Chronic Hepatitis C Associated Hospitalizations: A Birth Cohort Analysis with Implications for Screening

Journal:	*CMAJ Open*
Manuscript ID:	CMAJOpen-2013-0087
Manuscript Type:	Other
Date Submitted by the Author:	05-Dec-2013
Complete List of Authors:	Schanzer, Dena; Public Health Agency of Canada, Infectious Disease and Emergency Preparedness Branch Paquette, Dana; Public Health Agency of Canada, Lix, Lisa; University of Manitoba, Department of Community Health Sciences
Keywords:	Epidemiology, Hepatology, Infectious diseases, Public health, Statistics and research methods
More Detailed Keywords:	Chronic hepatitis C, Birth cohort, Cohort effect, Hospitalization, Trends and projections, Disease burden
Abstract:	Background: Much of the recent increase in chronic hepatitis C (CHC) mortality and morbidity rates in Canada is believed to be due to higher CHC prevalence among the baby boom population. We aimed to assess the current and potential future CHC-associated hospitalization burden by birth cohort and compare the cohort-specific rates. Methods: Hospital records of in-patients with a diagnosis of CHC and liver disease or liver cancer (CHC-LD) were extracted from the Canadian Discharge Abstract Database (DAD), for April 2004 to March 2011. Regression was used to estimate the temporal trend for each 5-year birth cohort from 1915 to 1984. These trends were used to predict future hospitalizations. Parametric bootstrap methods were used to calculate 95% confidence intervals (CIs) corresponding to the estimated rate ratios. Results: CHC-LD associated hospitalizations increased an average of 6.0% (95% CI, 4.4%-7.7%) per year over the study period. The CHC-LD associated morbidity burden was highest for the 1950-54 and 1955-59 birth cohorts at 18 (95%CI, 13-24) and 14 (95%CI, 10.3-18.2) times the rate for the 1970-74 birth cohort in 2010 respectively. Comparing rates at 75 years of age, the anticipated rate ratios declined to 3.6 (95%CI, 2.3-4.9) and 3.4 (95%CI, 2.1-4.7). Rate ratios at age 75 were statistically elevated for the four 5-year birth cohorts from 1950-69. Conclusions: Without further interventions, the CHC-LD disease burden will continue to increase for most birth cohorts, likely peaking after age 70. A significant disease burden is emerging in younger birth cohorts that should be monitored.

Title: Chronic Hepatitis C Associated Hospitalizations: A Birth Cohort Analysis with Implications for Screening

Authors:

Dena L. Schanzer[1], Dana Paquette[1], Lisa M. Lix[2]

Author Affiliations:

[1] Infectious Disease Prevention and Control Branch, Public Health Agency of Canada, Ottawa, Ontario, Canada

[2] Department of Community Health Sciences, University of Manitoba, Manitoba, Canada

Corresponding author:

Dena Schanzer, Infectious Disease and Emergency Preparedness Branch, Public Health Agency of Canada, 100 Eglantine Driveway, Tunney's Pasture, AL:0603B, Ottawa, Ontario, K1A 0K9, Canada

e-mail: dena.schanzer@phac-aspc.gc.ca

Short Title: Chronic HCV Disease Burden by Birth Cohort

Word count: Abstract: 249 Text: 2483

Number of Tables: 3

Number of Figures: 3

Potential conflicts of interest

None declared.

Financial support

Third party funding was not sought for this study. LML is supported by a Research Chair from the Manitoba Health Research Council.

Abstract

Background: Much of the recent increase in chronic hepatitis C (CHC) mortality and morbidity rates in Canada is believed to be due to higher CHC prevalence among the baby boom population. We aimed to assess the current and potential future CHC-associated hospitalization burden by birth cohort and compare the cohort-specific rates.

Methods: Hospital records of in-patients with a diagnosis of CHC and liver disease or liver cancer (CHC-LD) were extracted from the Canadian Discharge Abstract Database (DAD), for April 2004 to March 2011. Regression was used to estimate the temporal trend for each 5-year birth cohort from 1915 to 1984. These trends were used to predict future hospitalizations. Parametric bootstrap methods were used to calculate 95% confidence intervals (CIs) corresponding to the estimated rate ratios.

Results: CHC-LD associated hospitalizations increased an average of 6.0% (95% CI, 4.4%-7.7%) per year over the study period. The CHC-LD associated morbidity burden was highest for the 1950-54 and 1955-59 birth cohorts at 18 (95%CI, 13-24) and 14 (95%CI, 10.3-18.2) times the rate for the 1970-74 birth cohort in 2010 respectively. Comparing rates at 75 years of age, the anticipated rate ratios declined to 3.6 (95%CI, 2.3-4.9) and 3.4 (95%CI, 2.1-4.7). Rate ratios at age 75 were statistically elevated for the four 5-year birth cohorts from 1950-69.

Conclusions: Without further interventions, the CHC-LD disease burden will continue to increase for most birth cohorts, likely peaking after age 70. A significant disease burden is emerging in younger birth cohorts that should be monitored.

Keywords: Epidemiology; Hepatology; Infectious Diseases; Public Health; Statistics and research methods

Detailed Keywords: Birth Cohort; Chronic Hepatitis C; Cohort effect; Disease burden; Hospitalization; Trends and projections

Introduction

In August 2012, the US Center for Disease Control (US CDC) released recommendations to expand screening for the hepatitis C virus (HCV) to include a one-time blood test for all persons born between 1945 and 1965 (i.e., baby boom generation). This recommendation was based in part on estimates that this cohort accounts for three quarters of all HCV infections in the United States[1] and that of an estimated 4.3% of the population born in the 1950s who were infected[2], 50% were unaware of their HCV status[3]. Currently in Canada, screening recommendations for hepatitis C are based on an individual assessment of risk rather than the patient's age or year of birth[4]. The Canadian Health Measures Survey, a nationally representative household survey, estimated the seroprevalence for hepatitis C (HCV) in 2007 to 2011 at 0.5% (95%CI 0.3-0.9). However, only 30% (95% CI 16-51) were aware of their infection status, and prevalence was elevated among persons aged 50-79 years compared to persons aged 14-49[5].

Chronic hepatitis C (CHC) infections have resulted in a considerable morbidity and mortality burden in Canada[6-8]. Using health-adjusted life-years (HALY), a composite measure of premature mortality and reduced functioning due to disease, to estimate the disease burden associated with 51 infectious diseases in Ontario, Kwong and colleagues[9] found that HCV was the infectious agent that accounted for the largest proportion of the disease burden, surpassing HIV. Linking diagnostic and mortality data, a study in British Columbia found significantly elevated standardized mortality ratios (SMR) for both liver

related and drug related causes of death as well as all-cause mortality among persons who had tested positive for HCV compared to those who had tested negative for HCV[10].

The natural history of HCV is only partially understood, and the progression to liver cirrhosis is variable[11-13]. A small portion of persons clear their infection. For others, symptoms of the chronic infection often emerge 20 or more years after the initial infection. Disease progression from fibrosis to cirrhosis and hepatocellular carcinoma is not linear in time, with the rate of progression related to many factors, including time since infection, age and alcohol consumption.

This long delay from HCV infection to symptoms suggests that cohort-specific differences in CHC prevalence as well as the aging of these cohorts significantly influenced the observed trends in morbidity and mortality rates[6]. With access to detailed hospitalization data, we aimed to explore the effect of birth-cohort on the trends in hospitalizations associated with CHC and liver disease (CHC-LD); predict the future lifetime hospitalizations by 5-year birth cohort; and compare the disease burden for different birth cohorts.

Methods

Sources of data:

Hospital discharge records for patients admitted to an acute care hospital with a diagnostic code of CHC were extracted from the Canadian Institute of Health Information (CIHI) patient-specific Discharge Abstract Database (DAD)[8] from April 2004 to March 2011, a period when all DAD participating provinces used the *International Classification of Disease, Tenth Modification* (ICD-10)[14], Canadian version (ICD-10-CA)[15] for diagnostic coding. The province of Quebec does not participate in the DAD, hence the DAD includes approximately 75% of all acute care hospital separations in Canada. Hospitalizations were stratified by 5-year birth cohorts from 1915 to 1984, year of discharge (batch year: running from April until March of the following calendar year), discharge status (alive or deceased) and the presence of a co-diagnosis of liver diseases (ICD-10 codes K70-K77, R18) including hepatic carcinoma (ICD-10 code C22). CHC associated hospitalizations were identified by the ICD-10 code B18.2.

Population denominators for rate calculations were obtained from Statistics Canada population projections, medium growth scenario M1[16].

Analysis:

As a general outline, trends in the number of hospitalizations were estimated by birth cohort, and then these trends were used to predict the future burden in the younger birth cohorts as they aged. Next rates and rate ratios with the 1970-74 cohort as a reference

were calculated three different measures of the cohort effect: by year of hospitalization; at the same age; and future lifetime. Current year and near-term predictions focus on the visible burden. With new more effective treatments on the horizon, reducing the near-term burden is a more urgent concern. The same age comparison is a proxy measure of the relative prevalence. The future lifetime comparison is similar to the comparison used in cost-effectiveness analysis.

The first step was to estimate the trend in the number of CHC-LD associated hospitalizations for each 5-year birth cohort from 1915-19 to 1980-84. A generalized linear model (GLM) with a log link, Poisson distribution and dispersion parameter specified[17] was fit to the annual number of hospitalizations stratified by birth cohort with year of discharge (batch year) and a constant term as the model covariates. The quasi-Poisson regression model equation to predict the annual number of hospitalizations ($\boldsymbol{Hosp_{i,j}}$) for birth cohort $\boldsymbol{j}$ ($\boldsymbol{j}$ =1915-19 to 1980-84) in batch year $\boldsymbol{i}$ ($\boldsymbol{i}$ =2004 to 2010) is given by:

$$\log(Hosp_{i,j}) = \beta_{2,j} Year_i + \beta_{1,j} \quad (1)$$

The estimated trend parameter value ($\boldsymbol{\beta_{2,j}}$) and its standard error were converted to an average annual percentage change ($e^{\beta_{2,j}} - 1$) for each birth cohort. The same model was used to estimate the overall trend.

The second step was to use a parametric bootstrap approach, which involves generating simulated values of the parameters, to facilitate the calculation of confidence intervals (CI)

for the projected rate ratios. The bootstrap is a computationally intensive statistical technique that allows the researcher to make inferences from data with complex distributions (in this case, the ratios of projected rates)[17-19]. Random values were generated using the normal distribution with the mean and standard deviation given by the trend ($\boldsymbol{\beta_{2,j}}$) and standard error estimated in the quasi-Poisson regression model in the first step. The number of hospitalizations for each birth cohort in the last year of available data ($\boldsymbol{Hosp_{2010,j}}$) was also simulated from the distribution of uncertainty (standard error) associated with model predicted value for 2010. In the third step, the average age at hospitalization over the study period was calculated for each birth cohort and the simulated values for the cohort-specific trends ($\boldsymbol{\beta_{2,j}}$) were interpolated linearly to obtain trend estimates for each single year of age[17]. The fourth step was to project the number of hospitalizations until age 90 for each 5-year birth cohort and then sum the predicted number of hospitalizations for the time period of interest (for example, next 10 years, at age 75, or future lifetime) and calculate hospitalization rates. Future lifetime hospitalizations were calculated by summing the projected values from 2011 until age 90 and rates were calculated by dividing by the population in 2010. The 1970-74 birth cohort was selected as the reference for the rate ratios. Same-age rate ratios were reported for age 75, though with the methodology used same-age rate ratios would not be sensitive to this choice of age. The final step was to calculate the mean and standard deviation of the rate ratios from the previous step. Results from steps 1 (trends), 4(projections) and 5 (rate ratios) are reported. SAS Enterprise Guide 5.1 [17] was used for the analysis.

Results

The number of CHC-associated hospitalizations in the study area increased approximately 5% per year from 4700 in 2004/05 to 6400 in 2010/11. The rate of increase was more pronounced for CHC-LD associated hospitalizations at 6.0% (95% CI, 4.4%-7.7%) per year. The proportion of CHC-LD associated hospitalizations increased with increasing age from 5% for patients less than 30 years of age, reaching 60% by age 65. The fatality rate also increased with increasing age from 10% of CHC-LD associated hospitalizations for patients under the age of 30 years to 18% by age 65. The 'baby boom' cohort accounted for 75% of all CHC-LD associated hospitalizations in 2010, though by 2010 the number of CHC-LD associated hospitalizations among the 1965-69 birth cohort had already increased to levels seen 5 years earlier in the 1960-64 birth cohort (Figure 1).

Trends:

Statistically significant increases in the number of CHC-LD associated hospitalizations over the study period were detected for birth cohorts from 1950-54 to 1975-79, corresponding to an approximate age range of 25 to 60 years and statistically significant declines were detected for the 1920-24 and 1925-29 birth cohorts (Table 1). The rate of increase was highest at approximately 30 years of age (Table 1 and Figure 2).

Projections:

Applying these estimated trends to the historic hospitalization data produced a status quo projection which suggests that the 1950-54 and 1955-59 birth cohorts will continue to

experience the highest annual number of CHC-LD associated hospitalizations well past 2020 (Table 2, Figure 3a). The number of annual hospitalizations is projected to peak around age 70 to 80 (Table 1, Figure 3b). The 6.0% (95%CI, 4.1%-7.9%) annual increase observed over the study period for all 5-year birth cohorts (1915-1984) combined is projected to decline to 3% per year by 2020 and eventually plateau approximately 10 years later.

Ratio Ratios:

Over the next 10 years, the morbidity rate for the 1950-54 and 1955-59 cohorts is predicted to remain high at approximately 10.7 (95% CI, 6.7 -14.7) and 9.1 (95% CI, 5.8 – 12.4) times the rate for persons born between 1970 and 1974 respectively in 2020 (Table 2). The estimated rate ratios at age 75 can be considered a proxy for the relative prevalence of CHC in different cohorts, since age effects have been controlled for. The same-age ratios suggest that the CHC prevalence is approximately 3.6 (95% CI, 2.3 – 4.9) times higher for the 1950-54 birth cohort compared to the 1970-74 cohort, while the estimated ratio for the future lifetime morbidity burden is slightly lower at 2.4 (95% CI, 1.5 – 3.4). Though the disease burden for both 1960s birth cohorts is currently lower than for the two 1950s birth cohorts, the future lifetime burden is predicted to be similar for all four birth cohorts. It is uncertain whether the decline in prevalence seen in successive 5-year birth cohorts from 1955-59 to 1970-74 will continue with younger cohorts, though the future lifetime burden for persons born after 1970 is possibly elevated compared to persons born before 1944

(Tables 2). Table 3 provides summary classification of the relative disease burden by birth cohort.

Interpretation

The disease burden associated with CHC is significantly elevated for the 1950-54 and 1955-59 birth cohorts. Without further interventions, CHC-LD hospitalizations for these cohorts are expected to continue increasing before peaking at approximately 1.5 times the 2010 rate around 2025 to 2030. Despite the apparent lower prevalence of CHC among persons born in the 1960s, the potential to reduce the disease burden over a longer life span in younger cohorts suggests that the 60s cohorts could also benefit from earlier detection and treatment to stop disease progression. It is too early to fully assess the relative CHC prevalence and disease burden for persons born after 1974, though this analysis suggests continued monitoring of these younger birth cohorts would be appropriate. Both age and year of birth as a proxy for exposure contribute to the level of severe disease.

The rate of increase in CHC- and CHC-LD-associated admissions over the study period is considerably less than earlier estimates of 15% to 30% annual increases[6, 20]. The higher trends of the earlier studies can be explained in part by the combined effects of aging and differences in prevalence by birth cohort. In contrast to the increase in the disease burden, the number of new HCV diagnoses have been declining in recent years for most birth cohorts over the age of 30[21, 22]. Though the natural history of an infection with HCV is difficult to study and disease progression rates vary depending on the cohorts studied[11-13, 23], estimates of the rate of increase in disease burden by age alone are emerging. Zalesak and colleagues[24], in examining a Medicare claims database from the US, found that CHC patient populations have already started to decline for persons born before 1945

(aged 65+ in 2010). Our age-specific estimates of the rate of increase in patient populations followed by birth cohort are in close agreement, though we do not detect a statistically significant decline in the number of CHC-LD associated hospitalizations except for persons born before 1925.

Estimates from an American household survey found that persons born in the 1950s had the highest anti-HCV prevalence at 4.3 times that of persons born in the 1970s[2], whereas, we predict a CHC-LD burden for Canadians born in the 1950s of 3.5 times that for Canadians born between 1970 and 1974. The Canadian anti-HCV prevalence estimates from recent household surveys are however lower than the American estimate by a factor of 3 (0.5% versus 1.6%)[2, 5]. Our estimates of relative prevalence, combined with the CHMS estimate[5], suggest an anti-HCV Canadian household prevalence of approximately 1.1% for persons born in the 1950s and 0.5% and 0.3% for Canadians born in 1945-49 and the 1970s respectively. Household prevalence is, however, considered an underestimate of the national prevalence as groups such as the homeless and inmates are at high risk for HCV and were not included in the household surveys.

Limitations:

The primary limitation of this study is that to project the future disease burden, we assumed that the main driver of the birth-cohort specific trends in the annual number of CHC-LD associated hospitalizations was age combined with time since infection. As time since infection was not observed, it could be an important confounder. The relationship between age and time since infection is expected to be consistent across younger birth

cohorts for whom injection drug use is considered the primary risk factor for HCV infections. However, this may not be the case for older birth cohorts for whom blood transfusion, blood products, or organ transplant before 1992 are recognized sources of infection in Canada[4]. Later age at acquisition has been associated with a higher prevalence of cirrhosis 20 years later and faster rates of progression to cirrhosis[12, 25]. The source of the HCV infection is also known to influence the all-cause mortality rate[10]. As a result, the disease burden for persons born after 1950 may peak somewhat earlier and decline faster than suggested in Figure 3. Although improvement in treatment options over the study period have likely influenced the historic trends, significant future improvements in treatment options or the development of drug resistance could significantly alter the future disease burden and rate ratios. These sources of additional uncertainty were not included in the estimated confidence intervals for the rate ratios.

Conclusions:

In summary, this analysis has demonstrated an increasing burden of CHC-LD associated hospitalizations from 2004 to 2010. It is clear that without additional interventions, the disease burden of the 1950-54 and 1955-59 birth cohorts is especially high and will continue to be noticeably elevated over many years. The potential to reduce the disease burden over a longer life span in younger cohorts suggests that the potential benefits of earlier detection and treatment should be considered for younger birth cohorts as well. Analysis of birth cohort-specific trends has provided additional insight into the emerging disease burden due to CHC at the population level.

Acknowledgements

The authors acknowledge the support of the Canadian Institute of Health Information and all those involved in the collection and compilation of the Discharge Abstract Database. As well, the authors wish to thank the Data Coordination and Access Program of the Public Health Agency of Canada for providing access to this database. The cooperation of all involved in these activities is gratefully acknowledged.

Notes

Financial support

Third party funding was not sought. LML is supported by a Research Chair from the Manitoba Health Research Council.

Potential conflicts of interest

None declared.

Author contributions

DLS performed the analysis and drafted the manuscript. All contributed to the concept and design of the study, to the interpretation and presentation of study results. All authors revised the manuscript critically and all approved the final version submitted for publication.

Tables:

Table 1: Birth-cohort specific Average Annual Percentage Change in the Number of CHC-LD associated Hospitalizations from 2004/05 to 2010/11[1]

Birth Cohort	Average Age	Rate in 2010 (100,000) (95% CI)	Average Annual %Change	95% CI	p-value	Stat Sig.
1915 - 1919	89	8.9 (4.8, 16.6)	-6.8%	(-20.9, 9.4)	0.3902	
1920 - 1924	83	6.7 (4.5, 10.1)	-13.9%	(-22.0, -5.1)	0.0028	*
1925 - 1929	79	12.4 (9.8, 15.8)	-6.6%	(-12.3, -0.6)	0.0314	*
1930 - 1934	74	17.1 (14.2, 20.6)	3.5%	(-1.9, 9.1)	0.2095	
1935 - 1939	69	14.9 (12.5, 17.8)	1.1%	(-3.9, 6.2)	0.6786	
1940 - 1944	64	16.4 (14.1, 19.1)	1.6%	(-2.6, 5.9)	0.4715	
1945 - 1949	59	24.4 (21.9, 27.1)	2.2%	(-0.8, 5.3)	0.1594	
1950 - 1954	54	48.2 (45.0, 51.8)	6.6%	(4.4, 8.9)	<.0001	*
1955 - 1959	50	36.5 (33.9, 39.4)	8.9%	(6.5, 11.4)	<.0001	*
1960 - 1964	45	15.8 (14.2, 17.7)	11.5%	(7.7, 15.4)	<.0001	*
1965 - 1969	40	9.1 (7.8, 10.6)	12.7%	(7.4, 18.4)	<.0001	*
1970 - 1974	35	2.6 (1.9, 3.5)	10.1%	(0.7, 20.6)	0.0361	*
1975 - 1979	30	1.6 (1.0, 2.4)	33.6%	(14.3, 57.8)	0.0004	*
1980 - 1984	25	0.4 (0.2, 0.9)	25.0%	(-5.1, 69.3)	0.1244	
All Birth Cohorts: 1915-1984	55	8.9 (4.8, 16.6)	6.0%	(4.1, 7.9)	<.0001	*

Notes:

[1] Results from regression model

Table 2: Average Projected Ratios of Hospitalizations Rates Associated with CHC-LD with 95% Confidence Intervals

Birth Cohort	2010 (last year of Data)	2011 (1 year projection)	5 years[1]	2015	10 years[1]	2020	At age 75	Until Age 90[1]
1915 - 1919	2.9 (1.4, 6.1)	2.7 (0.9, 4.5)						
1920 - 1924	2.4 (1.4, 4.1)	2.1 (1.5, 2.8)	1.6 (0.5, 2.7)	1.2 (<2.3)				
1925 - 1929	4.4 (3.0, 6.4)	3.7 (2.3, 5.2)	2.4 (1.3, 3.6)	1.6 (0.6, 2.7)	1.6 (0.5, 2.6)	0.8 (<2.1)		
1930 - 1934	7.0 (5.0, 9.7)	6.1 (3.8, 8.3)	3.5 (2.0, 5.0)	2.2 (1.0, 3.4)	2.0 (1.0, 3.0)	0.8 (0.2, 1.4)		0.2 (0.1, 0.3)
1935 - 1939	4.7 (3.4, 6.6)	5.8 (3.4, 8.2)	4.1 (2.6, 5.7)	3.1 (1.8, 4.5)	2.6 (1.5, 3.7)	1.1 (0.4, 1.8)	0.8 (0.4, 1.2)	0.3 (0.1, 0.4)
1940 - 1944	6.3 (4.6, 8.6)	6.0 (4.3, 7.8)	4.7 (3.0, 6.4)	3.9 (2.3, 5.6)	3.5 (2.1, 5.0)	2.3 (1.1, 3.4)	1.0 (0.5, 1.5)	0.5 (0.2, 0.7)
1945 - 1949	8.8 (6.5, 11.8)	9.3 (6.2, 12.4)	6.9 (4.5, 9.4)	5.7 (3.5, 8.0)	5.3 (3.2, 7.4)	3.8 (2.0, 5.6)	1.6 (0.9, 2.3)	0.9 (0.5, 1.4)
1950 - 1954	17.6 (13.2, 23.5)	17.8 (10.9, 24.7)	14.0 (9.3, 18.6)	11.7 (7.3, 16.0)	10.7 (6.7, 14.7)	7.5 (4.0, 10.9)	3.6 (2.3, 4.9)	2.4 (1.5, 3.4)
1955 - 1959	13.7 (10.3, 18.2)	13.9 (9.7, 18.1)	11.5 (7.7, 15.3)	10.0 (6.3, 13.6)	9.1 (5.8, 12.4)	6.6 (3.7, 9.4)	3.4 (2.1, 4.7)	2.6 (1.6, 3.6)
1960 - 1964	5.6 (4.2, 7.6)	6.2 (4.5, 7.9)	5.6 (3.7, 7.5)	5.2 (3.2, 7.1)	4.8 (3.0, 6.6)	3.8 (2.2, 5.5)	2.2 (1.4, 3.1)	1.9 (1.2, 2.6)
1965 - 1969	3.4 (2.5, 4.7)	3.7 (2.5, 5.0)	3.4 (2.2, 4.6)	3.3 (2.1, 4.6)	3.2 (2.0, 4.4)	3.0 (1.8, 4.1)	2.1 (1.3, 2.8)	1.9 (1.2, 2.6)
1970 - 1974 (Reference)								
1975 - 1979	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)	0.6 (0.3, 1.0)	0.6 (0.2, 1.0)	0.6 (0.2, 1.0)	0.6 (0.2, 1.1)	1.1 (0.4, 1.8)	1.1 (0.4, 1.8)
1980 - 1984	0.1 (0.1, 0.3)	0.1 (<0.3)	0.3 (<0.6)	0.3 (<0.8)	0.3 (<0.7)	0.3 (<0.8)	0.7 (< 1.5)	1.0 (<2.5)

Notes:

[1] From 2011

Table 3: Classification of Disease Burden by Birth Cohorts

Relative Burden	Next 10 years	Lifetime
High	1950-59	1950-69
Medium High	1960-69	
Medium	1945-49, 1970-84	1945-49, 1970-84
Low	1925-44	1925-44

Figure Legends:

Figure 1: Annual chronic hepatitis C and liver disease associated hospitalizations by 5-year birth cohort, DAD participating hospitals (Canada, excluding the province of Quebec). Each data point corresponds to the annual number of hospitalizations with a contributing diagnosis of CHC and liver disease for the 5-year birth cohort identified in the legend (by batch year running from April to March). Data points are plotted against the average age at time of admission for the 5-year birth cohort on the x-axis. Data points corresponding to the same birth cohort have been joined. Each time series corresponds to years 2004/05-2010/11. The first data point in a time-series corresponds to the batch year of 2004/05. For successive birth cohorts, there is an overlap of two data points with the same age. The vertical space between the cohort-specific series at the same age is an indication of a cohort effect due to different levels of exposure to HCV as well as differences in the availability of treatments.

Figure 2: Rate of change in the number of chronic hepatitis C and liver disease associated hospitalizations, estimated by 5-year birth cohort and plotted by the average age of the cohort. The 95% confidence intervals are indicated by the vertical bars and were calculated by the regression model. The age indicated on the x-axis corresponds to the average age for the birth-cohort over the study period. (See Table 1)

Figure 3: Status quo projection of the number of chronic hepatitis C and liver disease associated hospitalizations. This is one of the simulated projections that illustrates the underlying cohort structure. In the calculations of rate ratios, the 1970-74 birth

cohort was used as the reference (dotted brown line). a) Projections are plotted against calendar year on the x-axis. For near term measures of disease burden, rate ratios were calculated for: the last year of data (2010); 1 year projection (2011); over the next 5 years (2011-2015); in 5 years (2015); over the next 10 years (2011-2020); and in 10 years (2020). b) Projections are plotted against the average age of the birth cohort on the x-axis. Rate ratios calculated for the same age (age 75 was used in the text) provide a measure of relative exposures closely related to the relative CHC prevalence. Future lifetime hospitalizations were calculated as the area under the curve from 2011 to age 90.

References

1. Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012;61:1-32.

2. Armstrong GL, Wasley A, Simard EP, et al. The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705-14.

3. Denniston MM, Klevens RM, McQuillan GM, et al. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology* 2012;55:

4. Pinette G, Cox J, Heathcote J, et al. Primary Care Management of Chronic Hepatitis C: Professional Desk Reference 2009. Public Health Agency of Canada: Available: http://www.catie.ca/sites/default/files/Primary-Care-Management-of-Chronic-Hepatitis-C-Professional-Desk-Reference.pdf (accessed 24Oct2013).

5. Rotermann M, Langlois K, Andonov A, et al. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. *Health Rep* 2013;24:3-13.

6. Myers RP, Liu M, Shaheen AA. The burden of hepatitis C virus infection is growing: a Canadian population-based study of hospitalizations from 1994 to 2004. *Can J Gastroenterol* 2008;22:381-7.

7. Canadian Vital Statistics - Death Database. Statistics Canada, Health Statistics Division: Ottawa; 2008.

8. Discharge Abstract Database. Canadian Institute for Health Information (CIHI): Ottawa; 1994-2010.

9. Kwong J, Ratnasingham S, Campitelli M, et al. The Impact of Infection on Population Health: Results of the Ontario Burden of Infectious Diseases Study. *PLoS ONE* 2012;7:e44103

10. Yu A, Spinelli JJ, Cook DA, et al. Mortality among British Columbians testing for hepatitis C antibody. *BMC Public Health* 2013;13:291.

11. Ascione A, Tartaglione MT, Giuseppe Di Costanzo G. Natural history of chronic

hepatitis C virus infection: HCV infection: a systemic disease Advances in pathophysiology, diagnosis and therapeutic approaches. *Digestive and Liver Disease* 2007;39, Supplement 1:S4-S7.

12. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;34:809-16.

13. Dusheiko GM. The natural course of chronic hepatitis C: implications for clinical practice. *J Viral Hepat* 1998;5 Suppl 1:9-12.

14. World Health Organization (WHO). ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. World Health Organization: Available: http://apps.who.int/classifications/apps/icd/icd10online/ (accessed 2011 Jun 16).

15. Canadian Institute for Health Information (CIHI). Errata in Canadian Coding Standards for Version 2009 ICD-10-CA and CCI. Canadian Institute for Health Information (CIHI): Available: http://www.cihi.ca/CIHI-ext-portal/internet/en/document/standards+and+data+submission/standards/classification+and+coding/bul_stand_01dec09 (accessed 2013 May 16).

16. Statistics Canada. Table052-0005 - Projected population, by projection scenario, sex and age group as of July 1, Canada, provinces and territories, annual (persons), CANSIM (database). Demography Division: Available: http://www5.statcan.gc.ca/cansim/pick-choisir?lang=eng&id=520005&pattern=520005&searchTypeByValue=1&p2=42 (accessed 2013 Nov 21).

17. SAS Institute Inc. *SAS Enterprise Guide 5.1,* Cary, NC: SAS Institute Inc.; 2006.

18. Haukoos JS, Lewis RJ. Advanced Statistics: Bootstrapping Confidence Intervals for Statistics with Difficult Distributions. *Acad Emerg Med* 2008;12:360-5.

19. Henderson AR. The bootstrap: A technique for data-driven statistics. Using computer-intensive analyses to explore experimental data. *Clin Chim Acta* 2005;359:1-26.

20. Grant WC, Jhaveri RR, McHutchison JG, et al. Trends in health care resource use for hepatitis C virus infection in the United States. *Hepatology* 2005;42:1406-13.

21. O'Brien SF, Fan W, Xi G, et al. Declining hepatitis C rates in first-time blood donors:

insight from surveillance and case-control risk factor studies. *Transfusion (Paris)* 2008;48:902-9.

22. Public Health Agency of Canada. Hepatitis C in Canada: 2005-2010 Surveillance Report. Centre for Communicable Disease and Infection Control, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada, Ottawa, Canada. 2011.

23. Sweeting MJ, De Angelis D, Neal KR, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. *J Clin Epidemiol* 2006;59:144-52.

24. Zalesak M, Francis K, Gedeon A, et al. Current and Future Disease Progression of the Chronic HCV Population in the United States. *PLoS ONE* 2013;8:e63959.

25. Thein H-H, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology* 2008;48:418-31.

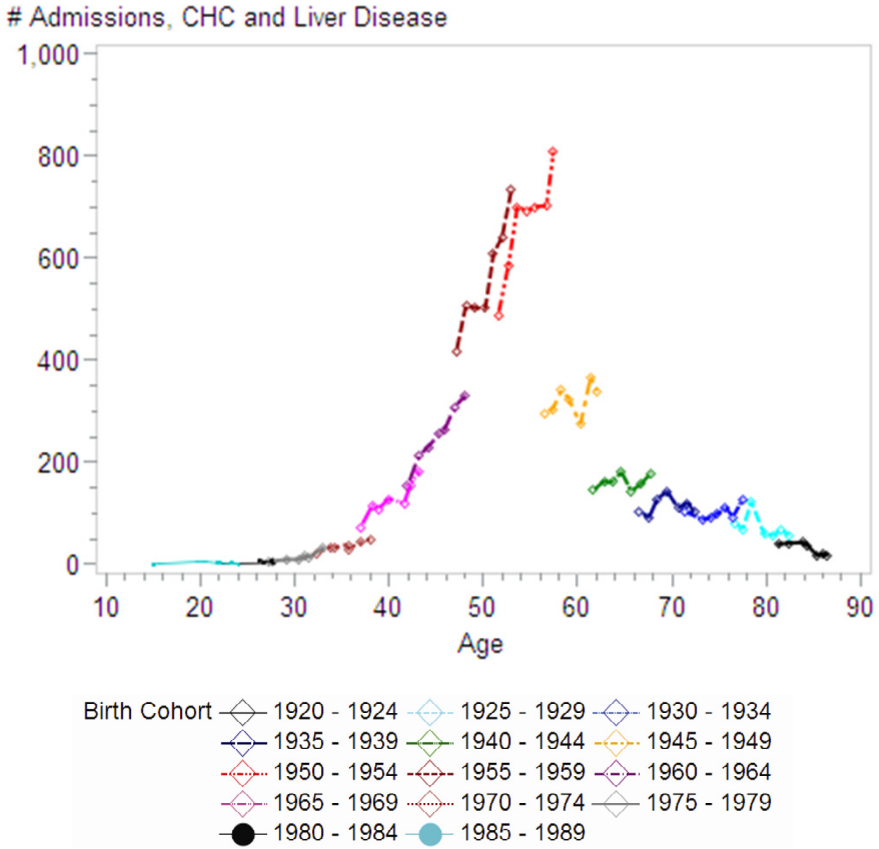
Admissions, CHC and Liver Disease
1,000
800
600
400
200
0
10
20
30
40
50
60
70
80
90
Age
Birth Cohort
1920 - 1924
1925 - 1929
1930 - 1934
1935 - 1939
1940 - 1944
1945 - 1949
1950 - 1954
1955 - 1959
1960 - 1964
1965 - 1969
1970 - 1974
1975 - 1979
1980 - 1984
1985 - 1989

Figure 1

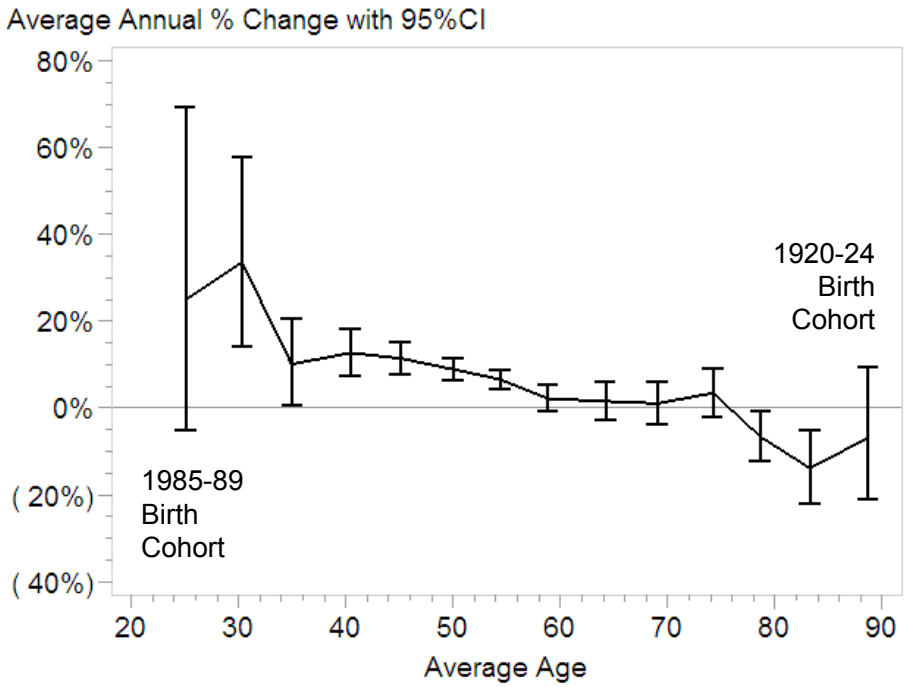

Figure 2

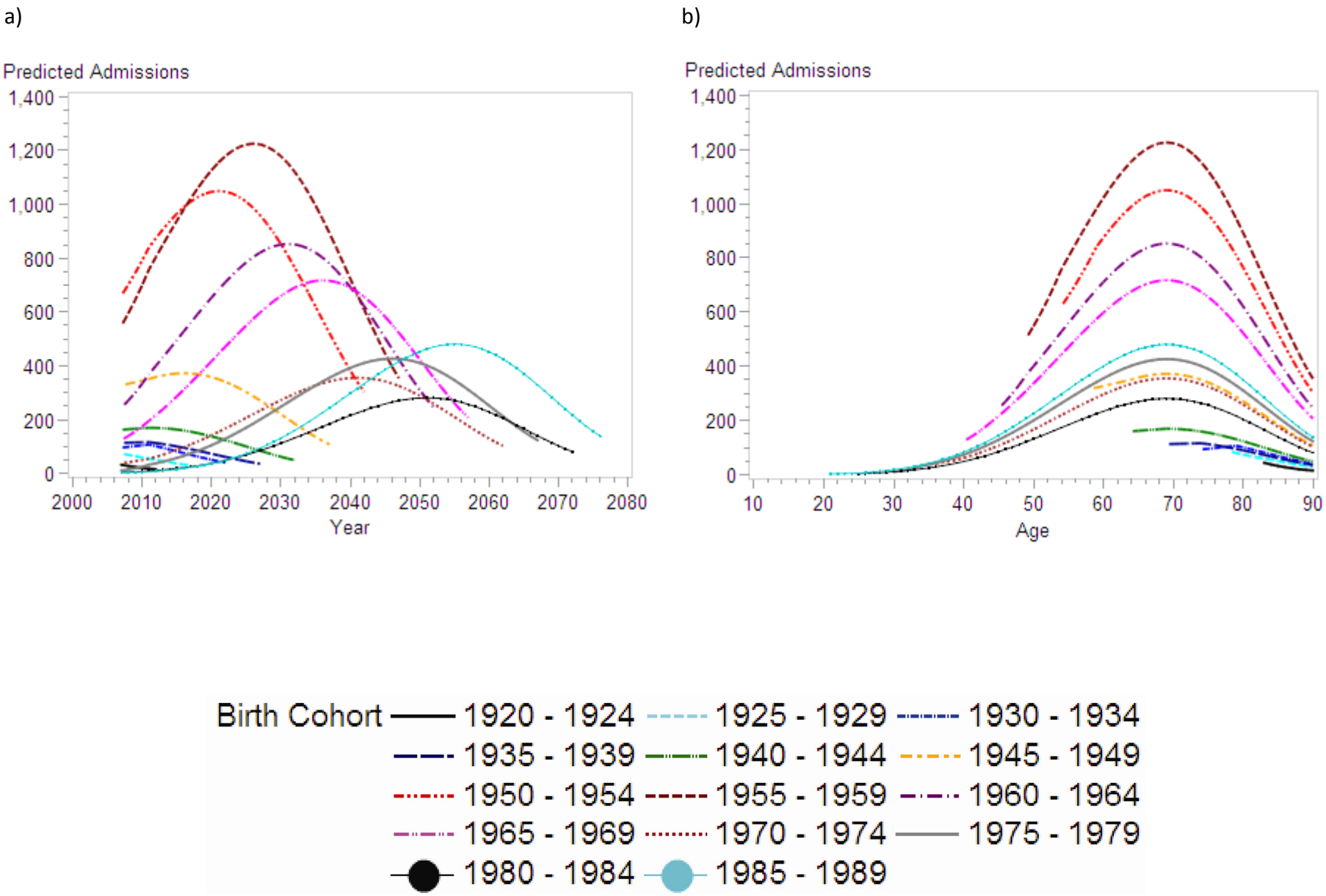
a)
Predicted Admissions
1,400
1,200
1,000
800
600
400
200
0
2000
2010
2020
2030
2040
2050
2060
2070
2080
Year
b)
Predicted Admissions
1,400
1,200
1,000
800
600
400
200
0
10
20
30
40
50
60
70
80
90
Age
Birth Cohort
1920 - 1924
1925 - 1929
1930 - 1934
1935 - 1939
1940 - 1944
1945 - 1949
1950 - 1954
1955 - 1959
1960 - 1964
1965 - 1969
1970 - 1974
1975 - 1979
1980 - 1984
1985 - 1989

Figure 3