SEROPREVALENCE OF HEPATITIS B IN PREVIOUSLY UNDIAGNOSED PATIENTS: A COMMUNITY SCREENING STUDY

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ABSTRACT

BACKGROUND: Forty percent of hepatitis B carriers have no knowledge of their diagnosis. A prior study in British Columbia suggested high rates of hepatitis B among immigrants. The authors undertook a large-scale screening study to validate these rates. METHODS: Attendees at Asian health fairs without knowledge of their hepatitis B status participated. They completed a questionnaire, and blood was drawn for HBV serologies. Active HBV was defined as HBV surface antigen positive. RESULTS: Of 2,726 patients, 1,704 (62.5%) were female and 1,022 (37.5%) male. Mean age was 62.7 (SD 22.1) years, and mean time of residing in Canada was 27.5 (SD 15.3) years. Most patients originated from China (1,042 patients, 38.2%) and Hong Kong (871, 31.2%). Fifty-six patients tested positive (seroprevalence rate 2.05%, 95% CI 1.52%–2.59%). Most seropositive patients were from China (28 patients, 50.0%). Mean time of residence in Canada for seropositive patients (23.8 [SD 2.1] y) was less than seronegative patients (27.6 [SD 0.3] y) (p = 0.06). There was a trend towards association of seropositivity with time of residence in Canada (OR 0.98, 95% CI 0.96–1.00, p = 0.09). 8 (14.3%) seropositive patients did not have family doctors, compared with 128 (4.8%) seronegative patients. Lack of a family doctor was strongly associated with seropositivity (OR 3.31, 95% CI 1.32–7.25, χ² = 10.42, p = 0.001). INTERPRETATION: The authors have shown that high risk immigrant populations may have seroprevalence rates as high as 2,700 per 100,000. Lack of a family physician was associated with seropositivity. These results should be used to design improved outreach programs.

KEYWORDS: hepatitis B; HBV; seroprevalence

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Dedication: We would like to dedicate this manuscript to the memory of Dr Francis Ho. Dr Ho passed away prior to submission of this manuscript. Dr Ho was a family physician of over 50 years duration, who served his community tirelessly. Dr Ho founded and served as Co-Chair of the Hep Beware project. He is
Undiagnosed hepatitis B seroprevalence

INTRODUCTION
Hepatitis B virus (HBV) in the immigrant population of Canada is a major public health concern. Up to 20.6% of Canadians were born outside the country, and this number is projected to double over the next two decades. China and the Philippines make up a substantial portion of these immigrants, with the majority choosing to settle in the Vancouver metropolitan area (1). These countries are known to be endemic for hepatitis B (2). It is estimated that only 30.0% of newborns in China had been vaccinated in 1992, and it was not until 2012 when 99.0% of all newborns were vaccinated. As such, there are still many individuals in China that are HBV carriers, with population seroprevalence rates up to 10.0% (3). Similar issues in the Philippines have resulted in seroprevalence rates as high as 16.0% in the adult population over the age of 20 (4). If left untreated, 20.0 to 30.0% of carriers will develop cirrhosis or hepatocellular carcinoma (HCC). It is estimated that there are 500,000 to 600,000 worldwide deaths per year directly attributable to HBV infection.

Overall seroprevalence of current HBV infection in Canada varies depending on population, and there is little data regarding HBV carrier rate in Canadian immigrants (5). Pre-vaccination era data screening 14,347 first generation immigrants to Canada showed 11.6% HBsAg positivity (6). Ideally all immigrants accepted to Canada with transmissible infection risk would be tested for hepatitis. However, only tuberculosis and HIV testing are mandatory (7). For chronic hepatitis, testing to identify carriers is at the discretion of the examining physician. Although guidelines to screen potential carriers exist, these are not always followed. Immigrant applicants may also not disclose health issues to physicians for fear of discrimination or to forgo personal costs associated with testing (8). Lastly, immigrants may have difficulty finding a family physician, leading to lack of follow-up and development of complications related to underlying hepatitis (9).

Given the high rate of immigrants from countries endemic for HBV, and the lack of a thorough screening program without longitudinal follow-up, it is likely that a substantial unknown HBV burden exists in the greater Vancouver area. A survey study from 2007 suggested the carrier rate amongst immigrants from China to be 6.0%, although carrier status was self-reported and up to 43% respondents were never tested (10). CDC data suggests that 1 in 12 Asian Americans have chronic HBV and over 50.0% may not be aware of their carrier status (11). Asian population screening in Southern California of 3,136 adult volunteers showed seroprevalence of 8.9%, with 65.4% not aware that they were carriers (12). A panel review conducted in 2012 by physicians prominently involved in treatment of hepatitis in greater Vancouver suggested that only 2,000 patients were being treated with a nucleotide analogue, a far below the expectation (unpublished data).

Taken together, this data suggests that a substantial number of HBV carriers in the Greater Vancouver area have not been identified and are not receiving proper follow up or therapy. The local burden of HBV related complications is substantial—for example, internal data suggests that Asian patients account for more than 50.0% of all HCC cases at the BC Cancer Agency. To identify carriers, and potentially reduce disease burden, the authors designed and conducted a large, prospective, community-based serologic screening study of patients who had no prior knowledge of their HBV status.

METHODS
Study design
The aim of this study was to estimate the seroprevalence of undiagnosed HBV in patients unaware of their carrier status in the greater Vancouver area. A central steering committee consisting of board members from the Canadian Liver Foundation (CLF) and expert physicians handled overall study design, ethics, and fundraising. Due to the scope of the project, a study coordinator handled logistics and overall project management. The study was approved by the University of British
Columbia (UBC) clinical research ethics board. All study sites consented to the use of their property for setup of mobile booths. Funds for this project were provided by the CLF and private donors. Data included in this study were collected prospectively from January 17, 2018 to September 2, 2019.

Study sites and mobile booths
Mobile booths were set up at various locations across the lower mainland where there was a high volume of foot traffic flow. Advertising campaigns announcing the date, time, and location of booths were carried out in advance to maximize participation. Locations included Asian-predominant shopping malls, community centres, large-scale community events such as health fairs, and large Catholic churches. Booths were staffed by volunteers and at least one certified technician and registered nurse for collection of blood samples. Standard lab needles and tubes were used for blood draws. Used needles were disposed of in a sharps box according to standard health care practice. A large screen was used to shield the participant having blood drawn.

Participants and consent
Participants of Asian background over the age of 18 who approached the booth and consented to the study were recruited for serologic testing. Only those participants who had no prior knowledge of their HBV status were recruited. Participation was completely voluntary. Study coordinators and volunteers explain the purpose and rationale of the study to participants, and all participants were required to complete consent forms. Patients consented to the recording of personal information, and to having one tube of blood (approximately 5 mL) drawn. The consent forms clearly described that the study was funded by a non-profit organization (CLF), was not connected with any government or pharmaceutical agencies, and that test results would not be disclosed to anybody aside from participants and, if requested, their family physician.

Data recording
Information recorded from participants included general demographics, place of birth, country of origin, years in Canada, and details regarding their family physician (if any). Data was entered into a program at the point of care and immediately transmitted to a server computer at a fixed location in real-time. The storage program was encrypted and password protected. Information sharing between the local computer and the server was done by a private Wi-Fi connection.

Laboratory analysis
Serum samples were transported to St. Paul’s hospital UBC virology laboratory. HBsAg determination was done with standard immunoassay under the supervision of medical microbiologists. HBsAb, and HBcAb (IgM and IgG) were done as part of the standard hepatitis B serological panel but not available for data analysis. Further testing such as HBV viral load was done only if initial screening was positive. Test characteristics of the HBsAg such as sensitivity and specificity are in line with literature values. (13,14) The virology lab also stored serum for further reference and retesting if required.

Follow-up of results
All consenting participants were provided an information sheet indicating the date of testing as well as a brief description of the study. Participants were informed via telephone and mail of test results. For those who tested positive, additional educational materials about HBV were provided. Those who tested positive were also given guidance about providing test results to their family physician for follow-up and disease evaluation.

Statistical analysis
Data were extracted from the central server and statistical analysis was carried out using Stata. Sample means were calculated for continuous variables, and categorical variables were tallied. Two tailed $t$-test was used to compare continuous variables, and two tailed $z$-test was used to compare proportions of categorical variables. Case control odds ratios for seropositive status based on presence or absence of having a family doctor were calculated using chi-squared test. Logistic regression was performed using seropositive status as the outcome of interest, with age and time of residence in Canada as independent variables. Tests were considered significant with a $p$-value less than 0.05.

RESULTS

Overall cohort
A total of 2,753 patients consented to the study and were recruited for blood draws (Figure 1). Of these, 26 patients were excluded due to incomplete data
entry or technical errors leading to aberrant test results. This left a total of 2,726 patients included for analysis (Table 1). Of these, 1,704 (62.5%) were female and 1,022 (37.5%) were male. Mean age was 62.7 [SD 22.1] years and was similar between females (62.3 y) and males (63.3 y). Mean time of residing in Canada was 27.5 [SD 15.3] years, also similar between females (27.0 y) and males (28.5 years). Of the total, 2,590 (95.0%) had regular family doctors. Most patients originated from China (1,042 patients, 38.2%) and Hong Kong (871, 31.2%) (Figure 2). Other highly represented countries included the Philippines (342, 12.5%), Taiwan (100, 3.7%), Canada (84, 3.1%) and Vietnam (74, 2.7%).

City of residence was most frequently Vancouver (1,372, 50.6%), Richmond (518, 19.1%), Burnaby (507, 18.7%), Surrey (120, 4.4%), Coquitlam (80, 3.0%), and New Westminster (71, 2.6%).

Seropositivity rate and associated factors
In total, 56 patients tested positive for HBV, giving an overall seroprevalence rate of 2.05% (95% CI 1.52%–2.59%). Of seropositive patients, 34 were female and 22 were male. Gender did not differ between seropositive and seronegative patients (p = 0.78). Mean age did not differ between seropositive patients (60.4 [SD 1.7] y) and seronegative patients (62.8 [SD 0.4] y) (p = 0.43). Mean time of residence in Canada for seropositive patients (23.8 [SD 2.1] y) was less than seronegative patients (27.6 [SD 0.3] y) and trended towards but did not reach significance (0.06). Logistic regression using seropositivity as the binary endpoint also revealed no association with age (OR 1.00, 95% CI 0.98–1.02, p = 0.806) and a trend towards association with time of residence in Canada (OR 0.98, 95% CI 0.96–1.00, p = 0.09). Of the 56 seropositive patients, 8 (14.3%) did not have family doctors, compared with 128 (4.8%) of the seronegative patients. Lack of a family doctor was strongly associated with seropositive status (OR 3.31, 95% CI 1.32–7.25, \( \chi^2 = 10.42, p = 0.001 \)). Comparison of the entire cohort, seronegative and seropositive patients is presented in Table 1.

Geographic features of seropositive patients
Of the 56 seropositive patients, most were from China (28 patients, 50.0%), Hong Kong (11 patients, 19.6%) or the Philippines (8, 14.3%) (Figure 3). This finding corresponded with seropositivity rates of 2.7% for China, 1.3% for Hong Kong, and 2.5% for the Philippines. Most frequent
cities of residence were Vancouver (33 patients, 58.9%), Richmond (10 patients, 17.9%) and Burnaby (9 patients, 16.1%). Comparison of country of origin by seropositive status revealed that patients from Burma ($p = 0.01$), Italy ($p = 0.06$), and Ivory Coast ($p < 0.01$) had a higher rate of seropositivity than would be expected based on immigration numbers, although overall number of patients from these countries were low. This trend was also observed in patients from China, although significance was not reached ($p = 0.07$). Comparison of city of residence by seropositive status revealed no differences.

**DISCUSSION**

To the authors’ knowledge, this study is the largest prospective, community-based HBV seroprevalence study ever carried out in Canada and, thus, likely reflects true prevalence rates in our population of interest. This study is also the only study directly assessing seroprevalence via lab testing, rather than surveys. British Columbia (BC) has
been estimated to have the highest chronic HBV rate in Canada, at 23.4 per 100,000 (15). The authors have demonstrated that this rate may be driven by populations such as immigrants, who exceed the overall BC rate by more than 10-fold (eg, 2,700 per 100,000 for patients from China). This data is concerning, as prior modelling data have shown that immigrants with chronic HBV lose an average of 4.6 life years relative to those not infected, likely due to cirrhosis or HCC (16,17). It is imperative that systemic factors contributing to such rates be addressed to reduce disease burden.

Joint 2018 guidelines from the Canadian Association for the Study of the Liver (CASL) and Association of Medical Microbiology and Infectious Disease Canada (AMMI) recommend that individuals at high risk of chronic hepatitis be screened (15). Screening serves to identify asymptomatic individuals in order to reduce transmission, monitor liver function, survey for HCC, and provide antiviral therapy when indicated. High risk individuals include those who were born or resided in an endemic area or those with household contacts known to be HBV carriers, particularly children of HBV-positive mothers. Screening such individuals prevents HBV-related deaths to a certain extent and is likely moderately cost-effective (18,19).

Despite these recommendations and associated benefits, many immigrants and their family members forego screening, both at time of immigration and at later time points. This lack of screening may, in part, be due to personal and socio-cultural factors such as education about the disease. Indeed, although many communities in BC are aware of HBV, their knowledge of its natural history and complications are poor, thus limiting their motivation to seek out screening (20,21). Stigma related to HBV infection also results in lower screening rates among immigrants (8). Acculturation and language barriers after successful immigration also likely contribute (9). Community-based efforts to increase knowledge and decrease stigma have promise in this regard (9).

Immigrants may face systemic issues that hinder screening such as reduction in clinician practice sizes and reduced number of physician-patient interactions (22). Immigrants also face increased barriers including limited knowledge of the health care system and inability to navigate the system due to language barriers (9). Prior analyses have demonstrated that the lack of a family physician in Canada leads to decreased rates of HBV screening (23). Although most patients in our study did indeed have access to a family physician, lack of a family physician was associated with higher rate of chronic HBV infection. Although this finding is not surprising, it is important to acknowledge the direct relationship between barriers to health care access and increased infection rate. Resources and strategies to increase access should be pursued.

It is very important to note that despite effective screening tests and vaccines, the overall health care burden of HBV in Canada remains high (24). Universal testing for viral hepatitis is not mandated upon immigration to Canada, even in those immigrating from endemic countries (7). Rather, current Canadian immigration policy dictates that in the absence of known liver disease or diagnosed risk factors (eg, HIV tuberculosis), evidence of liver disease be identified on history and physical examination, prior to screening. It is possible that certain migrants may not disclose a possible history of hepatitis, due to fear that it may prevent immigration, although a positive hepatitis test does not meet requirements for inadmissibility to Canada. Also very importantly, Canada does not yet have a universal birth vaccination program for HBV as proposed by the World Health Organization (25). As such, the onus of testing is not just on the primary care workforce themselves. A national, comprehensive unbiased and non-discriminative HBV screening and immunization program would be very beneficial to our patients and health care system as a whole.

LIMITATIONS

The main limitation of this study would be the possibility of volunteer bias, a type of selection bias. It is possible that those patients with greater underlying knowledge of HBV may have preferentially sought out testing at the booths.

CONCLUSION

In summary, the authors have conducted the largest prospective, community-based HBV seroprevalence study ever carried out in Canada, and the only study directly assessing seroprevalence in BC via direct serologic testing. The authors have shown that high risk populations, such as immigrants from China, may have seroprevalence rates as high as 2,700 per 100,000. The lack of a family physician was associated with seropositive status. The authors hope that this data can be used to design targeted educational
and screening efforts to identify unknown carriers, ultimately leading to therapy and a decrease in HBV related morbidity and mortality.

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