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Epidemiology of Hepatitis C over 28 years of monitoring Canadian blood donors: Insight into a low-risk undiagnosed population

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Abstract

Background Hepatitis C is a blood-borne infection with the hepatitis C virus (HCV) that can progress to cirrhosis and liver cancer. About 70% (50–80%) of infections become chronic and exhibit anti-HCV and HCV nucleic acid (NAT) positivity. Direct acting oral pan genotypic antiviral treatment became available in 2014 and was free for most Canadians in 2018. Clinical screening for HCV infection is risk-based. About 1% of Canadians have been infected with HCV, with 0.5% chronically infected (about 25% unaware) disproportionately impacting marginalized groups. Blood donors are in good health, are deferred for risks such as injection drug use and can provide insight into the low-risk undiagnosed population. Here we describe HCV epidemiology in first-time blood donors over 28 years of monitoring.

Methods All first-time blood donors in all Canadian provinces except Quebec (1993 to 2021) were analyzed. All blood donations were tested for HCV antibodies (anti-HCV) and since late 1999 also HCV NAT. A case-control study was also included. All HCV positive donors (cases) since 2005 and HCV negative donors (1:4 ratio controls) matched for age, sex and location were invited to complete a risk factor interview. Separate logistic regression models for anti-HCV positivity and chronic HCV assessed the association between age cohort, sex, region and neighbourhood material deprivation and ethnocultural concentration. Case: control data were analysed by logistic regression.

Results There were 2,334,238 donors from 1993 to 2021 included. Prevalence for anti-HCV was 0.33% (0.30,0.37) in 1993 and 0.07% (0.05,0.09) in 2021 ($p < 0.0001$). In 2021 0.03% (0.01,0.04) had chronic HCV. Predictors for both anti-HCV positivity and chronic HCV were similar, for chronic HCV were male sex (OR 1.8, 1.6,2.1), birth between 1945 and 1975 (OR 7.1, 5.9,8.5), living in the western provinces (OR 1.4, 1.2,1.7) and living in material deprived (OR 2.7, 2.1,3.5) and more ethnocultural concentrated neighbourhoods (OR 1.8, 1.3,2.5). There were 318 (35.4%) of chronic HCV positive and 1272 (39.6%) of controls who participated in case control interviews. The strongest risks for acquisition were injection drug use (OR 96.9, 22.3,420.3) and birth in a high prevalence country (OR 24.5, 11.2,53.6).

Conclusions Blood donors have 16 times lower HCV prevalence then the general population. Donors largely mirror population trends and highlight the ongoing prevalence of untreated infections in groups without obvious risks for acquisition missed by risk-based patient screening.

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Introduction

Hepatitis C is a blood-borne infection caused by the hepatitis C virus (HCV) that can progress to cirrhosis and liver cancer. Globally there are about 58 million people with chronic HCV, and about 1.5 million new infections each year. The World Health Organization has set a goal of eliminating HCV as a global threat by 2030 [1]. Recommendations to test patients are based on risk assessment. In 2015 the first all oral direct acting antiviral combination therapy was shown to be effective [2–4]. In the years following this interferon-free combination therapy and others were used clinically, and in 2018, provinces had removed reimbursement restrictions. This brought elimination of HCV within grasp, but case identification and linkage to care remain a challenge.

There are an estimated 204,000 (0.5%) of Canadians chronically infected of whom about a quarter are unaware of their infection [5]. Transmission is largely through blood exposure (people who inject drugs, blood transfusion before 1992, nosocomial infections) [5]. An age cohort of North American individuals born between 1945 and 1964 have higher seroprevalence primarily related to past injection drug use [6]. In Canada, the birth cohort of those born between 1945 and 1975 is associated with higher seroprevalence [7]. HCV is also associated with lower socioeconomic status and birth in countries with higher HCV prevalence [5, 8].

Blood donors are deferred for injection drug use, and sexual risks as well as cirrhosis, liver cancer, symptoms of hepatitis and known HCV infection. As such, blood donors are a low-risk segment of the population who do not think they could have HCV and are unlikely to be tested in a clinical setting. In Canada blood donations have been tested for HCV antibodies since 1990, with improved sensitivity of the assay in 1992. As 20 to 50% of acute infections resolve spontaneously, 50–80% (about 70%) of people who are anti-HCV positive are chronically infected [9]. Since late 1999 all blood donations were also tested for HCV nucleic acid. First-time donors who are both anti-HCV positive and HCV nucleic acid positive usually have chronic infections. Prior to implementation of testing, transfusion transmitted HCV (non-A non-B hepatitis as it was called) was considered a regrettable but unavoidable complication. Since 1992 when second generation anti-HCV testing was implemented there have been no cases of transfusion transmitted HCV in Canada [10].

We have previously reported declining anti-HCV positivity in first-time blood donors from the implementation of testing up to 2005 [11]. We now present an additional 16 years of HCV prevalence in blood donors and analyze the association with residential neighbourhood material deprivation and ethno-cultural concentration as well as age cohort. We also present risk factor data in a case control design subset of first-time donors.

Methods

There were two datasets analyzed. One includes all first-time donors from 1993 to 2021; the other is a case-control study of a subset of first-time donors from 2005 to 2021. These are described below.

CBS donors

Canadian Blood Services collects blood donations from all provinces in Canada except Quebec. Donors must be at least 17 years of age. Donors complete a screening questionnaire before each donation to assess safety of donation for the donor and risks for acquisition of infectious disease [12]. For the time period described in this study, donors were specifically asked about and deferred permanently for a history of injection drug use, for receiving payment or drugs for sex at any time in the past, for a positive test for HCV or hepatitis B virus, for ongoing sexual contact with a partner positive for HCV, and for cirrhosis or liver cancer. Male-to-male sex was permanently deferrable until 2003, and a temporary deferral period has been progressively reduced until removal in 2022, but effectively men who have sex with men were ineligible if they were in a relationship. During the study period donors were also asked about and deferred temporarily for jaundice or hepatitis, tattoo, skin piercing, acupuncture, transfusion, needlestick injury, previous sexual contact with a partner positive for HCV, household or sexual contact with someone with hepatitis of unknown cause, or paying money or drugs for sex [13]. For the study period, the Epidemiology Donor Database included each donors' date of birth, sex, and residential postal code as well as dates of donation and test results.

HCV testing

The screening and confirmatory assays in use over the time period of the study are summarized in Table 1. All donations that were positive on confirmatory testing were considered true positive results.

Case definition

Chronic HCV infection is defined as persistent, detectable serum HCV RNA for a period greater than 6 months with or without derangement of liver function [14]. In our study anti-HCV and HCV NAT were measured at a single time point, and as HCV NAT can be detected within 2 weeks of exposure and antibodies can

Table 1 Screening and confirmatory assays used by date range

Date HCV Antibody*	Screening Assay	Confirmatory Assay
1993 to mid-1996	Ortho Version 2.0 ELISA test system, (Ortho Clinical Diagnostics, Raritan, NJ)	the recombinant immunoblot second or third generation HCV assay (RIBA, Chiron Corp., Emeryville, CA)**
Mid-1996 to mid-2003	Ortho Version 3.0 ELISA test system, (Ortho Clinical Diagnostics, Raritan, NJ)	
Mid 2003 to December 2021	Abbott PRISM, Abbott Diagnostics Division, Wiesbaden, Germany	
Nucleic Acid Testing		
Late 1999 to early 2011	Roche Nucleic Acid Test (Roche Molecular Systems, Branchburg, NJ) (24 unit minipools)	Individual unit re-tested
Early 2011 to late 2017	Roche MPX on the cobas® s201 system (Roche Molecular Systems, Branchburg, NJ) (6 unit minipools).	Individual unit re-tested
Late 2017 to December 2021	Roche cobas® MPX Multiplex HIV, HCV & HBV nucleic acid test for use on the cobas® 6800/8800 Systems (Roche Molecular Systems, Branchburg, NJ) (6 unit minipool)	Individual unit re-tested

* Implementation dates are approximate due to roll-out by testing site

**All anti-HCV reactive donations were confirmed until May 2010. Thereafter, only those negative for HCV NAT were confirmed

be detected about 8–11 weeks post-exposure there is a period of about 3–4 months post-infection when the combination of both anti-HCV and HCV NAT positivity is related to an acute, rather than a chronic infection [15, 16]. However, as donors are free of symptoms and are deferred for recent risks for acquisition, the most likely clinical scenario for a first-time donor found to be anti-HCV and HCV NAT positive is chronic infection. We therefore refer to such cases as chronic HCV infections. Acute HCV will resolve spontaneously in 20–50% (about 30%) of acute infections and would present as anti-HCV positive but NAT negative [6, 9].

Case control study

From 2005 to 2021 all first-time donors with chronic HCV were invited to participate in a telephone interview about risks for acquisition. There was a 1:4 case: control ratio. For each case donor who participated, four control donors who had tested negative for HCV and all other markers matched according to age (+/- 5 years), sex, first-time donation status and geographic region were randomly selected. A standard notification letter was sent to all chronic HCV case donors informing them of their test results, advising them to seek medical attention and informing them that they were permanently deferred from blood donation. Donors were then sent a letter inviting them to participate in the telephone interview. Trained interviewers carried out telephone interviews using a pre-established script. For each completed interview with a case donor, control donors were selected and invited to participate in the same way. If a control donor refused to participate or could not be contacted, another control donor was randomly selected among the eligible donors until four control donors had been interviewed per case donor.

Data management and Statistical analysis

Analysis of the Epidemiology Donor Database (All first-time donors 1993–2021).

Socioeconomic status was estimated by the Pampalon Material Deprivation Index (MDI) [17, 18]. Material deprivation is associated with insecure job situation, insufficient income, and low education. The ethnic concentration was estimated using the CanMarg Ethnocultural Composition Index [19]. This index is based on the proportion of residents who are recently arrived from another country (in the last 5 years) and the proportion of people who are visible minorities [19, 20]. MDI and the Ethnocultural Composition Index were derived from the Statistics Canada census in 5 year periods. The donors' postal codes were aggregated to the dissemination area level (the smallest geographic unit available in the Canadian census, considering 400–700 persons) and were categorized into quintiles; from least deprived [1] to most deprived [5] (MDI), and from lowest ethnocultural concentration [1] to the highest [5] areas (Ethnocultural Composition Index). All analyses were carried out using SAS software (SAS Institute, NC).

The years of donation were grouped into four categories for anti-HCV analysis, (January 1, 1993 to February 1 2005; February 2, 2005 to June 1, 2010; June 2 2010-October 1 2015; October 2 2015 to December 31 2021), and in three birth cohorts (cohort 1: donors who were born before 1945; cohort 2: between 1945 and 1975; and cohort 3: after 1975) as those born between 1945 and 1975 have been reported to have higher HCV prevalence in Canada [7, 21]. Provinces with smaller populations were grouped together such that the Prairies region was comprised of Saskatchewan and Manitoba, and the Atlantic region of Nova Scotia, New Brunswick, Newfoundland, and Prince Edward Island. A logistic regression model was fitted with anti-HCV as the dependent variable and year, birth cohort, sex, region, material deprivation index and ethnocultural index as dependent variables. These variables

were included because they were plausible predictors of HCV positivity. A second multiple logistic regression was fitted with chronic HCV (HCV NAT positive and anti-HCV positive) as the dependent variable and year (October 1, 1999 – February 1 2005; February 2 2005 – June 1 2010; June 2 2010 – October 1 2015; October 2 2015 – December 31 2021), birth cohort, sex, region, material deprivation index and ethnocultural index as dependent variables. To compare finer slices of the age cohort the regression models with anti-HCV positivity and chronic HCV positivity were re-fitted with the birth cohorts of before 1945, 1945–1954, 1955–1964, 1965–1974, 1975–1984 and after 1984. Prevalence results were presented as the number per 100,000 donors because some values were small, but where presented in the text, the percentage was shown so that readers can easier compare with values in other populations. The percentage of anti-HCV positive donations that were also NAT reactive was calculated for each quarter year and assessed using an autoregressive integrated moving average (ARIMA) model. The model takes into account the correlation between time periods and the moving average takes into account trend while smoothing out random variation [22]. Interruption was included in 2014 when direct acting antiviral medications were first available in Canada and also with interruption in 2018 when direct acting antiviral medications became more widely available. Interruption tests whether the moving average changed at those time points.

Case – control study analysis

Risks for acquisition from the interviews were selected based on plausible association with HCV infection. Several univariable logistic regression models were constructed for risks for acquisition asked in the interview. Variables that were significant ($p<0.01$) in the univariate analysis were included in a multivariable logistic regression model. A variable for birth in an HCV highly endemic country (high risk country of birth) was constructed. Country of birth was classified as high risk if a donor reported that they were born in a country where HCV prevalence was 3% or higher [23, 24]. The logistic regression model was also fitted with the some of the key matching criteria (donor sex, age cohort and region) as a sensitivity analysis.

Results

There were 2,334,238 first-time donors from 1993 to 2021 included in the analysis. Prevalence for anti-HCV was 0.33% (0.30,0.37) in 1993 and 0.07% (0.05,0.09) in 2021 ($p<0.0001$). In 2000 0.09% (0.07,0.11) of first-time donors had a chronic infection and in 2021 0.03% (0.01,0.04). Table 2 shows the results of the logistic regression analysis with anti-HCV as the dependent variable. There were significant main effects for being male (OR=1.73, 95%CI 1.54–1.96), both older birth cohorts with the 1945–1975 birth cohort odds ratio being higher than for those born before 1945 (born before 1945 OR=4.22, 95%CI 2.60–6.86, born 1945–1975 OR=6.86, 95%CI 1.26–7.98), higher in British Columbia (OR=1.48, 95%CI 1.26–1.72) and Alberta (OR=1.30, 95%CI 1.11–1.53) compared with Ontario, but lower in the Prairies (OR=0.80, 95%CI 0.63–1.01) and Atlantic (OR=0.64, 95%CI 0.48–0.85) regions and higher odds ratios in those living in materially deprived neighbourhoods (OR=2.66, 95%CI 2.16–3.28) and neighbourhoods with higher ethnocultural concentration (OR=1.52, 95%CI 1.17–1.97). Figure 1 shows the numbers of first-time donations positive for HCV from 1993 to 2021 by birth cohort in which the larger number of anti-HCV positive donors born between 1945 and 1975 are visible. Univariate analysis is shown in the appendix (Table A1).

Table 3 shows the results of the logistic regression analysis with chronic HCV (positive for both anti-HCV and HCV NAT) as the dependent variable. There were significant main effects for being male (OR=1.84, 95%CI 1.60–2.13), both older birth cohorts with the 1945–1975 birth cohort odds ratio being higher than for those born before 1945 (born before 1945 OR=4.40, 95%CI 2.53–7.66, born 1945–1975 OR=7.10, 95%CI 5.92–8.52), higher in British Columbia (OR=1.44, 95%CI 1.20–1.72) and Alberta (OR=1.31, 95%CI 1.09–1.58) compared with Ontario, but lower in the Prairies (OR=0.55, 95%CI 0.40–0.76) and Atlantic (OR=0.62, 95%CI 0.45–0.87) regions, higher odds ratios in those living in materially deprived neighbourhoods (OR=2.71, 95%CI 2.12–3.45) and more neighbourhoods with ethnocultural concentration (OR=1.78, 95%CI 1.29–2.46). The univariate analysis is shown in the appendix (Table A2). Figure 2 shows the line graphs of the proportion of donors with chronic HCV by birth cohort, sex, material deprivation quintile, ethnocultural quintile from 2000 to 2021. Chronic HCV prevalence decreased over the period with the most notable difference between groups being between the 1945–1975 vs. after 1975 birth cohort. With finer slices of birth cohorts for both anti-HCV and chronic HCV the birth cohorts from 1945 to 1954 and 1955–1964 were the strongest predictors followed by 1965–1974 as shown in the appendix (Tables A3 and A4).

Figure 3 shows the percentage of anti-HCV positive donors who were also positive for HCV NAT from 2000 to 2021. There was a significant decrease ($p<0.001$) in the percentage over time from 0.71% (0.59,0.84) to 0.41% (0.11,0.71). Interruption of the time series in 2014 showed a more consistent decline from 2015 to 2021, but interruption in 2018 was not significant ($p>0.05$).

Tables 4a and 4b show the results of the logistic regression of case-control risks for acquisition. Of 898 chronic HCV positive donors, 318 (35.4%) participated, and of

Table 2 Multiple logistic regression with anti-HCV positivity as the dependent variable

Predictor (* indicates reference category)	Prevalence/100,000 and 95% CI	OR and 95% CI
Sex		
Female*	73.77(69.26,78.28)	
Male	147.85(140.95,154.75)	1.73(1.54,1.96)
Year		
January 1, 1993 to February 1, 2005	100.41(91.46,109.36)	1.47(1.25,1.73)
February 2, 2005 to June 1, 2010	74.30(66.47,82.12)	1.21(1.01,1.46)
June 2, 2010 to October 1, 2015	51.31(44.90,57.72)	0.94(0.78,1.14)
October 2, 2015 to December 31, 2021 *	49.60(43.72,55.49)	
Age Cohort		
Born before 1945	136.49(109.21,163.78)	4.22(2.60,6.86)
Born between 1945 and 1975	226.14(217.04,235.25)	6.86(5.90,7.98)
Born after 1975 *	21.70(19.35,24.05)	
Province		
British Columbia	135.42(121.78,149.07)	1.48(1.26,1.72)
Alberta	94.83(84.43,105.23)	1.30(1.11,1.53)
Prairies	57.09(46.48,67.71)	0.80(0.63,1.01)
Ontario *	88.00(81.90,94.10)	
Atlantic	58.67(47.40,69.94)	0.64(0.48,0.85)
Material Deprivation Quintile		
1 (least deprived) *	82.03(74.73,89.33)	
2	98.67(90.13,107.22)	1.35(1.11,1.63)
3	118.77(108.71,128.83)	1.89(1.57,2.28)
4	135.47(123.70,147.24)	1.98(1.63,2.42)
5 (most deprived)	151.19(137.02,165.35)	2.66(2.16,3.28)
Ethnocultural Composition Quintile		
1 * (lowest ethnocultural concentration)	79.21(68.26,90.15)	
2	99.70(90.17,109.23)	1.17(0.89,1.53)
3	124.53(115.05,134.01)	1.52(1.17,1.97)
4	108.89(100.26,117.53)	1.36(1.04,1.78)
5 (highest ethnocultural concentration)	149.36(138.92,159.80)	1.52(1.17,1.97)

3,209 controls invited, 1272 (39.6%) participated. The response rate was similar over the period. The strongest risks for acquisition were a history of injection drug use (OR=96.9, 95%CI 22.3,420.3) and birth in a high prevalence country (OR=24.5, 95%CI 11.2,53.6). The model was re-fitted with key variables on which cases and controls were matched (age, sex and region) but they were not significant predictors and did not alter the results substantively.

Discussion

Over 28 years of monitoring HCV infection in Canadian blood donors the proportion positive for HCV antibodies has declined. Higher HCV positivity was seen among those born between 1945 and 1975, in males, in the western provinces and in those living in materially deprived and ethno-cultural concentrated neighbourhoods. We report data since 1993 tested for HCV antibody, however acute HCV will resolve spontaneously in 20–50% (about 30%) of acute infections (thus would be anti-HCV positive but NAT negative) [6, 9]. The proportion of chronically infected individuals is better reflected by data since 1999 by those both HCV NAT and anti-HCV positive. These show similar trends to anti-HCV positive donors. In case control interviews injection drug use and birth in a high-prevalence country were the strongest risks for acquisition.

In 2014 DAA oral medications became available, displacing lengthier, more toxic, less effective interferon-based treatments [21]. These DAA agents were well tolerated by patients and resulted in a sustained virologic response for about 95% of infections [2, 3, 25]. Initially prescriptions were restricted to patients based on disease progression/fibrosis staging, but in 2018 were funded for all Canadians opening the door to widely available treatment for all Canadians with HCV infections [3]. HCV related hospitalizations have since decreased, although infections presenting late in the course of disease continue [25]. In the US a one-time screening of individuals born 1945 to 1965 was recommended, and later updated to include one-time testing of all adults [26–28]. In Canada a national task force recommended against such

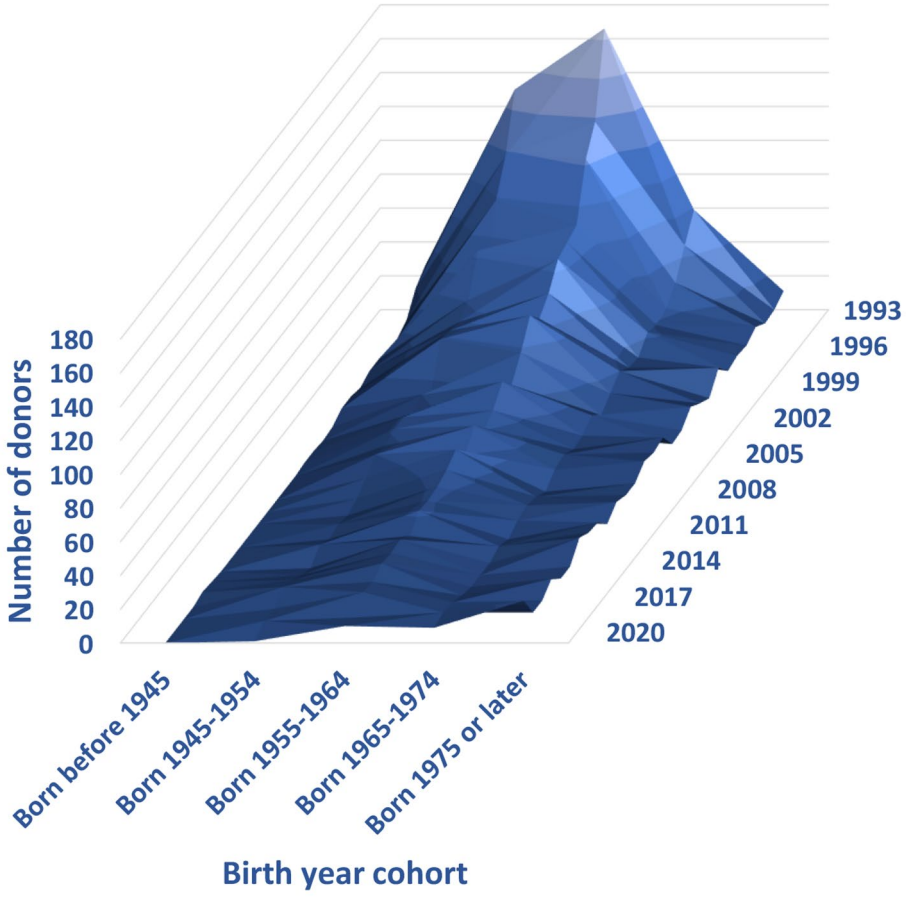

Fig. 1 Numbers of first-time donors by birth cohort from 1993 to 2021 who were hepatitis C positive

universal screening based on uncertain benefits but certainty of high usage of resources, and recommended risk-based screening (includes those transfused before 1992 in Canada) [29, 30]. The Canadian Network on Hepatitis C (CanHepC) and the Canadian Association for the Study of the Liver (CASL) countered with a recommendation of one-time testing of all individuals born between 1945 and 1975 [21]. Those in this birth cohort comprise a substantial proportion of people unaware of their infection, thus testing would be cost effective [20]. They, and those born in higher prevalence countries, face challenges being diagnosed [5, 31, 32].

Donors in the study period were deferred if they were aware that they were HCV positive, ever used injection drugs or received payment for sex. Temporary deferrals for percutaneous risks delay donation until an infection would be detectable by testing. In general, blood donors believe their blood is safe [33]. The proportion of donors with chronic HCV is 16 times lower than in the general population (0.03% vs. 0.5%), hence they are a low-risk population. First-time donors tend to be younger than the general population and are disproportionally from less materially deprived neighbourhoods, thus are not fully representative of Canadian demographics. Some countries, including the US and Canada, test for HCV in random cross-sectional general population samples drawn periodically [6, 34]. Prevalence models are based on these studies, passive surveillance of reported cases, studies in selected populations and administrative health record analyses [5]. Blood donor surveillance provides a rare opportunity to evaluate prevalence in a population segment without obvious risks for acquisition unaware of their infection and among the least likely to be diagnosed.

The proportion of first-time blood donors positive for HCV has declined in most high-income countries [35–39]. This is likely because the undiagnosed proportion of the general population has decreased, leaving only those still unaware of their infection to donate. In addition, there are more younger donors not in the high-risk birth cohort [40, 41]. A birth cohort of higher HCV prevalence among those born between 1945 and 1964 was identified in the US and in Canada, with Canadian analyses including a broader cohort of 1945 to 1975 [6, 7, 42]. Unsafe medical procedures may have contributed to this birth cohort HCV positivity but injection drug use

Table 3 Multiple logistic regression with chronic HCV positivity as the dependent variable

Predictor (* indicates reference category)	Prevalence/100,000 and 95% CI	OR and 95% CI
Sex		
Female*	34.56(31.03,38.08)	
Male	67.46(62.12,72.80)	1.84(1.60,2.13)
Year		
October 1, 1999 to February 1, 2005	79.21(71.26,87.16)	2.19(1.78,2.70)
February 2, 2005 to June 1, 2010	60.98(53.89,68.07)	1.89(1.50,2.38)
June 2, 2010 to October 1, 2015	35.88(30.52,41.24)	1.21(0.95,1.55)
October 2, 2015 to December 31, 2021 *	26.53(22.23,30.83)	
Age Cohort		
Born before 1945	83.70(42.70,124.70)	4.40(2.53,7.66)
Born between 1945 and 1975	114.71(106.67,122.76)	7.10(5.92,8.52)
Born after 1975 *	14.48(12.4,16.57)	
Province		
British Columbia	80.90(69.70,92.11)	1.44(1.20,1.72)
Alberta	58.85(50.08,67.62)	1.31(1.09,1.58)
Prairies	26.99(19.11,34.88)	0.55(0.40,0.76)
Ontario *	50.22(45.23,55.20)	
Atlantic	33.84(24.46,43.21)	0.62(0.45,0.87)
Material Deprivation Quintile		
1 (least deprived) *	34.36(29.15,39.57)	
2	42.22(36.07,48.37)	1.35(1.08,1.69)
3	56.53(48.91,64.16)	1.87(1.50,2.33)
4	57.43(49.02,65.84)	1.97(1.56,2.48)
5 (most deprived)	68.05(57.61,78.50)	2.71(2.12,3.45)
Ethnocultural Composition Quintile		
1 * (lowest ethnocultural concentration)	30.39(22.83,37.96)	
2	40.63(33.87,47.38)	1.34(0.96,1.88)
3	54.45(47.54,61.37)	1.86(1.34,2.56)
4	46.18(40.00,52.37)	1.55(1.11,2.16)
5 (highest ethnocultural concentration)	64.01(56.59,71.42)	1.78(1.29,2.46)

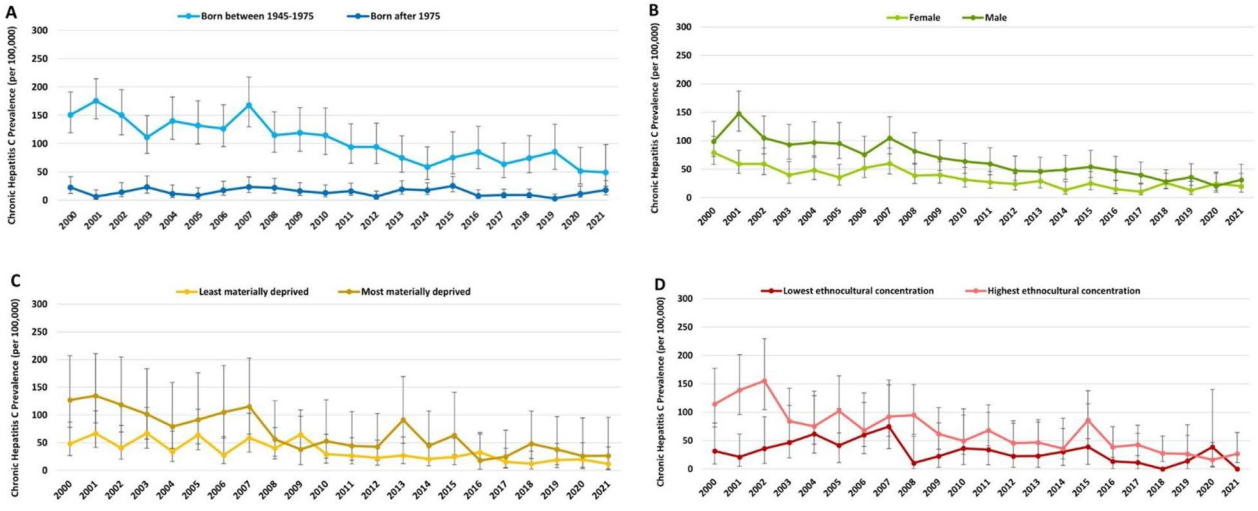

Fig. 2 Prevalence of chronic hepatitis C in donors from 2000 to 2021 by age cohort (Panel **A**), Sex (Panel **B**), Material Deprivation Index (Panel **C**) and Ethnocultural neighbourhood concentration (Panel **D**) 95% Confidence intervals shown in error bars

Table 4a Univariate odds ratios of case-control study with chronic HCV positivity as the dependent variable

Variable	Cases with risk (%)	Controls with risk (%)	Odds Ratio (OR)	95% CI
Intravenous drug use (ever)	16.7	0.2	126.78	30.69–523.73
Born in high risk country[1]	9.1	0.8	12.23	5.87–25.47
Transfusion (ever)	26.5	6.4	5.25	3.73–7.40
Sex with IVDU (ever)	14.8	1.1	16.21	8.57–30.65
Sex with someone who had hepatitis (ever)	3.6	0.3	11.15	3.408–36.51
Needlestick injury (ever)	16.6	4.2	4.50	2.98–6.81
Tattoo (ever)	27.4	14.3	2.27	1.69–3.04
Gonorrhea or other STD (ever)	17.6	5.7	3.53	2.42–5.15
Received money or drugs for sex (ever)	1.3	0.1	16.35	1.82–146.71
MSM or sex with MSM (ever)	3.3	1.2	2.81	1.21–6.57
Paid money or drugs for sex / Had sex with someone who received money or drugs for sex (ever)	7.4	1.5	5.10	2.72–9.56

[1] Born in higher prevalence country >= 3%

Table 4b Odds ratios of case-control study multivariable logistic regression model with chronic HCV positivity as the dependent variable

Variable	Cases with risk (%)	Controls with risk (%)	Odds Ratio (OR)	95% CI
Intravenous drug use (ever)	16.7	0.2	96.87	22.32–420.33
Born in high risk country[1]	9.1	0.8	24.48	11.18–53.61
Transfusion (ever)	26.5	6.4	7.79	5.27–11.53
Sex with IVDU (ever)	14.8	1.1	6.35	2.77–14.58
Sex with someone who had hepatitis (ever)	3.6	0.3	5.45	1.28–23.09
Needlestick injury (ever)	16.6	4.2	2.05	1.17–3.61
Tattoo (ever)	27.4	14.3	2.08	1.44–3.01
Gonorrhea or other STD (ever)	17.6	5.7	2.04	1.24–3.36

[1] Born in higher prevalence country >= 3%

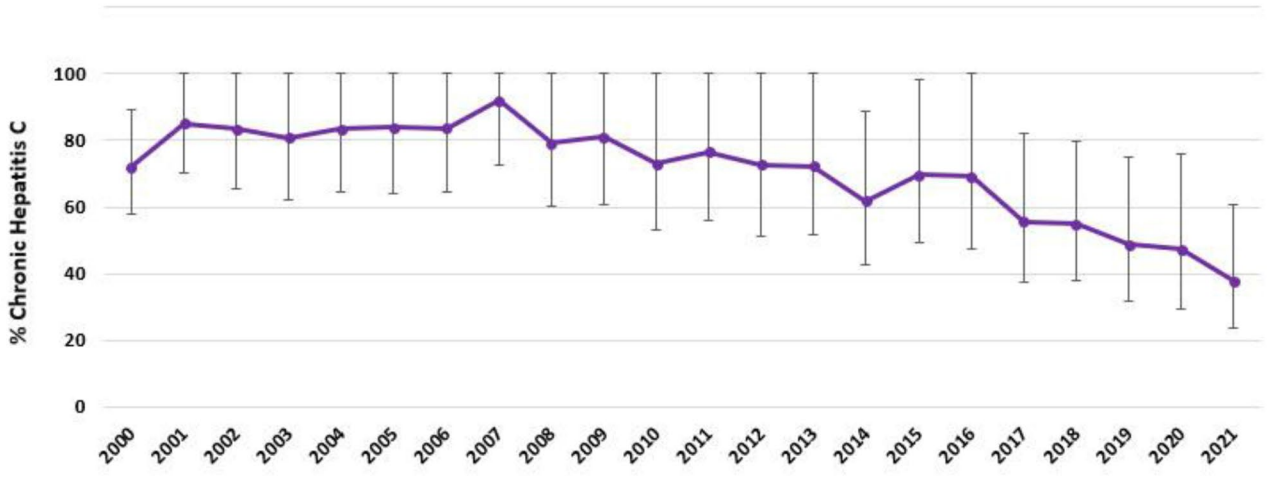

Fig. 3 Percentage of chronic hepatitis C infections among hepatitis C antibody positive donors in interrupted time series analysis the decline was greater after 2014 when direct acting antivirals became available ($p < 0.001$)

in the 1960's to 1980's prior to harm reduction strategies implementation were largely responsible [6, 43].

Despite denying it before donating, history of injection drug use was the strongest risk of acquisition from our donor interviews similar to the United Kingdom [44]. Donors may not understand the risk, they may not remember, or stigma may reduce willingness to disclose [45, 46]. Sexual transmission is rare and difficult to disentangle from people who will admit to sex with someone who uses injection drugs but not usage themselves [47]. Other risks for acquisition identified in our donors have been described in other settings. Tattoos in non-commercial or other unsterile settings may pose risk, but not licensed tattoo facilities where most tattoos now occur [47]. Needlestick injuries are a well described risk [30, 45]. Prior to 1992 blood transfusion was a common source of infection but has disappeared with the implementation of universal blood donation testing in Canada [10]. Blood transfusion may also be a surrogate marker for nosocomial transmission [48].

Racialized donors in other countries such as the US and the United Kingdom are more likely to be HCV positive [37, 38]. Nearly half (45%) of Canadians with HCV antibodies are individuals born in higher prevalence countries but comprise only 23% of the population [5, 49]. In higher prevalence countries unsterilized or inadequately sterilized medical, dental and surgical equipment, unsafe injections, infection from mother to child before or during birth and blood transfusion are the primary modes of transmission, hence many people from such countries do not have obvious risk s for acquisition. Birth in a higher prevalence country predicted HCV positivity in our interviewed donors. We report that donors living in higher ethno-cultural concentration neighbourhoods were associated with chronic HCV. Foreign-born Canadians are often not diagnosed until years after arrival [50, 51].

HCV disproportionally affects socio-economically marginalized people [51–57]. Injection drug use is associated with low income and lower levels of education, unemployment and history of trauma and family instability [57–59]. Injection drug use is responsible for close to half of all infections in Canada [5]. Our finding of chronic HCV in donors who live in materially deprived neighbourhoods is perhaps not surprising, although the infection will often have occurred decades before.

HCV is more common in males but the gap may be decreasing [7, 42, 53, 60]. In those born in higher prevalence countries infections are equally likely among females as males [50]. Infections in women tend to progress to fibrosis more slowly and may be undiagnosed for longer [61]. Hence both changing epidemiology related to immigration and delayed diagnosis may be at play.

We reported that a decreasing percentage of anti-HCV positive donors are chronically infected (HCV NAT positive), particularly after 2014 when DAA medications were available. Spontaneous viral clearance in chronic infection is rare [62–64]. There could be failure to disclose past infection after curative treatment [38]. However, a decrease was observed before the introduction of DAA medications in France and the United Kingdom [35, 37]. It is possible that as more people progress to liver disease they are diagnosed, reducing the chronically infected proportion unaware of infection who may donate, or that some people tested in clinical settings are either not told when they are anti-HCV positive if they are NAT negative, or are told they are not infected thus believe they are safe to donate.

An important strength of our study is the highly sensitive screening assays used over the period reported (>99% sensitivity). Indeed, no transfusion transmitted HCV has been reported since implementation of second generation testing [10]. We acknowledge some important limitations. Our study is observational in nature. We used neighbourhood indicators of material deprivation and ethnocultural status which may not describe individuals, and also donors from these communities may not be representative of their wider community. There is potential participation bias in the case-control study as only 35% of HCV positive donors completed an interview. In addition, as there may be stigma associated with some risks for acquisition, donors may not have disclosed these in the interview.

In summary, blood donors are screened for HCV risks for acquisition and have lower prevalence than the general population. Nevertheless, donors largely mirror trends in the general population and highlight the ongoing prevalence of untreated infections in groups less likely to have obvious behavioural risks for acquisition. Blood donor screening provides a rare opportunity to understand the potential impact a policy of testing all adults one time for HCV, as is done in the US, might have in Canada. Further evaluation is needed.

Abbreviations

Anti-HCV	Antibodies to the hepatitis C virus
ARIMA	Autoregressive integrated moving average
DAA	Direct acting antivirals
HCV	Hepatitis C virus
HCV NAT	Hepatitis C virus nucleic acid test
MDI	Material Deprivation Index

Supplementary Information

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Supplementary Material 1

Author contributions
SFO contributed to the conception, design, interpretation and prepared the first draft of the manuscript. BE contributed to analysis and interpretation. LO contributed to analysis and interpretation. WF contributed to analysis. MG contributed to the conception and interpretation. SJD contributed to the conception and interpretation. All authors contributed to the revision of the drafted manuscript.

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Data availability
Due to privacy constraints data are not publicly available, however data may be requested from Canadian Blood Services subject to institutional approval and research ethics approval. Sheila O'Brien (Sheila.obrien@blood.ca) may be contacted to request data from this study.

Declarations

Consent for publication
Not applicable.

Competing interests
Steven J Drews reports supplies provided by Abbott Laboratories and consulting fees provided by F Hoffmann-La Roche Ltd. Sheila O'Brien, Behrouz Ehsani-Moghaddam, Lori Osmond, Wenli Fan and Mindy Goldman have no competing interests to declare.

Ethics approval
The case: control study was approved by the Canadian Blood Services Research Ethics Board (REB 2018.040). Operational surveillance data are exempt from REB approval requirements.

Informed consent
Prior to donating blood all blood donors gave consent to donate and to have their blood tested. The case: control study participants gave informed consent to participate.

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