

Identifying and describing a cohort effect in the national database of HCV reported cases in Canada: 1991–2010

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Abstract (240 words)

The purpose of this analysis was to study the association of the birth year and reporting period with rates of reported HCV cases in Canada.

HCV cases with information on sex, age, year of report and jurisdiction reported to the Public Health Agency of Canada (PHAC) from 1991 through 2010 and estimates of age- and sex-specific populations in Canada were used to calculate sex-specific population rates (per 100,000) for 5-year age groups born between 1921 and 1990. Reported rates for 5-year birth cohorts were log-logit transformed and underwent the mean polish analysis.

Residuals from the mean polish analysis were plotted against birth cohorts in MS Excel to estimate the presence of a cohort effect in HCV cases. Rate ratios by birth cohort for the original HCV reported rates and their 95% confidence intervals were calculated, with males and females born in 1941–1945 utilised as reference birth cohort. Three-factor linear regression model, including cohort, period and their interaction, was fit for log-logit transformed HCV rates and their residuals.

Males born between 1946 and 1970 had 21 to 40% higher rates of HCV case reports, while females born between 1946 and 1975 accounted for 12 to 43% higher rates in comparison with rates in respective sexes born in 1941–1945.

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While our analysis suggests a cohort effect in HCV case reports among individuals born after 1945, further studies are required to estimate and validate the true burden of HCV infection in Canadian populations.

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Introduction

Increasingly, surveillance systems are being tasked not just to describe trends in the disease spread in terms of person, time and space, but to be used in more elaborate analyses to answer questions about the underlining reasons for such trends^{1,2}. One way to analyse rich historical data is to perform age-period-cohort analysis, although methodological issues and interpretation difficulties affected the usability of this approach³.

In the early 2012, the US Centres for Disease Control and Prevention reported increasing mortality from hepatitis C virus infection (HCV)⁴ and suggested that screening of cohorts of “baby boomers” (those born between 1945–1965) who may be heavily affected by HCV may not just be feasible, but also cost effective⁵. While in Canada similar work is in its early development, identifying birth cohorts potentially more affected by HCV morbidity may better focus public health activities and ensure cost-effectiveness of such interventions. The purpose of this analysis was to study the association of the birth year and reporting period with rates of reported HCV cases in the Canadian Notifiable Diseases Surveillance System (CNDSS).

Methods

HCV cases with information on sex, age, year of report and jurisdiction reported to the Public Health Agency of Canada (PHAC) from 1991 through 2010 were extracted from CNDSS. Sex-specific population rates for 5-year age groups born 1921–1990 were calculated per 100,000 by dividing age and sex specific HCV cases reported over 5-year period by the corresponding estimates of age- and sex-specific populations in Canada. Due to a considerable difference in the reported HCV rates among males and females, all analyses were done on sex-stratified subsets of the data. Year of birth was generated as a difference between the year of report and

reported age. A number of Canadian jurisdictions encompassing about 12% of the Canadian population have been submitting reports with aggregated only HCV data throughout the period of analysis (1991-2010). These data were not included in this analysis. Table 1 summarises the data used in the analysis.

Reported rates for 5-year birth cohorts were log-logit transformed and residuals from the mean polish analysis⁶, in which cohort and period mean values are subtracted from log-logit transformed rates, were plotted against birth cohorts in Excel to establish presence of the cohort effect. Rate ratios by birth cohort for the original HCV reported rates, their 95% confidence intervals and regression coefficients were calculated using STATA 11 (Stata Corp LP, College Station, TX). Cohorts of males and females born in 1941-1945 were utilised as reference categories for the calculation of rate ratios. The reference cohorts were chosen to separate cohorts of "baby boomers" from cohorts of individuals born before and after the "baby boom" period.

To assess the independent contribution of the individual components of the birth cohort - reporting period effect, a three factor linear regression model including cohort, period and their interaction was fit for log-logit transformed HCV rates and their residuals after the mean polish analysis following a normality check of their distribution.

Results

Figures 1 and 2 present the reported HCV rates in males and females for the period of 1991 through 2010 stratified by birth cohort and reporting period. While the HCV rates in male cases were on average twice as high as the rates in females for all age cohorts, the distribution of HCV rates by both age cohort and reporting period was strikingly similar: rates were the highest among those born between 1946 to 1970 in all four

reporting periods, the highest HCV rates were reported during the period of 1996 through 2000, the lowest HCV rates were reported during the earlier period of 1991 through 1995 and the remaining two reporting periods (2001-2005 and 2006-2010) had HCV reported rates somewhere in between. Of note, is the expanded shape of HCV rates distribution in the younger birth cohorts (those born after 1970) in both males and females.

Figures 3 and 4 present the HCV reported cases by age group and the reporting period. As was expected, the HCV rates distribution by reporting period was similar in both males and females, with the reporting period of 1995 through 2000 accounting for the highest HCV reported rates. However, the rate distribution by age group has shown both sex- and age-specific differences. While in both males and females the peak HCV rates seemed to be shifting towards older age groups over time, the relative contribution of younger cases (who were born after 1970) rates seemed to be higher in females than it was in males.

After performing the mean polish procedure on the log(-logit)-transformed HCV rates, a systematic deviation from zero indicative of the presence of a cohort effect was observed in both males (Figure 5) and females (Figure 6).

Table 2 presents ratios of HCV reported rates in males and females relative to rate in those born in 1941-1945. Males born between 1946 and 1965 had 21 to 40% increased rates of HCV case reports, while females of the same birth cohort, accounted for an additional 12 to 43% increase in the rates.

When linear models were fit to assess the independent contribution of the cohort and period components in the cohort effect on the log-logit transformed HCV rate (Table 3), the coefficients suggested a decrease in

the reported HCV rates from older to younger age cohorts and from earlier to later reporting periods.

After linear regression analysis was stratified by birth period, both cohort and period have shown to have a stable additive effect on the HCV rates in both males and females born after 1965, but not for those born before 1966 (Table 4).

We also fit three-factor linear models for residuals of log-logit transformed HCV rates after the "mean polish" procedure to assess the contribution of the systematic component of the cohort effect *without* the random component. Very similar results were obtained for both male and female cases (Table 5). Overall, models with and without interaction term were significant, however the amount of variance explained by the models increased by more than two-fold in both males and females.

Discussion

Rate ratios, the direction and the magnitude of the associations between age-cohort and period variables and the reported rates of HCV were similar in male and female subsets of the data. Our analysis suggests a possibly large pool of HCV cases in those born between 1946 and 1965. Over the four reporting periods (1991-1995, 1996-2000, 2001-2005 and 2006-2010), this cohort has contributed the most to the HCV reported rates in Canada. The HCV cohort effect seems to spread beyond the "baby boomers" birth cohorts: in males, the relative excess in HCV reported rates was found in those born up to 1970; while in females the effect was present in those born up to 1975 (Table 2). The period component of the age cohort-period effect appears to have an independent and significant effect after adjusting for the cohort component and the interaction of the two. We have also observed an association between HCV rates and a reporting period. The observed increase in the HCV case reports in the period of 1996-2000 is

likely due to a change in HCV testing and reporting practices and requires further examination.

Our findings are supported by the earlier HCV modelling work by Remis⁷, who estimated the peak of new HCV infections around 1980, and by the estimated average age at acute HCV infection at 25 to 34 years from the Enhanced Hepatitis Strain Surveillance System⁸. The scope of the “cohort effect” is generally in line with the “cohort effect” previously described in first-time blood donors⁹. The possible explanations for the observed findings include past exposure to injecting drug use, blood transfusions, other invasive procedures in health care settings, tattooing and high risk sexual exposure in the immunocompromised and persons co-infected with sexually-transmitted infections. These factors are explored in more detail below.

History of injecting drug use has been found to be the leading risk factor for HCV acquisition in a number of studies of HCV risk factors in first-time blood donors in Canada¹⁰. Injecting frequency notwithstanding, one other study suggested that the majority of injecting drug users become infected with HCV during the first year of injecting¹¹. High reported measures of injecting in Canadian “baby boomers” are evident in the findings of the 2004 Canadian Addictions Survey (CAS)¹², which reported the highest lifetime prevalence of injection drug use in those of 45-54 years of age, i.e. those born between 1950 and 1959. A shift from using injectable to non-injectable opioids in Canada, estimated by some at almost 25%¹³, may explain the reduction in the reports of HCV infections from recent drug use initiates in the last two reporting periods (2001-2010).

Canadian public health has documented examples of iatrogenic transmission of HCV to the Canadian populations. At least 30,000 HCV infections in Canada resulted from blood and blood products transfusions

that took place between 1986 and 1990 and become a discovery of the inquiry conducted by the Justice Krever Commission¹⁴. Blood transfusion has been implicated as a major risk factor for HCV acquisition in the look back studies in first-time donors in Canada⁹. As there is no evidence of sufficient precautionary measures for HCV transmission in the Canadian blood supply system existing before 1986 and worldwide reports of hepatocellular carcinoma found in patients whose only risk factor was transfusion-related hepatitis^{15,16}, it is possible that the beginning of the blood transfusion related risk period extends to before 1986.

Evidence documenting iatrogenic exposures to blood-borne pathogens has been published around the world^{17,18,19}. In Canada, reuse of syringes in the administration of BCG vaccinations²⁰ and sedation²¹ has been relatively common in some populations. Two modelling exercises estimated the risk of HCV transmission associated with syringe re-use in Canada in the ranges of 0.5-6.3 and 1.0-4.3 per 1,000,000 person-procedures with the ranges of probabilities for this practice to occur varying between 2.2 to 60% and 20 to 80%^{22,23}.

Although tattooing is not a universally acceptable practice and is more prevalent in specific populations, such as youth, prisoners, armed forces^{24,25} and law-enforcement personnel²⁶, the practice carries a considerable risk of HCV infection. A systematic review and meta-analysis of tattooing and risk of HCV transmission has reported the pooled odds ratios of 2.74 (95%CI: 2.38-3.15) across all studies in all persons and 5.74 (95% CI: 1.98-16.66) in those who did not report use of injectable drugs²⁷. Ten to 16% of youth aged 12 to 18 and between three to ten percent of the general population reported having permanent tattoos done²⁸ and an estimated 50 thousand new tattoos are being done every year in the United States²⁹. In Canada, between 10 and 12% of the Enhanced Street Youth

Surveillance (ESYS) respondents reported having a tattoo³⁰. While holding a low transmission probability, sexual transmission of HCV has been documented in persons with multiple sexual partners³¹ and co-infected with other sexually transmitted infections^{32,33}.

Overall, the reported rates of HCV infections are likely to underestimate the magnitude of HCV infections in the Canadian population. One of the reasons is the asymptomatic nature of the HCV infection resulting in a slow and often undetectable clinical course for the majority of infected individuals³⁴. Also, between 10 to 45% of HCV infections have the ability to clear spontaneously^{34,35,36}, with higher clearance rates in Aboriginal persons³⁷, females and younger individuals³⁸, so it is possible that cohort rates of HCV in these groups might have been overestimated. Also, our analysis was limited to the case-specific data submitted by jurisdictions accounting for about 88% of the Canadian population. In addition, overlapping adjacent birth cohorts and the choice of age categories (5 year) might have affected the precision of our estimates due to an averaging effect.

While the approach utilised in our analysis has been shown to be reliable, robust and relatively simple in identifying and measuring a cohort effect as an age by period interaction in comparison with other methods³⁹, our findings should be interpreted with caution and require further validation from both national and special population surveys. Also, sensitivity analyses and triangulation techniques are warranted to produce and validate age-specific estimates of the HCV burden in Canadians. Given the 20-year retrospective nature of our analysis, it is likely that the size of the HCV infected population who are not aware of their status among those born in 1946-1965 has decreased. This notion is supported by the decreasing measures of HCV infected individuals among "baby boomers" in

first-time donors⁹ and high estimates of awareness of HCV infection status (reported in the range of 40 to 60%) in the Canadian adult populations^{40,41,42}. The measures of awareness are likely to be considerably lower among youth and in socially excluded populations, such as street-involved people. Data from ESYS suggests HCV awareness levels at or below 10% of the sampled street youth aged 15 to 24³⁰.

Our analysis adds to what is already known⁹ about a cohort effect in Canadian “baby boomers” by using a nationally representative HCV data. Identifying a cohort effect may help to better target and shape public health activities to address the needs of the most affected populations. Further studies may help assess the feasibility and cost-effectiveness of public health strategies for identifying persons unaware of their HCV infection status and offering HCV treatment at a standard level of care in Canada.

References

1. Giesecke J. Modern infectious disease epidemiology. Arnold, Hodder Headline Group, 2001.
2. Tarling R. Statistical modelling for social researchers: principles and practice. Routledge, Taylor & Francis Group, 2009.
3. Keyes KM, Li G. A multiphase method for estimating cohort effects in age-period contingency table data. *Ann Epidemiol* 2010; 20:779-85.
4. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012; 156:271-8.

5. Rein DB, Smith BD, WittenbornJS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in US primary care settings. *Ann Intern Med* 2012; 156: 263-270.
6. Selvin S. *Statistical analysis of epidemiologic data*. New York: Oxford University Press, 2004.
7. Remis R. A study to characterize the epidemiology of hepatitis C infection in Canada, 2002. Available at: <http://www.phac-aspc.gc.ca/hepc/pubs/hepc2002/index-eng.php>, accessed September 12, 2012.
8. Public Health Agency of Canada. Enhanced Hepatitis Strain Surveillance System. Age-specific rates at acute HCV infection from 2007-2011 scaled by 2009 age-specific Canadian population. Unpublished document. PHAC, 2012.
9. 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* 2008; 48: 902-9.
10. Delage G, Infante-Rivard C, Chiavetta JA, et al. Risk factors for acquisition of hepatitis C virus infection in blood donors: results of a case-control study. *Gastroenterology* 1999; 116(4): 893-9.
11. Garfein RS, Vlahov D, Galai N, et al. Viral infections in short-term injection drug users: The prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health* 1996;86:655-61.
12. Adlaf, E.M., Begin, P., & Sawka, E. (Eds.). *Canadian Addiction Survey (CAS): A national survey of Canadians' use of alcohol and other drugs: Prevalence of use and related harms: Detailed report*. Ottawa: Canadian Centre on Substance Abuse, 2005.

13. Popova S, Patra J, Mohapatra S, et al. How many people in Canada use prescription opioids non-medically in general and street drug using populations? *Can J Public Health* 2009; 100(2): 104-8.
14. Krever H. The consequences of the contamination of the blood supply. In: Final report: Commission of Inquiry on the Blood System in Canada. Ottawa: The Commission; 1997. p. 708-18.
15. Kiyosawa K, Akahane Y, Nogata A, Furita S. Hepatocellular carcinoma after non-A, non-B post-transfusion hepatitis. *Am J Gastroenterol* 1984; 79: 777-81.
16. Gilliam JH III, Geisinger KR, Richter JE. Primary hepatocellular carcinoma after chronic NANB post-transfusion hepatitis. *Ann Intern Med* 1984; 101: 794-5.
17. Acharya SK, Madan K, Dattagupta S, Panda SK. Viral hepatitis in India. *Natl Med J India* 2006; 19(4): 203-17.
18. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 2002; 62(S1): 8-17.
19. Strickland GT. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. *Hepatology* 2006; 43(5): 915-22.
20. Young TK. BCG vaccination among Canadian Indians and Inuit: The epidemiological bases for policy decision. *Can J Public Health* 1985; 76: 124-9.
21. Government of Alberta. Provincial review of infection control practices complete. March 19, 2009.
22. Sikora C, Chandran AU, Joffee AM et al. Population risk of syringe reuse : estimating the probability of transmitting blood born disease. *Infection Control Hospital Epidemiol* 2010; 31(7): 748-54.

23. Oraby T, Elsaadany S, Gervais R, et al. Chapter 1. The Risk of Blood-Borne Viral Infection due to Syringe Re-Use. In: The Continuum of Health Risk Assessments, ISBN 980-953-307-582-7 (2012). Available at: <http://www.intechopen.com/articles/show/title/the-risk-of-blood-borne-viral-infection-due-to-syringe-re-use>, accessed September 12, 2012.
24. Gadd MC. A survey of soldiers' attitudes to tattooing. JR Army Med Corps 1992; 138(2): 73-6.
25. Armstrong ML, Murphy KP, Sallee A, Watson MG. Tattooed army soldiers: examining the incidence, behaviour and risk. Mil Med 2000; 165(2): 135-41.
26. Ho C. & McGinnis S. Keeping tattoos undercover. Ottawa Citizen, September 4, 2012. Available at: <http://www.ottawacitizen.com/life/Keeping+tattoos+undercover/7185822/story.html>, accessed, September 7, 2012.
27. Jafari S, Copes R, Baharlou S, et al. Tattooing and the risk of transmission of hepatitis C: a systematic review and meta-analysis. Int J Infect Dis 2010; doi:10.1016/j.ijid.2010.03.019.(in press)
28. Roberts TA, Ryan SA. Tattooing and high-risk behaviour in adolescents. Pediatrics 2002; 110 (6): 1058-63.
29. Adatto MA, Halachmi S, Lapidoth M. Tattoo removal. Curr Probl Dermatol 2011; 42: 97-110.
30. ESYS (Enhanced Street Youth Surveillance System). Public Health Agency of Canada/Centre for Communicable Diseases and Infection Control/Surveillance and Epidemiology Division, 2012. (unpublished data).
31. Brettler DB, Mannucci PM, Gringeri A, et al. The low risk of hepatitis C virus transmission among sexual partners of hepatitis C-infected males: an international, multicenter study. Blood 1992;80:540-3.

32. Sherman KE, Rouster SD, Chung RT, Rajcic N. Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: A cross-sectional analysis of the US Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002;34(6):831-7.
33. Wandeler G et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. *Clin Infect Dis*, online edition, 2012.
34. Seeff LB. The history of the « natural history » of hepatitis C (1968-2009). *Liver Int* 2009; 29(s1): 89-99.
35. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;34:809-16.
36. Mehta S, Cox A, Hoover D, et al. Protection against persistence of hepatitis C. *Lancet* 2002;359:1478-83.
37. Minuk GY, Uhanova J. Viral hepatitis in the Canadian Inuit and First Nations populations. *Can J Gastroenterol* 2003; 17(12): 707-12.
38. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000;284:450-456.
39. Keyes KM, Utz R, Robinson WR, Li G. What is a cohort effect? Comparison of three statistical methods to model a cohort effect in obesity prevalence in the United States, 1971-2006. *Soc Sci Med*. 2010;70:1100-1108.
40. Bowker SL, Smith LJ, Rosychuk RJ, Preiksaitis JK. A review of general hepatitis C virus lookback studies. *Vox Sanguinis* 2004; 86: 21-7.
41. M-Track: Enhanced Surveillance of Risk Behaviours among Gay, Bisexual and other men who have sex with men in Canada, Phase 1 (2005-2007).

Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control. August 2012. Unpublished data.

42. Poulin C, Alary M, Lambert G, et al. Prevalence of HIV and hepatitis C virus infection among inmates of Quebec provincial prisons. CMAJ 2007; 177(3): 252-6.

Table 1. Description of the data

Variable	Mean (SD)	Description	Sources
HCV rate	Males: 48.51 (44.73) Females: 25.76 (18.15)	Standardised sex- and age-stratified rates of HCV cases (per 100,000) reported to the Public Health Agency of Canada. Rates were calculated by dividing the aggregated 5-year sex-specific counts of HCV diagnoses in those born between 1921 and 1990 by the estimated sex-and age-specific population in Canada (Figures 1 and 2).	1. Canadian Notifiable Diseases Surveillance System for HCV case counts for the period of 1991-2010; 2. Statistics Canada' Population life tables (June estimates, 2012)
Log logit transformed HCV rate	Males: 0.55 (0.06) Females: 0.57 (0.04)	Original HCV reported rates were transformed as follows: $f(p) = \log(-\log(p/1-p))$	created
Residual	Males: 0 (0.31) Females: 0 (0.32)	Residuals of the log-logit transformed HCV rate after performing the mean polish procedure (Figures 5 and 6).	Created, according to (Selvin, 2004)
Birth cohort	Fourteen 5-year birth cohorts (1921-1925=1, ...	Categorical variable describing fourteen 5-year birth cohorts spanning 1921-1990.	created

	1986-1990=14)		
Reporting period	Four 5-year reporting periods (1991-1995, 1996-2000, 2001-2005, 2006-2010)	Categorical variable describing four 5-year reporting periods spanning 1991-2010.	created
Age cohort-period effect (interaction term)	Interaction = Cohort*period	An interaction term generated as a multiple of cohort by period to account for the interactive nature of the age cohort-period effect) in the 3-factor linear model.	created

Figure 1. HCV reported rates in Canadian males by birth cohort and reporting period (CNDSS, 2012)

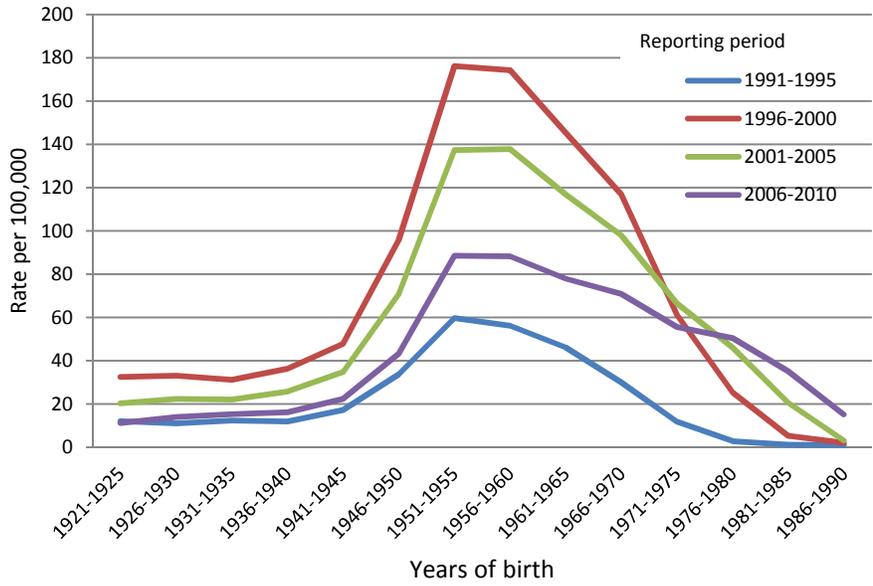


Figure 2. HCV reported rate in Canadian females by birth cohort and reporting period (CNDSS, 2012)

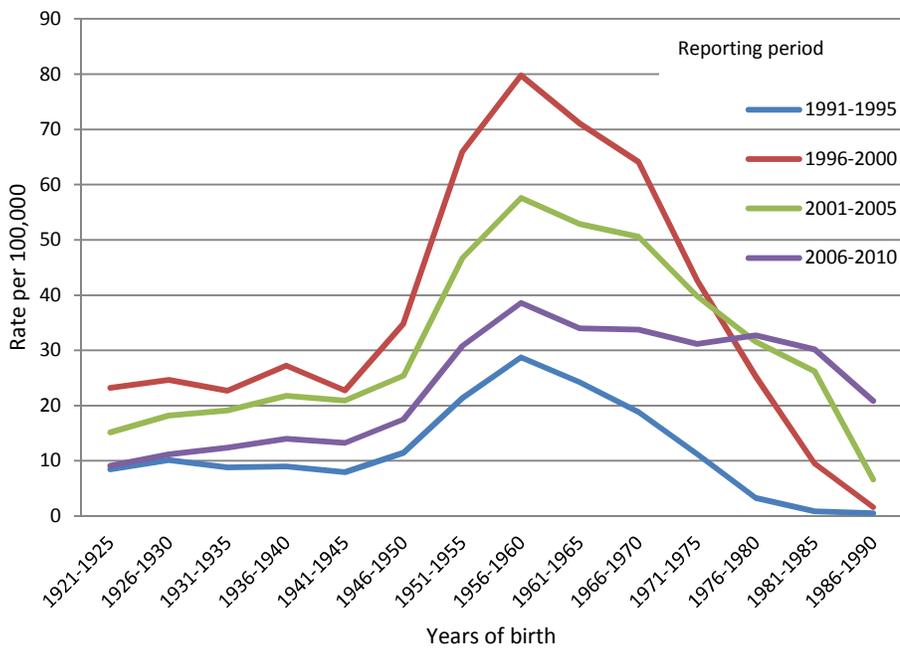


Figure 3. HCV reported rates in Canadian males by age group and reporting period (CNDSS, 2012)

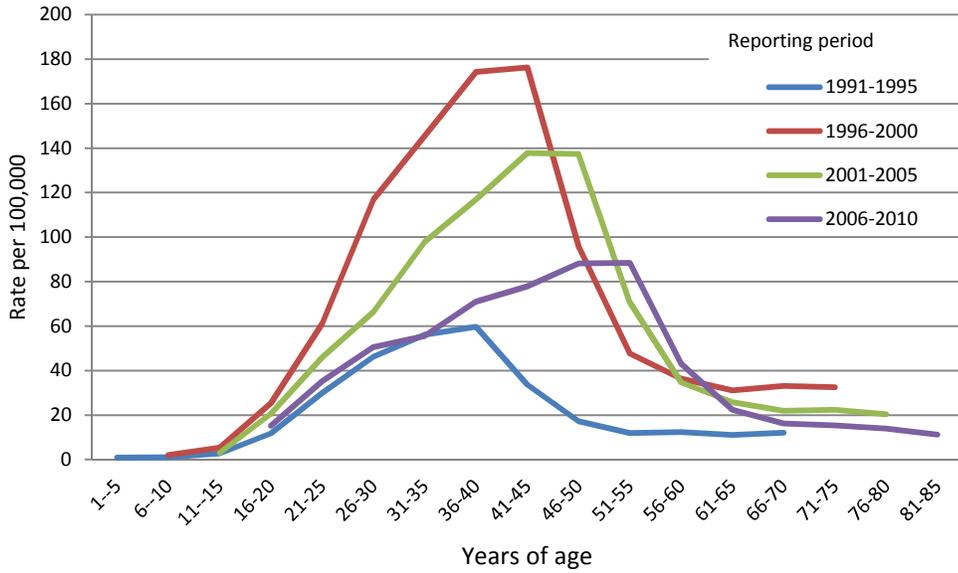
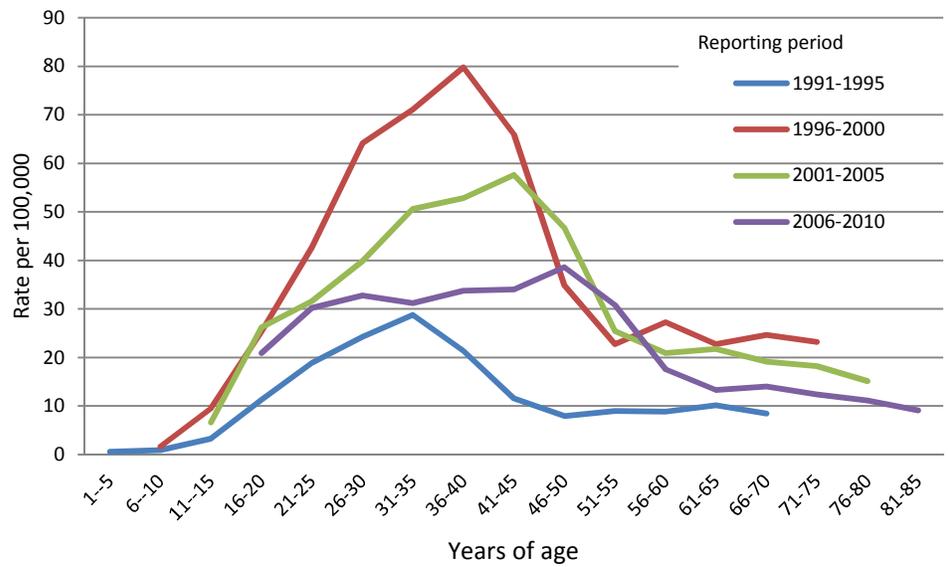


Figure 4. HCV reported rate in Canadian females by age group and reporting period (CNDSS, 2012)



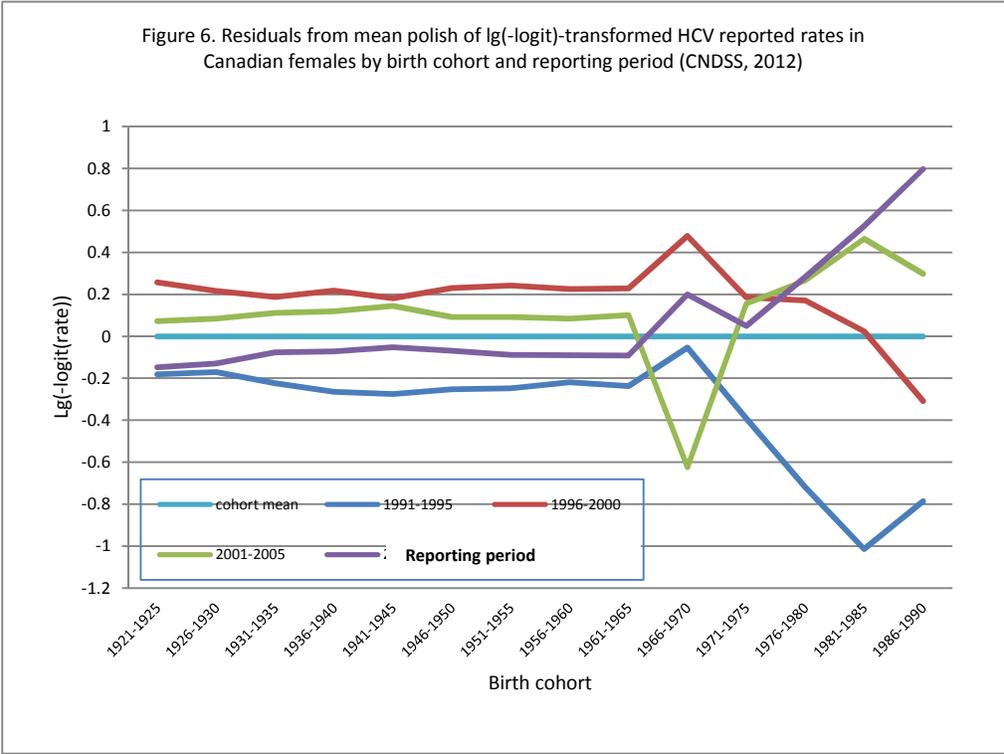
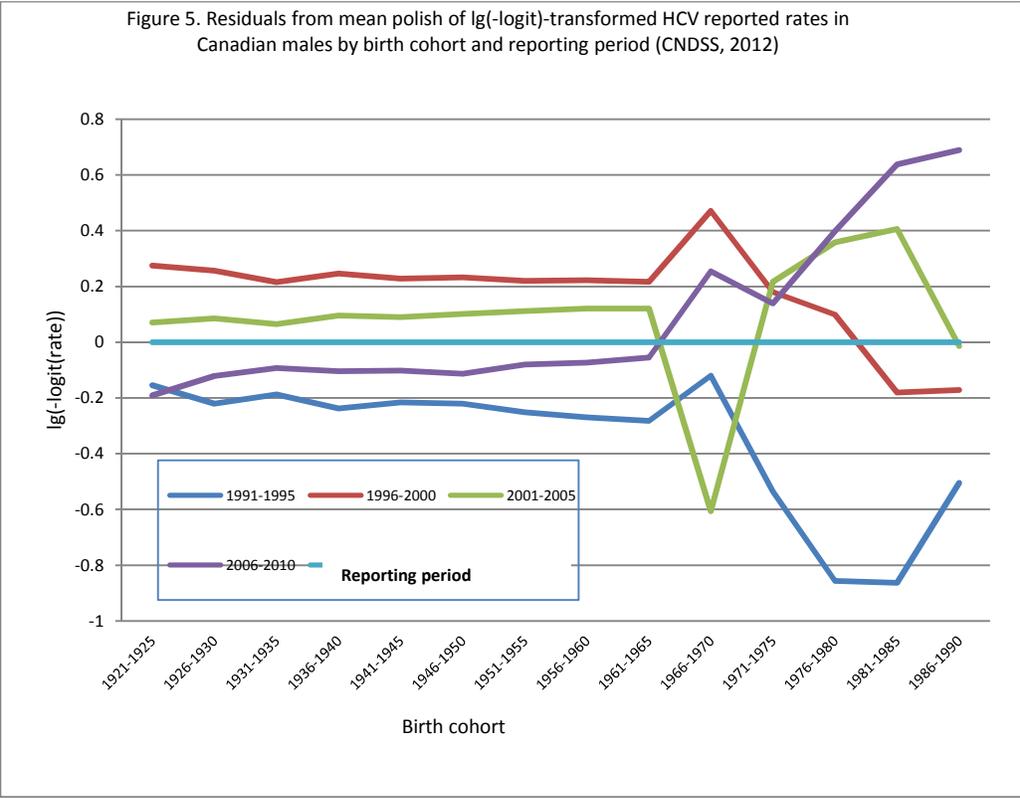


Table 2. Estimated RR and 95% confidence intervals for the effect of birth cohort on LN-transformed HCV reported rates in males and females

Birth cohort	RR (95%CI)	
	Males	Females
1921-1925	0.85 (0.80-0.91)	0.94 (0.86-1.02)
1926-1930	0.87 (0.84-0.90)	1.00 (0.93-1.07)
1931-1935	0.88 (0.87-0.89)	0.99 (0.96-1.03)
1936-1940	0.91 (0.88-0.93)	1.04 (1.01-1.06)
1941-1945	1 (reference)	1 (reference)
1946-1950	1.21 (1.18-1.23)	1.12 (1.07-1.16)
1951-1955	1.40 (1.35-1.45)	1.34 (1.26-1.42)
1956-1960	1.39 (1.34-1.44)	1.43 (1.32-1.53)
1961-1965	1.34 (1.29-1.39)	1.38 (1.29-1.47)
1966-1970	1.27 (1.20-1.34)	1.34 (1.29-1.39)
1971-1975	1.11 (0.94-1.27)	1.23 (1.16-1.29)
1976-1980	0.90 (0.55-1.25)	1.05 (0.77-1.32)
1981-1985	0.63 (0.18-1.07)	0.81 (0.30-1.32)
1986-1990	0.34 (-0.01-0.69)	0.44 (-0.12-1.01)

Table 3. Three factor linear regression modelling log-logit transformed HCV rates without (model 1) and with (model 2) an interaction term in males and females

Variables	Males		Females	
	Model 1	Model 2	Model 1	Model 2
Cohort	0.002 (0.33)*	0.011 (0.023)	0.001 (0.50)	0.010 (0.008)
Period	-0.013 (0.07)	0.014 (0.34)	-0.013 (0.021)	0.013 (0.24)
Interaction term (cohort*period)		-0.004 (0.039)		-0.003 (0.009)
R ²	0.08	0.15	0.10	0.21
P-value of F	0.12	0.036	0.06	0.006

*Values not in parentheses are regression coefficients, values in parentheses are p-values.

Table 4. Three factor linear regression modelling log-logit transformed HCV rates in males and females

Variables	Born in 1921-1945		Born in 1946-1965		Born in 1966-1990	
	Males	Females	Males	Females	Males	Females
Cohort	0.002 (0.89)*	0.003 (0.70)	-0.004 (0.84)	-0.014 (0.39)	0.058 (0.001)	0.060 (0.001)
Period	0.004 (0.33)	0.003 (0.74)	0.008(0.88)	-0.006 (0.88)	0.088 (0.20)	0.15 (0.026)
Interaction term (cohort*period)	-0.002 (0.70)	-0.002 (0.70)	-0.002 (0.79)	0.0004 (0.95)	-0.010 (0.08)	-0.015 (0.009)
R ²	0.04	0.08	0.14	0.27	0.759	0.723
P-value of F	0.93	0.73	0.61	0.26	<0.0001	0.0001

*Values not in parentheses are regression coefficients, values in parentheses are p-values.

Table 5. Three factor linear regression modelling residuals without (Model 1) and with (Model 2) an interaction term in males and females

Variables	Males		Females	
	Model 1	Model 2	Model 1	Model 2
Cohort	0 (1.00)*	-0.09 (<0.0001)	0 (1.0)	-0.08 (<0.0001)
Period	0.12 (0.001)	-0.13 (0.031)	0.12 (0.001)	-0.13 (0.051)
Cohort*period (interaction term)		0.034 (<0.0001)		0.033 (<0.0001)
R ²	0.19	0.44	0.19	0.41
P-value of F	0.003	<0.0001	0.004	<0.0001

*Values not in parentheses are regression coefficients, values in parentheses are p-values.