Prevalence of hepatitis B surface antigen in vaccinated children and controls in rural Nigeria

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Hepatitis B surface antigen;
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Summary

Objective: To determine the prevalence of hepatitis B surface antigen (HBsAg) amongst vaccinated children and controls aged 1—4 years in a rural community in mid-western Nigeria.

Methods: The vaccinated children had received at least three doses of hepatitis B vaccine. The vaccines included recombinant hepatitis B vaccine at birth and a combined diphtheria, tetanus, pertussis (whole cell) plus hepatitis B (DTPw-HBV) vaccine. HBsAg was determined by a rapid immunoassay method based on the immunochromatographic sandwich principle. Two hundred and twenty-three children and 219 controls were recruited into the study.

Results: The prevalence of HBsAg was significantly lower in the vaccinated group (1.3%) than in the control group (4.6%, p = 0.04). The prevalence rates were significantly higher in males (p = 0.02) and two-year birth cohort (p = 0.01). The controls were estimated to be at a six-fold higher risk of being positive for the surface antigen than the vaccinated children. The vaccine effectiveness was estimated to be approximately 80%.

Conclusion: These results confirm that hepatitis B vaccine protects against hepatitis B surface antigen carriage and confirm immunogenicity of the combined DTPw-HBV vaccine.

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Introduction

Hepatitis B (HB) infection is a serious public health problem, with two billion people infected worldwide and 350 million suffering from chronic HB infection. Globally it causes about 1.2 million deaths per year due to its various complications including chronic hepatitis, liver cirrhosis, and liver cancer. Hepatitis B infection is hyper-endemic in Nigeria. In children, the infection occurs early in life and studies report hepatitis B surface antigen (HBsAg) prevalence rates of 20%, while in adult populations, the rate varies from 10–38%. Hepatitis B is preventable through vaccination and studies have confirmed protection following vaccination in both industrialized and non-industrialized communities. Hence mass vaccination ought to become imperative on a global scale, as this will decrease the reservoir of chronic carriers able to spread the virus. Since 1992 the World Health Organization (WHO) has recommended the inclusion of hepatitis B vaccination in all national immunization programs independent of hepatitis B carrier rate.

GlaxoSmithKline Biologicals (GSK) developed the first diphtheria, tetanus, and pertussis (whole cell) - Hepatitis B combination (DTPw-HBV) vaccine, (TriantanrixTM-HB). Studies have shown it to be safe and immunogenic following a three-dose primary course. In Nigeria, since 1998 GlaxoSmithKline Biologicals has sponsored a vaccination programme at Sabongidda-Ora, in Owan west Local Government Area of Edo state in mid-western Nigeria. The programme offers vaccination against all the Expanded Programme on Immunization (EPI) diseases as well as against hepatitis B. The hepatitis B vaccination schedule includes a monovalent hepatitis B dose at birth and three doses using the combined vaccine given at 6, 10 and 14 weeks of age. Children who were older than six weeks at the time of registering into the programme did not receive the monovalent HB dose at birth as they were vaccinated against diphtheria, pertussis, tetanus and hepatitis B using the combined vaccine. The primary objective of the hepatitis B vaccination was to provide at least three doses of the vaccine to all children.

Sabongidda-Ora was the only community in Nigeria receiving hepatitis B vaccination at the time the study was conducted. Vaccination coverage for EPI antigens in this community in 1998 was 42% at a time when hepatitis B vaccine was not administered. A two-year post-programme evaluation showed that vaccination coverage for EPI antigens had increased to over 80% and hepatitis B vaccine coverage (three doses) was 58%. It is important to establish the benefit conferred by HB vaccination in this programme. Accordingly, the objective of this study was to investigate the prevalence of hepatitis B surface antigen in vaccinated children as compared to age-matched controls residing in the same area.

Methods

Study design

The study was conducted as a case control cross-sectional design. All children recruited into the study were aged between one to four years and were generally healthy as established from the medical history. The study took place between February and March 2001 at the local vaccination clinic. All subjects were required to visit the study site once during which the medical history was checked, physical examination and rapid blood test for HBsAg determination were carried out.

Ethical approval

Ethical approval for the study was obtained from The Research and Ethics Committee of the Lagos State University College of Medicine, the Primary Health Care Department of the Local Government and the community leaders in accordance with local customs. A cohort of unvaccinated children was chosen, as there were children who were older than the catchment age of the immunization programme in the community when it began and others who received vaccination excluding hepatitis B from other sources.

Study population

The children enrolled into the study were living in and around Sabongidda-Ora. They were invited through various community meetings, schools, religious meetings and home visits undertaken by the staff of the vaccination clinic.

The vaccinated group consisted of children with immunization cards or those registered on the clinic’s register with an immunization record. These children had received three or four doses of HB vaccine (either two doses of TritanrixTM-HB plus Engerix-BTM at birth or three doses of TritanrixTM-HB alone or three doses of TritanrixTM-HB plus Engerix-BTM at birth). Children in the control group were those whose records indicated they had not been vaccinated against hepatitis B and those who had not been registered at the study site. Recruitment was carried out consecutively as the children arrived at the clinic on each day of the study until the study sample size was achieved.
Children with protein-energy malnutrition (using the weight-for-age ratio, to calculate the cut-off limits, with the 50th percentile Harvard Boston standard as value) were excluded from the study as well as those with mothers unwilling to allow them to participate in the study. All mothers/guardians of participating children provided oral informed consent following a detailed explanation of the rationale, aims and objectives of the study. All oral consents were witnessed.

Sample size determination

The sample size was determined based on the following assumptions: the proportion of HBsAg in the vaccinated group was estimated at 2% and in the unvaccinated group at 20%. The power of the study was set at 99% to detect a true difference of 18% between both groups. A Fisher’s exact test with a 0.05 one-sided significance level was then applied and resulted in a minimum estimated sample size of 220 subjects in each group.

Laboratory assay

Blood samples for the assay were taken from a finger prick in each subject. Measurement of HBsAg was performed at the study site by the principal investigator (OOO) using the commercially available Trinity Biotech Uni-Gold™ HBsAg test kit (Trinity Biotech Plc, Co, Wicklow, Ireland) for the rapid in vitro, qualitative detection of HBsAg in whole blood.

This is a rapid immunoassay based on the immunochromatographic sandwich principle. The test kit is stable at temperatures of between 2—27 °C. The sensitivity of the test kit is >99.5% and specificity >99.5%.15

Data analysis

All data of subjects were collected along with the HBsAg status. These were then analysed using Epi-Info Version 6.04 b (CDC, USA & WHO Geneva, Switzerland) software. Age, gender, and HBsAg positivity status for both groups were analysed by birth cohort. Hepatitis B surface antigen prevalence was determined by groups. The level of significance was set at \( p < 0.05 \). The \( p \) values were one-sided.

Results

A total of 446 children, 227 vaccinated and 219 unvaccinated were recruited into the study. However, four subjects in the vaccination group were excluded from the final analysis as they were less than one year of age. Thus 442 subjects consisting of 223 (50.5%) vaccinated children and 219 (49.5%) unvaccinated were included in the analysis (Table 1). There were 214 (48%) females and 228 (52%) males in the study population, with the gender distribution being similar in each group. Other demographic characteristics of the two groups were similar except that the unvaccinated children were significantly older in age and weighed more (\( p = 0.001 \)) than the vaccinated group.

In the vaccinated cohort, one child (0.5%) received the monovalent HB dose at birth plus two doses of the combined vaccine; 106 (47.5%) received only three doses (omitting the dose at birth) of the combined vaccine and 116 (52%) received four doses (HB dose at birth plus three doses of the combined vaccine). The prevalence of HBsAg is shown on Table 2. Three subjects in the vaccinated group (1.3%) were positive compared to ten (4.6%) in the unvaccinated group (\( p = 0.04 \)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccinated N (%)</th>
<th>Controls N (%)</th>
<th>Fisher’s exact test p-value (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2/108 (1.9)</td>
<td>2/106 (1.9)</td>
<td>0.68</td>
</tr>
<tr>
<td>Male</td>
<td>1/115 (0.9)</td>
<td>8/113 (7.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1/89 (1.1)</td>
<td>0/26 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>2/87 (2.3)</td>
<td>7/50 (14.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0/45 (0.0)</td>
<td>3/73 (4.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>4</td>
<td>0/2 (0.0)</td>
<td>0/70 (0.0)</td>
<td>—</td>
</tr>
<tr>
<td>All subjects</td>
<td>3/223 (1.3)</td>
<td>10/219 (4.6)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
The age adjusted odds ratio for the unvaccinated cohort was 6.43 (95% confidence interval = 1.3 < OR < 27.6), and had a six-fold higher risk of being positive for the surface antigen. The risk was found to be significant (Mantel-Haenzel summary chi-square = 6.03; \( p = 0.01 \)). The prevalence of the surface antigen was significantly higher amongst males and the two-year birth cohort. The three vaccinated subjects who were positive for the surface antigen did not receive the hepatitis B dose at birth. There was no statistically significant difference in the prevalence rate of the surface antigen amongst vaccinated children who received the hepatitis B vaccine dose at birth and those who did not. Using a Poisson model with a correction for age, the vaccine effectiveness was 80.0% (20.0% < 95% CI < 95.0%).

Discussion

The HBsAg rate (4.6%) obtained amongst the unvaccinated children was much lower than previous reports amongst children (10–23%) in Nigeria.\(^2,3,5\) This could be explained as follows. First, the studies that report higher values are hospital-based and were conducted amongst sick children who may have had a higher level of exposure to the virus relative to the healthy children in the community. Thus, the actual HBsAg rate amongst children in the community may be much lower than has been previously reported. Secondly, the lower rates in this study may be due to the sensitivity of the test kit used, but this is unlikely as the manufacturers quote both sensitivity and specificity rates of 99.5%.

As was to be expected, the HBsAg rate amongst the vaccinated children was significantly lower than amongst the unvaccinated. At least 98% of the vaccinated group were negative for the surface antigen, while the unvaccinated children had a significant risk (six-fold) of being carriers of hepatitis B surface antigen. These results are similar to studies by other researchers who found significant reductions in the HBsAg rate post vaccination and a protective efficacy of between 67–94%.\(^8,16,17\) The 80% vaccine efficacy obtained in this study (though slightly lower than expected) is comparable to the 67% rate reported from Egypt,\(^17\) and like others confirms the immunogenicity of the combined DPTw-HB vaccine.\(^10,11\) Such a high level of vaccine efficacy is likely to impact positively and prevent the transmission of hepatitis B infection in the community.

The significantly higher proportion of males and children aged two years who were positive for the surface antigen may be related to a more intense level of exposure. Hepatitis B infection is more commonly transmitted in children through the horizontal route and this may explain the higher rates of the surface antigen in the two-year-olds as preschool activities start at this age. The low rates amongst the older children cannot be accounted for. The three cases of HBsAg in the vaccinated group are apparent vaccine failures. The failure rate of 1.3% is similar to rates of between 0.7–3% reported by other researchers.\(^16–18\) These three cases did not receive hepatitis B vaccine at birth and may have been exposed to the virus before vaccination. Furthermore, a hypothesis of an unproven intrauterine transmission of the virus from a carrier mother to her foetus has been proposed as one of the causes of vaccine failure.\(^19\)

In conclusion, this study found that the prevalence of HBsAg was significantly lower amongst vaccinated children compared with the unvaccinated group and that vaccine effectiveness was 80%. We suggest that more community-based studies be conducted amongst children to provide up-to-date information on HBsAg status in view of the low prevalence obtained in this study. In addition, we recommend that HB vaccination be commenced nationwide to further reduce the risks associated with the disease.

Limitations of the study

Serologic results presented in this study do not represent conventional evaluation of vaccine immunogenicity or efficacy but rather evaluation of the ability of the HB vaccination to provide protection and reduce susceptibility to the virus in vaccinated subjects. In addition, information on the HBsAg status of the children’s family members and exposure of the children to the virus were not available. These factors may have an impact on the results of the study as the intra-familial clustering of the infection is well known. The HBsAg prevalence in the unvaccinated group employed to determine the sample size was overestimated compared to the results of the study. This led to a sample size that was underpowered, though it was able to detect a statistically significant difference in the HBsAg prevalence between both vaccinated and unvaccinated children.

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Conflict of interest: All authors have either received payment for services to GlaxoSmithKline or are employees of the company.

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