Inside this issue: Hepatitis C

In this issue explore what we know about the Hepatitis C virus (HCV) in Canada. Since 1998, Canadian rates of reported HCV cases have declined over 50%, but certain populations remain at risk. An estimated 1% of people have been exposed to Hepatitis C in Canada. In our Useful Links section, find some good resources on Hepatitis C available from the Public Health Agency of Canada and see a recent summary on what is known about a new Hepatitis E vaccine currently under development. And for something completely different, see our Infectious Disease News Brief section to learn about the growth of "Big Data" and how this is being applied to infectious disease tracking.

Surveillance

ID News Briefs

Upcoming webinar

January 15, 2015, 1 pm EST: 2014 HIV & AIDS in Canada: Surveillance Reports to December 2013
https://gts-ee.webex.com/gts-ee/onstage/g.php?d=554298231&t=a

Useful links

Public Health Agency of Canada. Frequently Asked Questions about Hepatitis C
http://www.phac-aspc.gc.ca/hepc/faq-eng.php

Public Health Agency of Canada. Hepatitis C Resource Library
http://www.phac-aspc.gc.ca/hepc/rl-cd-eng.php

The Strategic Advisory Group of Experts (SAGE) on immunization. Hepatitis E vaccine in: World Health Organization's *Weekly epidemiological record*. No 50, 2014, 89: 573-575.
http://www.who.int/wer/2014/wer8950.pdf?ua=1

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Canada

Hepatitis C surveillance in Canada

Payne E[1], Totten S[1], Archibald C[1]

[1] Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, ON

*Corresponding author: elspeth.payne@phac-aspc.gc.ca

Abstract

Background: Hepatitis C is a highly transmissible virus that can lead to chronic liver disease. It continues to be a major public health concern in Canada.

Objective: To describe surveillance trends of reported cases of Hepatitis C virus (HCV) in Canada by age and sex from 1991-2012.

Methods: Cases of HCV reported to the Canadian Notifiable Disease Surveillance System were compiled at the national level. As most reported cases are not differentiated by acute or chronic HCV infection status, presented results are based on total HCV cases. Time trends are provided from 1991-2012, with a more detailed examination of age and sex patterns from 2005-2012.

Results: The rate of reported HCV infection increased sharply from 1991 (the year it was first notifiable) until 1998, when the highest overall rate of 66.9 per 100,000 was observed. From that time until 2012, rates of reported cases decreased in both sexes, but remained consistently higher among males than females. In 2012, the overall rate of reported HCV infection was 29.3 per 100,000. In younger age groups, rates among females were marginally higher, while males in older age groups (30 and above) exhibited substantially higher rates.

Conclusion: This surveillance summary presents the longer-term trends in reported cases and corresponding rates of HCV in Canada using national surveillance data. Canada continues to experience a downward trend in HCV rates; however, the burden of infection will continue to increase as chronically infected individuals develop severe illness.

Introduction

Hepatitis C is a highly transmissible virus, spread through contact with infected blood. Hepatitis C infection can lead to chronic liver disease and affects approximately 3% of the world's population (1). Globally, approximately 130-150 million individuals have a chronic Hepatitis C virus (HCV) infection and 350,000 to 500,000 people die annually from HCV-related illnesses (2). The seroprevalence of anti-HCV among the general public in Canada was recently estimated by the Community Health Measures Survey as 0.5% (3), while mathematical and epidemiologic models incorporating data from high-risk populations have estimated the seroprevalence of anti-HCV to be approximately 0.96% (4). In 2011, acute HCV infection was reported as the underlying cause of 35 deaths in Canada and chronic HCV infection as the underlying cause of 346 deaths (5). This may be an underestimate as deaths attributable to chronic HCV may have been coded as more proximal causes such as hepatocellular carcinoma or cirrhosis.

HCV was first identified in 1989, facilitating the development of HCV antibody and nucleic acid amplification screening methods that were implemented for screening the blood supply in Canada in 1990. Prior to this discovery, thousands of individuals were infected with HCV after receiving transfusions of blood components or products. The introduction of universal blood supply screening significantly improved the quality of Canada's blood supply and virtually eliminated this transmission risk (6).

However, certain populations continue to be at elevated risk for Hepatitis C infection. Transmission of HCV among people who inject drugs is now the most significant contributor to overall HCV rates; the majority of recent HCV infections in Canada occurred through the sharing of drug preparation and injection materials (7).

Less common routes of HCV transmission include contact with infected blood through sharing of sharp instruments, personal hygiene equipment (e.g., razors, toothbrushes, scissors and nail clippers) and vertical transmission from mother to child (8,9). While sexual transmission of HCV is uncommon, this mode of transmission has been observed among HIV-infected MSM (10).

HCV continues to be a major public health concern and was ranked first among 51 pathogens for its relative contribution to the overall burden of infectious diseases in Ontario (11). Hepatitis C is not preventable by vaccine and although some individuals will spontaneously clear and recover from their infection, up to 85% will progress to chronic infection with potentially life-threatening consequences (12). The health care burden presented by existing cases that progress to more serious sequelae continues to escalate.

The objective of this analysis was to describe trends in Hepatitis C cases reported to the Canadian Notifiable Disease Surveillance System (CNDSS) from 1991-2012, with a more detailed review of patterns by age and sex from 2005-2012.

Methods

Data sources
Data on HCV cases are reported to the CNDSS by provincial and territorial ministries of health, which in turn obtain data from local and regional health authorities. HCV infection has been nationally notifiable since 1991. Surveillance of Hepatitis C cases was phased in over time by provinces and territories, with all jurisdictions reporting cases by 1999. Nunavut data from 2007-2012 were not available for this analysis.

The HCV case definition used for national surveillance has evolved since 1991 (13), with revisions in 1999 (14), 2008 (15) and 2011 (*Unpublished update 2011. Public Health Agency of Canada. Case definitions for communicable diseases under national surveillance*). Most provinces and territories confirm cases using HCV antibody testing and do not currently distinguish reported HCV cases by infection status. Therefore, acute and chronic HCV cases were combined for analysis purposes.

Analysis
Descriptive analysis of HCV infection by year, age group and sex was conducted using data reported to the CNDSS. Analyses included all Hepatitis C cases reported to the CNDSS and rates are given per 100,000 population. Because Hepatitis C was not reported by all provinces and territories during some time periods, national rates for each year were calculated with denominators adjusted to include only those jurisdictions with available data. Demographic patterns in age and sex were examined in HCV cases reported for 2012 to provide a more detailed snapshot of the most recent available data.

Population data for the calculation of rates were obtained from Statistics Canada (16). The following estimates were used: for 2005, final intercensal estimates; for 2006, final postcensal estimates; for 2007-2010, final intercensal estimates; for 2011, final postcensal estimates; and for 2012, updated postcensal estimates. Rates, percentages and percent change in rates were calculated using unrounded numbers, and therefore presented results may differ compared to calculations based on rounded numbers. As population denominator data has been updated, rates reported may differ from previous reports.

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Results

Long-term trends (1991-2012)

Between 1991 and 1998, there was an overall increase in the rate of reported Hepatitis C cases. In 1991 there were 912 reported cases, corresponding to a rate of 5.2 per 100,000. By 1998, this rate had increased by over 1000%, to a rate of 66.9 per 100,000 and 19,379 cases. Throughout this time period, rates of reported cases of Hepatitis C were consistently higher among males than females (**Figure 1**).

From 1998-2012, the rate of reported cases of Hepatitis C decreased steadily among both males and females. In 2012, a total of 10,180 cases of Hepatitis C were reported, corresponding to a rate of 29.3 per 100,000 and a 56.2% decrease from 1998. Although the rates of reported cases of Hepatitis C were consistently higher among males than females over this time frame, the gap between the sexes narrowed over time. Among males, rates decreased by 58.6%, from 88.9 to 36.8 per 100,000; among females, rates decreased by 52.3%, from 45.0 to 21.5 per 100,000 (**Figure 1**).

Figure 1: Rates of reported cases of Hepatitis C in Canada[1] by sex, CNDSS[2], 1991-2012
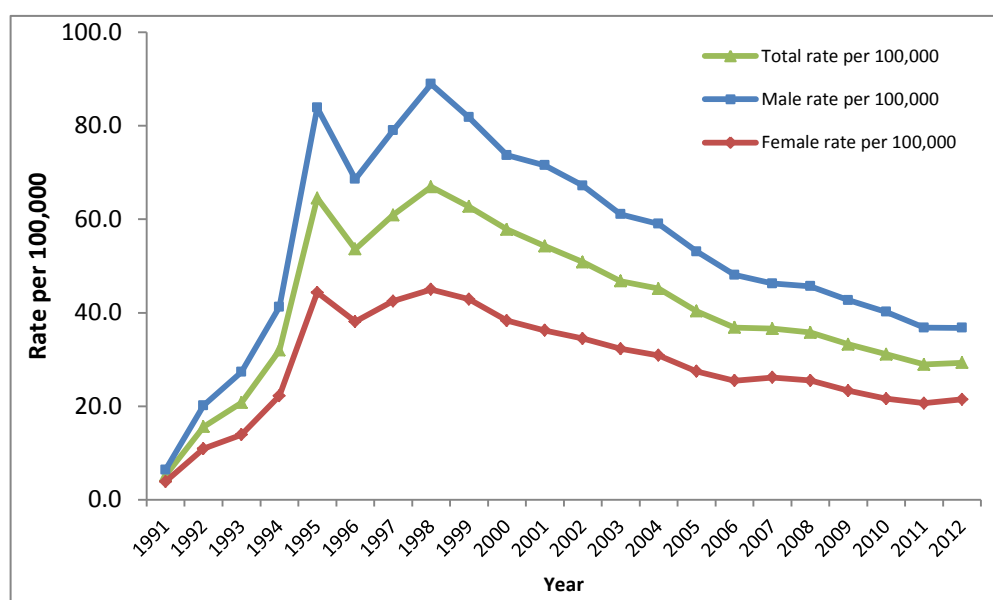
[1] Includes PEI, ON, SK, AB, BC 1991-2012; NL, NB, NT 1993-2012; YT 1994-2012; NS, QC 1996-2012; MB 1999-2012; NU 1999-2006. For rate calculation, population denominators were adjusted to include only those jurisdictions for which data were available in a given year.
[2] CNDSS = Canadian Notifiable Disease Surveillance System

Recent trends by age group and sex (2005-2012)

Between 2005 and 2012, males of all age groups experienced rate decreases, with the exception of those aged 60 and over who experienced a slight rate increase from 21.8 to 26.3 per 100,000. In males less than 15 years of age, HCV rates were less than 1.0 per 100,000 for all years. In 2005, males aged 40 to 59 years had the highest rate of reported acute HCV infection at 101.0 per 100,000. By 2012, this rate had decreased to 64.4 per 100,000. A large rate decrease was also observed among males aged 30 to 39; from 2005-2012 rates of HCV infection decreased from 83.9 to 51.7 per 100,000 (**Figure 2**).

Figure 2: Rates of reported cases of Hepatitis C in males in Canada[1] by age group, CNDSS[2], 2005-2012
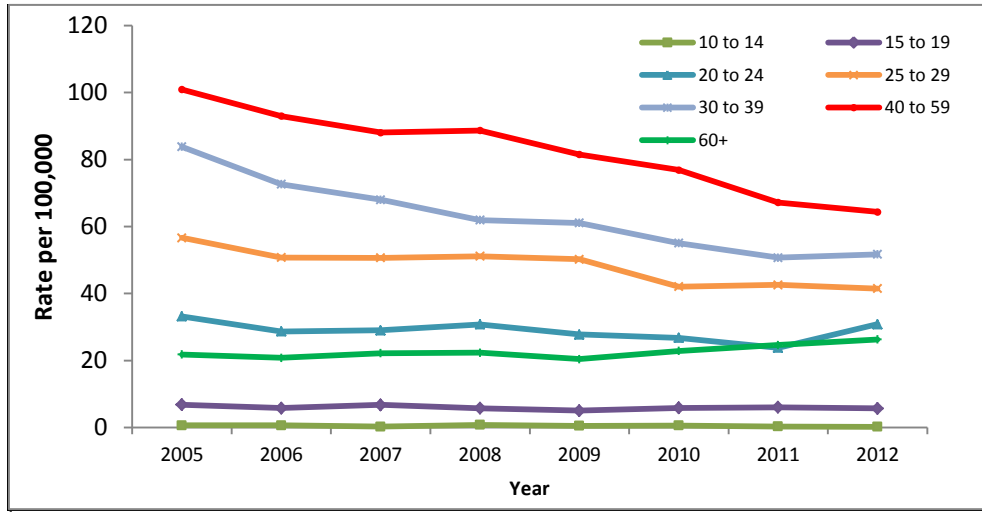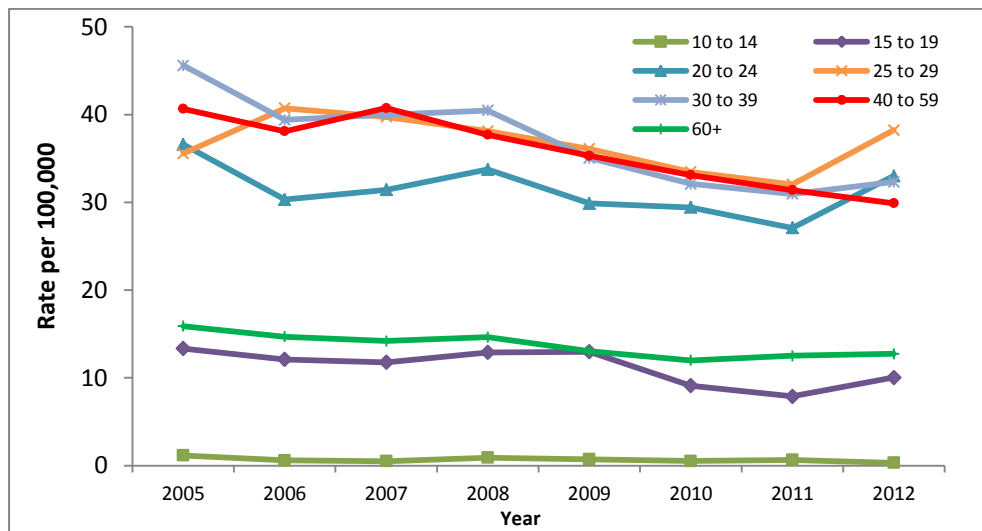

[1] Hepatitis C data were not available for NU from 2007-2012 at the time of analysis. The population has been removed from the denominator for rate calculation.
[2] CNDSS = Canadian Notifiable Disease Surveillance System

During the same time period, rate decreases were observed among females, with the exception of those in the 25 to 29 age group who experienced a rate increase from 35.6 to 38.2 per 100,000. The greatest rate decrease was observed among females between 10 and 14 years, from 1.2 to 0.3 per 100,000, though is largely reflective of the small HCV counts in this age group and the resulting instability in rates. Excluding females in the 10 to 14 age group, the largest rate decrease was noted among females aged 30 to 39, from 45.6 to 32.3 per 100,000 (**Figure 3**).

Figure 3: Rates of reported cases of Hepatitis C in females in Canada[1] by age group, CNDSS[2], 2005-2012
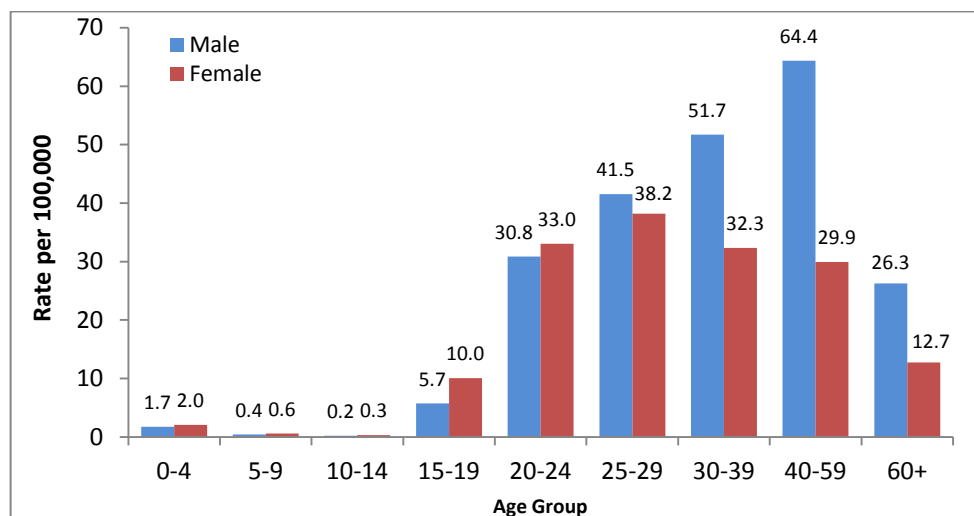

[1] Hepatitis C were not available for NU from 2007-2012 at the time of analysis. The population has been removed from the denominator for rate calculation.
[2] CNDSS = Canadian Notifiable Disease Surveillance System

In 2012, the highest rate of Hepatitis C was observed among males in the 40 to 59 age group, followed by males in the 30 to 39 age group (**Figure 4**). For both sexes, rates were higher among those over 19 years of age.

Differences in rates between males and females were more pronounced in older age groups (30 and above) with males exhibiting substantially higher rates.

Figure 4: Rates of reported cases of Hepatitis C in Canada[1] by age group and sex, CNDSS[2], 2012

[1] 2012 Hepatitis C data were not available for NU at the time of analysis and this population has been removed for rate calculation.
[2] CNDSS = Canadian Notifiable Disease Surveillance System

Discussion

This analysis provides the most up-to-date data currently available on reported cases and corresponding rates of HCV in Canada.

From 1991 to 1998, the rate of reported cases of Hepatitis C in Canada increased steadily as those infected through the blood supply were identified by look-back and trace-back procedures (17). Growing awareness of HCV transmission risk in light of the national inquiry conducted by the Krever Commission (18) and related media reports may have also impacted HCV testing rates, thus contributing to a rise in case reports over this time period. The implementation of HCV surveillance by provinces and territories across Canada should not have a significant impact on the increase in rates over this timeframe, as rates were calculated using adjusted denominators.

Since 1998, the rates of reported cases of HCV have declined by 56.2%, although certain populations continue to be at risk. Among newly acquired HCV cases with known risk factor information, 61% had reported a history of injection drug use (19). I-Track, the national behavioural and biological surveillance system that monitors HIV and Hepatitis C and associated risk behaviours among people who inject drugs in Canada, found the lifetime exposure to Hepatitis C (as measured by the presence of HCV antibody in a dried blood spot specimen) was 68% in Phase 3 of data collection conducted from 2010-2012 (20). In Phase 3 of I-Track, 68.2% of participants were male (20), indicating that a greater proportion of those who use injection drugs are male and potentially explaining why males continue to represent a larger proportion of reported HCV cases. However, differences in male and female rates of reported HCV have narrowed since 2005; females are more likely to be assisted with drug injection or be in sexual partnerships that are reliant on drug exchange and are at a higher risk for sharing drug-use equipment (21). Changing rates among males and females may also be a reflection of different serologic testing behaviours. Females are more likely to seek health care and be tested (22), leading to increasing reported rates of HCV detection.

An additional source of HCV cases may be immigration to Canada from countries where Hepatitis C infections are endemic, particularly from those regions where universal precautions to prevent the transmission of bloodborne infections are not routinely implemented (23). Household, vertical and sexual transmissions are less common in Canada and unlikely to contribute a significant number of cases to the national total.

An analysis of cohort effects among reported cases of HCV found that those born between 1946 and 1965 contributed more than half of all HCV cases reported between 1991 and 2010 in Canada (24). While the rate of reported cases in Canada appears to be decreasing, the number of individuals infected decades ago that develop sequelae is likely to increase over time as individuals advance to more severe stages of disease progression (25). In addition, undiagnosed cases represent an unknown future burden of illness (25).

While no vaccine exists, treatments are available for HCV infection. Previously, treatment was limited to pegylated interferon-α in combination with ribavirin (26). However, highly effective direct-acting antiviral agents (DAA) have recently been approved by Health Canada (27, 28) and more are in clinical development (29). Over time, increased availability of new treatments and implementation of other public health interventions (30) may reduce transmission and affect rates of newly reported cases.

Limitations

These findings need to be interpreted in light of several limitations of the data. First, the HCV case definition used for national surveillance and the reporting protocols used by provinces and territories have evolved since 1991, which may have affected case reporting over time. The case definition has consistently allowed confirmatory testing to be conducted using a second manufacturer's enzyme immunoassay (EIA). The lower sensitivity and specificity of first and second generations of these HCV assays have likely resulted in an unknown proportion of false positive HCV cases (31).

It is uncertain to what extent these data reflect true HCV incidence. Those with acute HCV infection are commonly asymptomatic and thus may not have been tested or diagnosed. According to results from the Community Health Measures Survey, only 30% of Canadian respondents who tested positive for a current HCV infection reported having been diagnosed with HCV (3). In addition, due to the long duration of infection, it is possible that an individual may be tested and diagnosed in more than one province or territory over time and consequently counted more than once in the CNDSS dataset.

Information on whether reported HCV cases were acute or chronic was not available from most provinces and territories and therefore, findings cannot shed light on potential current trends in transmission or the potential burden of HCV infection in Canada.

Finally, the data are limited to analysis by age and sex. At this time, there are no additional data elements in the CDNSS that could explain observed trends. Consequently, it is not clear what proportion of reported HCV infections are due to transmission through injection drug use or other risk factors.

Conclusion

Following an initial increase in cases during a period of increased screening, Canada continues to have a downward trend in the rate of new reported cases of HCV. Although there are significant limitations, these findings contribute to our understanding of HCV in Canada. Surveillance, supported by research that examines factors affecting observed trends, can contribute to the development of tailored HCV interventions in Canada.

Conflict of interest
None

Funding

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Estimated prevalence of Hepatitis C Virus infection in Canada, 2011

Trubnikov M[1*], Yan P[1], Archibald C[1]

[1] Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, ON

* Corresponding author: Maxim.Trubnikov@phac-aspc.gc.ca

Abstract

Background: Prevalence estimates contribute to our understanding of the magnitude of a particular health condition and in planning appropriate public health interventions.

Objective: To estimate the prevalence of chronic Hepatitis C virus (HCV) infection, anti-HCV-positive status (anti-HCV) and the proportion of undiagnosed HCV infections in Canada.

Methods: A combination of back-calculation and workbook methods was used. The back-calculation method estimated prevalent chronic HCV infection and the proportion undiagnosed using the Canadian Cancer Registry's data on hepatocellular carcinoma reported between 1992 and 2008 and the Canadian Notifiable Disease Surveillance System's data on Hepatitis C virus (HCV) cases reported between 1991 and 2009 in a Markov multi-state disease progression model with parameters adjusted to Canada. The workbook method divided the total population of Canada into population subsets and developed estimates of population size and anti-HCV prevalence for each. Sub-population size estimates were multiplied by anti-HCV prevalence measures to calculate the prevalence of anti-HCV by sub-population. A measure of spontaneous clearance was used to estimate the number of persons with chronic HCV from estimates of the number of anti-HCV-positive persons.

Results: The back-calculation method estimated the prevalence of chronic HCV infection at 0.64% and the proportion of undiagnosed chronic HCV infection at 44% in 2011. The workbook method estimated the anti-HCV prevalence at 0.96% (plausibility range: 0.61% to 1.34%) and chronic HCV infection at 0.71% (0.45 – 0.99%).

Interpretation: By combining mid-point estimates from both methods, it is estimated that between 0.64% to 0.71% of the overall Canadian population was living with chronic HCV infection in 2011 and 44% of these individuals were undiagnosed.

Introduction

Chronic Hepatitis C virus (HCV) infection affects an estimated 3% of the world's population (1). Approximately three out of four persons with acute HCV infection will not clear the virus spontaneously within six months and will develop chronic HCV infection with an array of long-term sequelae (2). The diagnosis of HCV infection is usually based on identifying antibodies to HCV (anti-HCV) and/or the viral material (i.e., HCV ribonucleic acid) (3) alongside certain liver function enzyme tests (4). A positive anti-HCV test result indicates past or current HCV infection since the HCV antibodies may remain after the virus has cleared. A positive HCV-RNA test suggests a current infection which may be acute or chronic, with chronic HCV infection being defined as a positive HCV-RNA test for more than six months since the presumed infection date.

National estimates of prevalence contribute to our understanding of the magnitude of a particular condition and can help in planning appropriate public health interventions (5). The prevalence of anti-HCV-positive persons in Canada was estimated at 0.78% of the total Canadian population in 2007, of whom 21% were considered not diagnosed at the time (6). Based on the data from Cycles 1 and 2 of the Canadian Health Measures Survey (2007-2011), Rotermann and colleagues estimate anti-HCV seroprevalence in the range of 0.3% to 0.9% with a mid-estimate of 0.5%. Approximately 70% of persons who tested anti-HCV-positive reported that they did not have Hepatitis C (7).

However, the Canadian Health Measures Survey did not cover non-household populations with a higher HCV burden (8) (e.g., prison inmates, homeless persons and residents of health care facilities) and, with a response rate of just above 52% (7), the Survey may have under-sampled household populations that were highly affected by HCV (e.g., people who use injection drugs (IDU), chronically ill persons on haemodialysis and immigrants who do not speak English or French). Therefore, the analysis by Rotermann and colleagues (7) likely underestimated the true anti-HCV seroprevalence in Canada.

Given the length of time since the last HCV prevalence estimates were developed in Canada (6) and the potential limitations of the analysis by Rotermann and colleagues (7), this review sought to update estimates of the prevalence of chronic HCV infection, anti-HCV-positive persons and the proportion of undiagnosed cases of chronic HCV infection in Canada.

Methods

Estimates of the prevalence of chronic HCV infection and anti-HCV-positive persons and the proportion of undiagnosed cases of chronic HCV infection in Canada were developed using a combination of back-calculation (9) and workbook (10) methods.

Back-calculation uses the observed occurrence of subsequent events to make inference about the incidence of the initiating events in the past that lead to them. This method was recently adopted to estimate the incidence of HCV infection in France (11) and England (12), where reported data on HCV-associated hepatocellular carcinoma and a Markov multi-state disease progression model were used to back-calculate the historical HCV incidence. We used a back-calculation method with Canadian Cancer Registry's data on hepatocellular carcinoma reported between 1992 and 2008 and a Markov multi-state disease progression model with parameters adjusted to Canada (13, 14) to estimate chronic HCV infection prevalence and the proportion of undiagnosed HCV infections in 2011. The prevalence of chronic Hepatitis C per 100 population was estimated with data stratified by 5-year birth cohort according to the date of birth. The overall prevalence was estimated using the same model with all birth cohorts combined. Another back-calculation process with data from the Canadian Notifiable Disease Surveillance System (CNDSS) on HCV cases reported between 1991 and 2009 was run in parallel to ensure the reliability of the estimates of the former. As record-level HCV data from CNDSS was only available for six Canadian provinces and territories that account for 88% of the Canadian population, estimates from the back-calculation were extrapolated to the whole Canadian population.

A workbook method was used to estimate the number of prevalent and undiagnosed anti-HCV-positive persons in Canada in 2011. Using this method, population size estimates were multiplied by anti-HCV seroprevalence measures (anti-HCV) to produce estimates of prevalent anti-HCV-positive persons. A value of 26% was used to describe the population's spontaneous HCV clearance and to estimate the chronic HCV infection prevalence from an estimate of anti-HCV-positive persons (15). Then, estimates of prevalent anti-HCV-positive persons were multiplied by the proportion of undiagnosed chronic HCV infection from the back-calculation method to produce the numbers of potentially undiagnosed persons.

The total population of Canada was divided into population subsets and size and anti-HCV prevalence estimates were developed for each subset population. Population size estimates were developed using data from published literature and a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey (*Unpublished data. Public Health Agency of Canada, available from the author upon request*). Sources are referenced in **Table 1**.

The MEDLINE, EMBASE, GLOBAL HEALTH, SCOPUS and PROQUEST PUBLIC HEALTH databases were searched for anti-HCV prevalence measures in the populations of interest in Canada and other developed countries through relevant papers published from 2000-2013 in English or French. Bibliographies of identified studies were also searched for relevant articles in addition to the electronic resources of Statistics Canada, Citizenship and Immigration Canada, Correctional Service Canada, the Public Health Agency of Canada (PHAC) and the Internet. Requests for information were sent to Canadian experts working in the fields of migration health, prison studies, substance abuse, mathematical modelling and Hepatitis C epidemiology.

During the review, anti-HCV seroprevalence measures were ranked as "under-estimates", "over estimates" or as "appropriate estimates" based on a subjective assessment of how representative the study sample was of the population of interest from the description of the study design in the methods section of the reviewed paper. The study outcomes assessed as likely over- or under-estimates were used to bound plausibility ranges of the appropriate estimates (10).

A number of population groups were assessed to have appropriately representative studies of anti-HCV prevalence, including foreign-born persons aged 14-79 years old, current and former injection drug users, homeless persons who do not use injection drugs, federal and provincial inmates and residents of long-term healthcare facilities. For these groups, prevalence estimates from the group of studies ranked as "appropriate estimates" were chosen if they were from cohort studies or systematic reviews, or, in the absence of such, from studies with more accurate geographical representation. For foreign-born persons, a range of anti-HCV prevalence measures at 1.90% (95%CI: 1.30-2.60) (suggested by Greenaway and colleagues) were used (16). For current injection drug users, including those of Aboriginal origin and homeless people who use injection drugs, a range of anti-HCV seroprevalence at 63%-69% were used (*Unpublished data. I-Track: Enhanced Surveillance of Risk Behaviours among People who Inject Drugs, Phases 1-3. PHAC. 2013*). For former injection drug users, a range of anti-HCV seroprevalence at 28.5% (95%CI: 10.8-46.3) from a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey were used (*Unpublished data, PHAC 2013*). For homeless people who do not use injection drugs, anti-HCV seroprevalence measures in the range of 0.8% (*Unpublished data E-SYS: Enhanced street youth surveillance system, Phase 6 (2009-2011). PHAC, 2013*) to 3.70% were used (17). For inmates of the federal penitentiaries, a point estimate of anti-HCV prevalence at 24.0% provided by the Correctional Service Canada for 2011 (*Unpublished data. Correctional Service Canada, 2013*) and a range of measures from a publication by De and colleagues at 18.10%-37.10% were used (18). For inmates of the provincial penitentiaries, a range of published measures of anti-HCV seroprevalence between 18.5% (19) and 28.0% were used (20). For residents of long-term care facilities, a range of published measures of anti-HCV seroprevalence between 1.4% (21) and 4.5% were used (20).

For the remaining population groups (including Aboriginal people who do not use injection drugs and Canadian-born persons of non-Aboriginal ancestry aged 0-13 and 80+ years old who do not use injection drugs), mid-point estimates and plausibility ranges were derived using indirect evidence on anti-HCV prevalence measures as compared to the anti-HCV prevalence estimates in populations with reliable estimates, such as rate ratios or higher or lower position in relation to anti-HCV prevalence rates measured in the comparison populations. Thus, the lower bound of the prevalence estimate (0.03%) for 14-44 years old from a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey (*Unpublished data. PHAC,2013*) was used as the upper bound for children 0 to 13 years old, while the lower bound was assigned as 0.01% and the mid-point estimated as the average of the two. For senior residents aged 80+ years old, the mid-point and range of prevalence in 14-44 years old from a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey (*Unpublished data PHAC, 2013*) (0.16% (0.03% to 0.29%) was assigned with the understanding that it should be lower than the prevalence in 45-79 years old (0.93% (0.33%-1.53%) but higher than that in the age group of 0-13 years old (0.02% (0.01%-0.03%) (as is evidenced from a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey (*Unpublished data. PHAC, 2013*).

For Canadian-born persons of non-Aboriginal ancestry who do not use injection drugs aged 14-79 years old, anti-HCV prevalence measures from a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey (*Unpublished data PHAC, 2013*) (0.20% (95%CI: 0.10-0.30%) were used. For Aboriginal persons who do not use injection drugs, a multiple of 2.5 (a coefficient found in the study of Uhanova and colleagues (23) times the seroprevalence rate from a custom tabulation of the Cycle 1 and 2 data from the Canadian Health Measures Survey (*Unpublished data, PHAC, 2013*) in Canadian-born persons of non-Aboriginal ancestry who do not use injection drugs aged 14-79 years old was used. Due to very limited data on anti-HCV-positive status awareness, a point estimate of undiagnosed chronic HCV infection from the back-calculation method was applied to the point-estimates of persons with chronic HCV infection from the workbook and back-calculation methods to calculate the range of undiagnosed persons with chronic HCV infection.

Results

The overall prevalence of chronic HCV infection (as estimated from the back-calculation) was 0.64% or 220,697 persons in 2011. In the previous 20 years, the country's prevalence of chronic HCV infection had changed in the range of 0.6% to 0.7% (**Figure 1**). The highest prevalence of chronic HCV infection occurred in the birth cohort 1955-59 (1.5%), followed by the birth cohorts 1950-54 (1.25%), 1960-64 (1.2%), 1965-69 (1.1%) and 1970-74 (0.8%). The prevalence of chronic HCV infection among those born before 1949 has declined from approximately 1% to below the overall prevalence rate in the past 20 years. The prevalence of chronic HCV infection among those born after 1965 has increased from below the overall prevalence rate to above it. The prevalence of chronic HCV infection in those born between 1950 and 1964 has remained above the overall prevalence rate throughout the 20 year period. The back-calculation method also estimated that 44% of those with chronic HCV infection were not diagnosed in 2011.

Figure 1: Estimated prevalence of chronic HCV[1] infection (per 100 population) in Canada from a back-calculation model[2]
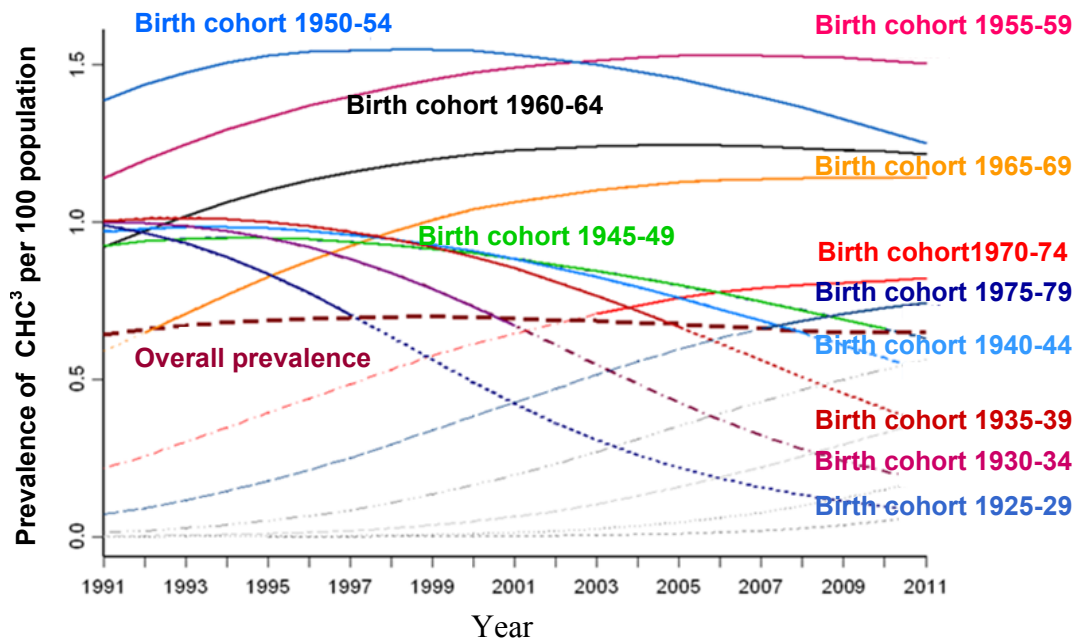
[1] HCV = Hepatitis C virus
[2] Note: Solid lines were used to reflect the birth cohort specific prevalence when it was above the overall prevalence. Dotted lines were used for when the prevalence was below the overall estimate.
[3] CHC = chronic Hepatitis C

The workbook method estimated the anti-HCV prevalence in Canada in 2011 at 0.96% with a plausibility range of 0.61% to 1.34% (**Table 1**). This range translates into an estimated 332,414 persons (plausibility range (persons): 210,753 to 461,517) who were anti-HCV-positive in 2011 (**Table 1**). After adjusting for an HCV clearance rate of 26%, the workbook method estimated 0.71% (plausibility range (%): 0.45 – 0.99) or 245,987 persons (plausibility range (persons): 155,957 to 341,522) had not cleared the virus and were considered living with chronic HCV infection in 2011.

Table 1: Estimated prevalence and the number of anti-HCV[1]-positive persons with associated plausibility ranges by key population in Canada in 2011

Population	Sources of populations (reference)	Size of population	Anti-HCV-positive prevalence (%)			Number of anti-HCV-positive persons[2]		
			Mid-Estimate	Lower bound	Upper bound	Mid-Estimate	Lower bound	Upper bound
Non-Aboriginal-non-Immigrant-non-IDU[3] 14-79 years old.	uCHMS[4]	19,855,629	0.20	0.10	0.30	39,711	19,856	59,567
male & female 0-13 years old.	Stats Canada (30), CHA[5] (32)	5,235,834	0.02[6]	0.01	0.03	1,047	524	1,571
male & female 80+ years old.	Stats Canada (30), CHA[5] (31)	1,141,489	0.16[6]	0.03	0.29	1,826	342	3,310
Foreign-born 14-79 years old.	Stats Canada (30), CIC[7] (32)	6,127,814	1.90	1.30	2.60	116,428	79,662	159,323
Aboriginal non-IDU[3]	Stats Canada (30) Remis (6)	1,223,081	0.50[6]	0.25	0.75	6,115	3,058	9,173
Former IDU[3] 14-79 years old.	uCHMS[4], Remis (6)	265,270	28.50	10.80	46.30	75,602	28,649	122,820
Current IDU[3]	CCSA[8] (33), Remis (6)	100,000	66.00[6]	63.00	69.00	66,000	63,000	69,000
Homeless non-IDU[3]	Pye (34), Laird (35), uI-Track[9]	180,969	2.25[6]	0.80	3.70	4,072	1,448	6,696
Federal inmates, including youth	Dauvergne (36), Prisonstudies.org (37), UBC[10] (38), prisonjustice.ca (39)	14,556	24.00	18.10	37.10	3,493	2,635	5,400
Provincial inmates, including youth		39,942	23.25[6]	18.50	28.00	9,287	7,389	11,184
Residents of nursing homes and long-term care hospitals	CHA[5] (31)	299,390	2.95[6]	1.40	4.50	8,832	4,191	13,473
Prevalence	Stats Canada (30)	34,483,975	0.96	0.61	1.34	n/a[11]	n/a[11]	n/a[11]
Number of anti-HCV[1]-positive[8]			n/a[11]	n/a[11]	n/a[11]	332,414	210,753	461,517

[1] HCV = Hepatitis C virus
[2] Note: Numbers may not add up due to rounding
[3] IDU= injection drug user
[4] uCHMS= unpublished custom tabulation of Canadian Health Measures Survey Cycle 1 and 2 data
[5] CHA = Canadian Healthcare Association
[6] Note: Calculated as an arithmetic average of the lower and upper bounds
[7] CIC = Citizenship and Immigration Canada
[8] CCSA = Canadian Centre on Substance Abuse
[9] uI-Track = unpublished data from I-Track (national behavioural and biological surveillance system)
[10] University of British Columbia
[11] N/A = not applicable

Discussion

By combining mid-points from both methods, between 0.64% to 0.71% of the overall Canadian population (from 220,697 to 245,987 persons) were living with chronic HCV infection in Canada in 2011. 44% of these individuals (ranging from 97,107 to 108,234) were likely undiagnosed. The estimated number of anti-HCV-positive persons was 332,414 (about 1% of the Canadian population) with a plausibility range from 210,753 to 461,517.

"Hidden" populations such as former and current injection drug users and homeless people (approximately 1% of the total Canadian population) account for almost 44% of total anti-HCV-positive persons. Foreign-born populations comprise an additional 35% of estimated anti-HCV-positive persons in Canada in 2011.

When compared with an estimated prevalence from a modelling exercise by Remis (6), which, like the back-calculation method used a Markov' multi-state disease progression model, mid-estimates of the prevalence of

anti-HCV and chronic HCV infection changed from 0.8% (6) to 1.0% and from 0.6% (6) to 0.7% respectively. This suggests that between 2007 and 2011, changes in anti-HCV and chronic HCV infection prevalence (if any) occurred in a narrow range and that the majority of anti-HCV-positive persons and those with chronic HCV infection were within a few key populations in Canada.

These prevalence estimates are comparable with estimates from an analysis of US data (24). In addition, the estimate of hidden populations accounting for 44% of total anti-HCV-positive persons is generally comparable with the estimate of 34% for comparable populations in the US (24).

Other important findings of this analysis include that the birth group of 1950-1970 currently encompasses the bulk of chronic HCV infection in Canada and that the new estimated proportion of persons with undiagnosed chronic HCV infection in 2011 was 44%. This new estimate is approximately twice as high as the one estimated by Remis for 2007 at 21% (6) and it falls between the estimates for populations which are expected to have high rates of HCV testing such as injection drug users at 20%-43% undiagnosed (*Unpublished data. I-Track: Enhanced Surveillance of Risk Behaviours among People who Inject Drugs, Phases 1-3. PHAC. 2013)* and populations expected to have lower rates of HCV testing such as hospital patients at 56% undiagnosed (25) and the weighted estimate for the Canadian household population of 14-79 years old at 69.5% undiagnosed (7). The estimate of 44% undiagnosed is also within the ranges of the proportion undiagnosed found in Canada in inmates (28-50%) (26), first time blood donors (42-58% undiagnosed) (27) and men who have sex with men (44-75% undiagnosed) *(Unpublished data M-Track: Enhanced Surveillance of Risk Behaviours among Men who Have Sex with Men, Phases 1-2 PHAC 2013*). It is also comparable with the US estimate of the proportion of undiagnosed with anti-HCV-positive status at 50.3% (28).

The two back-calculation processes used together provided an opportunity to internally calibrate the model outputs to improve the fit with the reported data on HCV cases and cases of hepatocellular carcinoma. The CNDSS data allowed for a more accurate estimate of recent trends, younger birth cohorts and the overall magnitude of the epidemic. The hepatocellular carcinoma data allowed for a more effective model of historical trends, older birth cohorts and disease progression, in a manner similar to that used by other researchers in the field (14). The use of the two data sets through an iterative process improved the overall model and made it less dependent on the limitations of any one data set. We also cross-validated the annual HCV prevalence predicted by the model with the prevalence from independent data sources, including the Canadian Health Measures Survey 2007-2011 data (7) and the reported HCV infections among healthcare patients from the CIHI Discharge Abstract Database (29). While absolute measures of HCV prevalence differed between the above data sources (possibly due to the differences in methodology and in how outcomes and geographic representation were defined) there was general agreement in the distribution of predicted/estimated HCV prevalent cases by year of report and birth cohort as well as for temporal trends.

These estimates may be affected by both data and methodological limitations such as under-reporting of outcomes; combining anti-HCV and HCV-RNA test results into a single outcome measure; and using record-level data from six Canadian jurisdictions to make inferences about HCV prevalence for all of Canada. Other limitations are due to value judgements in grading and choosing outcome measures for specific populations; the largely English-language focus of the review; not adjusting the back-calculation model for the effect of HCV treatment; and the many assumptions used in the estimation process. The methods used to develop HCV prevalence estimates described in this paper make maximum use of available data, are based on independent data sources and, when used jointly and iteratively, may compensate for individual deficiencies. Nonetheless, we anticipate the prevalence estimates will change as new and improved data on HCV prevalence in Canadian populations becomes available.

Acknowledgements

Conflict of interest

Funding

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Distribution of Hepatitis C virus genotypes among newly acquired HCV infections in British Columbia (2000-2013)

Andonov A[1*], Lin L[1], McGuinness L[2], Krajden, M[2]

[1] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg MB
[2] Public Health Microbiology and Reference Laboratory, British Columbia Centre for Disease Control, Vancouver, BC

* Corresponding author: Anton.Andonov@phac-aspc.gc.ca

Abstract

Background: Characterization of newly acquired Hepatitis C virus (HCV) infections is important in order to understand the epidemiology and spread of HCV.

Objective: To describe the Hepatitis C virus (HCV) genotype distribution of newly acquired HCV infections in the province of British Columbia for the period 2000-2013.

Methods: A descriptive cross-sectional analysis of multi-year data on HCV genotypes. Time trends for the proportion of different HCV genotypes are presented only for newly acquired (incident) HCV infections.

Results: For acute cases, genotype 1a remains the dominant HCV type in circulation (50%), followed by genotype 3a (34%). HCV genotype 1b declined, while genotype 2 was relatively stable. Phylogenetically-related clusters of HCV strains were observed indicating a common source of infection.

Conclusion: Enhanced hepatitis surveillance provides a mechanism for monitoring different HCV strains currently circulating in the community. While HCV genotype 1a continues to be the most prevalent, changes in the relative frequency of genotypes 1 and 3 have been observed. This may have important implications for the control and prevention of the infection.

Introduction

Hepatitis C virus infection (HCV) is a major cause of liver disease with a global prevalence of 2.8% affecting about 185 million people (1). In Canada HCV remains a major public health issue. A recent study from Ontario ranked HCV first among 51 pathogens based on their relative contribution to the overall infectious diseases burden (2). Hepatitis C virus is classified in the genus *Hepacivirus*, family *Flaviviridae* and is characterized by high genetic variability. According to the latest nomenclature there are seven genotypes and at least 67 subtypes (3). HCV genotypes differ in their geographical distribution based on disease endemicity and transmission route. In Europe genotype 3a became common in people who inject drugs (PWID), in some cases displacing the previously predominant genotypes 1b and 1a (4, 5). Studies in the US (6) and Canada (7) identified 1a as the predominant genotoype. An early genotyping study of chronic Hepatitis C patients in in British Columbia in the 1990s reported that the three main genotypes were genotype 1 (59.1%), genotype 2 (18.2%) and genotype 3 (22.7%) (8). Based on a re-analysis of this study using an up-to-date classification approach, genotypes 1a and 1b were almost evenly distributed (54% for HCV 1a and 46% for 1b respectively).

The infecting HCV genotypes and the viral load level are important for treatment with interferon-based therapies. For example, sofosbuvir is less effective in patients infected with genotype 3 and requires longer treatment regimens (9). HCV genotyping is also important as a laboratory tool to identify outbreaks and transmission clusters (10, 11).

Data available on HCV infection in Canada is based on mandatory reporting of cases to the Canadian Notifiable Disease Surveillance System (CNDSS) but it cannot identify incident infection rates (12). The Enhanced Hepatitis strain surveillance (EHSSS), involving the collection of additional epidemiological and laboratory information was designed to identify incident cases (13).

EHSSS was launched in Western Canada in 2000 and seven additional sites joined between 2004 and 2010 (Toronto, Hamilton, London, Thunder Bay, Montreal, Saskatoon and North West Territories).

The objective of this paper is to describe the Hepatitis C virus (HCV) genotype distribution of newly acquired HCV infections in the province of British Columbia for the period 2000-2013. The focus is on BC as it is the only province participating in the EHSSS where the entire population is covered.

Materials and methods

Study population
The BC EHSSS data were gathered by two sites: the Vancouver Coastal Health Authority (VCHA) which included the communities of Richmond, Vancouver, the North Shore, Sunshine Coast, Sea to Sky area, Powell River, Bella Bella and Bella Coola; and the BC Centre for Disease Control (BCCDC) which included VCHA and BCCDC for the rest of the province.

There were some important differences between the two sites. Between 2009 and 2011, for example, the rates for incident HCV in VCHA remained mostly unchanged; 4.42, 3.23 and 5.11 per 100,000, while the rates for the rest of BC were lower and declined further (2.15, 1.48 and 1.41 per 100,000) *(Unpublished EHSSS data)*. The incidence rate peaked in those aged 40-49 years for the VCHA population, compared to those aged 20-39 years for the rest of the province. More men than women were infected in VCHA; whereas the M:F ratio was lower in the rest of the province. Surprisingly 82% of the newly acquired HCV cases were among women aged 0-19 years. The main risk factor in the previous 12 months before diagnosis for both sites was injection drug use (IDU); 50% for VCHA and another 30% reported non-injection drug use (NIDU), while in the rest of the province, IDU was reported to be 70%. Another major risk factor identified was a history of incarceration (15%).

Data sources

Case definitions for acute HCV infection
In EHSSS, an acute HCV infection meets one of two criteria: (a) seroconversion from negative anti-HCV to positive within twelve months or (b) evidence of clinical Hepatitis C, requiring both clinical and laboratory criteria. Laboratory testing for HCV infection in the province of British Columbia is largely centralized at the BCCDC. Samples submitted for testing between January 2000 and March 2013 was used in this survey to identify anti-HCV seroconversion. From 2000-2001, the BCCDC collected information from all patients in the province with evidence of seroconversion and sent samples for genotyping to the National Microbiology Laboratory (NML). In 2002, the Vancouver Coastal Health Authority was also recruited to identify recent HCV cases based on the clinical case definition (b). The BCCDC continued to collect information and samples based on the laboratory criteria of anti-HCV seroconversion (a). Samples from incident HCV cases identified by VCHA were also referred to the NML for genotyping.

HCV genotype identification
HCV-RNA was extracted from 250 μL of sera using QIAamp viral RNA kit (QIAGEN Inc., Mississauga, Ontario, Canada) and/or the automated nucleic acid extraction system NucliSENS easyMag (bioMerieux Inc, Durham, US) and amplified by RT-PCR using primers specific for 5' non-coding region(5'-NCR), the core, E1 and NS5B genes (additional information is available upon request).

Amplicon products were gel purified prior to being Sanger sequenced. Sequence data were used to determine the HCV genotype of each viral sample and further analysis was performed to determine their phylogenetic relatedness. Genetic distances were estimated by Kimura two-parameter analysis and a phylogenetic tree was

constructed by the maximum likelihood method using MEGA 5.05 (8). Significant taxonomic relationships were obtained by bootstrap resampling analysis (200 replicates) using the maximum likelihood method.

Statistical analysis

The proportion of genotypes 1 and 3 were analyzed by the chi-square test. P values of <0.05 were considered to be significant. The robustness of phylogenetic reconstruction was evaluated by bootstrap analysis and clusters were identified with bootstrap thresholds > 90 % and a maximum genetic distance threshold of 0.05. Pairwise genetic distances of related sequences were assessed using MEGA 5.05.

Results

Between 2000 and 2013, 918 genotyped samples were analyzed; 258 from VCHA and 660 from the rest of BC. The cumulative HCV genotype distribution for the province is shown in **Figure 1.** Genotype 1a remained the dominant HCV type in circulation among the acute HCV cases (50%), followed by genotype 3a which accounted for 34% of the newly acquired HCV infections. HCV genotype 2 and genotype 1b were almost evenly distributed at 6% for 2a+2b and 5% for 1b respectively. A small proportion (3%) of cases had genotypes 1 and 3 dual infections which is consistent with these two genotypes being the two most commonly in circulation. There was no difference between the genotype pattern distribution when both geographic sites were compared.

Figure 1: HCV genotype distribution among cases of acute/recent HCV infection in British Columbia (2000-2013)
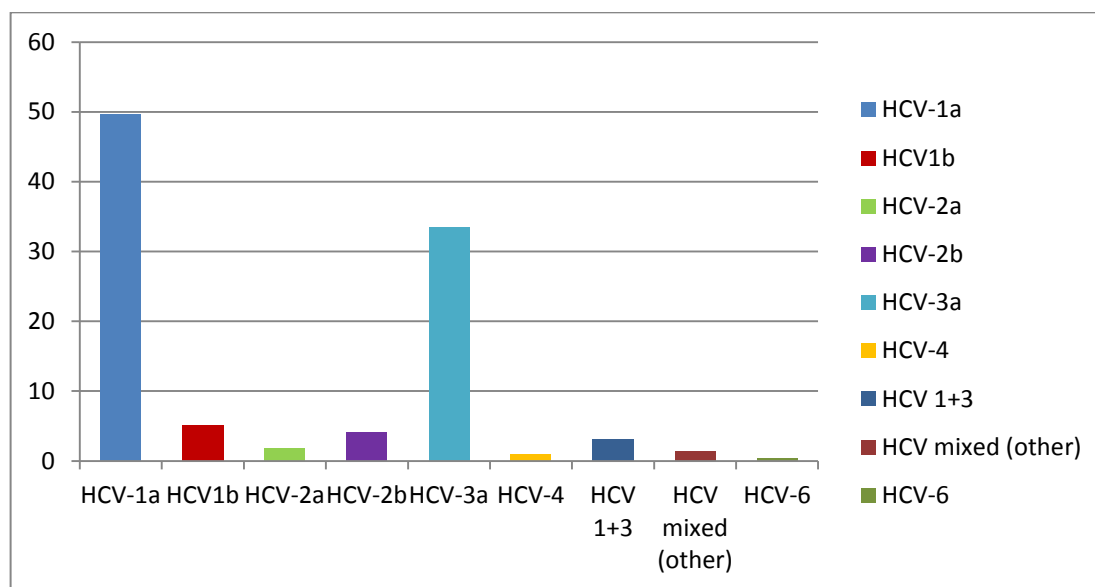
In 2000, HCV genotypes 1 and 3 were distributed equally among all acute HCV cases in the province (**Figure 2**), however during most of the following 13-year observation period, genotype 1 was significantly more common than genotype 3 (p<0.05). A notable exception is the two-year period 2007-2008 when the difference between genotype 1 (49%) and 3 (36%) was not statistically significant. Another important observation is the rise of genotype 3. When comparing the average proportion of genotype 3 for the period of 2001-2006 with that of 2007-2012, a statistically significant increase was observed at the 95% confidence level.

Figure 2: Proportion of HCV genotype 1 and 3a among cases of acute/recent HCV infection in British Columbia: 2000-2013
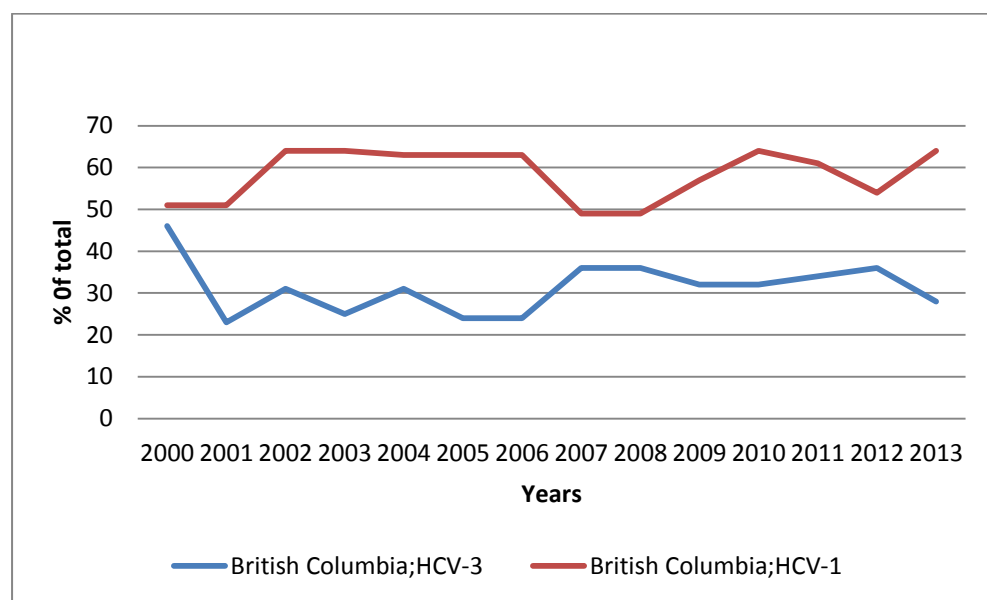
The third most common HCV genotype was two although it fluctuated from 0% to slightly over 10% throughout the observation period. Due to limited numbers, however, it is difficult to assess the trend. Comparing genotypes 1a and 1b reveals a trend toward a reduction of genotype 1b from an average of 13% for the first three years of the survey (2000-2002) to around 3% over the last ten years, while the level of 1a has increased since 2000 and remained relatively stable afterwards. The evaluation of the genotype distribution between the two sites demonstrates a similar pattern with slight year-to-year variations.

Sequence-based HCV genotyping of different genetic regions allows for accurate HCV genotyping and subtyping but also allows for phylogenetic analysis. **Figure 3** illustrates that phylogenetic analysis can lead to the identification of transmission clusters even without comprehensive epidemiological data. The circled areas identify identical or almost identical sequences that, when present in different specimens, indicate statistically plausible transmission from the same source.

Figure 3: Phylogentic tree based on Hepatitis C virus E1 gene
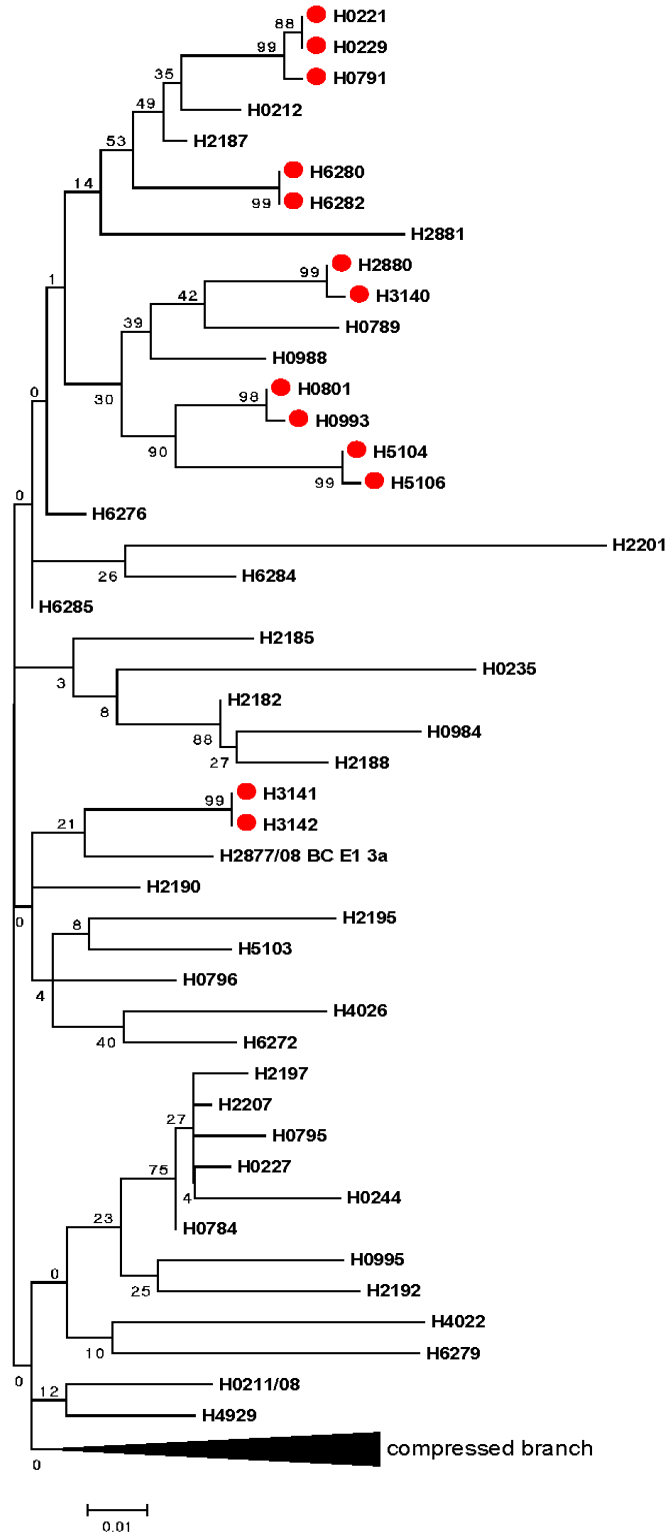
Discussion

Over the last 13 years, almost 90% of the newly acquired HCV infections in BC belong to genotypes 1 and 3. The prevalence of genotype 1a has remained stable during the last ten years, while genotype 3a has slowly increased. HCV genotype 1b has decreased significantly during the 13-year observation period. This identifies a shift in the epidemiology of HCV genotypes since the early 1990s among those acutely infected (14).

Compared with earlier studies done nationally (7) and in BC (14), HCV genotype 1a continues to be the dominant genotype in newly acquired HCV infection. In contrast, genotype 1b has declined in frequency over the last ten years. In prior decades this genotype was associated with blood product related transmission which has virtually been eliminated since 1990 as a result of blood screening.

The fact that the EHSSS was able to capture a change in the genotype pattern related to a modification of a particular risk factor (in this case blood product transfusion) highlights its capacity to track the changing epidemiology of incident HCV infections. In contrast to other cross-sectional studies reporting routine genotyping data, EHSSS monitors HCV incident trends and their association with risk activities.

In Europe, genotype 3a has been strongly associated with PWID and has been the predominant genotype during the last two decades (4, 15). In contrast, in BC genotype 1a has remained dominant although there were some years where there were similar rates of genotypes 1a and 3a (2000, 2007 and 2008). This suggests that genotype 3 transmissions may be slowly increasing over time.

The EHSSS study was able to identify clusters of related strains though phylogenetic analysis. A recent publication from the Vancouver Injection Drug Use Study (VIDUS) also identified clustering of extensive networks among PWID in Vancouver (11). In the VIDUS study, factors independently associated with clustering included age <40, HIV infection, HCV seroconversion and syringe-borrowing. In this study, most patients whose HCV strains were found in the same clusters **(Figure 3)** could not be located or refused to be interviewed, but collected epidemiologic data revealed at least two of the above mentioned risk factors. Of note, the VIDUS study also corroborates the findings on genotype distribution with 1a (48%), 1b (6%) 2a (3%), 2b (7%) and 3a (33%) (10).

An inherent limitation of any Hepatitis C surveillance system is that infections are rarely symptomatic and most cases remain undetected. This drawback is mitigated to some extent by the use of two case definitions for incident cases; the one based on seroconversion will identify asymptomatic infections especially among those whose continuous testing is driven by their own awareness of possibly being exposed to infection. In addition, not all incident cases respond favourably to requests for follow-up interviews and, as a result, risk factor information may be incomplete. The newly acquired HCV cases reported from some regions (Fraser Health Authority) are skewed due to the presence of federal and provincial correctional facilities located within that health authority. Finally, for cases with more than one risk factor, the analysis did not account for potential confounding by other possible factors.

Conclusion

The EHSSS data provides a comprehensive account of the HCV genotype distribution in acutely infected individuals in BC and underscores the value of sentinel surveillance for monitoring disease trends of public health importance. Monitoring these trends provides information on transmission dynamics and, when combined with phylogenetics, can enable the identification of transmission clusters in the absence of proper epidemiological data. This will help guide the selection and planning of direct-acting HCV antivirals and other future prevention and treatment strategies.

Conflict of interest

None

Funding

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ID News Briefs: Big Data

Ioannidis JPA, Khoury MJ. **Big data meets public health** Science 28 November 2014: Vol. 346 no. 6213 pp. 1054-1055. http://www.sciencemag.org/content/346/6213/1054.full?sid=775d7875-0e89-4618-bd28-04fb6f240c6e

The term "Big Data" refers to volumes of large, complex, linkable information. Beyond genomics and other "omic" fields, Big Data includes medical, environmental, financial, geographic, and social media information. Most of this digital information was unavailable a decade ago. This swell of data will continue to grow, stoked by sources that are currently unimaginable. Big Data stands to improve health by providing insights into the causes and outcomes of disease, better drug targets for precision medicine, and enhanced disease prediction and prevention. Moreover, citizen-scientists will increasingly use this information to promote their own health and wellness. Big Data can improve our understanding of health behaviors … and accelerate the knowledge-to-diffusion cycle… But the promise of Big Data is also accompanied by claims that "the scientific method itself is becoming obsolete" (and) "Big Error" can plague Big Data.

Pigott DM, Kraemer MU. **Enhancing infectious disease mapping with open access resources**. Euro Surveill. 2014; 19(49): pii=20989. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20989

The Spatial Ecology and Epidemiology Group (SEEG) at the University of Oxford … has collated a number of globally comprehensive and up-to-date databases from… three sources: (i) comprehensive PubMed searches, (ii) information from unpublished health surveys and entomological field studies made available by collaborators, and (iii) internet disease surveillance systems such as HealthMap….Disease and vector specific databases are then made openly available through online depositories which cover the diseases mentioned above…Future efforts include developing the Atlas of Baseline Risk Assessment for Infectious Diseases (ABRAID), an automated mapping platform which integrates the framework described above to generate spatially comprehensive, iteratively improving, evidence based maps of disease risk at the global level for a prioritised number of infectious diseases.

Iwasaki Y[1], Abe T, Wada Y, Wada K, Ikemura T.**Novel bioinformatics strategies for prediction of directional sequence changes in influenza virus genomes and for surveillance of potentially hazardous strains**. BMC Infect Dis. 2013 Aug 21; 13:386. doi: 10.1186/1471-2334-13-386. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3765179/

With the remarkable increase of microbial and viral sequence data obtained from high-throughput DNA sequencers, novel tools are needed for comprehensive analysis of the big sequence data. We have developed "Batch-Learning Self-Organizing Map (BLSOM)" which can characterize … millions of genomic sequences on one plane. .. Important issues for bioinformatics studies of influenza viruses are prediction of genomic sequence changes in the near future and surveillance of potentially hazardous strains… Millions of genomic sequences from infectious microbes and viruses have become available because of their medical and social importance, and BLSOM can characterize the big data and support efficient knowledge discovery.