Identification of Chronic Hepatitis B and Hepatitis C Co-infection in British Columbia from 1991 to 2007

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ABSTRACT

Objectives: To determine the chronic HBV/HCV co-infection identification rate in British Columbia, and examine the demographic characteristics, the order of virus identification, and trends of co-infection over time.

Methods: All newly identified cases of chronic HBV/HCV co-infection between 1991 and October 2007 were extracted from the BC integrated Public Health Information System. Differences according to sex and order of hepatitis identification were evaluated using chi-square, t-tests, and ANOVA.

Results: Of 1,815 HBV/HCV co-infected residents, 71.6% were male and the mean age at co-infection diagnosis was 40.5 years (95% CI, 40.0-41.0; range 3-85 years). Among all persons identified with HCV infection, 3.1% were identified as co-infected with HBV and 5.2% of all chronic HBV-infected were diagnosed with HCV. Annual co-infection identification rates peaked at 5.3 per 100,000 in 1996. Females were significantly younger when they were first diagnosed with a hepatitis virus ($p=0.0005$) at 35.2 years (95% CI, 34.0-36.5; range 3-79 years) than males at 37.9 years (95% CI, 37.0-39.7; range 4-85 years). The majority of co-infections consisted of concurrent diagnoses until 2003; since then, the number of co-infected cases identified with HBV first, HCV first and concurrent virus identification is similar.

Discussion: HBV/HCV co-infection identification rates have declined since the late 1990s, but appropriate testing and identification for both viruses are important. Some co-infection cases may be prevented through HBV vaccination and harm reduction activities for those with or at risk for HCV.

Key words: Hepatitis B; hepatitis C; British Columbia

La traduction du résumé se trouve à la fin de l'article.

Can J Public Health 2009;100(5):349-52.

Globally, viral hepatitis accounts for a considerable burden of morbidity and mortality. Hepatitis B (HBV) and hepatitis C (HCV) are the most common causes of chronic liver disease in different regions¹ and the majority of cirrhosis and hepatocellular carcinoma has been attributed to either virus.² In 2002, 103,000 and 53,000 deaths worldwide were estimated to be directly caused by HBV and HCV, respectively.³ There are an estimated 500,000 to 600,000 people in Canada infected with either HBV or HCV.⁴ Among individuals acutely infected with HBV, the risk of chronic HBV infection varies inversely with age; the risk among HBV-infected infants is 90% compared to 1-5% in adults.⁵ Among HCV-infected persons, 60-85% will develop chronic HCV infection.⁶ Because HBV and HCV share common risk factors and routes of transmission,^{1,7} co-infection is not uncommon.⁸ Co-infection with two or more hepatitis viruses is associated with poorer outcomes and accelerated progression of liver disease.^{1,7-9}

Although the burden of illness associated with HBV/HCV co-infection is substantial, few studies have detailed its epidemiology and none have described it in the general Canadian population. This study identifies chronic HBV/HCV co-infection among all HBV and HCV reported cases in British Columbia (BC) since 1991, probably the largest cohort from North America. In Canada, including BC, most HBV infections are identified in immigrants from endemic countries.¹⁰ Also, Vancouver continues to have the largest injection drug use problem among Canadian jurisdictions.¹¹ We determine HBV/HCV co-infections identified between 1991 and October 2007 and examine the order of virus identification, demographic characteristics at the time of co-infection identification, and observe temporal trends.

METHODS

Data source

All laboratories in BC routinely send HBV and HCV reports to the appropriate regional health authorities (HAs). Newly identified cases of HBV and HCV, who are BC residents and have not been reported elsewhere in Canada, are entered into the BC integrated Public Health Information System (iPHIS). Cases of chronic HBV and HCV reported 1991 to October 2007 were extracted from iPHIS.

Case identification and data management

Nominal data and Personal Health Number (PHN) from iPHIS were used to link reported cases of HBV and HCV to establish co-infection. For individuals entered into iPHIS with HBV or HCV more than once, the date of the first entry was used as the date of virus identification. Date of co-infection was the date when the second hepatitis virus was identified; if both HBV and HCV diagnoses were reported within 14 days, diagnoses were considered concurrent to account for laboratory testing and reporting delays. We included chronic HBV infection where the hepatitis B surface antigen (HBsAg) is present for over six months and undetermined where acute HBV infection was not identified through clinical history or laboratory tests. Cases reported as acute HBV only (i.e., not re-entered later as chronic HBV) were excluded because most acutely

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Acknowledgements: We thank Sunny Mak for his assistance.

Table 1. Demographic Characteristics of 1,815 Chronic HBV/HCV Co-infected, 31,346 Chronic HBV Mono-infected and 56,546 Chronic HCV Mono-infected British Columbia Residents between 1991 and October 2007

Characteristic	No. (%) of Cases		
	HBV/HCV Co-infection	HBV Only	HCV Only
Sex	1810	31,085	56,347
Male	1299 (71.6)	14,650 (52.9)	36,648 (65.0)
Female	511 (28.2)	16,434 (47.1)	19,693 (35.0)
Transgender*	0 (0.0)	1 (0.0)	6 (0.0)
Age at time of diagnosis (years)	1774	27,455	55,289
0-9	2 (0.1)	187 (0.7)	242 (0.4)
10-19	20 (1.1)	1632 (5.9)	827 (1.5)
20-29	236 (13.3)	5332 (19.4)	7598 (13.7)
30-39	611 (34.4)	7605 (27.7)	16,275 (29.4)
40-49	592 (33.4)	6968 (25.4)	18,835 (34.1)
50-59	221 (12.5)	3174 (11.6)	7673 (13.9)
60+	92 (5.2)	2557 (9.3)	3839 (6.9)
Residence at time of diagnosis	1815	31,346	56,546
Fraser Health Authority	529 (29.2)	9792 (31.2)	18,099 (32.0)
Interior Health Authority	223 (12.3)	535 (1.7)	8044 (14.2)
Northern Health Authority	119 (6.6)	356 (1.1)	3490 (6.2)
Vancouver Coastal Health Authority†	643 (35.4)	19,572 (62.4)	15,971 (28.2)
Vancouver Island Health Authority	301 (16.6)	1091 (3.5)	10,942 (19.4)

* Sex at birth unknown

† Includes City of Vancouver

infected adults do not develop chronic HBV. Once data linkage was performed using a computer algorithm, personal identifiers (first and last name and PHN) were deleted and anonymized data were analyzed. Data were cleaned of cases with probable data entry errors. BC guidelines recommend that testing of high-risk infants is performed 1-6 months after completion of HBV vaccine series (given at 0, 1 and 6 months); therefore HBV infections identified within seven months of birth were excluded. Babies at risk for maternal transmission of HCV should not be tested before six weeks of age; therefore cases identified within six weeks of birth were removed. To avoid bias to the sequence of virus identification, HBV and HCV diagnoses pre-1991 were excluded.

The study received ethical approval from the Behavioural Research Ethics Board at the University of British Columbia.

Statistical analyses

Data linkages and analyses were performed using SAS9.1 (Cary, NC). To determine the identification rate of HBV/HCV co-infection in BC, 2007 Population Estimates and Projections (P.E.O.P.L.E.32) were obtained from BC Stats. The mean population estimate during the observation period was used to calculate the cumulative identification rate. Data were available until October 2007; no seasonal variation was identified, therefore the annual identification rate and cases of virus identification for 2007 were pro-rated for the complete year. The order of hepatitis virus identification was compared by sex and residence using chi-square and by co-infection age using ANOVA. Sex differences were tested for age at co-infection, age at first hepatitis virus identification, and time from first virus to co-infection identification using *t*-tests. A two-sided *p*-value <0.05 was considered statistically significant. The distribution of age at co-infection identification was tested for normality using normal probability plots.

RESULTS

Between 1991 and October 2007, 1,815 BC residents were identified with HBV/HCV co-infection; the cumulative co-infection identification rate was 45.9 per 100,000 persons. The mean age at co-infection diagnosis was 40.5 years (95% CI, 40.0-41.0, SD=10.3, range 3-85 years) and 71.6% of cases were male (Table 1). Two thirds of cases resided in Vancouver Coastal Health Authority (VCHA) or Fraser Health Authority

Figure 1. Cumulative rate of HBV/HCV co-infection identification per 100,000 population and number of co-infections (#) by Health Authority in British Columbia between 1991 and October 2007

(FHA) at the time of co-infection diagnosis, with 26.6% living in the Vancouver Health Service Delivery Area (HSDA) (Figure 1). In comparison, among 55,289 BC residents identified with HCV but not HBV, the mean age of diagnosis was 41.3 years (95% CI, 41.2-41.4, SD=12.3, range 0-97 years) and 65% were male. Among the 27,455 identified cases of HBV but not HCV, the mean age at identification was 39.2 years (95% CI, 39.0-39.3, SD=14.2, range 0-95 years) and 52.9% were male.

Of all persons identified with HCV infection, 3.1% were identified as co-infected with HBV, and 5.2% of all chronic HBV-infected were diagnosed with HCV. The geographic distribution of HBV/HCV co-infection was similar to that of HCV (Table 1). The annual population rate of HBV/HCV co-infection identification decreased from 5.3 in 1996 to 1.02 per 100,000 in 2007 (Figure 2).

Overall, age-specific HBV/HCV co-infection identification rate was highest among BC residents aged 30-49 years; however, since 2005, the identification rate among individuals aged 20-29, 30-39, and

Table 2. Demographic Characteristics of HBV/HCV Co-infected British Columbia Residents Identified between 1991 and October 2007 by Order of Virus Identification

Diagnosis Order	Number (%) of Cases	Median Time Interval between HBV and HCV Identification (Days)	Sex No. (%) of Cases	
			Male	Female
HBV first	478 (26.3)	882.5	330 (69.3)	146 (30.7)
HCV first	432 (23.8)	773.0	267 (62.1)	163 (37.9)
HBV/HCV concurrently*	905 (49.9)	N/A	701 (77.7)	201 (22.3)

* This includes HBV and HCV infections diagnosed within 14 days.

Figure 2. Rate of HBV/HCV co-infection identification in British Columbia stratified by sex

Note: In 1996, persons who had received blood products between 1986 and 1990 were advised to seek HCV testing. Rates for 2007 are pro-rated to account for the fact that data were only available until October.

Figure 3. Number of HBV/HCV co-infection diagnoses annually based on sequence of virus identification in British Columbia

Note: In 1996, persons who had received blood products between 1986 and 1990 were advised to seek HCV testing. Numbers for 2007 are pro-rated to account for the fact that data were only available until October.

40-49 years was similar. Ages at infection were normally distributed. Females were significantly younger when they were diagnosed with the first hepatitis virus, mean age 35.2 years (95% CI, 34.0-36.5, SD=11.1, range 2-77 years) compared with 37.9 years (95% CI, 37.0-39.7, SD=10.5, range 2-84 years) among males ($p=0.0005$), and women were slightly younger when co-infection was identified, mean age 39.7 years (95% CI, 38.6-40.7, SD=12.0, range 3-79 years) compared with males, 40.8 years (95% CI, 40.2-41.4, SD=10.4, range 4-85 years) ($p=0.05$). Reported co-infection rates varied between HAs (Figure 1) and within HAs (data not shown).

Half (49.9%) of HBV/HCV co-infection cases consisted of concurrent identification of both viruses (Table 2). The mean age at co-infection diagnosis did not differ by order of virus identification ($p=0.72$). For those 478 (26.3%) persons where HBV was identified first, the median time to HCV identification was 882.5 days overall (887.5 days for males, 854.0 days for females). Among the 432 (23.8%) individuals identified with HCV first, the median time to HBV identification was 773.0 days overall (879.5 days for males, 615.0 days for females). Until 2003, the majority of co-infections consisted of cases diagnosed with HBV and HCV simultaneously. Since 2003, the number of co-infected cases by order of hepatitis identification (HBV first/HCV first or concurrent) was similar (Figure 3). Males had a higher rate of co-infection than females for all orders of diagnosis.

DISCUSSION

Identification of HBV and HCV depends on testing for these viruses. Half (48.5%) of all HBV reported infections in BC are male compared to two thirds (65.3%) of HCV infections. Between 1991 and October 2007, 1,815 cases of HBV/HCV co-infection were identified. The rate of HBV/HCV co-infection identification peaked during 1996-1999, following the 1996 notification of persons who had received blood products between 1986 and 1990 advising them to undergo HCV testing. Newly-identified HCV infections may be persons infected decades ago and now experiencing symptoms of liver damage/cirrhosis, or persons tested due to risk factors. Since 2003, BC Centre for Disease Control (BCCDC), where the majority of HCV testing is performed, has automatically tested HCV-reactive sera for hepatitis A virus and HBV immune status to determine vaccination eligibility. If HBV immunity is not identified, the specimen is tested for current infection. Automatic testing may account for some simultaneous identification, but does not appear to have affected the trends in simultaneous HBV/HCV identification. We used reporting within 14 days to determine concurrent identification; as date of diagnosis is used, delays in reporting will not affect the classification of order.

In BC, women have routine prenatal HBsAg testing but not HCV serology. However, a greater proportion of women than men had HBV identification secondary to HCV, suggesting follow-up of persons infected with HCV should be improved to ensure appropriate testing. Only 3.1% of persons with HCV infection were identified as co-infected with HBV; however, this underestimates past HBV infection by testing with hepatitis B core antibody (anti-HBc) as the virus is cleared in the majority of non-infant HBV infections. A study among HCV-infected northern Albertans found 44.3% had serologic evidence of past infection.¹²

HBV vaccination programs in BC may have contributed to the decline in HBV/HCV co-infection. In 1992, universal HBV vaccination for grade six students and provincially-funded HBV vaccine for injection drug users (IDUs) were introduced; HCV-reactive BC residents became eligible for HBV vaccine in 1997. An HBV vacci-

nation blitz in Vancouver's Downtown Eastside, an area home to many IDUs,¹³ was undertaken in 2000. Most chronic HBV cases in BC are immigrants; therefore, vaccination will have more effect on acute cases, but chronic HBV prevalence may decrease as endemic countries implement infant immunization programs. A universal infant HBV immunization program was introduced in BC in 2001.

The higher HBV/HCV co-infection rate among males is not surprising as 65% of all HCV cases identified in BC are male. The Provincial Laboratory of Northern Alberta also found the majority of HCV-positive individuals were male,¹² despite the fact that females were more likely to get tested.¹⁴ The majority of HCV cases diagnosed in Vancouver in 2005 and 2006 reported injection drug use,¹⁵ which is the leading cause of HCV infection.^{16,17}

Inmates of correctional facilities have a high prevalence of hepatitis. In Maryland correctional facilities, 56.1% of individuals positive for anti-HBs and anti-HBc were HCV-positive,¹⁸ and the prevalence of HCV among inmates in Ontario remand facilities is 22 times higher than that of the general population.¹⁹ HA of residence (including a correctional facility) at time of testing is reported into iPHIS. Admission to a correctional facility provides an opportunity for HCV testing; therefore some HCV infections reported in FHA may reflect persons tested within correctional facilities located there.

There are several limitations of the data. With administrative data based upon laboratory diagnosis of a chronic sometimes asymptomatic infection, the time of infection and incidence or prevalence of HBV/HCV co-infection cannot be determined. Some persons identified as HCV-reactive may have cleared the virus; others were infected years prior to testing, while others may be recent sero-conversions. Although most HCV testing is performed at the BCCDC provincial laboratory, allowing quality control, HBV testing is performed at hospitals and private laboratories throughout the province. Access to laboratory results from the whole province, including previous negative results, would improve incidence and prevalence data. HCV became a reportable disease in BC in 1992, resulting in the underestimation of HBV/HCV co-infection values for 1991 and 1992. The identification rate of HBV/HCV co-infection is likely an underestimate, especially given the asymptomatic nature of the infection and the need to present for testing.

Despite limitations, the ability to estimate the current and projected burden of HBV/HCV co-infection in BC is valuable so that HBV and HCV prevention and care programs can be improved and evaluated. Although the number of co-infections identified in BC has been declining since 2001, more effort could be made to address individuals at risk for co-infection and at-risk persons should be tested for the second virus. Some cases of co-infection could be prevented through HBV vaccination; automatic testing of HCV-positive sera identifies individuals eligible for immunization. Harm reduction activities should be accessible for those with or at risk for infection with blood-borne pathogens.

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Received: January 8, 2009

Accepted: June 24, 2009

RÉSUMÉ

Objectifs : Déterminer le taux de signalement des coinfections chroniques par le VHB et le VHC en Colombie-Britannique et en examiner le profil démographique, l'ordre dans lequel les virus sont signalés et les tendances des coinfections au fil du temps.

Méthode : Nous avons extrait du Système intégré d'information sur la santé publique de la Colombie-Britannique tous les cas nouvellement signalés de coinfections chroniques par le VHB et le VHC survenus entre 1991 et octobre 2007. Les écarts selon le sexe et l'ordre de signalement de l'hépatite ont été évalués à l'aide d'analyses du khi-carré, de tests t et d'analyses de la variance.

Résultats : Sur les 1 815 résidents coinfectés par le VHB et le VHC, 71,6 % étaient des hommes, et l'âge moyen lors du diagnostic de coinfection était de 40,5 ans (IC de 95 %, 40,0-41,0; intervalle de 3 à 85 ans). Parmi les sujets infectés par le VHC, 3,1 % étaient coinfectés par le VHB; 5,2 % des sujets présentant une infection chronique par le VHB avaient reçu un diagnostic d'infection par le VHC. Le taux de signalement annuel des coinfections a atteint un sommet de 5,3 p. 100 000 en 1996. À 35,2 ans, les femmes étaient significativement plus jeunes lors du premier diagnostic d'un virus de l'hépatite ($p=0,0005$) (IC de 95 %, 34,0-36,5; intervalle de 3 à 79 ans) que les hommes, à 37,9 ans (IC de 95 %, 37,0-39,7; intervalle de 4 à 85 ans). Jusqu'en 2003, dans la majorité des coinfections, les deux virus étaient diagnostiqués en même temps; depuis, le nombre de cas où le VHB est signalé en premier, le VHC en premier ou les deux virus en même temps est semblable.

Discussion : Les taux de signalement des coinfections par le VHB et le VHC diminuent depuis la fin des années 1990, mais il demeure important de dépister et de signaler convenablement les deux virus. Chez les sujets exposés ou infectés par le VHC, certains cas de coinfections peuvent être prévenus par le vaccin contre le VHB et par des mesures de réduction des méfaits.

Mots clés : hépatite B; hépatite C; Colombie-Britannique