The Impact of the Hepatitis B Virus Vaccine on the Incidence of Hepatitis B Virus–Associated Membranous Nephropathy

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**Background:** The hepatitis B virus (HBV) vaccine has resulted in a decline in the incidence of HBV carriage and hepatocellular carcinoma in southeast Asia. Vaccine efficacy in Africa has not been adequately assessed.

**Objective:** To report on the impact of HBV vaccination in South Africa on HBV-associated membranous nephropathy (MN) over 6 years.

**Methods:** King Edward VIII Hospital in Durban is the only tertiary referral center for the province of KwaZulu-Natal for children with renal diseases. The HBV vaccine was introduced into the South African Expanded Programme on Immunisation on April 1, 1995; vaccine coverage rates between April 1, 1995, and December 31, 2001, for children for the first, second, and third doses were 85.4%, 78.2%, and 62.0%, respectively. Hepatitis B virus status was determined using a radioimmunoassay (January 1, 1984–March 31, 1991) or an enzyme-linked immunosorbent assay. Membranous nephropathy was confirmed by the results of a renal biopsy. The hospital average annual incidence of HBV-associated MN was compared before and after vaccination and according to age groups.

**Results:** Between January 31, 1984, and December 31, 2001, there were 119 children with HBV-associated MN; their mean age was 7 years (range, 1-14 years), and 101 (84.9%) were males. The average annual rate ratio per 10^5 child population was 0.25. The overall incidence rate ratio showed a significant decrease from January 1, 2000, to December 31, 2001, compared with the preimmunization period (January 1, 1984–December 31, 1994) (incidence rate ratio, 0.12; 95% confidence interval, 0.03-0.50). Children from birth to the age of 4 years experienced no disease after 1998. Children aged 5 to 10 years showed a significant decrease in 2000-2001 compared with the prevaccination years (incidence rate ratio, 0.19; 95% confidence interval, 0.05-0.80).

**Conclusion:** The HBV vaccine, even at low coverage for the full South African Expanded Programme on Immunisation schedule, reduced the hospital incidence of HBV-associated MN over 6 years.


SEVERAL REPORTS of the impact of mass immunization with hepatitis B virus (HBV) vaccination on HBV carriage and hepatocellular carcinoma have documented a significant reduction in the prevalence of hepatitis B surface antigen (HBsAg) carriage and an accompanying decline in the annual incidence of hepatocellular carcinoma. After the introduction of immunization against HBV in July 1984 in Taiwan, an area of hyperendemic prevalence of HBV infection, HBV carriage in 6-year-old children declined from about 10% from 1981 to 1986 to between 0.9% and 0.8% from 1990 to 1994. Vaccination targets were progressively extended from newborns of HBsAg-positive mothers to all newborns in July 1986, and in 1987 to preschool-aged children as well.

Hepatitis B virus vaccine programs have been implemented in most countries. Hepatitis B virus infections, however, continue to pose a major public health problem and are present on all continents and in almost every country, with an estimated 320 million people with a chronic infection. In sub-Saharan Africa, rural communities seem to be at greater risk of exposure, and chronic viral infection has carriage rates between 8% and 15%. In South Africa, HBV is the main cause of liver-related diseases, especially among the black population. More than 70% of the South African black population has been exposed to HBV, with an estimated 10% being carriers (ie, positive for HBsAg) of the virus. The pattern of virus transmission contrasts with that in the Far East, with the predominant route being horizontal, especially between siblings. The mechanism of horizontal transmission of HBV in sub-Saharan Africa remains elusive.
of contracting the HBV infection. The chronic HBV carrier state declines rapidly with increasing age (82% in infants <6 months to 15% in children aged 2-3 years), with males being at higher risk for chronic HBV carriage.31

One of the major extrahepatic manifestations of chronic HBV carriage in children is HBV-associated nephropathy, particularly membranous nephropathy (MN).24-26 which develops in a few chronic HBV carriers.27 In Durban, up until April 1, 1995, HBV-associated nephropathy accounted for 86% of all cases of nephrotic syndrome (NS) in black children.28 Hepatitis B virus–associated MN accounts for a sizable proportion of childhood NS in other regions too (eg, Cape Province, Zambia, and Taiwan).24,28,30 The medium- to long-term impact of HBV vaccine programs, using an extrahepatic manifestation of HBV, HBV-associated MN, which is less frequent, as an end point, has not been assessed.

The HBV vaccine was incorporated into the South African Expanded Programme on Immunisation of children on April 1, 1995.31 This study examines the impact of HBV immunization on the incidence of HBV-associated MN in the ensuing 6 years following the introduction of the HBV vaccine.

METHODS

The province of KwaZulu-Natal is 1 of 9 provinces in South Africa and has a total child population (aged 0-14 years) of 2985708, based on the 1996 census figures.32 King Edward VIII Hospital is the tertiary referral center for the province of KwaZulu-Natal and the only center where tertiary nephrology services for children are available. All children with complex renal diseases, including NS, are referred to the hospital for assessment and treatment. Following the finding of the strong association between chronic HBV carriage and NS in children in KwaZulu-Natal, particularly in the black population, all patients with NS were screened for HBV carriage as part of a standard protocol.31 Thus, the number of new cases of NS associated with HBV carriage seen at the hospital is the nearest approximation available of the incidence of HBV-associated MN in the province. Experience with HBV-associated nephropathy over the past 3 decades has been reported27; to our knowledge, this is the largest series documented. The predominant histological form of NS in black children in Durban is MN, which accounts for more than 86% of all cases of HBV-associated NS.28 Hepatitis B virus–associated MN is the only histological type in which we assessed the impact of the HBV vaccine, because it is the lesion most clearly associated causally with chronic HBV infection. In the immediate postvaccination period, we extended our efforts to trace any residual cases of HBV-associated MN not already referred and also for information for further studies. From 1996 to 1997, requests were sent to all health centers in the province to refer children 10 years or younger with HBV-associated nephropathy to the tertiary center as part of a study on the biosocial background of this disease in households. To enhance the recruitment of index cases, in 1998, further requests were sent for children 16 years or younger with HBV-associated nephropathy to be referred to the tertiary center.

VIRAL STUDIES

Hepatitis B status was determined using a third-generation enzyme-linked immunosorbent assay (Auszyme Monoclonal; Abbott Laboratories, Abbott Park, Ill) from March 31, 1991, onward. From January 1, 1984, to March 31, 1991, HBV status was determined using a radioimmunoassay (Auszyme II Ansab HbeAg; Abbott Laboratories).

HISTOLOGICAL FEATURES

Hepatitis B virus–associated MN was defined by examination using light and electron microscopy, and by immunofluorescent staining of kidney biopsy specimens. Patients with HBV-associated MN have classic subepithelial deposits, with varying degrees of mesangial involvement, that may include proliferation.34,35

POPULATION ESTIMATES

The only reliable population data available are the 1996 census figures. Populations for the remaining years of the study were estimated based on a 3% growth rate per year. Two further denominators were used to assess the incidence of HBV-associated MN. These were the hospital admissions of all children from birth to the age of 14 years, and of children from birth to the age of 14 years with NS admitted to hospital during the period of the study. Information was obtained from the hospital registry.

HBV VACCINE

Starting April 1, 1995, all children born in South Africa since the beginning of that year were required to receive 3 doses of hepatitis B vaccine as part of their routine immunization schedule.31,36 The vaccine used for immunization is plasma derived and contains a lower dose of HBsAg (1.5 µg/0.5 mL per dose) than the other vaccines on the market. It is administered at 6, 10, and 14 weeks to infants in the anterolateral thigh. The doses are administered concurrently with the routine poliovirus vaccine live oral and diphtheria, pertussis, and tetanus immunizations.37 The average immunization coverage from April 1, 1995, to December 31, 2001, was 85.4% (first dose), 78.2% (second dose), and 62.0% (third dose).37

ETHICAL CONSIDERATIONS AND STATISTICAL ANALYSIS

Ethical approval for use of clinical data and registry records was obtained from the Ethics and Professional Standards Subcommittee, Faculty of Medicine, University of Natal. Statistical analysis was performed in consultation with the Institute of Biostatistics of the Medical Research Council using SAS statistical software, version 6 (SAS Institute Inc, Cary, NC).

The annual incidence of HBV-associated MN was determined by dividing the annual number of cases in children by the year-end population of children of the same age in KwaZulu-Natal. The effect of the vaccination program on the incidence of HBV-associated MN was assessed by Poisson regression. The Poisson model included the log of the population as an offset, and the age group as a covariate. Similar comparisons were made for hospital admissions of all children from birth to the age of 14 years and for all children with NS in the same age category. The number of cases occurring before vs after the introduction of the vaccine was compared using the Wilcoxon rank sum test.

RESULTS

One hundred and nineteen children, aged 1 to 14 years (mean, 7 years), with HBV-associated MN were the subjects of this study from January 1, 1984, to December 31, 2001; 101 (84.9%) were male. The average annual inci-
idence of HBV-associated MN (calculated as half the incidence over 2 years) during the study period was 0.25 per 10^5 children (range, 0.03-0.33 per 10^5 children) (Table 1). Following the introduction of the HBV vaccine in 1995, the average annual incidences in the immediate postimmunization period showed no significant decline, and were 0.43 per 10^5 for 1996-1997 and 0.25 per 10^5 from January 1, 1998, to December 31, 1999 (incidence rate ratio [IRR], 1.3; 95% confidence interval [CI], 0.9-1.9) when compared with the preimmunization period (1984-1995). However, when the average annual rate ratio of HBV-associated MN for the preimmunization period (1984-1995) (0.22) was compared with that from January 1, 2000, to December 31, 2001 (0.03), there was a sharp decline per 10^5 child population (IRR, 0.12; 95% CI, 0.03-0.50).

INCIDENCE OF HBV-ASSOCIATED MN

By Age Categories

The change in rate ratios differed significantly by age categories (Table 2). In children from birth to the age of 4 years, the average annual rate ratio was 0.16 per 10^5 in the preimmunization period and 0.20 per 10^5 in the years immediately thereafter (January 1, 1996–December 31, 1999) (IRR, 1.3; 95% CI, 0.5-3.0). All cases of HBV-associated MN occurred before January 1, 1997, and no cases occurred in the subsequent years (1998-2001). The probability of observing no cases in this period compared with the number of cases observed in the years before 1998, however, was statistically significant (P = .01).

In the 5- to 9-year-old category, the average rate ratio during the preimmunization period was 0.46, and during 1996-1999, it was 0.55 (IRR, 1.2; 95% CI, 0.7-2.0). When the average annual rate ratio for the preimmunization period (0.46) was compared with the average annual rate ratio for 2000-2001 (0.09), there was a statistically significant decrease (IRR, 0.19; 95% CI, 0.05-0.80).

In the 10- to 14-year-old group, the average annual rate ratio during the preimmunization period was 0.14, and during 1996-1999, it was 0.26 (IRR, 1.90; 95% CI, 0.85-4.10). No cases were observed during 2000-2001. The probability of observing no cases in this period compared with the number of cases observed in the years before 1998, however, was not statistically significant (P = .08).

The increase in the average annual rate ratios of HBV-associated MN during 1996 was most likely because of the active recruitment drive embarked on during this period for the purposes of another study, as described in the “Methods” section.38

By Pediatric Hospital Admissions

The incidence rate of HBV-associated MN as a proportion of hospital admissions showed a similar trend. There was no significant reduction in the incidence rate, from 520.7 in 1996 to 226.2 in 1999 (IRR, 0.43; 95% CI, 0.20-1.10). The decline in the incidence rates of HBV-associated MN was statistically significant from 1996 to 1997 and from 2000 to 2001 (IRR, 0.14; 95% CI, 0.02-0.60) (Table 3).

Table 1. Overall Average Annual Incidence Rates of HBV-Associated MN for the Population From Birth to the Age of 14 Years in KwaZulu-Natal, South Africa

<table>
<thead>
<tr>
<th>Year</th>
<th>Population Size</th>
<th>No. of Cases of HBV-Associated MN</th>
<th>Incidence Rate/10^5 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-1985</td>
<td>2,125,527</td>
<td>14</td>
<td>0.33 (0.2-0.6)</td>
</tr>
<tr>
<td>1986-1987</td>
<td>2,254,972</td>
<td>11</td>
<td>0.25 (0.1-0.4)</td>
</tr>
<tr>
<td>1988-1989</td>
<td>2,392,300</td>
<td>11</td>
<td>0.23 (0.1-0.4)</td>
</tr>
<tr>
<td>1990-1991</td>
<td>2,537,991</td>
<td>15</td>
<td>0.30 (0.2-0.5)</td>
</tr>
<tr>
<td>1992-1993</td>
<td>2,692,554</td>
<td>12</td>
<td>0.23 (0.1-0.4)</td>
</tr>
<tr>
<td>1994-1995</td>
<td>2,856,531</td>
<td>12</td>
<td>0.21 (0.1-0.4)</td>
</tr>
<tr>
<td>1996-1997</td>
<td>3,030,494</td>
<td>26</td>
<td>0.43 (0.3-0.6)</td>
</tr>
<tr>
<td>1998-1999</td>
<td>3,215,051</td>
<td>16</td>
<td>0.25 (0.1-0.4)</td>
</tr>
<tr>
<td>2000-2001</td>
<td>3,360,441</td>
<td>2</td>
<td>0.03 (0.0-1.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; MN, membranous nephropathy.

By Childhood NS

When the incidence rate of HBV-associated MN as a proportion of the number of cases of children with all histological types of NS admitted to the hospital was calculated, there was an unusual increase in incidence, from a low level of 12.0% in 1995 to 30.8% in 1996. This was because of hospital industrial action in the latter half of 1995, when nurses went on strike and all elective referrals were canceled. Again, the incidence rate per 100 showed a decline from January 1, 1999, to December 31, 2000 (IRR, 0.30; 95% CI, 0.03-1.40) (Table 3); no cases of HBV-associated MN were seen in 2001.

INCIDENCE OF UNRELATED CONDITIONS

We compared the annual incidences of 2 diseases that are the most common reasons for admission in children who are unlikely to have been affected by the HBV vaccine program in 1995. The incidence of pneumonia and gastroenteritis in children from birth to the age of 14 years admitted to the hospital remained steady during 1995-2001 (data not shown). These 2 conditions accounted, on average, for 38.2% and 24.4%, respectively, of all pediatric admissions.

The mortality in children with HBV-associated MN from 1984 to 1999 was 2.5% (a total of 3 deaths due to progressive renal failure). Neither of the 2 children with HBV-associated MN between 2000-2001 died.

COMMENT

The results of this study show that over 6 years following the introduction of the HBV vaccine into the routine childhood immunization schedule in South Africa, which corresponds to the earliest period of susceptibility of children to HBV-associated MN, the incidence of HBV-associated MN declined significantly. We assessed this trend by determining the proportion of HBV-associated MN differences using 3 denominators: (a) childhood population in the province, (b) hospital admissions of children with any disease, and (c) patients with childhood NS admitted to the hospital. The decline in HBV-
associated MN detected by population size was reinforced by similar trends for the other 2 denominators. These findings are in keeping with reports from southeast Asia, which show a decline in HBV carriage and hepatocellular carcinoma following the introduction of HBV immunization after 6 to 10 years of follow-up.3,10,13,39

In South Africa, HBV carriage in the black population is largely established in early childhood; the first (and largest) wave of HBV infection begins during the latter half of the first year of life, and high carrier rates are already present by the age of 3 to 5 years.19-22 The earliest age at onset of HBV-associated MN is around 1 year, while the peak age is around 7 years (range, 1-11 years), in keeping with reports24,25,40 from other centers. Therefore, we anticipated that there would be an intervening period of about 4 to 5 years before the effect of the vaccine on acquisition of new cases of HBV-associated MN could be detected among those earliest infected and in the peak age group.

The incidence of HBV-associated MN remained relatively constant up to 1999, 5 years after the implementation of the HBV vaccine; a significant decline in the incidence of HBV-associated MN was noted thereafter.

The success of HBV vaccination in decreasing the incidence of HBV-associated MN in South Africa may be because of the predominantly horizontal transmission of HBV, as seen in the rest of sub-Saharan Africa. The pre-immunization HBsAg carriage rate in 3-year-old black South African children is 12.8%.41 Following the introduction of the HBV vaccine in April 1995, with coverage rates of 85.4% (first dose), 78.2% (second dose), and 62.0% (third dose) in children aged 12 to 23 months,32 most children would have been already protected against HBV infection and, therefore, against HBV-associated MN, because there is overlap between the age periods of high HBV carriage (3-5 years) and the first appearance of HBV-associated MN (1-14 years). In the group from birth to the age of 4 years, which is the lowest age range at which HBV-associated MN develops in susceptible individuals, there was a significant decline in the incidence of HBV-associated MN following the implementation of the HBV vaccine in April 1995. It is likely that vaccination of this group directly protected them from HBV infection and resulted in a decreased incidence of HBV-associated MN.

The 5- to 9-year-old group (the group with the greatest susceptibility to HBV-associated MN) also showed a significant decline in the incidence of HBV-associated MN when the average rate ratios for the preimmunization
The incidence of HBV-associated MN closely parallels the incidence of HBV in the general population. Several reports have highlighted the impact of HBV vaccination on the incidence of HBV infection. To our knowledge, this is the first report of the impact of HBV vaccination on one of the most common extrahepatic manifestations of HBV infection (nephropathy). This report clearly demonstrates the effective control of HBV infection by immunization, which leads to a sharp decline in the incidence of HBV-associated MN in a hyperendemic region and, therefore, highlights the need for the implementation of such a vaccination program in areas endemic for the virus.

In conclusion, the results of this study indicate that the HBV vaccine given as part of routine immunization, even with low full coverage rates, is highly effective within the framework of the South African Expanded Programme on Immunisation in reducing the rate of HBV-associated MN.

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