

Liver Disease in Canada

A CRISIS IN THE MAKING



AN ASSESSMENT OF LIVER DISEASE IN CANADA

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CANADIAN
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EXECUTIVE SUMMARY

As the largest internal organ, the liver is tied into virtually every critical process of the body. Despite its vital role in maintaining overall health, the liver is routinely ignored by the majority of Canadians. Unfortunately dismissing the liver has dangerous consequences to quality of life and life expectancy but few understand just how high the stakes are.

Over a period of only eight years, the death rate from liver disease has risen nearly 30%. Those directly involved in the care of liver disease patients have seen this tragedy play out again and again in hospitals across the country. And yet there is no sense of urgency to collect or evaluate data to measure the true scope of the disease burden nor is there a sense of urgency to deal with it. Alcohol abuse does cause liver disease however a lack of data and a persistent assumption and stigma linking liver disease with only alcohol have made it difficult to overcome both public and government apathy.

It is estimated that one in 10 Canadians, or more than three million people, has some form of liver disease. The most common forms of liver disease – viral hepatitis, fatty liver disease and liver cancer – are all on the rise which means that the increase in death rates from these diseases and their complications will continue to climb if there is no effective intervention.

Liver disease should not be a death sentence. Effective screening, diagnostic and treatment options exist for many patients but without coordinated strategies, supportive government policies and financial investments in patient care and research, liver diseases will continue to strike from the shadows taking lives and exacting a high toll on the nation's health care systems. The key findings from this report highlight the gaps in care, missed opportunities for prevention and the human impact of liver disease.

VIRAL HEPATITIS

Viral hepatitis is a common infection in Canada. Although the precise prevalence is not known, it is likely that more than 500,000 people are chronically infected with the hepatitis B or hepatitis C virus. Viral hepatitis is much more common than HIV infection, the third major blood borne infection. Those who are infected with hepatitis B or hepatitis C are at risk for the development of cirrhosis, liver failure, and liver cancer. The death rate from chronic viral hepatitis exceeds, and will continue to exceed, that of HIV.

Surveillance: The prevalence of chronic hepatitis B and C and the mortality from these diseases is unknown. Data collected by the Public Health Agency of Canada (PHAC) on hepatitis B focuses on acute, not chronic, infection. However, most disease transmission is from individuals who are chronically infected, and mortality is mostly related to chronic viral hepatitis. Data collected by PHAC on hepatitis C also does not separate acute resolved infection from chronic infection. The lack of accurate data obscures the magnitude of the problem.

Modeling studies have suggested that mortality from hepatitis B and C is increasing, contributing to the general increase in deaths related to liver disease.

Screening: It is recommended that all pregnant women be screened for hepatitis B. Unlike some other jurisdictions, there are no official government recommendations regarding screening of other populations for either hepatitis B or hepatitis C. As a result opportunities to intervene are being missed.

Research: Canada has spent 10 times more on HIV research than hepatitis B research and 5 times more than on hepatitis C research, despite the fact that there are likely to be many more deaths annually from each of hepatitis B and hepatitis C than HIV.

Support: The Public Health Agency of Canada provides about \$10M/year for hepatitis C programs but little for hepatitis B. Some provincial governments have support programs for hepatitis B and C, but these are not comprehensive.

Treatment of both hepatitis B and hepatitis C is inadequate in Canada. Less than 10% of hepatitis B patients and less than 25% of hepatitis C patients have been effectively treated. There are multiple barriers to treatment.

Restrictive reimbursement policies: The reimbursement recommendations from the Canadian Drug Expert Committee (CDEC) and from most provinces leave many patients without access to treatment. These restrictions are not scientifically based, nor do they conform to clinical practice, but appear to be solely cost-based.

Hepatitis awareness: Patients and communities where these diseases are prevalent are not aware of the seriousness of these infections and their consequences. Part of this stems from lack of education in the immigrant communities, and part from cultural stigma and cultural concepts of medicine in these communities. There is a need for increased awareness on the part of family practitioners as to the significance of abnormal liver blood tests in patients with chronic viral hepatitis, and better understanding of the natural history of these infections.

Inadequate manpower: There are very few hospitals in Canada that have dedicated in-patients beds for patients with chronic liver disease. The number of physicians who are trained to undertake treatment of patients with liver disease, particularly hepatitis C and hepatocellular carcinoma is limited. Treatment of hepatitis C is complex and labour-intensive and requires nursing assistance. The majority of nurses in Canada who look after patients with hepatitis C are paid by the pharmaceutical industry, rather than, as with other diseases, by the provincial Ministries of Health.

Costs: Treatment of hepatitis B and hepatitis C is expensive, but the lifetime costs are less than the lifetime costs of treating HIV. Avoiding advanced liver disease will lead to future cost savings.

With all the restrictions on adequate care of chronic viral hepatitis, Canada faces an impending massive increase in deaths related to these conditions. Data from Statistics Canada already shows an increase in chronic liver disease deaths and an increase in deaths from liver cancer. Predictions are that viral hepatitis-related mortality will continue to increase beyond 2020. The death rate from liver cancer related to hepatitis B alone will increase by about 50%. There are also predictions of increases in death from hepatitis C. Hundreds of thousands of Canadians are at risk of these consequences ~ yet this outcome is largely preventable. There is excellent treatment for hepatitis B that will more or less permanently suppress the virus and reduce, or even eliminate, the risk of cirrhosis and liver cancer. Treatment for hepatitis C is improving, so that some forms of hepatitis C can be cured in about 70% of cases, and even better treatment is on its way. For those who have established cirrhosis or who are at higher risk of liver cancer, there are methods to provide long-term screening for cancer, and for curative treatment of most small cancers detected by screening.

In order to realize these potential gains however, Canada needs better surveillance, better data collection, better education, better access to treatment and more funding for research. Failure to institute these improvements will mean that there will be no reduction in mortality rates.

Governments elsewhere have recognized the threat posed by chronic viral hepatitis and have developed comprehensive programs to address it. There are no such programs in Canada.

NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is a result of accumulation of fat in the liver and has several causes, including obesity and diabetes. It is called non-alcoholic liver disease because the appearances of the liver under the microscope are identical to those seen in alcoholic liver disease, and yet this condition occurs in those who do not abuse alcohol. NAFLD is the most common liver disease in Canada, afflicting as much as 25% of the population. As with viral hepatitis, NAFLD is a progressive liver disease that over many years causes cirrhosis and liver cancer. With the increasing prevalence of obesity and diabetes, NAFLD is predicted to increase in prevalence and to contribute to liver-related deaths. The full impact of this form of liver disease is probably some years in the future as the current overweight generation ages. However, in time, non-alcoholic fatty liver disease will probably be the main contributor to the high prevalence of end-stage liver disease.

ALCOHOLIC LIVER DISEASE

Alcoholic liver disease is the result of excessive alcohol consumption and is seen in all social groups, including those who consume regularly, but who are not addicted to alcohol. There are two forms of alcoholic liver disease, acute alcoholic hepatitis and alcoholic cirrhosis. Both may co-exist and both are potentially fatal.

The consumption of alcohol is increasing in Canada. There is a direct relationship between overall alcohol consumption in a country or region and the incidence of alcohol-related liver disease. Therefore, alcoholic liver disease will likely also contribute to an increase in the liver disease death rate.

CIRRHOSIS

Cirrhosis is the final common pathway of most forms of liver disease. The term refers to a condition of heavy scarring of the liver characterized by a loss of liver cells, reduced blood flow through the liver and a reduced ability to regenerate. Initially, cirrhosis can be completely silent, with no abnormalities in blood tests or on imaging. Eventually there is loss of liver function and other complications such as an accumulation of fluid in the abdominal cavity, a confused mental state, and internal bleeding.

The incidence and prevalence of cirrhosis and of liver-related death has increased, and will continue to increase, along with the increase in the major causes of liver disease described above. The facilities available to manage end-stage liver disease are barely adequate at present, and are likely to become completely overwhelmed in future. The only treatment for end-stage liver disease is liver transplantation, and the magnitude of the problem can be gauged by the fact that there are over 5,000 liver deaths/year, and only about 400 transplants. Liver transplantation is clearly not the answer to chronic liver disease.

HEPATOCELLULAR CARCINOMA (HCC)

Chronic injury to the liver, from almost any cause, damages the liver in two ways – by laying down scar tissue leading to cirrhosis, and by inducing the development of liver cancer. There are two major forms of cancer that start in the liver, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Liver cancer is one of the few cancers that is increasing in incidence and in mortality. This is due to the increasing prevalence of the underlying liver diseases and the aging of the population that have those diseases.

However, unlike many other cancers, there are well-recognized methods to reduce liver-cancer-related mortality, namely prevention and treatment of the underlying liver disease. There are also methods to reduce mortality in those who develop HCC, in particular screening of at-risk patients. And yet, these measures are not being implemented on a wide scale.

RESOURCES

Facilities and resources in Canada to deal with end-stage liver disease are inadequate. There are insufficient hospital facilities and too few physicians and nurses trained to look after end-stage liver disease. Liver disease is becoming a very common reason for admission to hospital, with the attendant high costs. This will put additional pressure on already tight in-patient beds across the country. The costs of treatment of liver disease are high. A course of treatment for hepatitis C may cost \$20,000-70,000 depending on the subtype of the virus (genotype). Treatment of hepatitis B may cost between \$7,000-9,000/year for 10-20 years or more. Drug treatment for hepatocellular carcinoma costs \$6,000/month. Liver transplantation costs upwards of \$100,000 per case with ongoing costs for medical care and immunosuppressive drugs. Governments are going to have to better organize care for patients with these diseases, both to improve outcomes and reduce the associated costs. This document includes a number of recommendations that will improve the overall management of these diseases, and potentially reduce the costs of managing liver disease.

INTRODUCTION

The liver is vital to the day-to-day functioning of the body and yet it is routinely ignored or overlooked. This indifference coupled with the popular belief that liver disease affects only alcoholics and drug addicts has allowed people to dismiss this serious national health issue. With dramatic increases in death rates and burgeoning health care costs related to viral hepatitis and other forms of liver disease however, it is time to look beyond the stereotypes to see the complete picture of liver disease in Canada – before it is too late.

The Canadian Liver Foundation commissioned this report to show—for the first time – the true scope of liver disease in this country. Using information from various sources including government, academic and institutional databases and individual treating physicians, our experts collected facts and figures and extrapolated data on the most prevalent forms of liver disease. It was no easy task. Liver disease is often categorized under digestive ailments, infectious diseases or cancer or it may not be tracked at all. What we found was alarming and what we could not find even more so.

There are gaps in our knowledge about the prevalence, incidence and mortality associated with viral hepatitis and other forms of liver disease in Canada. Government databases focus on tracking acute infections rather than chronic conditions and data collection across all jurisdictions is inconsistent and incomplete. What is clear, however, is the devastating impact of liver diseases on individuals and families and the increasing burden on our health care system.

Canadians are suffering and dying from treatable and, in some cases, preventable liver diseases. The reasons why are complex but potential solutions are not insurmountable. Where we possess the knowledge and the tools to prevent or treat liver disease, what is lacking is equal access, coordination and a sense of urgency to intervene. And where we do not possess the knowledge or the resources, there is no strategy for change nor the political will to invest in one.

The reality is that Canada's health care system is failing Canadians with liver disease. To prevent tens of thousands of unnecessary deaths, federal and provincial governments need to recognize the magnitude of the problem and take action to improve surveillance, screening, access to treatment, patient care resources and research. Liver disease is too pervasive and deadly to be ignored any longer.

METHODS

The medical literature was reviewed for data pertinent to liver disease in Canada. Provincial and federal governments were asked to provide information about their policies regarding viral hepatitis and liver disease. Governments were also asked about program funding to deal with liver disease. Government websites were consulted to find information on drug approvals, prevalence incidence and mortality data, reimbursement conditions and government responses to the viral hepatitis epidemics (see later). Additional data was obtained from the pharmaceutical industry. A researcher was hired to document all the findings, and this information was collated for this report.

LIVER DISEASES

The major liver diseases that are responsible for the most morbidity and mortality are viral hepatitis (chronic hepatitis B and C), alcoholic liver disease, non-alcoholic fatty liver disease, cirrhosis and hepatocellular cancer. These conditions account for more than 95% of all deaths due to liver disease. Data will show that all are increasing in incidence. Each condition will be dealt with separately. Where relevant, the approach to managing hepatitis B and hepatitis C will be compared with HIV, the third major blood-borne disease. HIV is transmitted by the same routes as hepatitis B and C, and also causes chronic infection leading to death, and like hepatitis B and hepatitis C, is treatable.

CHAPTER I

HEPATITIS B

Viral hepatitis is an infection of the liver by a virus that causes inflammation and injury to the liver. In acute hepatitis the injury is usually mild and short-lived followed by a full recovery. In some cases however, the injury is severe enough to cause liver failure that may lead to death or to the need for liver transplantation. This is a rare outcome. In chronic viral hepatitis, the infection initially does not cause much injury, but the infection persists indefinitely and may, over many years, lead to cirrhosis, liver cancer and liver failure, ultimately leading to death. Although there are many viruses that infect the liver, the most common and potentially most deadly are hepatitis B and C. Therefore, this report will deal only with these two forms of viral hepatitis.

TRANSMISSION OF HEPATITIS B

Hepatitis B is a blood-borne infection. This means that the disease is transmitted through contact of body fluids with infected body fluids. All body fluids from an infected individual, including blood, saliva, semen and vaginal secretions, can contain the hepatitis B virus and are therefore potentially infectious. The virus is spread through close personal contact. Although the exact mechanism of transmission under these circumstances is not always clear, it presumably has to do with exposure to infected body fluids. The major routes of transmission are: amongst close family members, particularly between an infected mother and her very young children; sexual transmission; exposure to infected blood through injection drug use, tattoos or piercings or medical procedures with contaminated equipment or among health care professionals. Breast-feeding does not transmit infection. Hepatitis B is significantly more infectious than HIV.

NATURAL HISTORY OF HEPATITIS B

There are two forms of hepatitis B. Any new hepatitis B infection goes through an acute phase. By definition, acute hepatitis B resolves within six months, with eradication of the virus from the body, the development of immunity to future infection, and no long-term liver damage. However, persistence of infection beyond six months usually means life-long infection or chronic hepatitis B. In children, the initial infection is largely asymptomatic, whereas in adults the infection is more likely to provoke symptoms. If symptoms occur they may be non-specific or may include jaundice, abdominal pain and nausea. Most children who get infected are not diagnosed because of the absence of symptoms. Very young children (less than five years old) who become infected usually do not clear the virus and remain infected for life. In older children and in adults, the disease is more likely to be short-lived and resolve completely.

Chronic hepatitis B is defined as an infection that is present for more than six months. Most chronic infection is acquired in infancy or early childhood. The likelihood of chronicity after this period declines, until in adulthood the chronicity rate is less than 1%. Over about age 40-50, new infections are once more likely to become chronic.

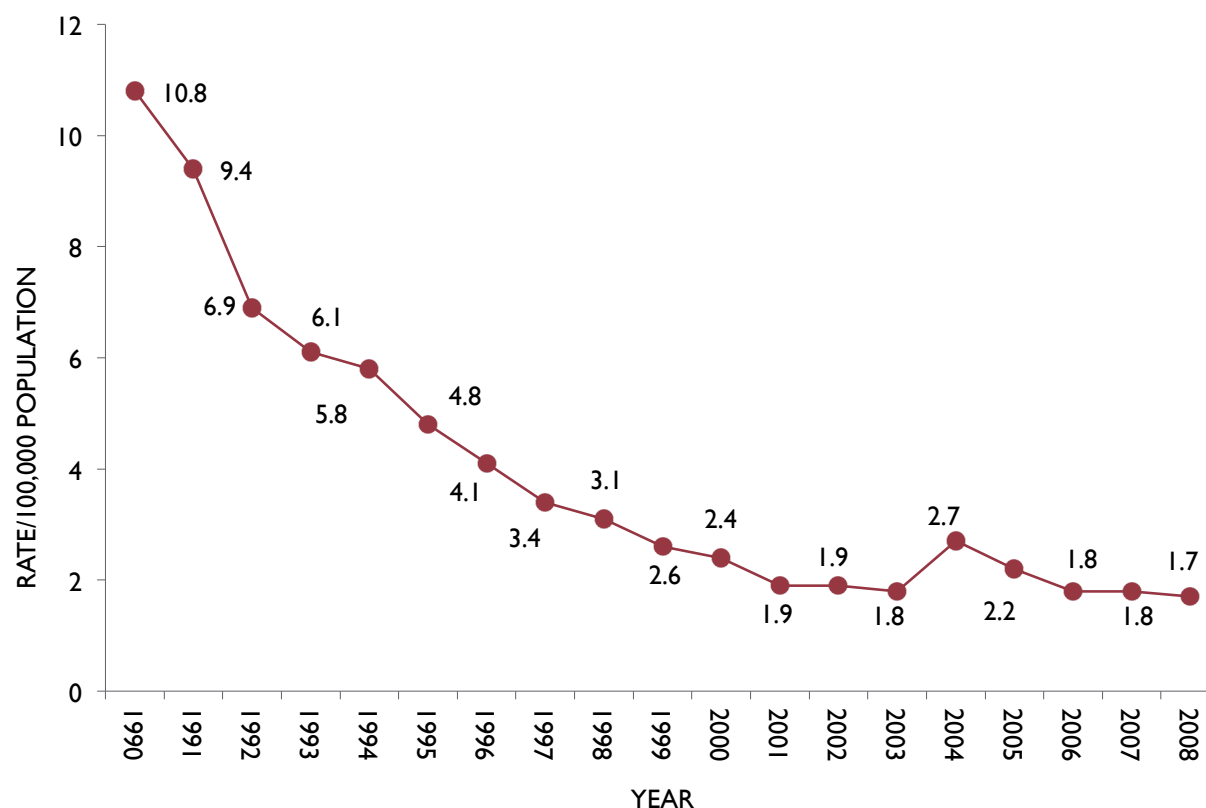
The outcome of chronic hepatitis B is variable. More than 50% of infections become more or less dormant with no long-term adverse consequences to the liver. However, over about age 40, the incidence of primary liver cancer is about 0.2-0.6%/year. Cirrhosis develops in about 15-20% cases and with the development of cirrhosis the risk of cancer increases to about 5-8%/year. Death from the complications of cirrhosis can also occur. Overall, about 25% of untreated males and about 8-10% of untreated women with chronic hepatitis B will die from complications of their disease.

EPIDEMIOLOGY OF HEPATITIS B IN CANADA

PREVALENCE AND INCIDENCE

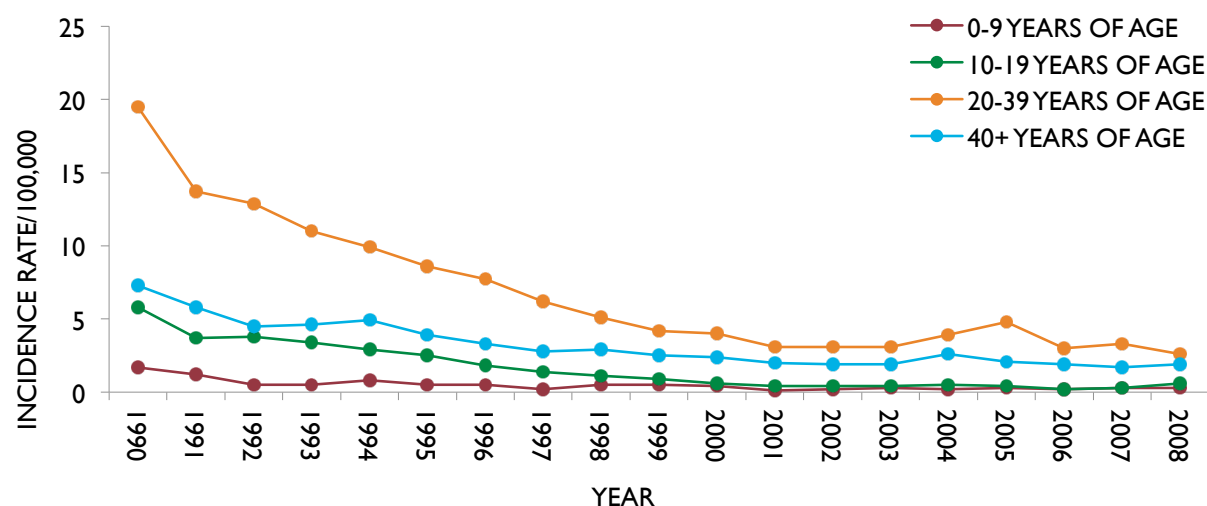
Hepatitis B infection is a reportable disease. All public health jurisdictions record all positive hepatitis B blood tests (HBsAg-positive, which is the marker for active infection) and report data on acute and “indeterminate” cases to the Canadian Notifiable Disease Surveillance System (CNDSS). Until recently, in addition to the CNDSS, the Enhanced Hepatitis Strain Surveillance System (EHSSS) (1) collected additional data from health regions that accounted for about 41% of the Canadian population. EHSSS has not published any data on chronic hepatitis B. EHSSS no longer exists, due to budget restraints. Data from both CNDSS and EHSSS confirms that the incidence of acute hepatitis B is falling (Figure 1). However, because of the asymptomatic nature of new infections, only recorded cases of acute hepatitis are shown in Figure 2 (1). Figure 2 shows that the greatest decline in incidence of acute hepatitis B has occurred in the age group that will have had universal vaccination (age 20-39), confirming the benefits of vaccination in reducing the incidence of acute symptomatic hepatitis B (however, this is not evidence of a reduction in prevalence of chronic hepatitis B, the main objective of hepatitis B vaccination).

FIGURE 1: RATE/100,000 POPULATION OF ACUTE & INDETERMINATE* HEPATITIS B⁽¹⁾



* Indeterminate cases are cases in which neither acute hepatitis B nor chronic hepatitis B could be determined with certainty. This may be due to confusing serological tests or to inadequate follow-up.

FIGURE 2: RATES OF ACUTE AND INDETERMINATE* HEPATITIS B CASES BY YEAR AND AGE GROUP⁽¹⁾



* Indeterminate cases are cases in which neither acute hepatitis B nor chronic hepatitis B could be determined with certainty. This may be due to confusing serological tests, or to inadequate follow-up.

The above data represents reported cases with acute hepatitis B. Reporting on chronic hepatitis B, however, is inadequate: The following quote is from the Public Health Agency of Canada (PHAC) (1):

“Aggregate data on HBV infection from all P/T’s [provinces and territories. ed] are sent to the Public Health Agency of Canada on a regular basis. However, reporting practices across P/T’s remain inconsistent because some jurisdictions report only acute HBV infection cases, while others report acute and indeterminate HBV infection cases together. Since 2004, chronic HBV infection cases are also being reported by some P/T’s. Efforts to investigate and remove duplicate HBV infection cases vary across jurisdictions” (1).

In the absence of official collection of data, seroprevalence studies may provide data. Unfortunately, there are only a few studies on the prevalence of hepatitis B in Canada, and these were undertaken many years ago. One study in a Northern Ontario town found a prevalence of 0.24-0.47% (2). However, a study in immigrants showed that the prevalence varied between 5-10% (3). A study in Vietnamese refugees coming to Canada found that 11.7% were hepatitis B-positive (4). Pregnancy screening in Nova Scotia showed a prevalence rate of 0.87% (5).

Given that none of these studies was representative of the general population, we can conclude that the prevalence of chronic hepatitis B in Canada is unknown. However, these studies strongly suggest that hepatitis B in Canada is highly prevalent amongst immigrant populations (5-12% prevalence vs. < 1% in the general population). This finding is reinforced by clinical experience. All liver disease clinics around the country that have a substantial number of hepatitis B patients report that the majority of these patients are immigrants. This is examined further below.

Most of the mortality and morbidity from hepatitis B occurs in those who are chronically infected, of whom up to 25% will die of their disease if untreated. Acute hepatitis B is usually asymptomatic, resolves spontaneously (particularly in adults), and the death rate is extremely low (32-47 cases/year in Canada)(7). Furthermore, since the period during which someone who is acutely infected can transmit disease is brief (no more than 3-4 months), the source of infection for most new cases of HBV infection is a chronically infected individual. Therefore, from a public health perspective, finding and documenting chronic hepatitis B would be more likely to have an effect on overall infection rates than tracking acute hepatitis B.

ROLE OF IMMIGRATION

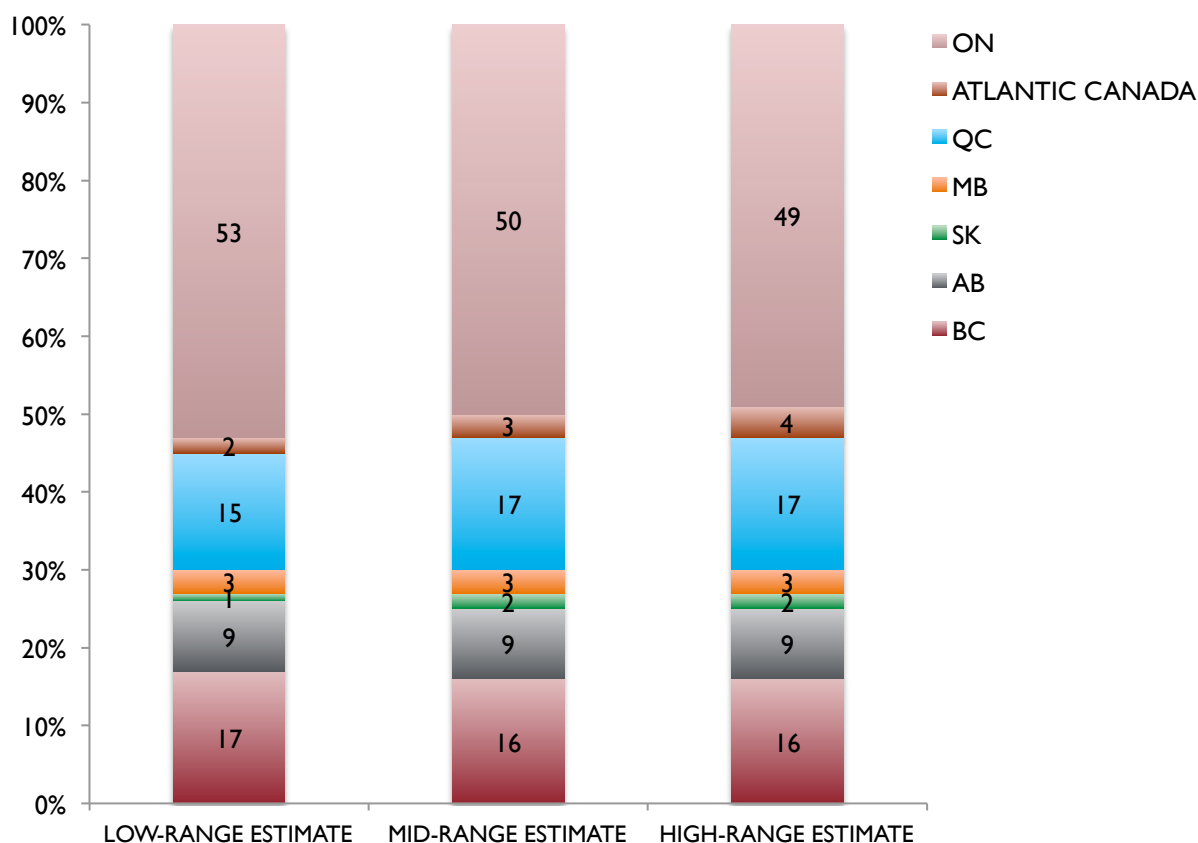
Canada draws a large proportion of its immigrants from areas of the world where hepatitis B is highly prevalent, including China, the Philippines, other areas of South East Asia, the Middle East and Africa. Studies based on the size and origin of the immigrant population from the 2006 census suggested there may have been anywhere between 242,749 to 444,500 hepatitis B-infected individuals in Canada, which corresponds to 0.81% to 1.44% of the Canadian population (6). Between 71% and 89% of these are immigrants (see Table 1). Because of the range of estimates in the home countries, the modeling study derived three estimates, representing the high range, medium range and low range possibilities.

TABLE 1: PREVALENCE OF CHRONIC HEPATITIS B IN CANADIAN IMMIGRANTS⁽⁶⁾

Country/Region	Immigrants alive in 2006	HBV carrier rates (%)			HBV carrier cases		
		Low	Mid	High	Low	Mid	High
North America	250,540	0.19	0.25	0.32	477	626	802
Central America	130,460	0.44	0.88	1.40	577	1,154	1,820
Caribbean	317,765	1.51	3.25	5.00	4,793	10,339	15,887
South America	250,710	0.59	1.16	1.74	1,477	2,916	4,366
Western Europe	424,645	0.32	0.56	0.83	1,356	2,374	3,525
Eastern Europe	511,095	2.12	2.76	3.39	10,838	14,086	17,318
Southern Europe	698,085	1.80	2.52	3.24	12,573	17,587	22,634
Northern Europe	644,530	0.30	0.53	0.59	1,925	3,438	3,827
West Africa	48,645	10.78	13.46	16.14	5,242	6,545	7,850
East Africa	129,920	6.58	9.22	11.87	8,548	11,983	15,420
North Africa	134,505	3.15	6.12	9.09	4,242	8,234	12,225
Central Africa	22,405	8.46	11.44	14.43	1,895	2,563	3,233
South Africa	39,090	4.68	6.20	7.71	1,829	2,424	3,014
West Central Asia and the Middle East	370,520	2.65	3.86	5.08	9,826	14,290	18,835
China and Hong Kong	682,375	11.70	12.25	12.80	79,837	83,590	87,343
Other Eastern Asia	191,995	10.63	11.17	11.71	13,121	14,083	15,055
Philippines	303,190	6.32	7.36	8.39	19,162	22,315	25,438
Other Southeastern Asia	257,800	7.80	8.94	10.09	24,583	27,862	31,138
India	443,690	2.92	3.23	3.55	12,956	14,331	15,751
Other Southern Asia	275,590	2.66	3.35	4.16	6,179	9,790	14,151
Oceania	59,410	1.96	3.13	4.30	1,034	1,652	2,270
Effect of vaccination up to 2006					-5,493	-5,876	-6,262
Total immigrants from all regions	6,186,950	3.65	4.38	5.13	216,977	266,306	315,640
Canadian-born	24,788,720	0.1%	0.35%	0.5%	25,772	90,201	128,860
Grand Total	30,975,670	0.81	1.17	1.44	242,749	356,507	444,500

The provincial distribution of hepatitis B-infected individuals is shown in Figure 3 (6). Whatever estimate of HBV prevalence is used, Ontario has 50% of all chronic hepatitis B, more than the next three provinces combined. Canada continues to absorb immigrants from countries where hepatitis B is common which means if the source countries and the numbers of immigrants from these countries remain constant, then, as shown in Table 2, the prevalence of hepatitis B will increase. There will be an increase of between 23,000 to 30,000 additional hepatitis B-infected persons in Canada to 2020. These numbers take into account the effect of hepatitis B vaccination in the source countries. This data suggests that the prevalence of chronic hepatitis B is increasing, and will continue to increase, as long as immigration patterns remain similar to what they are today. This is despite the introduction of hepatitis B vaccination.

FIGURE 3: DISTRIBUTION OF CHRONIC HEPATITIS B IN THE TOP 7 PROVINCES
(NUMBERS ROUNDED OFF) ⁽⁶⁾



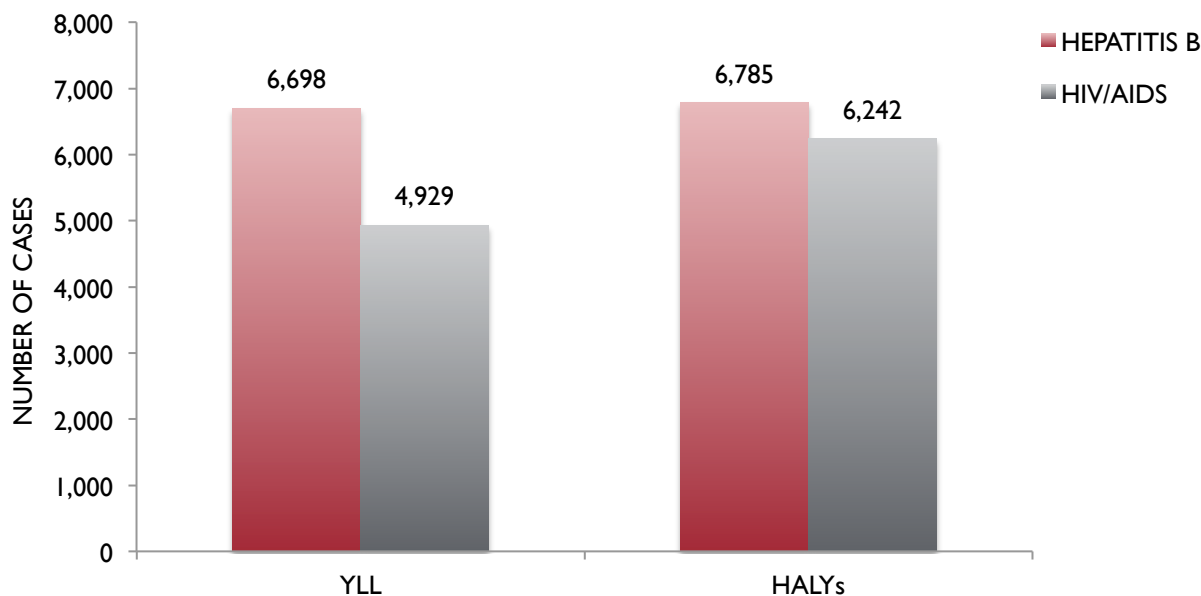
**TABLE 2: PREDICTED NUMBER OF HEPATITIS B-INFECTED PERSONS
IN CANADA TO 2020 ⁽⁶⁾**

Year	Low-range estimate	Mid-range estimate	High-range estimate
2006	242,749	356,507	444,500
2007	248,826	360,841	446,874
2008	251,556	363,575	449,907
2009	254,131	366,096	452,680
2010	256,550	368,403	455,190
2011	258,820	370,509	457,457
2012	260,952	373,355	459,497
2013	262,943	375,114	461,310
2014	264,802	376,697	462,911
2015	266,542	378,119	464,325
2016	268,144	379,366	465,512
2017	269,511	380,314	466,326
2018	270,718	381,038	468,882
2019	271,756	381,540	467,169
2020	272,640	380,710	467,222

HEPATITIS B-RELATED MORTALITY AND MORBIDITY

The death rate in Canada from hepatitis B-related diseases is unknown. Statistics Canada records deaths from viral hepatitis, but does not separate hepatitis B from hepatitis C (or D). Furthermore, deaths from viral hepatitis are recorded separately from deaths from cirrhosis and liver cancer that occur as a consequence of hepatitis B. Therefore, the recorded number of deaths from chronic hepatitis B (11-35 cases/year) represents a significant under-reporting of the actual consequences of the infection (7). Although there is no accurate data available, there have been some estimates based on modeling studies. The Ontario Burden of Infectious Disease Study (ONBOIDS) is the only Canadian study that has modeled the outcomes from hepatitis B (8). This analysis found that hepatitis B in Ontario ranks fifth as a cause of morbidity and mortality among all infectious diseases (Figure 4). There were nearly 7,000 years of life lost in the whole population and additional years of reduced functioning in the cohort. Since Ontario has about 50% of all hepatitis B infected individuals, the years of life lost (YLL) for Canada would be about double that figure.

FIGURE 4: MORTALITY AND MORBIDITY OF HEPATITIS B COMPARED TO HIV/AIDS IN YEARS OF LIFE LOST (YLL) AND HEALTH-ADJUSTED YEARS OF LIFE LOST (HALY)⁽⁸⁾



FUTURE MORBIDITY AND MORTALITY

Modeling data suggests that the absolute number of hepatitis B-infected individuals will continue to increase as a result of immigration, even after taking into account deaths due to hepatitis B and to competing causes (Table 2)(6). As the infected population ages, the incidence of liver disease complications will rise because it is directly related to the duration of infection. Leber et al (6) found that the death rate from hepatitis B-related hepatocellular carcinoma (HCC) in 2008 was about 5.5/100,000 and that the incidence and mortality from hepatitis B-related HCC will continue to increase over the next eight years or more (see Chapter 6: Hepatocellular carcinoma). The model did not include the effects of treatment of hepatitis B.

The Canadian Cancer Society, using Statistics Canada data, also reports that the incidence of HCC is increasing. This data does not indicate the cause of the underlying disease however, so it is difficult to determine the contribution of hepatitis B to these numbers (9).

Other independent modeling studies in the immigrant population have come to similar conclusions (10). This study showed that the mortality from hepatitis B-related liver disease in the hepatitis B-infected immigrants will rise sharply over the next 50+ years,

PRIMARY CARE MANAGEMENT OF HEPATITIS B

There is no data on how well patients with hepatitis B are cared for by their family physicians. The fact that hepatitis B-related hepatocellular carcinoma (HCC) seems to be on the rise and that most patients present with late stage cancer suggests that family physicians are missing opportunities to treat patients and opportunities to screen for HCC.

A survey among primary care residents in medical school showed very poor understanding of the management of hepatitis (11). This included failure to recognize cirrhosis, inappropriate referrals, and less-than-optimal understanding of serological markers of hepatitis B. The authors concluded that opportunities to provide potentially life-saving treatment were being missed.

Family physicians have a key role to play in early identification of hepatitis B. Since hepatitis B is highly prevalent within immigrant communities, most patients with hepatitis B are cared for by physicians from their community. If, as evidenced in the study noted above, family practice residents do not fully understand how to recognize and manage hepatitis B then it represents a challenge in ensuring that patients receive the timely care and referrals that they need. There are not enough specialists to care for the hepatitis B patient population so it is critical that family physicians and specialists are able to work together to address the care needs of these patients.

PATIENT AWARENESS OF HEPATITIS B

Patients lack awareness of hepatitis B and its consequences. A survey of Chinese women in Vancouver confirmed that although most were aware of the existence of hepatitis B, few were aware of how transmission occurred or of the consequences including cirrhosis and HCC. Hepatitis B awareness is impacted by level of education and the ability to speak English (12). Similar data has been reported from the U.S. (13). It is likely that Chinese immigrants elsewhere in Canada, and presumably other immigrant communities for whom English is a second language, would have the same difficulty in understanding the seriousness of hepatitis B. This represents a challenge for patient education.

DRUG THERAPY FOR HEPATITIS B

Hepatitis B treatment is suppressive which means that viral eradication is seldom possible, but viral replication and liver inflammation can be effectively suppressed so that there is no further liver damage. As with HIV infection, many patients with hepatitis B will need life-long therapy. Treatment of chronic hepatitis B has been shown to reduce progression of disease resulting in improved liver function, regression of fibrosis and even cirrhosis, and a reduced risk of developing HCC. There is a large amount of evidence to support this conclusion, although there is only a single randomized controlled study that compares outcomes in cirrhotic hepatitis B patients who were treated with antivirals (lamivudine) compared to untreated controls. This study showed that progression of disease occurred more frequently in the untreated group. Furthermore, when the treated group developed resistance to lamivudine, their prognosis worsened. There are no randomized controlled studies comparing survival in a treated group vs. an untreated group in non-cirrhotic patients. Nonetheless, there is sufficient evidence to suggest that treatment reduces mortality, even in non-cirrhotics and these results are widely accepted and reinforced by several meta-analyses and systematic reviews. The medical profession accepts that suppression of viral replication in chronic hepatitis B reduces mortality, in both cirrhotic and non-cirrhotic populations. Most recently, large-scale population studies from Taiwan have demonstrated that hepatitis B treatment in both cirrhotic and non-cirrhotic patients reduces the rate of development of HCC and reduces mortality (PJ Chen, personal communication).

Unfortunately, reimbursement agencies in Canada do not accept that treatment of hepatitis B reduces mortality in non-cirrhotic patients because there are no randomized controlled trials. However, it would be considered unethical to have a group with active HBV disease go untreated for anything more than a short period of time. There is considerable evidence from other kinds of studies that treatment of hepatitis B at any stage reduces the incidence of HCC. Clinical practice guidelines for the treatment of hepatitis B have been established by all the major international professional liver disease associations and by the Canadian Association for Study of the Liver, the Canadian professional association for hepatology (14-19). All these guidelines specifically state the indications for initiating treatment are active viral replication and ongoing liver injury regardless of the absence or presence of cirrhosis. Thus, reimbursement criteria for hepatitis B treatment in most provinces do not conform to accepted medical practice and scientific evidence.

About two-thirds of patients require public assistance to pay for their hepatitis B treatment. Therefore the restrictions on reimbursement severely limit the ability to treat these patients appropriately.

Currently, most private insurers continue to reimburse all hepatitis B treatments. This creates some inequity for those without private insurance plans. However, insurers are beginning to apply the provincial restrictions to their reimbursement policies. If fully implemented, this will remove the inequity, but to the disadvantage of privately insured patients.

AVAILABLE DRUGS

The drugs that are available to treat hepatitis B include standard and pegylated interferon alpha and drugs that block viral replication, including lamivudine, adefovir, telbivudine, entecavir and tenofovir. Interferons act primarily on the host immune system, although there is probably an antiviral effect as well. These are used for 6-12 months with some suppression of viral replication on therapy, but the majority of patients relapse after the course of therapy has been completed. The inhibitors of viral replication can sometimes be used for a limited period, but frequently these agents need to be used indefinitely.

LICENSING AND REIMBURSEMENT

The process of drug approval in Canada has been associated with long delays that prevent patients from getting access to important drugs in a timely manner. Delays in licensing by Health Canada are shown in Table 3. These delays are in part due to later submissions by the pharmaceutical company in Canada vs. the U.S., but also to delays in the approval process.

TABLE 3: DIFFERENCES IN TIME OF LICENSING DRUGS FOR HEPATITIS B IN CANADA COMPARED TO THE U.S. AND THE EU*

Total difference	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir	PEG-Int alfa
vs U.S.	21 days After	341 days After	444 days After	34 days After	508 days After	301 days After
vs EU	244 days Prior	174 days After	10 Days Prior	147 days Prior	406 days After	433 days After

* Information provided by Gilead Sciences Canada Inc.

On average, these agents were licensed in Canada 12-18 months after approval in the U.S. After licensing, additional approvals for reimbursement are required from CDEC, and from individual provincial drug review boards. Table 4 shows the length of time each drug was in the approval process at CDEC (20)

TABLE 4: TIME IN REVIEW

Therapeutic agent	Time in review (months)
Adefovir	18
Entecavir	11
Telbivudine	6 (not approved)
Tenofovir	6

Thus, it may be one to two years or more after licensing in the U.S. that drugs are available for reimbursement in Canada, if reimbursed at all.

Hepatitis B treatment is relatively expensive, but not as expensive as treatment for other infectious diseases such as HIV. Many provinces have restrictions on reimbursement for hepatitis B therapy, some based on recommendations from CDEC and some based on additional considerations. Reimbursement criteria vary by province. Only in Quebec is the reimbursement policy in line with clinical practice guidelines. The section that follows will describe the restrictions currently in place. It is worth noting that the reimbursement guidelines issued by CDEC are the most restrictive of public payers in the Western world. The guidelines on reimbursement in Ontario are the most restrictive in Canada. The guidelines in the different provinces are listed in Table 5. It is striking that there is no uniformity between provinces with regard to access to hepatitis B treatment.

TABLE 5: REIMBURSEMENT POLICIES FROM CDEC AND IN THE PROVINCES ²⁰⁻²⁹

Province	Available drugs to treat hepatitis B						
	Lamivudine (LAM)	Adefovir (ADE)	Entecavir (ETV)	Telbivudine (TEL)	Tenofovir (TDV)	Standard interferon	Pegylated interferon
CDEC	No recommendation*	For use in combination with LAM after development of LAM resistance	Recommended for cirrhosis only	Not to be listed	Recommended for patients with cirrhosis only	No recommendation*	No recommendation*
<i>*Licensed before establishment of CDEC</i>							
BC	ALT and viral load requirement, but no other restriction	For LAM failure only	As per CDEC	Not listed	As per CDEC	24 weeks, with one renewal if responding	Not listed
AB	Restricted to internal medicine specialists and designated prescribers	Restricted to internal medicine specialists and designated prescribers	Restricted to internal medicine specialists and designated prescribers	Restricted to internal medicine specialists and designated prescribers	Restricted to internal medicine specialists and designated prescribers	Not listed	Restricted to internal medicine and designated prescribers
SK	Special application but no restrictions	As per CDEC	As per CDEC	Not listed	As per CDEC	6 months only, but no other restrictions	48 weeks only. No other restrictions
MB	No restriction	As per CDEC, with exceptions	As per CDEC, with exceptions	Not listed	As per CDEC, with exceptions	Not listed	Not listed

Additional provinces listed on next page.

Province	Available drugs to treat hepatitis B						
	Lamivudine (LAM)	Adefovir (ADE)	Entecavir (ETV)	Telbivudine (TEL)	Tenofovir (TDV)	Standard interferon	Pegylated interferon
ON	F3 or cirrhosis and over age 40 only	LAM failure and F3 or cirrhosis only	Cirrhosis only (includes LAM resistance)**	Not listed	Treatment naïve - cirrhosis only. LAM resistance - F3 and cirrhosis only	24 weeks (HBeAg+ve) or 48 weeks (anti-HBe+ve). No cirrhosis.	Not listed
QC	No restrictions	Usual clinical restrictions only	Usual clinical restrictions only	Not listed	Usual clinical restrictions only	Usual clinical restrictions only	Usual clinical restrictions only
NB	Elevated ALT (No restrictions for specialists)	For LAM resistance only	As per CDEC	Not listed	As per CDEC	Not listed	LAM resistance only
NS ²³	Specialist application, usual clinical restrictions	Usual clinical restrictions only	As per CDEC	Not listed	As per CDEC	Specialist application	24weeks renewable x1
PEI	No information available***	No information available	No information available	No information available	No information available	No information available	No information available
NL ²⁴	No information available	As per CDEC	As per CDEC	As per CDEC	As per CDEC	No information available	No information available

** Ontario and other provinces allow entecavir to be used for LAM resistance despite the fact that all practice guidelines suggest that entecavir is not appropriate for LAM resistance (13)

*** Only 96 cases of hepatitis B reported in PEI. Treatment status not known.

As the province with the highest proportion of hepatitis B carriers in Canada (50%), Ontario is the only province that has attempted to determine the effect of hepatitis B on population morbidity and mortality. Hepatitis B infection is the fifth leading cause of morbidity and mortality among all infectious diseases in Ontario. And yet, Ontario has the most restrictive reimbursement criteria for hepatitis B drugs.

Ontario's listings are also contradictory. All the oral agents except lamivudine are restricted to those with advanced fibrosis (F3 or cirrhosis). Reimbursement for interferon for hepatitis B, in contrast, is only available for those without cirrhosis. Thus, the reimbursement criteria acknowledge on the one hand that patients with early stage disease need treatment (interferon), but then deny such treatment to those who would be treated with oral agents.

CDEC and many provincial governments (BC, SK, ON, NB, NL, PEI, NS) recommend reimbursement for oral agents only for patients with cirrhosis. However, delaying treatment until the development of cirrhosis is not without

consequences. The risk of developing liver cancer increases from less than 1% to more than 5%. Other complications of chronic liver disease also become more frequent once cirrhosis develops. In addition, the psychological cost to patients who cannot access treatment and know that their liver disease is progressing is enormous.

Some provinces insist on proof of elevated alanine aminotransferase (ALT) before providing reimbursement. This is an old concept left over from the days before HBV DNA measurements were available, and ALT measurement was the only way to assess response to treatment. Today, we recognize that ALT is not predictive of outcome or of the need for treatment. HBV DNA is recognized as a much more important predictor of outcome than ALT. Patients can develop fatal liver cancer or liver failure while the ALT remains normal.

The varying regulations in the different provinces mean that if the disease is less severe than cirrhosis, it can be properly treated in Alberta and Quebec, but not elsewhere. If the patient is under 40 in Ontario, there is no therapy available at all.

A cross-Canada study has shown that the major barrier to adequate care for hepatitis B remains the provincial restrictions on reimbursement (30). This study found that 64% of patients on hepatitis B treatment required reimbursement through public drug programs. The therapy that was provided varied depending on availability of public funding vs. private insurance. In 2009, 58% of patients with public coverage were treated with lamivudine, whereas only 10% of patients with private coverage were so treated. Lamivudine is the least expensive hepatitis B drug available, but it is no longer recommended as first-line treatment as there are more potent agents available with lower rates of antiviral resistance.

No other reimbursement agency in Western countries where there is public reimbursement for drugs has similar restrictions as those imposed by CDEC and most provinces.

UPTAKE OF HEPATITIS B TREATMENT IN CANADA

The number of patients with hepatitis B in Canada who are currently undergoing treatment is unknown. The only data that is available comes from IMS Brogan Inc., a company that buys prescription information from pharmacists. They obtain data from about 67% of private insurers and almost all prescriptions for medications reimbursed by government. Data is stratified by whether the prescriptions were new (first time) or repeat. Assessing the number of individuals under treatment is complicated by the fact that some drugs are used for more than one disease, and at similar doses (i.e. tenofovir). Other drugs such as lamivudine are dosed differently for different diseases. Given all these caveats, only a rough estimation of the number of treated patients can be made. According to this data, approximately 8,000 individuals are on treatment for hepatitis B each year. Since treatment is often life-long, this probably means that many of these are repeat prescriptions. However, data from the Ontario Public Drug Program over a single year shows that for drugs used only for hepatitis B (lamivudine in hepatitis B dosing and adefovir) only 841 recipients received reimbursement. For drugs used for hepatitis B and C (standard interferon, which must have been almost exclusively used for hepatitis B), another 126 individuals received reimbursement. For drugs used for hepatitis B and HIV (tenofovir), a further 1,755 received reimbursement (31). There is no way of knowing or estimating the split between hepatitis B and HIV, but assuming that 50% were for hepatitis B that would be another 877 individuals, for a total of 1,844 patients who received reimbursement. If this is 64% of all treated patients (those without private insurance) in Ontario, then the total number of treated patients is about 3,000 individuals. Given that Ontario has between a minimum of 128,000 and a maximum of about 250,000 hepatitis B-infected individuals, it is clear that there is a massive degree of under-treatment. It is not possible to assess the number of treated patients in other provinces, but the uptake of treatment is also likely to be low.

Up to 25% of patients with hepatitis B will die of their disease if left untreated. There are many studies that show that the mortality from hepatitis B can be reduced by treatment. In order to protect the 25% who are destined to die of their disease, we would have to treat more than 25% of all infected individuals. Therefore, if there are 120,000-500,000 hepatitis B infected in Canada, at least 40,000 to 125,000 patients should be undergoing treatment

HEPATITIS B VACCINATION

Vaccination against hepatitis B has been available since the mid-1980s and is very effective for children and adolescents. It protects a smaller proportion of patients when given to older populations. Vaccine protection is thought to be life-long, so that booster doses are not required. Most countries in the world have adopted neonatal vaccination and most infectious disease associations and pediatric associations recommend it. The National Advisory Committee on Immunization in Canada (NACI) advises universal vaccination either at birth or in adolescence (32). All the provinces have instituted universal vaccination, but policies differ. Some have introduced universal neonatal vaccination (BC, NB and PEI), while the others provide adolescent vaccination. The age at which adolescent vaccination is provided varies by province (Table 6).

TABLE 6: HEPATITIS B VACCINATION POLICIES IN THE DIFFERENT PROVINCES⁽³³⁻⁴²⁾

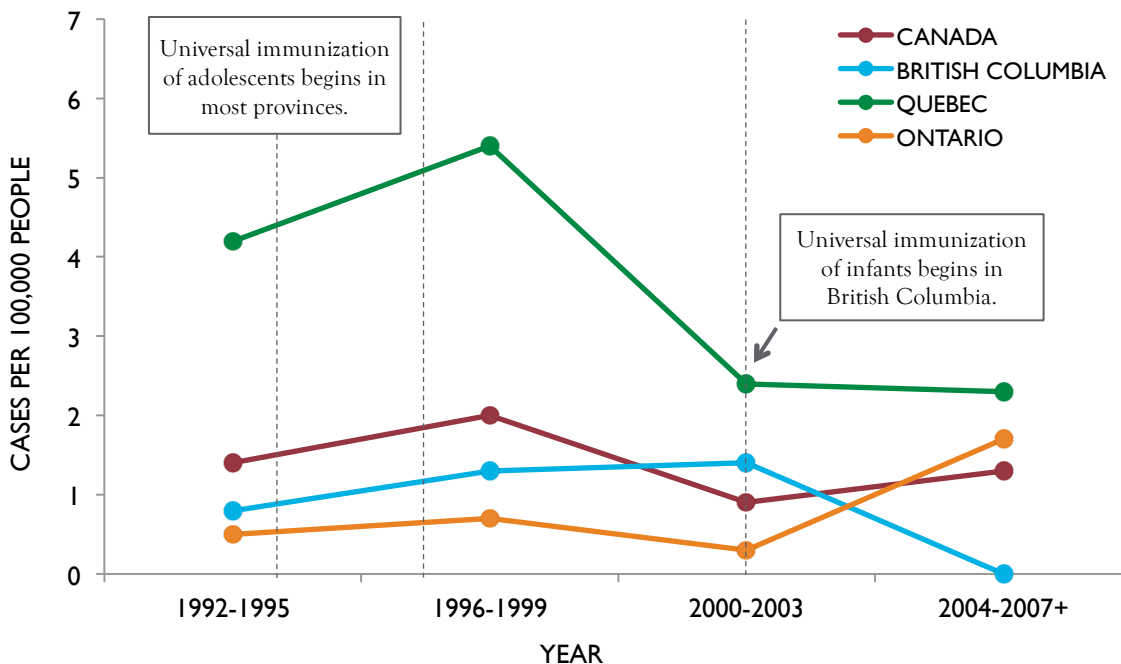
Province	Universal Immunization	Also paid by province
BC	Age 2,4 and 6 months (neonatal)	High risk groups
AB	Grade 5	High risk groups
SK	Grade 6	High risk groups
MB	Grade 4	High risk groups
ON	Grade 7	High risk groups
QC	Grade 4	High risk groups
NB	Neonatal and under 10	High risk groups
NS	Grade 7	High risk groups
PEI	2,4 and 15 months (neonatal)	Hepatitis C and frequent users of blood products
NL	Grade 6	High risk groups

The recommended vaccination schedule is neonatal vaccination at birth, 4 weeks and 6 months of age. Only BC adheres fully to the recommended schedule.

The definition of high-risk groups is not uniform across provinces.

The World Health Organization first recommended universal neonatal vaccination in 1997. Most jurisdictions around the world, including many low prevalence areas have followed that recommendation. In Canada, a comparison of neonatal vs. adolescent vaccination shows that acute hepatitis B in childhood is, if anything, increasing (43). Only in BC, where neonatal and adolescent vaccination is in place, is incidence of childhood hepatitis B falling. Elsewhere in Canada, the rates are either stable or rising (5).

FIGURE 5: REPORTED INCIDENCE OF ACUTE HEPATITIS B INFECTIONS AMONG INFANTS IN CANADA, 1992–2007 ⁽⁴³⁾



This data confirms that adolescent vaccination is not the best strategy to prevent hepatitis B transmission. There are many arguments to support neonatal vaccination as preferable to adolescent vaccination:

- Adolescents who acquire hepatitis B seldom develop chronic disease (<1%)(44). Almost all spontaneously clear the virus and become immune.
- The epidemiology of hepatitis B in Canada suggests that exposure is more frequent in neonates and very young children in immigrant families who are at the highest risk of developing chronic disease.
- Maternal screening for hepatitis B and vaccination of the newborn is universal, but if other members of the family are infected, such as fathers, siblings or grandparents the risk to the baby might not be recognized.
- Studies have shown that in circumstances of high HBV prevalence children of non-carrier mothers develop chronic hepatitis B at a significant rate (7% at age 10)(44).
- All professional medical associations, including pediatrics, infectious diseases, and hepatology, in North America, Europe and Asia recommend neonatal vaccination for hepatitis B as the most effective way of preventing transmission of disease and the development of chronic hepatitis B (46-49).
- The lack of uniformity between provinces puts children who move between provinces at risk of missing vaccination in their province of origin as well as the destination province.
- Canadian data exists that clearly demonstrates that neonatal vaccination is superior to adolescent vaccination (43).

HEPATITIS B-RELATED RESEARCH IN CANADA

Since 1990, research funding for hepatitis B awarded by federal agencies totaled \$11,243,554 (50)(compared to \$93,320,999 for hepatitis C and \$518,000,000 for HIV)(51,52). (For responses by other countries to hepatitis B and hepatitis C epidemics see Chapter 2, “Government responses elsewhere”)

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CHAPTER 2

HEPATITIS C

TRANSMISSION OF HEPATITIS C

Hepatitis C is a blood-borne infection. The virus infects the liver and causes inflammation, which in turn, leads to scarring that culminates in the development of cirrhosis and all its complications including liver failure and liver cancer. Hepatitis C exists in several genetic variants called genotypes. There are at least nine genotypes, but in Canada genotype 1 is the most common. The differences in genotype are not associated with differences in disease severity, but are associated with different sensitivity to current treatment.

Hepatitis C first came to medical attention as a post-transfusion infection, even before there was a diagnostic test. A diagnostic test for hepatitis C first became available in 1991. It soon became apparent that transfusion accounted for a minority of cases in Canada, perhaps 15% of all cases up to the mid 1990s when screening of donated blood for hepatitis C became very efficient. Since that time, transfusion of blood or blood products rarely transmits hepatitis C.

New infections of hepatitis C in Canada occur mostly in injection drug users. Hepatitis C infection occurs more frequently than HIV infection in this situation, and usually occurs within the first year of injection drug use. Although needle exchanges and safe injection sites have been shown to reduce the risk, these are not widely available. The notable exception is Vancouver, where a safe injection site was approved by the Supreme Court of Canada.

NATURAL HISTORY OF HEPATITIS C

A new hepatitis C infection is rarely symptomatic. It is therefore difficult for patients to identify when they became infected. Depending on the population, between 20-30% of those infected will spontaneously clear the virus within about 6-12 months, and will not develop chronic hepatitis C and hepatitis C-related liver disease. Those who develop jaundice with the initial infection are most likely to spontaneously clear the virus. Failure to clear the virus leads to chronic infection. With chronic infection, progression of liver disease is thought to be inevitable in all patients, but the rate at which the disease progresses is highly variable. Some patients might go from infection to cirrhosis in 20 years, however, many will take 40-60 years to develop cirrhosis. There is a perception that only a minority of patients with chronic hepatitis C develop progressive liver disease. This is based on old cross-sectional studies that did not have a time horizon sufficient to allow for detection of hepatitis C complications that might take 30-60 years to develop. It is not possible to predict the rate of progression in any one individual. Paired liver biopsies over time might give some sense of disease progression, but given that liver biopsy will under-estimate severity of disease in about 20-30% of cases, even paired biopsies cannot serve as reliable indicators.

Many patients with chronic hepatitis C complain of a variety of symptoms, ranging from fatigue to depression, itchiness, inability to concentrate and a myriad of other symptoms. These symptoms do not correlate with liver disease severity, concentration of virus in the blood, nor with the viral genotype. Despite the frequency of these symptoms in clinical practice, the vast majority of patients with hepatitis C have no symptoms. Furthermore, in those who do have symptoms, relief of symptoms following viral eradication is transient, suggesting that the symptoms are not due to hepatitis C.

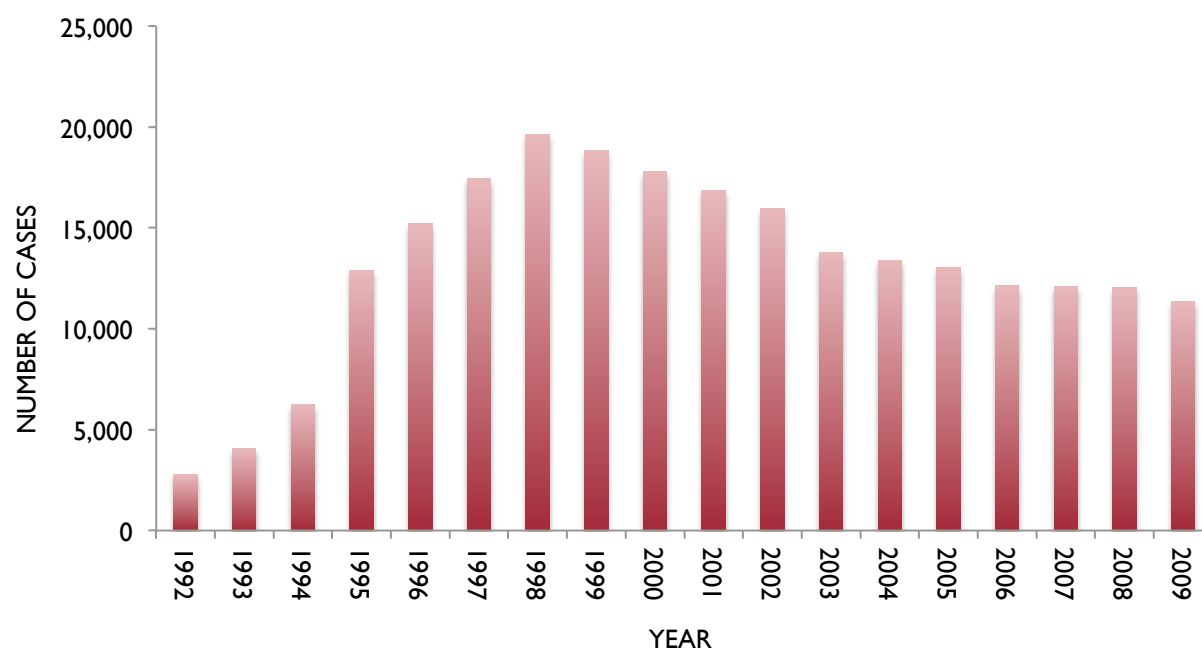
EPIDEMIOLOGY OF HEPATITIS C IN CANADA

PREVALENCE AND INCIDENCE

The prevalence of hepatitis C in Canada is unknown. Modeling studies from 2007 suggested that there were about 242,521 people in Canada infected with this virus (1). However, as of 2009, the Public Health Agency of Canada (PHAC) had records of 236,000 individuals who had been exposed to hepatitis C (2). Trends up to 2009 suggest that between 10,000 and 12,000 new cases are identified each year. Thus, the modeled total of 242,521 has likely been exceeded by now. If the current trend continues over the next 10 years, a further 50,000 or more new cases might be identified. This would suggest that the prevalence is likely much higher than previously thought. Secondly, prevalence in many other Western countries is considerably higher than the modeled data would suggest. In the U.S., it is estimated that there are 3.9 million cases. Since the epidemiology of hepatitis C in Canada is similar to the U.S., prevalence may be similar, i.e., about 350,000 to 400,000 cases – again much higher than previously estimated.

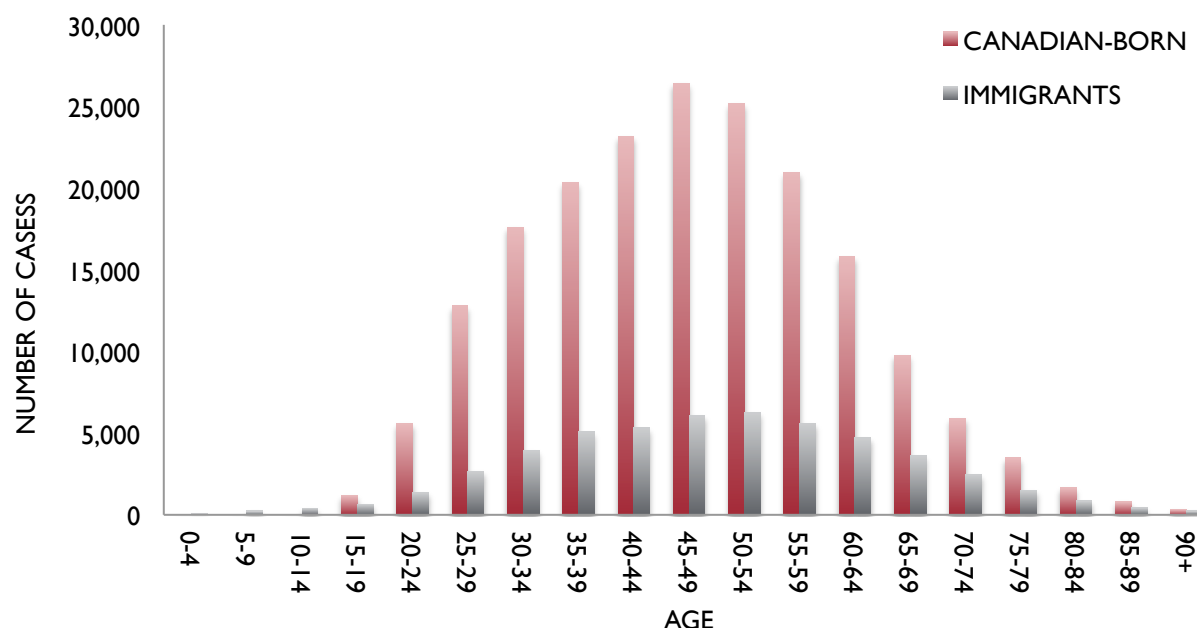
Figure 6 shows cases of hepatitis C notified to Health Canada by year, 1992-2009 (2). These figures do not distinguish between chronic infections and resolved infection. The cumulative totals do not take deaths from any cause into account. Some of these reported cases might have consequently cleared the virus, either spontaneously or with treatment. Some have certainly died from their disease. Therefore, this data cannot provide an accurate picture of the prevalence of hepatitis C in Canada, but does indicate the lowest possible prevalence rates.

FIGURE 6: CASES OF HEPATITIS C NOTIFIED TO HEALTH CANADA⁽²⁾



The PHAC data also does not distinguish whether the newly registered cases are newly infected or chronically infected but newly diagnosed. Given the epidemiology of hepatitis C, it is likely that most new notifications are patients who are chronically infected or previously exposed and newly diagnosed rather than newly infected. The graph above only shows those patients who have been diagnosed as anti-HCV-positive. Attempts to determine the total number of infected individuals have been undertaken, using modeling studies (1). The next two graphs (Figures 7 and 8) are derived from these studies, showing the distribution of chronic HCV infection by age, by immigration status and by province.

FIGURE 7: MODELED PREVALENCE OF HEPATITIS C IN CANADA⁽¹⁾



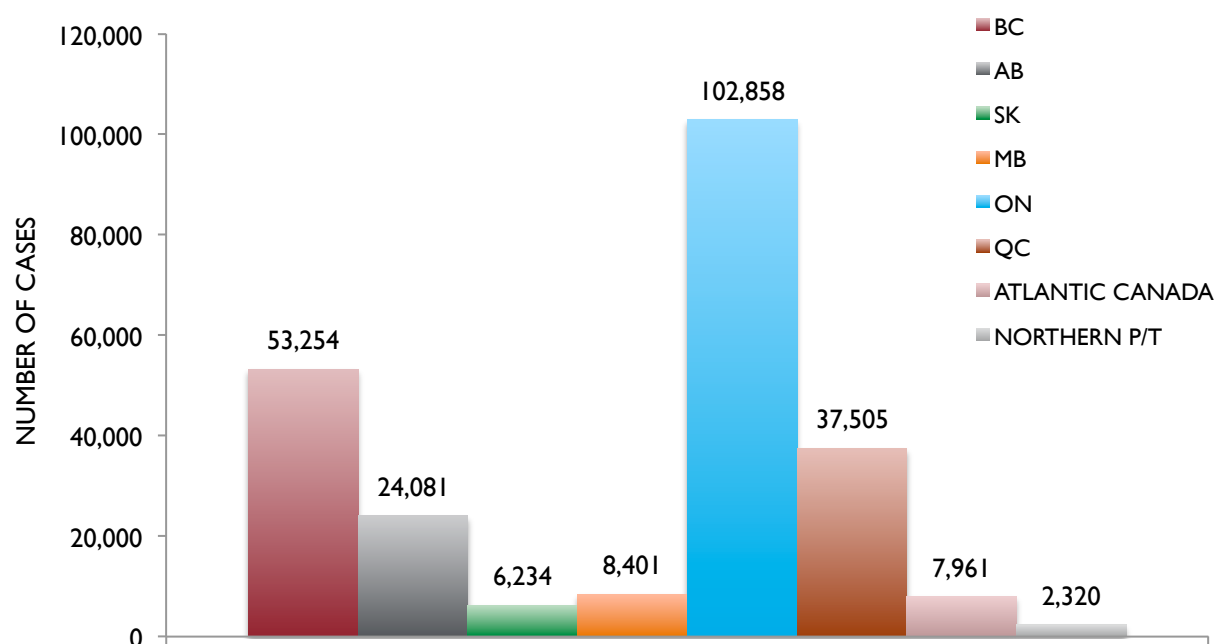
This graph suggests that in Canadian-born individuals, the peak prevalence is in the young and middle aged. In immigrants, the distribution of cases shows a similar pattern. Examination of data from PHAC confirms that the peak age of cases at the time of reporting is between ages 30-59.

Similar data in the U.S. prompted the Centers for Disease Control and Prevention (CDC) to recommend that all people born between 1945 and 1965 should undergo one-time screening for hepatitis C (3). PHAC (Canada's equivalent to CDC) has not issued any screening recommendations.

The provincial distribution of cases of hepatitis C is shown in Figure 8 (1). This data shows that as with hepatitis B, Ontario has the greatest number of cases.

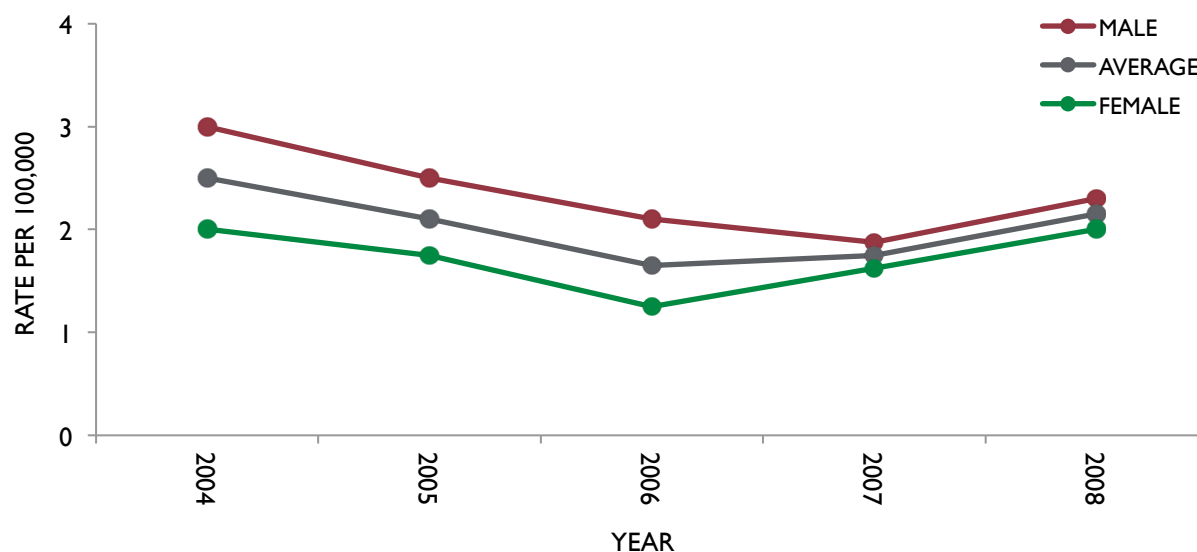
The contribution of immigration to the pool of hepatitis C infected individuals is unknown. The modeling study referred to above estimated that about 21% of hepatitis C occurred in immigrants (51,560 cases)(1). Other studies suggested that the proportion of all hepatitis C occurring in immigrants might be higher. Using methodology similar to that used for hepatitis B, one estimate suggests that there may be between 43,718 cases to as many as 291,162 cases in the immigrant community (4). Estimation of prevalence of hepatitis C in immigrants is likely to be less accurate than in hepatitis B because of a lack of uniformity in the age of infection. Some countries with high HCV prevalence, such as Pakistan, Vietnam, Somalia, Italy and Eastern Europe, contribute substantially to immigration in Canada. Identifying these patients and getting them into treatment represents a challenge because these populations are neither familiar with hepatitis C as a disease nor with its management. This population also does not access medical care as easily or as frequently as Canadian-born individuals.

FIGURE 8: PROVINCIAL DISTRIBUTION OF HEPATITIS C CASES⁽¹⁾



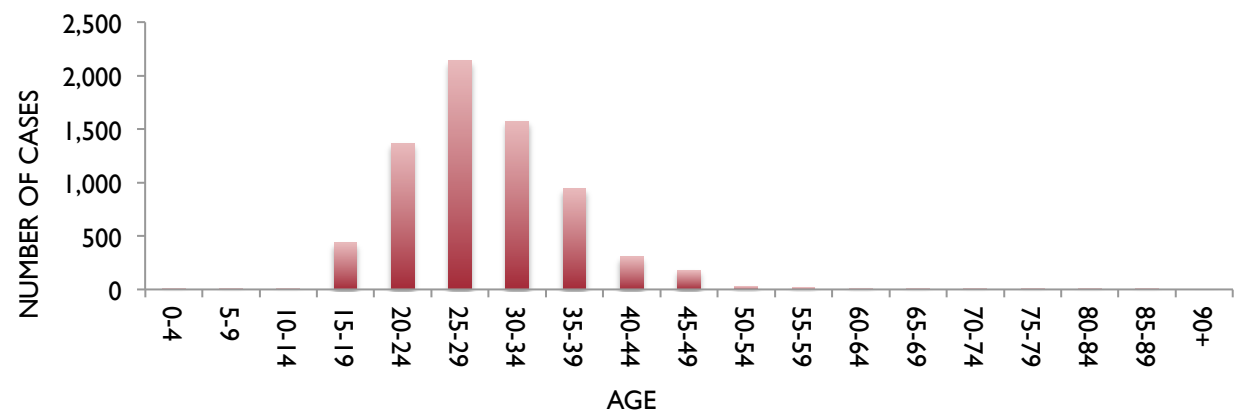
There is some incidence data on acute hepatitis C infection from EHSSS. Their data shows that the incidence of acute hepatitis C fell from 2004 to 2006, but then started to rise again. Whether this is a true rise in incidence or an artifact of data collection (inclusion of regions with higher hepatitis C incidence) is unknown. Figure 9 shows reported rates of acute hepatitis C from EHSSS for 2004-2008. This only shows those patients who have been diagnosed. Diagnosed cases represent an unknown fraction of all cases.

FIGURE 9: INCIDENCE OF ACUTE HEPATITIS C⁽⁵⁾



The total number of patients who develop acute hepatitis C each year is unknown, but has been modeled (1). The modeled number of acute cases/year in 2007 was about 7,000. Thus the notification rate may be as low as 10% of the actual rate. Figure 10 shows the age distribution of acute hepatitis C.

FIGURE 10: MODELED NUMBER OF CASES OF ACUTE HEPATITIS C BY AGE⁽¹⁾

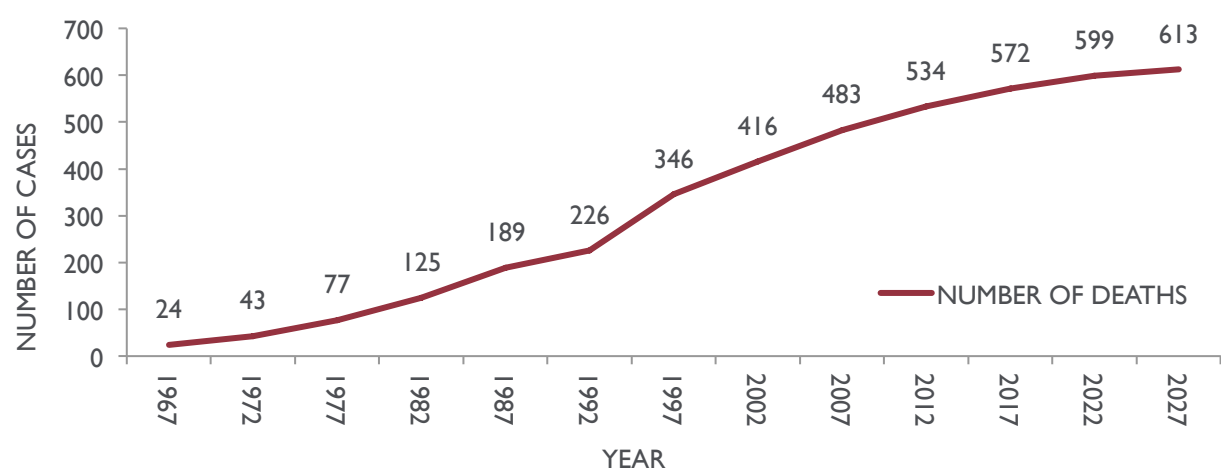


Note that the peak age of acute hepatitis C is about 20 years younger than the peak age of those chronically infected, suggesting that those who are currently chronically infected acquired their disease perhaps two decades ago. They will therefore be approaching the age when complications start to occur.

HEPATITIS C-RELATED MORTALITY AND MORBIDITY

The death rate in Canada from hepatitis C-related illness is unknown. However, liver failure due to hepatitis C infection is the most frequent indication for liver transplant. There are several publications from the U.S. and elsewhere that show that hepatitis C-related mortality is significant (6-10). There is also Canadian data showing that there is a significant death rate among hepatitis C infected individuals (1,11,12). Remis et al (1) estimated HCV prevalence and predicted HCC incidence and HCV-related deaths to 2020 (Figure 11). This analysis showed a continuously rising mortality to 2020 and beyond. This analysis did not take treatment of hepatitis C into account. Given the uncertainty about prevalence this projection might be an underestimate.

FIGURE 11: MODELED INCIDENCE OF HEPATITIS C-RELATED DEATHS⁽¹⁾



The Ontario Burden of Infectious Disease Study (12) found that chronic hepatitis C was the number one cause of mortality and morbidity among infectious diseases (14). This was also a modeling study that did not describe mortality, but rather expressed outcomes as years of life lost in the cohort.

FIGURE 12: YEARS OF LIFE LOST DUE TO PREMATURE MORTALITY (YLL), YEAR-EQUIVALENTS OF REDUCED FUNCTIONING (YERF) AND HEALTH-ADJUSTED LIFE YEARS (HALYS) FOR THE TOP 20 PATHOGENS, RANKED BY DISEASE BURDEN. ⁽¹²⁾

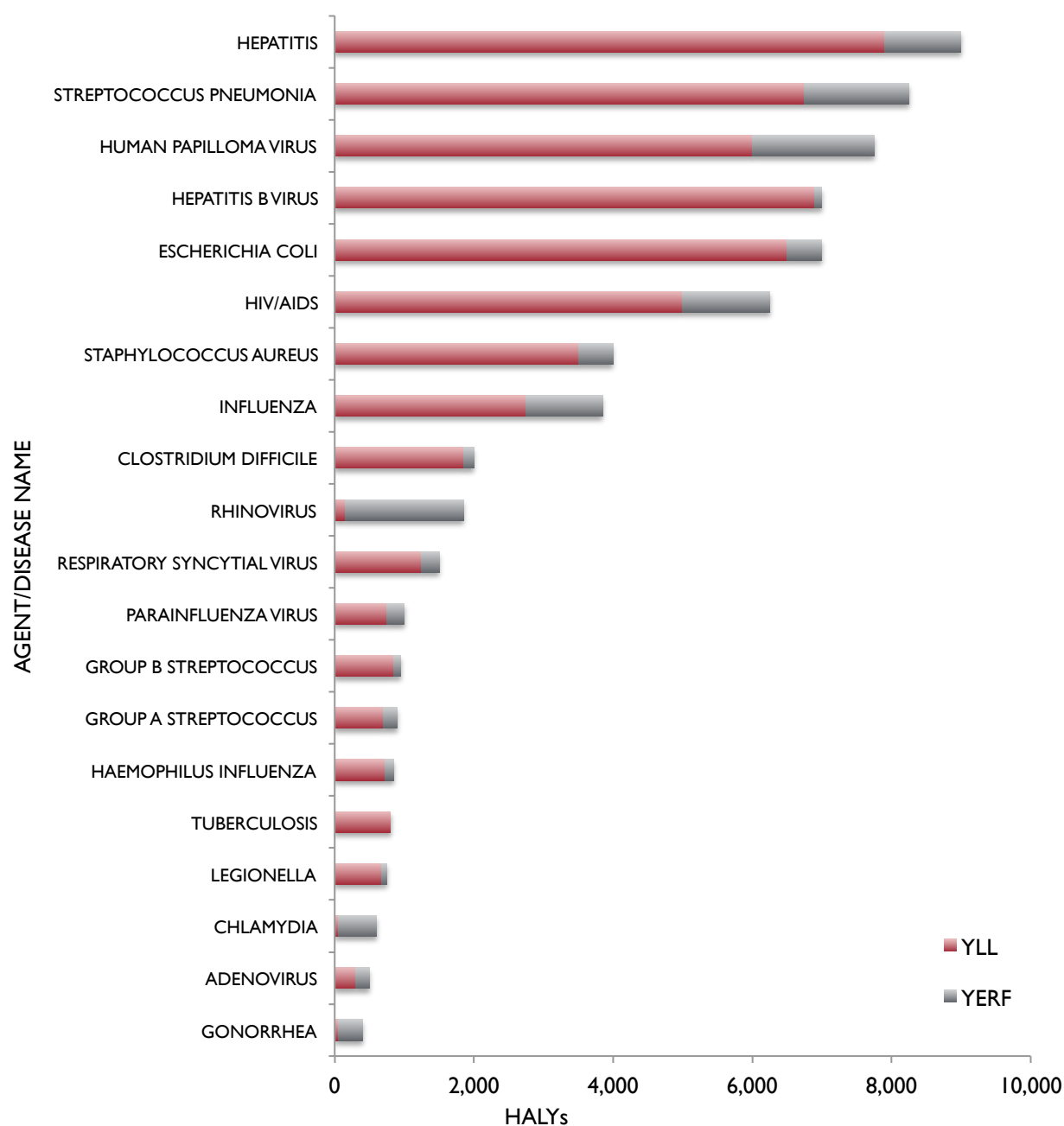
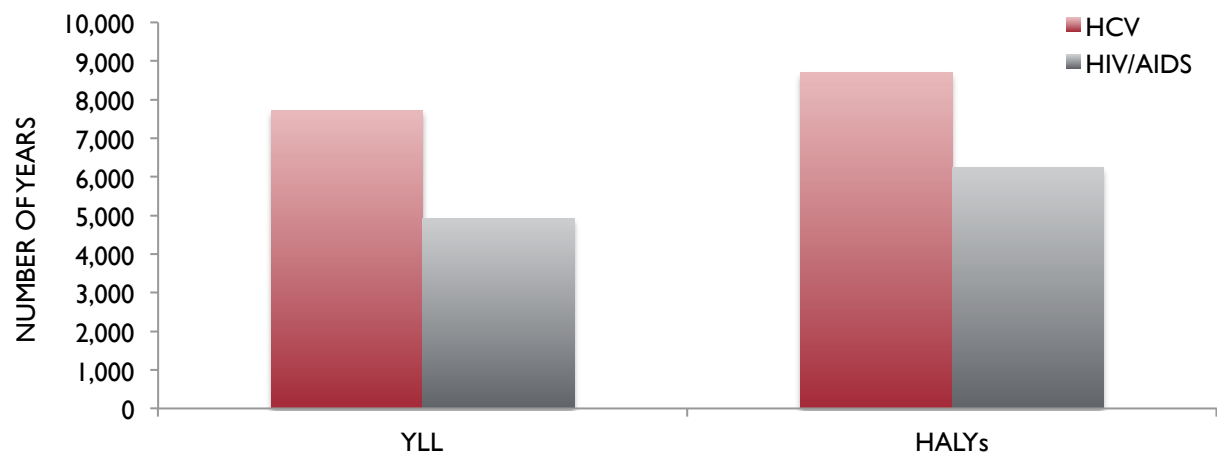


FIGURE 13: HEALTH OUTCOMES FOR HEPATITIS C AND HIV/AIDS IN ONTARIO ⁽¹²⁾

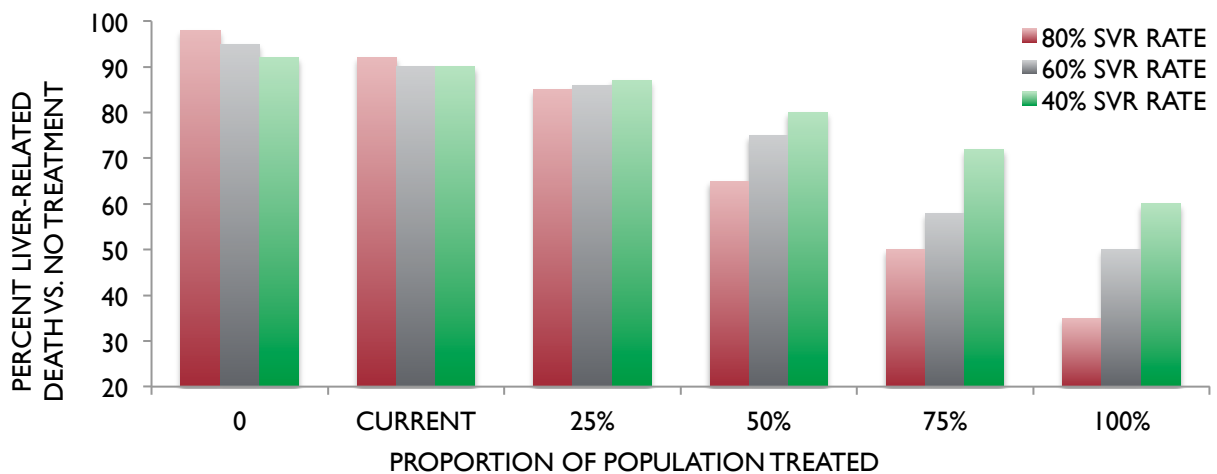


YLL - years of life lost HALYs Health adjusted years of life lost.
Figure 13 compares these outcomes for HIV and hepatitis C in the ONBOIDS study (12).

FUTURE MORBIDITY AND MORTALITY

Complications and death from hepatitis C are going to be an increasing problem well into the next decade based on the data in Figure 11. Modeling studies have suggested that an increase in the number of patients being treated and an improvement in the response rates for drug therapy could significantly reduce the death rate from hepatitis C. Figure 14 is taken from the modeling study, and indicates that under current circumstances, with less than 25% of patients treated and a response rate of <50% there will not be a substantial reduction in death rate. Fortunately, newly approved treatments and those still in development will increase response rates to 70% overall or more. However, since the number treated will still be less than 25%, even this improved response rate will not have a significant effect on mortality. Improving mortality will require a massive increase in the number of treated patients.

FIGURE 14: ESTIMATED REDUCTIONS IN LIVER-RELATED DEATH ASSUMING INCREMENTAL INCREASES IN PROPORTION OF INFECTED POPULATION TREATED AT DIFFERENT RESPONSE RATES ⁽¹³⁾



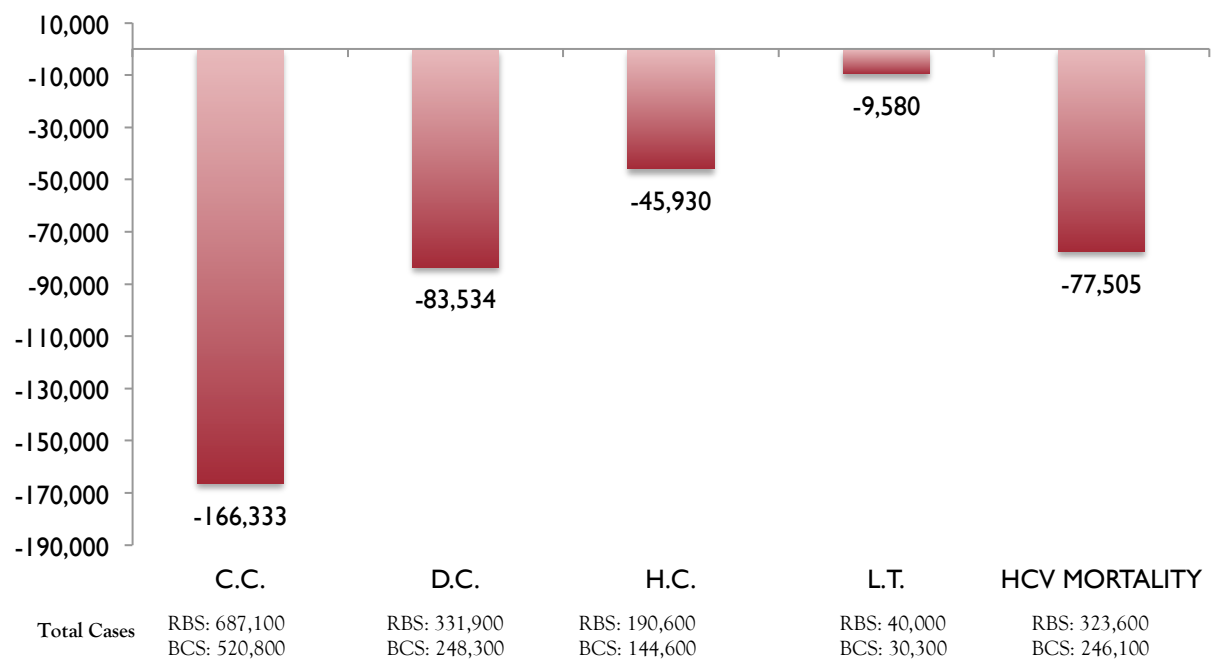
PRIMARY CARE MANAGEMENT OF HEPATITIS C

Management of chronic hepatitis C involves assessment of patients to determine whether they are candidates for treatment, to evaluate progression of disease, and to monitor for complications of cirrhosis. As discussed previously, family practice residents are not effective in identifying patients with cirrhosis. Hepatologists frequently report that patients who present with late stage disease have had their disease diagnosed many years previously, but were told that their slightly elevated ALT was “nothing to worry about.”

A recent IPSOS-Reid survey (14) conducted for the Canadian Liver Foundation found that awareness of hepatitis C in the general population was poor. Adults born between 1945-1965 claimed to be the most knowledgeable about hepatitis C but in fact actually knew the least of all Canadians surveyed. They were also less likely than younger generations to have been tested. The survey also revealed that only 35% of general practitioners felt that they knew a lot about the symptoms of hepatitis C and 57% did not know that hepatitis C could be cured. (14)

In 2012, the U.S. Centers for Disease Control and Prevention recommended that the members of the birth cohort 1945 to 1965 undergo a single screening for hepatitis C, as opposed to the current strategy of risk-based screening. The type of data on which this is based is demonstrated in Figure 15, which shows the reduction in various outcomes if universal screening was instituted and appropriate treatment provided (15).

FIGURE 15: REDUCTION IN OUTCOMES FOLLOWING UNIVERSAL HCV SCREENING VS RISK-BASED SCREENING IN THE USA⁽¹⁵⁾.



CC: Compensated Cirrhosis; DC: Decompensated Cirrhosis; HC: Hepatocellular Carcinoma; LT: Liver Transplant
RBS: Risk-based Screening Strategy; BCS: Birth-cohort Screening Strategy
Total Screened: 11,379,708 (RBS); 99,490,322 (BCS)
Total Diagnosed: 532,496 (RBS); 1,527,937 (BCS)
Total Treatment: 295,423 (RBS); 873,942 (BCS)

SPECIALIST CARE OF HEPATITIS C

Most hepatitis C treatment in Canada is provided by gastroenterologists, hepatologists, infectious disease specialists, and a few internists and family practitioners. According to industry sources, there are about 400 treating physicians in Canada. However, of these, fewer than 50 treat more than 50 patients/year. Current capacity for hepatitis C treatment can be gauged from the number of prescriptions written (7,000-8,000/year based on 2006-2010 data from IMS Brogan) which is fewer than the number of newly registered cases each year. More recently, the number of cases treated each year has dropped to less than 2,000. The reason for this decline is not clear, but may in part be due to doctors and patients delaying treatment until all-oral therapy is available. Given that there may be more than 200,000 individuals who still need treatment, it is clear that there are too few treating physicians for the number of patients with hepatitis C.

NURSING CARE OF HEPATITIS C

Treatment of hepatitis C is complex and time consuming and it is very difficult for physicians to see patients as frequently as necessary. Nursing care has become an essential part of the treatment of hepatitis C. Studies show that involvement of nurses improves patient adherence to therapy and increases the likelihood of achieving cure (16). Patient satisfaction also improves when nurses are involved. In Canada, nurses that provide hepatitis C care are funded by provincial governments and by the pharmaceutical industry. This represents a contribution to the health care system by the pharmaceutical industry of more than \$5 million. The number of nurses employed by the pharmaceutical industry is not known, but is likely at least equivalent to, or in excess of, the number funded by provincial governments.

PATIENT AWARENESS OF HEPATITIS C

Generally, patients know little about hepatitis C, its risk factors or how it is treated. In Canada, it may be that knowledge about hepatitis C is better than elsewhere, given all the publicity around transfusion-related hepatitis C and the 1997 Krever Commission Report on the Blood System in Canada. There has also been significant media coverage of the new hepatitis C drug treatments that are now available in Canada. Unfortunately, treating physicians still see a significant proportion of patients who are newly diagnosed and admit to injection drug use but are not aware that this is the likely source of infection.

Table 7 is taken from the U.S. Institute of Medicine Report on Viral Hepatitis and Hepatocellular Carcinoma, and it shows the proportion of U.S. population who are unaware of their disease. There is no equivalent data for Canada, but it is unlikely to be much different than the U.S. results (17). This conflicts with Canadian estimates of hepatitis C prevalence. If more than 236,000 individuals have been identified (1) and if, as in the U.S., this represents only 25% of all cases, then the prevalence of hepatitis C in Canada might be as high as 1,000,000 or about 3%. The U.S. prevalence is about 1.38%. If 50% of infected individuals are aware of their disease, this would suggest that there are about 472,000 cases in Canada, giving a prevalence of about 1.5%.

TABLE 7: PROPORTIONS OF THE INFECTED POPULATION WHO ARE NOT AWARE OF THEIR INFECTED STATUS (U.S. DATA)⁽¹⁷⁾

Virus	Percentage of Population Unaware of Infection Status
HBV	About 65%
HCV	About 75%

DRUG THERAPY FOR HEPATITIS C

Hepatitis C is a curable disease. Current therapy is not 100% effective, but when it works is able to clear the virus completely. The response rate to treatment varies by viral genotype. The backbone of therapy is pegylated interferon alpha and ribavirin. The interferon must be injected weekly, and the ribavirin is an oral medication. Interferon may have many side effects, some quite disabling, that make it difficult or even impossible for some patients to work or complete day-to-day tasks while on therapy. Recently, the first two therapies in a new class drugs called protease inhibitors have been licensed for use in Canada. They are effective only in genotype 1 infection but when given in addition to interferon and ribavirin, improve the cure rate compared to the older dual therapy. The protease inhibitors also come with potentially significant side effects. Fortunately, all the side effects are reversible on withdrawal of therapy.

AVAILABLE DRUGS

Since 2011, genotype 1 infection has been treated by a combination of interferon alpha, ribavirin and either of two protease inhibitors, boceprevir or telaprevir. These latter two act directly on viral replication. Boceprevir and telaprevir are oral agents. Responses to therapy determine the duration of therapy. Patients who are able to clear virus from serum after four weeks of triple therapy require 24-36 weeks of treatment while all others require 48 weeks of treatment. The overall cure rate is between 65-75%. Until the licensing of telaprevir and boceprevir, the cure rate for genotype 1 infection was about 40-50%.

Genotype 2 and 3 require 24 weeks of treatment with interferon alpha and ribavirin only. Those who clear the virus at four weeks need only 16 weeks of treatment. All other patients require 24 weeks of treatment. The cure rate for genotype 2 is close to 80%, and for genotype 3 is about 60%.

Genotypes 4-6 require treatment with interferon and ribavirin only for 48 weeks. The cure rates have not been well defined, but for genotype 4 is about 60%.

Within the next few years, there will be yet another new generation of treatment. Most patients will be treated with oral agents only that will be well tolerated and highly effective. Cure rates in excess of 80% are expected. Most patients will require only 12-24 weeks of therapy. The first of these new therapies is expected in 2015. While the new drugs will simplify treatment for the patient, the decision about which treatment to use will be more complex because of the patient and viral characteristics that favor one agent over another. Given the restrictions on the currently available drugs, it is not clear that reimbursement will be consistent with clinical indications.

As with hepatitis B, most private insurers continue to reimburse all hepatitis C treatments but this creates a level of inequity for those without private insurance plans. Insurers are beginning to apply provincial restrictions to reimbursement as well which, if fully implemented, will remove the inequity but to the disadvantage of private insured patients.

LICENSING AND REIMBURSEMENT

Pegylated interferon and ribavirin are recommended for reimbursement with restrictions by CDEC. Most provinces have restrictions on access in place, which often means patients with normal ALT values cannot obtain reimbursement. Since genotype 1 requires triple therapy and since the recommendation for the new protease inhibitors does not require an elevated ALT, this restriction now only applies to genotypes 2-6. Current reimbursement recommendations for protease inhibitors from CDEC also limit treatment to patients with disease that is at least moderate in severity (fibrosis stage 2 or higher). Patients with milder disease do not qualify for reimbursement for treatment.

TABLE 8: REIMBURSEMENT POLICIES FROM CDEC AND THE PROVINCES

Province	Available drugs to treat hepatitis C		
	Pegylated interferon and ribavirin	Boceprevir	Telaprevir
CDEC	No restriction	F2 fibrosis or higher, proven by biopsy	F2 fibrosis or higher, proven by biopsy
BC	ALT > 1.5xULN*	F2 fibrosis or higher or elevated ALT; no biopsy; HIV co-infection via adjudication	F2 fibrosis or higher
AB	Recognized prescribers	F0 or higher; no biopsy; null responders & HIV co-infection	Listed but no level of fibrosis specified
SK	No restrictions	As per CDEC; null responders; no biopsy	As per CDEC
MB	No restrictions	F2-F4; Metavir score or equivalent or ALT; null responders	As per CDEC
ON	ALT > 1.5xULN	F2 fibrosis or higher, any method of assessing fibrosis; HIV co-infection; Metavir score or equivalent	Null responders only
QC	No restriction	No restriction; no biopsy	No restriction; no biopsy
NB	Internal medicine specialty only	F2-F4 or specialist recommendation; biopsy/Fibroscan® only where available; null responders	As per CDEC
NS	Hepatology only	F2-F4 or specialist recommendation; biopsy/Fibroscan® where available; null responders	F2 fibrosis or higher
PEI	Individual request	Not listed yet	Not listed yet
NL	Internal medicine specialty only	Not listed yet	Not listed yet

* ULN= upper limit of normal.

Table 8 lists reimbursement restrictions for hepatitis C treatment by province and from CDEC.

The limitations on reimbursement are contradictory. Patients with genotype 2-6 infection can receive treatment whatever the level of fibrosis, but those with genotype 1 can only access treatment if they have F2 or higher fibrosis – despite the fact that there is no difference in the severity or outcomes between genotypes. In those provinces that still have the ALT restriction, genotype 1 patients with a normal ALT can access boceprevir or telaprevir, but not the interferon and ribavirin without which the protease inhibitors are ineffective. Genotype 1 patients with elevated ALT but less than F2 fibrosis can obtain reimbursement for interferon and ribavirin, but not boceprevir or telaprevir. In Ontario, telaprevir is approved for null responders including those with cirrhosis but no liver failure, despite data that shows that only 15% of these patients will respond to treatment.

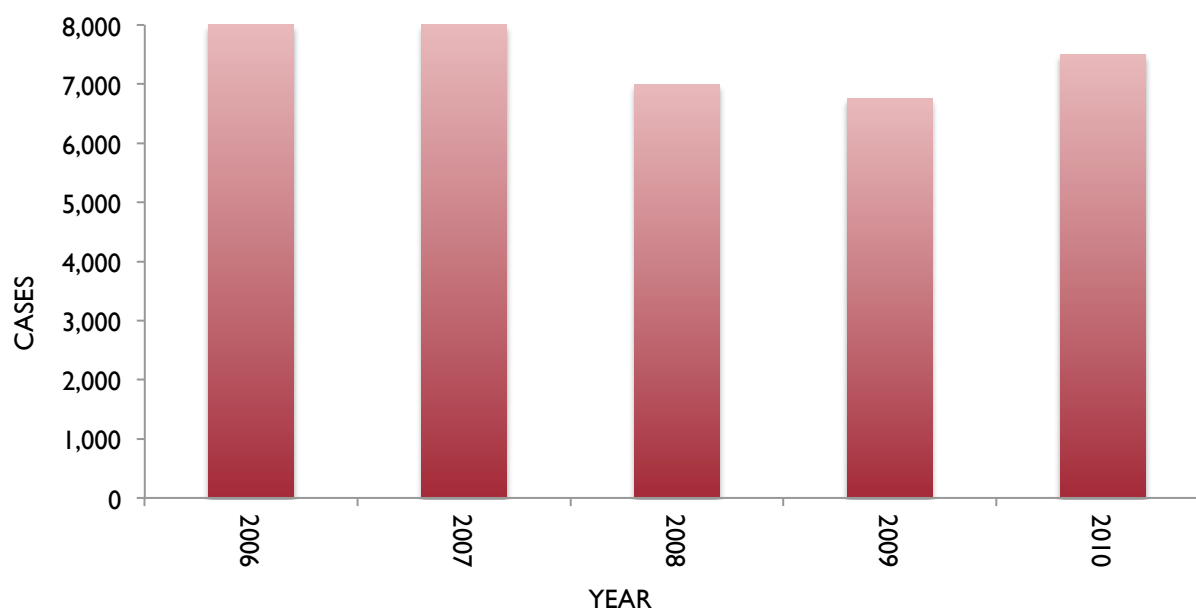
The ALT restriction is based on the fact that the initial interferon and ribavirin clinical trials used ALT as the marker of response because HCV RNA testing was not available. More recent studies have not required ALT to be elevated as an entry criterion to the study. Furthermore, it has been clearly shown that ALT is not a good marker of liver disease severity, nor of prognosis. Thus ALT does not discriminate as to who will develop complications of liver disease (and therefore should be treated), and who will not. However, in some provinces, the ALT remains in place despite this new information.

The scientific rationale for the restriction by disease severity on biopsy is not clear. Professional liver disease and infectious disease associations, including Canadian associations, recommend that all patients be considered for treatment (18-20). In Canada however, reimbursement conditions restrict availability of treatment. CDEC requires a liver biopsy to be performed in all patients prior to reimbursement. Reimbursement agencies in other countries do not have similar requirements. The decision to perform a biopsy is a medical decision between a doctor and patient, and not one that should be imposed. Under current guidelines for reimbursement, if the biopsy shows only mild disease then reimbursement will not be available and the biopsy would be in vain. Furthermore, in order to obtain funding for treatment, additional biopsies would be required to determine when stage 2 fibrosis has developed. These procedures would again not be clinically indicated. As liver biopsies are not universally available, some patients will be denied treatment reimbursement simply because a biopsy was not an option. Unfortunately, liver biopsy is not accurate, and about 20-30% of patients with stage 2 disease will have biopsies that show only stage 1 disease and thus will be denied reimbursement.

UPTAKE OF HEPATITIS C TREATMENT IN CANADA

Data from IMS Brogan suggests that about 7,000+ patients are treated for hepatitis C each year (i.e., about 37,000 patients treated between 2007 and 2010). This data is shown in Figure 16. Given the response rates, it is reasonable to assume that no more than 50% of these patients might have been cured. Assuming that between 2001 and 2007 a similar number of patients were treated with similar outcomes, this means that between 2001 and 2010 approximately 37,000 patients have been cured. Prior to 2001, treatment outcomes for genotype 1, the most common genotype, were closer to 30-35%. Fewer patients were treated each year at that time than are currently. A generous estimate would be that an additional 10,000 patients had been cured prior to 2001. Correcting for prescriptions not captured by IMS Brogan increases the total number cured to about 70,000. Correcting for patients captured by the PHAC data but who have died or spontaneously cleared virus, there remain more than 150,000 patients awaiting cure. This represents an enormous challenge.

FIGURE 16: PATIENTS TREATED FOR HEPATITIS C BY YEAR*



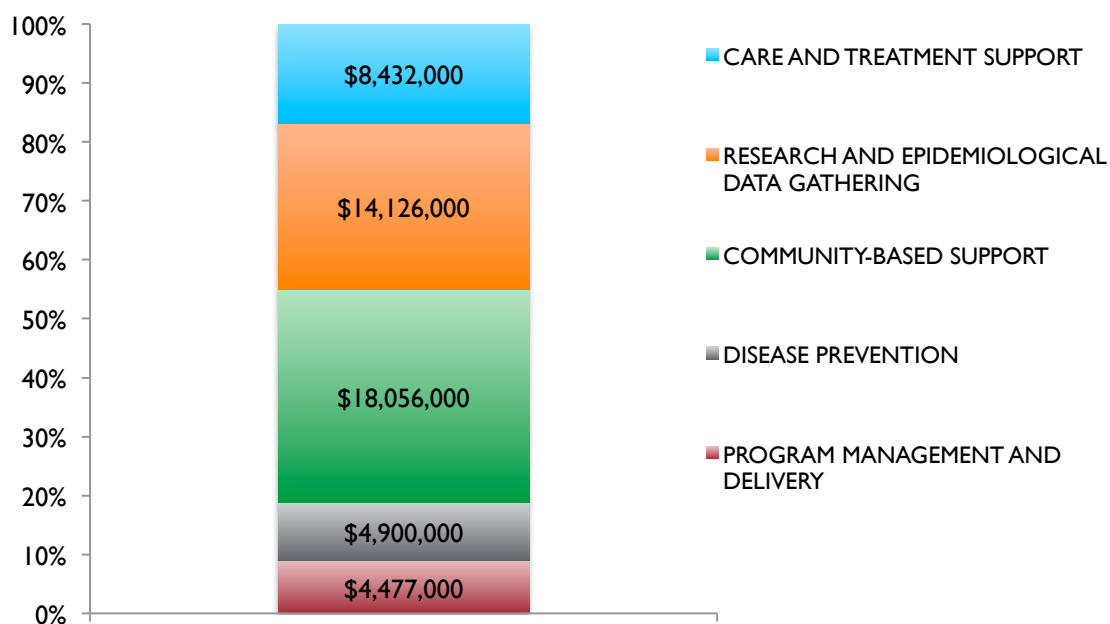
*Data from IMS Brogan Inc

Data from elsewhere is in conflict with the data from IMS Brogan Inc. For example, an abstract presented at the Annual Meeting of the American Association for Study of Liver Disease (AASLD) suggested that no more than 2,900 patients had been treated in 2009. In 2011, industry estimates were that no more than 2,000 patients had been treated.

GOVERNMENT RESPONSES TO HEPATITIS C

At the federal level, responsibility for hepatitis C rests with the Centre for Communicable Diseases and Infection Control (a division of the Public Health Agency of Canada). This division sponsors a single program centered on hepatitis C, the Hepatitis C Prevention, Support and Research Program. This program has a budget of approximately \$10,000,000/year (21). How the money was spent in the first five years is shown in Figure 17. More recent data is not available and what care and treatment support was provided within the time period is not specified.

FIGURE 17: EXPENDITURES ON HEPATITIS C PROGRAMS 1999-2004⁽²¹⁾



In addition to the PHAC program, some provincial governments have also established programs. These are listed in Table 9.

TABLE 9: GOVERNMENT RESPONSES TO HEPATITIS C

	Specific department/division	Activities	Budget
BC ²¹	BC Hepatitis Services	Surveillance, laboratory services, nursing services	\$1.36 M
AB	None	Support for 3 comprehensive hepatitis C clinics	Unknown
SK	None	None	None
MB	No information provided	Unknown	Unknown
ON	Hepatitis C services fall under Division of HIV/AIDS	Disease prevention, community and nursing support	Unknown
QC	No information provided	Unknown	Unknown
NS	None	Funding for hepatitis C clinic	\$210,000
NB	None	None	None
PEI	None	None	None
NL	Nurse practitioner support	Prepares care plans	\$100,000

MRC/CIHR PROGRAM AND HEPATITIS C RESEARCH IN CANADA

The Canadian Institutes of Health Research (CIHR)(previously known as the Medical Research Council of Canada) received \$12.25 M from the federal government in 1999, and added \$6.125 M for a program to enhance hepatitis C research capacity in Canada. The program was very successful in encouraging researchers who had not been in hepatitis C previously to become involved. Since 1990, CIHR has awarded \$93M for research projects directly related to hepatitis C (39,40). By comparison, the Government of Canada has spent \$518M on HIV research over the same period.

GOVERNMENT RESPONSES ELSEWHERE

UNITED STATES

In 2010, the Institute of Medicine (IOM) issued a report on viral hepatitis and its consequences. In its report, the IOM recognized the enormity of the epidemic of both hepatitis B and hepatitis C and issued recommendations to reduce the risk of death and chronic ill-health from these illnesses (25). The report concludes that the current approach to the prevention and control of chronic hepatitis B and hepatitis C is not working. As a remedy, the IOM recommends increased knowledge and awareness about chronic viral hepatitis among health care providers, social service providers, and the public; improved surveillance for hepatitis B and hepatitis C; and better integration of viral hepatitis services. The CDC Foundation (the independent non-profit partner of the Centers for Disease Control and Prevention), in partnership with CDC's Division of Viral Hepatitis, launched the Viral Hepatitis Action Coalition, to support specific studies and community action in support of the response to the IOM report (26). The Department of Health and Human Services in the U.S. has issued a blueprint for action describing how they plan to approach this epidemic (27). Most recently, the CDC has recommended that all baby boomers born between 1945 and 1965 should be screened for hepatitis C (3).

NEW ZEALAND

The Hepatitis Foundation of New Zealand is a charitable trust governed by a board of trustees in accordance with the Charitable Trusts Act of 1957 (28). Over the years, the Foundation has undertaken a number of major screening, vaccination and research programs in New Zealand, the Pacific Islands and Vietnam.

The Foundation has been carrying out follow-up of hepatitis B carriers in New Zealand since 1994. In June 1999, it

was contracted to deliver part of the national hepatitis B screening program, targeted to high-risk population groups, i.e., Maori, Pacific Island and Asian adults in the North Island. The Foundation is now contracted to the Ministry of Health as the national provider for long-term follow-up, with approximately 12,000 confirmed HBV carriers registered. Regular blood testing enables the early detection of complications such as liver inflammation and cancer. In recent years, increasing numbers of hepatitis C carriers have also registered with the Foundation for follow-up and information

AUSTRALIA

Australia has recently launched the 3rd National Hepatitis C initiative and the 1st National Hepatitis B Initiative. These major government programs include case finding, surveillance, treatment and research. (29,30)

FRANCE

France has had a National Hepatitis C Program for more than 10 years. This program includes education, data collection and research, as well as treatment support (31).

UNITED KINGDOM

A hepatitis C strategy was established in 2002 (32).

IRELAND

Ireland published their Hepatitis C Strategy in September 2012. (33)

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CHAPTER 3

ALCOHOLIC LIVER DISEASE

ALCOHOL CONSUMPTION AND ITS EFFECTS

The World Health Organization (WHO) has identified alcohol abuse as a leading cause of morbidity and mortality world-wide. Globally, alcohol has a much greater detrimental effect on health than other commonly recognized problems including obesity and elevated cholesterol. The impact of alcohol-related disorders is enormous. In 2004, 3.8% of all global deaths were attributable to alcohol, 6.3% for men and 1.1% for women. In the West, the alcohol-attributable mortality proportions were 9.0% for men and 1.8% for women. The majority of these deaths were due to cancer, cardiovascular diseases and cirrhosis, but alcohol was a contributing factor. The overall proportion of alcohol-attributable deaths has increased since 2000, mainly due to increases in the number of women drinking. Moreover, in 2004, 4.6% of the global burden of disease and injury, occurring mainly in individuals 15 to 30 years of age, was attributable to alcohol, 7.6% for men and 1.4% for women (1-6).

In Canada in 2002, alcohol-related costs to society were estimated to be \$14.5 billion. To offset this, alcohol sales contributed about \$7.7 billion to government revenue (2003) (7-9). Although these numbers each represent a single year, it is likely that subsequent numbers would be in the same range.

The overall impact of alcohol-attributable disorders can be appreciated by examining disability-adjusted life years (DALYs) which combine years of life lost due to premature death and years of life lived with disabilities as a unified measure of total lost years of full health from different causes. Table 10 illustrates such measures for alcohol-related disorders for 2004. The disease burden due to cirrhosis is enormous.

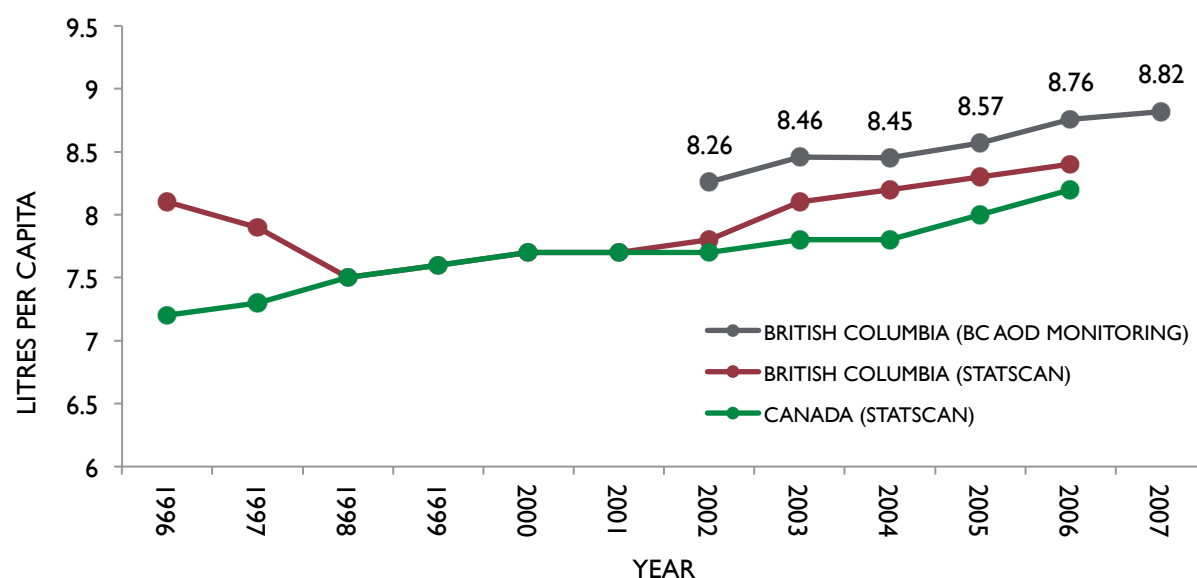
TABLE 10: ALCOHOL-ATTRIBUTABLE BURDEN OF DISEASE 2004⁽¹⁰⁾

Alcohol-attributable Disease/Disorder	DALYs (in 1,000s)
Neuropsychiatric disorders	26,682
Accidental injury	18,604
Intentional injury	7,660
Cirrhosis	6,945
Cardiovascular diseases	6,924
Cancer	6,268

In the West, 9.2% of all-cause DALYs were alcohol-related - 14.2% for men and 3.4% for women (10).

Cirrhosis mortality is directly related to per capita consumption rates, as is admission to hospital for alcohol-related illness. In Canada, each 1L increase in per capita consumption is associated with a 16% increase in cirrhosis deaths in men and 12% in women (10). This so-called 'alcohol effect' is stronger for alcohol-specific cirrhosis - 30% per litre for both men and women - but there is a 13% increase per litre in deaths due to cirrhosis coded as non-alcoholic as well. This likely reflects the negative synergistic effect of alcohol on the other common causes of cirrhosis, including chronic hepatitis C. Figure 18 shows the estimated increase in alcohol consumption between 1996 and 2007 in Canada and in British Columbia.

FIGURE 18: ESTIMATED INCREASE IN ALCOHOL CONSUMPTION BETWEEN 1996 AND 2007 IN CANADA AND BRITISH COLUMBIA⁽¹⁸⁾



Globally, the average annual per capita consumption in 2004 was 6.2 L of pure ethanol. Per capita rates vary substantially geographically. European rates are high at an average of 11.9 L while Eastern Mediterranean rates are low at 0.7L (14). In Canada, annual ethanol consumption rates have been slowly increasing. Per capita rates rose from 7.6L (16g/day) in 2000 to 8.2L (18g/day) in 2010. The Canadian Community Health Survey estimates of heavy drinking behavior show increases in both men and women from 2006 to 2010 by 5% and 12% respectively (14). The total number of heavy drinkers in Canada in 2010 was estimated at 4,743,655 (about 13% of the population). The average rates of ethanol consumption by individual Canadians over the age of 15 are at or near the accepted 'non-toxic' rates (13-26g/day) for liver disease but these rates must be interpreted in the context of a population expanded to a significant degree by immigrants from geographic regions with high rates of total abstinence and very low per capita consumption rates. In this context, the increasing levels of alcohol exposure are of major concern.

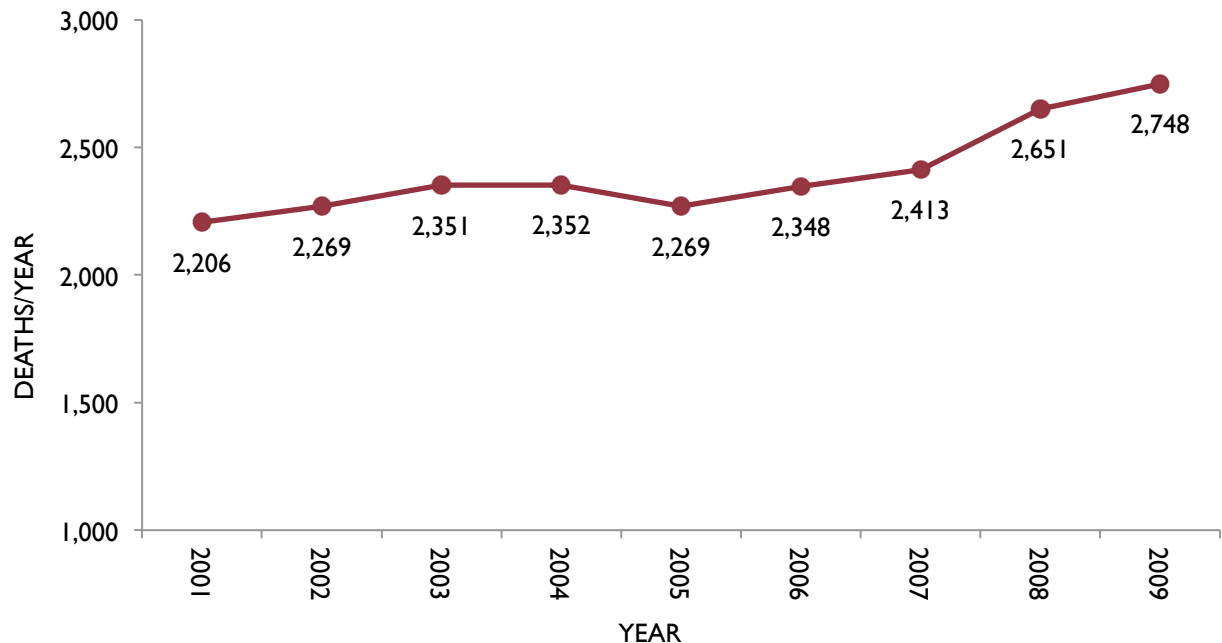
Alcohol toxicity is a known co-factor in the development of liver disease due primarily to other agents including chronic hepatitis C. It likely aggravates fatty liver disease related to insulin resistance in the metabolic syndrome. It is difficult to quantify the alcohol-attributable risk in these common conditions but one estimate suggests that 64% of male cirrhotic deaths recorded as non-alcoholic actually have some alcohol-attributable components.

EPIDEMIOLOGY

The increase in per capita consumption of alcohol in Canada has been accompanied by an increase in age-standardized cirrhosis death rates from 6 per 100,000 in 2004 to 6.5 per 100,000 in 2008 (15). For comparison, it is worth noting that death rates for diabetes, an extremely common chronic illness in the West, have actually declined in the same interval from 19.6 to 16.7 per 100,000. When segregated for alcoholic cirrhosis, the trend persists - 3.0 to 3.5 per 100,000 - accounting for over 50% of all cirrhosis deaths. These are likely underestimates. Autopsy studies have demonstrated that official mortality statistics may include less than 50% of actual cirrhosis deaths.

Figure 19 shows the increase in deaths from alcoholic liver disease over time. This includes alcoholic cirrhosis and alcoholic hepatitis. Either of these conditions is associated with prolonged illness and frequent hospitalizations.

FIGURE 19: DEATHS FROM ALCOHOLIC LIVER DISEASE⁽¹⁷⁾



NATURAL HISTORY OF ALCOHOLIC LIVER DISEASE

Alcoholic liver disease may present in several different ways. Acute alcoholic hepatitis is a condition characterized by clinical features of liver failure, jaundice and ascites and biochemical evidence of liver failure. It occurs as a result of prolonged heavy alcohol consumption. There may or may not be an underlying cirrhosis. This condition requires hospitalization for investigation, which may include a liver biopsy. There is the potential for recovery, which in some patients may be aided by administration of corticosteroid therapy. However, severe alcoholic hepatitis, particularly in the setting of cirrhosis, may be fatal. Assuming that recovery occurs, the ultimate outcome depends on whether the patient is able to maintain abstinence. If the patient has cirrhosis and is abstinent, they do not develop liver failure, but may still develop some of the complications of cirrhosis, such as hepatocellular carcinoma. If the patient continues to drink, the liver disease progresses and the patient will ultimately die of liver disease.

Lesser, but more prolonged drinking may also lead to cirrhosis, with presentation with the complications of cirrhosis, without going through the acute alcoholic hepatitis phase. Alcoholic cirrhosis has a bad prognosis. A recent study showed that about 47% of patients died within five years (16).

Liver disease induced by alcohol continues to be a major health problem. In addition, consumption of alcohol is likely a co-factor in the progression of other liver diseases that are not primarily due to alcohol. Alcohol consumption and alcohol-related liver injury are increasing in incidence in Canada and have major impacts on utilization of health care resources.

TREATMENT OF ALCOHOLIC LIVER DISEASE

Treatment of alcoholic liver disease is not very effective. Apart from steroids and/or pentoxiphylline for severe alcoholic hepatitis, there are no specific drug interventions that can modify the natural history of alcoholic liver diseases. The only long-term beneficial intervention is abstinence. Therefore, alcoholic liver disease continues to place demands on liver transplantation resources. Liver transplant units are reluctant to offer transplant to those are unable to maintain abstinence. As a result, in Canada, alcoholic cirrhosis, as a single attributable cause, accounts for only about 11% of all transplants undertaken.

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CHAPTER 4

NON-ALCOHOLIC FATTY LIVER DISEASE

EPIDEMIOLOGY

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Canada and is increasing in incidence. The long term consequence of this prevalence and rising incidence is unknown, but is likely to have a substantial impact on symptomatic liver disease, complications of liver disease, liver disease mortality and costs of care for liver disease.

NAFLD is a form of liver disease that microscopically resembles the injury seen in alcoholic liver disease. The disease includes three different stages: fatty liver, non-alcoholic steatohepatitis, and cirrhosis. In the first stage, fatty liver, the liver cells are swollen with fat but there is little or no inflammation and no fibrosis (scarring). In the second phase, the fat is accompanied by inflammation and death of liver cells. This is associated with a particular pattern of scarring, which if unchecked, results in the third stage, cirrhosis, which in turn leads to all the complications of cirrhosis (see Chapter 5).

The causes of NAFLD are obesity, diabetes, hyperlipidemia (increased levels of fat in the blood), and particularly hypertriglyceridemia (increased levels of triglycerides in the blood). However, not all patients with fatty liver disease have a clear predisposing cause. The underlying mechanism is a resistance to the effects of insulin and resulting high insulin levels.

The epidemiology of fatty liver disease in Canada is not known. However, given trends in diabetes and obesity, it is predictable that the prevalence of NAFLD and its consequences will increase.

Trends in obesity in Canada are shown in Figure 20 and trends in diabetes shown in Figure 21.

FIGURE 20: TRENDS IN OBESITY IN CANADA ⁽¹⁾

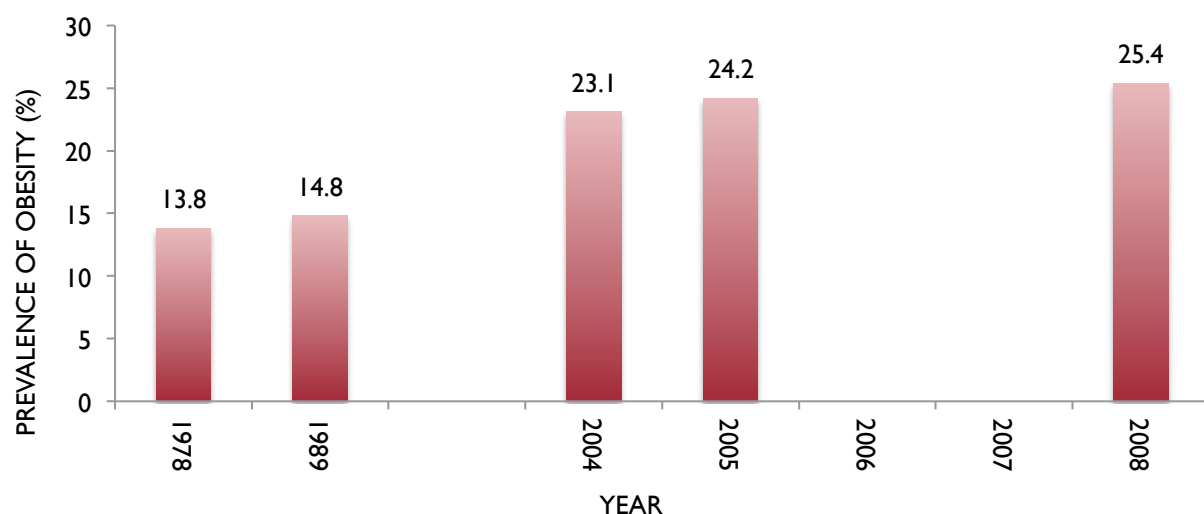
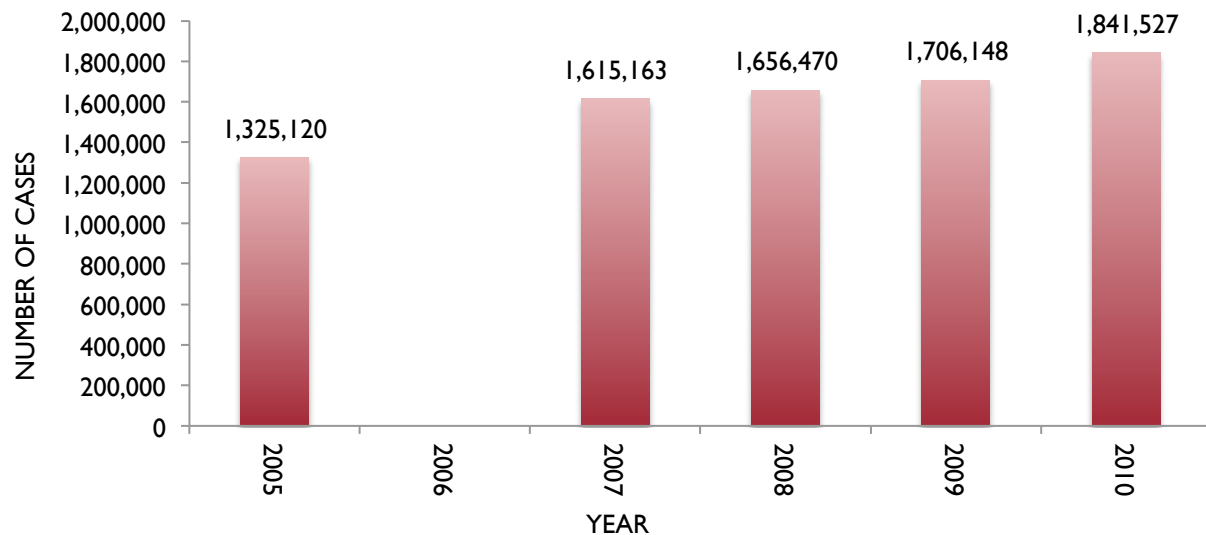


FIGURE 2I: CASES OF DIABETES BY YEAR⁽²⁾



There are rising trends in diabetes and in obesity that will result in a rising trend in NAFLD and subsequently an increase in incidence of cirrhosis and liver cancer.

NATURAL HISTORY OF NAFLD

About 15% of patients with NAFLD will develop cirrhosis and its complications. Many with NAFLD will die of other diseases related to obesity, diabetes, hypertension, heart attack and stroke before developing NAFLD complications. In the U.S., NAFLD is thought to afflict about 40% of the population. Assuming a similar proportion in Canada, about two million people would be expected to develop cirrhosis during their lives. Of these, about 1-5% will develop liver cancer (about 20,000-90,000 people), and an unknown proportion will develop other complications of cirrhosis.

DIAGNOSIS OF NAFLD

Fatty liver disease may come to attention through an abdominal ultrasound examination that documents fat in the liver. More frequently, abnormal liver blood tests are found on a routine physical evaluation and this in turn leads to an ultrasound being performed. However, the ultrasound appearance of fat in the liver is neither sensitive nor specific. This finding is very common and cannot be used to confirm NAFLD as the cause of liver blood test abnormalities. The distinction between steatosis and steatohepatitis can only be made on biopsy. There are non-invasive methods of assessing fibrosis, but their use in NAFLD still has to be validated.

TREATMENT OF NAFLD

The treatment of NAFLD is essentially lifestyle alteration – reduction in calorie intake through diet, and an increase in effective exercise. There are no drug treatments that have been shown to improve survival. However, Vitamin E and a drug called pioglitazone have been shown to improve the histological appearances of NAFLD. Coffee consumption also appears to reduce the severity of NAFLD. Other agents are currently being investigated. Bariatric surgery can be used to induce weight loss.

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CHAPTER 5

CIRRHOSIS AND ITS COMPLICATIONS

Cirrhosis is the end-stage of most liver diseases. The term originally referred to a particular pattern of scar tissue in the liver but has also come to be used to describe the consequences of this heavy scarring of the liver. These consequences include liver failure, as a result of replacement of functioning liver tissue by scar tissue, and an increase in the pressure in the veins leading into the liver (portal hypertension) as a result of (among other factors) destruction of blood vessels within the liver. Cirrhosis can be completely silent clinically, with no features on radiology or on blood tests to suggest that there is anything wrong with the liver. As a result, many patients with cirrhosis are not diagnosed until complications develop.

The most common complications of cirrhosis are internal bleeding from distended veins in the esophagus or stomach (bleeding varices), or an accumulation of fluid in the abdomen (ascites), or behavioural changes (hepatic encephalopathy). These are all features of both liver failure and portal hypertension. All patients with cirrhosis are also at risk for the development of liver cancer (hepatocellular carcinoma). This occurs at a rate of between 1-8%/year, depending on the severity of the underlying liver disease. Liver cancer is also silent for much of its development. Thus, with both the predisposing cirrhosis and the developing cancer being silent, most patients will only come to medical attention with the development of symptoms of liver failure, as the cancer replaces yet more functioning liver tissue, or with cancer symptoms, such as weight loss.

Usually cirrhosis is diagnosed by imaging only when the disease is sufficiently far advanced to change the outline of the liver or to cause the liver to shrink in size. Similarly, when the liver blood tests become abnormal in cirrhosis because of liver failure, this too represents late stage disease. Cirrhosis can be diagnosed before the onset of imaging or blood test abnormalities by liver biopsy, or by one of several non-invasive methods, such as Fibroscan[®] or Fibrotest[®]. However, none of these tests have very high sensitivity ($\leq 80\%$).

There is no data on the prevalence of cirrhosis in Canada. Statistics Canada (Statscan) has data on mortality from various liver diseases. However, the Statscan data records a number of different causes of death, other than cirrhosis, that are likely also due to cirrhosis. For example, patients who have chronic viral hepatitis listed as cause of death die either from cirrhosis or from liver cancer, since chronic viral hepatitis rarely causes death unless either of these two conditions is present. The same can be said of alcoholic liver disease, other forms of chronic hepatitis, and the other conditions listed in Table 11. Hepatic fibrosis is not a cause of death, unless it is extensive, in which case it qualifies as cirrhosis. Not all portal hypertension is related to cirrhosis, but more than 95% of portal hypertension is due to cirrhosis. Hepatorenal syndrome only occurs in cirrhosis. Therefore it is legitimate to lump these together when attempting to quantify mortality from cirrhosis. Figure 22 shows the increase in deaths from these conditions since 2000. Figure 23 shows the cumulative totals of deaths from malignant and non-malignant liver diseases.

TABLE 11: ICD CODES LISTED IN STATSCAN DATABASES THAT ARE LIKELY DEATH FROM CIRRHOSIS

Chronic viral hepatitis (B18)	Alcoholic liver disease [K70]
Chronic hepatitis (K73)	Fibrosis and cirrhosis of liver [K74]
Hepatic fibrosis [K74.0]	Hepatic failure not specified (K72)
Primary biliary cirrhosis [K74.3]	Secondary biliary cirrhosis [K74.4]
Biliary cirrhosis, unspecified [K74.5]	Other and unspecified cirrhosis of liver [K74.6]
Portal hypertension [K76.6]	Hepatorenal syndrome [K76.7]

FIGURE 22: DEATHS FROM LIVER DISEASE⁽¹⁾

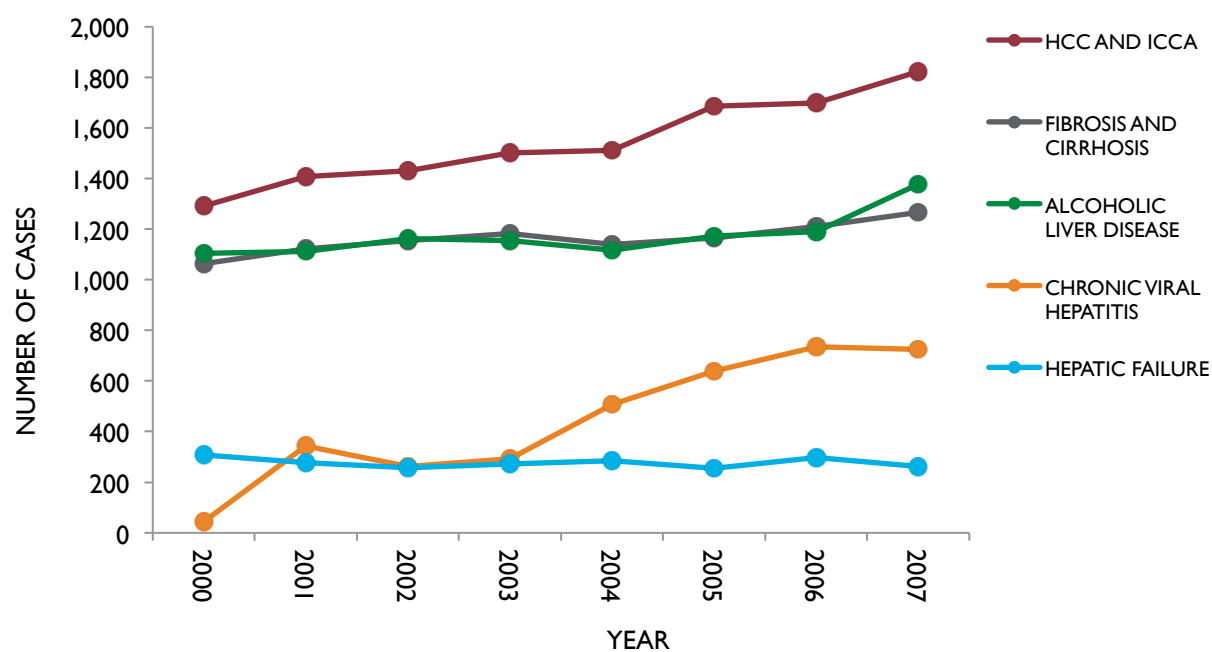
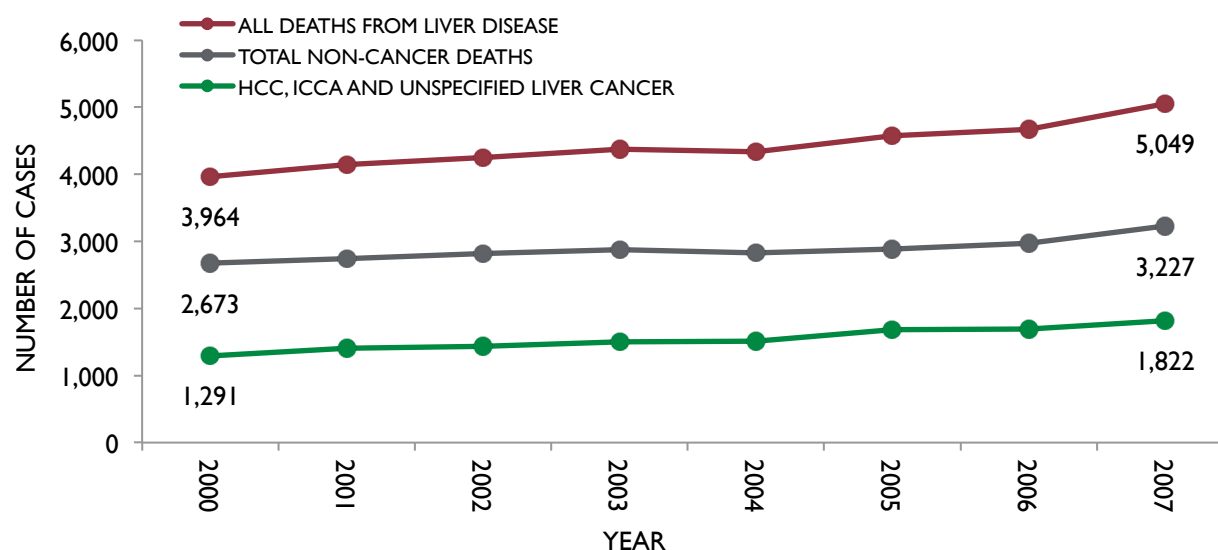


FIGURE 23: DEATHS FROM MALIGNANT AND NON-MALIGNANT LIVER DISEASE⁽¹⁾



Non-cancer liver-related deaths have increased from 2,673 to 3,227/year, an increase of 20.7%. All deaths from chronic liver disease have increased from 3,964 to 5,049/year, an increase of 27.9%. This is a stunning increase in mortality occurring over a period of only eight years.

HOSPITALIZATION FOR CIRRHOSIS

The development of ascites is a common consequence of liver failure. Ascites is usually managed initially on an out-patient basis. However, as the disease progresses, in-patient visits become more frequent so that patients with advanced liver disease may require many admissions to hospital before dying or receiving a liver transplant. Similarly, patients with hepatic encephalopathy require frequent hospitalizations. Patients with liver disease who require admission to hospital often have prolonged stays while those who present with variceal bleeding require urgent hospital admission. These patients seldom require repeated admissions for bleeding varices but they may require admissions for other complications. Thus, management of end-stage liver disease is expensive and consumes considerable hospital resources.

EFFECT OF CIRRHOSIS ON OTHER DISEASES

Cirrhosis is associated with dysfunction of other organ systems. Cirrhotic cardiomyopathy decreases cardiac capacity so that heart failure is more common when there is a stress on the heart, such as infection or surgery. Patients with cirrhosis are prone to serious bacterial infections. Often, what kills these patients is a form of kidney failure that is seen only in cirrhosis, the so-called hepatorenal syndrome. Other patients develop a particular form of lung disease. Finally, patients with cirrhosis do not tolerate surgery well. Patients with cirrhosis and normal liver function can expect an increased mortality from any major surgical procedure of about 5% over and above the usual mortality from that surgical procedure. Those with the most advanced liver disease can expect an increased mortality of up to 50%. Consequently, cirrhosis contributes to increased hospital stays and mortality in these patients as well. It is not clear how this contribution to mortality is captured in liver disease mortality statistics.

REFERENCES FOR CIRRHOSIS AND ITS COMPLICATIONS

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CHAPTER 6

HEPATOCELLULAR CARCINOMA

Note: This section deals only with cancers that arise in the liver (primary), not cancers that spread from elsewhere to the liver (secondary).

There are two common cancers that start in the liver. Hepatocellular carcinoma (HCC) arises from liver cells and makes up about 85% of all primary liver cancers. Intrahepatic cholangiocarcinoma (ICC) arises from bile duct cells and makes up about 15% of all cancers that arise in the liver. Both these cancers are increasing in incidence and mortality.

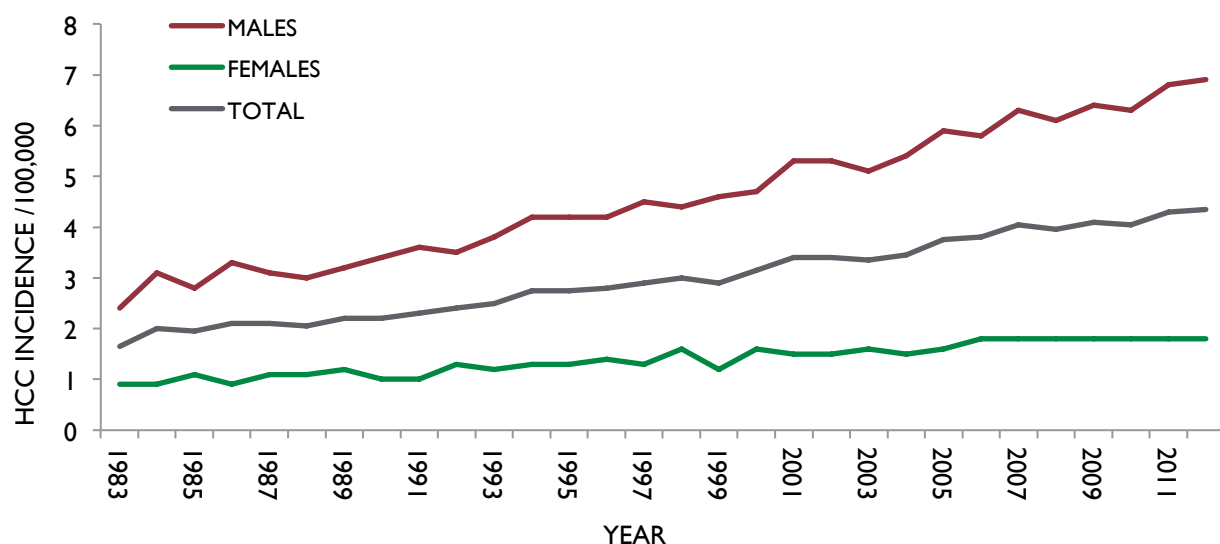
The vast majority of hepatocellular carcinomas develop in conjunction with chronic liver disease, most often cirrhosis, or pre-cirrhosis. As a result, the presence of chronic liver disease is the major risk factor for the development of hepatocellular carcinoma. ICCA is also seen more frequently in cirrhosis and hepatitis C, although not nearly as often as HCC.

EPIDEMIOLOGY

Data on the incidence of liver cancer is included as part of the annual cancer statistics published by the Canadian Cancer Society (CCS)(1). Statscan also keeps data on mortality from liver cancer (2). Data on HCC incidence and mortality secondary to chronic hepatitis B has been derived from modeling studies.

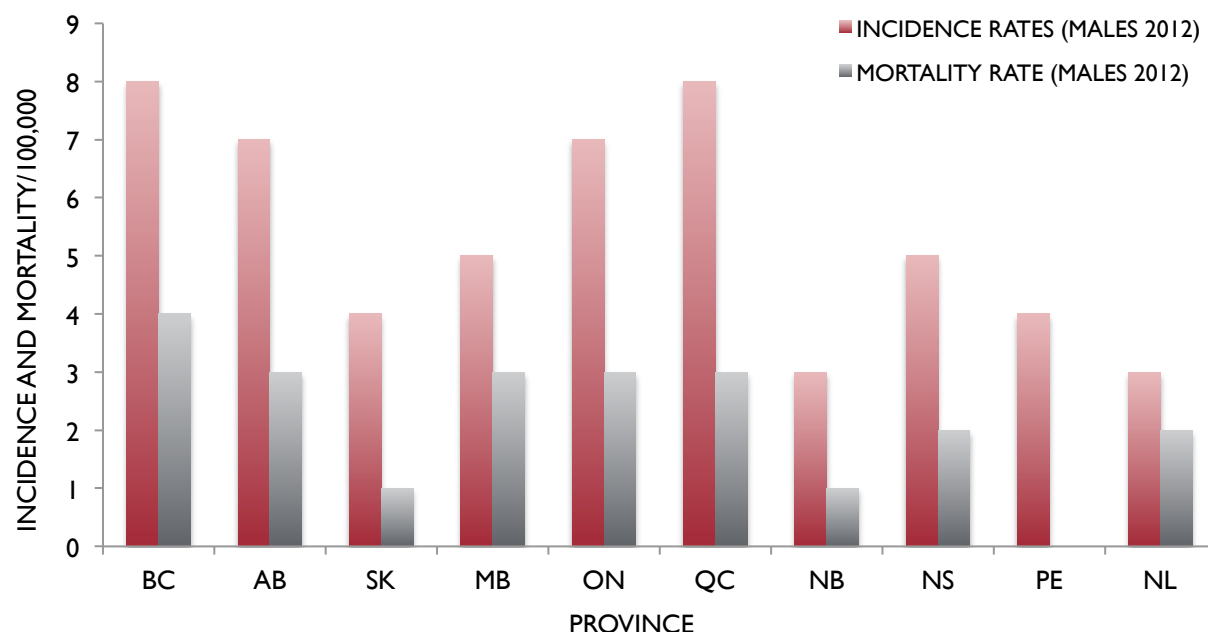
The CCS statistics coupled with the modeling studies confirm that HCC incidence is rising. Furthermore, HCC is the only cancer in Canada for which mortality is increasing.

FIGURE 24: HCC INCIDENCE WITH TIME IN CANADA ⁽¹⁾



Ontario, as the province with the largest population, has the highest number of cases of HCC, followed by Quebec. The HCC rate is highest in Quebec. This is shown in Figure 25.

FIGURE 25: HCC INCIDENCE RATES AND MORTALITY RATES BY PROVINCE (2012)⁽¹⁾



Modeling studies have suggested that the incidence of HCC related to hepatitis B and to hepatitis C is also increasing. This is shown in Figures 26-29. The modeling study in hepatitis B (3) showed that the mortality rate of hepatitis B-related HCC will increase by than more 50% to 2020 (Figure 28). Consequently, the increase in HCC deaths is not just due to a larger hepatitis B population, but also to an increased death rate within the population. Modeling studies in hepatitis C also suggest that the incidence of HCC will continue to rise to 2020 and beyond (Figure 29) (4).

The Canadian Cancer Society and Statistics Canada incidence data are likely to be an underestimate of the true HCC incidence. The data for these analyses comes from provincial cancer registries. However, to be entered into the register requires either a discharge diagnosis of HCC, or a pathological confirmation by biopsy. Since many patients do not get biopsies and may only be admitted for terminal care (often to a palliative care institution, rather than an acute care hospital), many cases are not captured. Often the discharge diagnosis and death certificate diagnoses do not mention liver cancer, but attribute death to liver failure, sepsis or variceal bleeding. Leber's analysis (2) describes as many cases of HCC from hepatitis B in 2007 as are recorded by the Canadian Cancer Society for HCC from all causes.

FIGURE 26: PROJECTED INCIDENCE OF HCC TO 2020 (CASE NUMBERS)⁽²⁾

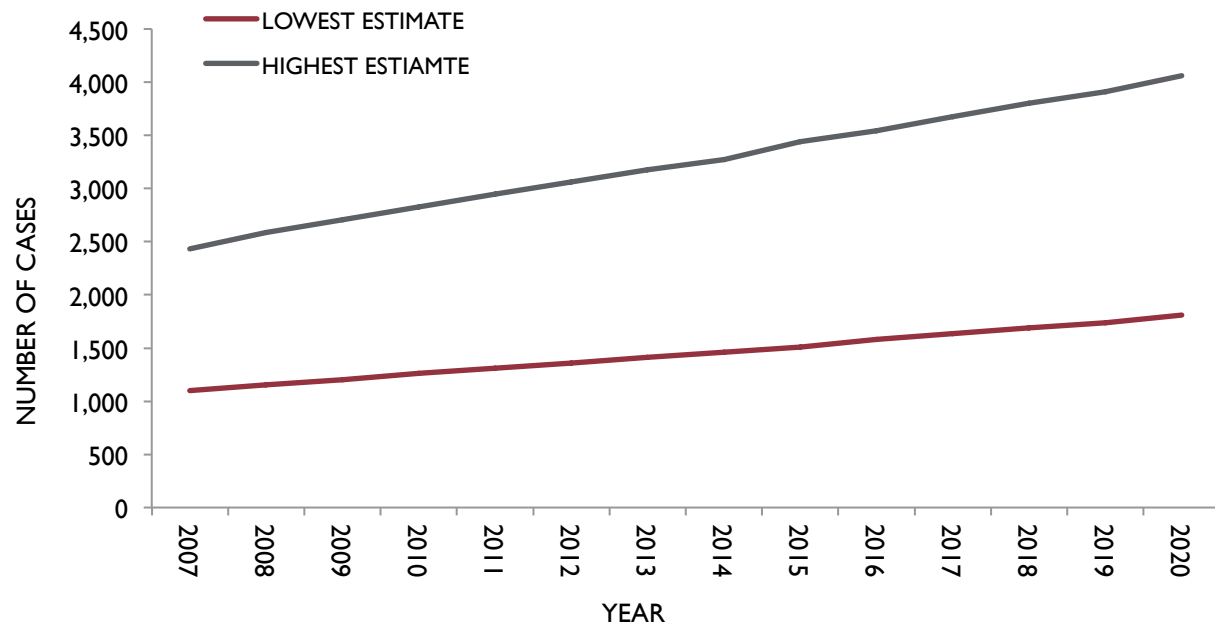


FIGURE 27: PROJECTED INCIDENCE OF HCC TO 2020 (RATE/100,000 POPULATION)⁽²⁾

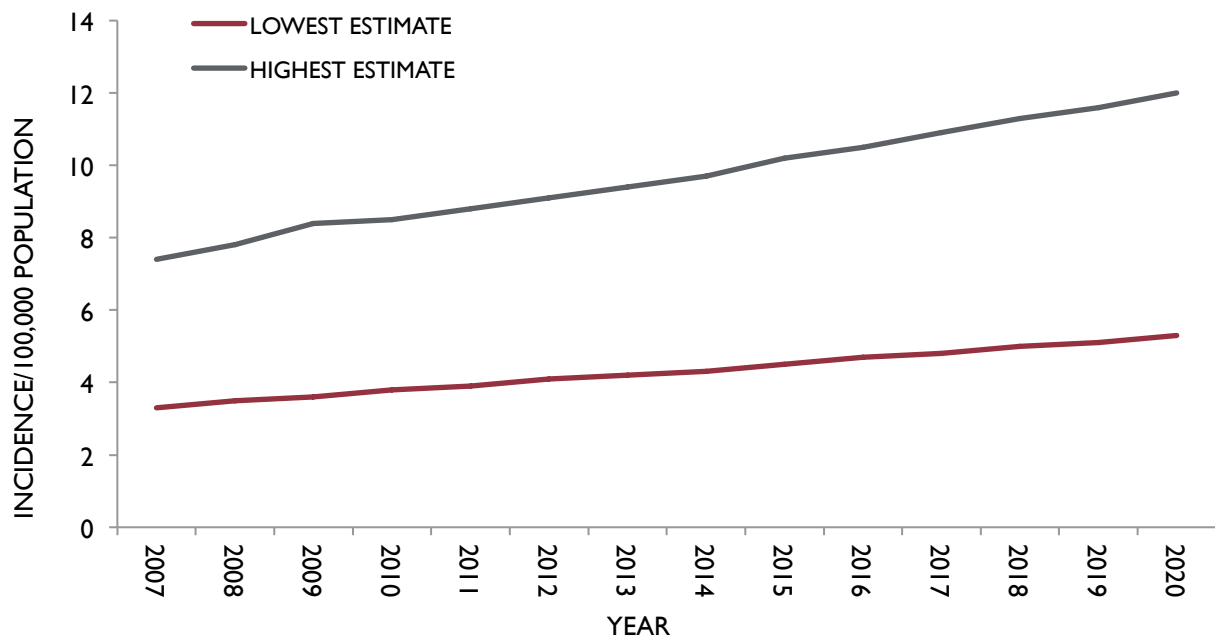


FIGURE 28: PROJECTED HBV-RELATED HCC MORTALITY TO 2020⁽²⁾

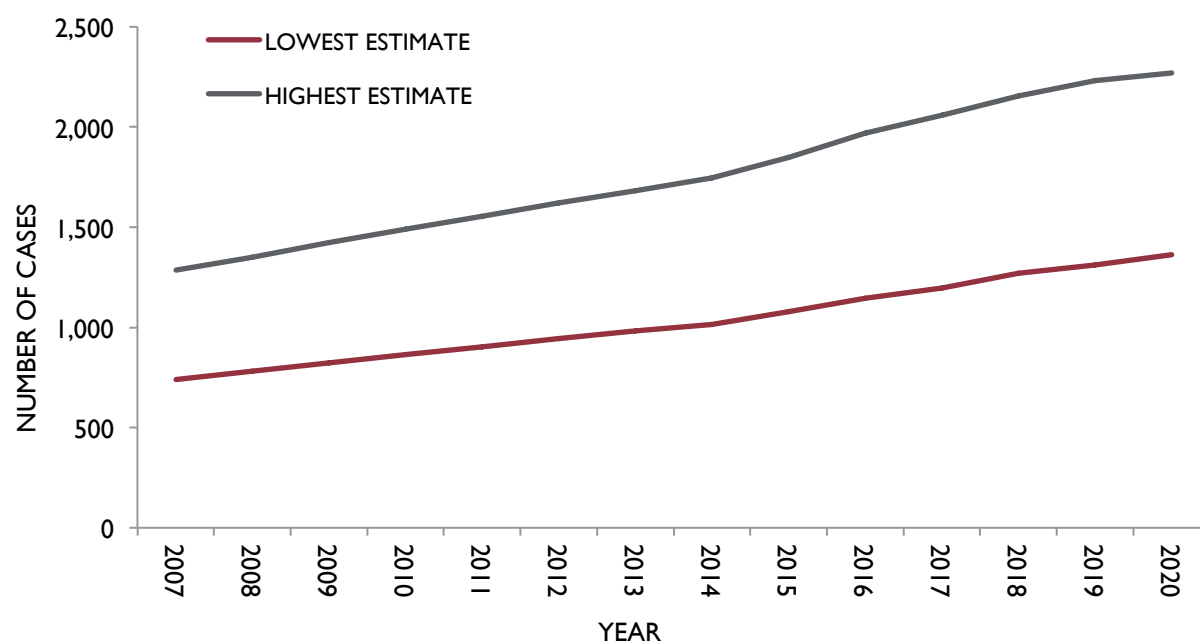
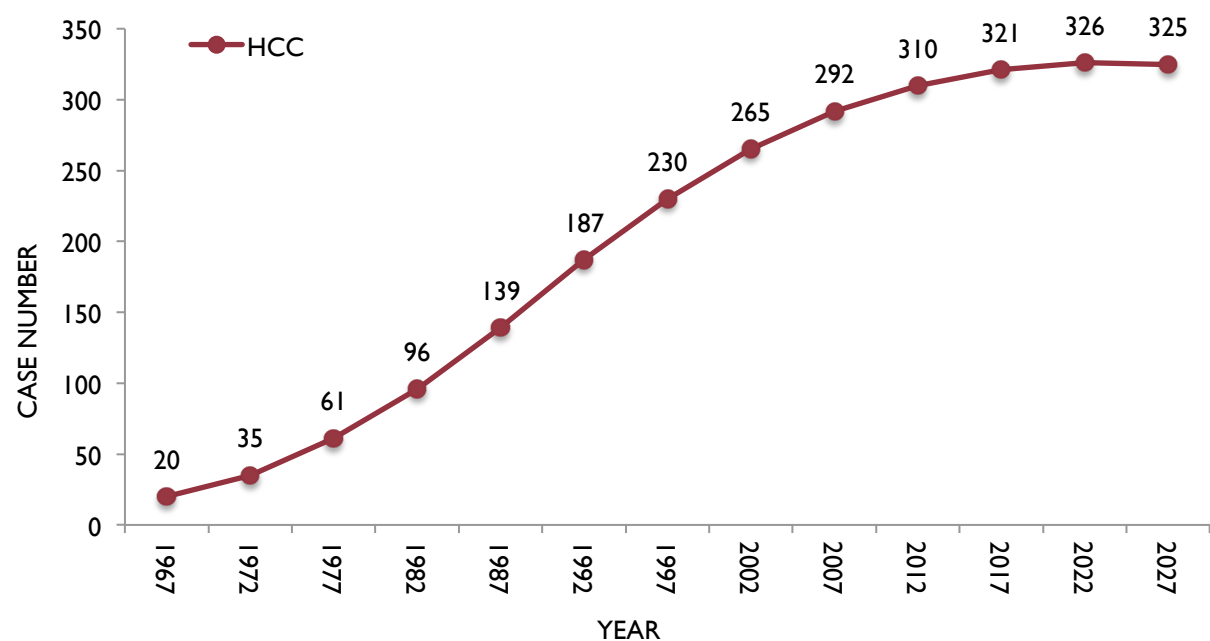


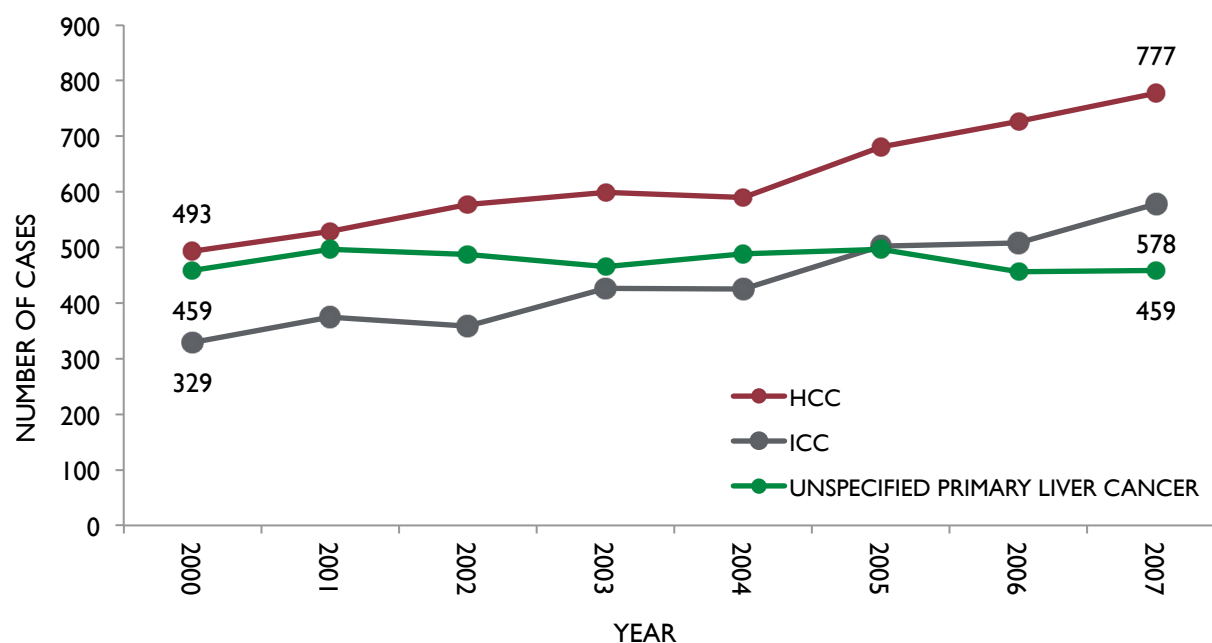
FIGURE 29: MODELED INCIDENCE OF HCC RELATED TO HEPATITIS C⁽³⁾



HCC MORTALITY

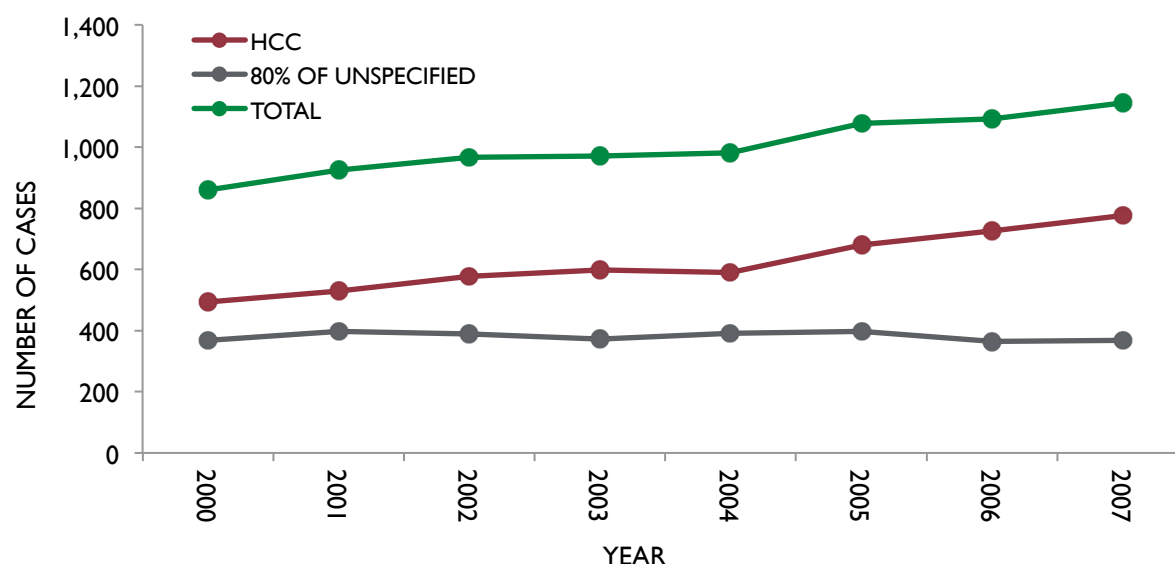
Statistics Canada has several categories for primary cancers of the liver. For the purposes of this report the categories for consideration are liver cell carcinoma (hepatocellular carcinoma), intrahepatic bile duct carcinoma (intrahepatic cholangiocarcinoma) and malignant neoplasm of the liver, unspecified. Figure 30 shows how the deaths from these cancers are changing over time.

FIGURE 30: MORTALITY FROM PRIMARY LIVER CANCERS⁽⁴⁾



The HCC data from Statscan is probably an underestimate in that most unspecified primary liver cancers are likely HCC. In clinical practice and in studies from elsewhere, the only two primary liver cancers that occur with any frequency are HCC and ICCA, and the ratio is more than 4:1. Fewer than 20% of all primary liver cancers are ICCA and more than 80% are HCC. If unspecified cases are counted as HCC, then the mortality rates from HCC are even higher. The reported HCC mortality rate compared to the “real” HCC mortality rate (including 80% of “unspecified” cancers) is shown in Figure 31.

FIGURE 3 I: MORTALITY FROM HCC CORRECTED FOR "UNSPECIFIED" LIVER CANCER⁽⁴⁾



SCREENING FOR HCC

Professional associations of liver disease experts all recommend that patients at risk for HCC should undergo regular screening to detect early stage disease. The reason for this is that the prognosis is poor in patients whose HCC is diagnosed because of the development of symptoms. These cancers are almost all advanced and beyond cure. However, in patients whose cancers are diagnosed early before the onset of symptoms, the cure rate may be as high as 90%. The benefits of HCC screening have been documented in a randomized controlled trial for patients with hepatitis B. While this kind of data is not available for hepatitis C or other causes of HCC, modeling analyses and indirect data have strongly suggested that screening is beneficial in reducing mortality in these conditions as well. Governments in Japan and Korea, where HCC is very common, have accepted the need for screening. However, no other government or health care authorities – including Canada – have endorsed screening.

National and international professional liver disease associations have issued practice guidelines with regard to screening for liver cancer. In the U.S., Europe and Canada, the recommendation is that patients at sufficient risk should be screened every six months with an ultrasound examination.

MANAGEMENT OF HCC

Since most patients with HCC have two diseases – cirrhosis and HCC – which have several different possible treatments, care ideally requires the expertise of a multidisciplinary group, including hepatologists, interventional radiologists, hepatobiliary surgeons, oncologists, radiation oncologists, pathologists, body imagers, and a liver transplant service. There are multidisciplinary groups managing HCC in most major cities in Canada (Vancouver, Edmonton, Calgary, London, Toronto, Montreal) but in the smaller cities HCC is managed essentially by the physician to whom the patient was initially referred. In many cities treatments essential for HCC management are not available. Chemoembolization, for example, is not available in Regina, Saskatoon or St. John's and liver transplant is only available in six centres in Canada (Vancouver, Edmonton, London, Toronto, Montreal and Halifax). Those units dealing with HCC are operating at or near capacity (see Chapter 7). Waiting times for some forms of HCC treatment in Toronto are unacceptably long. With current facilities, there is no capacity to treat large numbers of additional patients with HCC.

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CHAPTER 7

RESOURCES TO MANAGE LIVER DISEASE IN CANADA

With the care needs for a growing patient population on the rise, this report examines the facilities available to deal with liver disease in Canada in an attempt to determine whether the facilities are sufficient. The tables that follow look at the number of hepatologists, transplant programs, number of transplants done, deaths on the transplant waiting list, dedicated in-patient beds, and the costs of in-patient admissions for chronic liver disease. Table 12 shows the some of this data, broken down by province.

TABLE 12: RESOURCES TO MANAGE LIVER DISEASE ⁽¹⁾

	Full time Hepatologists	Liver transplantation program	Dedicated hospital beds for liver disease	Specialized liver pathology
BC	2	1	0	No
AB	20	1	shared with GI and other services	No
SK	0	0	0	No
MB	4	0	0	No
ON	20	2	For transplant only, shared	2
QC	14	2	Shared, but easy access	2
NB	0	0	0	No
NS	2	1	?	No
NL	1	0	0	No
PEI	0	0	0	No

In addition to hepatologists, chronic liver disease is also managed by gastroenterologists and internists. Unfortunately, there is no data on the numbers of these physicians who undertake care of patients with liver disease and the numbers of patients they care for. Viral hepatitis patients are also cared for by Infectious Disease (ID) specialists. Table 13 shows the number of gastroenterologists (including hepatologists) and ID physicians in each province. Once again, the number taking care of patients with liver disease is an unknown fraction of these.

The Canadian Association for Study of the Liver, the professional association for hepatologists and others involved in the care of, or research into, liver disease, is attempting to establish an Area of Focused Competence Diploma in Hepatology through the Royal College of Physicians and Surgeons of Canada. The plan is to have two tracks, the first as a specialization after gastroenterology training (as it currently is in most medical schools in Canada), and the second as an entry point after training in Internal Medicine. The hope is that this will encourage more physicians to become hepatologists. However, these measures, even if successful will not result in a large increase in the number of hepatologists in the near future.

TABLE 13: GASTROENTEROLOGISTS AND INFECTIOUS DISEASE SPECIALISTS IN CANADA BY PROVINCE

Province	Gastroenterologists/ hepatologists	IDs
AB	94	54
BC	71	36
MB	15	18
NB	8	5
NL	9	3
NWT/NUN	1	0
NS	16	10
ON	259	138
PEI	1	0
QC	133	59
SK	10	10
YK	0	0

The number of physicians who treat viral hepatitis is also not known. Table 14 shows estimated numbers from industry sources for hepatitis B. The number who treat hepatitis C is much smaller, about 400 in Canada.

TABLE 14: ESTIMATED NUMBER OF PHYSICIANS TREATING HEPATITIS B PATIENTS*

Province	All HBV Treating physicians
AB	90
BC	105
MN	21
NB	21
NL	6
NWT/NUN	?
NS	20
ON	253
PEI	?
QC	225
SK	29
YK	?

*Estimates from Gilead Sciences Canada Inc.

A patient with chronic liver disease that progresses to liver failure will usually end up in a liver transplant center. Data is available on the number of patients receiving liver transplants, the numbers on the waiting list, and the numbers who die while on the waiting list. However, there is no data on the numbers of patients who are referred for transplant but who do not qualify as candidates for various reasons. All of these patients will die of their liver disease, but what proportion of all liver deaths they might represent is unknown. Since the number of transplants per year (see Figure 32) is a small fraction of all liver deaths (about 400 transplants and about 5,000 liver deaths) this implies that the majority of patients with advanced chronic liver disease do not get transplants and die of their disease.

Figure 32 shows the number of liver transplants done in Canada from 2002-2010, and also shows the number of patients on the waiting list as of December of that year, and the number of deaths on the waiting list. This does not include deaths in patients who were once listed but subsequently de-listed over a three year period. Over the total period the number is more or less constant.

FIGURE 32: LIVER TRANSPLANTATION IN CANADA⁽²⁾

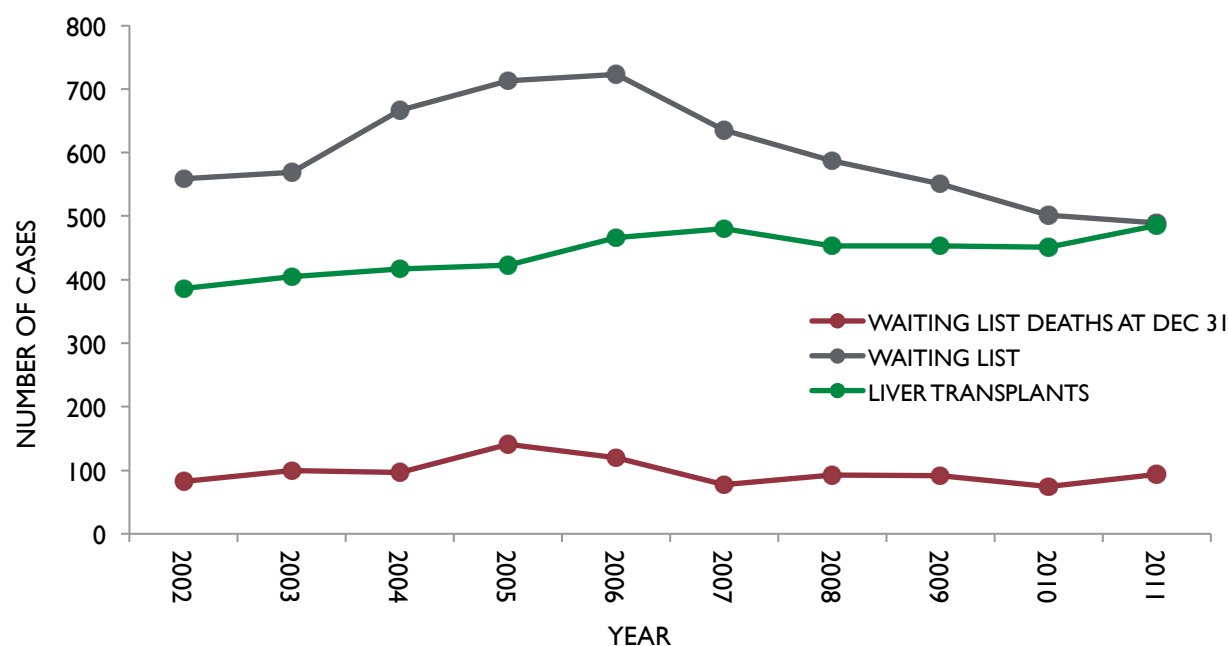


Figure 32 shows the rate of deaths on the liver transplant waiting list in Canada. This does not capture the fate of patients initially listed for transplantation, but de-listed for various reasons. This significant but unknown proportion of all patients initially listed.

Shortage of donor organs, expense and limited expertise are all major drawbacks to liver transplantation. Shortage of donor organs means that there is a significant drop-out on the waiting list as a result of patients dying or being disqualified because of progression of underlying liver disease to a state where the expected survival post-transplant is low.

SUMMARY

Given the high prevalence of liver disease, the lack of attention paid to these conditions is striking. There are very few beds dedicated to the care of these patients apart from beds reserved for liver transplant patients. Liver transplant is only available for a small minority of patients, so that the vast majority of patients who die of their liver disease do so without the benefit of a dedicated unit with expert nurses and physicians. The facilities to deal with the complications of end-stage liver disease are inadequate including a lack of expert physicians, resources, and availability of procedures such as radiofrequency ablation and chemoembolization. With the expected increase in frequency of end-stage liver disease that will occur in the decades to come, the current facilities will be overwhelmed. Training of new hepatologists will not be enough to address the demand for care. We need innovative ways to spread the expertise more widely and to limit the attendant costs.

REFERENCES FOR RESOURCES TO MANAGE LIVER DISEASE IN CANADA

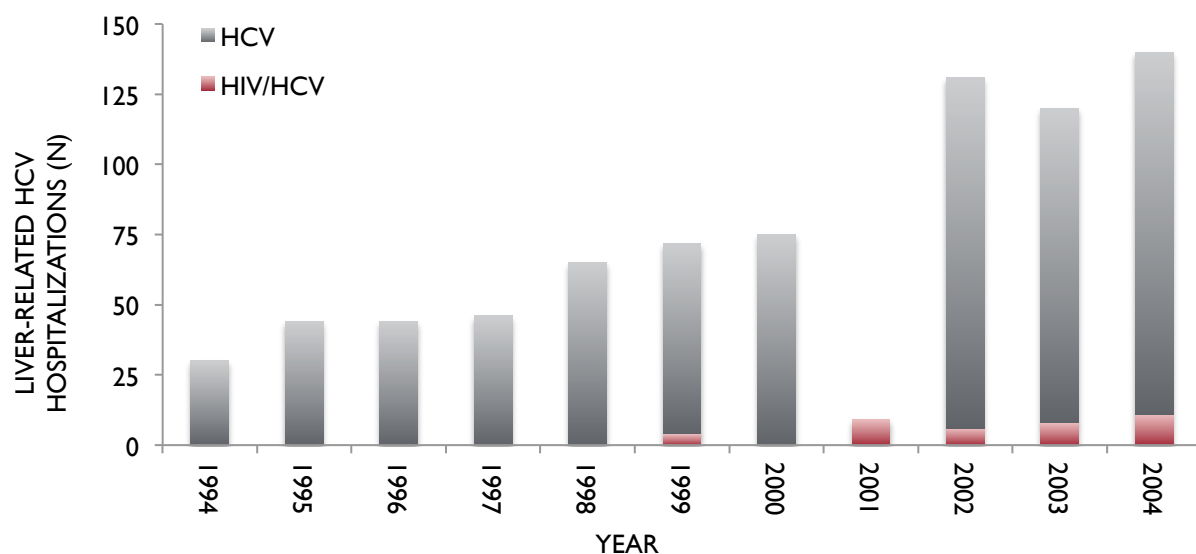
1. Drs Kevork Peltekian, Mang Ma, Vincent Bain, Les Lilly, Kelly Kaita, Helga Witt-Sullivan, Phil Wong, Bernard Willems, Jean-Pierre Villeneuve - personal communications.
2. Canadian Organ Replacement Registry annual report - 2010 and 2011
3. Gilead Sciences Canada Inc. -, personal communication
4. Michael Betel, personal communication

CHAPTER 8

COSTS OF LIVER DISEASE

There are no published studies of the costs related to all chronic liver disease in Canada. A study from Alberta showed that the number of hospital admissions for hepatitis C-related illness is increasing (1). This data is shown in Figure 33. Increased admission rates are associated with increased costs. Studies elsewhere have also documented substantial costs associated with management of liver disease but most focus on hepatitis C or liver transplantation.

FIGURE 33: ANNUAL NUMBER OF LIVER-RELATED HEPATITIS C VIRUS (HCV) HOSPITALIZATIONS IN THE CALGARY HEALTH REGION (1994 THROUGH 2004) ⁽¹⁾



Annual number of liver related hepatitis C virus (HCV) hospitalizations in the Calgary Health Region (1994 through 2004), stratified according to HIV status. This information was originally published in Can J Gastroenterol 2008;22(4):381-387

A study from BC showed that in the early phase of hepatitis C, the excess health care costs were about \$2,000/year/patient. In the mid-phase of the disease, the excess hepatitis C-related costs were \$5,500/patient/year. Although these costs are not large in themselves, multiplied by the number of cases in Canada (300,000+), the costs would be enormous. (This study also showed that less than 1% of patients were treated during this time, a disappointingly low proportion, emphasizing the massive task ahead of us to find and treat all patients with hepatitis C who might be at risk for end-stage liver disease). In the late stage of hepatitis C, the costs of cases and controls were similar. Data from the U.S. confirms that hospital costs are rising, and were about \$7 billion in 2009. For Canada, the equivalents costs might be about \$700 million.

In addition to the costs to the healthcare system the patients and their caregivers experience substantial costs in terms of time and out-of-pocket expenses (2). Depending on the stage of disease patients may spend anything up to 40 days a year attending doctors and hospitals. Their out-of-pocket costs also depend on stage of disease, but on average are about \$2,000/year. Their caregivers spend on average three weeks/year taking care of patients with hepatitis C. Patients who have been successfully treated have the lowest cost in terms of time and out-of-pocket expenses.

Figures 34 and 35 highlight data from the Canadian Institutes for Health Information (CIHI)(2). Figure 34 documents procedures performed in hospital in patients whose discharge diagnosis included some form of liver disease. There is a clear trend towards increased requirements for these procedures. There is a 19% increase in the number of gastroscopies and 18% increase over 4 years in the number of paracenteses, just two of the common procedures associated with the care of patients with liver disease.

FIGURE 34: PROCEDURES IN PATIENTS WITH LIVER DISEASE⁽²⁾

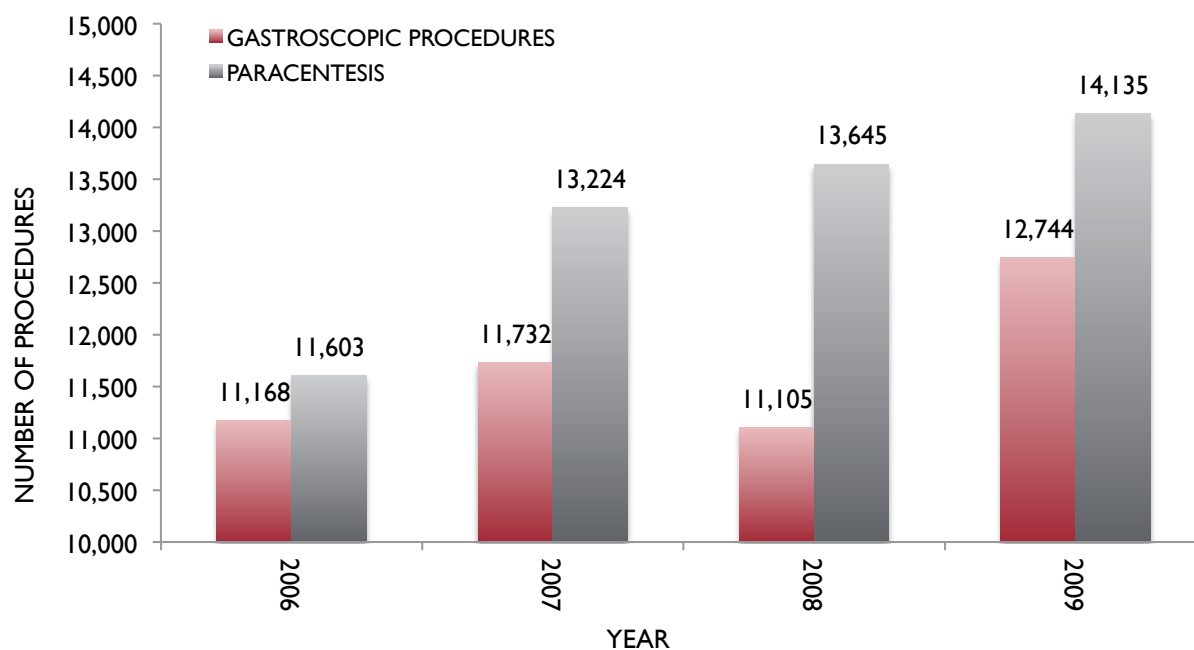
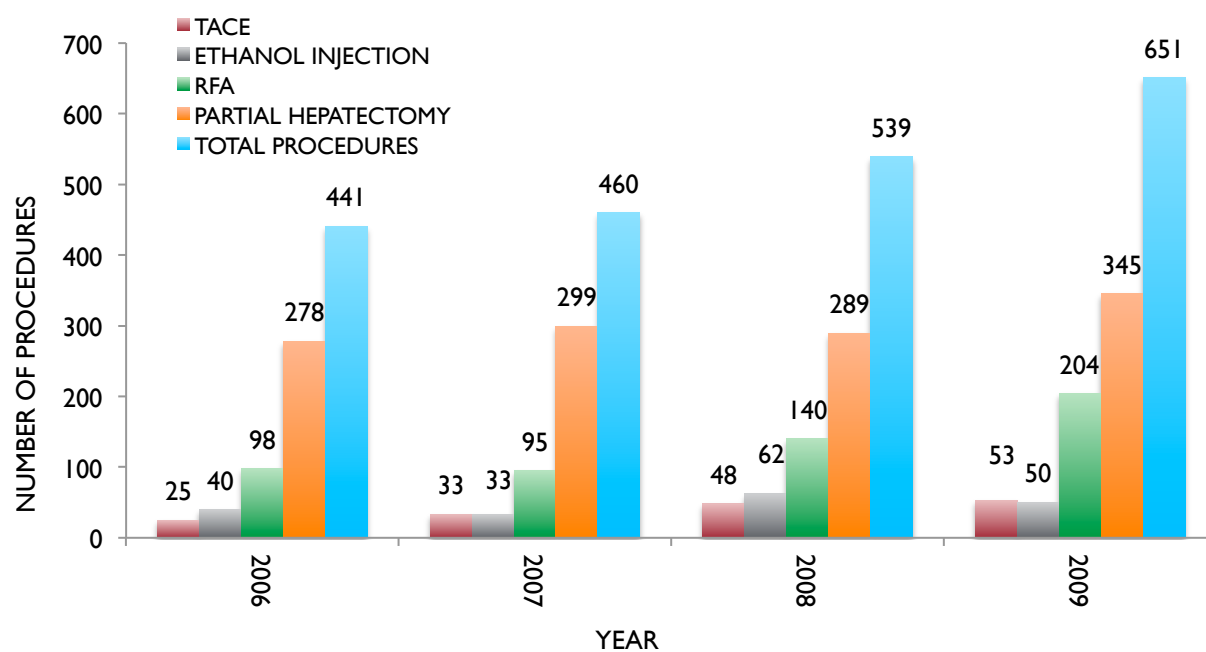


Figure 35 shows treatments performed for patients with liver cancer. The number of treatments performed each year is also rising. There is a 46% increase in delivery of cancer treatments over four years which represents a huge increase.

FIGURE 35: CANCER TREATMENT PROCEDURES IN PATIENTS WITH LIVER DISEASE⁽²⁾



Unfortunately, the CIHI data severely underestimates the real number of procedures. University Health Network (UHN) in Toronto, which is a referral center for HCC, has performed 476 trans-arterial chemoembolization (TACE) procedures from 2005-2011 (about 68/year), whereas CIHI has recorded between 25-53/year for the whole of Canada. UHN has performed 1,464 radiofrequency ablation (RFA) procedures since January 2006 (more than 200/year) whereas CIHI only lists up to 204/year for Canada. Underestimates of this magnitude suggest that the burden that HCC creates on the health care system is much bigger than previously thought.

Data provided by CIHI also allows calculation of costs related to hospitalization for liver disease. The data presented in Table 15 includes only the costs related to procedures required by in-patients with liver disease, and only the cases identified by CIHI. From the available data, it is not possible to capture all costs related to liver disease. Some of the in-hospital costs are shown in Table 15.

TABLE 15: IN-HOSPITAL COSTS FOR PROCEDURES REQUIRED BY LIVER DISEASE PATIENTS ACROSS CANADA ⁽³⁾

Diagnosis	In-Hospital costs
GI bleed	\$54,498,246
Liver transplant	\$28,521,333
Other major intervention	\$32,818,416
Cirrhosis/alcoholic hepatitis	\$31,000,037
Other liver disease (excluding malignancy)	\$10,266,708
Total	\$157,104,740

REFERENCES FOR COSTS OF LIVER DISEASE

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2. Federico CA, Hsu PC, Krajden M, Yoshida E, Bremner KE, Weiss AA, Anderson FA, 1-11Krahn M. Patient time and out-of-pocket costs in hepatitis C. *Liv Int*:2012:32:815-825
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CHAPTER 9

SUMMARY

There has been a nearly 30% increase in liver-related deaths over an eight year period. This is related to increases in incidence and prevalence of all the major liver diseases, including chronic viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease. This in turn has led to a dramatic increase in the incidence of cirrhosis and liver cancer.

However, there are major gaps in our knowledge about these conditions that hampers our ability to manage them effectively. There are an equal or greater number of barriers to control of these diseases – barriers that need not exist.

VIRAL HEPATITIS

1. The prevalence of chronic hepatitis B and chronic hepatitis C in Canada is unknown. Modeling studies suggest that there may be up to 700,000 people chronically infected with one of these viruses. Hepatitis B particularly, and to a lesser extent hepatitis C, disproportionately targets immigrant communities.
 - 1.1. Analyses suggest that without intervention there will be a increasing number of deaths in the infected populations over the next 10 years and more.
 - 1.2. Both hepatitis B and hepatitis C and the consequences of infection are under-recognized by the public and by family practitioners.
 - 1.3. The Public Health response to viral hepatitis at all levels of government is inadequate. The advent of SARS, H1N1 flu or new variant CJD (mad cow disease) all triggered much greater activity on the part of public health authorities, yet the mortality from these diseases was negligible compared to the mortality from hepatitis B and C.
 - 1.4. The costs of treating patients with viral hepatitis will be enormous and will likely draw funds from other disease areas. However, the financial and personal costs of not treating these diseases will be higher
2. Hepatitis B and C are vastly under-treated in Canada. The available data of 7,000-8,000 annual new prescriptions for hepatitis C is an under-estimate of the treated population, but is unlikely to be more than double this total. Fewer than 10,000 patients with hepatitis B are being treated in Canada.
 - 2.1. There are too few trained physicians and nurses to adequately care for patients with hepatitis B and C.
3. Reimbursement policies for drugs to treat hepatitis B and hepatitis C are restricted by CDEC and in most provinces. The restrictions frequently do not conform to medical practice guidelines or to scientific evidence. This begs comparison with HIV, another blood-borne disease. There are virtually no restrictions on reimbursement of HIV drugs. Total government expenditures for treating HIV exceed those for hepatitis B and hepatitis C despite the much higher prevalence of chronic viral hepatitis.
 - 3.1. Reimbursement agencies apply restrictions to hepatitis treatment that interfere with physician management of patients by requiring tests (such as liver biopsy) that are hazardous, and not always necessary for diagnosis or for disease staging.

4. Hepatitis B vaccination policies are not uniform in Canada, and do not reflect the demographics of the infected population (immigrants from endemic countries). Vaccination of adolescents targets the wrong population, one that does not develop chronic disease, and in whom hepatitis B-related morbidity and mortality is extremely low. In contrast, infant vaccination, which is recommended in most other countries, is not universal in Canada. As a result, childhood hepatitis B infection, which does lead to chronic disease and increased morbidity and mortality, is not declining, and may actually be increasing.
5. Provincial government funding for hepatitis B and C-related programs is virtually non-existent, except in British Columbia and Ontario.
6. Viral hepatitis is treatable. Treatment will prevent progression of disease to cirrhosis, liver cancer and death. And yet, current reimbursement policies, available manpower and other restrictions mean that there will be tens of thousands of unnecessary deaths from the consequences of viral hepatitis.

ALCOHOLIC LIVER DISEASE

1. Alcoholism is a major societal problem that will require long-term solutions.
2. The prevalence of alcoholic liver disease is unknown. However, with rising alcohol consumption, the prevalence of acute alcoholic hepatitis and alcoholic cirrhosis will rise contributing to the overall increase in liver-related deaths.
3. The contribution of alcohol-induced liver injury to progression of other liver diseases is likely substantial, but has not been measured.
4. There is no specific treatment for alcohol-induced liver disease, except abstinence.

NON-ALCOHOLIC FATTY LIVER DISEASE

1. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Canada, although the prevalence is unknown. It is a slowly progressive disease but may culminate in cirrhosis, liver failure, liver cancer and death. This condition is also increasing in frequency in correlation with the rise in prevalence of obesity and diabetes.
2. The increase in end-stage liver disease from non-alcoholic fatty liver disease will eventually overshadow the increase in end stage liver disease related to viral hepatitis.
3. There is no treatment for NAFLD except healthy living measures including weight loss and exercise. Patients with NAFLD are frequently not good candidates for liver transplantation because of co-morbid conditions, such as heart disease, hypertension, vascular disease and diabetes.

CIRRHOSIS AND ITS COMPLICATIONS

1. Cirrhosis can be the end-stage of a number of different types of liver disease.
2. Cirrhosis is preventable by treatment of the predisposing condition.
3. The increased incidence and prevalence of all major forms of chronic liver disease will result in an increase in the number of patients with cirrhosis. Cirrhosis is a potentially deadly condition that may cause death by liver failure, internal bleeding or the development of liver cancer. Patients with chronic liver disease die at a younger age than the population at large.

4. There is no treatment for cirrhosis, except for liver transplantation.
5. Care of patients with cirrhosis is time-consuming, expensive and demanding of physician time and hospital resources.
6. Facilities to manage cirrhosis are barely adequate at present in Canada. With the increase in cirrhosis incidence, current facilities will be overwhelmed. Care of patients with cirrhosis will draw resources from other chronic diseases.

HEPATOCELLULAR CARCINOMA

1. This is the most common cause of death in hepatitis B and a common cause of death from other chronic liver diseases. The incidence of hepatocellular carcinoma is increasing in Canada, and will likely continue to increase as a result of the increasing prevalence of the predisposing conditions.
2. Currently, most patients who get liver cancer present with symptoms, and early detection is uncommon, rather than the rule. When liver cancer causes symptoms it means the disease is advanced, treatment is usually futile, and death ensues rapidly.
3. Liver cancer is largely preventable, through prevention or treatment of the underlying liver disease. For those who develop liver cancer, routine screening can detect the cancer at a very early stage, when it is curable in most patients. Although advocated by the physicians who care for these patients and by professional associations no government in Canada supports screening for hepatocellular carcinoma.
4. Facilities to treat liver cancer are not universally available. Centres of expertise have developed but are restricted to major urban centers.

CHAPTER 10

RECOMMENDATIONS

All major forms of liver disease are increasing in frequency in Canada. Therefore, it is predictable that if the current state of resources for the management of liver disease remains unchanged, there will be substantial increases in the mortality from the complications of cirrhosis and from hepatocellular carcinoma. Barriers to access to treatment and care threaten the health and longevity of a large number of patients. The expanding epidemic of viral hepatitis and liver disease needs to be addressed in several areas to reduce potential mortality. Management of end-stage liver disease also needs to be addressed.

We therefore recommend that

1. Health Canada, in conjunction with the provinces must establish a national liver disease strategy. Without a national strategy as has been instituted in many other countries, we will not be able to optimize management of liver diseases.
2. Provinces where liver disease is particularly prevalent (Ontario, Quebec, Alberta and British Columbia) should establish agencies that manage liver disease, akin to the cancer agencies in each province. These would be responsible for determining priorities, for ensuring efficient use of public funds, and for establishing control programs. The agencies should have an external board of directors that determine policies and priorities. The board of directors should be independent of the Ministry and consist mainly of members of the public, and must include physicians who manage liver disease, as well as some with a background in epidemiology.

In addition, the following recommendations should be implemented:

LIVER DISEASE IN GENERAL

1. Testing of ALT should be part of the routine annual check up with the family practitioner. If more than 25% of the Canadian population has NAFLD or other liver diseases, routine testing is likely to allow for early intervention.
2. Family practitioners require additional education about the diagnosis of liver disease, assessment of liver disease severity, and outcomes of liver disease.

VIRAL HEPATITIS

1. Public health initiatives
 - a. A national seroprevalence survey should be undertaken with oversampling in high risk communities such as immigrants to more precisely determine the prevalence of hepatitis B and C in Canada and to pinpoint which communities require education of the patients and physicians.
 - b. Chronic hepatitis B should be a reportable disease with all notifications collected and collated by the Public Health Agency of Canada (PHAC). Notifications should include whether the patient was acutely or chronically infected and all jurisdictions should be obliged to report this data.
 - c. Reporting of chronic hepatitis C has to be improved. Data should be collected on those who are actively infected separately from those who have cleared virus. All jurisdictions should be obliged to report this data.

- d. All Canadians and permanent residents born between 1945 and 1975 should be tested once for hepatitis C. All immigrants should be screened for hepatitis B.
 - e. Deaths from the complications of hepatitis B and C must be tracked separately from deaths from other liver diseases.
 - f. The Federal Government must establish research programs aimed at better surveillance and innovative ways to deliver care for the massive numbers of infected individuals destined to impact the health care system in the future. The total amount of money invested by governments on programs should be proportionate with the prevalence of the diseases, compared to other infectious diseases.
 - g. Provincial governments should establish support systems for the treatment of viral hepatitis (different than support of community organizations). There should be an increase in the number of clinics, run mostly by nurses who can coordinate and provide care. The clinics should be capable of rapid through-put to increase the numbers of treated patients. Physicians alone cannot care for the more than 500,000 individuals with hepatitis B and hepatitis C and the few clinics that exist cannot possibly manage the total number of infected patients.
2. Treatment
- a. Restrictions on reimbursement for hepatitis B and C treatment must reflect modern approaches to the management of these diseases and must be based on need, not solely on minimizing costs. Restrictions based on ALT level and presence of cirrhosis must be abolished.
 - b. Treatment capacity has to be increased, either through recruitment of family physicians into hepatitis treatment groups, or by nurse practitioners. Waiting for capacity to increase through training of additional hepatologists, gastroenterologists and infectious disease specialists will take too long to solve the full scope of the problem.
 - c. Costs for nursing care for hepatitis C patients should be covered by provincial governments.
3. Vaccination
- a. Neonatal hepatitis B vaccination should be immediately introduced in all provinces, with a catch-up vaccination program in those provinces switching from adolescent vaccination to neonatal vaccination.
 - b. Programs for vaccination of high-risk individuals should be harmonized between provinces.
4. Research
- a. CIHR and PHAC need to establish a specific program to fund research into hepatitis B in a similar manner to what was done for hepatitis C. More research is badly needed.

ALCOHOLIC LIVER DISEASE

- 1. The ICD coding system does not adequately capture alcohol-attributable liver diseases. Steps should be undertaken to better capture information regarding the prevalence and costs of care of these patients.

NON-ALCOHOLIC FATTY LIVER DISEASE

1. There should be better documentation of the prevalence of NAFLD and its consequences, and of the health care costs associated with management of this condition (separate from the costs associated with management of associated conditions).

CIRRHOSIS AND ITS COMPLICATIONS

1. Provinces need to establish in-patient units staffed with trained physicians and nurses to care for patients with advanced liver disease. The consequences of not doing so will be a revolving door situation whereby patients frequently return to hospital within a short period after discharge.

HEPATOCELLULAR CARCINOMA

1. Too many patients who develop HCC present late with incurable disease. Governments need to establish HCC screening programs and keep track of the outcomes for quality assurance. This will require establishment of referral ultrasound units that specialize in HCC screening and have appropriate quality assurance protocols in place.
2. Resources (equipment and personnel) at existing regional cancer centers should be enhanced to facilitate the multidisciplinary care of liver cancer. The large university centres cannot take care of all HCC in Canada. Regional cancer centers should have access to all recognized modalities of HCC treatment.

CONCLUSION

WE NEED TO DO MORE TO FIGHT LIVER DISEASE...

AND WE NEED TO DO IT NOW.

Unlike other major diseases, there has been no national strategy put in place for a public health response to liver disease. Without a coordinated effort involving investment and resources for prevention, screening, treatment, patient care and research, thousands of Canadians will die needlessly. The Canadian Liver Foundation, in partnership with liver experts from across the country, is sounding the alarm and recommending short-term and long-term solutions to help defuse this ticking time bomb. We urge federal and provincial/territorial governments and health agencies to make liver disease a priority and to act to protect the health and well being of Canadians of all ages.

GLOSSARY OF ABBREVIATIONS

ADE	- Adefovir
ALT	- alanine aminotransferase
CASL	- Canadian Association for the Study of the Liver
CCS	- Canadian Cancer Society
CDC	- Centers for Disease Control and Prevention
CDEC	- Canadian Drug Expert Committee
CDR	- Common Drug Review
CIHI	- Canadian Institutes of Health Information
CIHR	- Canadian Institutes for Health Research
CLF	- Canadian Liver Foundation
CNDSS	- Canadian Notifiable Disease Surveillance System
DALYs	- disability-adjusted life years
EHSSS	- Enhanced Hepatitis Strain Surveillance System
ETV	- Entecavir
HALYs	- health-adjusted life years
HBV	- hepatitis B virus
HCC	- hepatocellular carcinoma
HCV	- hepatitis C virus
ICD	- International Classification of Diseases
ICCA	- intrahepatic cholangiocarcinoma
ID	- Infectious Disease
IOM	- Institute of Medicine (U.S.)
MRC	- Medical Research Council of Canada (was replaced by CIHR)
NACI	- National Advisory Committee on Immunization
NAFLD	- non-alcoholic fatty liver disease
ONBOIDS	- Ontario Burden of Infectious Disease Study
PHAC	- Public Health Agency of Canada
RFA	- radiofrequency ablation
SARS	- Severe Acute Respiratory Syndrome
TACE	- trans-arterial chemoembolization
TEL	- Telbivudine
TDV	- Tenofovir
UHN	- University Health Network
ULN	- upper limit of normal
YERF	- year-equivalents of reduced functioning
YLL	- years of life lost due to premature mortality

ABOUT THE CANADIAN LIVER FOUNDATION

Founded in 1969 by a group of doctors and business leaders concerned about the increasing incidence of liver disease, the Canadian Liver Foundation (CLF) was the first organization in the world devoted to providing support for research and education into the causes, diagnoses, prevention and treatment of all liver disease. Through its chapters across the country, the CLF strives to promote liver health, improve public awareness and understanding of liver disease, raise funds for research and provide support to individuals affected by liver disease.

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