INCOMPLETE PROTECTION AGAINST HEPATITIS B AMONG REMOTE ABORIGINAL ADOLESCENTS DESPITE FULL VACCINATION IN INFANCY

Elizabeth Dent, Christine E Selvey, Andrew Bell, Joshua Davis, Malcolm I McDonald

Abstract

The objective of this study was to determine long-term immunity to hepatitis B virus (HBV) in a cohort of adolescents who received plasma-derived HBV vaccine in 1989 and 1990 in a remote Australian Aboriginal community. This was done using a serological survey; primary outcome measures were cut-off titres of HBsAb, and the presence of HBeAb and/or HBsAg. Of 37 adolescents in the cohort, 4 (11%) had evidence of active infection, one with abnormal liver enzymes, 7 (19%) had evidence of past infection, 15 (41%) were HBsAb positive in low titre and 11 (30%) were classed as immune. It was concluded that there was relatively poor long-term serological immunity to HBV vaccination in this group; a finding which is in keeping with similar studies in Indigenous and remote populations elsewhere. This finding raises the concern that a significant proportion of Aboriginal adolescents in other remote communities (vaccinated in 1989 and 1990) were not adequately protected by the vaccine. If so, there will be an unexpected burden of chronic HBV infection in these settings and a substantial group who are non-immune, despite having received complete HBV vaccination courses as infants. The authors recommend follow-up serosurveys in remote Aboriginal communities to identify people with low HBsAb titres, especially those without an adequate anamnestic response to another dose of HBV vaccine. In addition, community-based active surveillance programs will be required to detect people with chronic HBV infection and provide access to monitoring and appropriate treatment.

Keywords: Indigenous, Australia, immunity, hepatitis, HBV

Introduction

The hepatitis B virus (HBV) vaccine was widely accepted and distributed soon after it became available in the early 1980s. Immunisation prevents HBV chronic liver disease and has dramatically reduced the incidence of hepatocellular carcinoma in vaccinated populations. HBV vaccination was introduced into the Northern Territory Childhood Immunisation Schedule at birth, 1 month and 6 months of age for Aboriginal neonates in April 1988. Several years later, it became universal across Australia.

Recent studies have suggested that immune responses to the early HBV vaccines may have been suboptimal in some Aboriginal communities. In addition to factors related to the vaccination process, investigators have suggested that genetic, developmental, and environmental factors may contribute to a poor response.

Studies in Mongolia and Indonesia have shown that improper storage and interrupted vaccine transport to remote settings can lead to freezing; this structurally destabilises the vaccine and reduces efficacy. A study in the Northern Territory, Australia, in 1994 documented freezing temperatures in 47.5% of vaccines, either in transfer or during storage. In rural China it was thought that similar transport factors could play a part, however it was found that genetic factors played a larger role, with a specific HLA haplotype predicting poor vaccine responses among the Han Chinese.

Two randomised controlled trials have reported long-term follow-up of high risk populations wherein a small percentage of vaccinated persons with initial seroprotection later developed HBeAb, indicating that some individuals either did not remain, or were never protected by the vaccine. Importantly, none of the subjects who developed HBeAb developed clinical hepatitis and the vaccine appears to have provided protection against chronic HBV disease. Maternal to infant transmission, prior to the first dose of vaccine, would also have been a plausible cause for the presence of HBeAb in these individuals.

In 2004, a well men’s check in one remote Indigenous community in the Northern Territory found a 14-year-old male with active HBV infection and abnormal liver function. A review of his medical record showed that he had received all 3 recommended vaccine doses, at the correct times, as an infant. Health centre staff knew of a second child of the same age in the community who had become HBV positive following contact with an
infected individual at age three. Both young people had also been fully vaccinated against HBV at the correct times. The hepatitis serology of their mothers at birth is unknown. These findings prompted the medical staff to conduct a serosurvey of children in the community who had been vaccinated in 1989 and 1990.

This Aboriginal population was among the first to receive routine infant HBV vaccination and this is the first report of long term follow-up in a remote setting. The aim was to determine immunity to HBV in adolescents vaccinated with plasma derived HBV vaccine in infancy over a 2-year period (January 1989 to December 1990). The outcome measures were:

1. the prevalence of HBV infection as indicated by a positive test for HBV surface antigen (HBsAg),
2. the rate of past exposure to HBV or vaccine as indicated by the titre of HBV surface antibody (HBsAb),
3. the rate of past HBV infection, indicated by the titre of HBV core antibody (HBcAb).

Methods

Ethics approval was granted by the human research ethics committee of the Menzies School of Health Research and the Northern Territory Department of Health and Families. The governing Health Board gave permission to access relevant laboratory results. A clinic nurse matched pathology results to vaccination history, de-identified the data and provided it to the principal investigator. Permission was given by the appropriate Aboriginal Health Board to publish the results. The community general practitioner (GP) used the computerised clinical records system to identify children born to families in the community and neighbouring communities in 1989 and 1990. HBV vaccination details were retrieved for each individual. An Aboriginal Health Worker identified vaccinated adolescents currently living in the community and located those who had left. Forty-eight teenagers were identified but 11 could not be located, leaving a cohort group of 37. The GP obtained informed consent, collected blood for serology between May and July 2005 (15–16 years post vaccination) and counselled each person about the reasons for the test and the potential meaning of results.

All samples were tested for HBsAb, HBcAb, and HBsAg. The Table outlines the relevance of each serological test. An HBsAb titre <10 mIU/ml with a negative HBcAb was taken as indication of immunity due to vaccination. Post-vaccine immunological memory is defined as the case where HBsAb titre < 10 mIU/ml and HBV exposure promotes a secondary immune response.\(^{12}\) Low HBsAb titre could represent a lack of initial immune response, waning immunity, or a latent immune response that would be re-activated with exposure to the virus or vaccine. Immunological memory can be measured by testing HBsAb titre after a booster dose.\(^{13}\)

Results of testing were explained to adolescents and their parents. Adolescents with evidence of current infection (positive HBsAg) were listed for regular follow-up. The GP arranged further liver function tests and counselled the adolescents, and their parents regarding the significance of the results.

Results

The GP screened 35 children, and two were tested by the school nurse at boarding school. The 11 adolescents who could not be located are being kept on a list for follow-up should they return to the community.

Of the 37 in the cohort, 4 (11%) had evidence of HBV infection, one with abnormal aminotransferase levels, 7 (19%) with evidence of past infection, 15 (41%) were considered not to have seroprotection (0 mIU/ml < HBsAb < 10 mIU/ml), and 11 (30%) were classed as having seroprotection according to the cut-off (Figure). Of the 11 adolescents with evidence of current or past HBV infection, all but one had received the first dose of vaccine at birth. One child had received the first dose at 1 month of age.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning of abbreviation</th>
<th>Explanation of HBV serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
<td>Presence indicates current infection</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Hepatitis B surface antibody</td>
<td>Presence indicates immunity</td>
</tr>
<tr>
<td>HBcAb Tot</td>
<td>Hepatitis B core antibody (total)</td>
<td>Presence indicates current or past infection</td>
</tr>
<tr>
<td>HBcAb IgM</td>
<td>Hepatitis B core antibody (IgM)</td>
<td>Presence indicates recent acute infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Hepatitis B e Antigen</td>
<td>Presence indicates highly infective stage</td>
</tr>
<tr>
<td>HBe Ab</td>
<td>Hepatitis B e Antibody</td>
<td>Presence indicates reduced infectivity status</td>
</tr>
</tbody>
</table>

Adapted from Western Diagnostic Pathology
Discussion

Eleven fully vaccinated children (close to 30%) in this cohort showed evidence of past infection with HBV, and 4 had ongoing infection as determined by positive HBsAg. This compares with the study of Wood et al (2008) (Australian Aboriginal Birth Cohort Study) who followed up 401 Aboriginal adolescents aged 16–20 years, vaccinated across 50 communities between 1987–1992. Evidence of past HBV infection was found in 21%, and 1.5% had persistent infection. Half were considered to have inadequate immunity and were given booster doses. In this cohort, only a third had received on-time childhood HBV vaccination in infancy.

Plasma derived vaccines were used before the introduction of recombinant vaccines in 1991, and when used in infancy, were accompanied by a relativity inferior anamnestic response. Moreover, evidence-based guidelines for storage and transport of vaccines were not developed by the World Health Organization until 1992/1993. A 1994 study conducted in the Northern Territory tagged 144 vials of HBV and 127 vials of poliomyelitis vaccine distributed to community settings. The cold chain was breached frequently with 23% of temperatures too high and 47.5% too low. The more stages there were in transportation, and the more remote the setting, the higher the risk of being exposed to freezing temperatures. As a result, inclusion of freeze monitors is now considered best practice. Awareness of freezing has increased since cold chain monitoring became policy in Australia in 2001. In 1989 and 1990, it is quite likely that some batches were frozen during transport or storage.

Another consideration would be persistent maternal–infant transmission despite proper vaccination. Hepatitis B immunoglobulin is recommended, in addition to infant vaccination, for the prevention of maternal–infant transmission. The HBsAg status of the mothers at the time of birth of the study adolescents is not known. However, HBV has high prevalence in Indigenous communities. In 1987, the prevalence of HBV infection among non-metropolitan Aboriginal women at prenatal screening in Western Australia was 3.6%. Estimates of the population prevalence of HBV infection among Aboriginal populations in Western Australia and the Northern Territory have varied from 3%–22%. A recent East Arnhem Land survey found a high prevalence of chronic infection, with a prevalence of HBsAg in 12% of adults.

Several studies have demonstrated that infant vaccination does not always prevent vertical transmission. In China, a long-term follow-up of 95 adolescents who were vaccinated with plasma derived hepatitis vaccine but not immunoglobulin at birth, 1 and 2 months, and whose mothers had HBV infection, found 9% had evidence of past infection (positive HBcAb), though none developed clinical hepatitis. In a similarly designed Canadian study, of 770 children who had been vaccinated at birth with immunoglobulin followed by the plasma derived vaccine at 0, 1 and 2 months, 5% had developed HBcAb when followed up at 8 years. Another 5-year follow-up study of vaccinated infants of carrier mothers using recombinant vaccine found that 12% (19/162) subsequently developed HBcAb by age 5 years (6/19 before age one) and that maternal HBcAb disappeared from the blood of the infant.
in 99% of children before age 2 years.\textsuperscript{25} While the post-birth period is the highest risk period for seroconversion, the infection might not be established or detected until as late as age two.\textsuperscript{25}

Low birth weight (LBW), with or without prematurity, is common among Indigenous infants, and failure to thrive occurs more commonly than in the general Australian population. In addition, many infants live in crowded conditions, exposed to multiple childhood infections and life stressors. Infant mortality is unacceptably high.\textsuperscript{26} Rates of seroprotection are lower for preterm compared with full term infants.\textsuperscript{27} Theoretically, lack of immunological maturity in LBW infants could compromise vaccine response; however, when infection and other co-morbid illnesses are excluded, there appears to be no difference.\textsuperscript{27} It is possible that prematurity, recurrent infection and ongoing poor nutrition in infants contribute to a suboptimal immune response.

Some studies have suggested that lower immune response among Indigenous infants is genetically determined.\textsuperscript{2–4} Additionally, HBV vaccine escape mutants can lead to vaccine failure.\textsuperscript{12,28} For practical reasons, neither HLA typing nor the presence of escape mutants could be assessed in this study setting.

The size of the cohort was small and 11 adolescents could not be located; this raises concerns of potential attrition bias. A sensitivity analysis suggests that if all the missing subjects had evidence of past infection, the proportion with hepatitis infection would be 22/48 (46%). If all 11 were immune, the proportion would have been 11/48 (23%), more in keeping with the expected infection rates in a population with a high rate of maternal infection.

The major limitation of this study is that the presence of immunological memory was not investigated for those adolescents with HBsAb <10 mIU/ml and HBsAg negative. Therefore, the immune status of this subgroup was unclear. A similar 15-year follow-up study of Micronesian infants illustrates the importance of checking for immunological memory. A group of 105 children were vaccinated with recombinant vaccine in infancy. HBcAb was determined at baseline, at 35 months, and again after 15 years.\textsuperscript{13} The rate of HBcAb in this study was much lower at 15 years post vaccination than in our study, 7.6% compared with 30%, and none became HBsAg positive. HBV booster doses were given to 96 subjects without HBcAb to investigate immune memory; 47.9% had an anamnestic response.\textsuperscript{13} If this study had tested immune memory in this way and found similar results, then around half the adolescents may have an anamnestic response.

No studies have demonstrated active HBV disease in vaccinated subjects (without renal failure) with initially documented seroprotection. Even though protective seroimmunity levels and the anamnestic response may wane over time,\textsuperscript{10,11} they do not necessarily constitute vaccine failure. There is probably still protection from progressive liver disease and hepatocellular carcinoma.\textsuperscript{10,11} Further investigation should examine the possible benefits of post-vaccination serological testing for high risk infants such as those in remote Aboriginal communities, as additional doses may result in seroconversion in a proportion of those who initially fail to respond to vaccination.

The results of this study are a cause for concern. There may be a significant proportion of Aboriginal adolescents vaccinated in 1989 and 1990 who have chronic HBV infection, and another substantial subset who are non-immune, despite having received complete HBV vaccination courses as infants. The authors recommend further investigation across remote Indigenous Australian populations to determine the proportion, location, and vaccine batch used in those whom vaccine failure has occurred and identify those who are not immune as well as those who are chronically infected. A systematic community-based program could be carried out as part of regular Adult Health Checks and is recommended to detect those with chronic HBV infection and provide access to ongoing monitoring and treatment.

Acknowledgements

Thanks to the Health Board and staff working at the community where this research was conducted: in particular the clinic staff who assisted with the project. Participants and their parents are thanked for the interest taken in their own health and the outcomes of this study.

Author details

Dr Elizabeth Dent, MPH Scholar\textsuperscript{1}
Dr Christine E Selvey, Senior Director\textsuperscript{2}
Dr Andrew Bell, Medical Director\textsuperscript{3}
Dr Joshua Davis, Infectious Diseases Physician\textsuperscript{1}
Dr Malcolm I McDonald, Physician\textsuperscript{1}

1. Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory
2. Communicable Diseases Branch, Queensland Health, Brisbane, Queensland
3. Katherine West Health Board, Katherine, Northern Territory
4. Top End Remote Health, Northern Territory Department of Health and Families

Corresponding author: Dr Elizabeth Dent, Concord Centre for Cardiometabolic Health in Psychosis, Concord Hospital, Hospital Road, CONCORD NSW 2139. Telephone: +61 2 9767 6027. Facsimile: +61 2 9767 7107. Email: libby.dent@usyd.edu.au
References


