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Serological and molecular epidemiological outcomes after two decades of universal infant hepatitis B virus (HBV) vaccination in Nunavut, Canada

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ABSTRACT

Chronic hepatitis B virus (HBV) infection within the Canadian Arctic is considered endemic (>2% prevalence). Within the Arctic region of Nunavut, a vaccination program targeted at newborn infants was initiated approximately 20 years ago, along with interim grade school catch-up programs, with the result that individuals born after 1980 are presumed vaccinated. This study investigates the effectiveness of these programs and is the first seroepidemiological survey to determine HBV prevalence in Nunavut in the post-vaccination era. Anonymized serum specimens scheduled for destruction following medical testing were collected between April 2013 and April 2014 from individuals granting consent. Specimens were tested for HBV antibodies, surface antigen (HBsAg), and HBV DNA to perform molecular characterization. Four thousand eight hundred and two specimens (13% of the population) were collected, with a resulting median age of 29 years (range 1 week to 93 years). The prevalence of antibody to the HBV core protein was 9.4%; however, a 10-fold decrease in the rate of HBV exposure was noted among those born after 1980 compared to those born before (1.8% vs. 19.8%, $p < 0.01$). HBsAg positivity was primarily documented in individuals born before 1980 (2.5%), although cases still occurred among the vaccine age cohort (0.3%). HBV subgenotype B5 (previously B6) was the most prevalent genotype observed (81.8%) indicating persistence of locally acquired infection. Vaccine-based antibody as the sole serological marker was evident in the vaccine age cohort, although the rate of decay with increasing age was much greater than predicted (less than 10% in those aged 5–19 years). Nearly two decades after the advent of HBV vaccination in Nunavut, HBV prevalence has decreased to 1.2%, indicating non-endemic prevalence. However, the persistence of infection and a lower than expected prevalence of vaccine-based immunity in the vaccine age cohort will require further investigation to understand the causes and consequences.

1. Introduction

The World Health Organization (WHO) recommends that all infants receive hepatitis B virus (HBV) vaccination at birth to prevent the development of chronic infection [1]. Universal newborn HBV vaccination has been shown to be highly cost effective and more feasible than only targeting at-risk populations [2], providing savings in medical care costs and lost productivity [3] based on a recent systematic review of the economic impacts of HBV vaccination [4]. HBV immunization programs in Canada, initiated in the 1990's, vaccinate infants with hexavalent vaccine or children aged 10–14 years old with monovalent vaccine [5]. Vaccination with hexavalent preparations starting at 2 months of age have been shown to elicit a robust response in Canadian infants [6], while adolescent vaccination programs have resulted in decreased HBV incidence rates over time among Canadian-born children [7–9]. The Arctic regions of Canada, including the Northwest

Abbreviations: anti-HBc, antibody to the HBV core protein; anti-HBs, antibody to the HBV surface protein; HBsAg, HBV surface protein, HBV, hepatitis B virus; GMT, geometric mean titer; WHO, World Health Organization.

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Territories and Nunavut, employ the recommended immunization schedule targeting neonatal infants at birth, due to historically observed endemic HBV infection (>2%) [10–12] with some regions of Nunavut having prevalence rates upwards of 12% [13,14]. The Nunavut HBV neonatal vaccination program began in 1995, with a concomitant catch-up program targeting grade 4 students, proceeding for approximately 10 years. Subsequently, a high school catch up program began in 1998 to target non-immunized high school students missed by the grade 4 program, running for approximately 3 years. Thus, it is expected that individuals born in Nunavut ≥1980 are vaccinated against HBV. The objectives of this study were to document the prevalence of antibody to the HBV surface protein (anti-HBs) in individuals born after 1980 to determine the vaccine-based immune rate and the current HBV exposure and chronic infection rates in the tested population, thus constituting the first seroepidemiological study investigating HBV prevalence and the level of protection against infection in Nunavut in the post-vaccination era.

2. Material and methods

2.1. Study design and sampling method

A cross-sectional survey was carried out in the Kivalliq and Qikiqtaaluk regions of Nunavut from April 2013 to April 2014 with the objective of collecting approximately 5000 samples. Convenience sampling of serum samples scheduled for destruction following unrelated medical testing was performed in all health care facilities in the two regions. Thus, eligible participants were those that had blood taken for an unrelated medical test, were informed of the study and had granted oral consent for their serum to be anonymously tested for HBV. Consented serum specimens in gel separator blood collection tubes (BD Diagnostics, Franklin Lakes, NJ) were stored at 4 °C for approximately 1–2 weeks, at regional medical testing laboratories in Iqaluit and Rankin Inlet, prior to shipment to the National Microbiology Laboratory (Winnipeg, MB, Canada) at 4 °C for HBV testing. Identifiers were removed from sample tubes, with the exception of birth date, gender and the community where the sample was collected. To reduce sample bias and ensure that only serum specimens from unique individuals were tested, subsequent specimens having the same three identifiers as a previously received specimen were assumed to originate from the same patient and were destroyed without testing.

2.2. Ethical approval

Ethical approval for this study protocol was obtained from the Research Ethics Boards of Health Canada and Public Health Agency of Canada and the University of Manitoba, and the research was registered with the Nunavut Research Institute. Nunavut communities were provided with information regarding the study through public service announcements and notices posted in four languages (English, French, Innuinnaqtun, and Inuktitut) in health centers or phlebotomy rooms. In accordance with ethical approval, all individuals were given the option to deny use of their blood sample through an informed oral opt-out procedure at the time of blood draw for unrelated medical testing.

2.3. Study population

The age of individuals from which specimens were collected was intended to represent the age distribution of the Nunavut population, which is the youngest population of any province or territory in Canada [15]. The estimated number of samples to be collected for each 10 year age range was established using the 2011 Nunavut census [16]. Once the quota for each age group was met, specimens from that age range were no longer tested throughout the year. As one of the study objectives was to document the prevalence of anti-HBs in individuals presumed to have been vaccinated starting at birth, power calculations were performed to determine the sample population size required to estimate the level of population protection based on the WHO recommendation that at least 80% of all infants in a population should have 3 doses of HBV vaccine [17]. Normally, estimated coverage is based on vaccination records; however, a surrogate measure of the Nunavut population is the prevalence of anti-HBs, as the sole serological marker, in age groups presumed to have been vaccinated. These calculations indicated that at least 810 samples (power = 99.9%) should be tested for anti-HBs antibody from individuals born after 1995 in order to determine a difference of at least 5% in vaccination coverage in the study population vs. the WHO-recommended level of 80%.

Results were analyzed by age cohort to correspond to the HBV vaccination programs offered in Nunavut since 1995. Therefore, samples from individuals born between 1995-01-01 and the period of the study (04-2013 to 04-2014) were considered to be within the universal infant HBV vaccination cohort, with individuals aged approximately 0–18 years old. Samples from individuals born between 1985-01-01 and 1994-12-31 were considered to be within the grade 4 catch-up HBV vaccination cohort, with individuals aged approximately 18–19 to 28 years old. Samples from individuals born between 1980-01-01 and 1984-12-31 were considered to be within the high school catch-up HBV vaccination cohort, with individuals aged approximately 28–29 to 33 years old. Samples from individuals born prior to 1980 were considered as within the non-vaccinated cohort.

2.4. Serological testing

All specimens were initially tested for anti-HBs, followed by antibody to the core (anti-HBc) protein. Specimens that were positive for anti-HBc antibody were further tested for the presence of surface antigen (HBsAg). All serological testing was performed using the Roche cobas e411 immunoassay analyzer (Roche Diagnostics, Laval, QC, Canada). Samples having an anti-HBs value ≥10 mIU/mL were considered to be positive. Anti-HBs quantities were converted to geometric mean titer (GMT), whether seropositive (>1000 mIU/mL equivalent to $\log_{10}$ 3) or seronegative (2.0–9.99 mIU/mL equivalent to $\log_{10}$ titer of 0.30–0.99) within the vaccination cohorts by each year of age. Anti-HBc antibody positive specimens with results close to the cutoff index (=1.0) were repeat tested, and HBsAg confirmatory testing was performed with all HBsAg positive/HBV DNA negative samples.

2.5. HBV DNA testing and characterization

Samples (150 μL) testing positive for HBsAg were extracted for HBV DNA [18] and amplified by PCR using primers targeting the HBsAg, precore/core genomic regions and full genome, as described previously [19,20] for sequence analysis. Phylogenetic investigation of HBV genotype was performed using maximum likelihood analysis by the DIVEIN web service [21] and substitution models chosen according to model estimation analysis of the alignment (MEGA6 [22]). HBV DNA viral load measurements of DNA positive specimens were performed using the RealStar HBV PCR 1.0 kit (Altona Diagnostics, Toronto, ON, Canada) according to the manufacturer's instructions.

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