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Sub-optimal protection against past hepatitis B virus infection where subtype mismatch exists between vaccine and circulating viral genotype in northern Australia

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ABSTRACT

Background: In Australia's Northern Territory, the hepatitis B virus (HBV) subgenotype A2 (subtype *adw2*) vaccine was introduced in 1988 for Indigenous infants. Subsequently, the circulating viral genotype has been identified as subgenotype C4 (subtype *ayw3*). We assessed HBV vaccine effectiveness (VE) in light of this subtype mismatch.

Methods: Participants of the Aboriginal Birth Cohort (ABC) study were recruited at birth (1987–1990), with HBV serology obtained at follow-up waves 3 (2005–2007) and 4 (2013–2015). Participants were immune if HBV surface antibody levels exceeded 10 IU/L. We determined the VE against any HBV infection (anti-HBc$^+$) and against chronic infection (HBsAg$^+$ or HBV DNA$^+$), comparing non-vaccinated participants with those fulfilling United States Centers for Disease Control and Prevention (CDC) criteria for full HBV immunisation.

Results: Of 686 participants in the ABC study, we obtained HBV serology from 388 at wave 4. 181 participants were immune to HBV and 97 had evidence of any infection. Seven participants were chronically infected, of whom five had received three vaccine doses, and anti-HBc seroconversion had occurred subsequent to the three vaccine doses for two of these seven participants. Comparing the 107 participants who had been vaccinated in accordance with CDC recommendations and 127 who had not been vaccinated, VE against any infection was 67% (95%CI, 43–104%). The odds of being anti-HBc$^+$ was 87% lower in participants raised in urban settings compared to those born into families from remote areas (OR, 0.1; 95%CI, 0.03–0.4).

Conclusions: In a setting where there exists a subtype mismatch between vaccine and circulating genotype, the vaccine was largely effective in preventing chronic infection but sub-optimal against any infection. The implications of a high prevalence of anti-HBc seropositivity in this population are unclear and require further study. The fact that anti-HBc seropositivity was strongly associated with remote dwelling suggests ongoing viral exposure in remote settings.

1. Introduction

Hepatitis B virus (HBV) is a global health problem with over two billion people affected and nearly 260 million chronically infected [1,2]. Morbidity and mortality are high, owing to increased lifetime risk of cirrhosis and hepatocellular carcinoma [3,4]. HBV surface antigen (HBsAg) was first isolated from an Indigenous Australian

Abbreviations: ABC, aboriginal birth cohort; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; CDC, United States center for disease control and prevention; 95%CI, 95% confidence interval; RDH, Royal Darwin Hospital; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IQR, interquartile range; OR, odds ratio; VE, vaccine effectiveness.

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in 1965, and called the 'Australia antigen' [5]. Although Australia as a whole is of low endemicity (1%), the burden of HBV remains significant among Indigenous people, with 2.2–4.0% chronically infected nationally [6,7], and prevalence up to 10% in remote communities [8,9]. Furthermore, Indigenous people from northern Australia are exclusively infected with the C4 genotype (subtype *ayw3*) [10].

The original HBV vaccine became available in the early 1980s and comprised HBsAg extracted from plasma of HBV-infected donors (genotype A2; subtype *adw2*) [11]. Taiwan and Alaska pioneered infant HBV vaccination programmes in 1984, and since then, both have recorded decreased prevalence of chronic infection and incidence of hepatocellular carcinoma [12–14]. Australia's Northern Territory, where approximately 30% of the population is Indigenous, began an HBV vaccination campaign for Indigenous children in 1988, and all children in 1990.

The Aboriginal Birth Cohort (ABC) study was initiated in 1987 to prospectively follow 686 infants born to Indigenous mothers at Royal Darwin Hospital (RDH); from a sample of 1238 babies born between January 1987 and March 1990 [15]. RDH serves a catchment area of approximately 400,000 km^2, encompassing Darwin, and rural and remote communities across the northern parts of the Northern Territory (the 'Top End'). During the recruitment phase, 90% of pregnant Indigenous women from the Top End delivered their babies at RDH [16]. Previous follow-ups of the ABC occurred at mean participant ages of 11 years (1998–2002; wave 2) [17] and 18 years (2005–2007; wave 3) [18]. Here we report the analyses of HBV serology collected between 2013 and 2015 (wave 4). Our aims were to determine vaccine effectiveness (VE) and define predictors of long-term immunity.

2. Methods

2.1. Data collection

Participants were contacted and provided blood for HBV serology. HBV vaccination histories were obtained from the Centre for Disease Control Immunisation Register, RDH and remote health clinics. Current United States Centers for Disease Control and Prevention (CDC) HBV immunisation guidelines recommend a birth dose of the vaccine. However, the ABC study began during an era when it was acceptable for this initial dose to be given up until 7 days of life [19,20]. Therefore we considered participants adherent to the CDC immunisation schedule if they received: the first dose within seven days of birth; the second dose before 3 months of age, at least 4 weeks after the initial dose; and third dose between 24 weeks and 18 months of age, at least 16 weeks after the initial dose and at least 8 weeks after the second dose [21]. We recorded whether participants had lived in urban or remote settings, and the communities their families were from. Urban locations included Darwin and townships up to 100 km away, as well as Katherine (300 km away) and Kununurra (800 km away). All other locations were considered remote.

2.2. Laboratory methods for serology

Wave 3 serology was performed at the Institute for Clinical Pathology and Microbiological Research at Westmead Hospital, Sydney, Australia and analysed on the Abbott Architect Automated Analyser i2000SR (Abbott Diagnostics, North Ryde, Australia). Wave 4 serology and viral loads were analysed at the Victorian Infectious Diseases Reference Laboratory at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia. The qualitative anti-HBV core antibody (anti-HBc) assay was a two-step competitive chemiluminescence immunoassay (Roche Diagnostics, Melbourne, Australia) where an "index value" <0.9 is considered positive and an index value >1 negative. Quantitative anti-HBV surface antibody (anti-HBs) testing was done using Elecsys Immunoassays (limits of detection, 3.5–1000 IU/L; Roche Diagnostics, Melbourne, Australia). We tested for HBV DNA viral load using the COBAS Ampliprep/Taqman Assay (lower limit of detection, 20 IU/mL; Roche Diagnostics, Melbourne, Australia) on pooled samples, with four samples per pool. Therefore, the detection limit for each sample in this pooled assay was 80 IU/mL, as each sample is in effect diluted 1:3. Individual samples from positive pools were then re-tested using an in-house assay [22] with confirmatory testing on the Realtime M2000 assay (Abbott Diagnostics, North Ryde, Australia).

Participants were classified as: (1) non-immune and non-infected (anti-HBs^-, $HBsAg^-$ and anti-HBc^-); (2) immune by vaccination ($HBsAg^-$, anti-$HBs^+ \geq 10$ IU/L and anti-HBc^-); (3) current or past infected (anti-HBc^+); and (4) chronically infected ($HBsAg^+$ or HBV DNA^+). The usual definition of chronic infection requires detection of HBsAg on two occasions at least six months apart. Where possible we reviewed the medical records of all those who were either $HBsAg^+$ or HBV DNA^+ at Wave 4 to determine if they satisfied the stricter definition of chronic infection. However, given the study design we were not able to ascertain the serial results for some participants and elected to define chronic infection based on a single result. An additional subgroup of participants were considered to have been exposed and transiently infected ('natural boosting') as indicated by an increase in anti-HBs level between wave 3 and wave 4 if: $\geq 4\times$ increased anti-HBs at wave 4 if <100 IU/L at wave 3, or $\geq 2\times$ increased anti-HBs at wave 4 if $\geq$100 IU/L at wave 3, and all other serological markers negative at wave 4 [23].

2.3. Ethics

Written informed consent was provided by participants and written support provided from each community's local governing bodies. Each wave of follow-up was approved by the Human Research Ethics Committee of Northern Territory Department of Health and Menzies School of Health Research, including the Aboriginal ethics sub-committee (wave 3 reference number 05/26 and wave 4 reference number 2013–2022).

2.4. Statistical analysis

We calculated VE with respect to protection against any (anti-HBc^+) and chronic ($HBsAg^+$ or HBV DNA^+) infection using the risk ratio with chi-square or Fisher's exact test for differences. Logistic regression was used to identify predictors of anti-HBc status. We used linear regression to identify associations with anti-HBs levels. We applied the natural logarithmic transformation on anti-HBs levels when this was the response variable [24]. By contrast, we used base two logarithmic transformations on anti-HBs levels when this was an independent variable to facilitate interpretation of regression models (it is simpler to consider doubling of an antibody level than unit increases, given the left-skewed distribution of the data). Statistical analyses were performed in R (version 3.3.2, the R Foundation for Statistical Computing). Results are presented as geometric means (with accompanying inter-quartile range; IQR) and odds ratios (OR), with accompanying 95% confidence intervals (95%CI).