those who have chronic hepatitis C as well as those who had been infected previously and spontaneously cleared the infection. Since 1995, when RNA assays had been introduced, specimens are considered positive only if both anti-HCV screen tests and confirmatory HCV-RNA tests are positive. Hence, cases reported from 1995 to 2002 are those with chronic hepatitis C. The data from the provincial Cadham laboratory (the testing facility for HCV in Manitoba) revealed that in 1995-2003 only

10% of all anti-HCV-positive specimens tested negative for HCV-RNA, indicating self-limiting infection (14% among First Nations and 10% among non-First Nations Manitobans)[140]. Hence, only a small fraction of 1991-1995 cases may not be chronic hepatitis C. For that reason, in the descriptive epidemiology section the term "HCV infection" as opposed to "chronic hepatitis C" is used. In addition, the incidence of HCV infection in 1995-2002, with all cases being chronic hepatitis C, is reported.

The date of the HCV infection was based on the date recorded in the original provincial Viral Hepatitis Surveillance Database. That date is entered into the database according to the notifications received by the Public Health unit of the Manitoba Health, where the date of the positive blood test is one of the required fields. The case is counted according to the year of the first ever positive HCV test result.

The annual incidence rates of HCV infection were calculated using the population of Manitoba for the corresponding year. The Manitoba Population Registry supplied the population counts for each year from 1991 to 2002 divided into demographic groups according to sex, treaty status, RHA, and the following 14 age groups: 0-10 yrs., 11-17 yrs., 18-24 yrs., 25-29 yrs., 30-34 yrs., 35-39 yrs., 40-44 yrs., 45-49 yrs., 50-54 yrs., 55-59 yrs., 60-64 yrs., 65-69 yrs., 70-74 yrs., and 75+ yrs.

Both crude and age/sex-adjusted incidence rates per 100,000 population were calculated to correct for the demographic differences between the First Nations and non-First Nations populations in Manitoba. Direct standardization was used for calculating

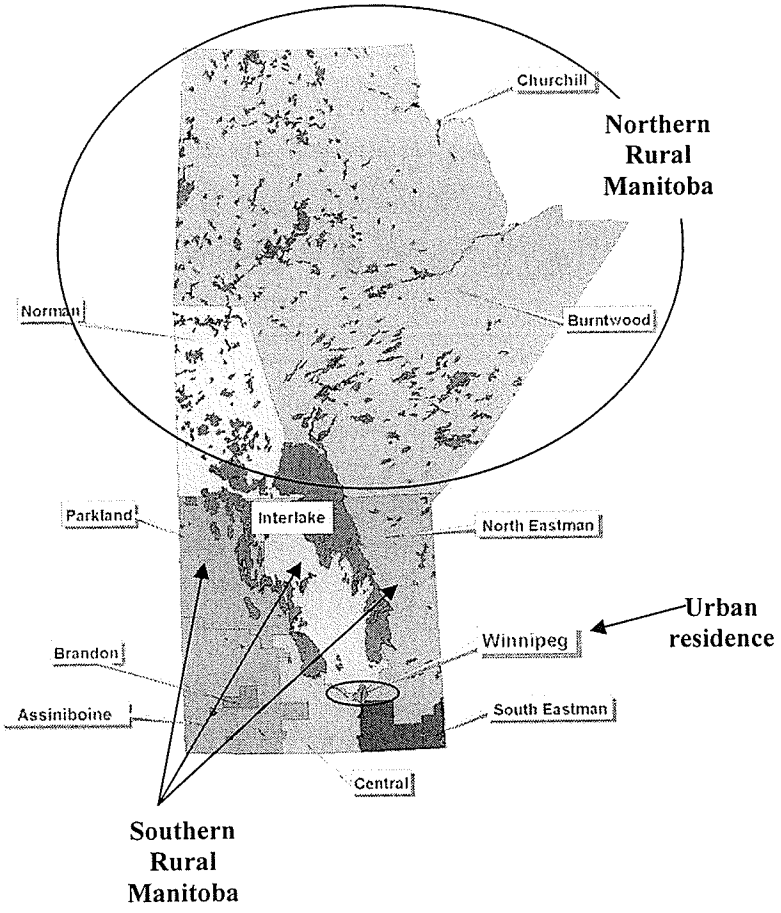
adjusted rates with the 1998 Canadian population (midpoint for the study) as the standard. FN-to-non-FN and female-to-male ratios of adjusted incidence rates with 95% CI were calculated.

The literature indicates a particular significance of cases of hepatitis C among males aged over 40 yrs. at diagnosis, therefore age-specific rates among FN and non-FN males and females were calculated to determine which demographic strata bear the most significant burden of infection.

Geographic distribution of cases was studied at several levels. To prevent instances of zero cell counts when breaking down the incident cases by year, region and FN status, the annual incidence was not calculated. Instead, the analysis included all cases (cumulative incidence) diagnosed during the study period (1991-2002) for each of the 12 regional health authority (RHA) areas. These RHA's included Winnipeg, Brandon, and 10 rural regions. Two of the northern RHAs of Burntwood and Churchill were combined due to the small population size in order to ensure that the calculated rates are stable. Next, the entire province was divided into urban (city of Winnipeg) and rural Manitoba. Winnipeg RHA was the only one classified as urban. Since the tertiary care hospitals, hepatologists, and the diagnostic laboratory for HCV are all located in Winnipeg and not in Brandon, the latter was included in Rural Manitoba. Finally, Rural Manitoba was divided into Northern rural and Southern rural according to the RHA's boundaries (Figure 3.3). The Northern rural RHAs included Norman and the combined Burntwood / Churchill RHAs. The Southern rural RHAs included Assiniboine, Brandon, Central, South Eastman, North Eastman, Interlake and Parkland.

Crude and age-adjusted cumulative incidence was calculated for each RHA, urban vs. rural and Northern rural vs. Southern rural areas as above. FN-to non-FN ratios of adjusted rates were calculated as well for each of the above areas.

Figure 3.3 Regional Health Authorities (RHA) regions of Manitoba



3.7 Analysis of the natural history of hepatitis C infection

3.7.1. Data sources

This analysis is based on data retrieved from utilization records contained in the Hepatitis C Research Database. Patients' medical histories and clinical data were obtained from the hospital discharge abstracts and physicians billing claims in order to determine each patient's disease stage and comorbidities. An exhaustive list of conditions was prepared. Diagnostic information was derived from ICD-9-CM coded diagnostic fields (up to 16 per record) in the hospital database and primary diagnosis field (one per record) in the physicians billing claims database. Relevant information on procedures was retrieved from ICD-9-CM coded procedures' fields (up to 10 per record) in the hospital database and tariff code (one per record) in the physicians billing claims. Each record in the hospital database is for a single admission, hence the study participants could have from zero corresponding records (if they did not use hospital services) to multiple records (if they were repeat users). Each physician's billing claim represents a single tariff for the service or procedure, and the individuals in the study may have from none to not only multiple records for multiple visits, but also multiple records for a single visit. All hospital discharge and medical services records between January1, 1991 and December 31, 2002 were included into the study database.

3.7.2 Key descriptive and outcome variables

To obtain as complete information as possible, a list of hepatitis C-related conditions and procedures was created with corresponding ICD-9-CM codes and tariffs and source a file (Appendix 2). This step was necessary in order to (a) examine conditions characteristic of

the natural history of chronic hepatitis C, such as cirrhosis, portal hypertension and its manifestations, hepatocellular carcinoma, as well as the number of liver transplants; and (b) to construct the indicator of decompensated cirrhosis by identifying records containing specific procedures and/or liver disease sequelae-related codes. Hospital abstracts contained the most detailed information on this with the 5-digit ICD-9-CM codes and 4-digit procedure codes. But since hospitalizations are not necessarily common and routine hepatitis C-related care is provided via outpatient and ambulatory visits, the physicians' claims data was used to obtain liver disease-related procedures' tariffs and, where possible, the 3-digit ICD-9-CM codes for the responsible diagnosis. However, the 3-digit codes did not allow for distinguishing between many forms of liver disease, hence only several broader categories were used in establishing the disease stage. To identify these events the following ICD-9-CM diagnostic codes were used for the primary diagnosis of hepatitis C: (070.41, 070.44, 070.51, 070.54, 070.7, 070.70, and 070.71, and V02.62). For conditions associated with the progression of chronic hepatitis C the following codes were used: cirrhosis of the liver without the mention of alcohol (571.5), portal hypertension (572.3) or any of its manifestations: hepatic encephalopathy (572.2), hepatorenal syndrome (572.4), ascites (789.5), or esophageal varices (456.0, 456.1, and 456.21), as well as hepatocellular carcinoma (155.0) and liver transplant (V427) (Appendix 2). In addition, a list of specific procedures used to treat complications of hepatitis C was developed for both hospital data {ICD-9-CM procedure codes for paracentesis (54.91), the treatment of varices (42.23, 42.33, 44.13, 45.13, and 42.91), transjugular intrahepatic portosystemic shunt (39.1)} as well as procedure tariffs {tariffs for paracentesis (3588, 3590), treatment of varices (3004, 3065), and transjugular

intrahepatic portosystemic shunt (2538, 7264)}. The list of conditions pertaining to hepatitis C or important in terms of comorbidities included complications of cirrhosis, other causes of liver disease, some viral infections and chronic conditions (Table 3.3).

Table 3.3 Clinical characteristics of hepatitis C in Manitoba

Diagnosis / Condition	
Chronic liver disease and cirrhosis (ICD-9-CM code "571")	
Sequelae of chronic liver disease (ICD-9-CM code "572")	
Other liver disease (ICD-9-CM code "573")	
Complications of chronic hepatitis C	
Cirrhosis	Hepatocellular carcinoma
Portal hypertension	Spontaneous bacterial peritonitis
Ascites	Hepatorenal syndrome
Esophageal varices	Orthotopic liver transplant
Hepatic encephalopathy	
Other causes of liver disease	
Alcohol dependence	Non-alcoholic fatty liver disease
Alcohol-induced liver disease	Hemochromatosis
Hepatitis A	Primary biliary cirrhosis (PBC)
Hepatitis B	Wilson's disease
Other viral hepatitis	Chronic non-viral hepatitis
	Liver abscess
Other conditions of interest	
Diabetes mellitus	EBV infection / persistence
HIV / AIDS	Hemophilia

Algorithms for combining all the sources into single indicators were developed for each condition. The codes were considered in any of the 16 diagnostic fields and any of the 10 procedure codes, as well as tariffs and responsible diagnosis. For example, a person was considered to have ascites if any of his/her hospital or physician visit record contained the following combination of diagnoses and procedures in any order and on any date: ICD-9-CM code 789.5 (ascites) from diagnostic field and/or 54.91 (paracentesis, percutaneous abdominal drainage) from the procedure field and/or tariffs 3588 (abdominal paracentesis, initial) or 3590 (abdominal paracentesis, subsequent). It should be noted that while it is possible to select the diagnosis of ascites from a 4-digit code in the hospital records, the physician services database allow only 3 digits for a single diagnosis as the reason for a visit. In this case, a 3-digit code would be "789 - Other symptoms of abdomen and pelvis", which is too broad and non-specific. Therefore, the diagnostic field on physicians' claims was excluded from the selection algorithm for ascites (Table 3.4). While potentially omitting some true cases with ascites, this strategy maintains high specificity of the selected cases. The date for the diagnosis is considered to be the earliest date of any record when corresponding codes or tariffs were encountered.

Table 3.4 Algorithm for selecting records of individuals with ascites

Item	Diagnosis or Procedure	Hospital abstracts		Diagnosis or Procedure	Physicians tariffs	
		code	Description		code	Description
Ascites	Diagnosis	789.5	Ascites	Diagnosis	--	--
	Procedure	54.91	Paracentesis (percutaneous abdominal drainage)	Procedure	3588 3590	Abdominal paracentesis, -initial -subsequent

The diagnoses of other forms of viral hepatitis (hepatitis A, hepatitis B, hepatitis D, hepatitis E, and other viral hepatitis); non-alcoholic cirrhosis, portal HTN, ascites, esophageal varices, hepatic encephalopathy, HRS, SBP, HCC, OLT, biliary cirrhosis, other liver disease and other sequelae of chronic liver disease, alcoholic liver disease, NAFLD, EBV/CMV infection, alcohol abuse, and diabetes were determined in the exact same fashion. The details of selection are presented in Appendix 2. If a person's utilization record contained any combinations of diagnostic and procedure codes or procedure tariffs for the following conditions: ascites, esophageal varices, hepatic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma or orthotopic liver transplant, such record was considered to be the record of decompensated cirrhosis.

Mortality data was obtained from the Registry file, because it is regularly updated against Vital Statistics files and is, therefore, most accurate. Cause of death is not recorded in the registry file. For the persons who died, the end-of-coverage date was considered the date of death. For in-hospital deaths, the patient's separation was examined and those who died had the separation date as the date of death. Those who were coded "deceased" in the registry file but did not have hospital record with "death" as separation code were considered "out- of hospital" death.

3.7.3 Statistical analysis

All statistical analyses were performed using SAS 9.1 statistical software for Windows. The proportions of hepatitis C patients who have also had cirrhosis, portal hypertension,

decompensated cirrhosis (ascites, esophageal varices, hepatic encephalopathy, HRS, SBP, HCC, and OLT); other liver diseases (co-infection with HBV, NAFLD, alcohol-induced liver disease, other viral hepatitis, chronic non-viral hepatitis, hemochromatosis, PBC, Wilson's disease and liver abscess); other related conditions (HIV coinfection, EBV, diabetes, alcohol abuse, hemophilia) were calculated for FN and non-FN individuals. The Chi-square test of association was used to examine the difference in the proportions between FN and non-FN groups. Fisher exact test was employed when the expected cell value was less than 5. Statistical significance was considered when a P-value fell below 5% in all analyses. The 95 percent confidence intervals for difference were computed. The sequelae of hepatitis C was examined by gender in a similar fashion.

Mortality (as the proportion of cases) was examined in several ways. With respect to the year of diagnosis, the proportion of cases in which the patient died was calculated (e.g. the percent of deaths among patients diagnosed in 1992 was determined, then among those diagnosed in 1993, then in 1994, and so on. Also, mortality according to the duration of time since the diagnosis of hepatitis C was computed, such as the percent of those dying in the year of diagnosis, in the second year after the diagnosis, and so on. Age-specific and sex-specific mortality was calculated. Standardized mortality ratio with the 95%CI was calculated for hepatitis C patients and non-infected controls using Canadian age-specific all-cause mortality rates for 1998[207].

Mortality rates per 1,000 person/years were calculated for FN and non-FN cases and controls, as well as for males and females.

To test for the association of the above mentioned conditions (decompensated cirrhosis, diabetes, etc.) and mortality (all-cause, in-hospital and "out of hospital") between FN and non-FN populations, Mantel-Haenszel adjusted odds ratios were calculated)[209]. This method accounts for the matched demographics of cases and controls and thus provides odds ratios adjusted for that matching. Adjusted odds ratios with the 95% confidence intervals were calculated for (a) all cases vs. all controls; (b) First Nations cases vs. FN controls; and (c) non-FN cases vs. non-FN controls. In addition, testing for the significance of the difference in adjusted odds ratios between FN and non-FN case-control populations was performed using ***proc phreg*** procedure. This was used to determine whether the odds of mortality, clinical manifestations and comorbidities are the same for FN and non-FN individuals with chronic hepatitis C as compared to the corresponding non-infected controls, or whether the odds are different and depend on whether the infected person is a First Nation or a non-First Nation individual. To summarize, the issue examined was whether there is an interaction between First Nations status and hepatitis C status.

3.8 ANALYSIS OF THE HEALTH CARE UTILIZATION

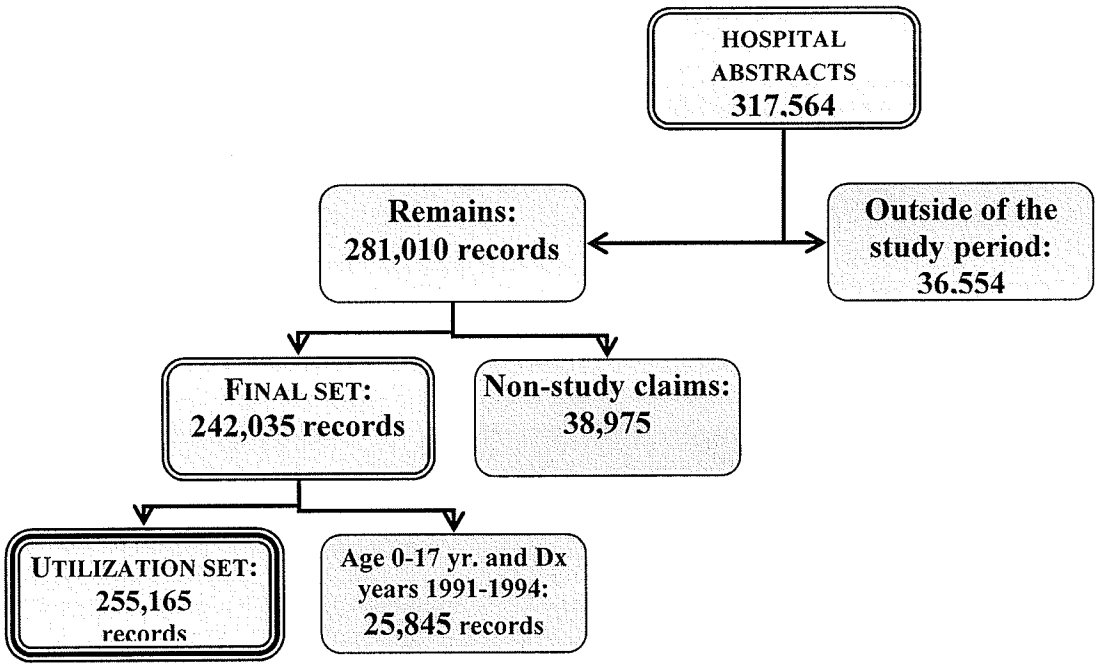
3.8.1 USE OF HOSPITAL SERVICES

3.8.1.1 Data Organization

To assess various characteristics of hospital services the information contained in the hospital abstract files was used. Each record in this database (for a total of 317,564) represents contact with hospital services that occurred during the study period among the members of the study population. An individual may have no records at all (did not use hospital services), have one record (had a single contact of any type), or have multiple records for repeated use of hospital services. Linked data provided all the information needed to identify admissions at the individual and aggregate levels (Figure 3.4).

For greater consistency, all utilization analysis is done on the subset of patients diagnosed in 1995-2002, because, as discussed earlier, the RNA confirmation of chronic infection was introduced in 1995. Hence, in the set of 1995-2002 yrs. of data all patients have chronic hepatitis C and all the individuals who might have had self-limiting infections are excluded. In addition, only those 18 years of age and older were included in the utilization analysis, since pediatric utilization is quite different than for adult individuals. Thus, anyone diagnosed with HCV infection in 1991-1994 and those who are 0-17 year of age are EXCLUDED from the analysis of health care use.

Figure 3.4 Selection of hospital records for the study population



All hospital admissions were classified on the basis of transaction code into inpatient and outpatient visits. All inpatient claims were further divided into "inpatient" with the total length of stay (LOS) of at least 1 day (overnight stay) and "day visits" for those inpatient claims where the admission and discharge dates were the same and the total days were reported as '0' on the hospital abstract.

All inpatient claims were further classified according to the LOS into short admissions with the LOS up to 30 days, and long admissions with the LOS>30 days. Length of each

hospital stay was calculated by subtracting the hospital admission date from the hospital separation date.

In-hospital deaths were ascertained from the patient's separation codes and the binomial variable was created for in-hospital death (Yes=1 / No=0).

For the hepatitis C cases, the date of the HCV-positive test result was set as the 'pivot date' for reference and further calculations. For the controls, the 'pivot date' was set at July 1 of the corresponding case's year (for example, the control of someone diagnosed in 1998 would have July 1, 1998 as the pivot date).

3.8.1.2 Person/Years calculation

To calculate annual rates of hospital services, the contribution of each person into person/years of follow-up was calculated. Patients' periods of follow-up varied substantially, depending on the date of hepatitis C diagnosis (hereafter called the "pivot date") and the end of the coverage. While some remained residents until the end of the study, others had died, moved out of the province, became clients of correctional facilities, etc. prior to the end of the study date. Therefore, the start and end dates of health coverage were calculated for each person in the study. The population registry provides the dates of coverage along with the reasons it was cancelled. However, according to the registry codes, 5% of the study participants (4,986 out of 99,300) had their health coverage terminated due to inability to locate an individual, and another ~0.7% (710/99300) had been recorded as "unknown". In addition, 54 cases had their

pivot date outside of the coverage date. In order to fill in this data, all the patients' utilization information was arrayed and the dates of the first ever and the last ever hospital service, physician visit claim, or prescription drug claim were recorded. Then, these dates were compared with the pivot date and coverage dates from the registry. The earliest date from the registry and the 3 utilization files was considered the "start of coverage date" and the latest of them was considered the "end of coverage date". Where the health coverage started prior to January 1, 1991, then the study start of coverage date was set to 01.01.1991. Where the health coverage continued beyond the study period, the end of coverage date was set at 12.31.2002. A person's date of death was considered end of coverage date. A person's time in the study was calculated by subtracting the coverage start date from the coverage end date.

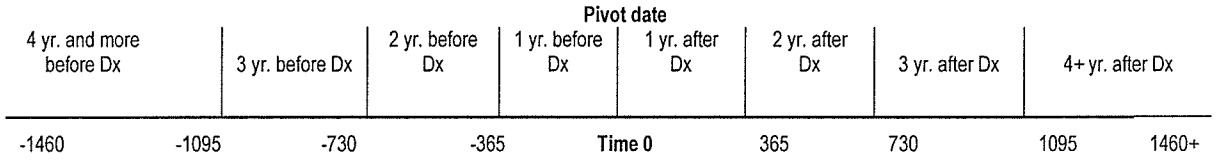
3.8.1.3 Annual Rate

For the annual rates of hospitalizations, outpatient visits, and day visits, a person-time for each calendar year was calculated; starting from the pivot date and ending with December 31 of each subsequent year in the study and so on, until the person's end of coverage or December 31, 2002, whichever came first. For instance, someone diagnosed with hepatitis C in July 1997 who moved out of province in April 1999 would have contributed 0.5 person/years in 1997, 1 person/year in 1998, and 0.25 person/years in 1999 for a total of 1.75 person/years. The denominator for each year from 1995 to 2002 was calculated by summing up corresponding values of person/years. The numerator is the number of services (hospitalizations, outpatient visits, and day visits) diagnosed each year for the same time period.

3.8.1.4 Rate by the year since diagnosis

Another way to assess the health care use was by the rates of service use in relationship to the date of the diagnosis. Thus, all individual's time in the study was divided into the time prior to and the time following diagnosis. The pivot date was time 0 and the time interval between 0 and -365 days was the year prior to diagnosis, the time between -366 and -730 days was two years prior to diagnosis, etc. Similarly, the time interval between 0 and 365 days was the first year since diagnosis, the time between 366 and 730 days was two years after diagnosis, etc. Time intervals were calculated for over 4 yrs., 3, 2, and 1 yr. prior to diagnosis and 1, 2, 3, and over 4 yrs. since the diagnosis. The person/years during these time intervals were calculated for each patient's record. The numerators were the number of services (hospitalizations, outpatient visits, and day visits) at each interval in relation to the pivot date instead of the calendar year (Figure 3.5). Trends in rates were examined to determine whether being diagnosed with chronic hepatitis C increased the use of health care services compared to pre-diagnosis years.

Figure 3.5 Defining the time intervals in relation to the pivot date



All analyses were performed comparing FN vs. non-FN cases as well as comparing FN cases vs. FN controls, and non-FN cases vs. non-FN controls. Calculations were made for total separation rates and rates for each type of hospital service: (1) hospitalizations, (2)

outpatient visits, and (3) day visits. These rates were calculated in two ways: annual rates and rates in relation to the time of diagnosis. Separation rates for (4) short stays and (5) long hospitalizations also were examined.

The overall hospital service use was examined by calculating the proportions of individuals among cases and controls who were hospitalized, had outpatient hospital visits, and had day visits. These were assessed by a Chi-square test or Fisher exact test if warranted. Average annual rates (of hospitalizations, day visits, total separations, etc.) were calculated by taking the mean of the corresponding individual annual rates. The overall rate was calculated by totaling all events, summing all the corresponding person-years, and taking the rate. Case-to-control ratios of rates were calculated separately for FN persons and for non-FN persons. The average and overall rates and the ratios of rates by the year before and after diagnosis were calculated in the same fashion. Quantification of the number of hospitalizations, outpatient, day, and physician visits per person were done by comparing the mean and the median number of hospitalization per person using t-test for means and Mann-Whitney U test (the non-parametric equivalent of t-test) for medians.

The following data were calculated for the hospital stays: total hospital days, LOS for short admissions, and LOS for long admissions. The differences in the lengths of hospitalization between cases and controls overall and by FN status were assessed with mean and median LOS using t-test (for means) and Mann-Whitney U test (for medians).

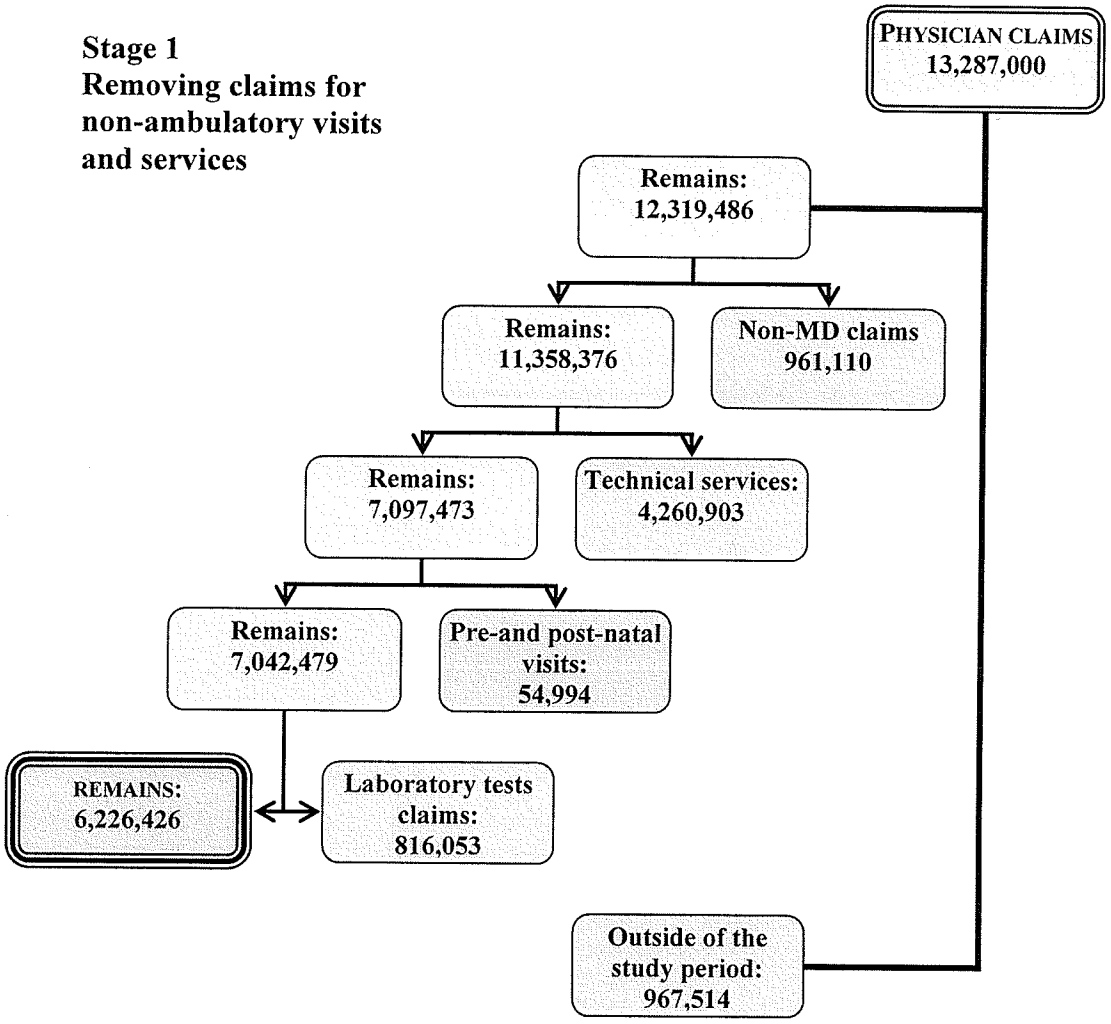
Frequencies of the *ICD-9-CM*-coded diagnostic categories of the most responsible admission diagnosis were assessed using $\chi 2$ test. Quantification of the number of diagnoses per person per admission was done by comparing the median number of hospitalization per person using Mann-Whitney U test as above.

3.8.2 USE OF PHYSICIAN AMBULATORY SERVICES

3.8.2.1 Data Organization

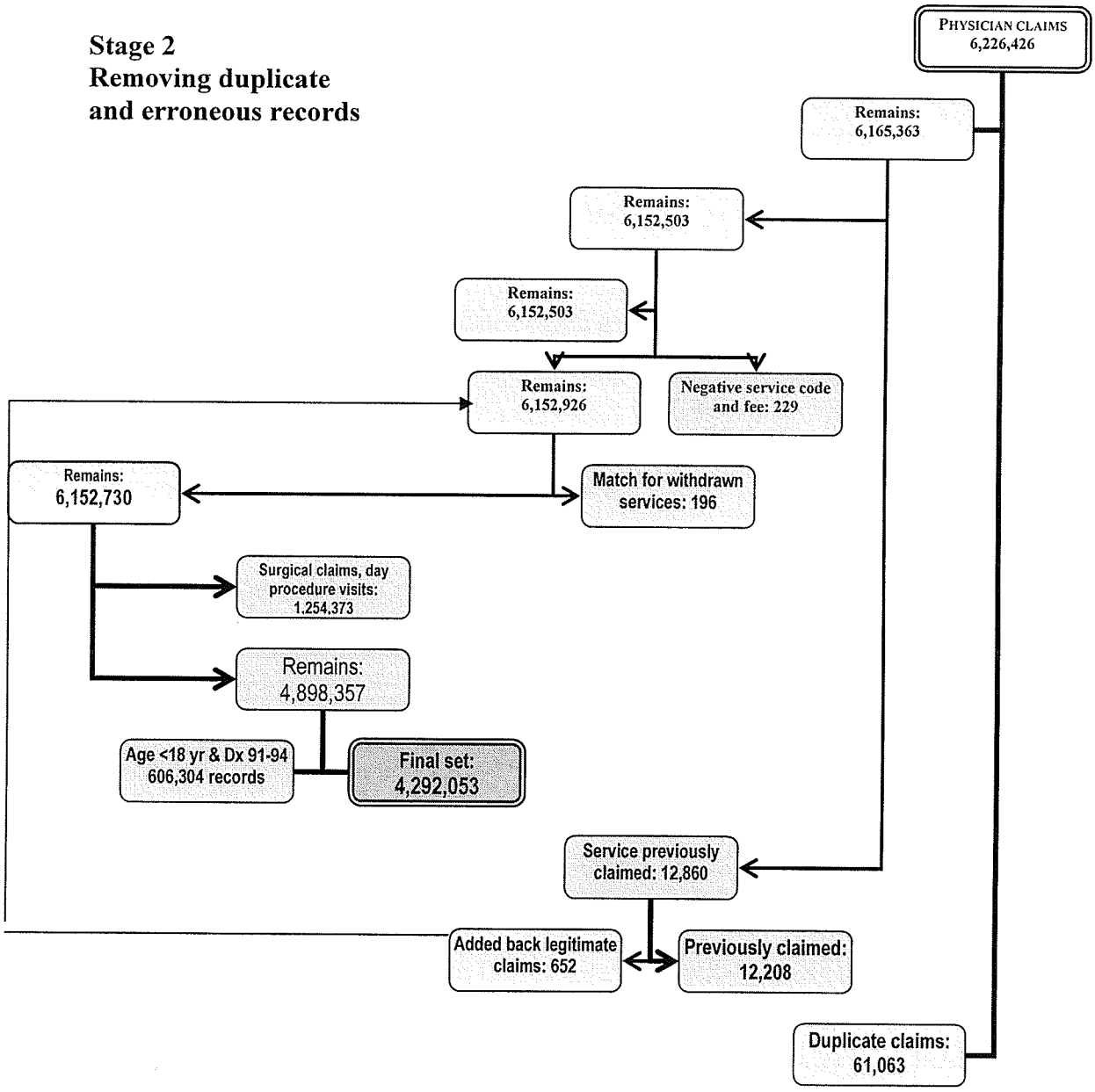
Physician services claims data set contained the largest number of records in the entire study database due to its design and functions. Each claim represents a service provided to the patient, and for a single claim only one tariff is allowed. Hence, multiple clams for one visit (one service date in the database) are quite common. A person may have no claim records at all (did not use physician services), have one record (had a single contact of any type with a single service provided by the physician), or have multiple records for multiple visits with one or more corresponding service claims. Prior to the analysis, the claim database needed intensive work in order to keep only appropriate records for the analysis (Figure 3.5). MCHP developed a list of exclusions based on the practice patterns, such as routine pre-and post-natal visits, and on claims by "technical" services, such as claims submitted for laboratory testing, radiology services, etc[208]. In addition, claims from chiropractors, optometrists, dental surgeons, and midwifes were removed. As the result of such exclusions, the size of the file was reduced to one half of its original size, from more than 13 million records to a little over 6 million records.

Figure 3.6 Stepwise cleaning of medical services claims file



Next, the records were examined for duplicates, erroneous entries, double billing (to prevent counting the same service twice) based on the disposal codes, services and negative fees[204] (Figure 3.6). The remaining set of physicians' claims contained 6,152,730 records for a total of 5,380,018 unique service dates (physicians' visits) with single (89%) or multiple claims per one service date.

Figure 3.6 Stepwise cleaning of medical services claims file



Further, all records or hospital outpatient and day surgery procedures, claims by surgical assistants and anesthesiologists (a total of 1,254,373) were removed. This step prevented a double-counting for surgeries and invasive diagnostic and treatment procedures, because for such services (for example, liver biopsy) the corresponding hospital records

are generated. Such records do not represent physician ambulatory care visit[208], but they are accounted for in the further analysis of liver disease-related care. As discussed previously, for the consistency of the study population anyone diagnosed with HCV infection in 1991-1994 and those who were 0-17 year of age were excluded from the analysis of physicians' services as well.

Rates of physicians' visits were calculated as were the hospital rates discussed above, per year prior to and since the diagnosis as well as annual rates of physicians' visits. The overall use of physician' services was calculated as the proportion of those who had at least one visit during the study period. Ambulatory visit rates to specialists and GPs were calculated, as well as physician' visit rates by cause (3-digit ICD-9-CM code) and rates by physician specialty.

Average annual rates of physician' visits were calculated by taking the mean of the corresponding individual annual rates. The overall rate was calculated by totaling all events and summing all the corresponding person-years and taking the rate. Case-to-control ratios of rates were calculated separately for FN persons and for non-FN persons. The average and overall rates and the ratios of rates by the year before and after diagnosis were calculated in the same fashion.

To compare mean and median numbers of physician visits per person the t-test for means and Mann-Whitney U test for medians were used. Physician visits by cause were

examined by calculating the proportions of visits by major diagnostic categories and assessing them by a Chi-square test (Fisher exact test if warranted).

3.8.3 ANALYSIS OF LIVER-DISEASE RELATED HEALTH CARE

Based on the most responsible diagnosis (Dx code number one) all hospitalizations, outpatient and day visits were divided into liver-related and non-liver-related. A hospital visit was considered to be liver-related if the most responsible diagnoses were: 070.xx – viral hepatitis; 155.xx – malignant neoplasm of the liver; 571.xx – chronic liver disease; 572.xx – sequelae of chronic liver disease; and 573.xx – other liver disease. Because the physicians' claims database has only 3-digit ICD-9-CM coding, for consistency in defining hospital and physician services for liver diseases, all liver-related visits were defined using these 3-digit codes. Moreover, other studies of liver-related health services utilization also employ the same 3-digit major codes, and such an approach therefore allows for comparisons between studies (see discussion chapter). Annual rates and rates in relation to the diagnosis date were calculated as previously described.

All diagnostic and treatment procedures related to chronic hepatitis C were identified and assessed. The following ICD-9-CM procedure codes from the discharge abstracts and physicians' tariffs were used to identify these procedures (Table 3.5):

Table 3.5 Liver disease-related diagnostic and therapeutic procedures

PROCEDURE	ICD-9-CM CODE	PHYSICIAN TARIFF
LIVER BIOPSY		
Closed (percutaneous) [needle] biopsy of liver	5011	3456
Transjugular liver biopsy	5013	3458
Laparoscopic liver biopsy	5014	
TREATMENT OF PORTAL HYPERTENSION		
Intra-abdominal venous shunt (porto-caval, mesocaval, etc.)	391	2538
T.I.P.S (Transjugular intra-hepatic portosystemic shunt)		7264
TREATMENT OF ASCITES		
Paracentesis (percutaneous abdominal drainage)	5491	3588/3590
TREATMENT OF ESOPHAGEAL VARICES		
Control of esophageal bleeding by endoscope, injection of esophageal varices by endoscope	4233	3065
Ligation of esophageal varices	4291	3004
HCC RELATED PROCEDURES		
Partial hepatectomy	5022	3464
Lobectomy of liver	503	3492, 3494
Open ablation of liver lesion or tissue	5023	
Percutaneous ablation of liver lesion or tissue	5024	
Laparoscopic ablation of liver lesion or tissue	5025	
Other and unspecified ablation of liver lesion or tissue	5026	
Other destruction of lesion of liver (cauterization, enucleation)	5029	
Other injection of therapeutic substance into liver	5094	3030
Radiofrequency ablation of liver tumor		3496, 3497
DIAGNOSTIC ENDOSCOPY		
Esophagoscopy, diagnostic	4223	3055
Gastroscopy, diagnostic (without or with biopsy)	4413, 4414	3121
Esophagogastroduodenoscopy (EGD) (without or with biopsy)	4513, 4516	3123
DIAGNOSTIC IMAGING		
C.A.T. scan of abdomen/biliary tract scan	8801	9966
Liver scan and radioisotope function study	9202	9925
Liver and spleen scan		9967
Dynamic liver scan		9968
Abdominal MRI	8897*	7510- 7512
Diagnostic ultrasound of abdomen and digestive system	8876, 8874	7310
Endoscopic ultrasound with biliary examination		3022

Note: ICD-9 codes for liver transplant were not included here as this procedure is not performed in Manitoba

**88.97 include all of the following: magnetic resonance imaging of other and unspecified sites: abdomen, eye orbit, face, neck*

Proportions of patients who had undergone each of the above procedures were calculated. The frequency of these was assessed by a Chi-square test or Fisher exact test. Average numbers of HCV-related diagnostic and treatment procedures per person were examined by comparing the median number per person using Mann-Whitney U test. The proportion of patients who had ever received treatment for their hepatitis C was calculated and assessed by a Chi-square test or Fisher exact test.

The length of liver-related vs. non-liver-related hospitalizations was examined by comparing the mean and median LOS using t-test for means and Mann-Whitney U test for medians.

For the hospital separations, in addition to liver-related stays, the proportion of those with liver disease as primary and secondary diagnosis (diagnoses from 2 to 16) was calculated.

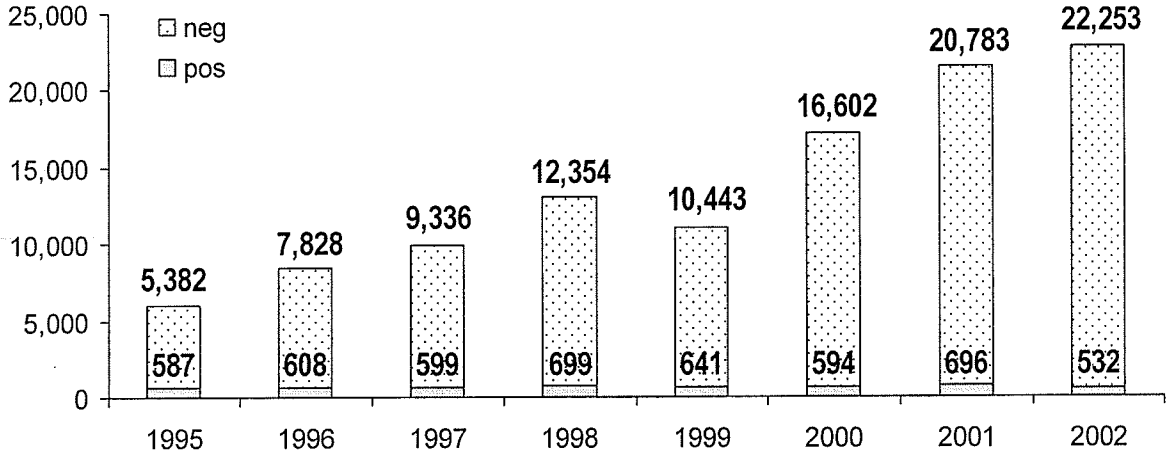
CHAPTER FOUR RESULTS

4.1 DESCRIPTIVE EPIDEMIOLOGY OF HCV INFECTION IN MANITOBA

4.1.1 Time trends in HCV testing and reporting

Cadham Provincial laboratory (CPL) started testing for HCV in July 1991[141]. The CPL performs all serological testing for HCV in Manitoba and reports all positive results directly to the Communicable Disease Control Unit of Manitoba Health. The first record of a positive anti-HCV result in the Communicable Disease Control Unit Surveillance Database dates back to 1991. Up until 1995 the HCV testing in the province was inconsistent. With the implementation of the qualitative HCV-RNA assay in 1995 and a broader recognition of issues around HCV infection among primary care physicians, the testing became more commonly used and is still increasing every year, while the detection of new HCV infections remains stable (Figure 4.1). The number of individuals tested for HCV in Manitoba almost quadrupled in eight years (1995-2002). This, however, did not translate into a similar (or any) increase in detecting new HCV infections, which, in fact, decreased 10% in 2002 compared to 1995.

Figure 4.1 Trends in Hepatitis C testing, Manitoba, 1995-2002



Source: Dawood et al., Can J Microbiol, 2006[141]

Information on a total of 5,018 cases of hepatitis C had been collected by the Communicable Diseases Control Unit of Manitoba Health between January 1, 1991 and December 31, 2002 (Table 4.1). The number was somewhat less than the total number of HCV-positive results identified by the CPL. At least some of the non-reported cases might be out- of-province cases. The percentage of cases not reported to Manitoba Health was quite steady across the entire study period (6%) and, surprisingly, did not decrease after 1999, when mandatory reporting of hepatitis C was instituted in Manitoba. In fact, under-reporting increased slightly from 4.6% in 1995-1998 to 7.4% in 1999-2002.

Table 4.1 Hepatitis C Testing and Reporting

	CPL data^			MB Health data		Not in
Year	Tested	Positive	% from Tested	Received reports	% from positive	MB Health Database*
1995	5,969	587	9.83	565	96.25	22
1996	8,438	608	7.21	550	90.46	58
1997	9,935	599	6.03	590	98.50	9
1998	13,053	701	5.37	676	96.43	25
1999#	11,084	641	5.78	572	89.24	69
2000	17,196	594	3.45	534	89.90	60
2001	21,479	696	3.24	685	98.42	11
2002	22,785	532	2.33	489	91.92	43
Total	***109,939***	***4958***	***4.51***	***4661***	***94.01***	***297***

Source: Dawood et al., Can J Microbiol, 2006[141]
**Out-of-province and/or not reported cases*
#*Year hepatitis C became reportable in Manitoba*

Up until 1998, the number of newly diagnosed cases of hepatitis C reported to the provincial Public Health Unit increased steadily from 565 cases in 1995 to the maximum of 676 cases in 1998, and then the number of reported cases decreased to the lowest of 489 in 2002, despite the already noted significant increase in the number of individuals

tested for hepatitis C (Table 4.1). With the exception of 2001, there seems to be a tendency towards a decrease in the number of new cases of hepatitis C of almost 28% in 2002 as compared to 1999.

The overall proportion of hepatitis C cases among First Nations individuals in Manitoba came to 13.4%, ranging from 3.3% in 1992 to 15.4% in 1995 (Table 4.2). This is more than twice the percentage of First Nations persons among the Manitoba population, according to the Manitoba Health plan Registry, where the proportion of First Nations counts as approximately 6%[204]. These data point towards a disproportionately high burden of chronic hepatitis C among Manitoba First Nations individuals, compared to the non-First Nations Manitobans. Furthermore, when administrative sources of information on Treaty status were combined with the self-reports from patients' interviews, the overall proportion of First Nations cases increased slightly to 15%.

Table 4.2 Annual number of HCV-positive cases by First Nations status

		First Nations		non-First Nations	
Year	**Total**	**n**	**% from total**	**N**	**% from total**
1991	1	0	0	1	100
1992	30	1	3.3	29	96.7
1993	87	7	8.0	80	92.0
1994	239	22	9.2	217	90.8
1995	565	87	15.4	478	84.6
1996	550	71	12.9	479	87.1
1997	590	87	14.7	503	85.3
1998	676	94	13.9	582	86.1
1999	572	87	15.2	485	84.8
2000	534	57	10.7	477	89.3
2001	685	89	13.0	596	87.0
2002	489	69	14.1	420	85.9
Total	***5,018***	***671***	***13.4***	***4347***	***86.6***

4.1.2 Incidence of newly diagnosed hepatitis C

The age and sex-adjusted annual incidence of newly reported hepatitis C among non-First Nations Manitobans was almost identical to crude rates, because the province's demographic distribution is based primarily on that very population (94% of Manitoba residence are non-First Nations) and is little affected by First Nations' demographics, whose proportion of population is only 6%. The opposite is true for Manitoba's First Nations peoples, whose demographic is different from the province's overall population structure, with a much younger population and fewer people over the age of 65. Hence, the directly adjusted (for age and sex distribution) annual incidence rates among First Nations people increased at an average of 21% above the corresponding crude rates (Table 4.3).

Table 4.3 Annual crude and age/sex-adjusted[#] incidence rates of HCV infection, FN vs. non-FN.

	First Nations populations				non-First Nations populations				
			Rate per 100,000				Rate per 100,000		Rate
Year	Cases	Population	Crude	Adjusted	Cases	Population	Crude	Adjusted	ratio*
1992	1	60,044	1.67	2.84	29	1,073,076	2.7	2.71	1.05
1993	7	61,357	11.41	19.61	80	1,075,500	7.44	7.34	2.7
1994	22	62,936	34.96	37.01	217	1,082,831	20.04	19.85	1.9
1995	87	64,107	135.71	141.56	478	1,082,888	44.14	43.8	3.2
1996	71	65,428	108.52	107.93	479	1,079,215	44.38	43.95	2.5
1997	87	66,591	130.65	140.66	503	1,079,740	46.59	46.21	3.0
1998	94	67,508	139.24	160.51	582	1,074,957	54.14	53.59	3.0
1999	87	68,786	126.48	144.96	485	1,075,638	45.09	44.53	3.3
2000	57	71,762	79.43	88.29	477	1,078,142	44.24	43.69	2.0
2001	89	73,449	121.17	146.85	596	1,079,532	55.21	54.36	2.7
2002	69	74,591	92.5	101.53	420	1,081,626	38.83	38.32	2.6
Total	***671***	***736,559***	***91.10***		***4346***	***11,863,145***	***36.63***		***2.5****

[#] *Rates adjusted by direct method*

* *FN-to-non-FN adjusted incidence rate ratio except for the total, where rates are crude*

During the entire study period, both crude and adjusted annual incidence of newly diagnosed hepatitis C was higher among First Nations Manitobans than among non-First Nations individuals virtually in any given year (Figure 4.2). In 1991 only one case was diagnosed. The incidence rates were relatively low among both populations during 1992-1994. Since 1995 there was a significant increase in the incidence of newly diagnosed hepatitis C, particularly amongst First Nations populations. Annual hepatitis C incidence rates were 2-3 times higher among First Nations than among non-First Nations Manitobans (table 4.4). The cumulative incidence rate was 2.5 times higher among First Nations than among non-First Nations populations of Manitoba.

Non-First Nations Population

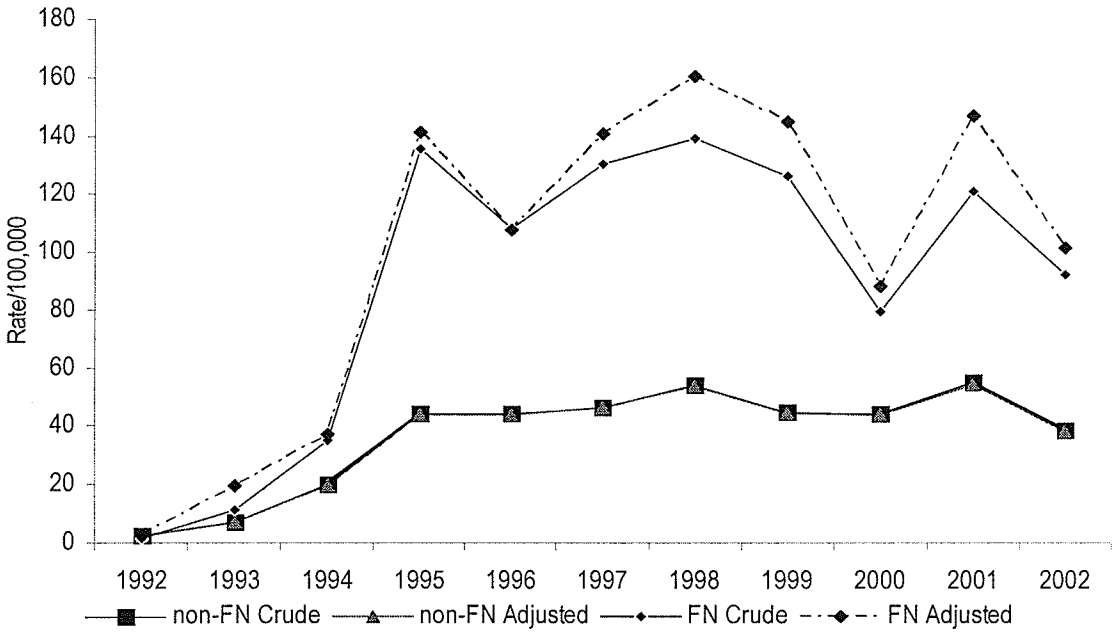
The directly age-and sex-standardized annual incidence of hepatitis C among non-First Nations was relatively constant at 43-46 cases per 100,000 population, except for 2 increases in 1998 and 2001 with the rates of 54.1 cases/100,000 population and 55.2 cases/100,000 population respectively and a slight decrease to 38.3 cases/100,000 population in 2002 (Figure 4.2). The overall incidence during the entire study period (1992-2002) was 36.6 cases per 100,000 population, but for the more representative 1995-2002 period it was 46.6 cases per 100,000 population.

First Nations Population

The age/sex-adjusted incidence of hepatitis C among First Nations individuals was much more variable than in Non-First Nations persons, fluctuating from 141.6/100,000 in 1995 to as high as 160.5/100,000 in 1998, decreasing to the lowest of 88.3/100,000 in 2000,

then rising and falling once again (Table 4.3). The overall incidence rate during the entire study period was 91.1 cases per 100,000 population, but for the year 1995-2002 it was 116.1 cases per 100,000 population.

Figure 4.2 **Crude and adjusted annual rates of hepatitis C, First Nations vs. non-First Nations**

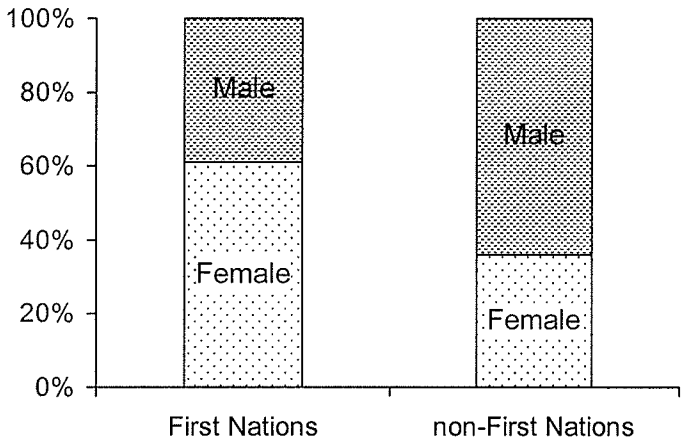


4.1.3 Gender distribution of hepatitis C patients

As expected, there was a male predominance in the study population. The overall percent of male patients was 61%, and the female-to male ratio was 0.64. However, when First Nations and non- First Nations subgroups were analyzed separately, proportions of males and females were reversed (Figure 4.3). In contrast with what might be expected based on

widely accepted HCV epidemiology, almost 60% of hepatitis C First Nations patients were females, thus bringing the female-to male ratio to 1.4. Conversely, the proportion of females in non-First Nations group was only 36%, and the female-to-male ratio was 0.6. The latter is consistent with the epidemiology of HCV infection as described to date.

Figure 4.3 Gender distribution of chronic hepatitis C cases, FN vs. non-FN



Sex-specific Incidence of hepatitis C

The crude and directly age-adjusted incidence rates of hepatitis C for FN and non-FN females and males are presented in Table 4.4. As already noted, the adjusted rates were almost identical to the crude rates in non-First Nations populations. In First Nations Manitobans, however, the age adjustment increased the rates at an average of 18% above the corresponding crude rates.

Table 4.4 Crude and age-adjusted incidence rates of hepatitis C, males vs. females

	First Nations						Non-First Nations					
	Females			Males			Females			Males		
Year	n	Crude	Adjusted	n	Crude	Adjusted	n	Crude	Adjusted	n	Crude	Adjusted
1992	0	0	0	1	3.3	5.5	8	1.5	1.5	21	4.0	3.9
1993	5	16.4	30.4	2	6.5	9.2	37	6.8	6.7	43	8.1	8.0
1994	14	44.7	40.8	8	25.3	32.4	83	15.1	15.3	134	25.1	24.6
1995	49	153.5	155.9	38	118.1	126.8	180	32.8	32.7	298	55.9	54.6
1996	41	125.8	120.9	30	91.4	94.4	182	33.2	33.2	297	55.9	54.7
1997	53	159.6	165.6	34	101.9	115.6	187	34.1	34.6	316	59.4	58.3
1998	57	169.0	194.0	37	109.5	125.8	201	36.8	37.0	381	72.0	70.5
1999	49	142.3	152.6	38	110.6	136.2	172	31.5	31.5	313	59.1	57.7
2000	34	94.5	102.8	23	64.3	73.2	159	29.1	29.0	318	59.9	58.3
2001	52	141.2	164.4	37	101.1	126.6	229	41.8	41.3	367	69.0	67.5
2002	38	101.4	105.6	31	83.5	97.7	137	25.0	25.1	283	53.1	51.6

Overall hepatitis C group

The annual incidence rates of hepatitis C in the overall cohort were higher among males than among females in any year during the study period (Figure 4.4). The overall incidence of hepatitis C among females was 30.8/100,000 as compared to 49.1/100,000 among males, with the female-to-male incidence rate ratio of 0.6. During the more representative 1995-2002 period the incidence rates of hepatitis C among females and males were 39.1/100,000 vs. 62.8/100,000 respectively, but the female-to-male incidence rate ratio was still 0.6 (Table 4.5). This shows that the gender composition of HCV-infected individuals (proportion of males and females) is relatively constant, regardless of the actual numbers of infected individuals.

Figure 4.4 Annual incidence of hepatitis C, females vs. males

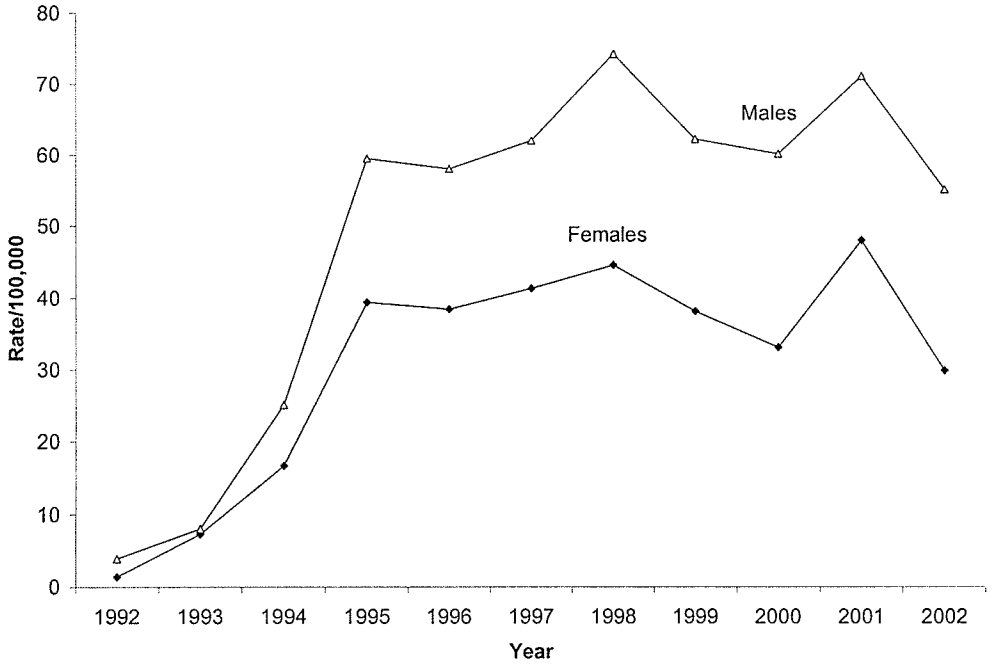
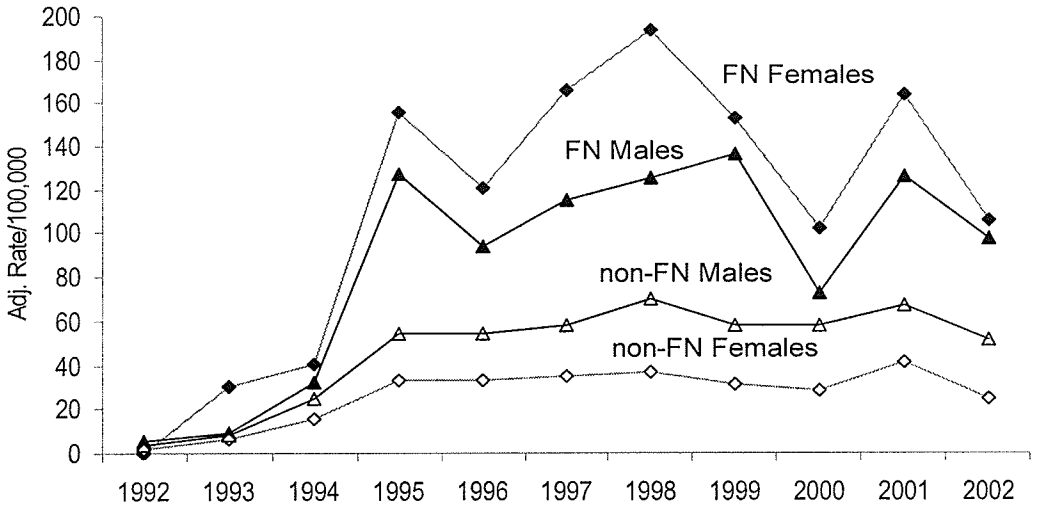


Table 4.5 Age-adjusted incidence of hepatitis C, females vs. males

	Females		Males		Rate	95% CI
Year	Cases	Incidence	Cases	Incidence	ratio*	
1992	8	1.4	22	3.9	0.35	0.16-1.08
1993	42	7.3	45	8.0	0.91	0.60-1.38
1994	97	16.7	142	25.1	0.67	0.51-0.86
1995	229	39.4	336	59.4	0.66	0.56-0.79
1996	223	38.4	327	58.0	0.66	0.56-0.78
1997	240	41.3	350	61.9	0.67	0.57-0.79
1998	258	44.5	418	74.2	0.60	0.51-0.70
1999	221	38.1	351	62.2	0.61	0.52-0.71
2000	193	33.1	341	60.2	0.55	0.46-0.68
2001	281	48.1	404	71.1	0.68	0.58-0.79
2002	175	29.8	314	55.1	0.54	0.45-0.62
Total	***1967***	***30.8***	***3050***	***49.1***	***0.63***	***0.59-0.67***
1995/2002	***1820***	***39.1***	***2841***	***62.8***	***0.62***	***0.59-0.66***

There was, however, a striking gender difference in the annual incidence of hepatitis C between First Nations and non-First Nations populations (Figure 4.5). The incidence for both sexes was higher among the First Nations populations, and the direction of the differences was reversed compared to non-First Nations individuals.

Figure 4.5 Incidence of hepatitis C by sex among First Nations vs. non- First Nations



Non-First Nations population

Predictably, the incidence rates among non-FN males were higher than amongst non-FN females from 1.6 times in 1994 to more than 2 times in 2000 and 2002 (Table 4.6). The overall incidence of hepatitis C among men was 47.4/100,000 as compared to 26.2/100,000 among women, and the female-to-male rate ratio was 0.55. The 1995/2002 incidence among men was 60.6/100,000 as compared to 33.0/100,000 among women, and again the female-to-male ratio was 0.55. Hence, at any given year proportionately more men than women were diagnosed with hepatitis C.

First Nations Population

The opposite was true for the First Nations peoples. First Nations females were diagnosed with hepatitis C more often than First Nations males. The annual incidence of hepatitis C was higher among females except for the year 2002, when it was quite similar between females and males (incidence of 105.6/100,000 and 97.7/100,000 respectively) and the corresponding rate ratio was 1.1. The cumulative incidence among females was 106.6/100,000 vs. 75.6/100,000 among males, while the female-to-male incidence rate ratio was 1.4. The 1995/2002 cumulative incidence among women was 135.1/100,000 as compared to 97.1/100,000 among men, and again the female-to-male ratio was 1.4.

Table 4.6 Age-adjusted incidence of hepatitis C by sex, FN vs. non-FN

	First Nations populations				Non-First Nations populations				TOTAL			
	Females		Males		Females		Males		Females		Males	
Year	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
1992	0	0.0	1	5.5	8	1.5	21	3.9	8	1.4	22	3.9
1993	5	30.4	2	9.2	37	6.7	43	8.0	42	7.3	45	8.0
1994	14	40.8	8	32.4	83	15.3	134	24.6	97	16.7	142	25.1
1995	49	155.9	38	126.8	180	32.7	298	54.6	229	39.4	336	59.4
1996	41	120.9	30	94.4	182	33.2	297	54.7	223	38.4	327	58.0
1997	53	165.6	34	115.6	187	34.6	316	58.3	240	41.3	350	61.9
1998	57	194.0	37	125.8	201	37.0	381	70.5	258	44.5	418	74.2
1999	49	152.6	38	136.2	172	31.5	313	57.7	221	38.1	351	62.2
2000	34	102.8	23	73.2	159	29.0	318	58.3	193	33.1	341	60.2
2001	52	164.4	37	126.6	229	41.3	367	67.5	281	48.1	404	71.1
2002	38	105.6	31	97.7	137	25.1	283	51.6	175	29.8	314	55.1
*1992-2002	39.2	112.1	25.4	85.7	143.2	26.2	251.9	46.3	178.8	30.8	277.3	49.1
**1995 / 2002	46.6	145.2	33.5	112.0	180.9	33.0	321.6	59.1	227.5	39.1	355.1	62.8

**Average of annual age-adjusted (direct) incidence rate per 100,000 population for the period from 1992 to 2002*

*** As above, but for the period from 1995 to 2002*

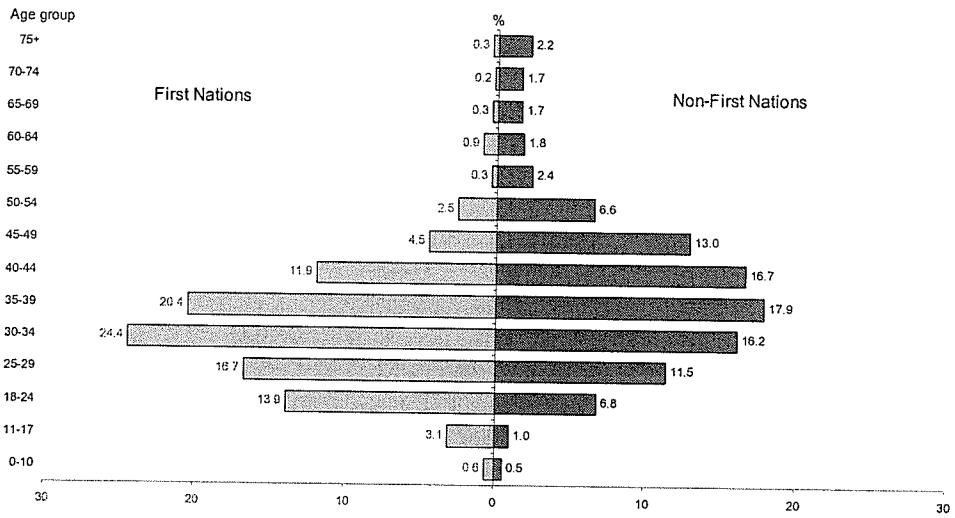
Generally, the highest incidence of hepatitis C was among First Nations females, followed by First Nations males, non-First Nations males, and the lowest incidence was among non- First Nations females (Figure 4.5). The cumulative incidence of hepatitis C among First Nations females was 4.1 times higher than the incidence among non-First Nations females. The difference was less dramatic among males, where overall incidence among First Nations males was 1.6 times the overall incidence among non- First Nations males.

4.1.4 The Age of Hepatitis C Patients

The mean age of patients at the time of their first ever positive HCV test result was 38.8±0.2 yr., and the median age in this study was 37 yr. old. First Nations persons were much younger than non-First Nations, with the mean ages of 33.0±0.4 vs. 39.7±0.2 years and the median ages of 33 vs. 39 years respectively. Only 4% of HCV-infected First Nations and 1.5% of non-First Nations individuals were children 0-17 years old (Figure 4.6). There were twice as many young adults 18-24 years of age among First Nations individuals (14%) compared to non-First Nations (7%). From all reported cases, the majority of First Nations patients (79%) were diagnosed with hepatitis C at an age younger than 40 years, while only 21% were diagnosed at the age of 40 years and older. Conversely, almost equal proportions of non-First Nations individuals were diagnosed with hepatitis C before (54%) and after (46%) the age of forty.

Overall, an increase in proportion of cases starts at the age of 18 years, reaches its peak at 30-39 years, and slowly decreases at 50-54 years of age, followed by relatively stable low proportions of cases at the ages 55 years and older.

Figure 4.6 Age distribution of hepatitis C cases (%), FN vs. non-FN



Females were slightly younger than males in both First Nations and non-First Nations groups. The median age of women was 32 yr. and for men it was 34 yr. among First Nations individuals vs. 37 and 39 yr. among non-First Nations women and men. At the average, First Nations females were 7 years younger than non-First Nations females, with the mean ages of 32±0.5 years vs. 39±0.4 years respectively. Likewise, First Nations males were 6 years younger than non-First Nations males, with the mean ages of 34±0.5 years vs. 40±0.2 years respectively.

4.1.4.1 Age- Specific incidence in men and women

Age-specific incidence of hepatitis C was higher among First Nations than non-First Nations individuals in almost all age groups (Table 4.7). The highest age-specific incidence among females (both First Nations and non-First Nations) was in the 30-39 year old age group. Among males, the highest incidence was in 30-44 year old First Nations men and in 35-49 year old non-First Nation men.

In First Nations people the incidence of hepatitis C was higher among females in all age groups except 40-44 and 50-54 yr. olds, where the rates were slightly higher among First Nations males (female-to male rate ratio of 0.9 and 0.8 respectively). The largest difference in incidence was in children 0-17 yr. of age and in 18-24 yr. old young adults, with female rates triple and double the rates of males respectively. In contrast, the incidence of hepatitis C was higher among non-First Nations males in all age groups except 0-24 yr. olds, where the rates were slightly higher among non-First Nations females. The largest difference in incidence was among those 45-54 years of age, with the incidence rate ratio of 0.3 (Table 4.7 and Figure 4.7).

The discrepancy in age-specific incidence of hepatitis C was particularly striking in women, with the overall incidence in First Nations females more than 4 times the incidence of non-First Nations females. The largest difference in incidence rates was among 11-17 year old girls with the FN-to-non-FN rate ratio of 7 and among 30-39 and 60-64- year old women with the rate ratio being greater than 5.

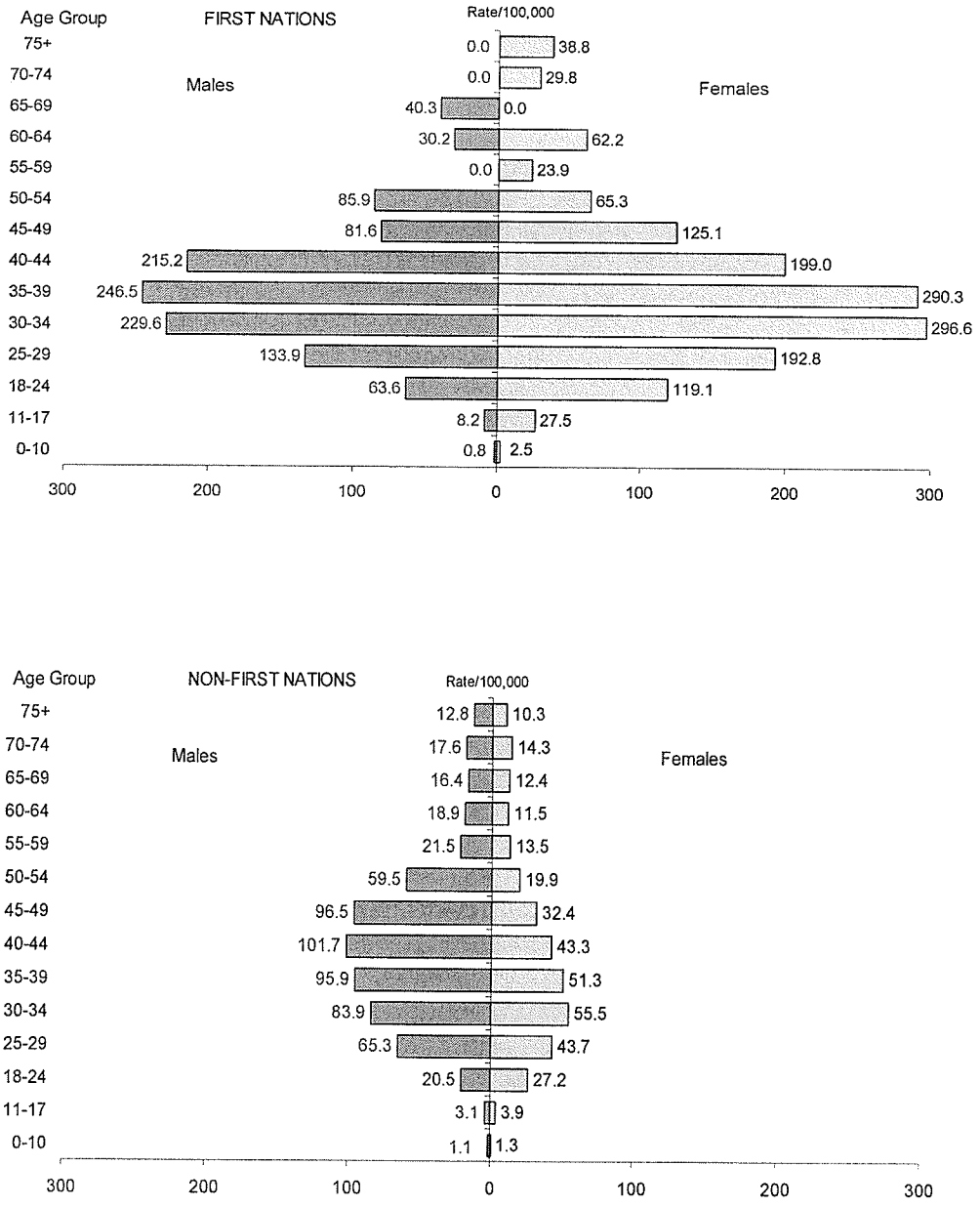
Such differences were much less pronounced in men, although still the incidence of hepatitis C in First Nations males was 1.6 times higher than in non-First Nations men.

The largest difference in incidence between First Nations and non-First Nations males was among 18-24 yr. olds with the rate ratio of 3.1. Interestingly, (aside from the 0-10 year old children), the incidence of hepatitis C in the 45-49 yr. old group was higher among non-First Nations males (rate ratio of 0.85), and there were no HCV-infected First Nations men older than 69 years of age.

Table 4.7 Age-specific incidence of hepatitis C

	First Nations		Non-First Nations		FN/non-FN
Age group (yr.)	Cases	Rate per 100,000	Cases	Rate per 100,000	Rate Ratio
Females					
0-10	3	2.48	12	1.28	1.94
11-17	16	27.54	24	3.94	6.98
18-24	61	119.05	166	27.24	4.37
25-29	68	192.77	199	43.74	4.41
30-34	95	296.57	278	55.53	5.34
35-39	76	290.29	270	51.30	5.66
40-44	39	198.97	216	43.32	4.59
45-49	18	125.06	142	32.36	3.87
50-54	7	65.31	72	19.85	3.29
55-59	2	23.86	40	13.46	1.77
60-64	4	62.23	31	11.47	5.42
65-69	0	0	33	12.37	-
70-74	1	29.77	37	14.35	2.08
75+	2	38.78	55	10.32	3.76
Total	***392***	***98.81***	***1575***	***23.99***	***4.12***
Males					
0-10	1	0.80	11	1.11	0.72
11-17	5	8.16	20	3.11	2.62
18-24	32	63.57	129	20.54	3.10
25-29	44	133.93	300	65.26	2.05
30-34	69	229.60	425	83.73	2.74
35-39	61	246.45	510	95.86	2.57
40-44	41	215.19	510	101.74	2.12
45-49	12	81.63	424	96.52	0.85
50-54	10	85.90	215	59.54	1.44
55-59	0	0	63	21.45	-
60-64	2	30.17	49	18.93	1.59
65-69	2	40.28	39	16.44	2.45
70-74	0	0	36	17.61	-
75+	0	0	41	12.75	-
Total	***279***	***70.01***	***2772***	***43.48***	***1.61***

Figure 4.7 Age-specific incidence of hepatitis C, males vs. females



Although different in magnitude, the age-specific incidence of hepatitis follows similar patterns in both groups (FN and non-FN) and in both sexes. Incidence increases sharply at the age of 18 years, reaches its peak in the 3rd and 4th decade of life, and than decreases with age (Figure 4.7).

4.2 GEOGRAPHIC DISTRIBUTION OF HEPATITIS C

Geographic location of hepatitis C cases was assigned according to the Regional Health Authority (RHA) at the time of the diagnosis. Residence was divided into 3 regions relative to the availability of various hepatitis C-related resources. Urban residence, where tertiary care and specialists (hepatologists) are available to provide regular care, includes Winnipeg only. Brandon (city with no hepatologists) was included in rural Southern Manitoba, together with North and South Eastman, Interlake, Central, Assiniboine, and Parkland RHAs. The third area, Rural Northern Manitoba, includes RHAs most remote from Winnipeg: Norman, Burntwood, and Churchill (Figure 3.3).

The vast majority of hepatitis C cases -83%- were from Winnipeg (Table 4.8). Another 21% of cases among First Nations and 16% of cases among non- First Nations were from rural Manitoba. Among those, an equal proportion of cases (12% of First Nations and 13% of non-First Nations) were among residents of rural Southern Manitoba. The proportion of cases from rural Northern Manitoba among First Nations -9%- was 3 times the proportion of cases among non-First Nations (3%).

The incidence of hepatitis C was the highest in Winnipeg, the only urban center in Manitoba. The overall incidence of hepatitis C among Winnipeg residents was 51.4 cases per 100,000 population, which was 3.4 times higher than the incidence among residents of rural Manitoba (including Brandon) at 15.0 cases per 100,000 population. Almost identical rates of 20-21 cases per 100,000 populations were in the RHA regions of North

Eastman, Interlake, and Burntwood/Churchill (Table 4.8). The lowest incidence of 8.8 cases per 100,000 population was in the Parkland RHA region (Figure 4.8).

While the incidence rates of hepatitis C were clearly higher among First Nations people in most regions of Manitoba and overall, in the North Eastman and combined Burntwood/Churchill area the rates were actually the same among both First Nations and non-First Nations residents (Table 4.8 and Figure 4.9). At the other end of the spectrum, First Nations Winnipeg residents had the highest incidence of hepatitis C (323/100,000), which was more than 7 times the incidence among non-First Nations urban residents (45.7/100,000). The incidence of hepatitis C among First Nations residents of southwestern Manitoba (Brandon, Assiniboine, and Central RHA) was more than 4 times the incidence of non-First Nations residents (Figure 4.9).

In summary, urban residents (both FN and non-FN) had the highest rates of hepatitis C, well above the corresponding provincial rates. The Parkland region enjoys the lowest rates of hepatitis C among both FN and non-FN residents. In the rest of Manitoba, geographic patterns between FN and non-FN populations varied. Thus, non-FN residents of Southern and Western Manitoba (Parkland, Brandon, Assiniboine, and Central RHAs) had the lowest incidence of hepatitis C, while those from the opposite geographic regions of Northeastern Manitoba (North Eastman and Burntwood/Churchill RHAs) had the highest incidence. Quite the opposite, FN residents of Northern Manitoba had the lowest incidence of hepatitis C, while those from Brandon and the Central regions had the highest incidence in rural Manitoba.

Table 4.8 Geographic location of hepatitis C cases

Region	First Nations			non-First Nations			FN / not FN	Total RHA		
		Rate/100,000		Ratio	Rate/100,000		Rate		Rate/100,000	
	n	Crude	Adjusted	n	Crude	Adjusted	Ratio	n	Crude	Adjusted
By RHA:										
Parkland	6	15.8	19.5	37	7.6	7.9	2.5	43	8.2	8.8
Assiniboine	10	27.6	39.8	76	9.1	9.4	4.2	86	9.9	10.4
South Eastman	0	0.0	0.0	81	13.0	13.2	-	81	13.0	13.2
Brandon	7	35.2	51.2	68	12.4	12.6	4.1	75	13.2	13.6
Central	22	39.5	57.3	129	11.8	12.5	4.6	151	13.1	14.0
Norman	10	17.1	21.1	37	15.1	14.6	1.4	47	15.5	15.6
Interlake	31	43.1	48.9	146	17.9	17.9	2.7	177	20.0	20.3
North Eastman	13	20.1	22.4	76	19.4	19.7	1.1	89	19.5	20.3
Burntwood / Churchill	42	15.2	19.9	54	20.5	20.4	1	96	17.8	20.6
Winnipeg	530	308.1	323.2	3643	47.7	45.7	7.1	4173	53.4	51.4
Manitoba	671	84.4		4347	33.6		2.5	5018	36.5	
By region:										
Urban (Winnipeg)	530	308.1	323.2	3643	47.7	45.7	7.1	4173	53.4	51.4
Rural	141	22.6	29.1	704	13.3	13.7	2.1	845	14.3	15.0
Rural Southern MB	*89*	*30.8*	*39.0*	*613*	*12.8*	*13.3*	*2.9*	*702*	*13.8*	*14.5*
Rural Northern MB	*52*	*15.5*	*20.3*	*91*	*17.9*	*17.4*	*1.2*	*143*	*17.0*	*18.5*
Manitoba	671	84.4		4347	33.6		2.5	5018	36.5	

Figure 4.8 Cumulative incidence of HCV infection by geographic region (rates per 100,000 population)

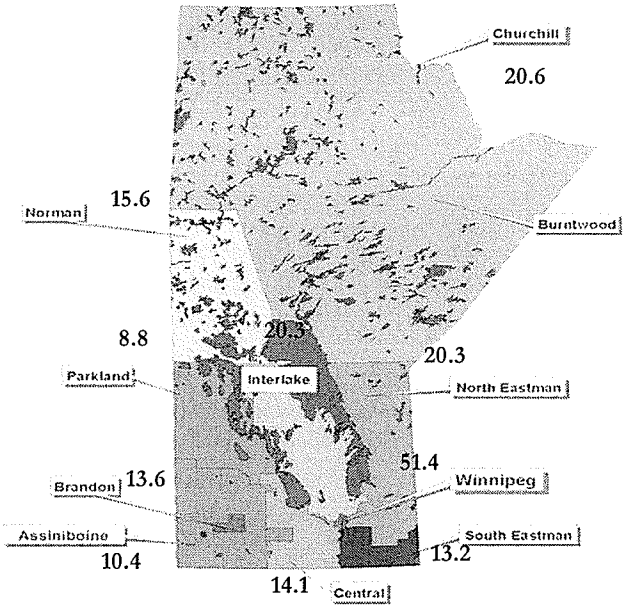
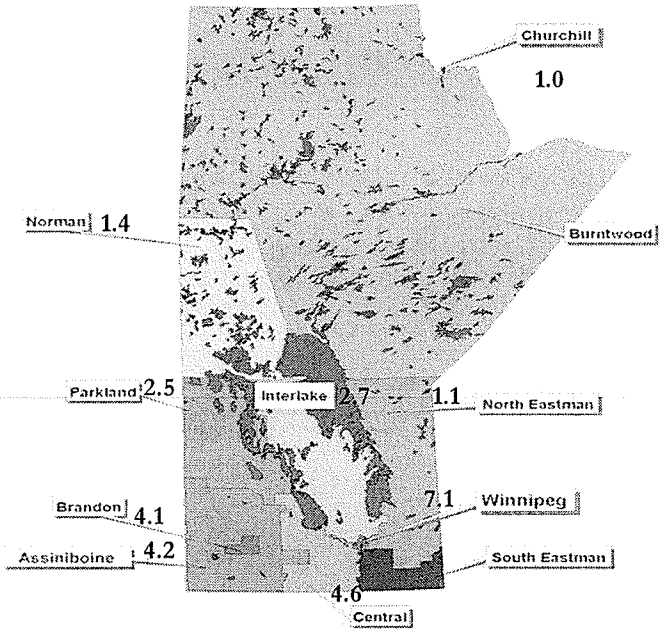


Figure 4.9 Geographic distribution of HCV infection in Manitoba by RHA: FN to non-FN Rate Ratio



4.3 SUMMARY

- The epidemiology of HCV infection is different when FN population is compared to non-FN population.
- The proportion of HCV-infected females in First Nations group was 60%, and the female-to-male ratio was 1.4. Conversely, the proportion of females in non-First Nations group was only 36%, and the female-to-male ratio was 0.6.
- FN HCV-infected persons were much younger than non-FN, and the majority of FN patients (79%) were diagnosed with hepatitis C at an age younger than 40 years, while just over 50% of non-FN persons were of this age.
- The age-specific incidence of HCV infection in FN females was the highest and was more than 4 times the incidence of non-FN females. The age-specific incidence of HCV infection in FN males was 1.6 times higher than in non-FN males.
- There are geographic variations in the incidence of newly diagnosed HCV infection, with the majority of cases coming from Winnipeg.

CHAPTER 5 NATURAL HISTORY OF THE DISEASE

5.1 DATA ORGANIZATION

As a result of the linkage, 98% of all cases were included in the utilization-based analysis (Figure 5.1). A total of 4924 records (98% of cases) containing ICD-9-CM–coded diagnostic information from either hospital abstracts or physician reimbursement databases formed the final set suitable for examining the clinical features and natural history of hepatitis C in the study cohort. These include all but one record from First Nation individuals (670 cases out of 671 recorded in the CDC database) and 97.9% of records of non-First Nations individuals (4254 cases out of 4347 recorded in the CDC database). Similarly, 98% of the records of controls were included in the natural history analysis Figure 5.2).

Figure 5.1 Structure of hepatitis C cohort (cases)

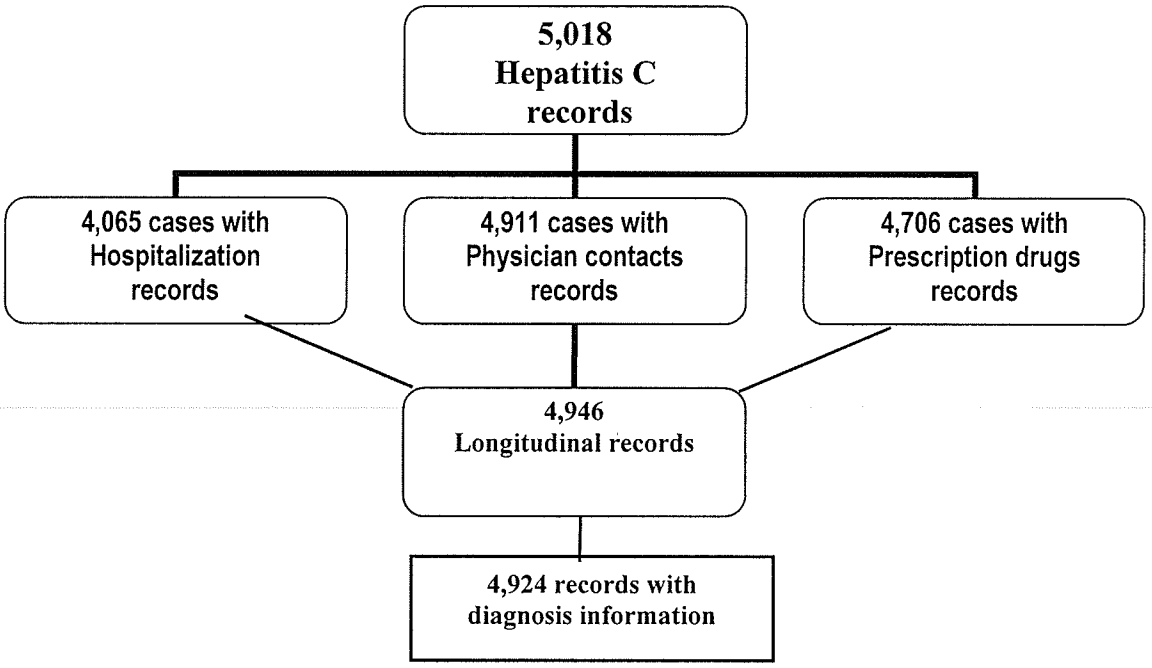
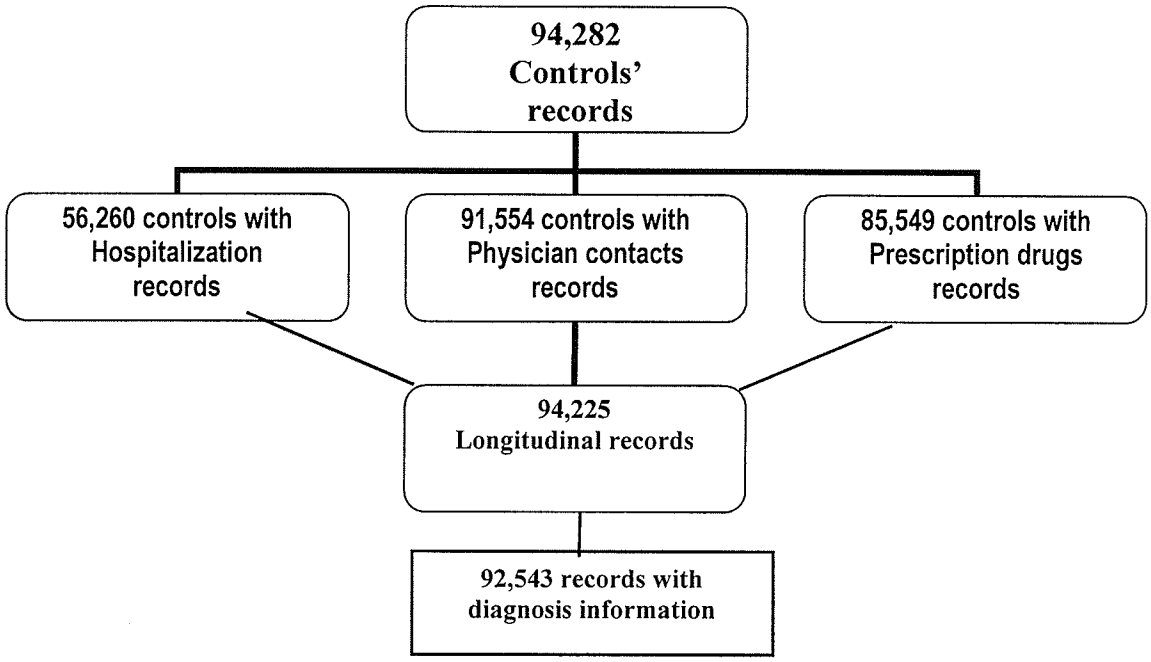


Figure 5.2 Structure of matched population-based control cohort



5.2 CLINICAL CHARACTERISTICS OF HEPATITIS C PATIENTS

A total of 74% of hepatitis C patients had liver disease-related (LDR) health care contacts during the study period. Clinical characteristics of First Nations and non-First Nations patients with chronic hepatitis C were remarkably similar. Only alcohol abuse, diabetes, and HIV infection were significantly more common among First Nations patients compared to non-First Nations individuals. Detailed information on clinical characteristics of Manitobans with chronic hepatitis C is presented below in Table 5.1. Orthotopic liver transplant, as treatment of decompensated liver disease, was included in the table under the "Complications of chronic hepatitis C" heading, because it indicated that the person had end stage liver disease.

Table 5.1 Clinical characteristics of hepatitis C patients in Manitoba

	FN (N=671)		NON-FN (N=4,347)		P	Total (N=5,018)	
VARIABLE	**n**	**%**	**n**	**%**		**n**	**%**
Total CLD and cirrhosis (code "571")[&]	116	17.3	807	19.0	0.212	923	18.7
Total sequelae of CLD (code "572")[&]	37	5.5	222	5.2	0.832	249	5.3
Total other liver disease (code "573")^	274	40.9	1953	45.9	0.015	2227	45.2
Complications of chronic hepatitis C							
Portal hypertension	38	5.7	238	5.5	0.791	276	5.5
Ascites	19	2.8	116	2.7	0.872	135	2.7
Esophageal varices	13	1.9	79	1.8	0.327	92	1.8
Hepatic encephalopathy	13	1.9	49	1.2	0.089	62	1.3
Hepatocellular carcinoma	3	0.4	55	1.3	0.059	58	1.2
Spontaneous bacterial peritonitis	6	0.9	41	1.0	0.866	47	1.0
Hepatorenal syndrome	1	0.1	11	0.3	0.594	12	0.2
[#]Orthotopic liver transplant	0	0.0	19	0.4	0.831	19	0.4
***Total Decompensated liver disease**	**33**	**4.9**	**213**	**4.9**	**0.73**	**246**	**4.9**
Other causes of liver disease and conditions of interest							
Alcohol dependence (AD)	402	60.0	1463	33.7	0.000	1865	37.2
Alcohol-induced liver disease	37	5.5	138	3.2	0.90	175	3.5
Alcohol-induced liver disease from AD	37	9.2	138	9.4	0.63	175	9.4
Diabetes mellitus	111	16.6	455	10.5	0.00001	566	11.3
HIV / AIDS	46	6.9	158	3.6	0.0001	204	4.1
Hepatitis B	27	4.0	126	2.9	0.138	153	3.1
Chronic non-viral hepatitis	9	1.3	90	2.1	0.185	99	2.0
EBV infection / persistence	7	1.04	52	1.2	0.739	59	1.2
Hemophilia	1	0.15	52	1.2	0.347	53	1.1
Non-alcoholic fatty liver disease	2	0.3	28	0.6	0.266	30	0.6
Hepatitis A	8	1.2	20	0.5	0.021	28	0.6
Other viral hepatitis	5	0.7	16	0.4	0.172	21	0.4
Hemochromatosis	0	0	12	0.3		12	0.2
Primary biliary cirrhosis (PBC)	0	0	4	0.1		4	0.1
Wilson's disease	0	0	1	0.02		1	0.02
Liver abscess	1	0.15	0	0		1	0.02

[#] Orthotopic liver transplant is included as a marker of hepatic decompensation
* The total is less than the sum of all conditions as individual patients may have several associated conditions
[&]ICD-9-CM code "571" - Chronic liver disease and cirrhosis; [&]ICD-9-CM code "572" - Liver abscess and sequelae of chronic liver disease; ^ICD-9-CM code "573" - Other disorders of liver

A total of 17% of First Nations and 19% of non-First Nations hepatitis C patients had chronic hepatitis and/or cirrhosis. There was no difference in the proportion First Nations and non-First Nations individuals with decompensated liver disease. Overall, at least 5% of First Nations and non-First Nations patients with chronic hepatitis C had one or another sign of decompensation (see Appendix 2 and Chapter 3 [*Methods* section] on the particulars of this data construction). There were no sex differences in the frequency of decompensation, with 5.9% of females and 6.2% of males developing clinically significant symptoms (p=0.66). The most common condition associated with progressive liver disease was portal hypertension, noted in at least 5.5% of all chronic hepatitis cases. Ascites at 2.7% and esophageal varices at 1.8% were next most common complications, and they were also observed with the same frequency among First Nations and non-First Nations patients. Hepatorenal syndrome was the least common complication. There were no liver transplant recipients among First Nations patients. Likewise, 95% of individuals with hepatocellular carcinoma were non-First Nations, yet the proportions of First Nations and non-First Nations patients who developed HCC were not statistically different.

Alcohol abuse was significantly more common among First Nations individuals compared to non-First Nations persons (60% vs. 34% respectively). 5.5% of FN and 3.2% of non-FN hepatitis C patients had co-existing alcohol-related liver disease. Interestingly, the proportion of alcohol abusers who developed alcohol-induced liver disease was the same in First Nations and non-First Nations patients (9.2% and 9.4% respectively). Decompensated liver disease also occurred with the similar frequency in First Nations (9.2%) and non-First Nations (9.8%) excessive alcohol users.

Concurrent presence of other liver diseases was relatively infrequent. Three percent of patients were co-infected with hepatitis B. One percent of hepatitis C patients have also had either hepatitis A or other forms of viral hepatitis, and an additional two percent had chronic non-viral hepatitis. Seven percent of First Nations patients and fewer than four percent of non-First Nations individuals had been co-infected with HIV ($p<0.0001$). First Nations individuals were also significantly more often affected by diabetes as compared to non-First Nations patients (16.6% vs. 10.7% respectively, $p<0.00001$). Approximately 1% of all diabetic patients had fatty liver as compared to 0.6% of non-diabetics with fatty liver; however, these are not reliable estimates, as fatty liver diagnoses are derived only from hospital records and can not be ascertained from physician visits data (see the forthcoming discussion of data limitations). There were just a few cases of hemochromatosis, primary biliary cirrhosis, and Wilson's disease (all among non-FN) and one case of liver abscess in a FN individual.

It is noteworthy that, while the disease features were largely similar between First Nations and non-First Nations individuals, liver biopsy was performed on fewer than 10% of First Nations persons as compared to 23% of non- First Nations individuals ($p<0.00001$).

A total of 41% of FN and 46% of non-FN individuals with chronic hepatitis C had medical visits for which the diagnosis was coded as "573 - Other disorders of liver", a code reserved for mostly vague and non-specified conditions. This may reflect initial visits to investigate abnormal liver function tests.

It is worth mentioning that the clinical characteristics of males and females were the same among FN and non-FN HCV-infected groups. A total of 17% of FN women and 13% of FN men had chronic hepatitis and/or cirrhosis, which was not different from non-FN women (15%) and men (16%). There was no difference in the proportion of First Nations and non-First Nations males and females with decompensated cirrhosis as well (Table 5.2). Overall, at least 5% of First Nations and non-First Nations patients with chronic hepatitis C had one or another sign of decompensation. Portal hypertension, ascites, esophageal varices, and hepatic encephalopathy were encountered with the same frequency in all four groups (FN females, FN males, non-FN females, and non-FN males) with hepatitis C. There were no sex differences in the frequency of most non-hepatic conditions as well. While alcohol abuse was twice as common among FN persons as it was among non-FN overall, males and females in each group had exact same proportion of alcohol abusers. Thus, 60% of FN males and females were abusing alcohol, as well as 33% of non-FN females and 34% of non-FN males. Likewise, HIV/AIDS was more prevalent in FN HCV-infected persons overall, but the same proportions of both sexes were co-infected in the FN group (7% of females and 6% of males were HCV/HIV co-infected) and in non-FN group (3% of females and 4% of males were HCV/HIV co-infected).

Only two conditions were more frequent among females than males. Almost 19% of FN females and 13% of FN males had diabetes ($p<0.05$). Similarly, more non-FN females had diabetes (12%) as compared to non-FN males (10%) ($p<0.04$). Liver diseases combined under ICD-9 code "573" were second most frequent condition after alcohol

abuse, with 51% of non-FN females vs. 42% of non-FN males and 44% of FN females vs. 36% of FN males having these conditions (Table 5.2).

Table 5.2 Clinical characteristics of hepatitis C patients in Manitoba by gender

	FN				non-FN			
	Females (N=392)		Males (N=279)		Females (N=1575)		Males (N=2772)	
	n	%	n	%	n	%	n	%
CLD and cirrhosis ("571")	65	16.6	35	12.5	242	15.4	446	16.1
Sequelae of CLD ("572")	16	4.1	9	3.2	56	3.6	110	4.0
Other liver disease ("573")*	174	44.4	100	35.8	800	50.8	1153	41.6
Complications of chronic hepatitis C								
Portal hypertension	22	5.6	16	5.7	78	5.0	160	5.8
Ascites	12	3.1	7	2.5	41	2.6	75	2.7
Esophageal Varices	7	1.8	6	2.2	26	1.7	53	1.9
Hepatic Encephalopathy	9	2.3	4	1.4	16	1.0	33	1.2
HCC	2	0.5	1	0.4	18	1.1	37	1.3
HRS	1	0.3	0		4	0.3	7	0.3
OLT	0		0		5	0.3	14	0.5
Decompensated cirrhosis	20	5.1	13	4.7	72	4.6	141	5.1
Other causes of liver disease and conditions of interest								
Alcohol abuse	236	60.2	166	59.5	512	32.5	951	34.3
Alcohol liver disease	24	6.1	13	4.7	38	2.4	100	3.6
DM#	74	18.9	37	13.3	185	11.7	270	9.7
NAFLD	0		2	0.7	11	0.7	17	0.6
HIV	29	7.4	17	6.1	53	3.4	105	3.8
HBV	21	5.4	6	2.2	65	4.1	61	2.2

**FN $p<0.02$, non-FN $p<0.0001$*

#FN $p<0.05$, non-FN $p<0.04$

5.3 Comparative clinical features between hepatitis C patients and demographically- matched population controls

Clinical characteristics of First Nations and non-First Nations patients with chronic hepatitis C and demographically-matched population controls are presented in Table 5.3. All conditions were more frequent among individuals with hepatitis C than among

controls without hepatitis C. When FN cases were compared to FN controls and non-FN cases were compared to non-FN controls, the odds of almost all conditions were higher among cases (those with hepatitis C), both FN and non-FN. The very few exceptions with no increase in the odds were EBV for both FN and non-FN; as well as diabetes, non-alcoholic fatty liver disease (NAFLD), spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS) for FN.

With respect to the relative increase in the odds for various conditions, however, two situations must be distinguished: on the one hand, the same increase in the odds among both FN and non-FN cases vs. respective controls, and on the other hand, a greater increase in the odds among non-FN as compared to FN cases vs. controls. For the most part, there was an interaction between race (FN vs. non-FN) and HCV infection (hepatitis C vs. no hepatitis C). While most conditions of interest were either more frequent or present with the same frequency in FN as compared to non-FN cases, in the corresponding controls all these conditions were almost universally less frequent in non-FN controls vs. FN controls. Hence, the relative increase in risk of such conditions was mostly higher among non-FN cases as compared to their corresponding controls. Hepatitis C seems to pose a greater relative risk for non-FN individuals when compared to uninfected controls, while having a relatively less significant effect on FN individuals. In general, FN individuals have a greater frequency of various comorbidities; hence the absolute difference between cases and controls is less for FN than non-FN individuals and the relative risk is greater for non-FN than FN persons.

Table 5.3 Adjusted odds ratios for selected conditions, FN vs. non-FN individuals

		CASES			CONTROLS			Adjusted OR				Difference	
		N	n	%	N	n	%	HR	95% CI		P	OR	P
Cirrhosis Total	Total	5018	324	6.46	94282	406	0.43	17.03	14.59	19.87	<0.0001		
	FN	671	40	5.96	9802	74	0.75	8.75	5.78	13.26	<0.0001		
	Non-FN	4347	284	6.53	84480	332	0.39	19.03	16.11	22.48	<0.0001	0.460	0.0007
Portal Hypertension	Total	5018	276	5.50	94282	389	0.41	14.70	12.50	17.28	<0.0001		
	FN	671	38	5.66	9802	72	0.73	8.37	5.48	12.77	<0.0001		
	Non-FN	4347	238	5.48	84480	317	0.38	16.26	14.65	19.38	<0.0001	0.515	0.0045
Hepatic Decompensation Total	Total	5018	246	4.90	94282	367	0.39	13.62	11.50	16.12	<0.0001		
	FN	671	33	4.92	9802	70	0.71	7.26	4.66	11.32	<0.0001		
	non-FN	4347	213	4.90	84480	297	0.35	15.24	12.70	18.30	<0.0001	0.476	0.0025
Ascites	Total	5018	135	2.69	94282	213	0.23	12.11	9.70	15.11	<0.0001		
	FN	671	19	2.83	9802	44	0.45	6.32	3.58	11.18	<0.0001		
	non-FN	4347	116	2.67	84480	169	0.20	13.73	10.80	17.46	<0.0001	0.460	0.014
Esophageal Varices	Total	5018	92	1.83	94282	110	0.12	15.86	11.96	21.04	<0.0001		
	FN	671	13	1.94	9802	27	0.28	6.84	3.47	13.49	<0.0001		
	non-FN	4347	79	1.82	84480	83	0.10	19.31	14.12	26.41	<0.0001	0.355	0.007
Hepatic Encephalopathy	Total	5018	62	1.24	94282	53	0.06	23.05	15.73	33.78	<0.0001		
	FN	671	13	1.94	9802	21	0.21	9.40	4.47	19.77	<0.0001		
	non-FN	4347	49	1.13	84480	32	0.04	32.06	20.36	50.48	<0.0001	0.293	0.006

		CASES			CONTROLS			Adjusted OR				Difference	
		N	n	%	N	n	%	HR	95% CI		P	OR	P
Hepatocellular Carcinoma	Total	5018	58	1.2	94282	61	0.1	18.4	12.80	26.46	<0.0001		
	FN	671	3	0.5	9802	5	0.1	8.1	1.85	35.33	<0.0055		
	non-FN	4347	55	1.3	84480	56	0.1	19.5	13.37	28.34	<0.0001	0.415	0.258
Spontaneous Bacterial Peritonitis	Total	5018	47	0.9	94282	224	0.2	3.8	2.75	5.21	<0.0001		
	FN	671	6	0.9	9802	45	0.5	1.6	0.65	3.90	0.3053		
	non-FN	4347	41	0.9	84480	179	0.2	4.5	3.21	6.37	<0.0001	0.352	0.138
Orthotopic Liver Transplant	Total	5018	19	0.4	94282	15	0.02	23.1	11.69	45.77	<0.0001		
	FN	671	0	0.0	9802	2	0.02						
	non-FN	4347	19	0.4	84480	13	0.02	27.7	13.67	56.25	<0.0001		
Hepatorenal Syndrome	Total	5018	12	0.2	94282	15	0.02	15.5	7.19	33.56	<0.0001		
	FN	671	1	0.2	9802	4	0.04	3.4	0.33	34.24	0.307		
	non-FN	4347	11	0.3	84480	11	0.01	20.3	8.76	46.85	<0.0001	0.165	0.581
Chr. liver disease and cirrhosis (ICD-9 code "571")	Total	5018	788	15.7	94282	963	1.0	19.6	17.69	21.76	<0.0001		
	FN	671	100	14.9	9802	210	2.1	9.0	6.82	11.75	<0.0001		
	non-FN	4347	688	15.8	84480	753	0.9	22.5	20.10	25.15	<0.0001	0.398	0.0002
Sequelae of chronic liver disease (ICD-9 code "572")	Total	5018	191	3.8	94282	196	0.2	19.8	16.07	24.34	<0.0001		
	FN	671	25	3.7	9802	50	0.5	7.6	4.57	12.61	<0.0001		
	non-FN	4347	166	3.8	84480	146	0.2	24.4	19.38	30.70	<0.0001	0.312	0.0001
Other disorders of the liver (ICD-9 code "573")	Total	5018	2227	44.4	94282	1748	1.9	45.3	41.97	48.93	<0.0001		
	FN	671	274	40.9	9802	299	3.1	24.1	19.59	29.61	<0.0001		
	non-FN	4347	1953	45.9	84480	1449	1.7	49.7	45.81	54.01	<0.0001	0.484	0.0000

		CASES			CONTROLS			Adjusted OR				Difference	
		N	n	%	N	n	%	HR	95% CI		P	OR	P
Alcohol abuse	Total	5018	1865	37.2	94282	6598	7.0	9.55	8.92	10.22	<0.0001		
	FN	671	402	59.9	9802	2556	26.1	4.73	3.99	5.61	<0.0001		
	non-FN	4347	1463	33.7	84480	4042	4.8	10.72	9.97	11.53	<0.0001	0.441	0.0005
Alcohol-related liver disease (ARLD)	Total	5018	175	3.5	94282	289	0.3	12.29	10.09	14.97	<0.0001		
	FN	671	37	5.5	9802	91	0.9	7.00	4.59	10.69	<0.0001		
	non-FN	4347	138	3.2	84480	198	0.2	14.51	11.62	18.13	<0.0001	0.482	0.001
ARLD from those with alcohol abuse	Total	1865	175	9.4	6598	289	4.4	2.26	1.98	2.50	0.005		
	FN	402	37	9.2	2556	91	3.6	2.75	2.01	3.45	0.005		
	non-FN	1463	138	9.4	4042	198	4.9	2.02	1.51	2.51	0.005	1.361	0.765
Diabetes	Total	5018	566	11.3	94282	7753	8.2	1.39	1.26	1.52	<0.0001		
	FN	671	111	16.5	9802	1701	17.4	0.90	0.72	1.12	0.348		
	non-FN	4347	455	10.5	84480	6052	7.2	1.54	1.39	1.71	<0.0001	0.580	<0.0001
Non-alcoholic fatty liver	Total	5018	30	0.6	94282	84	0.1	6.52	4.28	9.93	<0.0001		
	FN	671	2	0.3	9802	26	0.3	1.04	0.25	4.44	0.956		
	non-FN	4347	28	0.6	84480	58	0.1	9.61	6.12	15.11	<0.0001	0.108	0.004
Hemophilia	Total	5018	53	1.1	94282	39	0.0	25.8					
	FN	671	1	0.2	9802	0	0.0						
	non-FN	4347	52	1.2	84480	39	0.1	26.21					
Hemo-chromatosis	Total	5018	12	0.2	94282	9	0.0	25.11					
	FN	671	0	0.0	9802	0	0.0						
	non-FN	4347	12	0.3	84480	9	0.0	25.98					

		CASES			CONTROLS			Adjusted OR				Difference	
		N	n	%	N	n	%	HR	95% CI		P	OR	P
Viral infections:													
HIV / AIDS	Total	5018	204	4.07	94282	135	0.14	29.49	23.63	36.79	<0.0001		
	FN	671	46	6.86	9802	25	0.26	30.13	18.20	49.90	<0.0001		
	non-FN	4347	158	3.63	84480	110	0.13	29.38	22.96	37.59	<0.0001	1.026	0.929
Hepatitis B	Total	5018	153	3.05		n/a							
	FN	671	27	4.02									
	non-FN	4347	126	2.90									
Hepatitis A	Total	5018	28	0.56	94282	21	0.02	25.19	14.10	45.00	<0.0001		
	FN	671	8	1.19	9802	13	0.13	10.44	4.22	25.86	<0.0001		
	non-FN	4347	20	0.46	84480	8	0.01	49.32	21.59	112.66	<0.0001	0.212	0.473
Epstein-Barr virus	Total	5018	59	1.18	94282	1203	1.28	0.92	0.71	1.20	0.447		
	FN	671	7	1.04	9802	73	0.74	1.44	0.66	3.18	0.738		
	non-FN	4347	52	1.20	84480	1130	1.34	0.88	0.66	1.17	0.516	1.634	0.815

5.3.1 CHRONIC HEPATITIS C AND ITS SEQUELAE

Conditions such as chronic hepatitis and cirrhosis are not specific to viral hepatitis only and do have other etiologies. Hence, we expect population controls to be affected by liver diseases other than hepatitis C. These diseases are included in ICD-9-CM under the rubrics "Chronic liver disease and cirrhosis (571)", "Sequelae of chronic liver disease (572)" and "Other disorders of the liver (573)". As expected, the prevalence of conditions associated with progressive hepatitis and cirrhosis was significantly higher among cases (hepatitis C cohort) than among non HCV-infected controls, both among FN and non-FN persons (Table 5.3 and Figure 5.3). Nonetheless, the relative increase in risk of having these conditions due to chronic hepatitis C, expressed as an adjusted the odds ratio (AOR), was significantly higher in non-FN as compared to FN individuals. For FN cases, the adjusted odds of having the diagnosis of chronic liver disease* were 9 times the odds of FN controls. For non-FN cases, the odds of this diagnosis were 22.5 times the odds of corresponding controls (Figure 5.4). The AOR among FN was only 40% of the AOR among non-FN ($p<0.0002$).

Similarly, the odds of sequelae of chronic liver disease[*] were 7.6 times higher for FN cases as compared to FN controls. However, this is only 1/3 of the respective odds for non-FN cases, whose odds of sequelae of chronic liver disease were 24.4 times the odds for corresponding controls ($p<0.0001$).

Finally, the odds of having other disorders of the liver[#] had a 24-time increase for FN cases compared to FN controls. But the same the odds among non-FN cases were twice as high: AOR of other liver disorders were 50 times the odds for corresponding controls.

**ICD-9-CM code "571"; [*]ICD-9-CM code "572"; [#] ICD-9-CM code "573"*

Figure 5.3 Prevalence (%) of liver disease among hepatitis C cases and controls

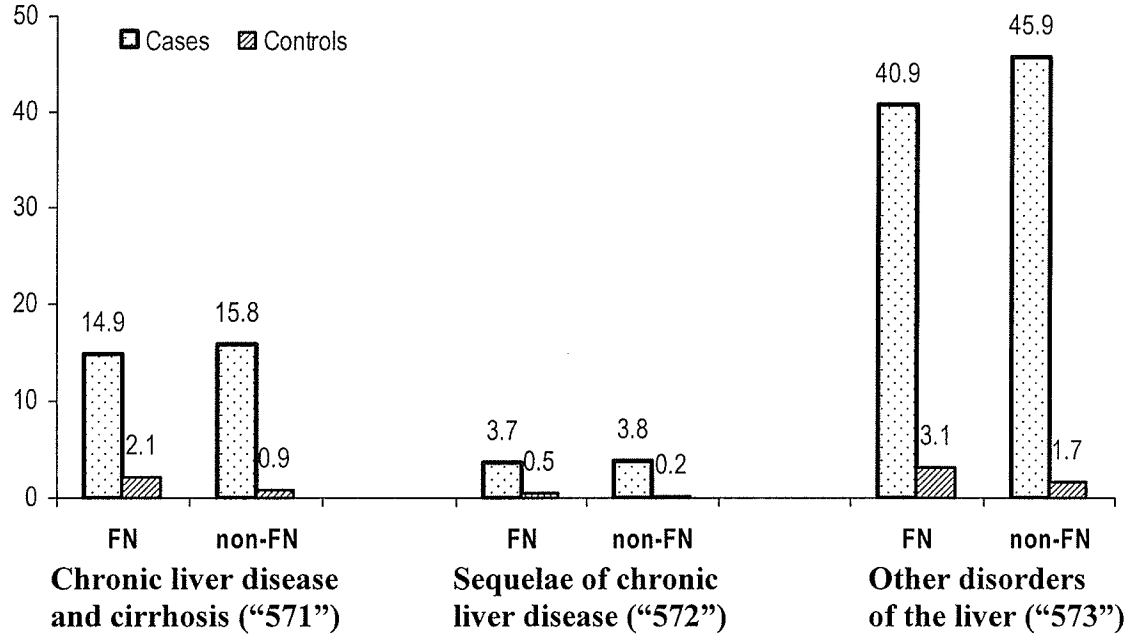
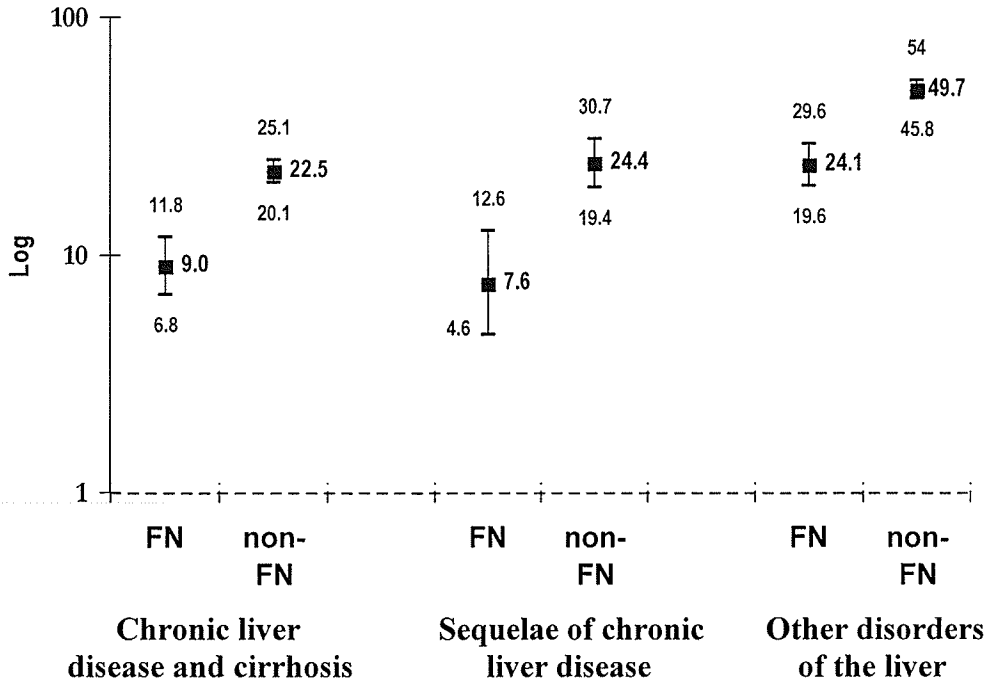


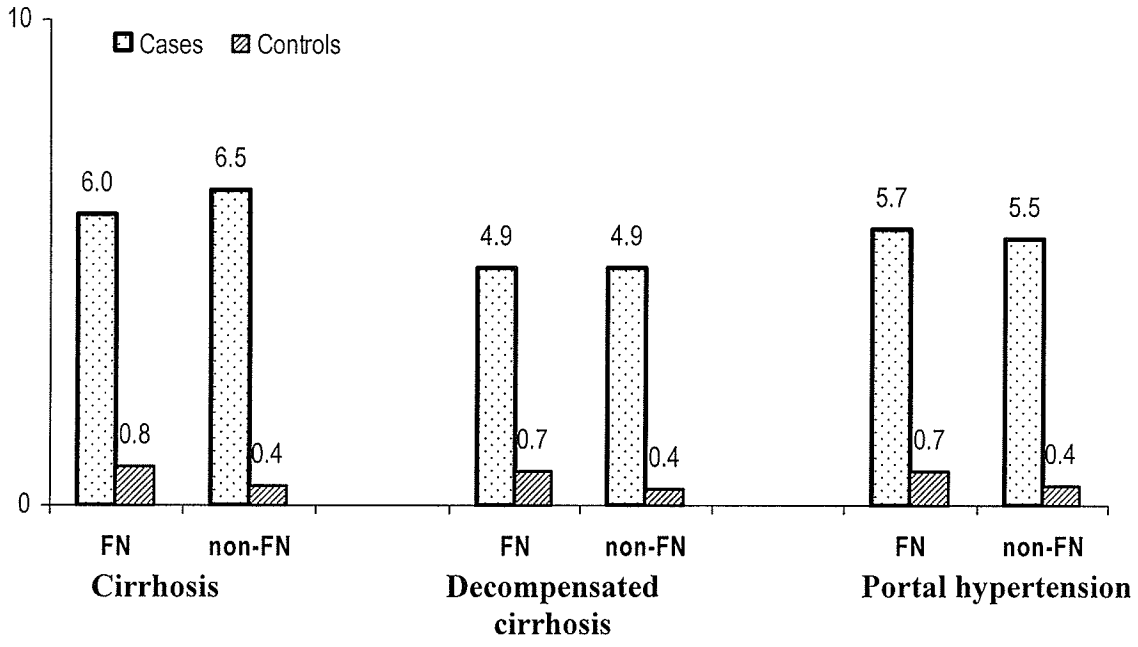
Figure 5.4 Adjusted Odds Ratios with 95% CI for liver diseases, FN vs. non-FN



5.3.2 PROGRESSIVE AND DECOMPENSATED LIVER DISEASE

Five percent of the study population had progressed to decompensated liver disease or end-stage liver disease (ESLD). This manifested in ascites, esophageal varices, hepatic encephalopathy, HRS, HCC, or a combination of these conditions. The prevalence of decompensated disease was the same for FN and non-FN patients with chronic hepatitis C. Fewer than 1% of FN controls and less than 0.5% of non-FN controls also had decompensated liver disease (Figure 5.5).

Figure 5.5 Prevalence (%) of cirrhosis and portal hypertension among hepatitis C cases and controls



Despite the same prevalence among cases, the AOR of hepatic decompensation were significantly higher for non-FN hepatitis C patients than for FN patients with hepatitis C when compared to corresponding controls. This was caused by the less frequent presence

of decompensated liver disease among the non-FN control population as compared to FN control population. This was true not only for hepatic decompensation overall, but for each individual condition associated with progressive liver disease, such as ascites, esophageal varices, etc. The corresponding adjusted odds ratios for FN populations were half the odds ratios of non-FN populations (Table 5.3 and Figure 5.6).

There were no increases in the odds of SBP and HRS among FN persons, while among non-FN individuals these odds were much higher as compared to corresponding controls (Table 5.3). A relatively small number of cases of hepatic encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma resulted in the odds ratios with wide confidence intervals, providing imprecise estimates of the adjusted odds (Figure 5.6). Hence, while the OR seems to be dissimilar, there were no statistically significant differences in the odds ratios of SBP, HCC, or HRS between FN and non-FN individuals (Figure 5.6).

Figure 5.6 Adjusted Odds Ratios with 95% CI for selected conditions

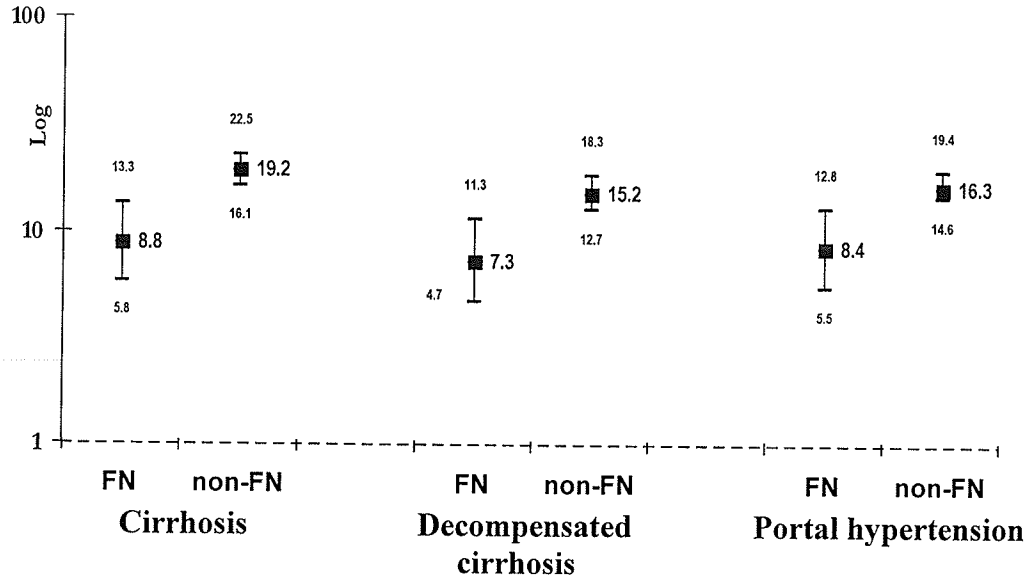
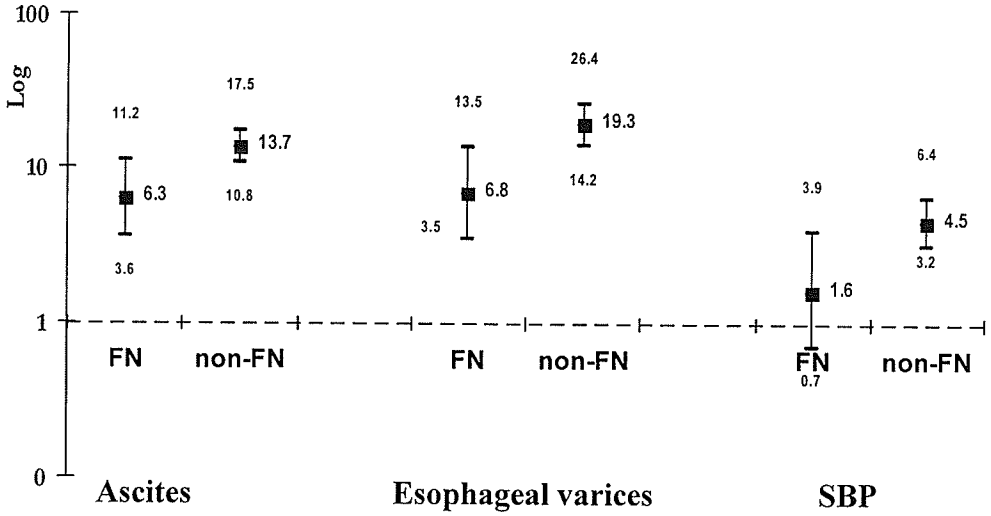
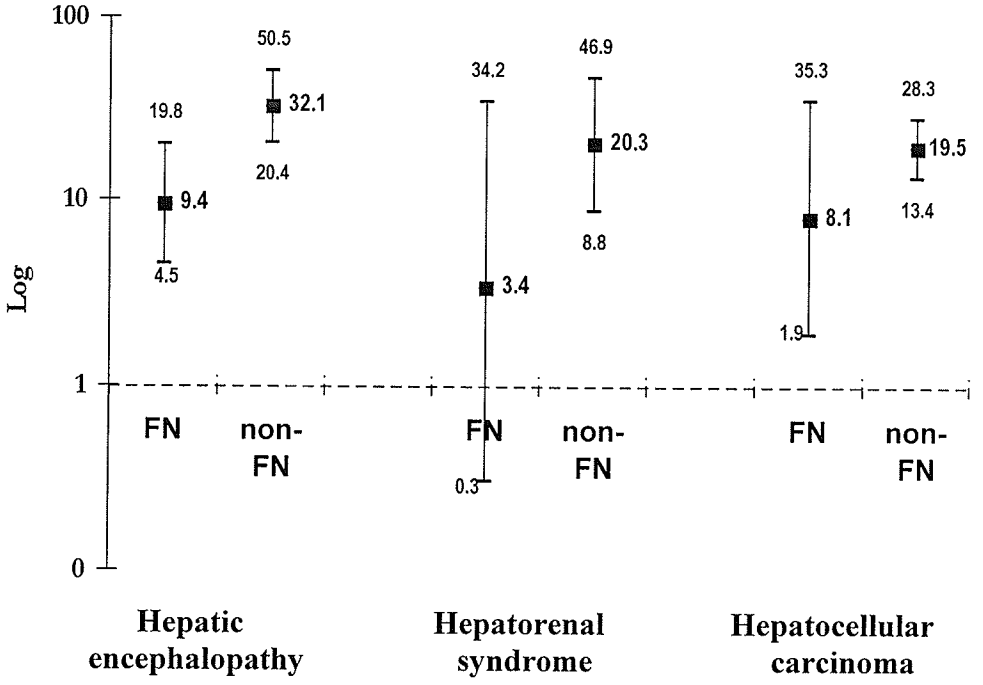


Figure 5.6 cont'd



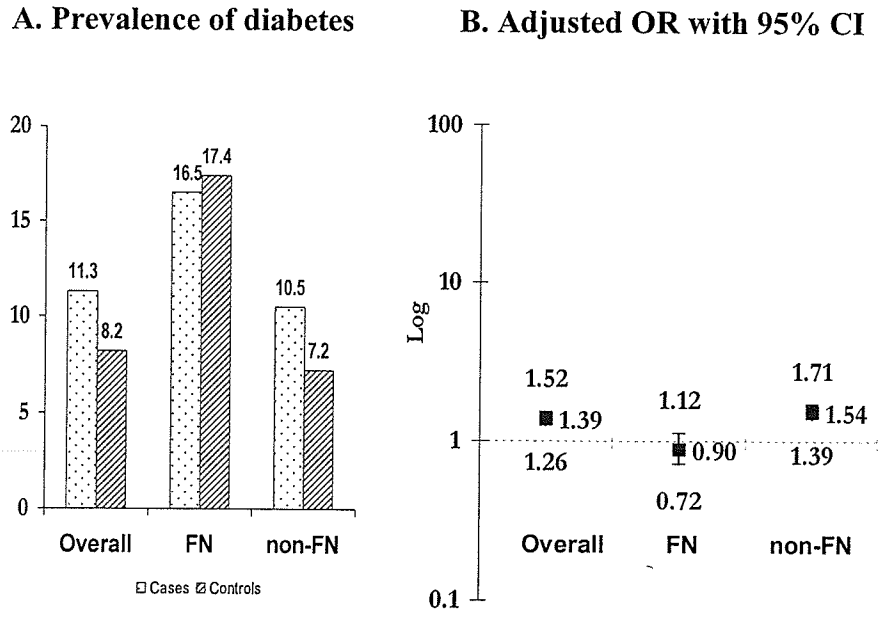


5.3.3 CHRONIC HEPATITIS C AND OTHER IMPORTANT COMORBIDITIES.

5.3.3.1 DIABETES

Diabetes mellitus is an important condition thought to be associated with hepatitis C. It is also well known that FN populations are disproportionately affected by diabetes. In this study, the overall prevalence of diabetes was 11.3% among cases and 8.2% among controls (OR 1.4, $p<0.001$). There was no difference in the prevalence of diabetes among FN cases (16.5%) and controls (17.4%), with the corresponding OR of 0.9 ($p<0.35$). On the other hand, non-FN individuals with chronic hepatitis C had the odds of diabetes 1.5 times the odds of non-FN controls ($p<0.001$). In other words, due to the already high prevalence of diabetes in FN populations, chronic hepatitis C does not result in an increase in the odds thereof, while for non-FN individuals with hepatitis C the odds of diabetes are increased in relation to the non-infected individuals (Table 5.2, Figure 5.7).

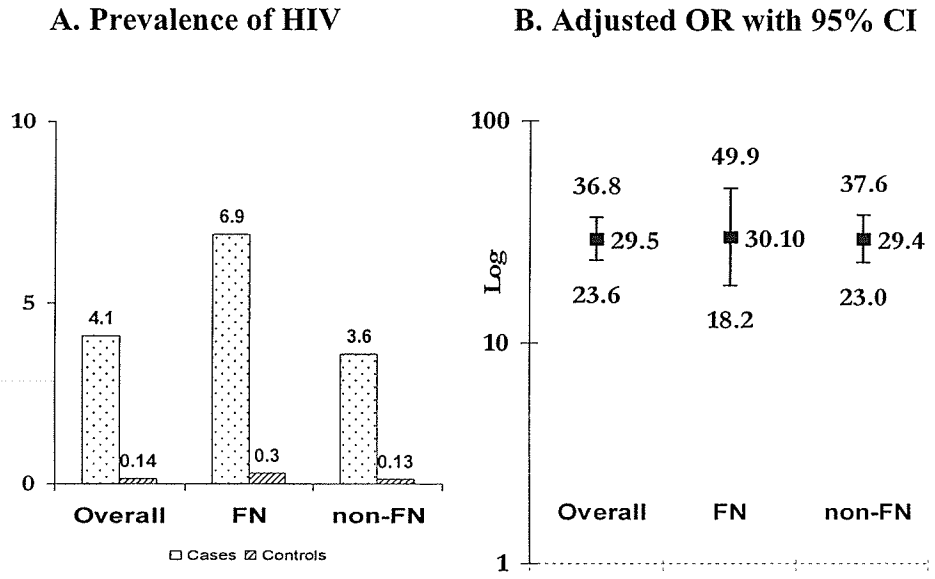
Figure 5.7. Prevalence and AOR of diabetes among hepatitis C cohort and controls



5.3.3.2 HCV/HIV COINFECTION

Co-infection with hepatitis C and HIV causes particular concern for clinicians, because HIV is known to accelerate the progression of hepatitis C to severe hepatitis and cirrhosis[199]. Moreover, the need for anti-retroviral therapy combined with hepatitis C treatment may create a certain clinical challenge. As discussed in chapter two, there is an alarming over-representation of HCV/HIV co-infected individuals of aboriginal descent even among populations of similar risk. In keeping with this general tendency, the prevalence of HIV in this study was 6.9% among FN cases and 3.6% among non-FN cases. The prevalence of HIV infection among controls was 0.3% in FN and 0.1% in non-FN persons. The adjusted odds ratios, however, were the same for FN and non-FN individuals, indicating a 30-times increase in the odds of having HIV for those with hepatitis C as compared to individuals without hepatitis C (Table 5.2 and Figure 5.8).

Figure 5.8 Prevalence and OR of HIV infection among hepatitis C and control cohorts



5.3.3.3 ALCOHOL ABUSE AND ALCOHOL-RELATED LIVER DISEASE

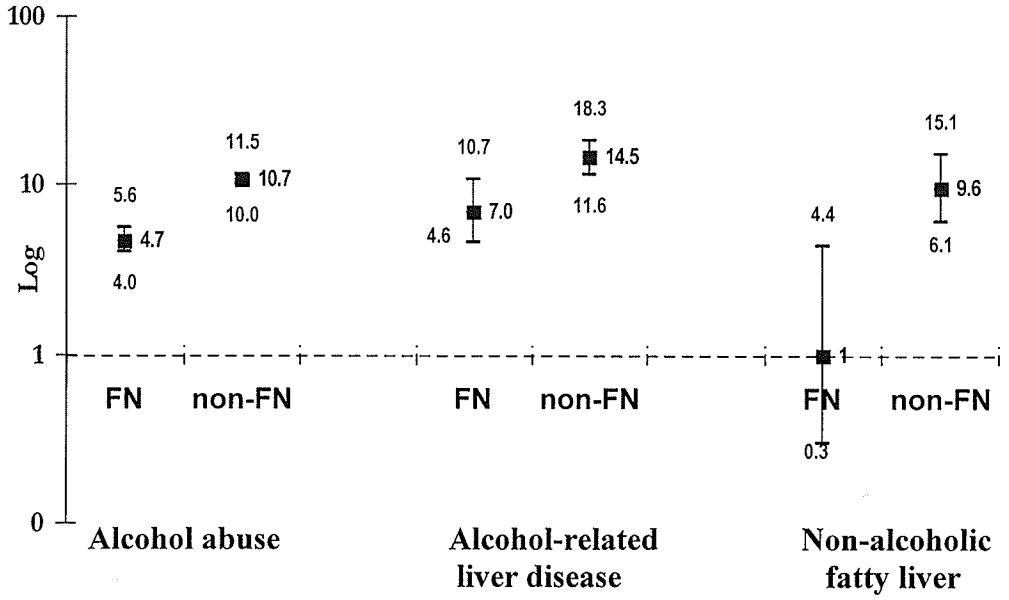
Alcohol abuse is a very important risk factor for the progression of hepatitis to end-stage liver disease. Patients with chronic hepatitis C who are heavy alcohol users are at an increased risk for developing cirrhosis of the liver and its complications (see discussion of this topic in chapter 2). As with diabetes and HIV, alcohol abuse was much more prevalent in the study's FN population vs. non-FN individuals, in both cases and controls. Thus, 60% f FN vs. 34% of non-FN persons with chronic hepatitis C were alcohol abusers ($p<0.00001$). Prevalence of alcohol abuse was 26% among FN controls and less than 5% among non-FN controls (Table 5.2). Because alcohol abuse was so common in FN individuals, among cases and controls alike, the relative increase in the odds thereof for FN cases was much smaller than the relative increase in the odds for non-FN individuals. On the other hand, the difference in prevalence of alcohol abuse among non-FN cases and controls (34% vs. 4.8%) was much greater, which resulted in a much larger AOR of 10.7 (Figure 5.9). Likewise, the odds of alcohol-induced liver disease were twice as high in non-FN cases (AOR of 14.5) as in FN hepatitis C patients (AOR of 7) when compared to their respective non-infected controls (Figure 5.9).

5.3.3.4 NON-ALCOHOLIC FATTY LIVER

The diagnosis of fatty liver is not readily discernable from administrative data, hence there were fewer cases than one would expect based on literature and clinical experience. As a result, there was no increased risk identified in FN cases vs. controls (AOR 1.04, $p<0.96$). Non-FN cases had an increase in the odds of having fatty liver as compared to

corresponding controls (AOR=9.6, p<0.0001). However, due to the small numbers, the confidence interval for AOR was wide, indicating unstable the odds (Figure 5.9)

Figure 5.9. Prevalence and OR of diabetes among hepatitis C cohort and controls



5.4 REASONS FOR HOSPITAL VISITS

During the study period, 81% of cases and 60% of controls had hospital contacts. Diagnostic categories for the principal reasons for these contacts are presented in the Table 5.3. For cases, the most common reasons were: injury and poisoning (27%), diseases of the digestive system, which include all *ICD-9-CM* codes for liver diseases (26.5%), and infectious and parasitic diseases, which include *ICD-9-CM* codes for viral hepatitis (23.8%). The same conditions were among five most frequent reasons for admissions among FN and non-FN cases. The causes were just slightly different for the controls (Table 5.4):

Table 5.4 Major reasons for hospital visits, FN vs. non-FN, cases vs. controls

FN cases		non-FN cases		FN controls		non-FN controls	
Injury/Poisoning	(44%)	Digestive	(26%)	Injury/Poisoning	(27%)	Digestive	(15%)
Digestive	(30%)	Infections	(25%)	Digestive	(22%)	Genitourinary	(15%)
Mental	(22%)	Injury/Poisoning	(24%)	Genitourinary	(17%)	Neoplasms	(10%)
Genitourinary	(19%)	Mental	(19%)	Respiratory	(11%)	Injury/Poisoning	(9%)
Infections	(17%)	Genitourinary	(19%)	Mental	(9%)	Cardiovascular	(6%)

Considering the risk factors for hepatitis C and its social aspects, it is not unexpected that 24% of non-FN individuals with hepatitis C had hospital contacts due to injury and poisoning, as well as almost twice as many FN cases (44%) (Table 5.4). Among the control population, the difference between FN and non-FN was even greater: just under 9% of non-FN vs. 27% of FN had been in the hospital due to injury and poisoning. Hence, once again, the odds were higher among non-FN (AOR=3.4) vs. FN (AOR=2.2) cases as compared to respective controls (Table 5.5).

Mental disorders appear to be a significant health problem for hepatitis C patients but not for controls. While mental disorders were 3rd most common reason for hospital visits for FN cases (22.5%) and 4th for non-FN cases (19.4%), it was a relatively infrequent cause for visits among both FN (8.8%) and non-FN (3.7%) controls. Individuals with chronic hepatitis C were 5.5 times more likely to have mental health problems as compared to controls without hepatitis C (AOR 5.54, 95% CI 5.13 – 5.99, $p<0.0001$).

Hepatitis C infection was not associated with any increase in the odds of malignancy. Also, there were no increase in the odds of digestive, genitourinary, nervous system, and endocrine disorders among FN cases vs. controls. Conversely, non-FN cases had increased the odds of these conditions as compared to non-FN controls (Table 5.5).

Table 5.5 Hospital contacts by the most responsible diagnosis

	CASES			CONTROLS						
	N	n	%	N	n	%	AOR	95% CI		P
INJURY AND POISONING (800-999)										
Total	5018	1353	26.96	94282	10013	10.62	3.16	2.95	3.38	<0.0001
FN	671	296	44.11	9802	2631	26.84	2.16	1.83	2.54	<0.0001
non-FN	4347	1057	24.32	84480	7382	8.74	3.43	3.19	3.70	<0.0001
DISEASES OF THE DIGESTIVE SYSTEM (520-579)										
Total	5018	1331	26.52	94282	14806	15.70	1.96	1.83	2.09	<0.0001
FN	671	199	29.66	9802	2126	21.69	1.51	1.26	1.81	0.307
non-FN	4347	1132	26.04	84480	12680	15.01	2.05	1.90	2.20	<0.0001
INFECTIOUS AND PARASITIC DISEASES (001-139)										
Total	5018	1195	23.81	94282	1803	1.91	16.61	15.30	18.03	<0.0001
FN	671	114	16.99	9802	325	3.32	6.06	4.78	7.67	<0.0001
non-FN	4347	1081	24.87	84480	1478	1.75	19.37	17.74	21.15	<0.0001
MENTAL DISORDERS (290-319)										
Total	5018	995	19.83	94282	4008	4.25	5.54	5.13	5.99	<0.0001
FN	671	151	22.50	9802	863	8.80	3.00	2.46	3.66	<0.0001
non-FN	4347	844	19.42	84480	3145	3.72	6.27	5.77	6.82	<0.0001
DISEASES OF THE GENITOURINARY SYSTEM (580-629)										
Total	5018	751	14.97	94282	9985	10.59	1.50	1.38	1.63	<0.0001
FN	671	130	19.37	9802	1632	16.65	1.18	0.95	1.46	0.1272
non-FN	4347	621	14.29	84480	8353	9.89	1.57	1.43	1.73	<0.0001
DISEASES OF THE RESPIRATORY SYSTEM (460-519)										
Total	5018	594	11.84	94282	5635	5.98	2.08	1.90	2.28	<0.0001
FN	671	99	14.75	9802	1059	10.80	1.39	1.11	1.75	0.0049
non-FN	4347	495	11.39	84480	4579	5.42	2.27	2.05	2.51	<0.0001
DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE (680-709)										
Total	5018	536	10.68	94282	6057	6.42	1.75	1.59	1.92	<0.0001
FN	671	74	11.03	9802	823	8.40	1.38	1.07	1.78	0.0135
non-FN	4347	462	10.63	84480	5234	6.20	1.82	1.65	2.02	<0.0001
DISEASES OF THE CIRCULATORY SYSTEM (390-459)										
Total	5018	476	9.49	94282	5573	5.91	1.77	1.60	1.97	<0.0001
FN	671	50	7.45	9802	485	4.95	1.50	1.09	2.07	0.0132
non-FN	4347	426	9.80	84480	5088	6.02	1.81	1.62	2.03	<0.0001
NEOPLASMS (140-239)										
Total	5018	473	9.43	94282	8771	9.30	1.05	0.94	1.16	0.393
FN	671	36	5.37	9802	610	6.22	0.80	0.56	1.15	0.226
non-FN	4347	437	10.05	84480	8161	9.66	1.05	0.95	1.17	0.367

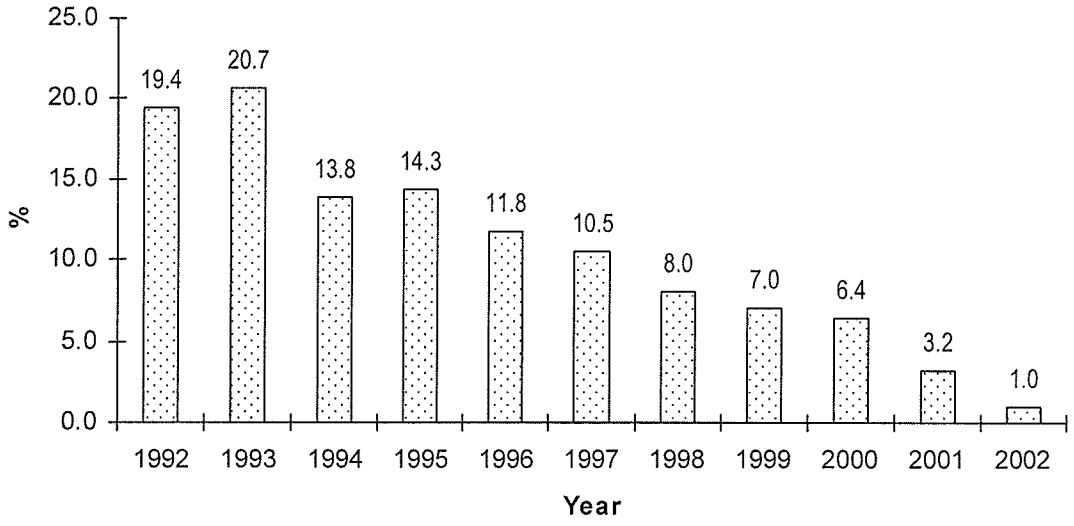
Table 5.5 cont'd

	CASES			CONTROLS						
	N	n	%	N	n	%	AOR	95% CI		P
DISEASES OF THE NERVOUS SYSTEM AND SENSE ORGANS (320-389)										
Total	5018	355	7.07	94282	5128	5.44	1.36	1.21	1.52	<0.0001
FN	671	38	5.66	9802	581	5.93	0.95	0.67	1.33	0.750
non-FN	4347	317	7.29	84480	4547	5.38	1.43	1.26	1.62	<0.0001
ENDOCRINE, NUTRITIONAL AND METABOLIC DISEASES, AND IMMUNITY DISORDERS (240-279)										
Total	5018	145	2.89	94282	1132	1.20	2.38	1.99	2.85	<0.0001
FN	671	20	2.98	9802	258	2.63	1.09	0.68	1.75	0.713
non-FN	4347	125	2.88	84480	874	1.03	2.86	2.36	3.47	<0.0001
DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS (280-289)										
Total	5018	115	2.29	94282	552	0.59	3.94	3.20	4.85	<0.0001
FN	671	15	2.24	9802	92	0.94	2.09	1.15	3.79	0.015
non-FN	4347	100	2.30	84480	460	0.54	4.39	3.52	5.48	<0.0001
SYMPTOMS, SIGNS, AND ILL-DEFINED CONDITIONS (780-799)										
Total	5018	559	11.14	94282	5449	5.78	2.05	1.86	2.25	<0.0001
FN	671	86	12.82	9802	999	10.19	1.28	1.00	1.63	0.0505
non-FN	4347	473	10.88	84480	4450	5.27	2.26	2.04	2.51	<0.0001
SUPPLEMENTARY CLASSIFICATION OF FACTORS INFLUENCING HEALTH STATUS (V01-V89), and EXTERNAL CAUSES OF INJURY AND POISONING (E800-E999)										
Total	5018	837	16.68	94282	10799	11.45	1.56	1.44	1.69	<0.0001
FN	671	113	16.84	9802	1612	16.45	0.98	0.79	1.22	0.8476
non-FN	4347	724	16.66	84480	9187	10.87	1.69	1.55	1.84	<0.0001

5.5 MORTALITY

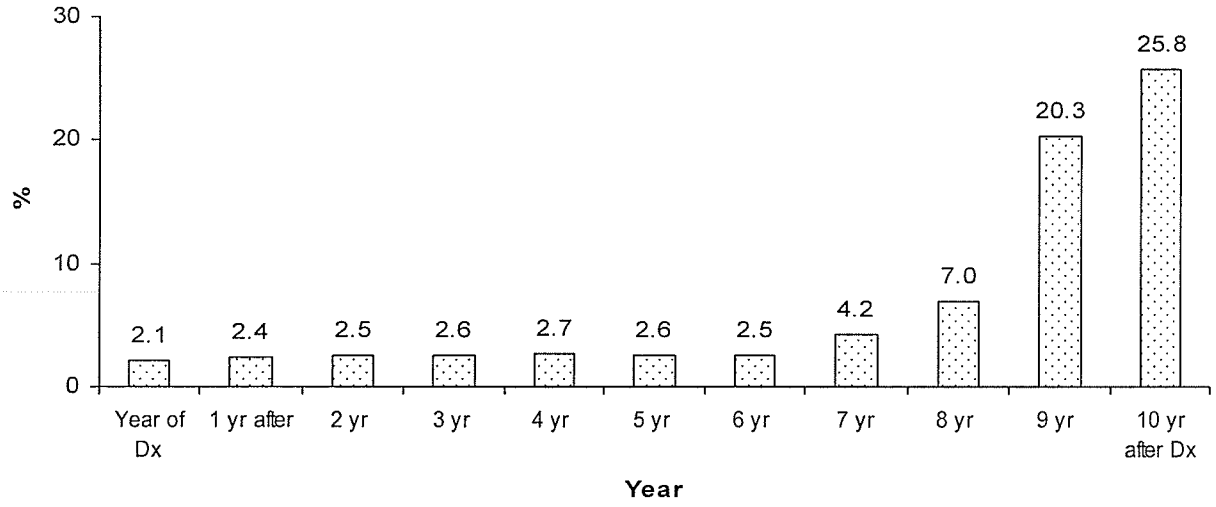
There were a total of 420 deaths among 5018 chronic hepatitis patients and 2047 deaths among 94282 controls during the study period. The proportion of individuals with chronic hepatitis C who died declined from the earliest years towards the more recent years, as the follow-up period shortened. Thus, twenty percent of those diagnosed with hepatitis C during 1991-1993 died by the end of the study period (December 31, 2002), while only 1% of people diagnosed in 2002 died by the same date (Figure 5.10).

Figure 5.10 Mortality (%) in the hepatitis C cohort by year of diagnosis



Two percent of the patients died in the same year their hepatitis C was diagnosed (Figure 5.11). The proportion of cases who died was stable in the first six years following the diagnosis (2.4%-2.7%), then increased to 4% and 7% at the years 7 and 8, and up to 26% among those few who were followed for 10 years.

Figure 5.11 Mortality (%) in the hepatitis C cohort by year since diagnosis



Total all-cause mortality among chronic hepatitis cases was much higher than among controls (8.4% vs. 2.2%, p<0.0000). Hepatitis C cases had 2.25 times the risk of dying as compared to controls without hepatitis C (AOR 2.25, 95% CI 2.13 – 2.37, p<0.0000). Mortality was the same among First Nations and non-FN cases (8% and 8.4% respectively) and for First Nations and non-FN controls (2.5% and 2.1% respectively). Both FN and non-FN cases had similarly increased odds of dying as compared to respective controls (Table 5.6). Standardized mortality ratio (SMR) was greatly increased in hepatitis C patients as compared to non-infected controls (Table 5.8). However, there was no significant difference in the SMR between FN and non-FN cases (96.6 vs. 51.6 respectively). The 95% confidence intervals of the SMR were inflated in FN cases due to the small numbers, thus making estimates of the SMR imprecise.

There were no sex differences in mortality between First Nations and non-FN hepatitis C patients, with 9% of First Nations men and 7.4% of First Nations women dying as compared to 8.9% and 7.6% of non-First Nations men and women respectively. Similarly, there was no sex difference in mortality in the control cohort. Mortality was 2.9% and 2.1% among First Nations males and females respectively as compared to 2.2% and 2.1% of non-First Nations men and women respectively. As with the cases and controls overall, both FN and non-FN males with chronic hepatitis C had 2.1 times the risk of dying as compared to FN and non-FN male controls without hepatitis C (Table 5.6). Similarly, FN and non-FN females with chronic hepatitis C had 3.0 and 2.4 times the risk of dying respectively as compared to corresponding female controls without hepatitis C (Table 5.6).

Table 5.6 All-Cause Mortality (%) in hepatitis C cohort and controls, 1991-2002

		CASES			CONTROLS						
		N	n	%	N	n	%	AOR	95% CI		P
ALL CAUSE MORTALITY											
Total		5018	420	8.4	94282	2047	2.2	2.25	2.1	2.37	<0.000
FN		671	54	8.0	9802	241	2.5	2.56	2.2	2.98	<0.000
non-FN		4347	366	8.4	84480	1806	2.1	2.2	2.1	2.33	<0.000
In-HOSPITAL MORTALITY											
Total		5018	246	4.9	94282	1045	1.1	4.57	4.3	4.89	<0.000
FN		671	34	5.1	9802	104	1.1	6.13	5.0	7.61	<0.000
non-FN		4347	212	4.9	84480	941	1.1	4.39	4.1	4.72	<0.000
Out-of-HOSPITAL MORTALITY											
Total		5018	174	3.5	94282	1002	1.1	4.87	4.5	5.22	<0.000
FN		671	20	3.0	9802	137	1.4	4.75	3.9	5.76	<0.000
non-FN		4347	154	3.5	84480	865	1	4.85	4.5	5.22	<0.000
MORTALITY among FEMALES											
Total		1967	148	7.5	36244	733	2	2.48	2.3	2.71	<0.000
FN		392	29	7.4	5613	120	2.1	3.03	2.5	3.75	<0.000
non-FN		1575	119	7.6	30631	613	2	2.38	2.2	2.61	<0.000
MORTALITY among MALES											
Total		3051	272	8.9	58038	1314	2.3	2.1	1.98	2.26	<0.000
FN		279	25	9.0	4189	121	2.9	2.1	1.68	2.63	<0.000
non-FN		2772	247	8.9	53849	1193	2.2	2.1	1.97	2.27	<0.000

AGE-SPECIFIC MORTALITY PER 1000 POPULATION

		CASES			CONTROLS				
	Age group	N	n	Rate/ 1000	N	n	Rate/ 1000	FN to non-FN Rate Ratio Cases	Controls
FN	18-29	205	8	39.0	3370	54	16.0	1.03	4.4
non-FN		794	30	37.8	15055	55	3.7		
FN	30-39	301	20	66.4	4121	85	20.6	1.3	2.8
non-FN		1483	77	51.9	29083	214	7.4		
FN	40-49	110	12	109.1	1539	55	35.7	1.55	2.6
non-FN		1292	91	70.4	25199	345	13.7		
FN	50-59	19	6	315.8	220	22	100.0	2.5	3.6
non-FN		390	50	128.2	7521	209	27.8		
FN	60-69	8	6	750.0	104	16	153.8	2.5	1.7
non-FN		152	45	296.1	2920	258	88.4		
FN	70+	3	1	333.3	16	4	250.0	0.8	1.1
non-FN		169	73	432.0	3286	722	219.7		

As expected, the age-specific all-cause mortality was steadily increasing with age (Table 5.6). The highest age-specific mortality was among FN cases, followed by non-FN cases, followed by FN controls; the lowest of all was the mortality among non-FN controls. The highest peak of mortality noted in the 50-59 yrs. and 60-69 yrs. age groups among FN cases is due to the very small number of individuals who belonged to these age groups, hence even a few events (deaths in this case) with a fairly small denominator resulted in inflated rates.

5.4.1 Mortality rates

Persons with CHC had increased overall mortality, both FN and non-FN. Mortality rate was 20.7 per 1000 P/Yrs. among FN cases and 22.6 per 1000 P/Yrs. among non-FN cases, whereas rates were 6 per 1000 P/Yrs. among FN cases and 5.4 per 1000 P/Yrs. among non-FN controls over the entire study period (Table 5.7). Case-to-control mortality rate ratio was 3.5 among FN persons and 4.2 among non-FN persons. Mortality rates were only slightly higher among males, FN and non-FN alike, both cases and controls. Female-to-male mortality rate ratio was 0.7 among FN controls, 0.8 among FN and non-FN cases, and 0.9 among non-FN controls (Table 5.7).

Table 5.7 Mortality rates overall and by sex, FN vs. non-FN

		FN				non-FN				FN /
		P/Yrs	deaths	Rate per 1,000*	F/M RR#	P/Yrs	deaths	Rate per 1,000	F/M RR#	nFN RR^
Cases	F	1566.9	29	18.5		6170.2	119	19.3		1.0
	M	1044.4	25	23.9		10024.5	247	24.6		1.0
	Total	2611.3	54	20.7	0.8	16194.6	366	22.6	0.8	0.9
Controls	F	23068.1	120	5.2		125391.7	613	4.9		1.1
	M	17425.1	121	6.9		211810.8	1193	5.6		1.2
	Total	40493.2	241	6.0	0.7	337202.4	1806	5.4	0.9	1.1

**Rate per 1,000 Person/Years*

#Female-to-male Rate Ratio

^FN-to-non-FN Rate Ratio

5.6 CAUSE-SPECIFIC DEATHS AMONG CHC PATIENTS.

Five percent of individuals with chronic hepatitis C died during hospitalization, and the proportion of in-hospital death was the same for both First Nations and non- First Nations patients (5.1% vs. 4.9% respectively). Approximately 1% of patients had died within 48 hours of admission. At the average, FN individuals with hepatitis C who died in the hospital were 11 years younger than non-FN patients who died (47 yr. vs. 58 yr. old respectively).

Forty percent of all deaths occurred during liver disease-related hospitalizations of patients with hepatitis C, and the proportion of such deaths was similar among First Nations and non-First Nations patients (48% vs. 39% respectively, $p<0.202$). Out of 246 in-hospital deaths, 116 deaths (47.2%) were directly attributed to liver disease as per most responsible and primary diagnoses on the discharge abstract, and another 21.5% had

liver disease as contributing factor. Deaths from liver disease (as per most responsible diagnosis) were much more common among non-First Nations (26.9%) then among First Nations (5.9%) persons who died during hospitalization (Table 5.8).

Table 5.8 Characteristics of hospital deaths among hepatitis C patients

	FN		NON-FN		P	Total	
VARIABLE	**n**	**%**	**n**	**%**		**n**	**%**
Total deaths	**54**	**8.0**	**366**	**8.4**	**0.746**	**420**	**8.4**
Males (from all males)	25	9.0	247	8.9	0.934	272	8.9
Females (from all females)	29	7.4	119	7.6	0.916	148	7.5
Age, mean (SD)	43.6	(13.4)	53.6	(17.4)	**0.000**		
SMR (95% CI)	96.6	(7.4 - 185.9)	51.6	(37.4 - 65.9)		34.2	(22.8 - 45.5)
In-hospital death	34	5.1	212	4.9	0.907	246	4.9
In-hospital death, age, mean (SD)	46.8	(14.5)	57.8	(17.5)	**0.000**		
Cause of death during hospitalization and associated conditions							
	FN		**non-FN**		**P**	**Total**	
	n	**%**	**n**	**%**		**n**	**%**
Death during liver disease-related hospitalization	26	3.9	143	3.3	0.434	169	3.4
- from total deaths	26	48.1	143	39.1	0.202	169	40.2
- from hospital deaths	26	76.4	143	67.4	0.393	169	68.7
Liver disease as most responsible Dx. (% from hospital deaths / total deaths)	2	5.9 / 3.7	57	26.9 / 13.7	0.147	59	24.0 / 14.0
Liver disease as primary Dx. (% from hospital deaths / total deaths)	16	47.1 / 29.6	41	19.3 / 11.2	0.847	57	23.2 / 13.6
Liver disease as secondary Dx. (% from hospital deaths / total deaths)	8	23.5 / 14.8	41	19.3 / 11.2	0.497	49	19.9 / 11.7
Liver disease as complication	0	0.0	4	1.9 / 1.1		4	1.6 / 1.0

Dx. - diagnosis

More than one half of patients with the sequelae of chronic liver disease and decompensated disease died during the study period (Table 5.9). Fifty six percent of patients with clinical decompensation died. Overall, 50% of women and 60% of men

with decompensated liver disease died (p 0.33). Among the specific disease categories, deaths occurred with similar frequencies among First Nations and non-First Nations persons. The only difference was that the proportion of deaths among First Nations individuals with 'other liver disease (code "573")' was higher as compared to non-First Nations individuals (21% vs. 13% respectively). As expected, the highest mortality was among those with hepatorenal syndrome (all but one patient died), followed by hepatic encephalopathy, ascites, hepatocellular carcinoma, portal hypertension and esophageal varices (85%, 73.3%, 69.0%, 63.8%, and 57.0% died respectively). Also, 57% of individuals with alcohol-induced liver disease died.

5.7 SUMMARY

- There were no differences between FN and non-FN HCV-infected individuals in clinical characteristics of their liver disease, with similar proportions of persons having decompensated cirrhosis
- Alcohol abuse, diabetes mellitus, and co-infection with HIV were more frequent among FN persons as compared to non-FN individuals
- Decompensated cirrhosis was as frequent in females as it was in males, both FN and non-FN
- All conditions were more frequent among individuals with hepatitis C than among controls without hepatitis C.

- Most conditions were more frequent or equally present in FN as compared to non-FN cases, in the corresponding controls all these conditions were almost universally less frequent in non-FN controls vs. FN controls.
- Mortality rates were significantly higher among hepatitis C cases than among non-Infected controls. Mortality rates ratio was 3.5 in FN persons and 4.2 in non-FN persons.
- Mortality rates (per 1000 P/Yrs.) were similar between men and women, FN and non-FN alike
- Mortality was highest in persons with decompensated cirrhosis, particularly hepatorenal syndrome and hepatic encephalopathy.

Table 5.9 Cause-specific deaths among CHC patients

	FN			NON-FN				Total		
VARIABLE	**N**	**n**	**%**	**N**	**n**	**%**	**P**	**N**	**n**	**%**
Total CLD and cirrhosis (code "571")[&]	116	37	31.9	807	218	27.0	0.32	923	255	27.6
Total sequelae of CLD (code "572")[&]	37	20	54.1	222	130	58.6	0.74	259	150	57.9
Total other liver disease (code "573")^	274	58	21.2	1953	262	13.4	0.001	2227	320	14.4
Portal hypertension	33	18	54.5	196	128	65.3	0.32	229	146	63.8
Ascites	19	12	63.2	116	87	75.0	0.42	135	99	73.3
Esophageal varices	18	9	50.0	89	52	58.4	0.69	107	61	57.0
Hepatic encephalopathy	13	11	84.6	49	42	85.7	0.91	62	53	85.5
Hepatocellular carcinoma	3	2	66.7	55	38	69.1		58	40	69.0
Spontaneous bacterial peritonitis	6	1	16.7	41	25	61.0		47	26	55.3
Orthotopic liver transplant	0	0		19	5	26.3		19	5	26.3
Hepatorenal syndrome	1	1	100.0	11	10	90.9		12	11	91.7
Total Decompensated liver disease**	45	23	51.1	305	172	56.4	0.613	350	195	55.7
Alcohol dependence (AD)	402	80	19.9	1463	263	18.0	0.89	1865	343	18.4
alcohol-induced liver disease from AD	37	20	54.1	138	81	58.7	0.75	175	101	57.7
decompensated liver disease from AD	37	20	54.1	143	88	61.5	0.55	180	108	60.0

	FN			NON-FN				Total		
VARIABLE	**N**	**n**	**%**	**N**	**n**	**%**	**P**	**N**	**n**	**%**
HIV	46	14	30.4	158	44	27.8	0.69	204	58	28.4
HBV	27	5	18.5	126	30	23.8	0.73	153	35	22.9
Chronic non-viral hepatitis	9	5	55.6	90	28	31.1	0.27	99	33	33.3
Non-alcoholic fatty liver disease	2	1	50.0	28	5	17.9		30	6	20.0
HAV	8	2	25.0	20	4	20.0		28	6	21.4
Other viral hepatitis	5	1	20.0	16	3	18.8		21	4	19.0
Hemochromatosis	0	0		12	3	25.0		12	3	25.0
Primary biliary cirrhosis	0	0		4		0.0		4	0	0.0
Wilson's disease	0	0		1		0.0		1	0	0.0
Liver abscess	1	1	100.0	0	0			1	1	100.0
EBV	188	27	14.4	1001	114	11.4	0.31	1189	141	11.9
Diabetes mellitus	111	26	23.4	455	134	29.5	0.25	566	160	28.3

*Include any type of hospital visit: inpatient, outpatient, emergency room visit

** The total is less than the sum of all conditions as individual patients may have several conditions

[&]ICD-9-CM code "571" – Chronic liver disease and cirrhosis

[&]ICD-9-CM code "572" – Liver abscess and sequelae of chronic liver disease

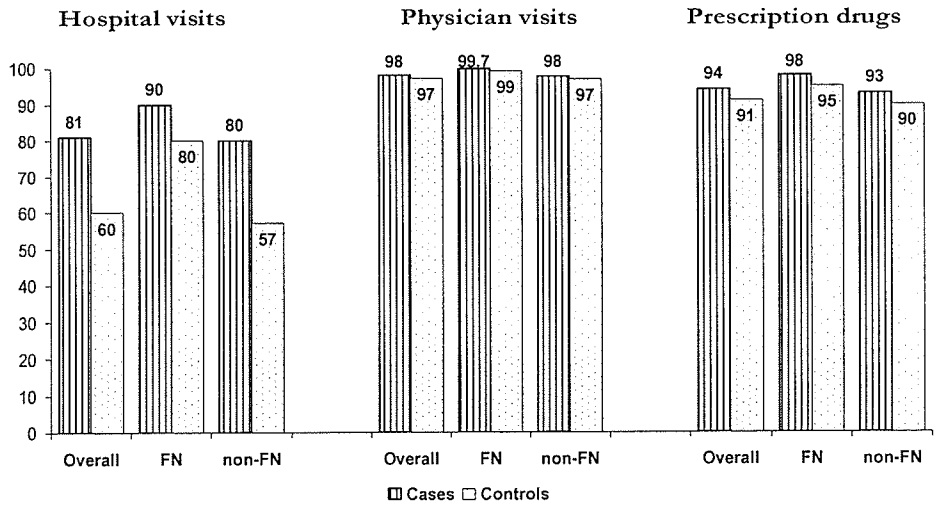
[^]ICD-9-CM code "573" – Other disorders of liver

CHAPTER 6 HEALTH CARE UTILIZATION

6.1 UTILIZATION RECORDS

Longitudinal utilization records were constructed for all patients who had positive HCV-RNA test results and were therefore reported to the Public Health CDC Unit. The records were constructed by combining physician, hospital, and prescription drug databases. Such records were constructed also for population-based matched controls. Eighty one percent of the hepatitis C cohort members had a corresponding hospital record, 98% had at least one record of physician contact, and 94% of patients had records of prescription drugs. Similarly, 97% and 91% of population controls had records of physician contacts and prescription drugs, while only 60% had at least one hospital record each (Figure 6.1).

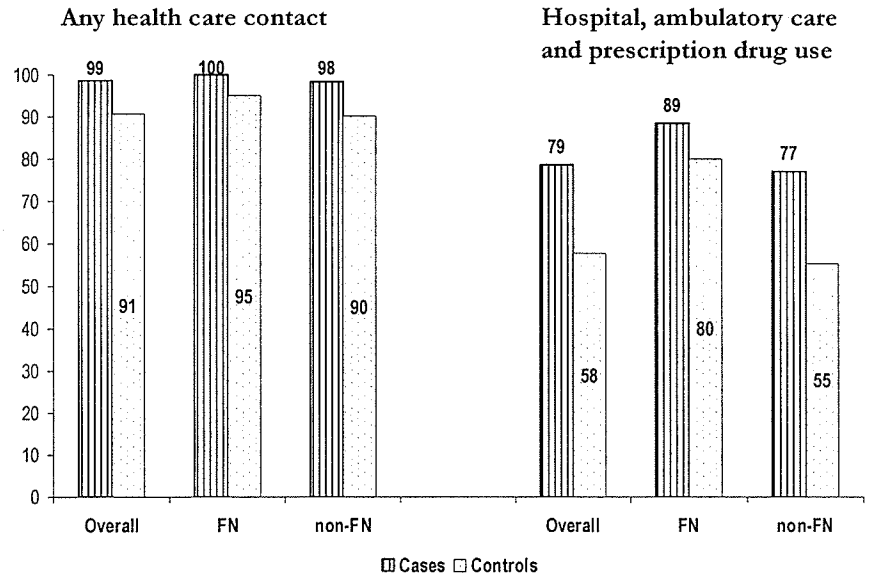
Figure 6.1 Percentage of individuals with health care utilization records



To sum up, virtually all cases (100% FN and 98% of non-FN) and 90% of controls (95% FN and 90% of non-FN) had at least one record each of health care contact during the study period (Figure 6.2). Moreover, 89% of FN and 77% of non-FN cases had records of

all three types of contacts with the health care system as compared to 80% of FN and 55% of non-FN controls (Figure 6.2).

Figure 6.2 Proportion of individuals with at least one type and all three types of health care utilization records



There was a significant difference between First Nations and non-First Nations patients in the use of health care resources. While 20% of non-First Nations individuals had no records of hospital inpatient stays or outpatient visits, only 10% of First Nations patients did not have any contacts with the hospital (Table 6.1). Similarly (although to a much lesser extent), only 2.4% of non-First Nations individuals did not have any physician visits, while among First Nation patients there were only 2 persons without such records (0.3%). Finally, 93% of non-First Nations as compared to 98% of First Nations patients had at least one prescription medication filled during the study period.

Table 6.1 Proportion of HCV-infected persons who did not have records of contact with the health care system during the study period

1991-2002	FN (N=671)		non-FN (N= 4347)		P	Total (N=5018)	
VARIABLE	n	%	n	%		n	%
No hospital separations	68	10.1	885	20.4	0.0000	953	19.0
No physician claim records	2	0.3	105	2.4	0.0004	107	2.1
No prescription drugs records	13	1.9	299	6.9	0.0000	312	6.2
No either phys. or hosp. contact	1	0.1	93	2.1	0.0004	94	1.9
No any of the 3 types of utilization record	0	0.0	72	1.7	0.001	72	1.4

Compared to controls, more FN and non-FN patients with hepatitis C utilized hospital care and filled prescriptions for drugs, while the proportion of individuals who had physician visits did not differ between FN and non-FN patients (Table 6.2). First Nations and non-First Nations CHC patients had the odds of having used all three types of services 2.2 and 2.7 times respectively compared to matched controls without hepatitis C.

Table 6.2 Health care contacts among HCV-infected cases and controls

	CASES			CONTROLS			P
	N	n	%	N	n	%	
No utilization record	5018	72	1.4	94282	2329	2.5	0.004
FN	671	0	0	9802	63	0.6	
non-FN	4347	72	1.7	84480	2266	2.7	0.000
Hospital record present	5018	4065	81.0	94282	56260	59.7	0.000
FN	671	603	89.9	9802	7851	80.1	0.000
non-FN	4347	3462	79.6	84480	48409	57.3	0.000
Physician record present	5018	4911	97.9	94282	91554	97.1	0.98
FN	671	669	99.7	9802	9720	99.2	0.87
non-FN	4347	4242	97.6	84480	81834	96.9	0.36
Prescription drug record present	5018	4706	93.8	94282	85549	90.7	0.000
FN	671	658	98.1	9802	9323	95.1	0.001
non-FN	4347	4048	93.1	84480	76226	90.2	0.001
Any of the 3 types of record present	5018	4946	98.6	94282	91953	97.5	0.87
FN	671	671	100	9802	9739	99.4	0.79
non-FN	4347	4275	98.3	84480	82214	97.3	0.97
All 3 records present	5018	3943	78.6	94282	54454	57.8	0.000
FN	671	594	88.5	9802	7642	78.0	0.000
non-FN	4347	3349	77.0	84480	46812	55.4	0.000

6.2 HOSPITAL SEPARATIONS

There were a total of 281,010 hospital separations for the entire study population. Nineteen (19%) percent of FN cases (953 out of 5,018) and 40% of controls (38,022 out of 94,282) did not have any contact with a hospital during the study period. There were 25,125 hospital separations among 4,065 persons with hepatitis C (the mean of 6.1 separations per person who used the services and 5.0 separations per person overall). The non-infected controls had 216,910 hospital separations among 56,260 individuals (the mean of 3.8 separations per person who used hospital services and 2.3 separations per person overall). Infected persons used hospital services more than twice as often as the control population.

Removing the records of children under the age of 18 yrs. and those diagnosed with HCV infection before 1995 left 4,579 cases and 86,013 controls. The mean of hospital services use per service user and per person overall remained exactly the same in the subgroup of controls, while among CHC patients the mean number of services per user decreased from 6.2 to 4.9, while the overall proportion of users remained the same. Overall, 80% of cases and 60% of controls used hospital services (Table 6.3).

Table 6.3 Use of hospital services among CHC persons and non-infected controls

		All ages, 1991-2002		Age 18+yrs., 1995-2002	
		N	%	N	%
Cases	N	5,018		4,579	
	Separations	25,125		22,179	
	Non-users	953	19.0	893	19.5
	Service users	4,065	81.0	3,686	80.5
	Mean per user	6.2		4.9	
	Mean per pt overall	5.0		4.8	
Controls	N	94,282		86,013	
	Separations	216,910		197,224	
	Non-users	38,022	40.3	34,869	40.5
	Service users	56,260	59.7	51,144	59.5
	Mean per user	3.9		3.9	
	Mean per pt overall	2.3		2.3	

6.2.1 ANNUAL TOTAL SEPARATION RATES

Total separation rates per 1,000 person-years (P/Yrs) combine all types of hospital care for which there was a record of hospital discharge. These include outpatient services, day admissions, and hospitalizations.

Annual separation rates were highest among FN individuals with CHC during 1997-2002 but not in 1995 or 1996, and they fluctuated during the study period from 710 separations per 1000 P/Yrs in 1995, increasing to the highest of 890 separations per 1000 P/Yrs in 1997, then falling to as low as 583 separations per 1000 P/Yrs in 1995 and then increasing again to 755 per 1000 P/Yrs in 2002 (Table 6.4 and Figure 6.3). The mean annual rate was 698 separations per 1000 P/Yrs, and the average variation between the

annual rates was 20%. The overall 1995/2002 rate of hospital separations among FN cases was 684 per 1000 P/Yrs.

The separation rates for non-infected non-FN controls were the lowest among the four groups and were, on average, 4 times lower than the rates for non-FN cases. There were no variations in the total separation rates for non-FN controls, and the rates were essentially the same (Table 6.4 and Figure 6.3). The difference between the separation rate of 163.1 per 1000 P/Yr in 1995 and 158.5 per 1000 P/Yr in 2002 was only 2.8%, the same as the mean variation of rates. The differences in the rates between non-FN cases and controls were much more pronounced than the differences between FN cases and controls. Thus, the mean case-to-control rate ratio among non-FN persons was 4.0 as compared to 1.7 among FN cases and controls. The non-FN rate ratio varied from as high as 7.3 in 1995 (1192.3 vs. 163.1 per 1000 P/Yr) to the lowest of 3.0 in 2002 (472 vs. 158.5 per 1000 P/Yr) (Table 6.4). Since there were no variations in the annual rates, the mean and the 1995-2002 overall rate of hospital separations among FN cases were the same (166.8 and 166.5 per 1000 P/Yr.).

In general, the non-infected controls (particularly the non-FN ones) had much lower and less variable total separation rates in any given year as compared to CHC individuals.

Table 6.4 Annual rates (per 1000 p/yr.) of total hospital separations, outpatient, day, and inpatient separations, 1995-2002

TOTAL HOSPITAL SEPARATIONS													
	Chronic hepatitis C						Population controls						Case-to-control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total separations	Rate*	Person/ Years	Total separations	Rate	Person/ Years	Total separations	Rate	Person/ Years	Total separations	Rate	FN	non-FN
1995	36.6	26	710.2	203.0	170	837.6	508.9	252	495.2	4523.7	718	158.7	1.4	5.3
1996	106.6	71	666.2	669.9	482	719.5	1437.6	549	381.9	13191.6	2160	163.7	1.7	4.4
1997	175.2	156	890.3	1081.8	693	640.6	2441.5	1097	449.3	21740.4	3629	166.9	2.0	3.8
1998	252.8	184	727.9	1532.9	977	637.3	3721.7	1555	417.8	31106.5	5450	175.2	1.7	3.6
1999	337.7	197	583.4	1969.7	1044	530.0	5159.1	2127	412.3	40363.6	6876	170.4	1.4	3.1
2000	391.8	248	632.9	2319.5	1310	564.8	6379.3	2776	435.2	48582.5	8364	172.2	1.5	3.3
2001	447.4	278	621.3	2718.7	1423	523.4	7315.2	3169	433.2	57587.5	9465	164.4	1.4	3.2
2002	507.2	383	755.1	3074.2	1451	472.0	8078.9	3547	439.0	65568.2	10394	158.5	1.7	3.0
Mean	281.9	192.9	698.4	1696.2	945	621.8	4380.3	1884.0	433.0	35333.0	5882.0	166.2	1.6	3.7
Overall	2255.3	1543.0	684.2	13569.7	7560	557.1	35042.1	15072.0	430.1	282663.8	47056.0	166.5	1.6	3.3

OUTPATIENT HOSPITAL SEPARATIONS													
	Chronic hepatitis C						Population controls						Case-to-control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total separations	Rate	Person/ Years	Total separations	Rate	Person/ Years	Total separations	Rate	Person/ Years	Total separations	Rate	FN	Non-FN
1995	36.6	0	0.0	203.0	1	4.9	508.9	49	96.3	4523.7	36	8.0	0.0	0.6
1996	106.6	11	103.2	669.9	11	16.4	1437.6	143	99.5	13191.6	53	4.0	1.0	4.1
1997	175.2	14	79.9	1081.8	2	1.8	2441.5	255	104.4	21740.4	120	5.5	0.8	0.3
1998	252.8	10	39.6	1532.9	19	12.4	3721.7	391	105.1	31106.5	195	6.3	0.4	2.0
1999	337.7	23	68.1	1969.7	35	17.8	5159.1	633	122.7	40363.6	270	6.7	0.6	2.7
2000	391.8	52	132.7	2319.5	131	56.5	6379.3	804	126.0	48582.5	384	7.9	1.1	7.1
2001	447.4	50	111.8	2718.7	116	42.7	7315.2	1025	140.1	57587.5	402	7.0	0.8	6.1
2002	507.2	82	161.7	3074.2	100	32.5	8078.9	1243	153.9	65568.2	471	7.2	1.1	4.5
Mean	281.9	30.3	87.1	1696.2	51.9	23.1	4380.3	567.9	118.5	35333.0	241.4	6.6	0.7	3.5
Overall	2255.3	242.0	107.3	13569.7	415	30.6	35042.1	4543.0	129.6	282663.8	1931.0	6.8	0.8	4.5

HOSPITAL DAY ADMISSIONS

YEAR	Chronic hepatitis C						Population controls						Case-to-control Rate Ratio	
	FN			non-FN			FN			non-FN				
	Person/ Years	Total day admissions	Rate	Person/ Years	Total day admissions	Rate	Person/ Years	Total day admissions	Rate	Person/ Years	Total day admissions	Rate	FN	non-FN
1995	36.6	8	218.5	203.0	70	344.9	508.9	34	66.8	4523.7	309	68.3	3.3	5.8
1996	106.6	13	122.0	669.9	181	270.2	1437.6	101	70.3	13191.6	944	71.6	1.7	3.8
1997	175.2	33	188.3	1081.8	281	259.7	2441.5	215	88.1	21740.4	1634	75.2	2.1	3.5
1998	252.8	46	182.0	1532.9	414	270.1	3721.7	349	93.8	31106.5	2536	81.5	1.9	3.3
1999	337.7	48	142.2	1969.7	467	237.1	5159.1	399	77.3	40363.6	3267	80.9	1.8	2.9
2000	391.8	43	109.7	2319.5	559	241.0	6379.3	536	84.0	48582.5	4108	84.6	1.3	2.9
2001	447.4	49	109.5	2718.7	623	229.2	7315.2	607	83.0	57587.5	4380	76.1	1.3	3.0
2002	507.2	67	132.1	3074.2	573	186.4	8078.9	593	73.4	65568.2	4841	73.8	1.8	2.5
Mean	281.9	38.4	150.5	1696.2	397.25	261.0	4380.3	354.3	79.6	35333.0	2752.4	76.5	1.9	3.4
Overall	2255.3	307.0	136.1	13569.7	3178	234.2	35042.1	2834.0	80.9	282663.8	22019.0	77.9	1.7	3.0

INPATIENT HOSPITAL SEPARATIONS

YEAR	Chronic hepatitis C						Population controls						Case-to-control Rate Ratio	
	FN			non-FN			FN			non-FN				
	Person/ Years	Total hospitalizations	Rate	Person/ Years	Total hospitalizations	Rate	Person/ Years	Total hospitalizations	Rate	Person/ Years	Total hospitalizations	Rate	FN	non-FN
1995	36.6	18	491.7	203.0	99	537.0	508.9	169	332.1	4523.7	393	86.9	1.5	5.6
1996	106.6	47	441.0	669.9	290	432.9	1437.6	350	243.5	13191.6	1163	88.2	1.8	4.9
1997	175.2	109	622.1	1081.8	410	379.0	2441.5	627	256.8	21740.4	1875	86.2	2.4	4.4
1998	252.8	128	506.4	1532.9	544	354.9	3721.7	815	219.0	31106.5	2719	87.4	2.3	4.1
1999	337.7	126	373.1	1969.7	542	275.2	5159.1	1095	212.2	40363.6	3339	82.7	1.8	3.3
2000	391.8	153	390.5	2319.5	620	267.3	6379.3	1436	225.1	48582.5	3872	79.7	1.7	3.4
2001	447.4	179	400.1	2718.7	684	251.6	7315.2	1537	210.1	57587.5	4683	81.3	1.9	3.1
2002	507.2	234	461.4	3074.2	778	253.1	8078.9	1711	211.8	65568.2	5082	77.5	2.2	3.3
Mean	281.9	124.3	460.8	1696.2	495.9	337.7	4380.3	967.5	238.8	35333.0	2890.8	83.7	1.9	4.0
Overall	2255.3	994.0	440.7	13569.7	3967.0	292.3	35042.1	7740.0	220.9	282663.8	23126.0	81.8	2.0	3.6

LIVER DISEASE-RELATED HOSPITAL SEPARATIONS													
	Chronic hepatitis C						Population controls						Case-to control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Liver separations	Rate	Person/ Years	Liver separations	Rate	Person/ Years	Liver separations	Rate	Person/ Years	Liver separations	Rate	FN	non-FN
1995	36.61	6	163.9	203.0	58	285.8	508.9	0	0.0	4523.7	2	0.4		646.3
1996	106.57	9	84.5	669.9	103	153.8	1437.6	6	4.2	13191.6	4	0.3	20.2	507.1
1997	175.22	8	45.7	1081.8	131	121.1	2441.5	7	2.9	21740.4	7	0.3	15.9	376.1
1998	252.78	20	79.1	1532.9	163	106.3	3721.7	13	3.5	31106.5	11	0.4	22.7	300.7
1999	337.67	16	47.4	1969.7	197	100.0	5159.1	12	2.3	40363.6	17	0.4	20.4	237.5
2000	391.82	22	56.1	2319.5	177	76.3	6379.3	5	0.8	48582.5	22	0.5	71.6	168.5
2001	447.42	14	31.3	2718.7	205	75.4	7315.2	14	1.9	57587.5	26	0.5	16.3	167.0
2002	507.2	23	45.3	3074.2	216	70.3	8078.9	17	2.1	65568.2	39	0.6	21.6	118.1
Mean	281.9	14.8	69.2	1696.2	156.3	123.6	4380.3	9.3	2.2	35333.0	16.0	0.4	27.0	315.2
Overall	2255.3	118.0	52.3	13569.7	1250	92.1	35042.1	74.0	2.1	282663.8	128.0	0.5	24.8	203.4

Table 6.5 Rates (per 1000 p/yr) of outpatient, day, inpatient and total hospital separations by the time since CHC diagnosis, 1995-2002

TOTAL HOSPITAL SEPARATIONS													
	Chronic hepatitis C						Population controls						Case-to control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total Sep#.	Rate	Person/ Years	Total Sep.	Rate	Person/ Years	Total Sep.	Rate	Person/ Years	Total Sep.	Rate	FN	non-FN
4+ yrs prior to Dx	3025.62	1950	644.5	16812.63	6074	361.3	43604.41	25301	580.2	341339.77	61124	179.1	1.1	2.0
3 yrs prior to Dx	614.04	281	457.6	3553.11	1188	334.4	8937.58	4139	463.1	71903.2	11658	162.1	1.0	2.1
2 yrs prior to Dx	615	367	596.7	3636.61	1213	333.6	8953.6	4039	451.1	73196.49	12242	167.2	1.3	2.0
1 yr prior to Dx	615.32	438	711.8	3758.22	1531	407.4	8969.86	3783	421.7	74794.77	12626	168.8	1.7	2.4
Year of Dx	563.66	514	911.9	3575.63	2629	735.3	8482.86	3838	452.4	71390.1	11953	167.4	2.0	4.4
2nd yr post-Dx	475.58	337	708.6	2937.23	1627	553.9	7466.33	3239	433.8	59948.44	10025	167.2	1.6	3.3
3 yrs post-Dx	393.45	265	673.5	2334.1	1154	494.4	6384.39	2797	438.1	48700.32	8239	169.2	1.5	2.9
4+ yrs post-Dx	821.3	424	516.3	4714.45	2187	463.9	12689.5	5258	414.4	102459.63	16963	165.6	1.2	2.8
Mean	890.5	572.0	652.6	5165.2	2200.38	460.5	13186.1	6549.3	456.9	105466.6	18103.8	168.3	1.4	2.7
Overall	7124.0	4576.0	642.3	41322.0	17603	426.0	105488.5	52394.0	496.7	843732.7	144830.0	171.7	1.3	2.5

OUTPATIENT HOSPITAL VISITS														
	Chronic hepatitis C						Population controls						Case to control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	FN	non-FN
4+ yrs prior to Dx	3025.62	496	163.9	16812.63	286	17.0	43604.41	7595	174.2	341339.8	2199	6.4	0.9	2.6
3 yrs prior to Dx	614.04	67	109.1	3553.11	45	12.7	8937.58	1127	126.1	71903.2	424	5.9	0.9	2.1
2 yrs prior to Dx	615	95	154.5	3636.61	54	14.8	8953.6	1100	122.9	73196.49	419	5.7	1.3	2.6
1 yr prior to Dx	615.32	97	157.6	3758.22	148	39.4	8969.86	996	111.0	74794.77	464	6.2	1.4	6.3
Year of Dx	563.66	63	111.8	3575.63	117	32.7	8482.86	1126	132.7	71390.1	491	6.9	0.8	4.8
2nd yr post-Dx	475.58	51	107.2	2937.23	59	20.1	7466.33	958	128.3	59948.44	351	5.9	0.8	3.4
3 yrs post-Dx	393.45	47	119.5	2334.1	27	11.6	6384.39	843	132.0	48700.32	338	6.9	0.9	1.7
4+ yrs post-Dx	821.3	77	93.8	4714.45	211	44.8	12689.5	1612	127.0	102459.6	751	7.3	0.7	6.1
Mean	890.5	124.1	127.2	5165.2	118.375	24.1	13186.1	1919.6	131.8	105466.6	679.6	6.4	1.0	3.8
Overall	7124.0	993.0	139.4	41322	947	22.9	105488.5	15357	145.6	843732.7	5437	6.4	1.0	3.6

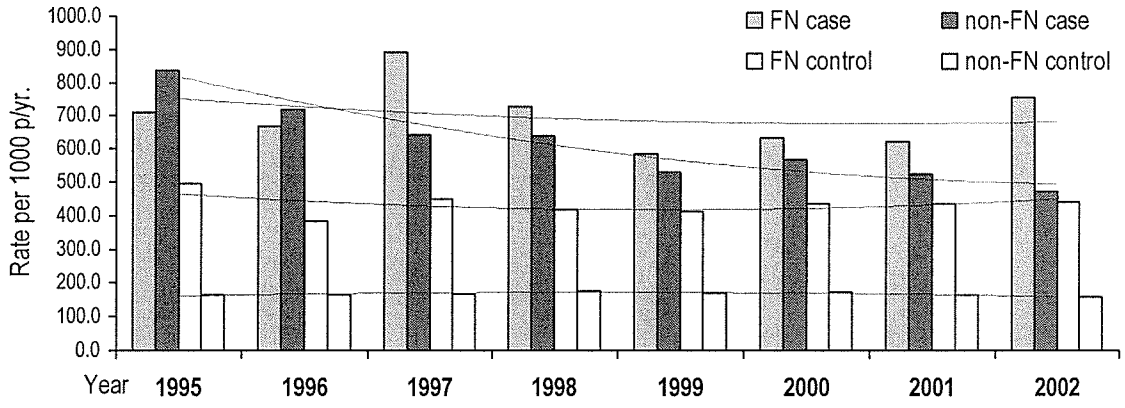
HOSPITAL DAY ADMISSIONS														
	Chronic hepatitis C						Population controls						Case-to control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Day Adm&.	Rate	Person/ Years	Day Adm.	Rate	Person/ Years	Day Adm.	Rate	Person/ Years	Day Adm.	Rate	FN	non-FN
4+ yrs prior to Dx	3025.62	224	74.0	16812.63	1728	102.8	43604.41	3530	81.0	341339.8	25184	73.8	0.9	1.4
3 yrs prior to Dx	614.04	50	81.4	3553.11	396	111.5	8937.58	708	79.2	71903.2	5339	74.3	1.0	1.5
2 yrs prior to Dx	615	68	110.6	3636.61	458	125.9	8953.6	743	83.0	73196.49	5704	77.9	1.3	1.6
1 yr prior to Dx	615.32	75	121.9	3758.22	498	132.5	8969.86	684	76.3	74794.77	5983	80.0	1.6	1.7
Year of Dx	563.66	107	189.8	3575.63	1029	287.8	8482.86	702	82.8	71390.1	5462	76.5	2.3	3.8
2nd yr post-Dx	475.58	85	178.7	2937.23	780	265.6	7466.33	673	90.1	59948.44	4644	77.5	2.0	3.4
3 yrs post-Dx	393.45	44	111.8	2334.1	516	221.1	6384.39	509	79.7	48700.32	3826	78.6	1.4	2.8
4+ yrs post-Dx	821.3	70	85.2	4714.45	845	179.2	12689.5	949	74.8	102459.6	8085	78.9	1.1	2.3
Mean	890.5	90.4	119.2	5165.2	781.25	178.3	13186.1	1062.3	80.9	105466.6	8028.4	77.2	1.5	2.3
Overall	7124.0	723.0	101.5	41321.98	6250	151.3	105488.5	8498.0	80.6	843732.7	64227.0	76.1	1.3	2.0

HOSPITALIZATIONS (Inpatients)														
	Chronic hepatitis C						Population controls						Case-to control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total Hosp^.	Rate	Person/ Years	Total Hosp.	Rate	Person/ Years	Total Hosp.	Rate	Person/ Years	Total Hosp.	Rate	FN	non-FN
4+ yrs prior to Dx	3025.62	1230	406.5	16812.63	4060	241.5	43604.41	14176	325.1	341339.8	33741	98.8	1.3	2.4
3 yrs prior to Dx	614.04	164	267.1	3553.11	747	210.2	8937.58	2304	257.8	71903.2	5895	82.0	1.0	2.6
2 yrs prior to Dx	615	204	331.7	3636.61	701	192.8	8953.6	2196	245.3	73196.49	6119	83.6	1.4	2.3
1 yr prior to Dx	615.32	266	432.3	3758.22	885	235.5	8969.86	2103	234.5	74794.77	6179	82.6	1.8	2.9
Year of Dx	563.66	344	610.3	3575.63	1483	414.8	8482.86	2010	236.9	71390.1	6000	84.0	2.6	4.9
2nd yr post-Dx	475.58	201	422.6	2937.23	788	268.3	7466.33	1608	215.4	59948.44	5030	83.9	2.0	3.2
3 yrs post-Dx	393.45	174	442.2	2334.1	611	261.8	6384.39	1445	226.3	48700.32	4075	83.7	2.0	3.1
4+ yrs post-Dx	821.3	277	337.3	4714.45	1131	239.9	12689.5	2697	212.5	102459.6	8127	79.3	1.6	3.0
Mean	890.5	357.5	406.3	5165.2	1300.75	258.1	13186.1	3567.4	244.2	105466.6	9395.8	84.7	1.7	3.0
Overall	7124.0	2860.0	401.5	41321.98	10406	251.8	105488.5	28539.0	270.5	843732.7	75166.0	89.1	1.5	2.8

LIVER DISEASE-RELATED HOSPITAL SEPARATIONS														
	Chronic hepatitis C						Population controls						Case-to control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total Sep.	Rate	Person/ Years	Total Sep.	Rate	Person/ Years	Total Sep.	Rate	Person/ Years	Total Sep.	Rate	FN	non-FN
4+ yrs prior to Dx	3025.62	14	4.6	16812.63	105	6.2	43604.41	52	1.2	341339.77	120	0.4	3.9	17.8
3 yrs prior to Dx	614.04	1	1.6	3553.11	32	9.0	8937.58	7	0.8	71903.2	22	0.3	2.1	29.4
2 yrs prior to Dx	615	2	3.3	3636.61	26	7.1	8953.6	16	1.8	73196.49	34	0.5	1.8	15.4
1 yr prior to Dx	615.32	6	9.8	3758.22	45	12.0	8969.86	16	1.8	74794.77	45	0.6	5.5	19.9
Year of Dx	563.66	53	94.0	3575.63	490	137.0	8482.86	25	2.9	71390.1	32	0.4	31.9	305.7
2nd yr post-Dx	475.58	26	54.7	2937.23	340	115.8	7466.33	18	2.4	59948.44	30	0.5	22.7	231.3
3 yrs post-Dx	393.45	16	40.7	2334.1	165	70.7	6384.39	12	1.9	48700.32	20	0.4	21.6	172.1
4+ yrs post-Dx	821.3	23	28.0	4714.45	253	53.7	12689.5	19	1.5	102459.63	46	0.4	18.7	119.5
Mean	890.5	17.6	29.6	5165.2	182	51.4	13186.1	20.6	1.8	105466.6	43.6	0.4	16.6	116.5
Overall	7124.0	141.0	19.8	41321.98	1456	35.2	105488.5	165.0	1.6	843732.7	349.0	0.4	12.7	85.2

**Rate – rate per 1000 P/Yrs.; #Sep. – separations; &Adm. - admissions; ^Hosp. – hospitalizations; Dx – diagnosis.*

Figure 6.3 Annual total separation rates per 1,000 P/Yrs., CHC cases and controls, 1995-2002



6.2.2 ANNUAL RATES OF OUTPATIENT VISITS

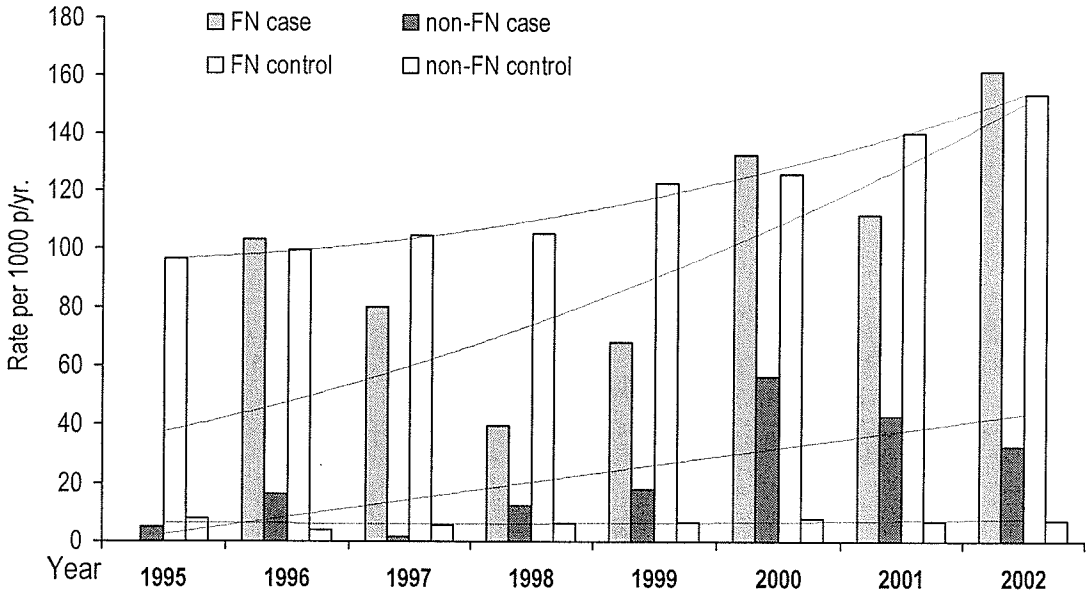
Rates of outpatient hospital visits per 1,000 P/Yr were based on the separation abstracts contained in the hospital database with a code for outpatient services and a total stay of zero days. Unlike the annual total separation rates, the highest outpatient rates were observed among non-infected FN controls, followed by FN persons with chronic hepatitis C. Also, unlike the total separation rates, the outpatient hospital rates of FN individuals, both cases and controls, increased significantly over time (Figure 6.4). For instance, the rate of outpatient hospital visits among FN persons with CHC increased by 57% in 2002 as compared to 1996 (Table 6.4 and Figure 6.4). There was much variation in the rates from year to year among FN cases, whose outpatient visit rates ranged from 0 in 1995 to 103 in 1996, then dropped to the low of 39.6 in 1998, then started to rise again in the following year, reaching the highest rate of 161.7 visits per 1,000 P/Yr. in 2002. The rates among FN controls showed a stable increase from year to year between 1995 and 2002.

The rate of outpatient visits among FN controls increased by 60% in 2002 as compared to 1995.

The hospital outpatient rates of non-FN cases were variable as well, but the actual rates were closer to the rates among non-FN controls than to those of FN cases. As with FN cases, the rates of outpatient hospital visits were highly inconsistent from year to year, rising and falling from 4.9 in 1995 to 1.8 in 1997 to as high as 56.5 in 2000 and back to 32.5 per 1,000 P/Yr. in 2002 (Figure 6.4, Table 6.4).

The annual rates of hospital outpatient visits amongst non-FN controls were the lowest of the four groups, and were the only constant rates throughout the study years, much like with the total separation rates. There were no variations, and the average and overall rates were the same (6.6 and 6.8 visits per 1,000 P/Yr.). The 1995-2002 overall rate of 6.8 outpatient hospital visits per 1,000 P/Yr. among non-infected non-FN persons was 15.7 times, 4.5 times, and 19.0 times lower than the corresponding overall rates of 107.3, 30.6, and 129.6 per 1,000 P/Yr. amongst FN cases, non-FN cases, and FN controls respectively (Table 6.4). In general, the rates of outpatient hospital care were highly inconsistent from year to year among all but the non-infected non-FN individuals. The higher rates experienced by FN cases and controls may have been the result of a generally higher burden of illness in the FN populations as compared to the general population of Manitoba.

Figure 6.4 Annual rates of outpatient hospital visits per 1,000 P/Yrs., CHC cases and controls, 1995-2002



6.2.3 ANNUAL RATES OF DAY VISITS

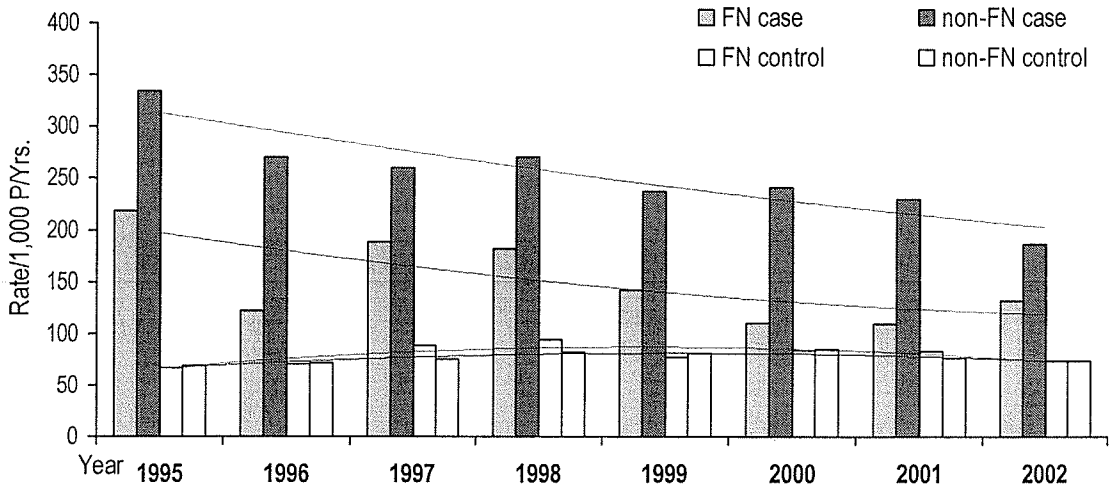
The rates of day visits per 1,000 P/Yrs. are calculated for hospital visits with admission and separation on the same date and no overnight stays (length of stay: zero).

Interestingly, the annual day visit rates were highest among non-FN individuals with chronic hepatitis C, followed by FN persons with CHC (Figure 6.5). In these two groups, the annual rates decreased from 394.1 and 218.5 per 1,000 P/Yr. in 1995 to 186.4 and 132.1 per 1,000 P/Yr. in 2002 among non-FN and FN cases respectively (Table 6.4). These rate decreases totaled 53% amongst non-FN cases and 40% among FN cases.

The annual rates of day admissions were the same for FN and non-FN controls. The rates did not vary much from year to year, and displayed remarkable similarities for the two

groups. The annual rates were the lowest in 1995, with 66.8 day admissions per 1000 P/Yrs. among FN controls and 68.3 admissions per 1000 P/Yrs. among non-FN controls. In the following years, the rates of day admissions amongst FN controls peaked at 93.8 per 1000 P/Yrs. in 1998 and then decreased again to a low of 73.4 per 1000 P/Yrs. in 2002. Similarly, the rates of day admissions amongst non-FN controls increased to the highest of 84.6 per 1000 P/Yrs. in 2000 and decreased to 73.8 per 1000 P/Yrs. in 2002. However, because the day admission rates were so much higher among non-FN cases than among controls, the resulting case-to-control rate ratios were much higher among non-FN individuals than among First Nations persons. Thus, the highest case-to control rate ratios for both populations were in 1995, but it was 3.3 among First Nations persons vs. 5.8 among non-FN individuals (Table 6.4). In 2000 and 2001, the case-to-control rate ratio of 1.3 among FN people was the lowest. Among non-FN people, the lowest rate ratio was 2.5 in 2002 (Table 6.4).

Figure 6.5 Annual rates of day admissions per 1,000 P/Yrs., CHC cases and controls, 1995-2002



6.2.4 ANNUAL HOSPITALIZATION RATES (INPATIENT ADMISSIONS)

The rates of hospitalizations per 1,000 P/Yrs. were calculated for all inpatients with the length of stay of at least one day (overnight admissions). Multiple admissions for the same person were counted as separate events, while multiple transfers during one continuous event were counted as one admission[202,206].

Annual rates of hospitalizations were highest among FN individuals with chronic hepatitis C, followed by non-FN persons with CHC, while the lowest rates were, as with all the other types of hospital separations, among the non-infected non-FN controls (Figure 6.6). Interestingly, the hospitalization rates among FN and non-FN cases were virtually the same in 1995 (819.4 vs. 793.2 per 1000 P/Yr. respectively) and in 1996 (441.0 vs. 432.9 per 1000 P/Yr. respectively) (Figure 6.6.). Since 1997, however, the rates of hospital stays among FN and non-FN cases diverged significantly. While the rates of hospitalization among non-FN cases continued to drop throughout the study years, the rates amongst FN cases fluctuated (Figure 6.6). The non-FN hospitalization rates decreased 68% in 2002 as compared to 1995, to a low of 253.1 hospitalizations per 1,000 P/Yrs. The annual inpatient rates among FN cases fluctuated during the study period from the highest of 819.4 separations per 1000 P/Yrs. in 1995, falling to a low of 441 separations per 1000 P/Yrs. the following year, then increasing again to 622.1 per 1000 P/Yr in 1997. From 1997 to 1999 the rates decreased to the lowest of 373.1 per 1000 P/Yr., and then rose again to 461.4 per 1000 P/Yr. at the end of the study period in 2002. The mean variation between the annual rates was 22.1%.

The inpatient admission rates of non-infected FN controls were the second lowest among the four groups and were, on average, 2.1 times lower than the rates for FN cases. The rates of hospitalization among the non-infected FN persons did not vary much, and over the years the rates decreased from 338 hospitalizations per 1000 P/Yrs. in 1995 to 211.8 hospitalizations per 1000 P/Yr in 2002, amounting to a decrease of 37%.

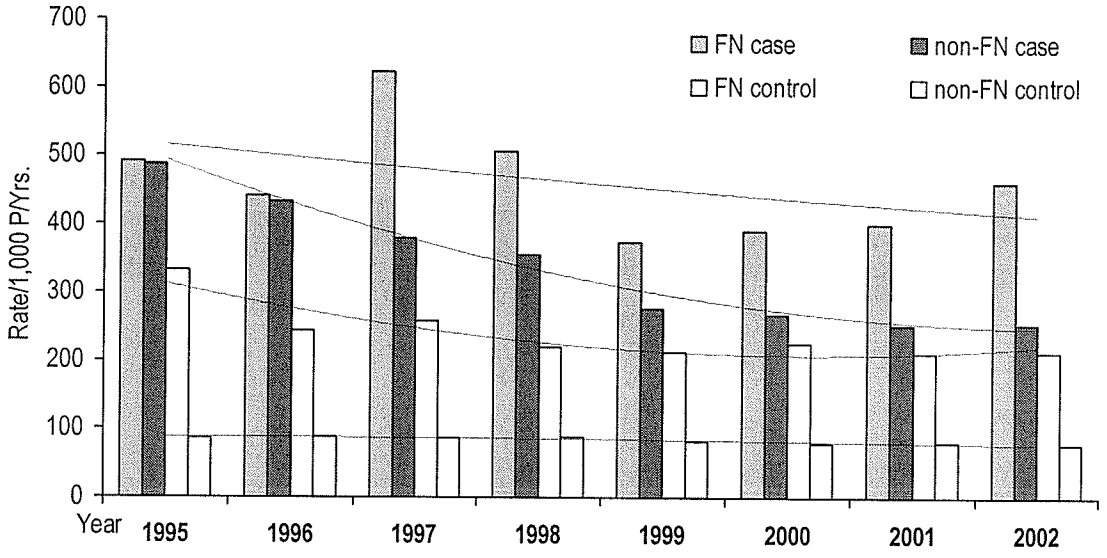
The rates of hospitalization among non-infected non-FN controls were the lowest for the four groups and were overall 3.6 times lower than the rates among non-FN cases. The rates were highly consistent right through the study period and decreased only slightly from 86.9 per 1000 P/Yrs. in 1995 to 77.5 hospitalizations per 1000 P/Yrs. in 2002 (Table 6.4).

Both FN and non-FN CHC cases had much higher rates of hospital admissions than their corresponding population controls. The case-to-control rates ratios amongst FN populations ranged between 2.4 in 1995 and 1997 to 1.7 in 2000 (the mean of 2.1). The difference was even greater in the non-FN populations. The case-to-control rate ratio among non-FN persons varied from a striking 9.1 in 1995 to 3.1 in 2001, with the mean of 4.5 and the overall rates ratio of 3.6 (Table 6.4).

In general, the non-infected controls (particularly the non-FN ones) had much lower and less variable rates of hospitalizations in any given year compared to individuals with chronic hepatitis C. The difference in hospitalization rates between CHC and non-

infected non-FN individuals was greater than that between chronically infected and non-infected FN persons.

Figure 6.6 Annual hospitalization rates (per 1,000 P/Yrs.), CHC cases and controls, 1995-2002



6.3 Rates by Time since Diagnosis

For persons with chronic hepatitis C the rates were calculated in relation to the date of diagnosis. For the corresponding controls, the "pivot date" as a substitute for the diagnosis date (see detailed description in Chapter 3, "Methodology") was used for computing corresponding date.

6.3.1. TOTAL SEPARATION RATES

There was a clear pattern of hospital services use among patients with chronic hepatitis C in relation to the time of diagnosis. While non-infected individuals, non-FN in particular, had strikingly stable hospital total separation rates throughout the study period, those with chronic hepatitis C had an arch-shaped pattern of such rates throughout the same period (Figure 6.7).

For the FN cases, the total separations rates were 644.5 per 1000 P/Yrs. for up to 4 years prior to the CHC diagnosis and 457.6 per 1000 P/Yrs. in the third year prior to the diagnosis. Rates began to rise again two years prior to the diagnosis, and peaked at 911.9 per 1000 P/Yrs. during the year in which the CHC diagnosis was made. During the second year after the diagnosis the rates decreased to the level of the year preceding CHC diagnosis (708.6 per 1000 P/Yrs.), and further declined to 516.3 total separations per 1000 P/Yrs. 4 years after the diagnosis and thereafter.

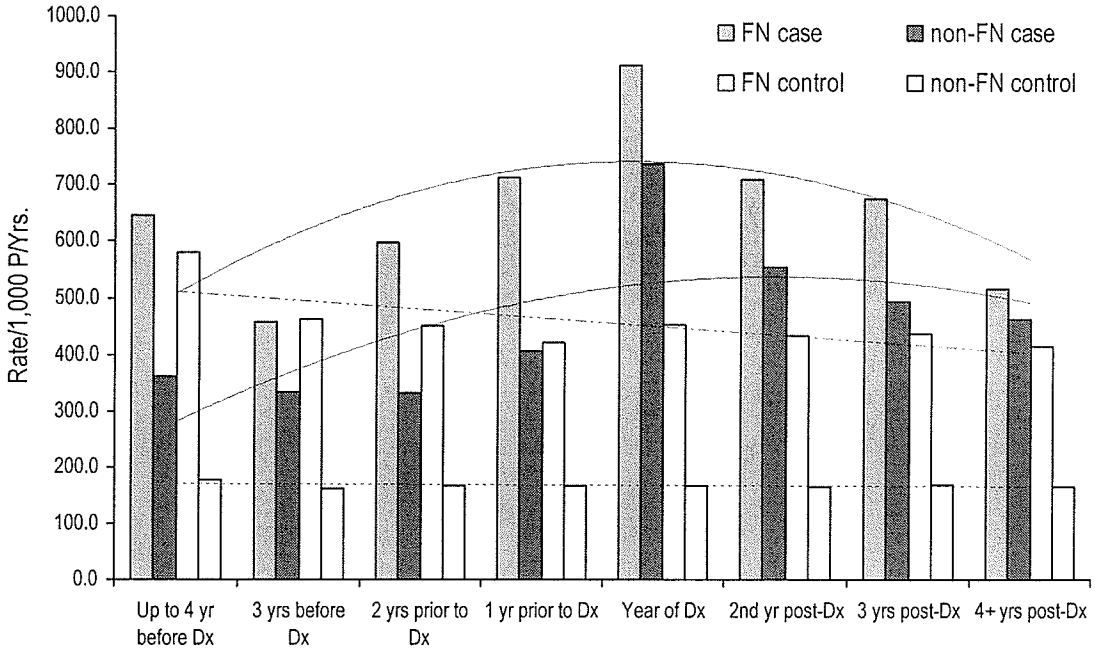
The rates of total hospital separations amongst non-FN cases were fairly similar up to a year before diagnosis, when they increased from 360-330 separations per 1000 P/Yrs. in previous years to 407.4 separations per 1000 P/Yrs. During the first year after the diagnosis the rates soared to 735.3 separations per 1000 P/Yrs., then decreased during the following years to 463.9 total separations per 1000 P/Yrs., but did not reach the lower pre-diagnosis levels (Table 6.5 and Figure 6.7).

Non-infected FN individuals had the same rates of total separations as did FN persons for up to 3 years before their diagnosis. After that, the rates remained largely the same

among FN controls while rising among FN cases. Finally, the non-infected non-FN controls had remarkably steady total separations rates throughout the study, ranging from 179 to 162 separations per 1000 P/Yr.

The overall case-to-control ratio of rates was 1.3 among FN and 2.5 among non-FN persons, indicating a greater difference in hospital use between non-FN persons with CHC and their corresponding controls as compared to FN populations of cases and controls (Table 6.5).

Figure 6.7 Total hospital separation rates (per 1,000 P/Yrs.) among cases and controls in relation to the date of CHC diagnosis for cases and 'pivot' date for controls

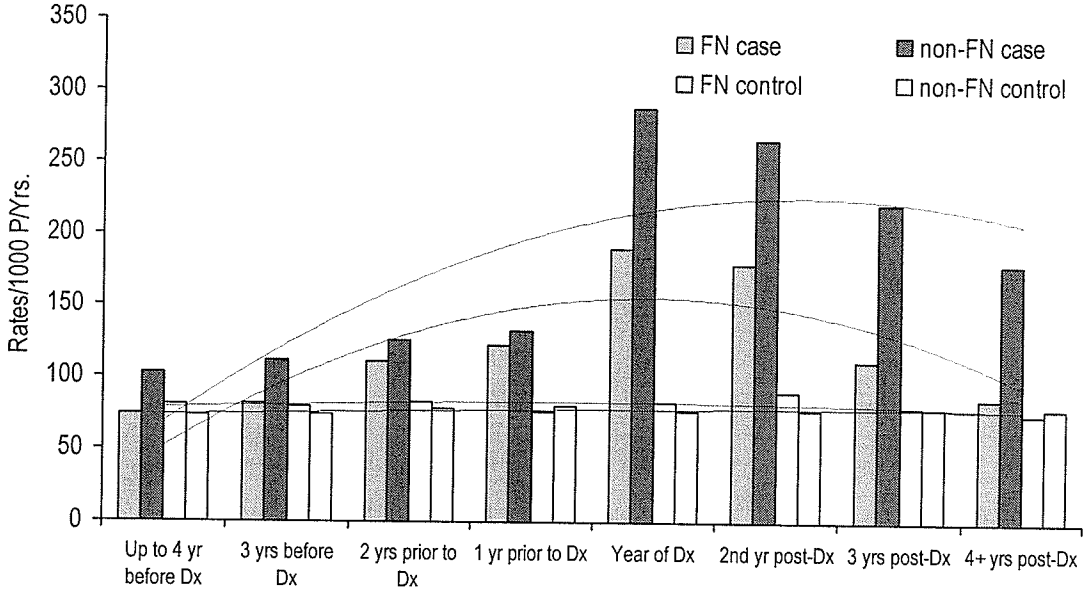


6.3.2 RATES OF DAY VISITS

As my earlier analysis of the annual rates of day visits has already shown, the highest rates of day admissions were among non-FN individuals with chronic hepatitis C, followed by the FN persons with CHC (Figure 6.8). In these two groups, the rates increased slightly from $\geq$ 4 yr. prior to the diagnosis of CHC until 1 year before the diagnosis (Figure 6.9, Table 6.5). There was a dramatic increase in the rates of day admissions during the year of the diagnosis compared to the preceding year (2.6 times among FN cases and 2.8 times among non-FN cases). In the following years, the rates decreased in both FN and non-FN cases, but reached the same level as up to 4 years prior to the diagnosis in FN cases only (74 day admissions per 1,000 P/Yrs. four and more years before the diagnosis and 85.2 admissions per 1,000 P/Yrs. 4 years and up after the CHC diagnosis). Among non-FN cases, however, the rates of day procedures, while also decreasing, stayed significantly above the pre-diagnosis levels (Figure 6.8).

The rates of day admissions were very similar among FN and non-FN controls, and they did not vary much across the timelines in this study. It appears that non-FN persons with chronic hepatitis C underwent an increased amount of hospital day procedures after their CHC diagnosis was made.

Figure 6.8 Rates of day admissions (per 1,000 P/Yrs.) among cases and controls in relation to the date of CHC diagnosis for cases and 'pivot' date for controls



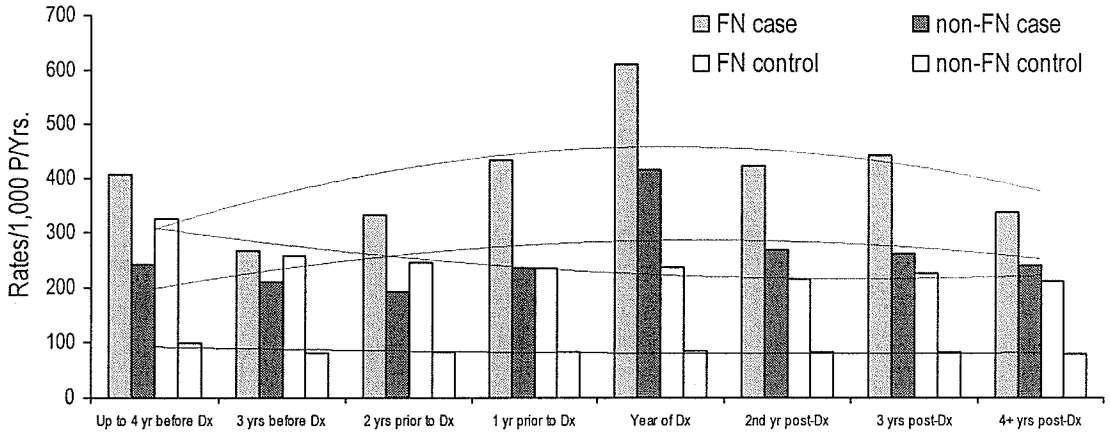
6.3.3 HOSPITALIZATION RATES (INPATIENT ADMISSIONS)

Persons with chronic hepatitis C had higher rates of hospitalizations. This was true for both FN and non-FN groups. The rates varied in relation to the time of the diagnosis, but during each time interval the FN CHC cases had the highest rates of hospitalizations.

Having the lowest rates of inpatient care 3 years prior to the CHC diagnosis at 267.1 hospitalizations per 1000 P/Yrs., the FN persons experienced an increase in hospitalizations, peaking at 610.3 hospitalizations in the year of the CHC diagnosis, followed by a decline to almost the same levels as 3-4 years before the diagnosis (Figure 6.9 and Table 6.5). Rates of hospitalizations among non-FN cases followed exactly the same pattern; although the rates themselves were 30-40% lower than those of FN cases.

The non-infected controls, both FN and non-FN, had fairly stable rates during the study, except ≥4 years prior to the "pivot" date. Those rates were 17% higher than the rates during the subsequent time interval (3 years prior to the "pivot" date) for both FN and non-FN controls. Overall, the inpatient rates declined 35% for non-FN controls from 325.1 to 212.5 hospitalizations per 1000 P/Yr; and 20% for FN controls from 98.8 to 79.3 hospitalizations per 1000 P/Yr during the study period (Figure 6.9).

Figure 6.9 Inpatient rates (per 1,000 P/Yrs.), among CHC cases and controls relative to the date of CHC diagnosis for cases and 'pivot' date for controls



6.4 LIVER DISEASE RELATED SEPARATION RATES

Hospital services due to liver disease were calculated based on a 3-digit ICD-9-CM code for diseases of the liver (571-573), viral hepatitis (070), and liver cancer (155), as discussed in the "Methodology" section of Chapter Three.

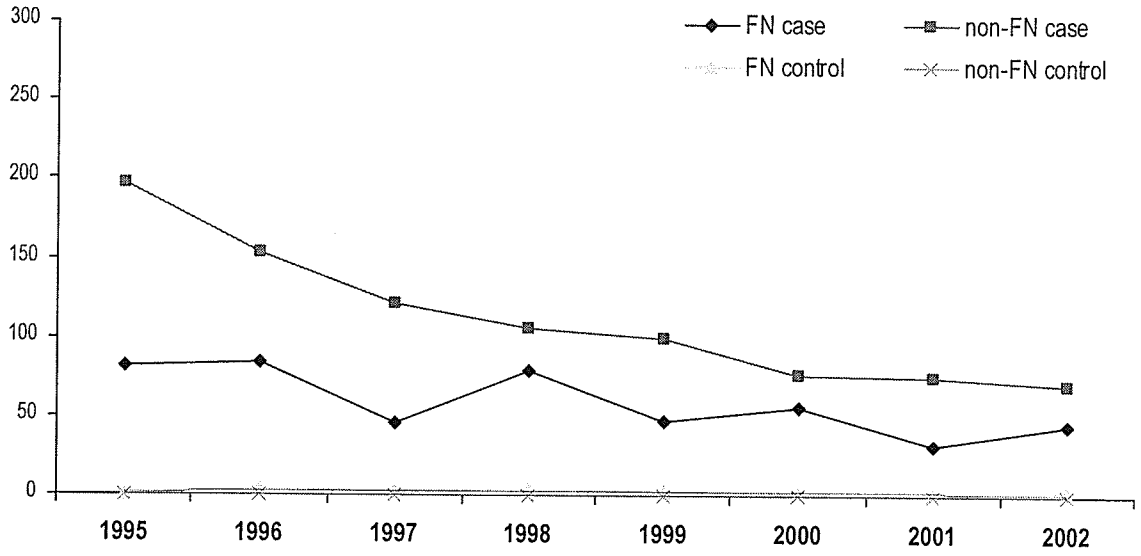
A total of 7.6% of hospital separations among FN cases and 16.4% of such separations among non-FN cases were due to liver disease, compared to 0.5% and 0.3% among FN and non-FN controls (P<0.0000). Another 3.5% of total hospital separations among FN persons with CHC and 6% among non-FN CHC patients had liver disease as one of the diagnoses on their discharge records.

Annual hospital separation rates for liver disease were low for non-infected controls, although somewhat higher among FN vs. non-FN non-infected individuals (Table 6.6). Thus, the annual rates of liver-related hospital use ranged from 0.8 per 1000 P/Yrs in 2000 to 4.2 per 1000 P/Yrs in 1996, with the average of 2.2 liver-related hospital separations per 1000 P/Yrs among FN non-infected controls. The corresponding rates among non-FN controls varied much less during the study period and ranged from 0.3 per 1000 P/Yrs in 1996 to 0.6 separations per 1000 P/Yrs in 1996, with the average of 0.4 liver-related hospital separations per 1000 P/Yrs among FN non-infected controls.

Among persons with CHC, higher liver-related separation rates were observed among non-FN individuals when compared to FN individuals with chronic hepatitis C. During the study period of 1995-2002, the rates declined from the highest level of 197.1 liver separations per 1000 P/Yrs in 1995, falling to 100 separations per 1000 P/Yrs in 1999, and continued to decline to 70.3 liver disease hospital separations per 1000 P/Yrs in 2002 (Table 6.6). The rates of hospital separations for liver disease among FN persons with CHC also declined during the study, but had some variability from year to year. The rates started to decline from 84.5 separations per 1,000 P/Yrs in 1996 to 45.7 separations per

1,000 P/Yrs in 1997. Next, the rate increased to 79.1 separations per 1,000 P/Yrs in 1998, then declined again to 47.4 separations per 1,000 P/Yrs in 1999. The rate then alternated between rise and fall for the next 3 years (Figure 6.10).

Figure 6.10 Annual total separation rates for liver disease per 1,000 P/Yrs., CHC cases and controls, 1995-2002



The higher liver disease hospital separation rates were reflected in the FN-to-non-FN ratios of annual rates, which varied throughout the study from 0.4 in 1997 and 2001 to 0.7 in 1998 and 2000. The overall and mean rate ratios during 1995-2002 were 0.6 and 0.5 respectively (Table 6.6).

Table 6.6 Annual rates of total hospital separations due to liver disease among persons with CHC and among non-infected controls, 1995-2002

	Chronic hepatitis C						Population controls						FN / non-FN RR
	FN			non-FN			non-FN			non-FN			
YEAR	P/Yrs	N	Rate	P/Yrs	N	Rate	P/Yrs	N	Rate	P/Yrs	N	Rate	
1995	36.6	3	81.9	203.0	40	197.1	508.9	0	0.0	4523.7	2	0.2	0.4
1996	106.6	9	84.5	669.9	103	153.8	1437.6	6	4.2	13191.6	4	0.3	0.5
1997	175.2	8	45.7	1081.8	131	121.1	2441.5	7	2.9	21740.4	7	0.3	0.4
1998	252.8	20	79.1	1532.9	163	106.3	3721.7	13	3.5	31106.5	11	0.4	0.7
1999	337.7	16	47.4	1969.7	197	100.0	5159.1	12	2.3	40363.6	17	0.4	0.5
2000	391.8	22	56.1	2319.5	177	76.3	6379.3	5	0.8	48582.5	22	0.5	0.7
2001	447.4	14	31.3	2718.7	205	75.4	7315.2	14	1.9	57587.5	26	0.5	0.4
2002	507.2	23	45.3	3074.2	216	70.3	8078.9	17	2.1	65568.2	39	0.6	0.6
Mean	281.9	14.4	58.9	1696.2	154	112.5	4380.3	9.3	2.2	35333.0	16	0.4	0.5
Overall	2255.3	115	51.0	13569.7	1232	90.8	35042.1	74	2.1	282663.8	128	0.5	0.6

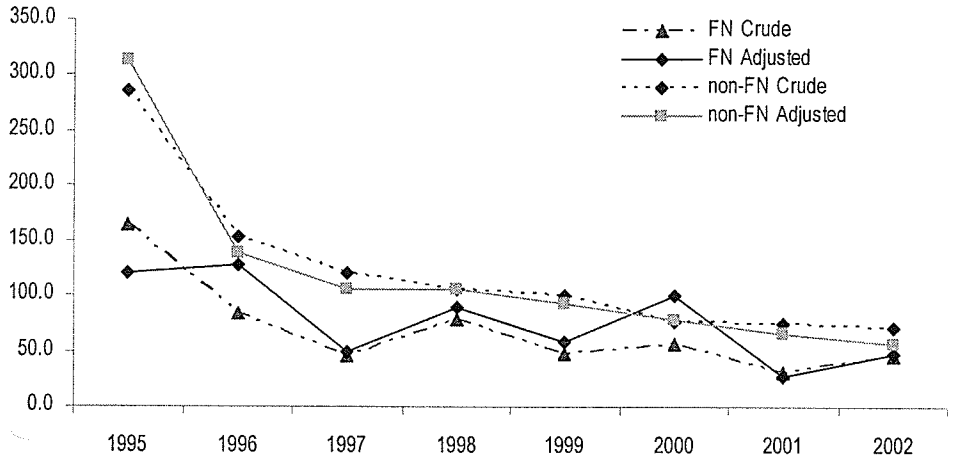
6.4.1 Age adjusted rates of liver disease-related hospital separations

Age adjustment of annual rates of hospital separations for liver disease did not change the direction of differences between FN and non-FN persons with chronic hepatitis C. Both crude and adjusted rates were higher for non-FN persons with CHC. The rates of liver-related hospital separations among FN CHC patients varied through the study period, while the rates among non-FN persons were steady declining since 1995 (Figure 6.11).

The highest age-adjusted rates of liver-related visits were in 1995 for both FN and non-FN persons (over 300 separations per 1000 P/Yrs. among non-FN persons and over 100 separations per 1000 P/Yrs. among FN persons). The following year the rate for non-FN persons dropped considerably to 138 liver disease separations per 1000 P/Yrs. and continued to drop thereafter to 57 separations per 1000 P/Yrs. in 2002. Age-adjusted rates

of liver separations among FN cases fluctuated throughout the study period, peaking in 1996 at 128 separations per 1000 P/Yrs. and reaching the lowest level of just 28 liver disease separations per 1000 P/Yrs. in 2001 (Figure 6.11).

Figure 6.11 Crude and age-adjusted annual separation rates for liver disease per 1,000 P/Yrs., 1995-2002

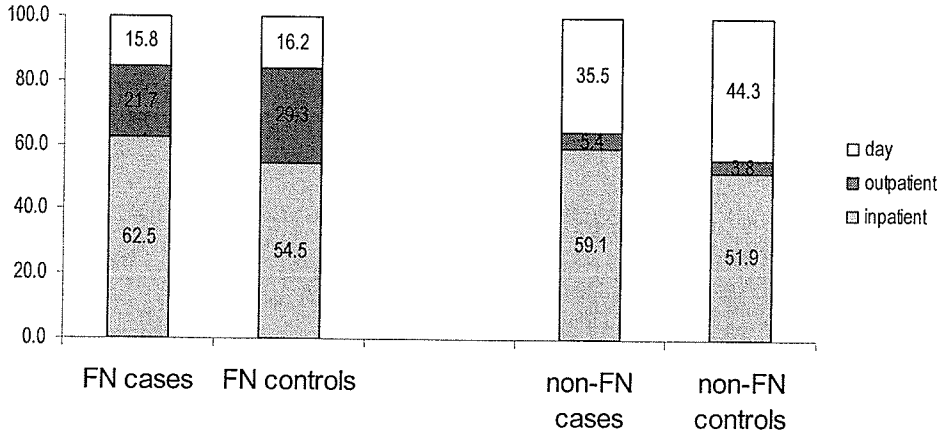


6.5 USE OF HOSPITAL CARE AND LENGTH OF HOSPITALIZATIONS

As shown above, hospital inpatient admissions were only part of the services provided by the hospitals. From all separations during the study period, hospitalizations accounted for 62.5% and 59% of services to FN and non-FN individuals with CHC respectively, as well as for 54.5% and 52% of services to non-infected FN and non-FN individuals respectively (Figure 6.12). Interestingly, both FN cases and controls used outpatient care much more often (22% and 29% respectively), while outpatient care among non-FN cases and controls comprised only 5% and 4% of all hospital services by this population

(Figure 6.12). The opposite was true for day admissions: day admissions are recorded much more frequently for non-FN cases, and even more so for non-FN controls, as compared to both FN cases and FN controls. Day admissions, while requiring formal admittance to the hospital, did not contribute to the total number of in-patient days, as the length of stay (LOS) in such admissions is counted as 0.

Figure 6.12 Overall proportions of various types of hospital services used by individuals with chronic hepatitis C and non-infected controls, 1995-2002, Manitoba



6.5.1 LENGTH OF HOSPITALIZATION

The overall length of hospitalization (total number of days spent in the hospital as inpatient) among the study population was 7.72 days per hospitalized patient. However, this included a proportion of cases with prolonged stay in the hospital. To separate "regular" hospitalizations from the prolonged ones, all admissions were divided into short stays – up to 29 days in duration, and long stays of 30 and more days as inpatient. Long admissions comprised 3 % of all admissions. The average stay during regular admissions was shorter for both FN cases and controls (6.3 and 4.9 days) compared to their non-FN

counterparts (8.5 and 8.7 days) (Table 6.7). For the long admissions, the mean LOS was longest for non-FN controls (P<0.001).

Table 6.7 Total days and the mean LOS of hospitalizations, cases and controls

	Inpatient stays	Total days	LOS per inpatient	Long stays	% of total hospitalizations	Total days	LOS per inpatient
FN case	2860	17977	6.3	84	2.9	7325	87.2
FN control	28539	141223	4.9	569	2.0	47423	83.3
non-FN case	10406	88380	8.5	527	5.1	43932	83.4
non-FN control	75166	655734	8.7	3715	4.9	351078	94.5

Liver-related admissions comprised less than 1% of total hospitalizations. Ninety seven percent of non-liver disease-related and 92.5% of liver disease-related admissions were short stays up to 29 days (Table 6.8). FN persons with CHC stayed in the hospital on average 3.34 days, which is 0.8 day longer than FN controls (2.55 days, P<0.001). Non-FN cases also stayed in the hospital 0.5 days longer than their corresponding controls (P<0.002).

Regular (up to 29 days) hospital stays for liver diseases on average were longer than non-liver disease-related stays (Table 6.9). Thus, FN cases stayed in the hospital due to liver disease 8.4±7.0 days (median 8.0), while non-FN cases stayed 6.6±5.65 (median 5.0). FN and non-FN controls had an average stay of 7.9±6.6 days (median 6.0) and 7.25±7.3 (median 4.0) respectively. None of these stays were significantly different from one another.

A higher proportion of liver disease-related admissions resulted in long stays compared to admissions not related to liver disease (7.5% vs. 2.9%, P<0.000). Although both the

mean and the median LOS during long liver-related admissions appears to be not as long as LOS of non-liver hospitalizations, none differences were significant (Table 6.8).

Table 6.8 Average length of hospitalizations for liver disease and all other conditions among persons with CHC and non-infected individuals during short and long stays

SHORT ADMISSIONS (LOS <29 DAYS)									
				% of			95% CI		
		Total	N	total	Mean	SD	LCL	UCL	Median
Non Liver admissions	FN Cases	1503	1459	97.1	3.34	4.6	3.08	3.60	2.0
	FN Controls	15075	14899	98.8	2.55	3.6	2.48	2.62	1.0
	non-FN Cases	7411	7145	96.4	3.07	4.9	2.95	3.20	1.0
	non-FN Controls	47123	45593	96.8	2.49	4.5	2.44	2.53	0.0
Liver admissions	FN Cases	55	49	89.1	8.44	7.0	6.44	10.45	8.0
	FN Controls	67	66	98.5	7.88	6.6	6.16	9.60	6.0
	non-FN Cases	229	210	91.7	6.60	5.6	5.83	7.37	5.0
	non-FN Controls	78	72	92.3	7.25	7.3	5.53	8.97	4.0

LONG ADMISSIONS (LOS >30 DAYS)										
				% of			95% CI			Max
			N	total	Mean	SD	LCL	UCL	Median	days
Non Liver admissions	FN Cases	1503	44	2.9	102.0	180.3	51.31	152.64	46.0	1041
	FN Controls	15075	176	1.2	98.04	205.1	68.03	128.06	50.5	2494
	non-FN Cases	7411	266	3.6	72.74	80.9	63.25	82.23	49.0	824
	non-FN Controls	47123	1530	3.2	89.41	173.7	80.74	98.08	54.0	3395
Liver admissions	FN Cases	55	6	10.9	72.00	40.7	29.30	114.70	62.0	129
	FN Controls	67	1	1.5	62.50	68.2	5.48	119.50	40.0	213
	non-FN Cases	229	19	8.3	79.68	61.4	50.10	109.20	57.0	266
	non-FN Controls	78	6	7.7	57.33	22.5	33.67	80.99	51.5	93

6.6 PHYSICIAN AMBULATORY VISITS

There were a total of 4,898,357 physician's claim records for 99,300 patients (average of 4.1 claims per patient per year). After excluding 8,708 records of individuals younger than 18 yr. of age and of those diagnosed with HCV infection before 1995 with their corresponding billing claims (606,304), the final set of data for 89,757 individuals had 4,292,053 corresponding physician claims for an average of 5.9 claims per person per year.

The use of physician services during the study period was very high, with 97% of persons overall having at least one visit during the study period. Three percent of persons (2.2% of cases and 3% of controls) did not have any physician billing claims during the study period (Table 6.9). Ninety five percent of individuals had multiple visits during the study period. For the majority of visits (95.5%) there had been one claim submitted per visit, and another 4% had two claims per visit.

Two thirds of CHC patients had liver disease-related physician visits, compared to less than 3% of controls. To compare CHC visits with another chronic infection (HIV) and a common chronic condition (diabetes mellitus), visits for these two conditions were also calculated. Individuals with chronic hepatitis C had significantly more physician visits due to HIV infection (3%) compared to non-hepatitis C controls (0.1%). On the other hand, similar proportion of cases (11%) and controls (9%) had diabetes-related visits during the study period (Table 6.9). In approximately one percent of cases the reason for the visit was not known (ICD-9-CM code was left blank on the record).

Table 6.9 Physician visits total and by selected causes

			No visits		1 visit		2 or more visits	
		N	n	%	n	%	n	%
CHC	all	4,579	103	2.2	35	0.8	4,403	96.2
Controls	visits	86,013	2,541	3.0	1,302	1.5	81,373	94.6
Total		90,592	2,644	2.9	1,337	1.5	85,776	94.7
CHC	Liver	4,579	1,485	32.4	505	11.0	2,551	55.7
Controls	disease	86,013	82,959	96.4	1,304	1.5	953	1.1
Total	visits	90,592	84,444	93.2	1,809	2.0	3,504	3.9
CHC	HIV	4,579	4,418	96.5	39	0.9	84	1.8
Controls	visits	86,013	85,126	99.0	41	0.05	49	0.1
Total		90,592	89,544	98.8	80	0.1	133	0.1
CHC	DM	4,579	4,071	88.9	143	3.1	327	7.1
Controls	visits	86,013	78,432	91.2	2,206	2.6	4,578	5.3
Total		90,592	82,503	91.1	2,349	2.6	4,905	5.4

6.6.1 RATES OF PHYSICIAN VISITS BEFORE AND AFTER HEPATITIS C DIAGNOSIS

There was an obvious pattern in the use of physician services by patients with chronic hepatitis C relative to the time of diagnosis. While the rates of physician visits among non-infected individuals, both FN and non-FN, had declined over time 28% and 23% respectively, the pattern of decline was linear in the non-FN controls and slightly curved in the FN controls (Figure 6.13). Among the cases, the pattern was clearly dome-shaped, with the peak during the year of diagnosis (Figure 6.13).

For the FN cases, the rates were 9.1 physician visits per person-year up to 4 years prior to CHC diagnosis, and rose steadily to the highest level of 14.4 visits per person-year during

the year of CHC diagnosis. Subsequently, the rates began to decline during the second year since diagnosis and reached exactly the same level 4 and more years after CHC diagnosis as it was up to 4 years prior to diagnosis (Table 6.10). The rates of physician visits amongst non-FN cases followed exactly the same pattern, except that the actual rates were on average 20% lower than those of FN cases (ranging between 15% and 25%). The overall case-to-control ratio of physician visit rates was 1.6 among FN and 2.0 among non-FN persons, indicating a greater difference in the use of physician services between non-FN persons with CHC and their corresponding controls compared to the FN populations of cases and controls (Table 6.10).

Figure 6.13 Rates of physician ambulatory visits by the time since diagnosis

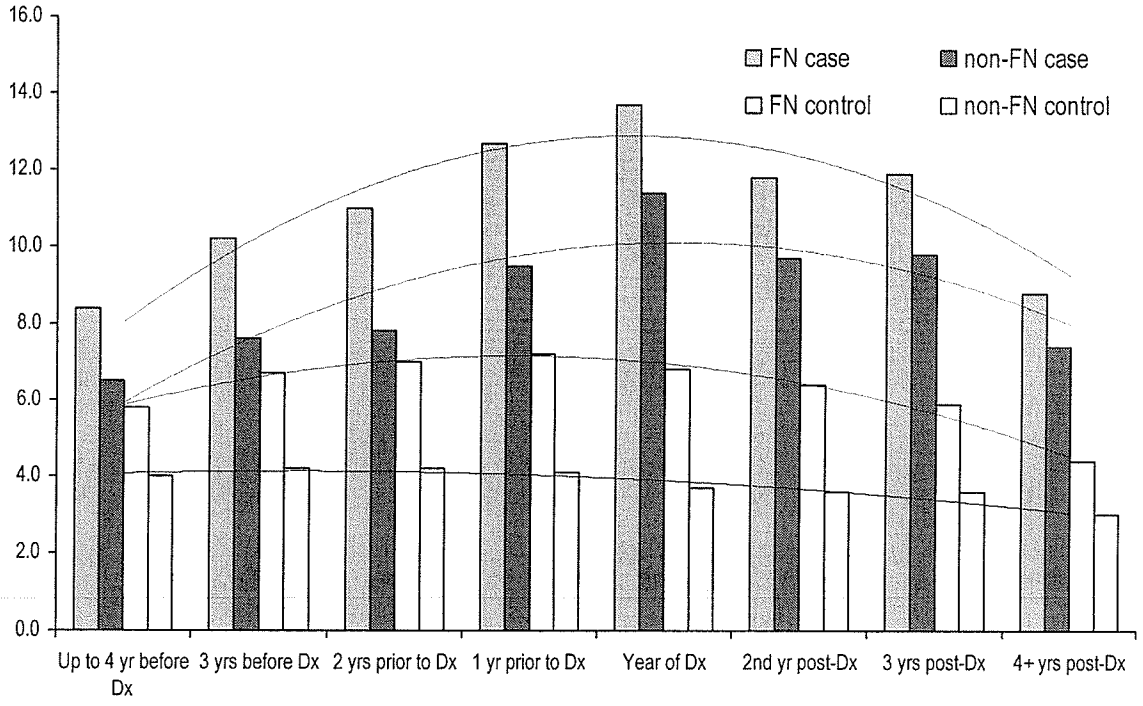


Table 6.10 Rates of physician visits per person/year by the time since diagnosis and annual rates

	Chronic Hepatitis C						Non-Infected Controls						Case to control Rate Ratio	
	FN			non-FN			FN			non-FN				
Time interval	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	FN	non-FN
4+ yr before Dx	3025.6	25439	8.4	16812.6	108981	6.5	43604.4	254940	5.8	341339.8	1380345	4.0	1.4	1.6
3 yr before Dx	614.0	6272	10.2	3553.1	26901	7.6	8937.6	59607	6.7	71903.2	299009	4.2	1.5	1.8
2 yr prior to Dx	615.0	6770	11.0	3636.6	28438	7.8	8953.6	62410	7.0	73196.5	306201	4.2	1.6	1.9
1 yr prior to Dx	615.3	7840	12.7	3758.2	35753	9.5	8969.9	64207	7.2	74794.8	303173	4.1	1.8	2.3
Year of Dx	563.7	7725	13.7	3575.6	40645	11.4	8482.9	58092	6.8	71390.1	266879	3.7	2.0	3.0
2 yr post-Dx	475.6	5622	11.8	2937.2	28581	9.7	7466.3	48151	6.4	59948.4	216761	3.6	1.8	2.7
3 yr post-Dx	393.5	4674	11.9	2334.1	22821	9.8	6384.4	37908	5.9	48700.3	175221	3.6	2.0	2.7
4+ yr post-Dx	821.3	7193	8.8	4714.5	34819	7.4	12689.5	55686	4.4	102459.6	302345	3.0	2.0	2.5
Mean	890.5	8941.9	11.1	5165.2	40867.4	8.7	13186.1	80125.1	6.3	105466.6	406241.8	3.8	1.8	2.3
Overall	7124.0	71535.0	10.0	41322.0	326939	7.9	105488.5	641001.0	6.1	843732.7	3249934.0	3.9	1.7	2.1

	Chronic Hepatitis C						Population Controls						Case-to-control Rate Ratio	
	FN			non-FN			FN			non-FN				
YEAR	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	FN	non-FN
1995	36.6	448	12.2	203.0	2611	12.9	508.85	3641	7.2	4523.7	17519	3.9	1.7	3.3
1996	106.6	1369	12.8	669.9	8249	12.3	1437.62	10084	7.0	13191.6	52904	4.0	1.8	3.1
1997	175.2	2553	14.6	1081.8	13354	12.3	2441.49	17521	7.2	21740.4	89295	4.1	2.0	3.0
1998	252.8	3700	14.6	1532.9	18925	12.3	3721.7	26610	7.1	31106.5	132363	4.3	2.0	2.9
1999	337.7	4422	13.1	1969.7	22105	11.2	5159.06	35882	7.0	40363.6	170884	4.2	1.9	2.7
2000	391.8	5352	13.7	2319.5	26184	11.3	6379.31	45568	7.1	48582.5	203705	4.2	1.9	2.7
2001	447.4	6325	14.1	2718.7	30218	11.1	7315.19	50709	6.9	57587.5	242451	4.2	2.0	2.6
Mean	249.7	3452.7	13.6	1499.4	17378	11.9	3851.9	27145.0	7.1	31013.7	129874.4	4.1	1.9	2.9
Overall	1748.1	24169.0	13.8	10495.5	121646	11.6	26963.2	190015.0	7.0	217095.6	909121.0	4.2	2.0	2.8

Annual rates (per person/year) of physician visits by sex

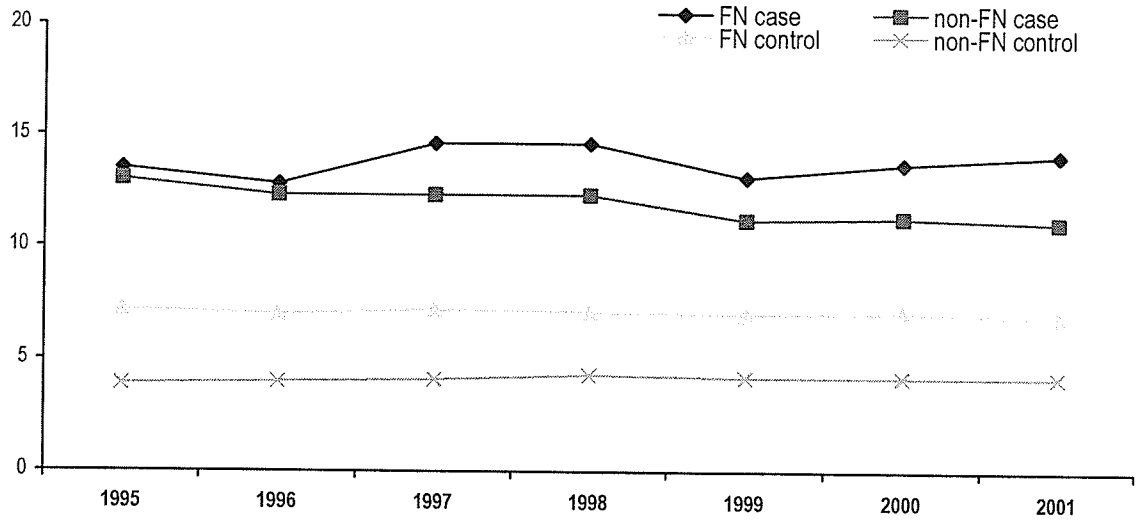
	CHRONIC HEPATITIS C						POPULATION CONTROLS						Case-to-control Rate Ratio	
	non-FN						non-FN							
	Males			Females			Males			Females				
YEAR	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	Person/ Years	Total visits	Rate	FN	non-FN
1995	15.33	22	1.4	21.28	33	1.6	126.36	266	2.1	76.62	162	2.1	0.7	0.7
1996	47.73	45	0.9	58.84	76	1.3	411.65	869	2.1	258.25	527	2.0	0.4	0.6
1997	74.18	59	0.8	103.39	81	0.8	664.86	1004	1.5	416.96	699	1.7	0.5	0.5
1998	103.39	76	0.7	149.38	177	1.2	951.64	1775	1.9	581.3	1138	2.0	0.4	0.6
1999	142.32	81	0.6	195.35	187	1.0	1241.78	1961	1.6	727.95	1186	1.6	0.4	0.6
2000	165.1	141	0.9	226.73	288	1.3	1468.02	2632	1.8	851.46	1545	1.8	0.5	0.7
2001	186.75	143	0.8	260.67	329	1.3	1702.72	3364	2.0	1015.93	1901	1.9	0.4	0.7
Mean	105.0	81.0	0.9	145.1	167.3	1.2	938.1	1695.9	1.8	561.2	1022.6	1.9	0.5	0.6
Overall	734.8	567.0	0.8	1015.64	1171	1.2	6567.0	11871.0	1.8	3928.47	7158	1.8	0.4	0.6

6.6.2 ANNUAL RATES OF PHYSICIAN VISITS PER PERSON-YEAR

Annual rates of physician visits per person-year were highest among FN individuals (except in 1995) with chronic hepatitis C, followed by the non-FN persons with CHC, while the lowest rates were, as with the hospital separations, amongst the non-infected non-FN controls (Figure 6.14). The physician visit rates among non-FN cases were higher than among FN cases in 1995 (26.1 vs. 24.9 per person-year respectively). During 1996-2001 the rates were similar, with a slight decline in use by FN and non-FN persons with CHC and non-infected individuals (Figure 6.14). Compared to 1996, the rates in 2001 declined 14.5% from 5.4 to 4.6 visits per person-year among non-FN controls and 15.3% from 18 to 15.2 visits per person-year among FN cases. The steepest decline of 25% in ambulatory visit rates occurred among non-FN CHC persons: from 16 visits per P/Yrs in 1996 to 12 visits per P/Yrs in 2001. The 20-percent decline in physician visit rates among FN cases from 9 to 7 visits per person-year during 1996-2001 period was second largest decline (Figure 6.14, Table 6.10).

Overall, the rates of ambulatory visits were much higher among FN and non-FN persons with CHC than amongst their corresponding population controls. The case-to-control rates ratios of visits amongst FN persons ranged from 1.8 to 2.1 during 1995-2001 (the mean rate ratio of 1.9). The difference was larger in the non-FN populations, with the case-to-control rate ratio variations from 3.2 in 1995 and 3.0 in 1996-97 to 2.4 in 2001 and the mean rate ratio of 2.8 (Table 6.10).

Figure 6.14 Annual rates of physician visits per person/year



6.6.3 PHYSICIAN VISITS BY CAUSE

The main reason for physician visits was determined based on the diagnostic code from the billing claims. These codes were divided according to the 19 major Chapters of the ICD-9-CM coding system (Appendix 3).

The two principal reasons for physician visits in this study were mental disorders and diseases of respiratory tract, with 14.8% of total visits each. The top five reasons for physician visits were exactly the same for both CHC cases and non-infected controls, except for a minor variation in the order of complaints. Thus, at 22%, mental illness was the top reason for physician visits among persons with CHC. It was the most common cause of physician visits with almost twice as many visits as for the second-ranked cause – respiratory diseases – at 11.4% of the total visits by patients with chronic hepatitis C.

Mental illness was also the second most frequent reason for visit among non-infected controls at 14% (Figure 6.15 and Table 6.11). Respiratory disorders, the main reasons for visits among controls, comprised 15% of all visits by non-CHC individuals, while being the second most frequent cause of visits among those with CHC at 11.4%. Injury and poisoning, musculoskeletal diseases and symptoms and ill-defined conditions comprised the remaining categories for the top five reasons for physician visit (Table 6.11).

Figure 6.15 Causes of physician visits for CHC and non-infected persons, Manitoba, 1995-2002

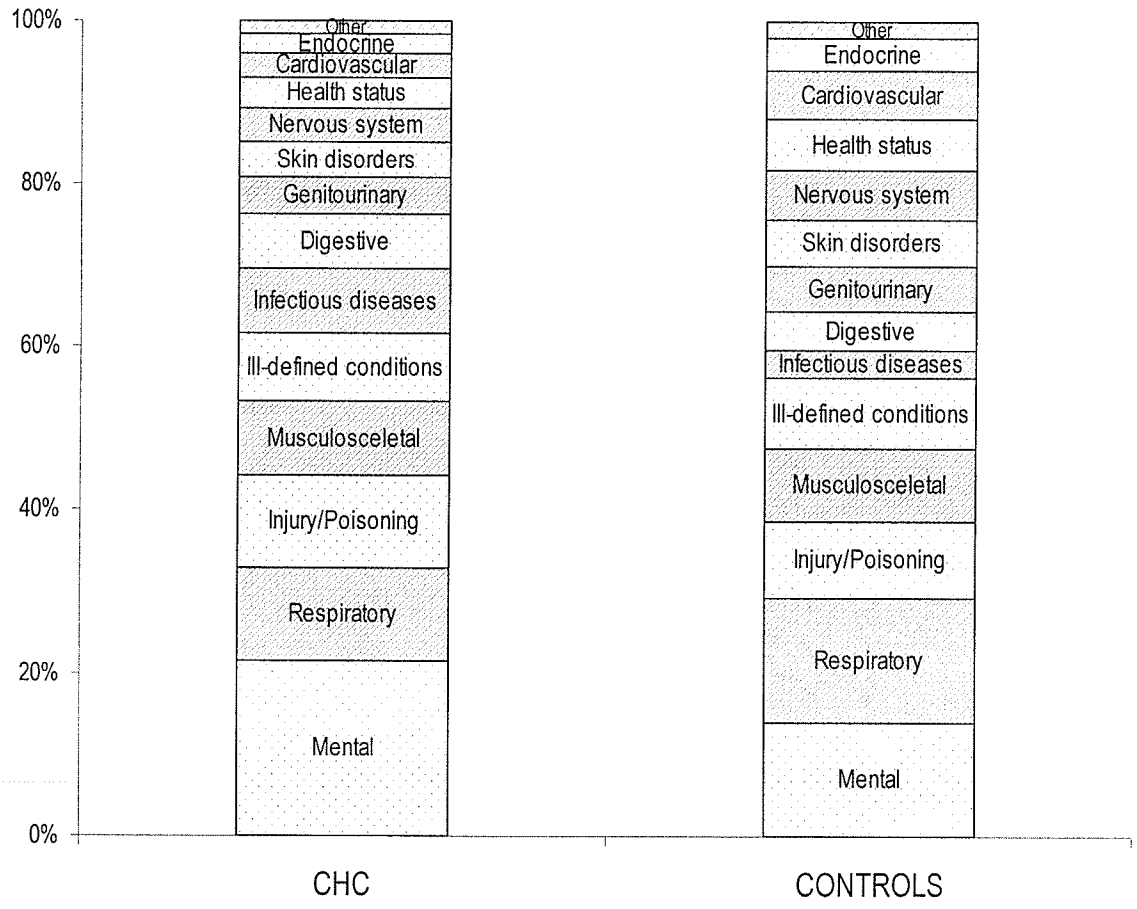


Table 6.11 Reasons for physician visits among persons with CHC, non-infected controls and overall (percent from total visits and ranking)

CONDITIONS	CHC		CONTROLS		TOTAL	
	%	rank	%	rank	%	Rank
Mental disorders	21.6	1	14.1	2	14.8	1-2
Respiratory disorders	11.4	2	15.2	1	14.8	1-2
Injury and Poisoning	11.1	3	9.4	3	9.6	3
Musculoskeletal diseases	9.1	4	9.0	4	9.0	4
Symptoms and Ill-defined conditions	8.4	5	8.6	5	8.6	5
Infectious and parasitic diseases	7.9	6	3.4	13	3.8	13
Digestive diseases	6.7	7	4.7	11	4.9	11
Genitourinary diseases	4.6	8	5.5	10	5.4	10
Skin and subcutaneous tissue disorders	4.3	9	5.7	9	5.6	8-9
Nervous system disorders	4.2	10	6.2	7	6.0	7
Conditions influencing health status	3.7	11	6.5	6	6.2	6
Cardiovascular diseases	3.1	12	5.9	8	5.6	8-9
Endocrine and metabolic diseases	2.3	13	4.1	12	3.9	12
Other conditions	1.6	14	1.9	14	1.8	14

Of the already mentioned top five causes for physician visits, mental illness and respiratory disorders were among the top five for both males and females, and for both cases and controls of both genders. Injury and poisoning was also among the top three reasons for all but non-infected females (Table 6.11). Musculoskeletal diseases were among top five reasons for visits among males, while genitourinary diseases were among top five causes among females.

Females most often saw a physician due to mental disorders, respiratory disorders, symptoms and ill-defined conditions, genitourinary diseases. Approximately 30% of all visits (33% among females with CHC and 28% among non-infected females) were due to mental illness and respiratory disorders. Injury and poisoning was the third top cause of

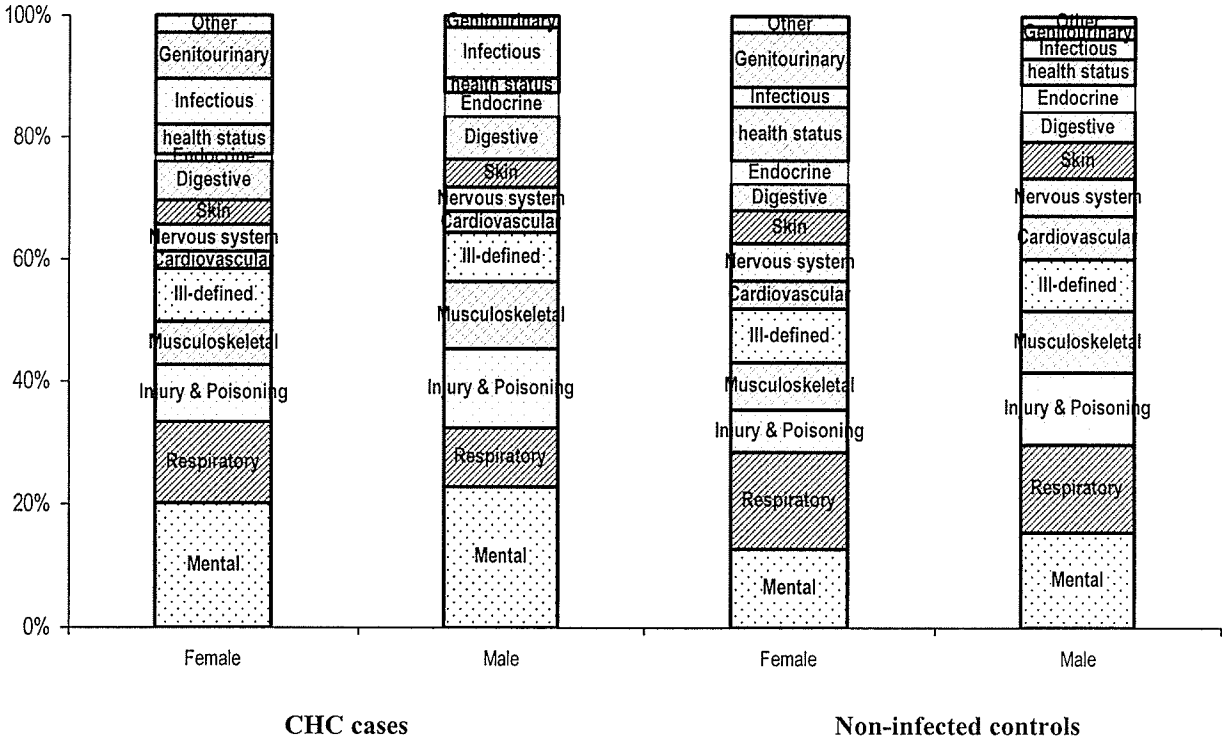
physician visits for females with CHC but not for non-infected females. Infectious and parasitic diseases were the final group in the top 5 for the females with chronic hepatitis C, while it was next to last for non-infected females (Table 6.12, Figure 6.16).

Males saw physicians for mental disorders, respiratory disorders, injury and poisoning, musculoskeletal diseases and infectious and parasitic diseases (CHC cases) and ill-defined conditions (non-infected controls). The non-infected controls was the only group who had cardiovascular diseases as an important reason for visits (ranked sixth), while for all other groups (CHC males and females and non-infected females) it was outside of the top ten.

Table 6.12 Causes of physician visits for males and females

CONDITIONS	CHC				Controls			
	Females		Males		Females		Males	
	%	rank	%	rank	%	rank	%	rank
Mental disorders	20.1	1	22.9	1	12.7	2	15.4	1
Respiratory disorders	13.3	2	9.6	4	15.8	1	14.4	2
Injury and Poisoning	9.2	3	12.9	2	6.9	7	11.7	3
Symptoms and Ill-defined conditions	8.8	4	8.0	6	8.7	3-5	8.5	5
Infectious and parasitic diseases	7.5	5-6	8.3	5.0	3.4	13	3.3	12
Genitourinary diseases	7.5	5-6	1.9	13	8.9	3-5	2.2	13
Musculoskeletal diseases	7.1	7	11.0	3	7.8	6	10.2	4
Digestive diseases	6.4	8	7.0	7	4.4	11	5.1	9
Conditions influencing health status	5.0	9	2.4	12	8.8	3-5	4.2	11
Nervous system disorders	4.4	10	3.9	10	6.1	8	6.2	7
Skin and subcutaneous tissue disorders	4.0	11	4.6	8	5.4	9	5.9	8
Other conditions	2.9	12	0.0	14	2.7	14	1.5	14
Cardiovascular diseases	2.7	13	3.5	11	4.7	10	7.0	6
Endocrine and metabolic diseases	1.1	14	4.0	9	3.7	12	4.4	10

Figure 6.16 Causes of physician visits for CHC and non-infected persons by sex, Manitoba, 1995-2002



6.6.4 AMBULATORY VISITS PROVIDERS

In terms of health care providers, the majority of physician visits were provided by general practice physicians (general practitioners and family physicians). Overall, 84% of all ambulatory visits were to general practitioners, 79.5% of visits among cases and 84.3% of visits amongst controls ($p<0.000$). There was, as expected, a difference in the proportion of specialist visits between FN and non-FN individuals. Thus, only 9% of all ambulatory visits by FN persons with CHC and 7% of visits by FN controls were provided by specialist physicians, compared to 23% of visits by non-FN individuals with CHC and 17% of visits by non-FN controls.

The proportions of visits to specialists reflect the remoteness of residence. Thus, amongst Winnipeg residents with CHC, 78% of visits were to general practitioners compared to 84% of visits by those residing in rural Southern Manitoba and 92% of visits by residents of Northern Manitoba (P for trend 0.000) (Table 6.13, Figure 6.17).

A higher proportion of visits due to liver disease by non-FN persons with CHC from Winnipeg and Southern Manitoba were to specialist physicians compared to their FN counterparts. Thus, 64% of non-FN vs. 45% of FN with CHC from Winnipeg and 60% of non-FN vs. 40% of FN from Southern Manitoba had specialist visits for their liver disease (P 0.000 for each). In Northern Manitoba, however, both FN and non-FN persons with CHC had similar proportion of liver disease-related visits managed by specialists (46% vs. 43% respectively, P<0.51).

Figure 6.17 Ambulatory visits to specialists by the region

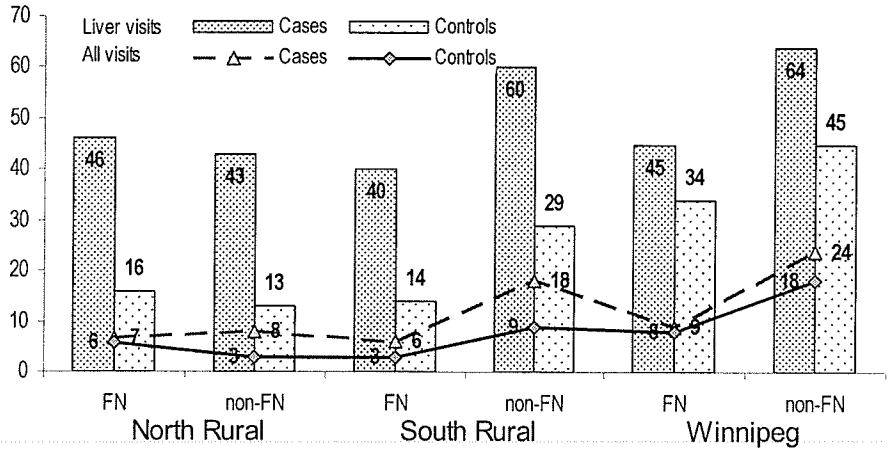
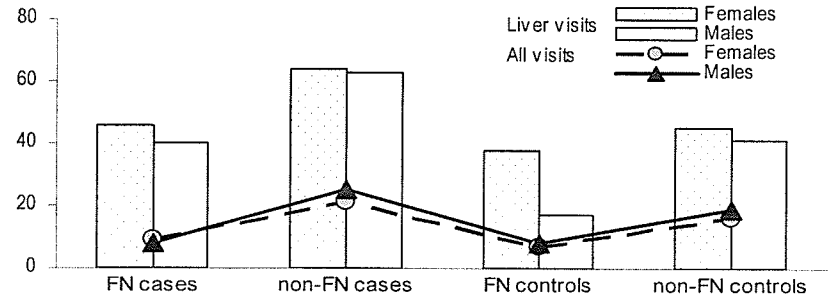


Table 6.13 Ambulatory visits by provider

	Cases						Controls					
	FN			Non-FN			FN			Non-FN		
	North	South	WPG	North	South	WPG	North	South	WPG	North	South	WPG
All visits												
Visits (N)	4656	9341	68785	7972	44049	335935	40872	92472	591931	68454	456968	3168496
GP: n	4350	8785	62399	7306	36141	255365	38558	89732	544084	66331	415911	2568945
%	93.4	94.0	90.7	91.6	82.0	76.0	94.3	97.0	91.9	96.9	91.0	81.1
Specialist: n	306	556	6386	666	7908	80570	2314	2740	47847	2123	41057	599551
%	6.6	6.0	9.3	8.4	18.0	24.0	5.7	3.0	8.1	3.1	9.0	18.9
Liver disease-related visits												
	106	370	1870	554	3634	23172	32	93	1118	178	470	5230
GP: n	57	222	1034	317	1438	8303	27	80	740	155	332	2891
%	53.8	60.0	55.3	57.2	39.6	35.8	84.4	86.0	66.2	87.1	70.6	55.3
Specialist: n	49	148	836	237	2196	14869	5	13	378	23	138	2339
%	46.2	40.0	44.7	42.8	60.4	64.2	15.6	14.0	33.8	12.9	29.4	44.7

There were no sex differences in the proportion of total visits to specialists among FN cases or controls. Among non-FN cases and controls, males had slightly more specialists' visits than females did (25% vs. 21% and 19% vs. 16% respectively, p=0.000 for both). Conversely, females had more specialists' visits for liver disease, except in the case of non-FN persons with CHC, where males and females had the same frequency of specialist-managed liver disease-related visits (63% and 64% respectively). Among the non-infected FN, females had twice as many visits to specialists for their liver disease (other than hepatitis C) as males (38% vs. 17%, P 0.000). Also, 46% of liver disease visits among FN females with CHC were managed by specialists, compared to 40% of such visits by FN males with CHC ($p<0.004$), and 45% vs. 41% ($p<0.01$) of liver visits among females were managed by specialist, compared to 41% of such visits by FN males with CHC ($p<0.004$) (Figure 6.18).

Figure 6.18 Ambulatory visits to specialists by sex



Females	46	64	38	45
Males	40	63	17	41
Females	9	21	7	16
Males	8	25	8	19

6.6.5 LIVER DISEASE-RELATED VISITS

Physician visits for liver disease comprised approximately one percent of all physician visits. But, as expected, there was a significant difference in the populations of cases and controls in terms of such visits. Both FN and non-FN controls had 0.2% of their respective total visits due to liver diseases. Non-FN persons with CHC had 14% of the total visits due to liver disease, which is more than twice the proportion of liver disease-related visits among the FN individuals with hepatitis C (Table). Annually, between 5% and 8% of physician visits by FN persons with CHC were due to liver disease, while non-FN persons with CHC had between 11% and 16% of annual visits because of their liver disease (Table 6.14).

Table 6.14 Proportion of liver disease-related physician visits from the total visits among persons with CHC and non-infected controls

	CHRONIC HEPATITIS C						POPULATION CONTROLS					
	FN			non-FN			FN			non-FN		
	Total	Liver		Total	Liver		Total	Liver		Total	Liver	
YEAR	visits	visits	%	visits	visits	%	visits	visits	%	visits	visits	%
1995	495	55	11.1	2611	428	16.4	3641	5	0.1	17519	26	0.1
1996	1389	121	8.7	8249	1396	16.9	10084	20	0.2	52904	74	0.1
1997	2553	140	5.5	13354	1703	12.8	17521	46	0.3	89295	150	0.2
1998	3700	253	6.8	18925	2913	15.4	26610	50	0.2	132363	225	0.2
1999	4422	268	6.1	22105	3147	14.2	35882	66	0.2	170884	310	0.2
2000	5352	429	8.0	26184	4177	16.0	45568	100	0.2	203705	436	0.2
2001	6325	472	7.5	30218	5265	17.4	50709	122	0.2	242451	544	0.2
Mean	3462.3	248.3	7.7	17378.0	2718.4	15.6	27145.0	58.4	0.2	129874.4	252.1	0.2
Overall	24236	1738	7.2	121646	19029	15.6	190015	409	0.2	909121	1765	0.2

As expected, the rates of liver disease-related physician visits in the non-infected population were very low and comprised 0.01 and 0.02 visits per person-year among FN and non-FN population controls respectively. Annual rates of liver disease-related visits per person-year were much higher among non-FN individuals with chronic hepatitis C compared to their FN counterparts. The pattern of rates over time was the same, while the value was different. The annual rate of ambulatory visits for liver disease amongst FN cases ranged from 1.8 visits per person-year in 1995 to 0.9 visit per person-year in 1997 to 1.1 visits per P/Yrs in 2001 (Table 6.15). The rates of liver disease-related visits among non-FN persons with CHC varied from the highest of 3 visits per P/Yr. in 1995 to a low of 1.6 visits per P/Yrs in 1999 to 2 visits per P/Yrs in 2001. The mean FN-to-non-FN case rate ratio was 0.6 (Table 6.15).

Even after adjustment for age, the annual rates of ambulatory physician visits for liver disease were still significantly higher among non-FN persons with CHC as compared to FN patients. During 1995-2002, a non-FN person had an average of 2.4 liver disease-related visits per P/Yr., while a FN person had 1.2 visits per P/Yr. The FN-to-non-FN rate ratio remained stable over the entire study period with the mean of 0.5 and the range of 0.4 to 0.6 (Figure 6.19, Table 6.15).

Figure 6.19 Crude and age-adjusted rates of liver-related physician visits, FN and non-FN CHC patients (per P/Yr.)

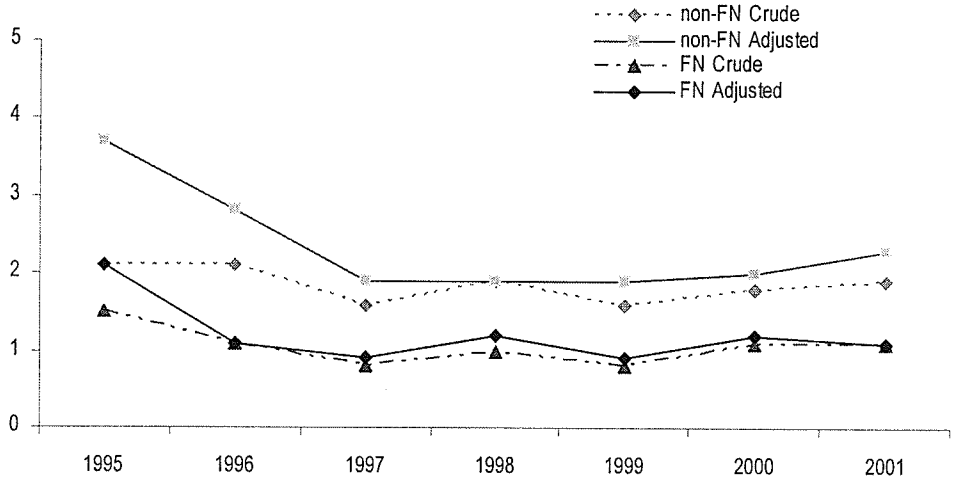


Table 6.15 Crude and age-adjusted rates of liver disease-related physician visits

	CHRONIC HEPATITIS C						FN TO
	FN			non-FN			non-FN
YEAR	Liver visits	Crude Rate	Adjusted Rate	Liver visits	Crude Rate	Adjusted Rate	Rate Ratio
1995	55	1.5	2.1	428	2.1	3.7	0.57
1996	121	1.1	1.1	1396	2.1	2.8	0.39
1997	140	0.8	0.9	1703	1.6	1.9	0.47
1998	253	1.0	1.2	2913	1.9	1.9	0.63
1999	268	0.8	0.9	3147	1.6	1.9	0.47
2000	429	1.1	1.2	4177	1.8	2.0	0.60
2001	472	1.1	1.1	5265	1.9	2.3	0.48
Mean	248.3	1.1	1.2	2718.4	1.9	2.4	0.5

The rates of liver-disease-related physician visits were higher for both non-FN males and females compared to their FN counterparts (Figure 6.20, Table 6.16). The FN–to-non-FN ratio of liver-related ambulatory visits for males was 0.4-0.5 throughout the entire study period. The same ratio for females varied from 0.7 in 1996-96 to 0.5 in 1997 to back to 0.7 in 2001.

There were no differences in the annual rates of liver disease-related visits between non-FN males and females; the overall male-to-female ratio of rates was 1.0. Conversely, FN females with CHC had higher rates of liver visits than FN males did with the male-to-female ratio ranging from 0.8 in 1995 to 1.0 in 1997 to 0.6 in 2001; the overall male-to-female ratio of rates was 0.7.

Figure 6.20 Rates of liver-related physician visits among persons with CHC by sex

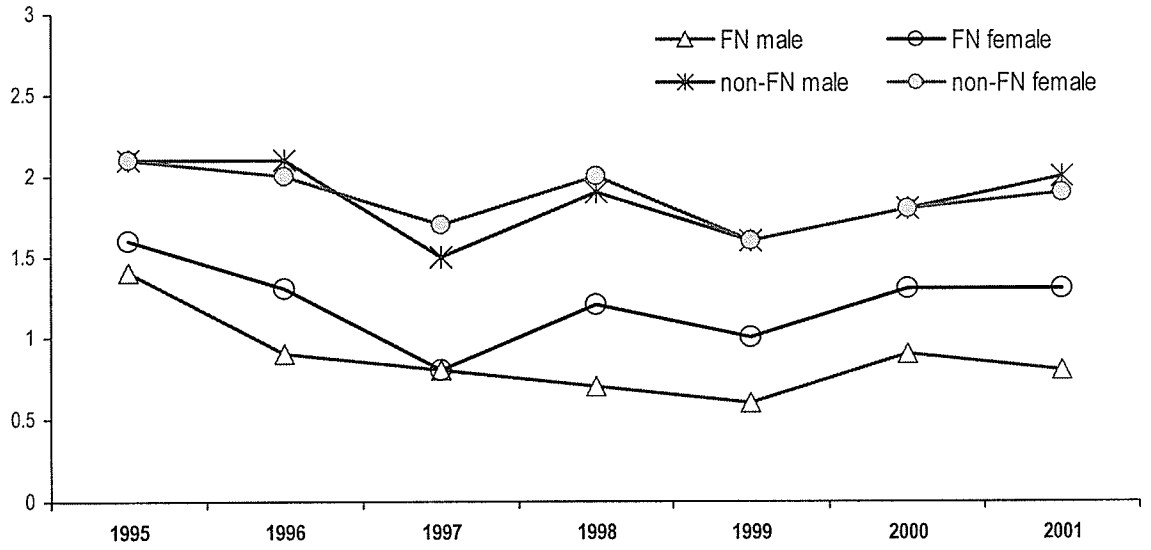


Table 6.16 Rates of liver disease-related physician visits among CHC and non-infected persons

	CHRONIC HEPATITIS C						FN TO	POPULATION CONTROLS					
	FN			non-FN			non-FN	FN			non-FN		
YEAR	Person/ Years	Liver visits	Rate	Person/ Years	Liver visits	Rate	Rate Ratio	Person/ Years	Liver visits	Rate	Person/ Years	Liver visits	Rate
1995	36.6	55	1.5	203.0	428	2.1	0.7	508.9	5	0.01	4523.7	26	0.01
1996	106.6	121	1.1	669.9	1396	2.1	0.5	1437.6	20	0.01	13191.6	74	0.01
1997	175.2	140	0.8	1081.8	1703	1.6	0.5	2441.5	46	0.02	21740.4	150	0.01
1998	252.8	253	1.0	1532.9	2913	1.9	0.5	3721.7	50	0.01	31106.5	225	0.01
1999	337.7	268	0.8	1969.7	3147	1.6	0.5	5159.1	66	0.01	40363.6	310	0.01
2000	391.8	429	1.1	2319.5	4177	1.8	0.6	6379.3	100	0.02	48582.5	436	0.01
2001	447.4	472	1.1	2718.7	5265	1.9	0.5	7315.2	122	0.02	57587.5	544	0.01
Mean	249.7	248.3	1.1	1499.4	2718.4	1.9	0.6	3851.9	58.4	0.01	31013.7	252.1	0.01
Overall	1748.1	1738.0	1.0	10495.5	19029	1.8	0.5	26963.2	409.0	0.02	217095.6	1765.0	0.01

6.7 SUMMARY

- Hospital separation rates were much higher among FN cases than among non-FN cases.
- Hospital separation rates follow an arched pattern, with an increase in utilization 1-2 yrs. preceding the diagnosis of CHC, then a peak in the year of diagnosis, followed by a decrease during the second year after CHC diagnosis.
- FN persons, cases and controls alike, used much more outpatient care as compared to non-FN persons.
- Non-FN cases and controls had significantly more day admissions as compared to FN persons.
- FN persons with CHC had higher rates of visits to physicians (per P/Yr.) overall as compared to non-FN CHC patients. However, the rates of visits for liver disease were higher among non-FN CHC patients compared to FN CHC patients.

CHAPTER 7 LIVER DISEASE-RELATED HEALTH CARE UTILIZATION FOR PERSONS WITH CHRONIC HEPATITIS C

7.1 LIVER DISEASE-RELATED HOSPITAL CARE

Individuals with CHC used hospital resources extensively. Overall, a total of 90% of FN persons with CHC and 79% of non-FN persons were either hospitalized or had outpatient and/or day admissions (Table 7.1). In addition to a much higher proportion of hospital users, those FN CHC patients who used hospital care did so more often than non-FN patients. Thus, FN persons with CHC had an average of 8.4 separations per service user as compared to 5.6 separations per patient among non-FN CHC patients who received hospital care (Table 7.1). Also, a much higher proportion of FN patients with CHC had been hospitalized compared to non-FN patients (81.4% vs. 63.2%, p=0.00). Similarly, amongst those who had been hospitalized, FN and non-FN persons averaged 5.7 vs. 4.2 hospitalizations per service user respectively. Also, significantly more FN patients with CHC had outpatient hospital visits compared to non-FN CHC patients (14.4% vs. 2.6%, p=0.00), with the mean of 11 visits per FN outpatient vs. 9.3 visits per non-FN outpatient. More than one half of FN and non-FN patients had day admissions, but this was higher for non-FN CHC patients (57%) as compared to FN (52%), with 2.8 vs. 2.2 day admissions per non-FN and FN respectively.

Despite the higher all cause hospital separations, FN persons had significantly fewer hospital visits due to their hepatitis C. Thus, 24% of non-FN and 14% of FN patients had hospital visits for CHC and CHC-related conditions. This translates into 30% of all hospital visits by non-FN CHC patients being due to their liver disease, compared to only

16% of such visits amongst FN persons with CHC (p=0.00) (Table 7.1). In addition, there were significantly more day admissions for CHC among non-FN persons (21%) compared to FN persons (9%). A total of 6% of FN and 4% of non-FN patients were hospitalized for their CHC-related problems, and 4.5% of both FN and non-FN patients also had outpatient visits due to CHC.

Table 7.1 Overall and liver disease-related hospital use by persons with CHC

	FN (N=617)			NON-FN (N=3,962)			
VARIABLE	n	%	visit per person	n	%	visit per person	P
HOSPITAL SEPARATIONS TOTAL	555	90.0	8.4	3131	79.0	5.6	0.00
- inpatient (hospitalizations)	502	81.4	5.7	2504	63.2	4.2	0.00
- day admissions	322	52.2	2.2	2256	56.9	2.8	0.05
- outpatient visits	89	14.4	11.0	102	2.6	9.3	0.00
- long hospitalizations	52	8.4	1.6	317	8.0	1.7	0.78
HOSPITAL SEPARATIONS FOR LIVER DISEASE	89	14.4	1.6	934	23.6	1.6	0.00
Liver separations from total sep (%)		16.0			29.8		0.00
- Liver disease inpatient	39	6.3	1.9	176	4.4	1.8	0.051
- Liver disease day admissions	56	9.1	1.2	815	20.6	1.4	0.00
- Liver disease inpatient non-primary	27	4.4	2.3	177	4.5	1.7	0.98

Significantly higher proportions of hospitalizations and day admissions were among FN females than males. Thus, 72% of all hospitalizations of FN CHC persons were among females and only 28% of all hospitalizations were among FN males (Table 7.2). Similarly, 67% of all FN day admissions were female admissions. Conversely, 44% of all day admissions among non-FN CHC patients were female admissions; and just slightly more than one half (51.5%) of all non-FN hospitalizations were among non-FN females.

Conditions related to pregnancy, childbirth, and the postpartum period were by far the most common reasons for both hospitalizations and day admissions, totaling almost 1/3 of all inpatient and day admissions among females (Table 7.2). Thus, 45% of hospitalizations and 29% of day admissions amongst FN females with CHC were due to these reasons. Among non-FN females, 34% of all hospitalizations and 17% of day admissions were also due to complications during pregnancy, childbirth, and postpartum period.

When these conditions were removed from the analysis, the most common reasons for hospitalizations were injury and poisoning, digestive diseases, and mental illness (Table 7.3 and Figure 7.1). For day admissions, the three most common reasons were infectious and parasitic diseases (non-FN), symptoms and conditions influencing health status, digestive diseases, and genitourinary diseases (FN). Mental illness, while being one of the most common reasons for hospitalizations, was the least common reason for day admissions. Conversely, while infectious and parasitic diseases were among the most common reasons for the day admissions, they were relatively infrequent causes for hospitalizations among CHC patients (Table 7.3)

Table 7.2 Reasons for hospitalizations and day admissions among CHC patients

	HOSPITALIZATIONS						DAY ADMISSIONS						TOTAL		
	FN (N=2860)			non-FN (N=10406)			FN (N=723)			non-FN (N=6252)			N=20241		
Conditions	n	%	#	N	%	#	n	%	#	n	%	#	n	%	#
Females	2051	71.7		5355	51.5		484	66.9		2754	44.0		10406	51.4	
Pregnancy	922	45.0	1	1844	34.4	1	139	28.7	1	468	17.0	2	3373	32.4	1
Mental Dx	356	12.4	4	2142	20.6	2	0	0.0	14	44	0.7	14	2542	12.6	2
Digestive Dx	358	12.5	3	1076	10.3	4	99	13.7	2	951	15.2	3	2484	12.3	3
Injury & poisoning	435	15.2	2	1438	13.8	3	52	7.2	6	270	4.3	11	2195	10.8	4
Infections	72	2.5	8	276	2.7	12	58	8.0	5	1074	17.2	1	1480	7.3	5
Health status	71	2.5	9	343	3.3	10	95	13.1	3	561	9.0	4	1070	5.3	6
Genitourinary Dx	109	3.8	6	430	4.1	7	76	10.5	4	452	7.2	5	1067	5.3	7
Respiratory Dx	155	5.4	5	572	5.5	5	32	4.4	9	159	2.5	13	918	4.5	8
Cardiovascular	56	2.0	11	528	5.1	6	13	1.8	13	285	4.6	9	882	4.4	9
Musculoskeletal	43	1.5	12	395	3.8	9	45	6.2	7	389	6.2	7	872	4.3	10
Symptoms	86	3.0	7	406	3.9	8	20	2.8	11	249	4.0	12	761	3.8	11
Skin	66	2.3	10	327	3.1	11	34	4.7	8	276	4.4	10	703	3.5	12
Neoplasms	21	0.7	14	248	2.4	13	22	3.0	10	409	6.5	6	700	3.5	13
Nervous system	27	0.9	13	125	1.2	14	19	2.6	12	310	5.0	8	481	2.4	14
*Other	83	2.9		256	2.5		19	2.6		355	5.7		713	3.5	

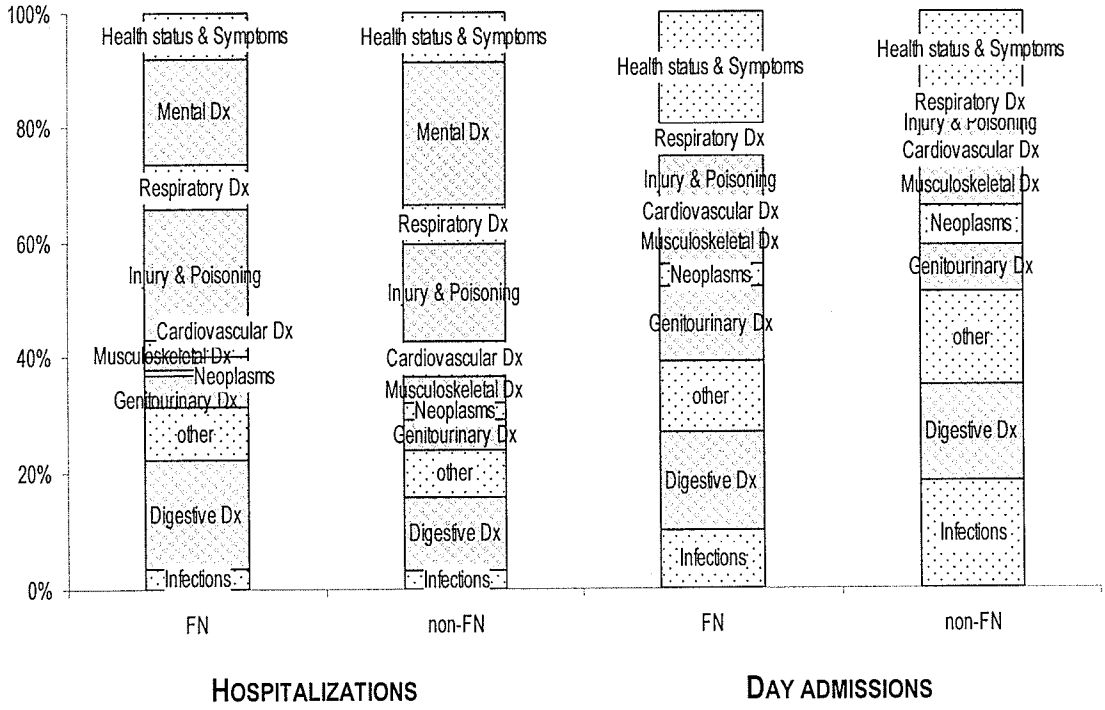
**Other includes endocrine and metabolic conditions, disorders of blood and blood forming organs, congenital anomalies.*

Table 7.3 Reasons for hospitalizations and day admissions among CHC patients without pregnancy-related conditions

	HOSPITALIZATIONS						DAY ADMISSIONS					
	FN (N=1938)			non-FN (N=8562)			FN (N=584)			non-FN (N=5784)		
	n	%	rank	N	%	rank	n	%	rank	n	%	rank
Injury & Poisoning	435	22.4	1	1438	16.8	2	52	8.9	5	270	4.7	8
Digestive diseases	358	18.5	2	1076	12.6	3	99	17.0	2	951	16.4	2
Mental diseases	356	18.4	3	2142	25.0	1	0	0		44	0.8	10
Health status & symptoms	157	8.1	4	749	8.7	4	115	19.7	1	810	14.0	3
Respiratory diseases	155	8.0	5	572	6.7	5	32	5.5	7	159	2.7	9
Genitourinary diseases	109	5.6	6	430	5.0	7	76	13.0	3	452	7.8	4
Infections & parasitic Dx	72	3.7	7	276	3.2	9	58	9.9	4	1074	18.6	1
Cardiovascular diseases	56	2.9	8	528	6.2	6	13	2.2	9	285	4.9	7
Musculoskeletal diseases	43	2.2	9	395	4.6	8	45	7.7	6	389	6.7	6
Neoplasms	21	1.1	10	248	2.9	10	22	3.8	8	409	7.1	5
*Other	176	9.1		708	8.3		72	12.3		941	16.2	

**Other includes endocrine and metabolic conditions, disorders of blood and blood forming organs, congenital anomalies, disorders of skin and subcutaneous tissues, and nervous system disorders, .*

Figure 7.1 Ten top reasons for hospitalizations and day admissions among CHC patients excluding pregnancy-related conditions



7.2 LIVER DISEASE-RELATED AMBULATORY VISITS

More than 99% of FN and almost 97% of non-FN persons with CHC had ambulatory physician visits (Table 7.4). A total of 63% of FN patients and 67% of non-FN patients with CHC had ambulatory visits due to liver disease, and non-FN persons had more such visits per person compared to FN persons (8.6 vs. 5.3 liver disease-related visits per person). Similarly, a higher proportion of non-FN CHC patients had physician visits for viral hepatitis compared to FN persons (56.4% vs. 48.3%, $p<0.0002$). Moreover, among those who had hepatitis-related visits, non-FN persons had an average of 7 visits per person while FN had an average of 4 visits due to viral hepatitis per person (Table 7.4).

Similar proportions of FN and non-FN patients with chronic hepatitis C had physician visits due to their chronic liver disease (15% vs. 14% respectively, p<0.6). Likewise, 3.2% of non-FN CHC patients and 2.8% of FN CHC patients had ambulatory physician visits due to progressive liver disease and liver cancer. Interestingly, 39% and 41% of FN and non-FN persons respectively with CHC had visits for other liver diseases (Table 7.4). Overall, while a large number of patients did have liver disease-related hospital admissions and physician visits, it was not the largest part of the overall health care use by persons with CHC. Liver disease-related hospitalizations comprised only 4% of all hospitalizations among FN persons and 3.5% of hospitalizations among non-FN patients with CHC. Likewise, liver disease-related physician visits totaled only 3% and 4% of all physician visits amongst FN and non-FN patients with CHC respectively (Table 7.5). On the other hand, 11% of all hospital day admissions among FN and 20% of all day admissions amongst non-FN CHC patients were due to liver disease (p=0.00) (Table 7.5).

Table 7.4 Ambulatory visits overall and for liver disease among persons with CHC

	FN (N=617)		NON-FN (N=3,962)		P
VARIABLE	**n**	**%**	**n**	**%**	
Physician visits total	613	99.4	3826	96.6	0.0003
Physician visits for liver disease	387	62.7	2669	67.4	0.03
Liver disease visits per person	5.3		8.6		
Physician visits for viral hepatitis	298	48.3	2233	56.4	0.0002
Visits for viral hepatitis per person	*3.9*		*7.1*		
Physician visits for liver cancer	2	0.3	29	0.7	0.04
Visits for HCC per person	*3.5*		*4.5*		
Physician visits for chronic liver disease (CLD)	91	14.7	547	13.8	0.57
CLD visits per person	*2.8*		*3.3*		
Physician visits for sequelae of CLD	15	2.4	97	2.4	0.91
Sequelae of CLD visits per person	*2.7*		*2.8*		
Physician visits for other liver diseases	238	38.6	1636	41.3	0.22
other liver diseases visits per person	*2.3*		*2.7*		

Table 7.5 Proportion of health care hospitalizations, day admissions, and physician visits due to liver disease (from the totals)

Condition	HOSPITALIZATIONS					DAY ADMISSIONS					AMBULATORY VISITS				
	FN (N=1938)		non-FN (N=8562)		P	FN (N=584)		non-FN (N=5784)		P	FN (N=71537)		non-FN (N=641072)		P
	n	%	n	%		n	%	n	%		n	%	n	%	
Viral hepatitis	11	0.6	73	0.9	0.26	51	8.7	943	16.3	0.00	1216	1.7	16219	2.5	0.00
Liver cancer	3	0.2	23	0.3	0.51	0	0.0	2	0.0		7	0.01	135	0.02	0.06
Chronic liver disease	38	2.0	120	1.4	0.08	6	1.0	125	2.2	0.09	263	0.4	1882	0.3	0.001
Sequelae of CLD	17	0.9	61	0.7	0.54	6	1.0	58	1.0	0.87	47	0.1	303	0.05	0.04
Other liver disease	7	0.4	19	0.2	0.39	2	0.3	8	0.1	0.52	575	0.8	4601	0.7	0.01
Subtotal liver disease	*62*	*3.2*	*200*	*2.3*	*0.00*	*14*	*2.4*	*191*	*3.3*	*0.29*	*885*	1.2	*6786*	1.1	*0.00*
TOTAL	76	3.9	296	3.5	0.35	65	11.1	1136	19.6	0.00	2108	2.9	23140	3.6	0.00

7.3 LIVER DISEASE-RELATED DIAGNOSTIC AND TREAMENT PROCEDURES

Various liver disease-related procedures were performed when individuals were admitted to a hospital either as inpatients (with at least one overnight stay) or for the day admissions. No such procedures were done on an outpatient basis (or at least none were listed in the outpatient hospital abstracts - as mentioned earlier, over 40% of outpatient abstracts had no diagnostic or procedure information). The list of diagnostic and treatment procedures for viral hepatitis and liver disease from both hospital discharge data (coded according to ICD-9-CM) and physician claims (tariff codes) is presented in Table 7.6.

While there were many physician claims for such procedures as liver biopsy, paracentesis, treatment of varices, diagnostic endoscopies, etc., none of these are

ambulatory office procedures and consequently, these claims had corresponding claims from the hospital for inpatient day visits. Thus, the physician tariff claims were used to determine liver-disease-related and non-liver visits, but were not used in calculating the rates of the procedures.

All the procedures were performed during admissions classified as "liver-related admissions" as described earlier, because the most responsible diagnosis and the main procedure listed in the hospital abstracts were related to liver disease. Therefore, the rates for the most commonly performed liver procedures were calculated per 1000 hospital liver-disease related visits with the exclusion of outpatient visits from the totals.

Liver biopsy was the most common diagnostic procedure performed on CHC patients. There was a significant difference in the proportion of persons who had undergone this procedure depending on their FN status. Only 9% of FN compared to 23.5% of non-FN persons had undergone liver biopsy (Table 7.7). The rate of liver biopsy per 1000 liver disease-related hospitalizations and day visits was 534 for FN and 827 for non-FN CHC patients (Table 7.7).

Table 7.6 Codes of the liver disease-related diagnostic and treatment procedures

PROCEDURE	ICD-9-CM CODE	PHYSICIAN TARIFF
LIVER BIOPSY		
Closed (percutaneous) [needle] biopsy of liver	5011	3456
Transjugular liver biopsy	5013	3458
Laparoscopic liver biopsy	5014	
TREATMENT OF PORTAL HYPERTENSION		
Intra-abdominal venous shunt (porto-caval, mesocaval, etc.)	391	2538
T.I.P.S (Transjugular intra-hepatic portosystemic shunt)		7264
TREATMENT OF ASCITES		
Paracentesis (percutaneous abdominal drainage)	5491	
Abdominal paracentesis, initial / subsequent		3588/3590
TREATMENT OF ESOPHAGEAL VARICES		
Control of esophageal bleeding by endoscope, injection of esophageal varices by endoscope	4233	3065
Ligation of esophageal varices	4291	3004
HCC RELATED PROCEDURES		
Partial hepatectomy	5022	3464
Lobectomy of liver	503	3492, 3494
Open ablation of liver lesion or tissue	5023	
Percutaneous ablation of liver lesion or tissue	5024	
Laparoscopic ablation of liver lesion or tissue	5025	
Other and unspecified ablation of liver lesion or tissue	5026	
Other destruction of lesion of liver (cauterization, enucleation)	5029	
Other injection of therapeutic substance into liver	5094	3030
Radiofrequency ablation of liver tumor		3496, 3497
DIAGNOSTIC ENDOSCOPY		
Esophagoscopy, diagnostic	4223	3055
Gastroscopy, diagnostic (without or with biopsy)	4413, 4414	3121
Esophagogastroduodenoscopy (EGD) (without or with biopsy)	4513, 4516	3123
DIAGNOSTIC IMAGING		
C.A.T. scan of abdomen/biliary tract scan	8801	9966
Liver scan and radioisotope function study	9202	9925
Liver and spleen scan		9967
Dynamic liver scan		9968
Abdominal MRI	8897*	7510- 7512
Diagnostic ultrasound of abdomen and digestive system	8876, 8874	7310
Endoscopic ultrasound with biliary examination		3022

Note: ICD-9 codes for liver transplant not included here as this is not done in Manitoba
**88.97 include all of the following: magnetic resonance imaging of other and unspecified sites: abdomen, eye orbit, face, neck*

Ascites was present in 3% of FN and 2.5% of non-FN persons with CHC ($p<0.6$). Ascites was treated with paracentesis in 67% of FN and 79% of non-FN persons. Paracentesis was performed slightly more often in non-FN persons than in FN, with the mean number of the treatments of 2.5 per non-FN person with ascites compared to 1.6 procedures per FN person with ascites. The rates of paracentesis were similar for FN and non-FN persons (161.0 and 152.4 procedures per 1000 liver-related hospital visits).

Fewer than 2% of persons with CHC had esophageal varices, and 78% of FN and 83% non-FN persons with this condition had haemostatic treatment to control the bleeding. Persons who underwent such treatment had on average 2.1 (FN) and 2.7 (non-FN) procedures (injection, ligation, or banding of esophageal varices). As with paracentesis, the rates of endoscopic treatment of esophageal varices were similar for FN and non-FN CHC persons, with 127.1 and 114.7 procedures per 1000 liver-related hospital visits respectively.

There were only 2 cases of HCC in FN persons with CHC, and they did not receive any related procedures for it. Among non-FN persons with CHC, 1.2% had HCC, and 22% of them had either surgical resection or ablative therapy for the lesions.

There were no differences in the proportion of persons receiving diagnostic imaging and endoscopic procedures. Thus, 10% FN and 11% of non-FN individuals with CHC had diagnostic EGD, 4.5% had abdominal/liver CT/MRI scan, and 2% had abdominal ultrasound (Table 7.7). However, the rates of these procedures per 1000 liver disease-

related hospital visits were higher among FN compared to non-FN persons. Thus, rate ratios ranged from 1.2 for abdominal US to 1.5 for diagnostic EGD to 1.9 for abdominal/liver scan to 2.2 for diagnostic ES (Table 7.7).

Table 7.7 Diagnostic and treatment procedures among patients with CHC (Proportion of persons with the condition and percent of persons with the condition who got the procedure)

	FN					NON-FN						
Procedure	**Persons**		**Visits**			**Persons**		**Visits**				
				mean					mean			Rate
	n	**%**	**#**	**per pt**	**Rate**	**n**	**%**	**#**	**per pt**	**Rate**	**P**	**Ratio**
LIVER BIOPSY	57	9.2	63	1.1	533.9	932	23.5	1031	1.1	826.8	0	0.6
PORTAL HYPERTENSION	32	5.2				198	5.0				0.58	
Portocaval shunt or TIPS	0					7	0.2	7	1.0	5.6		
% treated		0				3.5						
ASCITES	18	2.9				98	2.5				0.61	
Paracentesis	12	1.9	19	1.6	161.0	77	1.9	190	2.5	152.4		1.1
% with procedure		66.7				78.6						
ESOPHAGEAL VARICES	9	1.5				64	1.6				0.91	
Injection, ligation, banding of varices	7	1.1	15	2.1	127.1	53	1.3	143	2.7	114.7		1.1
% treated		77.8				82.8						
HEPATOCELLULAR CARCINOMA	2	0.3				46	1.2					
Lesion excision, injection, ablation	0					10	0.3	10	1.0	8.0		
% treated		0					21.7					
DIAGNOSTIC ENDOSCOPY												
Diagnostic esophagoscopy	6	1.0	7	1.2	59.3	24	0.6	34	1.4	27.3	0.43	2.2
Diagnostic gastroscopy	8	1.3	9	1.1	76.3	94	2.4	165	1.8	132.3	0.12	0.6
Esophagogastroduodenoscopy	63	10.2	108	1.7	915.3	423	10.7	748	1.8	599.8	0.78	1.5
DIAGNOSTIC IMAGING												
Abdominal MRI	0					12	0.3	12	1.0	9.6		0.0
Abdominal/liver scan (CAT scan)	27	4.4	42	1.6	355.9	182	4.6	238	1.3	190.9	0.89	1.9
Abdominal ultrasound (US)	10	1.6	11	1.1	93.2	78	2.0	94	1.2	75.4	0.97	1.2

Interestingly, there were no differences in the use of diagnostic and treatment procedures between males and females with CHC. Only 10% of FN females and 8% of FN males undergone biopsy procedure compared to 24% of non-FN males and females each (Table 7.8). Nonetheless, the rate of liver biopsy per 1000 liver disease-related hospitalizations and day visits was 526 and 550 for FN females and males respectively vs. 822 and 826 for non-FN females and males (Table 7.10).

Ascites was present in 3.4% and 2.3% of FN females and males respectively; and 2.5% of non-FN females and males each. Non-FN males had an average of 2.9 paracenteses per person, while FN males were on the opposite end of the spectrum with 1.3 procedures per person, with FN and non-FN females in the middle with 1.8 and 1.6 treatments per person respectively. Similarly, non-FN males had the most treatments for esophageal varices - 3.2 per person. Non-FN females had 1.5 treatments per person, FN females and males had 2.0 and 2.3 haemostatic procedures respectively.

There were no differences in the proportion of persons receiving diagnostic imaging and endoscopic procedures. Thus, 10% FN and 11% of Diagnostic EGD received 10% of persons with CHC, FN and non-FN males and females alike (Table 7.10).

7.4 Pharmacological Treatment of chronic hepatitis C

Interferon was licensed for the treatment of CHC in 1996 in Canada. Since then, many patients with chronic hepatitis C have been treated within industry sponsored clinical

trials of various antiviral regimens, doses and forms of interferon (standard and later pegylated) and ribavirin. The database of prescriptions filled in the community pharmacies was not designed to capture this information, and the number of patients who had been treated for their CHC had to be interpreted accordingly.

IFNα as a single agent was used from 1996 to 1998. Combination therapy with IFN and ribavirin became available in 1998 and continued until 2002, when a new generation of treatment became available. Pegylated IFNα in combination with ribavirin is the current standard treatment of chronic hepatitis C and became available in Manitoba in May 2003 (thus being outside of the scope of this study).

During 1996-2002, of the two treatments - IFNα as a single agent and IFNα in combination with ribavirin, a total of 6% of individuals received treatment outside of clinical trials, 69% of them receiving combination therapy (Table 7.8). A significantly smaller proportion of FN individuals with CHC were treated – 2.3% vs. 6.9% of non-FN persons with CHC ($p<0.00002$). The length of treatment with the combination therapy appears to be similar between FN and non-FN individuals (7.6 vs. 8.5 prescriptions per person respectively). With the IFNα as the single agent the length of treatment seems to be significantly longer in non-FN individuals, with 5 refills per FN person treated and 9 refills for non-FN person treated. While FN patients stopped this type of treatment earlier, some non-FN individuals appear to have gone on to maintenance therapy with IFNα, as is evident from a maximum number of 70 refills for a single person (Table 7.8)

Table 7.8 Treatment of CHC

	FN N=617		non-FN N=3962			Total N=4579	
	n	%	N	%	P	n	%
No prescription drugs	11	1.8	255	6.4	0.0000	266	5.8
IFN + Ribavirin	9	1.5	180	4.5	0.0005	189	4.1
# of prescriptions	68		1538			1606	
refills per person (max)	7.6 (21)		8.5 (26)			8.5 (26)	
IFN α2B	5	0.8	64	1.6	0.18	69	1.5
# of prescriptions	24		585			609	
refills per person (max)	4.8 (10)		9.1 (70)			8.8 (70)	
IFN α2A	0		28	0.7		28	0.6
# of prescriptions			190			190	
refills per person (max)			6.8 (23)			6.8 (23)	
Peg IFN α2B	0		1	0.03		1	0.02
# of prescriptions			18			18	
refills per person (max)			18 (18)			18 (18)	
Total Treated	14	2.3	273	6.9	0.00002	287	6.3
# of prescriptions	92		2331			2423	
refills per person (max)	6.6 (21)		8.5 (70)			8.4 (70)	

A total of 6% of individuals received treatment, 69% of them received combination therapy (Table 7.9). A significantly smaller proportion of FN individuals with CHC got treated – 2.3% vs. 6.9% of non-FN persons with CHC ($p<0.00002$). The length of treatment with the combination therapy appears to be similar between FN and non-FN individuals (7.6 vs. 8.5 prescriptions per person respectively). With the IFN as a single agent the length of treatment seems to be significantly longer in non-FN individuals, with 5 refills per FN person treated and 9 refills for non-FN individual treated. While FN patients stopped this type of treatment earlier, some of non-FN individuals appear to go on to a maintenance therapy with IFN, as evident from a max number of 70 refills in a single person (Table 7.9)

A higher proportion of males than females did not have any prescription drug during the study period. Thus, 8% of non-FN males compared to 3.4% of non-FN females ($p<0.000$) as well as 3.4% of FN males vs. 0.6% of FN females ($p<0.02$) did not have any prescription filled in the community pharmacy (Table 7.10). There was no sex difference in the proportion of treated cases among non-FN CHC persons, with 6.6% of females and 7% of males being treated for their CHC (Table 7.10). Among the FN persons with CHC, 3.4% of females and only 0.8% of males received antiviral treatment, but that was not statistically significant due to small numbers ($p<0.06$).

Table 7.9 Treatment of CHC by sex, FN vs. non-FN

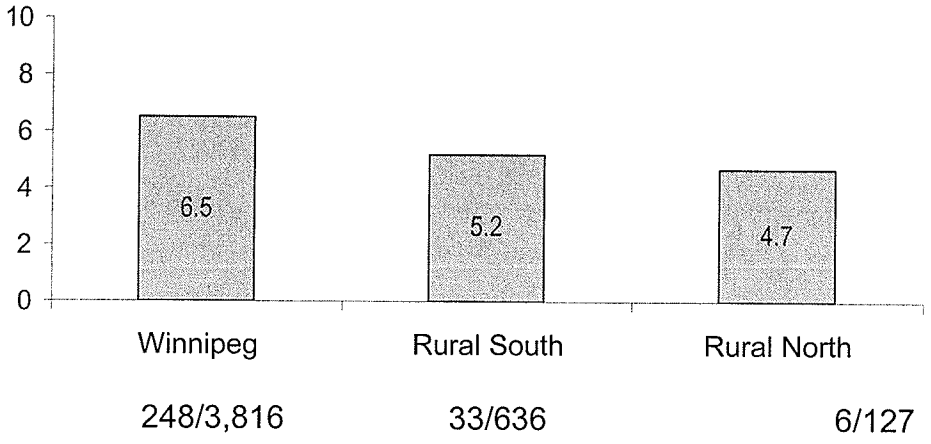
	FN				non-FN			
	Females N=355		Males N=262		Females N=1,414		Males N=2,548	
	N	%	N	%	n	%	n	%
No prescription drugs	2	0.6	9	3.4	48	3.4	207	8.1
IFN + Ribavirin	8	2.3	1	0.4	64	4.5	116	4.6
# of prescriptions	64		4		462		1,076	
refills per person (max)	8 (21)		4 (4)		7.2 (20)		9.3 (26)	
IFN α2B	4	1.1	1	0.4	20	1.4	44	1.7
# of prescriptions	22		2		145		440	
refills per person (max)	5.5 (10)		2 (2)		7.3 (28)		10 (70)	
IFN α2A	0		0		10	0.7	18	0.7
# of prescriptions					60		130	
refills per person (max)					6 (13)		7.2 (23)	
Peg IFN α2B	0		0		0		1	0
# of prescriptions							18	
refills per person (max)							18 (18)	
Treatment total	12	3.4	2	0.8	94	6.6	179	7.0
# of prescriptions	86		6		667		1,664	
refills per person (max)	7.2 (21)		3 (4)		7.1 (20)		9.3 (70)	

As expected, the majority of treated patients were from the urban centre (86%), with only 2% of treated persons coming from Northern Manitoba. However, the relative frequency

of treatment was not very different in the three areas (Figure 7.1). The proportion of treated CHC patients from Winnipeg (6.5%) was not statistically different from the proportions of southern rural (5.2%) and northern rural (4.7%) residents who received treatment for their CHC ($p>0.2$).

Figure 7.1 Proportion of persons receiving treatment for CHC by residence

(% of persons who had prescriptions for antivirals from the total numbers of persons with CHC from each residence)



7.5 SUMMARY

- Persons with CHC use health care resources extensively
- Diagnostic and treatment procedures (except for liver biopsy) were used with the similar frequency for FN and non-FN CHC patients, as well as males and females in these two groups
- Treatment for hepatitis C appears to be quite low and even more so among FN persons

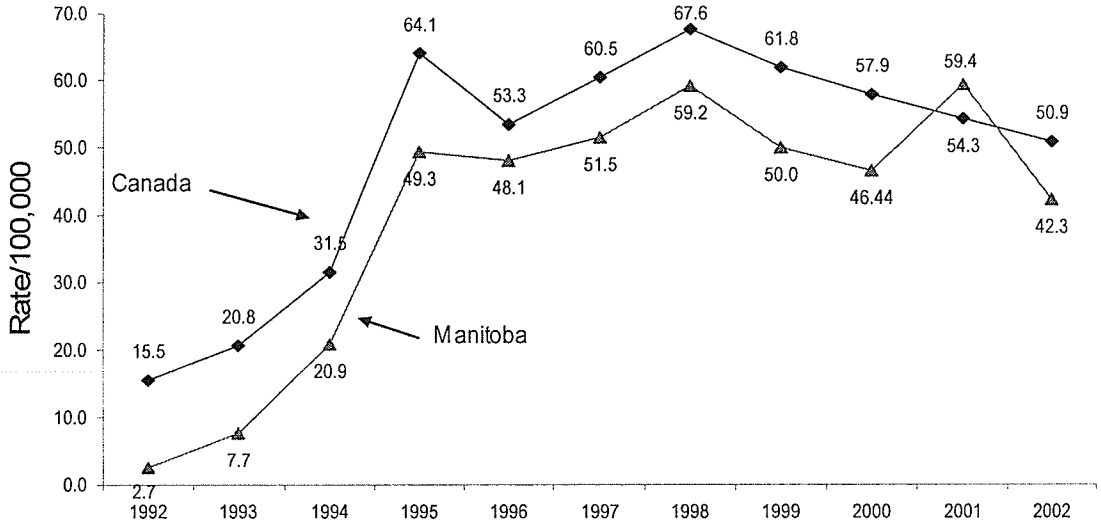
Table 7.10 Diagnostic and treatment procedures among patients with CHC, males vs. females

Procedure	FN										NON_FN									
	Females					Males					Females					Males				
	persons		visits			persons		visits			persons		visits			persons		visits		
	n	%	#	per pt	Rate	n	%	#	per pt	Rate	Rate Ratio	n	%	#	per pt	Rate	n	%	#	per pt	Rate	Rate Ratio
Cirrhosis	21	5.9				13	5.0					80	5.7				153	6.0				
Decompensation	18	5.1				10	3.8					59	4.2				119	4.7				
Portal hypertension	19	5.4				13	5.0					64	4.5				134	5.3				
Liver biopsy total	37	10.4	41	1.1	525.6	20	7.6	22	1.1	550	1.0	333	23.6	352	1.1	822.4	599	23.5	679	1.1	826.0	1.0
Portal hypertension	19	5.4				13	5.0					64	4.5				134	5.3			0.0	
Shunt or TIPS	0					0						1	0.1	1	1.0	2.3	6	0.2	6	1.0	7.3	
% treated													1.6					4.5			0.0	
Ascites	12	3.4				6	2.3					35	2.5			0.0	63	2.5				
Paracentesis	8	2.3	14	1.8	179.5	4	1.5	5	1.3	125	1.4	25	1.8	39	1.6	91.1	52	2.0	151	2.9	183.7	0.5
% with procedure		66.7					66.7						71.4			0.0		82.5				
Esophageal varices	5	1.4			0.0	4	1.5			0		18	1.3			0.0	46	1.8			0.0	
Tx of varices	4	1.1	8	2.0	102.6	3	1.1	7	2.3	175	0.6	15	1.1	23	1.5	53.7	38	1.5	120	3.2	146.0	0.4
% treated		80.0			0.0		80.0			0			83.3			0.0		82.6			0.0	
HCC	2	0.6				0						14	1.0			0.0	32	1.3			0.0	
HCC Tx	0											1	0.1	1		2.3	9	0.4	9	1.0	10.9	
% treated													7.1			0.0		28.1			0.0	
Dix endoscopy																						
Esophagoscopy	3	0.8	4	1.3	51.3	3	1.1	3	1.0	75	0.7	11	0.8	16	1.5	37.4	13	0.5	18	1.4	21.9	1.7
Gastroscopy	6	1.7	7	1.2	89.7	2	0.8	2	1.0	50	1.8	38	2.7	68	1.8	158.9	56	2.2	97	1.7	118.0	1.3
Diagnostic EGD	35	9.9	65	1.9	833.3	28	10.7	43	1.5	1075	0.8	154	10.9	285	1.9	665.9	269	10.6	463	1.7	563.3	1.2
Dx imaging																						
Abdominal MRI	0				0.0	0						5	0.4	5		11.7	7	0.3	7	1.0	8.5	1.4
Liver scan	17	4.8	29	1.7	371.8	9	3.4	13	1.4	325	1.1	74	5.2	103	1.4	240.7	108	4.2	135	1.3	164.2	1.5
Abdominal US	8	2.3	9	1.1	115.4	2	0.8	2	1.0	50	2.3	37	2.6	45	1.2	105.1	41	1.6	49	1.2	59.6	1.8

8.1 EPIDEMIOLOGY OF HCV INFECTION IN MANITOBA.

The present study revealed several important features of HCV infection in Manitoba. The incidence of newly diagnosed cases during 1991-2002 was very consistent with the national trends reported by the Public Health Agency of Canada *(Disease Surveillance, Notifiable Diseases On-Line).* Thus, the number of reported cases steadily increased since 1992 reaching the highest incidence of 67.6 per 100,000 population nationally and 59.2 per 100,000 population in Manitoba in 1998. That rise was mainly due to the recognition of previously acquired infection[78]. Between 1999 and 2002, the incidence of newly reported hepatitis C decreased 25% to 50.9 per 100,000 in Canada and, with the exception of 2001, decreased 28% to 42.3 cases per 100,000 population in Manitoba (Figure 8.1).

Figure 8.1 Time trend in annual reporting of hepatitis C, Canada and Manitoba, 1992-2002



Source: PHAC, Disease Surveillance, Notifiable Diseases On-Line[78]

This trend reflects the development of laboratory assays for HCV and time lag needed for broad recognition of hepatitis C by health care providers. Thus, since the time the HCV was discovered (1989) and the first generation immunoassay become available (1991), the testing and the number of positive cases slowly increased. In 1995, when the third generation immunoassay and qualitative tests for HCV-RNA became licensed, the testing increased drastically, and the incidence of the newly reported cases more than doubled compared with the previous year (Figure 8.1). On the level of a broader medical community, the guidelines for HCV testing were developed, outlining important features of natural history, transmission patterns, and risk groups for acquiring HCV. The decrease in the incidence of reported cases continued beyond 2002 (to 45.0 and 44.7 cases per 100,000 population in Canada and 38.8 and 38.2 cases per 100,000 population in Manitoba in 2003 and 2004 respectively) because, according to the latest 2007 Canadian consensus guidelines on Management of chronic hepatitis C, the majority of estimated cases of HCV infection in Canada - approximately 65% - had been identified[77]. The data from Dawood et al. confirm this statement. The volume of testing for HCV in Manitoba more than quadrupled between 1995 and 2003, yet this did not translate into increase in the incidence of positive cases, with the numbers ranging between 530 and 690 HCV-positive cases per year[141]. If anything, the increase in the testing resulted in the decrease of the percent of HCV-positive samples. The part of this increase in testing is due to repeat tests among those who is on treatment or had been treated, but, as this work shows, such numbers account only for a small minority of tests and the increase do represent a true increase in the number of tested individuals.

The present work showed a significantly higher incidence of HCV infection among FN Manitobans compared to their non-FN counterparts. This is similar to the data reported from the other provinces in Canada and in the USA. In the three Prairie Provinces, incidence of the newly diagnosed HCV cases among FN populations was on average 2.5 times, 2.7 times, and 4 times the incidence of HCV infection among non-FN populations in Manitoba (1991-2002), Saskatchewan (1995-1998), and Alberta (1998-2001) respectively[137-139]. Similar results are reported by Wu et al. in their study of newly acquired HCV infection and acute hepatitis. The analysis of data collected by the Enhanced Hepatitis Strain Surveillance System (EHSSS) during 1999-2004 showed that the incidence of newly acquired HCV infection was 6.7 times higher in Aboriginal than in non-Aboriginal Canadians (18.9 vs. 2.8 cases per 100,000 population respectively)[88]. The reasons for such significant difference in rates of hepatitis C between FN and non-FN populations could be (1) that FN populations are tested in a disproportionally high numbers compared to non-FN populations, resulting in the inflated rates or (2) that the rates of HCV infection are truly higher in this population. Although there are no data available to confirm or disprove the former (that would require to know the actual numbers of unique samples submitted for testing from FN and non-FN individuals), it seems unlikely that the high rates of hepatitis C in FN population are just the result of increased case finding. The two principal reasons for HCV testing are clinical (when the person has symptoms or biochemical profile consistent with hepatitis C) or if the person belongs to a so-called "high risk" group for HCV infection. The other reasons comprise a small proportion of those tested. Indeed, the data from a small sample (~5%) of persons with CHC reported to MB Health who completed an interview by a public health nurse

and listed reasons for testing revealed that 27% of FN and 32% of non-FN persons had clinical reasons for testing, 50% of FN and 35% of non-FN had risk factors, 6% and 10% respectively were requested by patient, with the remaining 17% and 23% being blood donation, needle stick injury and unspecified. In a sample of 413 CHC persons from Alberta in 1998 the reasons for testing were reported as symptomatic - 16% of patients; ordered by physician (presumably related to risk factors and/or clinical reasons) - 27% of cases, and in 30% it was patient's request, the remaining unspecified or unknown[99]. Thus, even if we assume increased testing of FN persons, it does not seem to be caused by more liver disease, for we'd expect the proportion of persons with decompensated disease to be higher in FN vs. non-FN, which is not the case based on the results of the current study. Rather it is likely to be due to the higher prevalence of risk factors among FN populations, which, in turn, would explain the higher rates of infection among FN persons by an increased "opportunity" to be infected. Hence the second explanation seems likely to be true.

Indeed, it is well documented that FN populations have a higher prevalence of risk factors associated with the transmission of HCV compared to non-FN populations. Certain populations have specific risks associated with bloodborne pathogen acquisition (including HCV) as a result of behaviour, lifestyle or occupation, such as illicit drug users, health care workers, or recipients of tainted blood[83,103,155-159]. The single most important population at risk for acquiring the hepatitis C virus (not counting those who acquired the disease via transfusions of infected blood or blood products prior to the screening of donated blood for HCV becoming standard procedure) are those injection

drug users[143-145,155-156,210-216]. Injection drug use is prevalent among prison inmates, street-connected people, those of low socioeconomic status, socially disadvantaged individuals, etc.[143-145,155-159]. In this context, sharing drug injecting equipment, which provides an opportunity for contracting hepatitis C, is very likely. And it is also well documented that all the aforementioned factors place a disproportionately heavy burden upon Canadian Aboriginals, and First Nations in particular, as described in the background section of this work. High rates of involvement in injection drug use among Aboriginal youth are well-documented[143-146,149,155-159]. In a study of risk behaviour among Aboriginal youth in seven Canadian cities, 21% of 15-24 year olds reported injecting drugs[211]. In various studies of IDU and street-connected people, Aboriginal clients are represented in disproportionately high numbers in the study populations relative to their population size[142,147,148,155]. In the *AT-Risk Youth Study*, 27% of youth who injected drugs were anti-HCV positive compared to only 1.4% among those who did not use injection drugs[156]. As many as 40-50% of drug users report sharing needles (both lending and borrowing), thus effectively propagating the infection among the IDU community[149,156]. In addition, participating in traditional rituals such as skin cutting, tattooing, and body piercing with shared instruments, sharing drug snorting paraphernalia, sexual activity with multiple partners, and household sharing of items of personal hygiene are behaviors not uncommon in the FN populations (as they are not uncommon in other populations of similar risk) and pose an additional, although comparatively a much smaller, risk of hepatitis C transmission[212]. The high rate of migration of First Nation individuals between reserves and urban centers is well documented[16,150,154,163,210]. As many drug users are highly mobile, reside in hotels, shelters or are homeless, and move in and out of

reserves, for as long as this situation persists the reservoir of HCV infection in FN populations will not only persist but might also bring infection into previously unaffected communities[210]. Because sharing of drug equipment (or participating in skin-cutting rituals) happens mostly within communities of shared ethnicity, an individual who belongs to an FN community has a higher chance to acquiring HCV within a smaller population of FN persons than a non-FN individual. Another factor which may contribute to the increased incidence of HCV infection among FN populations is an apparent widespread lack of awareness about hepatitis C transmission, an issue which is both pointed out by Aboriginal leaders and found in several studies. Where there is no understanding of the risks for HCV acquisition, there can be no efforts on the part of an individual to prevent the infection. For instance, the *WIDE* Study found that while almost 80% of participants reported having been tested for HIV at least once, only 45% reported having been tested for HCV and 36% for HBV, highlighting a relative lack of awareness or a perceived low priority regarding viral hepatitis B and C in this segment of the population, of which many members were Aboriginal[149]. Hepatitis C is a lower priority for many members of "high risk" groups (street–involved, homeless, etc), who are faced with such immediate problems as getting food, clothing or shelter, as was found while conducting needs assessments within hepatitis C program evaluation in Manitoba[164]. These are the groups which would benefit from education about hepatitis C the most, but these are also the very groups which are most likely disconnected socially and do not have any regular contact with the health care system, making education about HCV infection problematic. Consequently, they might not perceive a risk of HCV for themselves or others. It is particularly important to educate Aboriginal youth before they

become involved in high risk activities and may become infected, since as demonstrated by Roy et al., the first 4 years after injection is initiated pose the greatest risk of contracting HCV infection[213].

The present study also demonstrated that the majority of FN persons with HCV infection are females (60% of cases in Manitoba), which is the opposite of the gender distribution of HCV infection described in the literature and noted in the non-FN populations (fewer than 40% females). Also, FN persons with HCV were significantly younger than non-FN individuals. The most likely reason for such epidemiology is the earlier involvement in high risk activities, and also the predominance of FN females of younger age among IDU populations. For instance, the aforementioned *WIDE* study found a clear trend towards young drug users being females. Thus, 41% of Aboriginal females vs. 25% of males in this study were under the age of 30 years, with the overall proportion of Aboriginal females in the study's IDU cohort of being 52%[149]. As reported by Callaghan et al., among Canadian Aboriginal individuals admitted to the inpatient substance abuse detoxification programme in Prince George, BC, females were younger than males and received proportionately higher rates of cocaine and opiate detoxification diagnoses, the proportion being the highest among females 18-25 years of age. The same study found that a much higher proportion of female detoxification clients reported having hepatitis C as compared to male clients (29% vs. 21% respectively)[214]. Others reported greater stress, more medical problems, and greater addiction severity in females entering addiction treatment than in males. In *the Cedar Project* from British Columbia, a community-based cohort of IDU and/or non-injection street drug users included young

Aboriginal women between the ages 14 and 30, 65% of which used drugs and the duration of injecting was between 0.1 and 13(!) years, pointing to a very early age of involvement in IDU among at least some Aboriginal females[215]. The same project specifically studied gender differences in HIV and hepatitis C related vulnerabilities among Aboriginal young people who use street drugs and found that the proportions of individuals positive for HIV and HCV were significantly higher among young Aboriginal women. The proportion of HIV-positive individuals was 13.1% in women as compared to 4.3% in men, and the proportion of HCV-infected individuals was 43.6% in women as compared to 25.4% in men. Restricting analysis to young injection drug users resulted in the same trend that the proportions HIV-positive and HCV-positive were significantly higher among Aboriginal females[216].

Similar findings were reported in Australia. A number of studies of Aboriginal communities found that the involvement in injection drug use was increasing among Australian Aboriginal people, particularly among females. In the US, it was reported that 3% of American Indian women screened during routine pre-natal care were anti-HCV-positive. All these various findings together points to a two distinctive features of the epidemiology of HCV infection in Aboriginal populations in general and among Canadian FN populations in particular, namely: (1) that the majority of HCV-infected individuals are females, and (2) that this population of HCV-infected persons is much younger than what is reported in general literature about HCV infection.

8.2 The Natural history of chronic hepatitis C infection in FN and non-FN populations

Two interesting features emerged from among the findings of the present study: that the clinical manifestations (e.g. decompensated disease) of hepatitis C were remarkably similar between (a) FN and non-FN persons, as well as between (b) males and females. With regard to the former, 5.7% of FN and 5.5% of non-FN patients had portal hypertension, and 5% in each group had decompensated liver disease. Also, 17.3% of FN and 19% of non-FN patients had records with the diagnostic code "*571- Chronic liver disease and cirrhosis*". HCC was diagnosed in 0.4% of FN and 1.3% of non-FN persons. As was pointed out in the literature review section, the estimates of the CHC progression depend on the type of study cited: population samples tend to have lower rates of cirrhosis and decompensated disease as opposed to the studies from tertiary care centers where HCV-infected individuals have already established disease. The present study includes a heterogeneous cohort of CHC patients who had been investigated for HCV infection primarily due to either clinical or risk behavior reasons. Hence, the results of the present study lie somewhere between those reported by Gordon et al.[175] (persons with established chronic hepatitis C) and Niderau et al.[217] (HCV-RNA positive persons referred for therapy) with 37% and 17% of respective study patients having cirrhosis and 4% and 1.6% developing HCC, and the results reported in the UK in the cohort of 684 recipients of tainted blood found via "look back" programme reported by Brant et al.[218]. In this cohort, severe liver disease was present in 3.2% of cases with liver biopsy (less than half of this cohort), revealing cirrhosis in 7.5% of cases. Also, ascites and

esophageal varices were fairly infrequent at 0.7% and 0.6% respectively, and there were no cases of HCC.

To date, there is no literature available on the course of hepatitis C infection among Canadian FN populations, and therefore no prior findings with which the results of this study could be directly correlated. However, some evidence can be found to support the similarities in clinical features of CHC between FN and non-FN populations. Thus, Cooper et al. studied the outcomes of treatment of CHC in Aboriginal and non-Aboriginal patients for the Canadian Pegasys Study Group. They found no differences in presenting status between the two groups (with the exception that the proportion of Aboriginal patients among those treated for CHC was too small)[219]. Liver biopsy was performed on 98% of Aboriginal and 85% of non-Aboriginal patients, and the fibrosis scores on the biopsy were the same for the two groups. Thus, 63% of Aboriginal and 60% of non-Aboriginal patients had mild fibrosis (Metavir fibrosis stage 0 to 2), 21% and 20% of Aboriginal and non-Aboriginal patients respectively had stage 3 fibrosis, and 12% of Aboriginal and 17% of non-Aboriginal patients had stage 4 fibrosis (cirrhosis of the liver). These findings support the results of the present study that the severity of CHC among FN and non-FN populations was similar.

One finding of the present study which was somewhat surprising is to find no differences in the clinical manifestations of CHC in FN and non-FN Manitobans. Considering that alcohol abuse was twice as common among FN persons with CHC (60%) as among non-FN persons with CHC (34%), and it is one of the major factors known to be associated

with the progression of CHC to cirrhosis, one would expect the severity of the disease would be at least somewhat different in the two groups. While it was not possible to directly assess the severity of the disease in the two groups, the indirect indicators, such as the proportion of those developing complications, e.g. cirrhosis-associated portal hypertension, variceal bleeding, ascites, and such conditions as spontaneous bacterial peritonitis, HCC, and so on, were compared and found to be present with the same frequencies in the two groups. Interestingly, the proportion of alcohol abusers who developed alcohol-induced liver disease was also the same among FN and non-FN persons with CHC (9.2% and 9.4% respectively). Moreover, decompensated liver disease also occurred with the same frequency in First Nations (9.2%) and non-First Nations (9.8%) excessive alcohol users. Poynard et al. in the prospective study of hepatitis C reported that daily alcohol consumption>50 g was independently associated with progression[196]. The fact that the proportion of FN CHC patients with an unfavorable prognostic factor (alcohol abuse) was doubled but the proportion of decompensated disease was the same points toward the possibility that CHC might have a somewhat milder course in FN patients as compared to their non-FN counterparts. Moreover, other factors with known potential to negatively affect the course of CHC, such as HIV confection and diabetes mellitus (due to insulin resistance), were also significantly more prevalent among FN patients. Hence, the high prevalence of prognostically unfavorable factors does not seem to be reflected in the progression of disease among FN CHC patients. The higher proportion of younger people among the FN CHC cohort may partially account for the similarities in the prevalence of decompensated cirrhosis. The role of age in the natural history of HCV infection is well researched and described in

numerous publications, as background information chapter of this study explicates. The older the age of HCV acquisition (after 40 yrs.) and the longer the duration of infection, the greater is the risk of developing cirrhosis and its complications. Since 79% of FN persons were diagnosed with CHC at the age younger than 40, while only 54% of non-FN persons were younger than 40 yrs. old at the time of their CHC diagnosis, and since the mean age of FN females was 32 years old vs. 37 for non-FN females respectively and the mean age of FN males was 34 years old vs. 39 for non-FN males respectively, fewer FN than non-FN CHC patients could be expected to develop cirrhosis and hepatic decompensation. Both older age and male gender are repeatedly found to be independently associated with the progression of CHC to cirrhosis[193]. Hence, the larger proportion of females (60%) among FN CHC patients as opposed to non-FN CHC patients (40%) would imply that fewer cases of cirrhosis and decompensated disease would be expected in the younger and female-predominant FN CHC cohort as compared to the older and male-predominant non-FN CHC cohort.

This brings us to the second point made in the beginning of this section – that the proportion of decompensated cirrhosis was the same among males and females, both in FN and non-FN cases. As the literature on the natural history of HCV infection illustrates, the course of infection is thought to be milder in women than in men. This study, however, demonstrated no significant difference in the proportion of CHC cases with decompensated liver disease between males and females. It appears that once cirrhosis develops, there are no gender differences in the progression towards the decompensated stage as manifested in ascites, esophageal varices, hepatic

encephalopathy, and the occurrence of HCC. The present study demonstrates that in persons who had been diagnosed with CHC, gender does not seem to influence the outcome of the disease, for females had the same frequency of complications as did males, with the exception of HCC. In the aforementioned study of the Aboriginal clients of an inpatient addiction treatment programme, a similar proportion of males (8%) and females (6%) had cirrhosis[214]. The results of this study are in contrast with those of Poynard et al., who reported the rates of progression to cirrhosis in men with risk factors to be 13 years and for women without risk factors to be 42 years, as well as with the two large cohort studies of pregnant women infected with HCV via contaminated Rh immunoglobulin (704 women in Ireland and 917 women in Germany), which found that chronic hepatitis C developed in 55% of women and only ~2% developed cirrhosis after 17 and 20 years of follow-up respectively[168-169]. On the other hand, Seeff et al. reported 15% of cirrhosis in patients with transfusion-associated hepatitis after 20 years of follow-up[177]. The results of the present study fall somewhere in between these two extremes. Here, similar proportions of males and females, both FN and non-FN, had evidence of cirrhosis and advanced liver disease with complications. Thus, 5.6% of FN females and 5.7% of FN males vs. 5% of non-FN females and 5.8% of non-FN males had portal hypertension, 6.1% and 5.7% of FN females and males respectively vs. 6.3% and 6.6% of non-FN females and males respectively had cirrhosis, and 5.1% and 4.7% of FN females and males respectively vs. 4.6% and 5.1% of non-FN females and males respectively had decompensated liver disease. It is possible, in theory, that the young age and female gender in the FN cohort (both favorable factors in the rate of the CHC progression to cirrhosis) are negated by the alcohol consumption, diabetes, HBV and HIV co-infection

(unfavorable factors), which resulted in the similar rates of the progression to cirrhosis and decompensated cirrhosis. However, alcohol abuse was as frequent among females as it was among males, both FN and non-FN, as was the frequency of HIV co-infection, while diabetes was only slightly more prevalent among females. Thus, the similar rates of progression of CHC to the decompensated stage require more detailed investigation.

When FN cases were compared to FN controls and non-FN cases were compared to non-FN controls, the odds of all conditions were higher among cases (those with hepatitis C) then they were among controls, both FN and non-FN. With respect to the relative increase in the odds, however, two situations were observed: (1) a similar increase in the odds for FN and non-FN cases relative to their corresponding controls, (2) a greater increase in the odds for non-FN cases vs. non-FN controls as compared to FN cases vs. FN controls. For example, the odds of alcohol-related liver disease were the same for FN cases relative to FN controls (2.75) as they were also for non-FN cases relative to non-FN controls (2.02). Similarly, the odds of having been co-infected with HIV were 30 for FN cases relative to FN controls and 29 for non-FN cases relative to non-FN controls. For the other conditions (such as cirrhosis and hepatic decompensation, or diabetes and alcohol abuse, etc.) the increases in the odds were much greater for non-FN cases. Such interaction between CHC and race was due to the increased prevalence of the above conditions among FN controls as compared to FN cases. It is well documented, and once again confirmed by the present study, that many diseases, such as diabetes, substance abuse, HIV/AIDS, viral hepatitis and many others are generally more prevalent in FN populations than in non-FN populations. Since the higher proportions of non-infected FN

individuals had such conditions compared to non-FN non-infected persons, the relative increase once the person was infected was smaller in FN vs. non-FN persons.

The present study also documented that the various forms of liver disease were more common among the FN population than among the non-FN general population represented by the sample of non-infected individuals. Thus, 2.1% of FN vs. 0.9% of non-FN controls had chronic liver disease (CLD) and cirrhosis, 0.5% of FN vs. 0.2% of non-FN controls had decompensated liver disease, and 3.1% of FN vs. 1.7% of non-FN controls had other liver disease. Conditions indicative of hepatic decompensation (ascites, esophageal varices, hepatic encephalopathy, etc.) were also at least twice as frequent among FN non-infected controls as compared to non-FN non-infected controls. Similarly, death from liver disease was far more common among FN than among non-FN uninfected persons. Thus, 15.4% of all hospital deaths among non-infected FN controls were from liver disease (as per the most responsible diagnosis) as compared to just over 3% among non-infected non-FN controls. These findings are in agreement with the well documented fact that the prevalence of chronic liver disease (CLD) in the North American indigenous populations far exceeds the prevalence of these conditions in the general population. In the US, liver disease is the 5th most common cause of deaths among American Indians/Alaska Natives (AI/AN) populations, while it is the 12th cause of mortality in the general population in the US and the 13th cause of death in Canada. As reported by Scott and Garland, the mortality from CLD in the general US population declined 4.5% in 1990-1998 while increasing 11% among the AI/AN[220]. Other researchers have consistently found that alcohol-induced liver disease was the major

cause of CLD and related mortality among AI/AN and Canadian FN[221-222]. Autoimmune hepatitis and NAFLD were also more common in the aboriginal North American populations in both the US and Canada[223]. The results of the present study confirmed that, indeed, CLD overall and various liver diseases (e.g. portal hypertension, alcohol-related liver disease, ascites, encephalopathy, esophageal varices, as explained in detail in chapter 5) except HCC were at least twice as common in FN persons not infected with HCV as they were in non-FN non-HCV infected persons.

The present study found excessive all cause mortality among persons with CHC, both FN and non-FN. Mortality rates were 24 cases per 1000 person/years among FN and 27 cases per 1000 person/years among non-FN cases. Case-to-control mortality rates ratios was 3.5 among FN and 4.2 among non-FN populations, possibly pointing towards a more detrimental effect of chronic hepatitis C on non-FN persons. Interestingly, the mortality patterns of males and females were very similar, with the female-to male mortality rates ratio of 0.8 for both FN and non-FN cases, and 0.7 and 0.9 for FN and non-FN controls respectively. A total of 7.5% of females and 9% of males with CHC died during the study period (the proportions were the same among FN and non-FN populations), while 2% of non-infected females and 2.3% of non-infected males died in the same period. Hence, the mortality of males and females with CHC is very similar and, as in the case of decompensated liver disease discussed earlier, there is no evidence that females had different outcomes as compared to males.

Since the cohort of FN cases was the smallest in size compared to non-FN cases as well as FN and non-FN controls, the relatively small number of deaths in this cohort resulted in unstable annual mortality rates, making reliable interpretation difficult. The annual mortality rates of non-FN cases ranged from 19.5 to 30.5 deaths per 1000 P/yrs. and were much higher than the total mortality rates of 8 deaths per 1000 residents reported in Manitoba in 1990-1999 by Martens et al.[224]. The annual mortality rates of non-FN controls ranged from 4.7 to 6.5 deaths per 1000 P/yrs., and the mortality rates of FN controls ranged from 5.4 to 8.2 deaths per 1000 P/yrs. This is somewhat lower than the aforementioned Manitoba mortality rate, although higher than mortality rates reported nationally (3.4 and 1.7 per 1000 populations among males and females). The lower all-cause mortality rates among the study's control populations, both FN and non-FN, are likely to be the result of the study demographics. Thus, the study population included only hepatitis C cases and demographically matched controls, and the age distribution of the study population differs from the age structure of the overall Manitoba population. While just under 60% of the study population were persons of 41 yrs. and older, 50% of the Manitoba's persons were of the same age, hence it was not unexpected that fewer deaths would occur in the control groups comprised of younger persons. Mortality among Manitobans with CHC was lower than the one reported by Brant [218](14.7%) or Serfaty et al.[225] (16%), but similar to the all-cause mortality (9%) reported by Fattovich et al.[182] in the cohort of persons with compensated cirrhosis. However, the comparisons here are only approximate since all of the mentioned studies had different periods of follow-up and none reported mortality rates, just the total percent of deaths among the study groups.

There were 246 in-hospital deaths during the study period, 169 of which occurred during liver-related hospitalizations, i.e. 68.7% of in-hospital deaths were liver disease-related. Similar results were reported in the US by Kim et al., who studied a 1995 inpatient sample of the Healthcare Cost and Utilization Project database that included data from over 900 hospitals in 19 states[226]. In that study, the proportion of in-hospital deaths during liver-related hospitalization was 66.6%. Seeff et al.[227] reported death from liver-related causes in 3.3% of persons with transfusion-associated hepatitis C after ~18 yrs. of follow-up, while Brant reported 1.2% of persons dying directly from liver disease and another 3.5% had liver disease as a contributing cause of death after more than 10 yrs. of follow-up. Although it is not possible to determine the exact proportion of persons who died as the result of their liver disease in the present study, the results seems to be quite similar despite a shorter follow-up. Thus, considering the diagnoses of those who died during hospitalization revealed that at least 1.3% of non-FN and 0.3% of FN CHC patients died from their liver disease. Moreover, when the most responsible diagnosis and the first primary diagnosis are combined, the proportion of those who died from liver-related causes increases to 2.3% of non-FN persons and 2.7% of FN persons with CHC. These results are also consistent with and fall between those reported by Koretz et al. [172] and Mattson et al. [173] with 1.3% and 1.6% of liver deaths respectively and those reported by Di Biscegle et al.[174] and Tremolada et al. [171] with 3.7% of liver deaths.

In the present study, FN patients who died in the hospital were much younger than their non-FN counterparts; the mean age at death was 47 yrs. for FN and 58 yrs. for non-FN persons. The latter figure is the same as the median age of in-hospital deaths reported by

Kim et al. (57 yrs.). The younger age at death among the FN populations is not a new observation. Martens et al. reported that during 1995-1999, FN Manitobans experienced an 8-year gap in life expectancy as compared to non-FN Manitobans, had double the premature mortality rate, and more than double potential years of life lost (PYLL)[228]. Numerous reports have shown that mortality is much higher in FN persons in Canada and in other indigenous minorities throughout the world. Death at a much younger age is one of the most dramatic representations of the health status disparity between FN and non-FN populations.

8.3 Health care utilization among persons with chronic hepatitis C and non-infected population controls

8.3.1 Hospital services use

The overall use of hospital services was much higher among the CHC population as compared to non-infected controls. The fact that the same proportions of users and non-users of hospital services were during the whole study period (1991-2002) and the period where only confirmed chronic hepatitis C cases were reported (1995-2002) suggests that the population of those infected with HCV had mostly been the ones with chronic infection.

The results of this study revealed that the intensity of use of hospital resources by persons with CHC, FN and non-FN alike, far exceeded the rates of hospital use among the general populations of Manitoba. Furthermore, the hospital separation rates among FN

non-infected persons were more than double of both the rates of the non-FN controls and the overall provincial rates. While the provincial annual separation rates were fairly stable over time and were reported to be 167.9, 156, and 170.3 separations per 1000 residents in 1994-1996, 1998/99 and 1999-2001 respectively, only the rates among non-FN controls were at the same level (the mean 1995-2002 rate was 166.2 separations per 1000 person/years). The mean total hospital separation rates among non-infected FN controls (430 per 1000 P/yrs), FN CHC cases (698.4 per 1000 p/yrs), and non-FN CHC cases (621.8 per 1000 p/yrs) were more than 2.5 times, 4.1 times, and 3.7 times higher than the reported Manitoba rates respectively. Moreover, the rates among FN controls were also higher than the rates reported by Martens et al. for Manitoba's FN population in 1998/99 at 348 separations per 1000[229].

The annual rates of hospital outpatient visits were highly inconsistent from year to year among all but the non-infected non-FN individuals, and increased over time for all but the non-infected non-FN persons, the only group with the stable rate of an average of 6.6 visits per 1000 p/yrs. The fact that not only FN cases but also FN controls had similarly high rates of outpatient visits points to the generally higher burden of illness in the FN populations compared to the general population of Manitoba. In contrast, a much greater increase in the annual rates of outpatient visits among non-FN CHC patients relative to non-FN controls most likely reflects disease-related management visits. For instance, during antiviral therapy a person is seen weekly for the first month, every two weeks for the next two months, and monthly thereafter for the duration of treatment[230]. The fact that

over 95% of persons who received treatment for CHC in Manitoba are non-FN individuals supports this explanation.

Annual rates of day admissions were consistent and very much essentially the same among FN and non-FN controls, but were much higher among FN cases and the highest among non-FN cases, although with the trend towards an overall decrease in those with CHC. Both the decrease in day admissions over time and the higher rates of these among non-FN cases possibly reflect the differences in CHC investigations. Thus, liver biopsy, a procedure performed during inpatient day admission, was performed significantly more often on non-FN (24%) than on FN (9%) patients, and the number of procedures alone – 1031 vs. 63 respectively – would result in the very different rates. On the other hand, while in the early era of CHC a liver biopsy was required to assess a person's eligibility for treatment, this is no longer the case, and liver biopsy rates may drop as the result of patients' decisions to forgo this procedure.

Both FN and especially non-FN CHC cases had much higher rates of hospital inpatient stays than their corresponding population controls, particularly non-FN cases. The mean case-to-control rates ratio among FN populations was 2.1, and the difference was even greater among the non-FN population with the mean case-to-control rate ratio of 4.5. In general, the non-infected controls (particularly the non-FN ones) had much lower and less variable rates of hospitalizations in any given year as compared to individuals with chronic hepatitis C.

Total hospital separation rates, day admission rates, and the rates of inpatient hospital stays among persons with CHC all increased significantly in the year the diagnosis of CHC was made and decreased thereafter, but not to the pre-diagnosis level. This was particularly evident in the case of day admissions, which started to increase slightly 1-2 years before the CHC diagnosis, then peaked in the year of diagnosis (rates more than doubled for both FN and non-FN CHC patients), then decreased but remained above the pre-diagnosis levels, reflecting hepatitis-associated care. The rates were much higher among non-FN cases, and did not change over time intervals among FN and non-FN controls. Overall, FN persons used proportionally more outpatient hospital care, while non-FN persons used more day admissions; hospitalizations comprised approximately 60% of all hospital care for CHC persons and slightly more than 50% for non-infected controls.

Similarly to the published reports from Canada, the US and European countries, there was a considerable increase in the number of liver disease-related hospital separations over time. The present study found that the number of liver-related separations among persons with CHC in Manitoba increased 3.7 times in 2002 compared to 1995, and this increase was similar for FN and non-FN CHC persons. The average growth in the number (not rate) of hospital separations was 23%. These results are similar to the report from Calgary by Myers et al., who studied liver-related hospitalizations among HCV-infected persons and found a 4-fold increase in hospitalizations in 2004 compared to 1994[231]. Likewise, Grant and colleagues reported a 4.2-fold increase in liver-related hospitalizations among HCV-infected persons in 2001 as compared to 1994[232]. The

observed increase in hospitalizations seems to be primarily due to the fact that more persons are becoming known to have HCV infection, and more health care resources are required to serve the increasing pool of persons with CHC. The logical explanation wood seems to be that person with CHC got sicker over time, but it is not supported by the results of the present study. For this explanation to hold, not only the number of hospital visits but also the annual rates per p/yr. would have to increase over time, which was shown not to be the case by the present study.

The length of stay during liver-related hospitalizations in Manitoba the median stay of 6 days for non-FN and 8 days for FN persons) was comparable to those reported in Calgary (7 days) and San Francisco (7.7 days). The HCUP study group observed a decrease in the LOS from 8.5 days in 1994 to 6.9 days in 2001.

8.3.2 Physician services use

The use of physician services in the present study was high, with 97% of participants using such services, which is higher than the provincial use of 83% reported by MCHP in 1995-2001. It is also higher than 78.2% of physician services users among Manitoba FN and 82.7% of users for Manitoba overall reported by Martens et al. in their study of health and health services use of registered FN living in Manitoba. Moreover, the annual rates of physician visits among non-FN controls (4.2 visits per p/yr) in the present study were slightly lower than the rates reported in the aforementioned study by Martens (4.9 visits per person per year), whereas the rates among FN controls (7.1 per p/yr) were

slightly above the Manitoba FN rate of 6.1 per person per year. As for CHC persons, the annual rates of physician visits were almost 3 times higher among non-FN cases as compared to the rates among their corresponding controls, and for FN cases the rates were double the rates of their corresponding FN controls. Among persons with CHC, the rates of physician visits were increasing and peaked in the first year since the diagnosis of CHC, decreasing to the pre-diagnosis levels thereafter. A similar trend was found by Nguyen and Jacobs et al., who studied the costs of hepatitis C-related health care in Alberta, but his reported numbers of visits per person (not rate) were somewhat higher than what was found in the present study[99]. Nguyen reported 11.4 physician visits per person in the year before the diagnosis (vs. 12.7 and 9.5 visits per p/yr. among FN and non-FN CHC patients respectively in Manitoba), 19.9 visits during the first year after diagnosis (vs. 13.7 and 11.4 visits per p/yr. among FN and non-FN patients respectively in the present study), and 18.3 visits per person in the second year after diagnosis (vs. 11.8 and 9.7 visits per p/yr. among FN and non-FN CHC patients respectively in Manitoba).

The annual number of physician visits for liver-related problems among Manitobans with CHC increased by 64% in 2001 as compared to 1995. Similarly, Grant at al. found a 36% increase in physician visits for CHC in 2001 as compared to 1994 in HCUP mentioned above.

8.3.3 Reasons for hospital and physicians visits

The top reason for physician visits among persons with CHC was mental illness, with 22% of all physician visits made for this reason. This was by far the most common cause

of physician visits; almost twice as frequent as the cause ranked second – respiratory diseases – at only 11.4% of the total visits by patients with chronic hepatitis C. This observation is very similar to the findings of Nguyen and colleagues, that the highest of all was the cost associated with mental illness[99]. After respiratory diseases just mentioned, injury and poisoning ranked as the last in the top three reasons for visits in Manitoba. This finding is also comparable to the results of the Alberta study. In their paper, Jacobs et al. described injury and poisoning along with respiratory diseases as two other major sources of cost (presumably due to being second and third most frequent causes of physician visits). Also similar to both studies was the finding of the present study that the liver-related visits were not the largest portion of health care consumed by the persons with CHC. Rather, they had a multitude of various health needs.

Also similar in both studies was the finding that the liver-related visits were not the largest portion of health care consumed by the persons with CHC. Rather, they had a multitude of various health needs.

8.3.4 Overall Health care use

Overall, there is a strong relationship between chronic hepatitis C and hospital separation rates and physician visits rates. Both FN and non-FN persons with CHC have much higher health care utilization rates compared to corresponding non-infected controls. It indicates the high burden of illness among persons with CHC as compared to non-infected controls.

Also, the relative difference in the hospital separation rates and the rates of physician visits seems to be different when FN and non-FN cases are compared to their corresponding controls. Thus, the relative difference in the hospital separation and physician visits rates was smaller among FN cases and their corresponding controls and larger among non-FN cases vs. their corresponding controls. Most likely, this is related to the overall higher levels of various comorbidities and the need for care among the FN population in general when compared to the general Manitoba population in general. Conversely, when the generally healthier non-FN persons contract CHC, the relative burden of disease for such persons increases substantially.

8.3.5 The treatment of CHC

The proportion of CHC patients who received antiviral treatment appears to be low with only 6% of persons with CHC receiving treatment. Compared to non-FN patients, of whom 7% were treated, an even smaller proportion - only 2.3% - of FN persons with CHC were treated. Among all persons who received treatment for their CHC, the proportion of FN persons was just under 5%, which is higher than what had been reported by the Pegasys study group with only 1.7% of Aboriginal persons among those enrolled in the extended treatment access program[233].

Two explanations suggest themselves as to why FN persons are not receiving treatment in the same numbers as non-FN persons with CHC. Either FN patients with CHC (1) need to be treated but for whatever reasons are not receiving treatment or, (2) although

infected, do not need to be treated as often as non-FN patients do. Several reasons could account for this. First, viral hepatitis C is a relatively new disease (the virus was isolated by Cho in 1989). During the mid-nineties, the first treatment - with standard interferon - became available for patients with CHC. Because the early treatment results were so dismal (the treatment success with IFN monotherapy was ~20-25%), the clinical trials of antiviral drugs and regimens continued throughout the nineties and into the early part of this decade. Therefore, some patients with chronic hepatitis C received treatment within these industry-sponsored clinical trials and did not have to get a prescription for antivirals. Such information is not captured in the database of prescriptions filled in community pharmacies in Manitoba. Hence, the numbers of patients actually treated for their chronic hepatitis C is higher than 6%.

Second, during the earlier times of HCV disease recognition, there were numerous contraindications for treatment, and they were not all based on the patient's disease status. Two principal "non-clinical" contraindications at that time (and to a lesser degree now) were active intravenous drug use and active alcohol abuse. Since antiviral therapy requires extended commitment from the patient, those actively involved in IDU and alcohol users are likely not to adhere to a treatment schedule (which is 24-48 weeks long) and were not eligible for the treatment. Because the results of this study indicate that the proportion of those with substance abuse among FN persons was more than twice that of non-FN, it is reasonable to assume that a much higher proportion of FN persons with CHC had these contraindications for treatment. Active IV drug users and those who snort drug also run a risk of re-infection due to persistent drug use. Thus, in a single-centre

study of antiviral treatment, the most common contraindications for treatment were non-compliance with the pre-treatment evaluation procedures (37%), active substance/alcohol abuse (13%), and patient's refusal (11%)[233]. The two latter reasons were also recorded in Winnipeg at 12.3% and 5.2% respectively[230]. In the study of inner city residents in Vancouver, the uptake of treatment was reported to be only 1.1%, even though most patients reported having access to health care. Notably, only 27% of persons completed the treatment[3]. In this study, Aboriginal ethnicity and current crack cocaine use were associated with lower treatment uptake[224].

Third, there is an extensive list of medical contraindications for antiviral therapy, such as active psychiatric disease, anemia, decompensated liver disease, etc. Mental illness was more prevalent in FN CHC patients compared to non-FN counterparts, as were other comorbidities, such as diabetes. It is possible that a higher proportion of FN persons might have had their treatments delayed in order to stabilize their underlying medical problems first.

Furthermore, to be eligible for the province-funded antiviral therapy, which is both lengthy and expensive, one needed to have the results of a liver biopsy indicating that the course of the disease was progressive (grade 2 inflammation and/or stage 2 fibrosis on the METAVIR scale)[230]. While a liver biopsy is no longer a pre-requisite in order to be eligible for treatment, during the study period (1995-2002) a liver biopsy was required. The results of the present study show that 2.5 times fewer FN patients had liver biopsies compared to non-FN patients; this is concordant with the 3-fold difference in the proportion of those who received treatment. This could be both an explanation and a

consequence of the perceived non-eligibility for treatment. If a physician assessed a person not to be eligible for the treatment, no biopsy was pursued. On the other hand, if a patient did not want to proceed with the liver biopsy (and there is a view that FN individuals are less acceptant of such an invasive procedure), the treatment would likely not be initiated. Hence, the low rates of biopsy could also suggest that a much smaller proportion of FN individuals were assessed for treatment.

In addition, the treatment of chronic hepatitis C infection is provided primarily by three Winnipeg hepatologists. Hence, persons residing outside of Winnipeg had a remote chance of being treated. Indeed, 86% of the persons treated were from Winnipeg and only 2% were from Northern Manitoba. Access to treatment could be an issue with remote residence, although the fact that residents of rural Northern and Southern Manitoba received treatment in similar proportions suggests otherwise (6.5% of CHC patients from Winnipeg vs. 5.2% of persons from Southern rural vs. 4.7% of CHC patients from Northern rural Manitoba were treated).

An alternative explanation of lower rates of treatment in FN persons with CHC compared to non-FN CHC patients could be that FN individuals with chronic hepatitis C may have a more favorable course of disease and may not require treatment in the same proportions as members of other populations might require. For example, alcohol abuse has long known been known to be an unfavorable prognostic factor which accelerates the progression of chronic hepatitis C to cirrhosis. However, with twice as many alcohol abusers, the FN population had the same proportion of patients with portal hypertension

and hepatic decompensation as the non-FN population. Also, the present study revealed that FN CHC patients had a much higher prevalence of confection with HIV and a higher prevalence of diabetes and some other important comorbidities that are usually associated with a less favorable course of the disease, yet there was no evidence of an increased number of cases with end stage liver disease and the mortality was the same. One may argue that since FN individuals do have more of the other comorbidities that which would be considered as contraindications for the treatment (severe psychiatric conditions, seizures, anemia, hepatic decompensation, etc.), one would expect a higher proportion of progressive disease in such persons who would otherwise be treated. However, as mentioned above, the proportion of individuals who developed conditions associated with the progression to end stage liver disease (ascites, esophageal varices, HCC, hepatic encephalopathy) was the same among FN and non-FN patients. It seems that CHC does not progress as one would expect it would in the presence of all these unfavorable prognostic factors. Moreover, since FN CHC patients were much younger than non-FN persons the median age was 33 vs. 39 years of age), the disease might have a more benign course.

While all the above might be true, the question of unequal rates of liver biopsy and treatment in FN persons compared to non-FN individuals with CHC merits further investigation. Assuming that needed resources exist and are allocated, a functioning system of delivery is in place, the required drug is abundant, and the public is educated, then it can be argued that treatment uptake depends primarily on a population's willingness to obtain the available service. Success of treatment will ultimately depend

on whether eligible persons with CHC would seek treatment or choose not to do so for whatever reasons. Access to prescribed health services could be formally the same for all population categories, but in itself it can not guarantee equality of use by the consumers of those services. If an intervention is available but is not perceived as accessible, or if a person is indifferent to the consequences of a disease or risk behaviour, or if health-seeking is not a part of an individual's personality, or if a person beliefs he or she does not need treatment due to cultural leaning towards a traditional, holistic and less invasive health care, than the formal access does produce desired result, for it is not acted upon. Unfortunately, it is well documented (and described in detail in the background section of this work) that poor health status, addictions and mental health problems, etc., and such social issues as poverty, low education level, and high unemployment among Aboriginal people may lead to an early and more regular involvement in high-risk activities which are not conducive to health seeking or health maintenance practices. The very same factors which put First Nations persons at increased risk of acquiring HCV could also be responsible for the decreased uptake of treatment by that hard- to- reach population.

CHAPTER NINE STRENGTHS AND LIMITATIONS

9.1 STRENGTHS

The first stage of this work was the development of a comprehensive hepatitis C research database, which is a major strength of this study. The extensive administrative data for a cohort of CHC patients and population-matched controls has made it possible to examine various epidemiological, clinical, and health services aspects of hepatitis C in Manitoba.

Population-based administrative data in general have numerous advantages for conducting population health research, such as making it possible to generate denominators for calculating rates, offering a relatively large number of cases, and providing information for assessing various comorbidities. Such data make it possible to utilize existing information without embarking on a complex and lengthy process of data collection. When linked with readily available demographic information (such as age, sex, residence, treaty status, etc.), administrative data facilitate comparing individuals of varying demographic strata with regard to rates of disease, comorbidity, treatments, and such outcomes as hospital admissions and mortality, to name a few. Merging hospital abstracts of outpatient, day, and inpatient admissions, physician billing claims, and prescription drugs data allowed for the construction of fully comprehensive longitudinal records of each type of health care contact for each member of the study and control cohorts. Twelve years of data made it possible to assemble longitudinal utilization histories for persons diagnosed with CHC in Manitoba, and to assess the health care use prior to and after the diagnosis of CHC.

Linking public health surveillance database with the population registry and the above-mentioned administrative databases provided additional advantages. Using public health data to identify cases proved to be superior to creating the disease cohort based on ICD-9-CM coding. Since physician claims data use only the first 3 digits of ICD codes, it would have been impossible to distinguish between hepatitis C and other viral hepatitis (A, B, D, and E) in persons who had not been hospitalized. The public health surveillance data effectively removed this problem. Moreover, since the only laboratory which conducts HCV testing also reports the data to the Public Health authorities, there was very strong agreement between the testing facility data and the public health surveillance data. Thus, 94% of cases tested positive for HCV were reported to the CDC which formed the study cohort. Furthermore, there were only 2 cases of CHC and 3 cases of acute hepatitis C in the hospital abstracts from the control cohort, which is less than 0.006%. That the data was highly specific was indirectly confirmed by the fact that there was not a single record of a prescription for Rebetron (used for antiviral therapy for CHC during the study period) among non-infected controls. Moreover, in the study conducted by the Viral Hepatitis Investigative Unit (VHIU) in Winnipeg[230] (the unit responsible for the care of nearly 90% of those with CHC in Manitoba), the number of patients treated corresponds with the number of treatments in the present study. Thus, of 331 patients treated in 1998-2003 in VHIU, 269 received either IFNά or IFNά in combination with ribavirin, while in the present study the number of persons treated with the same regimens was 286. Hence, the cohort of HCV-infected persons truly represents the number of hepatitis C cases identified in Manitoba during 1991-2002. Finally, selection

of demographically matched population controls provided the means for determining the impact of CHC on health services utilization.

Another important advantage of this study is the large number of variables explored in it. A vast amount of information from the public health database on clinical presentation, hepatitis screening test results, and risk factors - information not routinely available in health research - was used in this work. Furthermore, in the analysis of health care utilization, restricting the study population to cases 18 years of age and older diagnosed during 1995 – 2002 afforded two advantages: (1) to minimize the differences in diagnostic and treatment practices between persons diagnosed as anti-HCV positive by the 1st or 2nd generation immunoassay without RNA testing and those diagnosed as having chronic hepatitis C based on the 3rd generation immunoassay and confirmatory testing for HCV-RNA, initiated in 1995; and (2) to eliminate the bias arising from the differences in health care use among pediatric and adult patients.

9.2 LIMITATIONS

Turning now to potential limitations of this study, what deserves mention first is that administrative data, including those used in this study, have the following potential drawbacks. To begin with, there is some probability of linking incorrect records while conducting probabilistic linkage of multiple records based on scores. There is also a possibility of miscoding in the source databases.

Further, the data may lead us to underestimate the comorbidities associated with chronic hepatitis C. The severity of the disease is not captured in administrative data. This may produce biased estimates of the natural history of the disease, since only the stage of hepatic decompensation (which requires extensive medical management) can be ascertained from administrative data. Minimal disease, chronic hepatitis, and uncomplicated cirrhosis cannot be reliably identified from such data.

Moreover, the study population includes only persons who tested positive for HCV. Therefore, because the work does not include infected persons who have never been tested, it does not represent the true annual incidence of HCV infection or the true prevalence of CHC. Further, the study period is restricted to 1991-2002, and treatment practices have changed since. Because the current standard therapy (Pegylated IFNά in combination with ribavirin) was licensed in 2003, and also because some of the relative contraindications to treatment have been reconsidered, the proportion of treated persons has since increased. All the same, the differences in utilization of drug therapy by different subpopulations are likely to persist over time, even as overall rates of drug utilization increase.

The only Aboriginal group which can be readily identified from the administrative sources is the Registered First Nations Manitobans. In the present study, the term "First Nations" refers only to them. The current registry undercounts approximately 1/3 of First Nations people. As reported by the group of MCHP researches led by Martens, the Registered First Nations count in the 1999 Manitoba Health population registry was 69,526, while the First Nations and Inuit Health Branch (FNIHB) count was 101,407, a

difference of 35%[228, 234]. The problem with under-counting is particularly severe among the off-reserve populations, with almost 50% of urban and rural off-reserve First Nations populations not identified in the Provincial sources. For the most part this problem was caused by a significant number of individuals, particularly women and children, regaining their First Nations Status. These individuals are accounted for by the Indian and Northern Affairs Canada (INAC) and FNIHB registries, such as the Status Verification System (SVS). These files, however, are not available to provincial bodies for a number of political reasons. Hence, the provincial registry is not updated and is not entirely accurate in accounting for the First Nations, to say nothing of other aboriginal groups[234]. This means that the results of the present study, because based on the only available definition of First Nations individuals (about 65% of all registered First Nations), need to be interpreted with some caution when applied to other aboriginal groups and communities. The results derived from this study are representative of other First Nations populations because those who are identified as "Registered First Nations" almost certainly are, in fact, persons of First Nations ancestry. Hence the results are based solely on First Nations population, and when differences between the two study groups (First Nations and non-First Nations individuals) are found, the direction of the differences will not be affected. If anything, the magnitude of differences between the two groups has likely been underestimated as a result of misclassification of non-Registered First Nations, for had we had the correct classification of all FN persons as FN, such differences would have been even larger.

Finally, certain geographic and cultural differences may have an impact on the utilization of health services. For example, remote residence, the absence of physicians in the area, the individual's level of education, etc., may contribute to the distribution of the outcomes of the study. However, the inclusion of both FN and non-FN persons with hepatitis C and population controls matched by age, gender, and residence has minimized the impact of this variable.

9.3 APPLICATIONS

The data generated in the present study are confined to the population of Manitoba and may not be readily applicable to all Aboriginal individuals elsewhere in the country. Aboriginal cultures vary from east to west and from north to south. Aboriginal Peoples on the west and east coasts were sea-oriented, whereas the people in the southern geographical region of Ontario developed a more sedentary farming life while other groups were less sedentary and more mobile[226]. The lifestyle and health-related practices vary widely between First Nations societies and communities, as does reliance on traditional vs. western style health care, which may have an impact on both the prevalence of the disease and the use of health services even when these are available.

Obviously, geographic and cultural differences influence the utilization of health services. Services available in one province may not be the same in another, and within each province what is available in urban centers or in close proximity to them may not be available or readily accessible by the residents of remote or isolated communities. Moreover, the Prairies (and Manitoba in particular) have the highest concentration of

Aboriginal populations. First Nations comprise 14% of Manitoba's population (although only 6% according to administrative sources), the same as that of Saskatchewan, but less than 2% of Ontario's total population. Similarly, 8% of Winnipeg residents and 9% of Saskatoon residents are First Nations, compared to only 0.3% in Montréal and 0.4% in Toronto. This definitely affects health care utilization patterns because urban residence opens more opportunities for regular interaction with the health care system, as opposed to remote residence which would have an impact on both the frequency and the nature of health care contacts (specialist care vs. generalist, physician vs. nurse, etc). Hence, provincial trends in health care utilization may differ in these areas. However, the participation of non-First Nations HCV-infected individuals as well as the selection of non-HCV infected population-based controls (to the degree permissible by the administrative sources), matched by age group, gender, residence and Registered First Nation status, have minimized the impact of these variables.

Although similar in many ways, First Nations are different in that the conditions in which communities live are different. The reality is that even within the same province some communities are very poor and have many social, environmental, and health problems, whereas others have a much higher standard of living and a wider range of opportunities, with the correspondingly higher level of general well-being and health. Calculated on the basis of the 2001 Census data, the so-called Community Well-Being (CWB) Index, which combines 4 indicators (education, labor force activity, income and housing) allows for comparisons across First Nations communities[236]. Communities with lower well-being are more prevalent in the Prairie Provinces, including Manitoba, while there are

many communities with higher well-being in Atlantic and Pacific Canada, Ontario, and the Territories (Appendix 4). The well-being of First Nations varies both between provinces and between communities within the same province. The average level of well-being is also lower for those living in reserve communities or settlements as compared to First Nations individuals living off a reserve. In general, then, the results of this study should be interpreted while keeping in mind the environment of the particular population.

Patterns of risk may be different in different communities. In North America risk is largely associated with injection drug use. In other countries (Taiwan, for example) the exposure of isolated populations to inadequately sterilized reusable hypodermic needles at a limited number of clinics and pharmacies resemble needle-sharing among groups of intravenous drug addicts. Yet others (South America, for example) report that the very socioeconomic conditions and the marginalization of indigenous people are responsible for their being excluded from the medical system, thus sparing them from the infection which was, in many cases, spread iatrogenically.

The results of this study are applicable elsewhere only to the degree that the other country's organization, prosperity, and health care delivery are similar. For example, Canada, Australia, and New Zealand have comparable health care delivery, while in the USA, particularly in urban settings, private medical insurance is not attainable for many Aboriginal individuals, leaving their health care confined to emergency visits. Similarly, Canadian results are unlikely to have relevance for populations of much poorer countries

(South America, Africa), where GDP is low and resources are lacking to deliver quality health care to the majority of the countries' populations.

Conclusions (1) The comprehensive database developed for this project is useful for a multitude of purposes and for many future research endeavors. This database makes it possible to design many subsequent projects to further examine various epidemiological, clinical and health care aspects of chronic hepatitis C in Manitoba. Further, it can form the basis for projections regarding the future burden of the disease and for formulating specific health programmes of prevention and care.

(2) While of course not universally applicable, the results of this analysis offer multiple potential benefits to the Canadian Health care system, to the Aboriginal populations of Canada, and to those populations internationally which meet the similarity criteria as discussed above.

CHAPTER TEN FUTURE OPPORTUNITIES

The present study was designed to determine (1) whether there is an increase in the incidence of newly diagnosed HCV infection in First Nations individuals compared to the rest of Manitobans; (2) whether there is a difference in clinical manifestations and the natural history of HCV infection in First Nations as compared to non-First Nations persons with CHC; and (3) whether chronic hepatitis C imposed an additional burden on the health care system compared to the health care use by non-infected Manitobans. The enormous database developed for this project makes it possible to design many projects to scrutinize from numerous angles every aspect of clinical management or health care use in both CHC patients and non-infected controls. Of the many avenues made available for pursuit by the database, I chose for this work to focus on the issue all other projects would have first need to have determined if there were, indeed, differences that would warrant further in-depth analysis of various aspects of HCV infection in the First Nations populations as compared to the rest of Manitobans. It turns out that the results of this study suggest that there are indeed some distinct features in the epidemiology of HCV infection and in the management of the disease among Manitoba's First Nations populations. Hence, the results of this study enhanced our understanding of the epidemiology as well as of the diagnostic and therapeutic resource utilization in both FN and non-FN persons with CHC, and now additional work can be done in order to further assess the differences and to develop strategies (if needed) to minimize these differences. I would suggest that the next project in the research programme dedicated to studying chronic hepatitis C in Manitoba, based on the Hepatitis C Research Database completed for the present study, would be to link it with the clinical data from the Viral Hepatitis

Investigative Unit database and to examine the natural history of CHC in Manitoba in greater depth. Also important would be a study of health care use and clinical outcomes in persons with CHC who have comorbidities that may influence the natural history of CHC and its clinical management, such as co-infections with HIV and HBV as well as alcohol abuse – all factors known to affect the progression of the disease. The study would compare these issues with regard to the differences between FN and non-FN persons with CHC. An in-depth look into HCV-related care in various demographic groups as well as a study of the association between HCV infection and other chronic conditions (diabetes mellitus, hypercholesterolemia, etc) and comparing the epidemiology of such conditions in non-infected controls are some of the other themes which it would be fruitful to look into further within the context of the viral hepatitis research program developed by the candidate. Overall, the present study (and the further research outlined here which utilizes the Hepatitis C Research Database) not only enhances our understanding of the epidemiology, natural history, and health services utilization associated with CHC in Manitoba's First Nation and non-First Nation populations, but are also essential for designing specific public health programmes related to HCV infection prevention and care. Finally, this study contributes to research on aboriginal health, to which the Canadian scientific community is strongly committed.

REFERENCES

1. WHO/CDS/CSR/EDC/2000.7 Hepatitis A. Web accessed June 24, 2008 http://www.who.int/csr/disease/hepatitis/HepatitisA_whocdscsredc2000_7.pdf
2. Krajden M. Hepatitis. Can J Infect Dis 2001; Vol. 12 No 6:329-331
3. WHO. Viral Cancers. Web accessed June 24, 2008 http://www.who.int/vaccine_research/diseases/viral_cancers/en/print.html
4. Lavanchy D. Global surveillance and control of hepatitis C: report of a WHO. 1999; (6):35-47
5. WHO/CDS/CSR/LYO/2002.2: Hepatitis B Web accessed June 24, 2008 http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf
6. Centers for Disease Control and Prevention. Deaths, percent of total deaths, and death rates for the 15 leading causes of death: United States and each State, 2005. http://www.cdc.gov/nchs/data/dvs/LCWK9_2005.pdf
7. Statistics Canada. Leading causes of death, total population, by sex, Canada, provinces and territories, annual. http://cansim2.statcan.gc.ca/cgi-win/cnsmcgi.pgm#TFtn
8. Murray CJL and Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease study. Lancet 1997; 349:1269-76
9. Maynard JE. Hepatitis B: global importance and need for control. Vaccine 1990; 8 (supplement):518-20
10. WHO. Revised GBD 2002 Estimates for Countries Accessed July 5, 2008 http://www.who.int/healthinfo/statistics/gbd1990regionmortality2002.xls

11. Cohen J. The Scientific Challenge of Hepatitis C. Science, 1999;Vol 285, Issue 5424, 26-30

12. Choo QL, Kuo G, Wiener AJ et al. Isolation of a cDNA clone derived from a bloodborne non-A non-B viral hepatitis genome. Science 1989; 244:359-362

13. Division of Blood-borne Pathogens - LCDC - Health Canada: Report on the Meeting of the Expert Panel on Hepatitis C Epidemiology, June 17-18, 1998. http://www.cihr-irsc.gc.ca/e/documents/identificationhepc_e.pdf

14. Durie MH. The Health of Indigenous Peoples Depends on Genetics, Politics, and Socioeconomic factors. BMJ 2003; 326:510-511.

15. Indigenous issues. International Work Group on Indigenous Affairs.

16. Aboriginal peoples of Canada: A demographic profile January 2003. Catalogue no. 96F0030XIE2001007 http://www12.statcan.ca/english/census01/products/analytic/companion/abor/pdf/96F0030XIE2001007.pdf

17. Words First. An Evolving Terminology Relating to Aboriginal Peoples in Canada. INAC, September 2004. http://www.ainc-inac.gc.ca/pr/pub/wf/index_e.html Catalogue No.R2-236/2002E-IN, ISBN 0-662-33143-5

18. AFN Communications Unit. Fact Sheets. http://www.afn.ca/cmslib/general/FS-TM-e.pdf

19. Indian and Northern Affairs Canada, 2001, Basic Departmental Data 2001, Catalogue no. R12-7/2000E

20. Cunningham C and Stanley F. Indigenous by Definition, Experience, or World View. Links between people, their land, and culture need to be acknowledged. BMJ 2003; 327:404-405.

21. Schwartz R. S. Racial Profiling in Medical Research. The New England Journal of Medicine 2001; 344 (18): 1392-1393.

22. Knowler WC, Saad MF, Pettitt DJ, Nelson RG, Bennett PH. Determinants of diabetes mellitus in the Pima Indians. Diabetes Care 1993;16:216-227.

23. Rahman N, Stratton MR. The genetics of breast cancer susceptibility. Annu Rev Genet 1998;32:95-121

24. Warmkssel KE. Expediting Genetic Research with Help from the Amish. Dr. Shuldiner's work with the Amish. http://www.umm.edu/amish_research.pdf

25. Aborsangaya KB, Dembinski I, Alphonse MP, Khatkar S, Nickerson P and Rempel JD. The impact of Aboriginal ethnicity on HCV Core induced IL-10 synthesis: interaction with IL-10 gene polymorphisms. Hepatology. 2007; 45:623-630.

26. Albuquerque AG, Moraes M, Vanderborght PR, Romero M, Santos AR, Moraes MO, et al. Tumor necrosis factor and interleukin-10 gene promoter polymorphisms in Brazilian population and in Terena Indians. Transplant Proc 2004;36:825-826.

27. Vozarova B, Fernandez-Real JM, Knowler WC, Gallart L, Hanson RL, Gruber JD, et al. The interleukin-6 (-174) G/C promoter polymorphism is associated with type-2 diabetes mellitus in Native Americans and Caucasians. Hum Genet 2003;112:409-413.

28. Hoffmann SC, Stanley EM, Cox ED, DiMercurio BS, Koziol DE, Harlan DM, et al. Ethnicity greatly influences cytokine gene polymorphism distribution. Am J Transplant 2002;2:560-567.

29. Torkildsen O, Utsi E, Harbo HF, Mellgren SI, Vedeler CA, Myhr KM. Ethnic variations of IL-10 polymorphisms in a Sami and Norwegian population. Scand J Immunol 2005;62:71-74.

30. Larcombe L, Rempel JD, Dembinski I, Tinckam K, Rigatto D, Nickerson P. Differential cytokine genotype frequencies among Canadian Aboriginal and Caucasian populations. Genes Immun. 2005; 6:140-144.

31. Fleckenstein J., Chronic Hepatitis C in African Americans and Other Minority Groups, Current Gastroenterology Reports 2004, 6: 66-70.

32. De Maria N., Colantoni A., Idilman R., Friedlander L., Haring J., Van Thiel D. H., Impaired Response to High-dose Interferon Treatment in African-Americans with Chronic Hepatitis C, Hepato-Gastroenterology 49 (2000):788-792.

33. Sherman K. E. Implications of Peginterferon Use in Special Populations Infected with HCV, Seminars in Liver Disease 2003:Volume 23, Supplement 1: 47-52.

34. Zeuzem S., Heterogeneous Virologic Response Rates to Interferon-Based Therapy in Patients with Chronic Hepatitis C: Who Responds Less Well?. Ann Intern Med 2004; 140:370-381.

35. Pawlotsky J-M., Hepatitis C Virus Resistance to Antiviral Therapy, Hepatology 2000; 32 (5): 889-896.

36. Muir A. J., Bornstein J. D., Killenberg P. G., Peginterferon Aalfa-2a and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites, The New England Journal of Medicine: 2265-2271.

37. Morelli J., Kim C. Y., Willner I. R. U. S. Veterans' Experience With Rebetron in a Nonstudy Environment: Success or Failure? The American Journal of Gastroenterology 2002; 97 (9): 2379-2382.

38. Reddy KR, Hoofnagle JH, Tong MJ, Lee WM, Pockros P, Heathcote EJ, Albert D, Joh T. Racial differences in responses to therapy with interferon in chronic hepatitis C. Consensus Interferon Study Group. Hepatology. 1999 Sep;30(3):787-93.

39. Theodore D., Shiffman M. L., Sterling R. K., Bruno C. J., Weinstein J., Crippin J. S, et al. Intensive Interferon Therapy Does Not Increase Virological Response Rates in African Americans with Chronic Hepatitis C. Digestive Diseases and Sciences 2003; 48 (1): 140-145.

40. Kinzie J. L., Naylor P. H., Nathani M. G., Peleman R.R., Ehrinpreis M. N., et al. African Americans with genotype 1 treated with interferon for chronic hepatitis C have a lower end of treatment response than Caucasians. Journal of Viral Hepatitis 2001; 8: 264-269.

41. McHutchison J. G., Poynard T., Pianko S., Gordon S.C., Reid A. E., et al. The Impact of Interferon Plus Ribavirin on Response to Therapy in Black Patients With Chronic Hepatitis C. Gastroenterology 2000; 119: 1317-1323.

42. Kimball P., Elswick R.K., Shiffman M. Ethnicity and Cytokine Production Gauge Response of Patients with Hepatitis C to Interferon-α Therapy. Journal of Medical Virology 2001; 65:510-16.

43. Sugimoto K., Stadanlick J., Ikeda F., Brensinger C., Furth E. E., Alter H. J., Chang K-M., Influence of Ethnicity in the Outcome of Hepatitis C Virus Infection and Cellular Immune Response. Hepatology 2003; 37:590-9

44. Dev A. T., McCaw R., Sundararajan V., Bowden S., Sievert W. Southeast Asian Patients With Chronic Hepatitis C: The Impact of Novel Genotypes and Race on Treatment Outcome. Hepatology 2002; 36 (5): 1259-1265.

45. Nguyen M. H., Keeffe E. B. Chronic Hepatitis B and Hepatitis C in Asian Americans. Reviews in Gastroenterological Disorders 2003; 3 (3):125-134.

46. Luo S, Cassidy W, Jeffers L, Reddy KR, Bruno C, Howell CD. Interferon-stimulated gene expression in black and white hepatitis C patients during peginterferon alfa-2a combination therapy. Clin Gastroenterol Hepatol. 2005;3(5):499-506

47. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999 Aug 19;341(8):556-62.

48. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The Prevalence of hepatitis C virus infections in the United States, 1999 through 2002. Annals of Internal Medicine 2006;144:705-14.

49. Minuk GY, Uhanova J. Viral hepatitis in the Canadian Inuit and First Nations populations. Can J Gastroenterol 2003;17:707-712.

50. Minuk GY, Zhang M, Wong SG, Uhanova J, Bernstein CN, Martin B, et al. Viral hepatitis in a Canadian First Nations community. Can J Gastroenterol 2003;17:593-596.

51. Hill W, Butt G, Melanson P, Crosby M, Mahoney C, Panessa C, et al. Spontaneous clearance of hepatitis C virus among Aboriginals in British Columbia. Can J Infect Dis Med Microbiol 2006;17:67A.

52. Scott JD, McMahon BJ, Bruden D, Sullivan D, Homan C, Christensen C, et al. High rate of spontaneous negativity for hepatitis C virus RNA after establishment of chronic infection in Alaska Natives. Clin Infect Dis 2006; 42:945-952.

53. Grebely J, Conway B, Raffa J, Lai C, Krajden M, Kerr T, et al. Natural history of hepatitis C virus infection among injection drug users in Vancouver, Canada Hepatology 2006;42:230A.

54. Pearce N., Foliaki S., Sporle A., Cunningham C. Genetics, race, ethnicity, and health. British Medical Journal 2004; 328: 1070-1072.

55. Ring I., Brown N. The health status of indigenous peoples and others. The gap is narrowing in the United States, Canada, and New Zealand, but a lot more is needed. British Medical Journal 2003; 327: 404-405.

56. Brown R and Gaglio P. Scope of worldwide hepatitis C problem. Liver Transpl 2003;9:S10-S13.

57. The Global Burden of hepatitis C working group. Global Burden of disease (GBD) for hepatitis C. J Clin Pharmacol 2004;44:20-29.

58. Madhava V, Burgess C, Drucker E. Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. Lancet Infect Dis. 2002 May;2(5):293-302.

59. Guidance for the Prevention, Testing, Treatment & Management of Hepatitis C in Primary Care, Royal College of General Practitioners (2007) http://www.patient.co.uk/

60. Dubois F, Desenclos JC, Mariotte N, Goudeau. A Hepatitis C in a French population-based survey, 1994: seroprevalence, frequency of viremia, genotype distribution, and risk factors. Hepatology 1997; 25(6):1490-6.

61. Sy T, Jamal MM. Epidemiology of hepatitis C Virus (HCV) Infection. Int J Med Sci 2006;3(2):41-46

62. Stvilia K, Tsertsvadze T, Sharvadze L, Aladashvili M, del Rio C et al. Prevalence of Hepatitis C, HIV, and Risk Behaviors for Blood-Borne Infections: A Population-Based Survey of the Adult Population of T'bilisi, Republic of Georgia. J Urban Health 2006; Vol. 83, No. 2

63. Tulisov A, McMahon BJ, Koch A, Minuk G, Chulanov V, Bruce MG, Uhanova J et al. Viral hepatitis in the Arctic. A review from a Circumpolar Workshop on Viral hepatitis, ICCH13. Alaska Med. 2006;49 (2 Suppl):193-203.

64. WHO. Hepatitis C. Fact sheet N°164. Accessed 01/08/2004 http://www.who.int/mediacentre/factsheets/fs164.

65. Takahashi M, Nishizawa T, Gotanda Y, Tsuda F et al. High prevalence of antibodies to hepatitis A and E viruses and viremia of hepatitis B, C, and D viruses among apparently healthy populations in Mongolia. Clin Diagn Lab Immunol. 2004 Mar;11(2):392-8.

66. Amin J, Gidding H, Gilbert G, Backhouse J et al. Hepatitis C prevalence – a nationwide serosurvey. Commun Dis Intell 2004;28:517-521.

67. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999 Aug 19;341(8):556-62.

68. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The Prevalence of hepatitis C virus infections in the United States, 1999 through 2002. Annals of Internal Medicine 2006;144:705-14.

69. Kamal SM. Acute Hepatitis C: A Systematic Review. Am J Gastroenterol 2008;103:1283-97.

70. Wasley A, Miller JT, Finelli L. Surveillance for Acute Viral Hepatitis—United States 2005. MMWR 2007; MAR 16;56(3):1-24.

71. Alter MJ. The epidemiology of acute and chronic hepatitis C. Clin Liver Dis; 1997: 1(3):559-68

72. Centers for Disease Control and Prevention, Division of Viral Hepatitis, http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/index.htm

73. MMWR, Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System, 1996-2006. http://www.cdc.gov/mmwr/preview/mmwrhtml/figures/s702a1t2.gif

74. Robotin MC, Copland J, Tallis G, Coleman D, Giele C et al. Surveillance for newly acquired hepatitis C in Australia. Journal of Gastroenterology and Hepatology 2004; 19:283–288.

75. Mohamed MK, Abdel-Hamid M, Mikhail NN et al. Intrafamilial transmission of hepatitis C in Egypt. Hepatology 2005;42:683-7.

76. Alter MJ, Hutin YJF, Armstrong GL. Epidemiology of hepatitis C. Chapter 9, p. 169-184 in Hepatitis C. Biomedical research reports. Editors Liang TJ and Hoofnagle JH. 2000 Academic Press.

77. Sherman M, Shafran S, Burak K et al. Management of chronic hepatitis C: Consensus guidelines. Can J Gastroenterol 2007;21(Suppl. C):25C-34C.

78. PHAC, Disease Surveillance, Notifiable Diseases on Line, http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/index_e.html

79. Canadian Association for the Study of the Liver. Management of Viral Hepatitis: A Canadian Consensus 2004. Accessed 20.08.2004 http://www.hepatology.ca/cm/FileLib/consensus_English_Aug_04.pdf

80. MRC of Canada: Identification of a Research Agenda for the Diagnosis, Care and Prevention of Hepatitis C in Canada, report to the Minister of Health, June 1999.

81. Gully PR, Tepper ML. Hepatitis C. Can Med Assoc J 1997; 156 (10): 1427-28.

82. Manuel DG., Johnson I., Fearon M., Hoskin J. The Prevalence of Hepatitis C in a Community -Based Population, Ontario, 1996. Can-Commun-Dis-Rep. Dec 1999; Vol 25-23: 1-7.

83. Sherman M. How Significant is Hepatitis C Infection in Canada? The HepNet - Hepatitis Update 1 – fall 1995.

84. Gudelines and recommendations on the prevention and control of hepatitis C. LCDC, Can-Commun-Dis-Rep. 1995 Jul; 21 Suppl 2: 1-18, 1-21.

85. Zou S, Zhang J, Tepper M, et al. Enhanced surveillance of acute hepatitis B and C in, 1998 to 1999. Can J Infect Dis 2001; Vol. 12 No 6:357-63

86. Health Canada. Blood-borne pathogens routine surveillance system report. Health Canada: Ottawa, Ontario, 2002 (Cat. No H39-603/2002E).

87. Remis RS. A Study to Characterize the Epidemiology of Hepatitis C Infection in Canada, 2002. Final Report. HP40-31/2008E-PDF 978-0-662-48672-5 http://www.phac-aspc.gc.ca/hepc/pubs/hepc2002/index-eng.php

88. Wu H-X, Wu J, Wong T, Donaldson T, Dinner K, Andonov A et al. Enhanced surveillance of newly acquired hepatitis C virus infection in Canada, 1998 to 2004. Scandinavian Journal of Infectious Diseases 2006; 38(6): 482 — 489.

89. Saab S and Busuttil RW. Practical management of liver transplant recipients for hepatitis C. Minerva Chirurgica 2003 Aug; 58(4):479-89.

90. Fattovich G, Giustina G, Degos F. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112:463-472

91. Zou S, Tepper M, El Saadany S. Prediction of Hepatitis C Burden in Canada. Can J Gastroenterol 2000; Vol. 14 (7): 575-80.

92. Davis GL. Chronic Hepatitis C and Liver Transplantation. Reviewes in Gastroenterological Disorders 2004; 4 (1):7 - 17.

93. Stell DA, McAlister VC, Thorburn D. A comparison of disease severity and survival rates after liver transplantation in the United Kingdom, Canada, and the United States. Liver Transplantation 2004; 10 (7): 898 - 902.

94. Yoshida EM, Caron NR, Buczkowski AK, Arbour LT, Scudamore CH, Steinbrecher UP, Erb SR, Chung SW. Indications for liver transplantation in

British Columbia's Aboriginal population: a 10-year retrospective analysis. Canadian Journal of Gastroenterology 2000 Oct; 14 (9):775-9.

95. Dore GJ, Law M, MacDonald M, Kador JM. Epidemiology of hepatitis C virus infection in Australia. J Clin Virol 2003;26:171-84

96. CDC. Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease. October 16, 1998 / 47 (RR19); 1-39.

97. Jacobs P., Golmohammadi K, Minuk G, Adams J. The Cost of Stages of Hepatitis C in Canada. First Canadian Therapeutics Congress, 2004, June 6-8, Winnipeg; Abstracts 155: 79.

98. Rakela J., Vargas H. E. Hepatitis C: Magnitude of the Problem. Liver Transplantation 2002; 8 (10), Suppl 1: S3-S6.

99. Nguyen TH, Jacobs P, Hanrahan A, Fraser-Lee N, Wong W, Lee B, Ohinmaa A.J Viral Hepat. 2008 Apr 22. Health care costs of persons with newly diagnosed hepatitis C virus: a population-based, observational study.

100. Wong J. B., McQuillan G. M., McHutchison J. G., Poynard T. Estimating Future Hepatitis C Morbidity, Mortality, and Costs in the United States. American Journal of Public Health 2000; 90: 1562-1569.

101. Hepatitis C Prevention, Support and Research Program. Community Acquired Infections Division. Centre for Communicable Diseases and Infection Control. Infectious Disease and Emergency Preparedness Branch. Public Health Agency of Canada. Ottawa, ON K1A 0K9. Published by authority of the Minister of Health. Cat.: HP40-32/2008E ISBN: 978-0662-48874-3

102. Zou S, Tepper M, Giulivi A. Hepatitis C in Canada. In Viral Hepatitis and Emerging Bloodborne Pathogens in Canada. CCDR 2001; Volume: 27S3. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/01vol27/27s3/27s3f_e.html

103. Remis RS. Final Report: Estimating the Number of Persons co-infected with Hepatitis C Virus and Human Immunodeficiency Virus in Canada. http://www.phac-aspc.gc.ca/hepc/pubs/hivhcv-vhcvih/index-eng.php

104. Yeung LTF, King SM, Roberts EA. Mother-to-Infant Transmission of Hepatitis C Virus. Hepatology 2001; 34 (2):223-29.

105. Infectious Diseases and Immunization Committee, Canadian Paediatric Society (CPS). Vertical transmission of the hepatitis C virus: Current knowledge and issues. Paediatrics & Child Health 1997;2(3):227-31.

106. National Institutes of Health. Consensus Conference Statement, June 10-12, 2002. Consensus Statement on Management of Hepatitis C: 2002. http://consensus.nih.gov/2002/2002HepatitisC2002116html.htm

107. Kamal SM, Amin A, Madwar M, Graham CS, et al. Cellular Immune Responses in Seronegative Sexual Contacts of Acute Hepatitis C Patients. J Virol. 2004; 78(22):12252–12258.

108. Tetrault N. Sex and hepatitis C. Am J Gastro 2005 (100(4):825-6

109. Tahan V, Karaca C, Yildirim B, Bozbas A, Ozaras R, Demir K et al. Sexual transmission of HCV between spouses. Am J Gastroenterol. 2005 (4):821-4

110. Alary M, Joly JR, Vincelette J, Lavoie R, Turmel B, Remis RS. Lack of evidence of sexual transmission of hepatitis C virus in a prospective cohort study of men who have sex with men. Am J Public Health. 2005;95(3):502-5

111. Lin HH, Li YH, Yu JH, Wang YW, Lua AC, Huang LC, Huang SC, Lee ML. Ethnic and geographic variations in the prevalence of hepatitis A, B and C among aboriginal villages in Hualien, Taiwan. Infection 2000 Jul-Aug;28(4):205-8

112. Shen CY, Lee HS, Huang LC, Tsai KS, Chen DS, Cheng AT. Alcoholism, hepatitis B and C viral infections, and impaired liver function among Taiwanese aboriginal groups. American Journal of Epidemiology 1996 May 1;143(9):936-42

113. Chang SJ, Chen HC, Ying J, Lu CF, Ko YC. Risk factors of hepatitis C virus infection in a Taiwanese aboriginal community. Kaohsiung J Med Sci 1996 Apr;12(4):241-7

114. Wu JS, Lu CF, Chou WH, Chen HY, Lee HF, Wu YC, Lin SY. High prevalence of hepatitis C virus infection in aborigines in Taiwan. Jpn J Med Sci Biol 1992 Aug;45(4):165-74

115. Butler T, Spencer J, Cui J, Vickery K, Zou J, Kaldor J. Seroprevalence of markers for hepatitis B, C and G in male and female prisoners--NSW, 1996. Aust N Z J Public Health 1999; 23(4):377-84

116. Butler TG, Dolan KA, Ferson MJ, McGuinness LM, Brown PR, Robertson PW. Hepatitis B and C in New South Wales prisons: prevalence and risk factors. Med J Aust 1997;166(3):127-30.

117. Day C, Ross J, Dolan K. Characteristics of Aboriginal Injection Drug Users in Sydney, Australia: Prison history, hepatitis C status and treatment experiences. http://www.haworthpressinc.com/store/ArticleAbstract.asp?ID=40029

118. National American Indian and Alaska Native Heritage Month. Centers for Disease Control and Prevention, Division of Viral Hepatitis. http://www.cdc.gov/ncidod/diseases/hepatitis/spotlights/ai_an.htm

119. US department of human services, Office of Minority Health. Viral Hepatitis. http://www.omhrc.gov/templates/content.aspx?ID=6494

120. McMahon BJ, Hennessy TW, Christensen C, Bruden D et al. Epidemiology and Risk Factors for the Hepatitis C in Alaska Natives. Hepatology 2004; 39:325-32.

121. McMahon BJ. Viral hepatitis in the Arctic. Int J Circumpolar Health. 2004;63 Suppl 2:41-8.

122. Tulisov A, McMahon BJ, Koch A, Minuk G, Chulanov V, Bruce MG, Uhanova J et al. Viral hepatitis in the Arctic. A review from a Circumpolar Workshop on Viral hepatitis, ICCH13. Alaska Med. 2006;49 (2 Suppl):193-203.

123. Neumeister AS, Pilcher LE, Erickson JM, Langley LL, Murphy MM, Haukaas NM, Mailliard ME, Larsen JL. Hepatitis-C prevalence in an urban native-American clinic: a prospective screening study. J Natl Med Assoc. 2007;99(4):389-92.

124. Leon P, Venegas E, Bengoechea L, Rojas E, Lopez JA et al. Prevalence of infections by hepatitis B, C, D and E viruses in Bolivia. Rev Panam Salud Publica 1999 Mar;5(3):144-51

125. Soares MC, Menezes RC, Martins SJ, Bensabath G. Epidemiology of hepatitis B, C and D viruses among indigenous Parakana tribe in the Eastern Brazilian Amazon Region. Bol Oficina Sanit Panam 1994 Aug;117(2):124-35

126. Ferrari JO, Ferreira MU, Tanaka A, Mizokami M. The seroprevalence of hepatitis B and C in an Amerindian population in the southwestern Brazilian Amazon. Rev Soc Bras Med Trop 1999 May-Jun;32(3):299-302

127. Blitz-Dorfman L, Monsalve F, Atencio R, Porto L, Monzon M, Favorov MO et al. Serological survey of markers of infection with viral hepatitis among the Yukpa Amerindians from western Venezuela. Ann Trop Med Parasitol. 1996;90(6):655-7

128. Echevarria JM, Blitz-Dorfman L, Pujot FH. Infection by hepatitis virus among the indigenous populations of South America: a review of the problem. Invest Clin 1996 Sep;37(3):191-200

129. Ohba K, Mizokami M, Kato T, Ueda R, Gurtsenvitch V et al. Seroprevalence of hepatitis B virus, hepatitis C virus and GB virus-C infections in Siberia. Epidemiol Infect 1999; Vol. 122 (1):139-43

130. Netesova IG, Iaroslavtseva OA, Dryga SA, Posukh OL, Osipova LP et al. Frequency of encountering markers of viral hepatitis A, B, and C in the aboriginal inhabitants of the northwest region of Siberia. Vopr Virusol 1995 Jul-Aug;40(4):172-4.

131. Langer BC, Frosner GG, von Brunn A. Epidemiological study of viral hepatitis types A, B, C, D and E among Inuits in West Greenland. J Viral Hepat 1997 Sep;4(5):339-49

132. Hepatitis C – Statistics. Australian Federation of AIDS Organizations Submission: Review of the 4th National HIV/AIDS Strategy. 31 May 2002. http://www.ntac.org.au/hepc_stats.htm

133. P.Riben, G.Bailey, S.Hudson, K.McCulloch, T.Dignan, D.Martin. Hepatitis C in Canada's First Nations and Inuit Populations: An Unknown Burden. Can J Public Health 2000; Vol. 91 (Supplement 1): S16-S17.

134. J. Wu, S. Zou, A. Giulivi. Current hepatitis A status in Canada. Can J Infect Dis 2001; Vol. 12 No 6:341-4

135. J Zhang, S Zou, A Giulivi. Epidemiology of hepatitis B in Canada. Can J Infect Dis 2001; Vol. 12 No 6:345-50

136. G Minuk, J Uhanova. Chronic hepatitis B Infection in Canada. Can J Infect Dis 2001; Vol. 12 No 6:351-6

137. AT RISK, Recommendations for a Strategy on HIV, Blood-borne Pathogens and Injection Drug Use. A*ccessed 7.02.2008* http://www.health.gov.sk.ca/mc_dp_skhlth_at_risk_booklet.pdf

138. Alberta Blood-borne Pathogens Surveillance Working Group. Alberta Blood-borne Pathogens Surveillance Report 2003. Edmonton, AB. Alberta Health and Wellness. http://www.health.alberta.ca/resources/publications/BBP03.pdf

139. MB Health, Reportable Diseases Manitoba: CDC Unit Annual Review and monthly reviews; http://www.gov.mb.ca/health/publichealth/cdc/surveillance/

140. Patrick DM, Tyndall MW, Cornelisse PG, Li K, Sherlock CH, Rekart ML et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. CMAJ. 2001 Oct 2;165(7):889-95.

141. Dawood M, Smart G, Wood M, Wu H-X, Paton S, Wu J. Hepatitis C virus infection among First Nation and non-First Nation people in Manitoba, Canada —

a public health laboratory study. Canadian Journal of Microbiology, Volume 52, Number 10, 1 October 2006 , pp. 999-1005(7).

142. Forrester L. The Incidence of acute hepatitis C Infection in the Canadian Aboriginal Population, 1999-2001. Proceedings from the First Aboriginal Hepatitis C Conference, April 30 – May 3, 2002, Edmonton

143. Moses S., Mestery K., Kaita KDE., Minuk GY. Viral Hepatitis in a Canadian Street-Involved Population. Can J Public Health 2002; Vol. 93 (2):123-8.

144. Siushansian J, Vooght M, Archibald C.P., Young E., Bangura H., Hudson S., Horsman G., Lior L.Y., Allen M., Whitehead S., Nowgesic E., Sutherland D. The Prince Albert Seroprevalence Study (PASS), 02/1996 – 05/1997.

145. Higgins B. Issues relating to hepatitis C and HIV infection in prison. Proceedings from the First Aboriginal Hepatitis C Conference, April 30 – May 3, 2002, Edmonton.

146. The Lethbridge connection. http://www.lethbridgehiv.com/ *Accessed 27.07.2008*

147. Elias BD. The influence of the social environment on the health of Manitoba First Nations Communities. PhD Dissertation, Chapter 2.

148. Heath K, Li K, Muller J, Hogg R et al. Honouring the Warrior Spirit: Bringing Change Through Protecting, Preparing and Providing: A collaborative report on the occurrence of HIV, HCV and TB in Aboriginal injection drug users in Vancouver. The Evidence Speaks. Monograph Series Number 9 www.cheos.ubc.ca

149. Elliott L, Blanchard J, Dawood M, Beaudoin C, Dinner K. The Winnipeg Injection Drug Epidemiology (WIDE) Study. Public Health Branch, Manitoba Health

150. Northern Health Research Unit, University of Manitoba (J. O'Neil et al). Research on HIV/AIDS in Aboriginal People. A Background Paper. Medical Services Brunch, Health Canada. Cat. No.: H34-94/1998E, ISBN 0-662-83281-7

151. Carl Orr. Patient Advocate Developer for the Northwest Region of the Ontario Aboriginal Health Advocacy Initiative (OAHAI). www.niichro.com

152. Health Canada, Annual report of HIV/AIDS among Aboriginals (1999-2000) http://www.hc-sc.gc.ca/fnihb/cp/annualreview/hiv_aids.htm, *accessed 01.09.2007*

153. Health Canada, Management Guidelines for the HCV/HIV Co-Infected Adults. Recommendations of a multidisciplinary expert panel, October 31, 2000. http://www.hc-sc.gc.ca/hppb/hepatitis_c/pdf/careGuideMgmt.pdf, *accessed 01.09.2007*

154. Walk The Red Road. Chee Mamuk Aboriginal program. BCAAAP/HOS Hepatitis C Teaching Toolkit: www.bccdc.org

155. Shields S. Enchanced Surveilance of Canadian Street Youth – Phase II Self-Identified Aboriginal Youth. Division of STD Prevention and Control, Bureau of HIV/AIDS, STD&TB, 2000.

156. Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML et al. Needle exchange is not enough: lessons from the Vancouver injecting drug use study. AIDS 1997 Jul;11(8):F59-65

157. Ford PM, White C, Kaufmann H, et al. Voluntary anonymous linked study of the prevalence of HIV infection and hepatitis C among inmates in a Canadian federal penitentiary for women. CMAJ 1995; Dec.1; 153 (11):1605-9

158. Ford PM, Pearson M. et al. HIV, Hepatitis C and risk behaviour in a Canadian medium-security federal penitentiary. QJM 2000; 93:113-119

159. Lior L and Stratton E. Seroprevalence of HIV, hepatitis B and hepatitis C viruses and high risk behavior among IDU and sexual partners of IDU, October 1996-February 1997. Halifax, NS Department of Health report.

160. A Health Care Needs Assessment of Federal Inmates. Can J Public Health 2004; 95 Supplement 1.

161. YouthCO AIDS Society Vancouver, BC (p.104) in Collection of Project Case Studies. Hepatitis C Prevention, Support and Research Program www.healthcanada.ca/hepc

162. Kingston Street Health Centre (p.27) in Collection of Project Case Studies. Hepatitis C Prevention, Support and Research Program www.healthcanada.ca/hepc

163. Fisher DG, Fenaughty AM, Paschane AA, Paschane DM, Cagle HH, Orr SM. Hepatitis C Virus Infection among Alaskan Drug Users. Am J Public Health 1997; Vol. 87 (10): 1722-4.

164. Wiebe J. Profile of Hepatitis &Injection Drug Use in Canada. A Discussion Paper. September 2000. www.hc-sc.gc.ca

165. Taylor L. Manitoba Hepatitis C Needs Assessment, 2001. Commissioned by the Hepatitis C Society of Canada, Manitoba Chapter

166. Nicole Eshkakogan, AYN Writer, Edmonton (Nov.10, 2003). Hepatitis C: A Mystery to Many Aboriginal Youth. www.niichro.com

167. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology 2002;36:S21-S29.

168. Kenny-Walsh Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 1999;340(16):1228-33

169. Muller, R. The natural history of hepatitis C: clinical experiences. J. Hepatol. 24(2 Suppl):52-54, 1996.

170. Vogt M, Lang T, Frösner G, Klingler C, Sendl AF, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med. 1999; 341(12):866-70.

171. Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, Realdi G. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. J Hepatol. 1992;16(3):273–281.

172. Koretz RL, Abbey H, Coleman E, Gitnick G. Non-A, non-B post-transfusion hepatitis. Looking back in the second decade. Ann Intern Med. 1993 Jul 15;119(2):110–115.

173. Mattson L, Sonnerborg A, Weiland O. Outcome of Acute Symptomatic Non-A, Non-B Hepatitis - A 13- Year Follow-Up Study of Hepatitis-C Virus Markers. Liver 1993;13:274-8.

174. Di Bisceglie AM, Goodman ZD, Ishak KG et al. Long term clinical and histopathological follow up of chronic posttransfusion hepatitis. Hepatology 1991; 14: 969-74.

175. Gordon, S. C., Elloway, R. S., Long, J. C. & Dmuchowski, C. F. The pathology of hepatitis C as a function of mode of transmission: blood transfusion vs. intravenous drug use. Hepatology 1993;18: 1338–1343.

176. Tong MJ. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995; 332(22): 1463-6

177. Seeff, L.B., Miller, R.N., Rabkin, C.S., Buskell-Bales, Z., Straley-Eason, K.D., Smoak, B.L. et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. Ann. Intern. Med. 2000;132:105-111

178. Wilson C. Hepatitis C Infection and Type 2 Diabetes in American-Indian Women. Diabetes Care 2004; 27:2116–2119

179. Conjeevaram HS, Kleiner DE, Everhart JE, Hoofnagle JH, Zacks S et al. Viral hep-C Study Group. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. Hepatology 2007;45(1):80-7

180. Jian Wu Y, Shu Chen L, Gui Qiang W. Effects of fatty liver and related factors on the efficacy of combination antiviral therapy in patients with chronic hepatitis C. Liver Int. 2006;26(2):166-72.

181. Soresi M, Tripi S, Franco V, Giannitrapani L, Alessandri A at al. Impact of liver steatosis on the antiviral response in the hepatitis C virus-associated chronic hepatitis Liver Int. 2006;26(9):1119-25.

182. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112(2):463–472.

183. Piperno A, Sampietro M, D'Alba R, Roffi L, Fargion S, Parma S et al. Iron stores, response to alpha-interferon therapy, and effects of iron depletion in chronic hepatitis C. Liver 1996 Aug;16(4):248-54

184. Management of Hepatitis C. NIH Consens Statement Online 1997 Mar 24-26; 15(3): 1-41.

185. Angelucci E, Muretto P, Nicolucci A, Baronciani D, Erer B, Gaziev J et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood 2002; 100(1):17-21.

186. S D Ryder, on behalf of the Trent Hepatitis C Study Group. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Gut 2004;53:451-455

187. McCaughan GW and George J. Fibrosis progression in chronic hepatitis C virus infection. Gut. 2004 Mar;53(3):318-21.

188. Ghany MG, Kleiner DE, Alter H, et al. Progression of fibrosis in chronic hepatitis C. Gastroenterology 2003;124:97–104

189. Fontaine H, Nalpas B, Poulet B, et al. Hepatitis activity index is a key factor in determining the natural history of chronic hepatitis C. Hum Pathol 2001;32:904–9.

190. Lagging LM, Westin J, Svensson E, et al. Progression of fibrosis in untreated patients with hepatitis C virus infection. Liver 2002;22:136–44.

191. Sharma P, Balan V, Hernandez J, Rosati M, Williams J, Rodriguez-Luna H et al. Hepatic Steatosis in Hepatitis C Virus Genotype 3 Infection: Does It Correlate with Body Mass Index, Fibrosis, and HCV Risk Factors? Digestive Diseases and Sciences 2004; Vol. 49, No. 1: 25-9.

192. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, Marinos G, Kaldor JM. Estimating Progression to Cirrhosis in Chronic Hepatitis C Virus Infection 1: Hepatology 2001;34(4 Pt 1):809-16.

193. Dore GJ, Freeman AJ, Law M, Kaldor JM. Is severe liver disease a common outcome for people with chronic hepatitis C? J Gastroenterol Hepatol. 2002 Apr;17(4):423-30.

194. Scott JD, McMahon BJ, Bruden D, et al. High rate of spontaneous negativity for hepatitis C virus RNA after establishment of chronic infection in Alaska Natives. Clin Infect Dis. 2006;42:945–52.

195. Grebely J, Raffa JD, Lai K, Krajden M, Conway B, Tyndall MW. Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. Can J Gastroenterol. 2007 July; 21(7): 447–451.

196. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349(9055):825–832.

197. Deuffic S, Buffat L, Poynard T, Valleron AJ. Modeling the hepatitis C virus epidemic in France. Hepatology 1999;29(5):1596–1601.

198. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology 1998;28(3):805–809

199. Soto B, Sánchez-Quijano A, Rodrigo L, del Olmo JA, García-Bengoechea M, Hernández-Quero J, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997;26(1):1–5.

200. MCHP Population Health Research Data Repository. Medical Services file. http://umanitoba.ca/faculties/medicine/units/mchp/resources/repository/health_medical.html Accessed April 13, 2009.

201. Manitoba Physician's manual. Issued by The Minister of Health www.manitoba.ca/health/manual

202. MCHP Population Health Research Data Repository. Hospital abstracts. http://umanitoba.ca/faculties/medicine/units/mchp/resources/repository/health_hospital.html Accessed April 13, 2009.

203. Metge C., Black C., Peterson S., Kozyrsky A. The Population Use of Pharmaceuticals. Med Care Suppl, Vol 37 (6): 42-59.

204. Manitoba Health. Population tables www.manitoba.ca/health

205. Statistics Canada, 2006 Census. http://www.gov.mb.ca/contact/faq.html

206. Roos LL, Walld R, Wajda A, Bond R, Hartford K. Record Linkage Strategies, Outpatient Procedures, and Administrative Data. Medical Care 1996; 34 (6): 570-82.

207. Statistics Canada. Age-specific all-cause mortality rates for Canadian population, 1998. http://www.statcan.gc.ca/start-debut-eng.html

208. MCHP Concept Dictionary. Service Types, Physician Visits. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1225#a_concepts

209. SAS manual. Proportional hazard regression. http://www.sas.com

210. Callaghan RC, Tavares J, Taylor L. Mobility Patterns of Aboriginal injection drug users of between on -and off-reserve settings in northern British Columbia. Int J Circumpolar Health 2007; 66(3): 241-247

211. S.Shields, T.Wong, J.Mann, A.Jolly, D.Haase, S.Mahaffey et al. Prevalence and correlates of chlamydia infection in Canadian street youth. Journal of Adolescent Health 2004; 34 (5): 384-390

212. Get The Facts. Hepatitis C Prevention, Support, and Research Program. Health Canada. http://www.phac-aspc.gc.ca/hepc/pubs/iduyth-udijns/pdf/aboutFactsSheet2.pdf accessed 03.11.2006

213. Roy E, Boudreau J-F, Boivin J-F. Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. Drug and Alcohol Dependence 2009;102 (1-3):158-61.

214. Callaghan RC, Cull R, Vettese LC, Taylor L. A gendered analysis of Canadian Aboriginal individuals admitted to inpatient substance abuse detoxification: a three-year medical chart review. The American Journal of Addictions 2006; 15:380-86.

215. Mehrabadi A, Craib K J P, Patterson K, Warner A, Moniruzzaman A, Ward-Burkitt B et al. The Cedar Project: a comparison of HIV-related vulnerabilities

amongst young Aboriginal women surviving drug use and sex work in two Canadian cities. The International journal on drug policy 2008;19(2):159-68.

216. Mehrabadi A, Paterson K, Pearce M, Patel S, Craib KJP, Moniruzzaman A, et al. for the Cedar Project Partnership. Gender Differences in HIV and Hepatitis C Related Vulnerabilities among Aboriginal Young People Who Use Street Drugs in Two Canadian Cities. Women & Health 2008; Vol.48 (3): 235 – 260.

217. Niederau C, Lange S, Heintges T et al.: Prognosis of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998; 28: 1687-1695.

218. Brant L, Harris HE, Ramsay ME, Grieve R, Roberts J on behalf of the HCV National Register Steering Group. Pathways of care and resource utilization in a national cohort of patients with transfusion-acquired hepatitis C. Journal of Viral Hepatitis, 2005, 12, 618–626

219. Cooper CL, Bailey RJ, Bain VG, Anderson F, Yoshida EM, Krajden M, Marotta P; Canadian Pegasys Study Group.Outcomes of peginterferon alpha-2a and ribavirin hepatitis C therapy in Aboriginal Canadians. Can J Gastroenterol. 2008 ;22(8):677-80

220. ScottJD , Garland N. Chronic liver disease in Aboriginal North Americans. World J Gastroenterol 2008; 14(29): 4607-4615

221. Mendenhall CL, Gartside PS, Roselle GA, Grossman CJ, Weesner RE, Chedid A. Longevity among ethnic groups in alcoholic liver disease. Alcohol Alcohol 1989; 24: 11-19

222. Denny CH, Holtzman D, Cobb N. Surveillance for health behaviors of American Indians and Alaska Natives. Findings from the Behavioral Risk Factor Surveillance System, 1997-2000. MMWR Surveill Summ 2003; 52: 1-13

223. Yoshida EM, Caron NR, Buczkowski AK, Arbour LT, Scudamore CH, Steinbrecher UP, Erb SR, Chung SW. Indications for liver transplantation in British Columbia's Aboriginal population: a 10-year retrospective analysis. Can J Gastroenterol 2000; 14: 775-779

224. Martens PJ, Fransoo R, The Need to Know Team. The Manitoba RHA Indicators Atlas: Population-Based Comparison of Health and Health Care Use. http://mchp-appserv.cpe.umanitoba.ca/deliverablesList.html

225. Serfaty L, Aumaitre H, Chazouillers O at al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998; 27:1435-40.

226. Kim WR, Gross JB, Poterucha JJ, Locke GR, III, Dickson ER. Outcome of Hospital Care of Liver Disease Associated With Hepatitis C in the United States. Hepatology 2001;33:201-6

227. Seeff LB, Buskell-Bales Z, Wright EC, Durako SJ, Alter HJ et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. The National Heart, Lung, and Blood Institute Study Group. N Engl J Med. 1992; 327(27):1906-11.

228. Martens PJ, Bond R, Jebamani L, Burchill C, Roos NP, Derksen S, Beaulieu M, Steinbach C, MacWilliam L, et al. The Health and Health Care Use of Registered First Nations People Living in Manitoba: A Population-Based Study http://mchp-appserv.cpe.umanitoba.ca/deliverablesList.html

229. Fransoo R, Martens P, The Need to Know Team, et al. Sex Differences in Health Status, Health Care Use, and Quality of Care: A Population-Based Analysis for Manitoba's Regional Health Authorities http://mchp-appserv.cpe.umanitoba.ca/deliverablesList.html

230. Kaita KDE, Wong S, Renner E, Minuk GY. Treatment outcomes in a centralized specialty clinic for hepatitis C virus are comparable with those from clinical trials Can J Gastroenterol. 2006 February; 20(2): 87–90.

231. Myers et al. The burden of hepatitis C virus infection is growing: A Canadian population-based study of hospitalizations from 1994 to 2004. Canadian Journal of Gastroenterology, 2008;22(4):381-387

232. Grant WC, Ravi R. Jhaveri, G. McHutchison, Schulman K, Kauf TL. Trends in Health Care Resource Use for Hepatitis C Virus Infection in the United States. Hepatology 2005; 42 (6):1406-13

233. Grebely , Raffa JD , . Lai C, M. Krajden,, T. Kerr , B. Fischer, Tyndall MW. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. J Vir Hepatitis2009; 16(5)352-358

234. Jebamani. LS, Burchill CA, and Martens PJ. Using data linkage to identify First Nations Manitobans. Can J Public Health 2005; 96 (Suppl.1):S28-S32.

235. M. Sinclaire and K. Storm. First Nations Culture and Elders. U of M Aboriginal Student Centre. Cultures

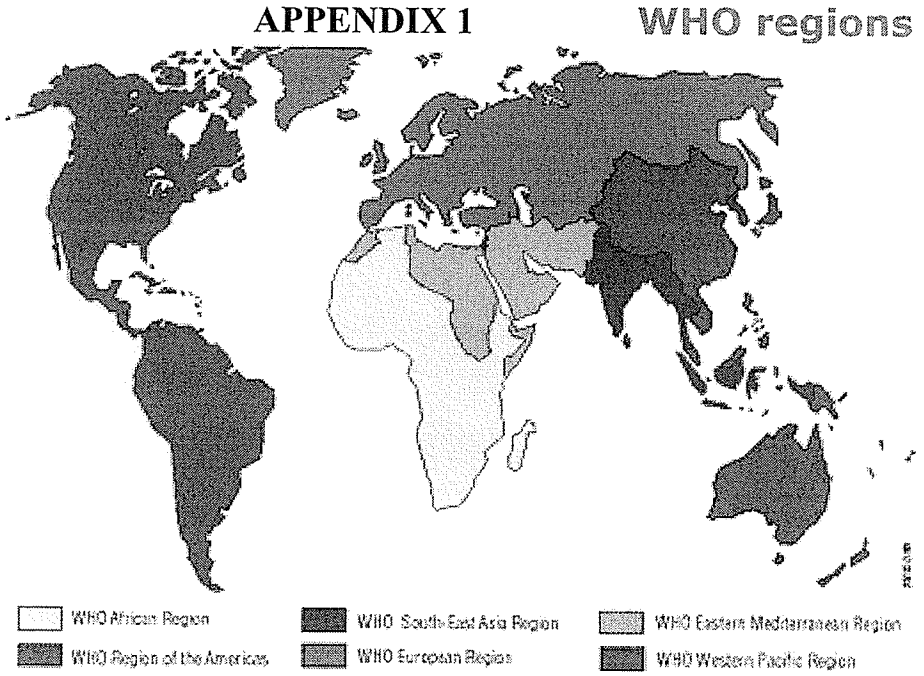
236. INAC. Measuring First Nations well-being. http://www.ainc-inac.gc.ca/pr/ra/index_e.html

237. Ho MS, Hsu CP, Yuh Y, King CC, Tsai JF, Mau LC et al. High rate of hepatitis C virus infection in an isolated community: Persistent hyperendemicity or period-related phenomena? J. Med. Virol. 1997; 52:370-376.

238. Stephenson P. Hepatitis C Carriers Must Be Found and Treated to Avert Crisis. British Medical Journal 2004 May; 328:1031.

239. Manitoba Health. The Descriptive Epidemiology of Sexually Transmitted Infections and Blood-Borne Pathogens in Manitoba: 2002–2003. http://www.gov.mb.ca/health/publichealth/cdc/surveillance/desti.pdf accessed 03.11.2006

APPENDIX 1



Countries in the WHO African Region

- Algeria
- Angola
- Benin
- Botswana
- Burkina Faso
- Burundi
- Cameroon
- Cape Verde
- Central African Republic
- Chad
- Comoros
- Congo
- Côte d'Ivoire
- Democratic Republic of the Congo
- Equatorial Guinea
- Eritrea
- Ethiopia
- Gabon
- Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Kenya
- Lesotho
- Liberia
- Madagascar
- Malawi
- Mali
- Mauritania
- Mauritius
- Mozambique
- Namibia
- Niger
- Nigeria
- Rwanda
- Sao Tome and Principe
- Senegal
- Seychelles
- Sierra Leone
- South Africa
- Swaziland
- Togo
- Uganda
- United Republic of Tanzania
- Zambia
- Zimbabwe

Countries in the WHO Region of the Americas

- Antigua and Barbuda
- Argentina
- Bahamas
- Barbados
- Belize
- Bolivia
- Brazil
- Canada
- Chile
- Colombia
- Costa Rica
- Cuba
- Dominica
- Dominican Republic
- Ecuador
- El Salvador
- Grenada
- Guatemala
- Guyana
- Haiti
- Honduras
- Jamaica
- Mexico
- Nicaragua
- Panama
- Paraguay
- Peru
- Saint Kitts and Nevis
- Saint Lucia
- Saint Vincent and the Grenadines
- Suriname
- Trinidad and Tobago
- United States of America
- Uruguay
- Venezuela

Countries in WHO South-East Asia Region

- Bangladesh
- Bhutan
- Democratic People's Republic of Korea
- India
- Indonesia
- Maldives
- Myanmar
- Nepal
- Sri Lanka
- Thailand
- Timor-Leste

Countries in the WHO European Region

- Albania
- Andorra
- Armenia
- Austria
- Azerbaijan
- Belarus
- Belgium
- Bosnia and Herzegovina
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Georgia
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Israel
- Italy
- Kazakhstan
- Kyrgyzstan
- Latvia
- Lithuania
- Luxembourg
- Malta
- Monaco
- Montenegro
- Netherlands
- Norway
- Poland
- Portugal
- Moldova
- Romania
- Russian Federation
- San Marino
- Serbia
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- Tajikistan
- The former Yugoslav Republic of Macedonia
- Turkey
- Turkmenistan
- Ukraine
- United Kingdom
- Uzbekistan

Countries in the WHO Eastern Mediterranean Region

- Afghanistan
- Bahrain
- Djibouti
- Egypt
- Iran (Islamic Republic of)
- Iraq
- Jordan
- Kuwait
- Lebanon
- Libyan Arab Jamahiriya
- Morocco
- Oman
- Pakistan
- Qatar
- Saudi Arabia
- Somalia
- Sudan
- Syrian Arab Republic
- Tunisia
- United Arab Emirates
- Yemen

Countries in the WHO Western Pacific Region

- Australia
- Brunei Darussalam
- Cambodia
- China
- Cook Islands
- Fiji
- Japan
- Kiribati
- Lao People's Democratic Republic
- Malaysia
- Marshall Islands
- Micronesia (Federated States of)
- Mongolia
- Nauru
- New Zealand
- Niue
- Palau
- Papua New Guinea
- Philippines
- Republic of Korea
- Samoa
- Singapore
- Solomon Islands
- Tonga
- Tuvalu
- Vanuatu
- Viet Nam

APPENDIX 2. **CODES FOR VARIOUS HEPATITIS C-RELATED CONDITIONS**

		Hospital abstracts		Physicians tariffs	
Item	***D/P**	**code**	**description**	**code**	**description**
Liver biopsy	P	5011	Closed (percutaneous) [needle] biopsy of liver	3456	Needle biopsy
		5012	Open biopsy of liver / Wedge biopsy	3457	Open needle biopsy, when exposed at other operation
		5013	Transjugular liver biopsy	3459	Excisional open biopsy when exposed at other operation
		5014	Laparoscopic liver biopsy	3458	Transjugular liver biopsy
HAV	D	0700	Viral hepatitis A with hepatic coma	070*	Viral hepatitis
		0701	Viral hepatitis A without mention of hepatic coma		
Viral hepatitis B	D	*0702*	*Viral hepatitis B with hepatic coma:*	070*	Viral hepatitis
		07020	- acute or unspecified, without mention of hepatitis delta		
			- acute or unspecified, with hepatitis delta		
		07021	- chronic, without mention of hepatitis delta		
			- chronic, with hepatitis delta		
		07022	*Viral hepatitis B w/out mention of hepatic coma*		
		07023	- acute or unspecified, without mention of hepatitis delta		
		0703	- acute or unspecified, with hepatitis delta		
		07030	- chronic, without mention of hepatitis delta		
			- chronic, with hepatitis delta		

		07031 07032 07033 07042 07052 V0261	Active hepatitis B disease with hepatic coma Hepatitis delta with hepatitis B carrier state Hepatitis delta without mention of active hepatitis B disease or hepatic coma Hepatitis B carrier		
Viral hepatitis C	D	07041 07044 07051 07054 0707 07070 07071 V0262	Acute hepatitis C with hepatic coma Chronic hepatitis C with hepatic coma Acute hepatitis C without mention of hepatic coma Chronic hepatitis C without mention of hepatic coma Unspecified viral hepatitis C Unspecified viral hepatitis C without hepatic coma; Unspecified viral hepatitis C not otherwise specified (NOS) Unspecified viral hepatitis C with hepatic coma Hepatitis C carrier	070*	Viral hepatitis

		Hospital abstracts		Physicians tariffs	
Item	**D/P**	**code**	**description**	**code**	**description**
HEV	D	07043 07053	Hepatitis E with hepatic coma Hepatitis E without mention of hepatic coma	070*	Viral hepatitis
EBV/CMV	D	075.xx 0785	Epstein-Barr virus Cytomegaloviral disease		
Other viral hepatitis	D	07049 07059 0706 0709	Other specified viral hepatitis with hepatic coma Other specified viral hepatitis without mention of hepatic coma Unspecified viral hepatitis with hepatic coma Unspecified viral hepatitis without mention of hepatic coma		
Cirrhosis	D	5715	Cirrhosis of liver without mention of alcohol	571*	Chronic liver disease and cirrhosis
Hepatic coma	D	5722	Hepatic coma; Hepatic encephalopathy; Hepatocerebral intoxication; Portal-systemic encephalopathy		

		Hospital abstracts		Physicians tariffs	
Item	**D/P**	**code**	**description**	**code**	**description**
Portal HTN	D	5723	Portal hypertension		
	P	391	Intra-abdominal venous shunt (mesocaval; portacaval; portal vein to inferior vena cava; splenic and renal veins; transjugular intrahepatic portosystemic shunt (TIPS)	2538 7264	Shunt porto-caval T.I.P.S (Transjugular intra-hepatic portosystemic shunt)
HRS	D	5724	Hepatorenal syndrome		
Ascites	D	7895	Ascites		Other symptoms of abdomen and pelvis
	P	5491	Paracentesis (percutaneous abdominal drainage)	3588 3590	Abdominal paracentesis, -initial -subsequent
Varicies	D	4560 4561 4562	Esophageal varices with bleeding Esophageal varices without bleeding Esophageal varices in diseases classified elsewhere		
	P	4223 4233 4413 4513 4291	Endoscopic excision or destruction of lesion or tissue of esophagus; Control of esophageal bleeding by endoscope, Esophageal varices by endoscope; Injection of esophageal varices by endoscope Ligation of esophageal varices	3065 3004	Esophagoscopy with injection of varices or band ligation Hemostasis G. I. Tract by any endoscopic method or technique (e.g., cautery, injection, banding)

		Hospital abstracts		Physicians tariffs	
Item	**D/P**	**code**	**description**	**code**	**description**
Alcoholic Liver Disease	D	5710 5711 5712 5713	Alcoholic fatty liver Acute alcoholic hepatitis Acute alcoholic liver disease Alcoholic cirrhosis of liver; Alcoholic liver damage, unspecified		
LD: other sequelae	D	5728	Other sequelae of chronic liver disease	572*	Liver abscess and sequelae of chronic liver disease
HCC	D	1550 1552 V1007	Malignant neoplasm of liver, primary Liver, not specified as primary or secondary Personal history of malignancy – Liver	155*	Malignant neoplasm of liver and intrahepatic bile ducts
	P	502 5022 503 5029 5094	Local excision or destruction of liver tissue or lesion Partial hepatectomy Lobectomy of liver Other destruction of lesion of liver (Cauterization of hepatic lesion, Enucleation of hepatic lesion) Other injection of therapeutic substance into liver	3464 3494 3492 3491 3030 3496 3497	Partial hepatectomy hepatic lobectomy left hepatic lobectomy right tri-segmentectomy Injection into one or more of the following– metastases, nodes, masses, or celiac plexus Radiofrequency ablation of single liver tumor Ablation of a second or subsequent tumor

		Hospital abstracts		Physicians tariffs	
Item	**D/P**	**code**	**description**	**code**	**description**
Other liver diseases	D	573.xx 5730 5731 5732 5733 5734 5738 5739 5719	Other disorders of liver - Chronic passive congestion of liver - Hepatitis in viral diseases classified elsewhere (Excludes: viral (070.0-070.9) - Hepatitis in other infectious diseases - Hepatitis, unspecified; Toxic hepatitis - Hepatic infarction Other specified disorders of liver; hepatoptosis Unspecified disorder of liver Unspecified chronic liver disease w/out mention of alcohol	573	Other disorders of liver
Fatty Liver	D	5718	Chronic yellow atrophy (liver) Fatty liver, without mention of alcohol		
Biliary cirrhosis	D	5716	Chronic nonsuppurative destructive cholangitis Cirrhosis: cholangitic; cholestatic		

		Hospital abstracts		Physicians tariffs	
Item	**D/P**	**code**	**description**	**code**	**description**
Liver transplant	D	E8780 *	Surgical operation with transplant of whole organ (heart; kidney; liver)		
		V427	Liver transplant		
		V4983	Awaiting organ transplant status		
		V5844	Aftercare following organ transplant		
		99682	Complications of transplanted Liver		
	P	505	Liver transplant		
		5051	Auxiliary liver transplant		
		5059	Other transplant of liver		
		5092	Extracorporeal hepatic assistance (Liver dialysis)		
Chronic hepatitis	D	5714	Chronic hepatitis		
		57140	Chronic hepatitis, unspecified		
		57141	Chronic persistent hepatitis		
		57149	Other Chronic hepatitis: Active; Aggressive Recurrent hepatitis		
SBP	D	56723	Other suppurative peritonitis		

		Hospital abstracts		Physicians tariffs	
Item	**D/P**	**code**	**description**	**code**	**description**
HIV/ AIDS	D	042 07953 V08	Human immunodeficiency virus [HIV] disease Acquired immunodeficiency syndrome (AIDS) AIDS-like syndrome AIDS-related complex (ARC) HIV infection, symptomatic Human immunodeficiency virus type 2 [HIV-2] Asymptomatic HIV infection status		
Alcohol abuse	D	303.xx 291.xx 3050 2918 2919	Alcohol dependence syndrome Alcohol-induced mental disorders Alcohol abuse Other specified alcohol-induced mental disorders Unspecified alcohol-induced mental disorders	303 291	Alcohol dependence syndrome Alcohol-induced mental disorders
Diabetes mellitus	D	250.xx	Diabetes mellitus	250	Diabetes mellitus

***D – Diagnosis**
P- Procedure

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