

# Preimmunization Epidemiology of Hepatitis B Virus Infection in South African Children

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The prevalence of hepatitis B surface antigen (HBsAg) was determined in a community-based, cross-sectional, age-stratified sample of children from 0 to 6 years of age ( $n = 2,299$ ) from the Eastern Cape Province of South Africa. The purpose of the study was to investigate the epidemiology and the age of acquisition of hepatitis B virus (HBV) infection in children, thus providing a preimmunization baseline measure of this infection in the population targeted for HBV immunization in South Africa. Overall, 10.4% (95% CI, 9.2–11.7) of the children tested were HBsAg-positive. There was a high rate of positivity in the 0–6- and 7–12-month age groups at 8.1% (95% CI, 5.5–11.7) and 8.9% (95% CI, 6.1–12.7), respectively, suggesting a higher rate of early acquisition of this infection than previously reported in South Africa. The proportion of HBsAg-positive children increased significantly with increasing age ( $\chi^2_{\text{trend}} = 5.9$ ,  $df = 1$ ,  $P = 0.02$ ), reaching 15.7% in the 61–72-month age group. This is the highest rate of HBV infection reported in community-based children from South Africa, indicating a significant burden of this infection. The difference in HBsAg prevalence between urban and rural children was not statistically significant ( $\chi^2 = 0.32$ ,  $df = 1$ ,  $P = 0.57$ ). There was also no difference in positivity between males (10.5%; 95% CI, 8.7–12.5) and females (9.8%; 95% CI, 8.1–11.7), ( $\chi^2 = 0.006$ ,  $df = 1$ ,  $P = 0.94$ ). This study provides the most recent preimmunization, community-based baseline investigation of the epidemiology of HBV infection in children targeted for universal immunization in South Africa. *J. Med. Virol.* 58:111–115, 1999.

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## INTRODUCTION

Infection with hepatitis B virus (HBV) poses a significant public health problem in many parts of the world, particularly in sub-Saharan Africa [Kire, 1993]. Worldwide, more than 300 million people are estimated to be chronic carriers of the virus and about 30% of these carriers who survive for 30 years or more may subsequently die of the chronic sequelae of HBV infection, cirrhosis, and hepatocellular carcinoma [Maynard, 1990]. Almost 90% of infants infected with HBV at a young age will become chronic carriers, whereas 10% or less of adults develop the carrier state [Hyams, 1995]. Therefore, immunization in infancy and childhood remains the most effective intervention to prevent the transmission of HBV and the sequelae associated with early acquisition of infection and the carrier state [World Health Organization, 1992; Kane, 1995].

The epidemiology of HBV varies greatly in different parts of the world. Nevertheless, it is possible to classify broadly geographical regions according to the prevalence of HBV infection. In areas of high endemicity, defined as regions in which more than 75% of adults have serological evidence of past or current infection with HBV [Edmunds et al., 1996], infection primarily occurs during childhood. Within South Africa, which is identified as highly endemic for HBV infection [Dusheiko et al., 1989a, 1989b, Kew, 1992] most children acquire the infection by as yet largely undescribed horizontal routes between the ages of 1 to 5 years. Vertical transmission appears to be rare, with estimates of highly infectious hepatitis B e antigen (HBeAg)-positive pregnant women ranging from 4.6% to 10.3% [Prozesky et al., 1983; Guidozi et al., 1992], compared to South East Asia, where greater than 40% of preg-

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nant women are HBeAg-positive [Stevens et al., 1975; Edmunds et al., 1996]. Presumably, perinatal and neonatal infection still occur at a low rate in South Africa [Kew, 1992].

Details regarding the epidemiology of hepatitis B virus infection in children from Southern Africa has been reported in a number of published studies [Prozesky et al., 1983; Botha et al., 1984; Di Bisceglie et al., 1986; Abdool Karim et al., 1988, 1989; Dusheiko et al., 1989a, 1989b; Joubert et al., 1991; Schoub et al., 1991, 1993; Schoub, 1992]. Previous exposure to HBV as measured by HBsAg positivity ranges from 0.97% in urban black children [Di Bisceglie et al., 1986] to 25.1% in institutionalized children from Kwazulu-Natal [Abdool Karim et al., 1988]. The results from these studies form the basis on which South African health policy decisions have been made considering the inclusion of hepatitis B virus immunization for children. However, each of these studies has limitations, which restricts its use as a reliable, recent, community-based preimmunization baseline estimate of HBV infection in infants and children from South Africa. The most important constraints are very small sample sizes [Prozesky et al., 1983; Botha et al., 1984; Schoub et al., 1991]; samples were taken from diversely different groups (urban, rural, institutions, and undefined) [Botha et al., 1984; Abdool Karim et al., 1988; Schoub et al., 1993] and various age groups were examined, which included mainly older children and adults and not children less than 6 months of age [Di Bisceglie et al., 1986; Abdool Karim et al., 1989; Dusheiko et al., 1989a, 1989b; Joubert et al., 1991]. In addition, all these studies were done in the late 1980s and early 1990s. Since then, there have been considerable sociopolitical changes in South Africa, with significant changes in economic and cultural activities, increased population mobility, and blurring of strict urban/rural boundaries, which may impact on the epidemiology of infectious diseases, particularly HBV infection.

The introduction of universal infant HBV immunization in South Africa [Department of Health South Africa, 1995; Kane, 1995], which would undoubtedly alter the characteristics of natural HBV infection, and the inadequate existing baseline data on the epidemiology of HBV in the group targeted for universal HBV immunization prompted the present study. Our aim was to provide a recent preimmunization quantitative assessment of the burden of HBV infection in children between the ages of 0 to 6 years and to approximate the age of acquisition of this infection, thus providing a community-based baseline estimate of HBV infection against which to measure the impact of the South African HBV infant immunization strategy in the future.

## MATERIALS AND METHODS

### Study Population

The study was done in the Mdantsane district of the Eastern Cape Province, which includes both urban and rural communities. A large, densely populated urban township is located in the center of the district. Most

inhabitants of the township live in brick houses or backyard shacks and have access to basic amenities such as electricity, water, and sanitation [Orkin et al., 1997]. The township is surrounded by a sparsely populated rural area made up of isolated traditional settlements. Few rural households have electricity, water is obtained from local rivers or springs, and pit latrines are the predominant form of sanitation [Orkin et al., 1997]. In 1996, it was estimated that a total of 359,978 children under 5 years of age live in Mdantsane district, approximately 67% of whom are from rural communities [Department of Health, 1996].

Health services in the district are provided by Cecilia Makiwane Hospital (CMH), with a capacity of 1,000 beds and 18 primary health care clinics associated with the hospital. Eleven of these clinics are located within the township of Mdantsane and seven are in the surrounding rural areas. Four urban clinics and three rural clinics were selected for the study. The clinics were selected for logistic reasons in that their immunization days were staggered throughout the 5-day working week. Nevertheless, the clinics were thought to be representative of others in the district.

The study population consisted of children visiting the primary health clinics for routine primary care, between the ages of 0 to 72 months from July 1995 to April 1996. Children were included if there was no history of hepatitis B immunization. This was checked with the parent or guardian and confirmed by examining the Road to Health card, a patient-held record of immunizations and birth data. Children older than 72 months or those that had been already immunized against hepatitis B were excluded from the study. The purpose of the study was explained to the parent or guardian of each eligible child. Children were then included if the mother or guardian gave written consent for their participation. The study aimed to obtain a cross-sectional, age-stratified sample of 2,000 children equally stratified into the following age groups; 0–6, 7–12, 13–24, 25–36, 37–48, 49–60, and 61–72 months. Two registered nurses from the area (field workers) recruited the subjects, documented the relevant demographic information, and took the blood samples.

Clearance from the Committee for Research on Human Subjects and Ethics at the University of the Witwatersrand Johannesburg was obtained (protocol number M951029) and human experimentation guidelines as specified by this committee were followed in the conduct of the clinical research. Permission to conduct the study was also obtained from the Ethics Committee at Cecilia Makiwane Hospital and the Department of Information, Eastern Cape Province, South Africa.

### Sample Collection

Heel or finger prick blood specimens were obtained from children less than 24 months of age, using Microtainer tubes. The maximum volume of blood that these tubes contain is 700  $\mu$ l and this was the maximum limit set for children below 24 months of age. Children

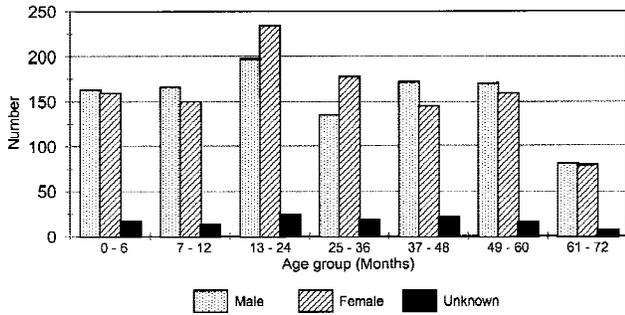


Fig. 1. Age and Sex Distribution of Sample

over the age of 24 months had either a heel/finger prick specimen taken or formal venepuncture from the ante-cubital fossa with a maximum volume of 5 ml allowed. Strictly hygienic and safe conditions were maintained at all times during blood sample collection. Name, age, gender, district, and immunization histories were recorded on standardized patient information forms. Blood specimens were kept in a cooler box on wet ice blocks at each clinic and transported back to Cecilia Makiwane Hospital to be stored at 4°C. At the end of each week, the specimens were sent to the National Institute for Virology (NIV) in Johannesburg by overnight courier for analysis. On arrival at the NIV, the serum was separated and the specimens were labeled and stored at -20°C until testing.

### Serological Testing

Serum samples were batched and tested for HBsAg using an enzyme immunoassay (EIA) kit Wellcozyme HBsAg. Murex Laboratories, UK). The manufacturer's conditions for the tests were strictly adhered to at all times and positives were defined according to the kit instructions.

### Statistical Analysis

SAS statistical software was used for all the analysis. The 95% confidence intervals for the proportions positive per age group stratum and for the whole group were calculated [Fleiss, 1981]. Differences in prevalence between gender and rural/urban groups were evaluated for significance using the  $\chi^2$  test. The  $\chi^2$  test for trend with one degree of freedom was used to evaluate linear trends for the age-stratified results.

## RESULTS

A total of 2,299 serum samples were tested. The age and sex distribution of the children tested are shown in Figure 1. In total, 47.1% of the sample were boys, 48.0% were girls, and information on gender was missing for 114 children (4.9%). The proportion of girls and boys were similar in each stratum. Children in the 13–24-month age group were slightly overrepresented, whereas there were fewer children in the 61–72-month group.

The proportion of HBsAg-positive children in each age group is shown in Table 1. The differences between

TABLE I. Proportion of HBsAg-Positive Tests per Age Group

Age group (months)	Total	HBsAg-positive	
		Number	% (95% Confidence interval)
0–6	333	27	8.1% (5.5; 11.7)
7–12	326	29	8.9% (6.1; 12.7)
13–24	453	45	9.9% (7.4; 13.2)
25–36	329	42	12.8% (9.5; 17.0)
37–48	337	27	8.0% (5.4; 11.6)
49–60	344	42	12.2% (9.0; 16.3)
61–72	166	26	15.7% (10.7; 22.3)
Total	2,288	238	10.4% (9.2; 11.7)

TABLE II. Proportion of HBsAg-Positive Tests

	Total	HBsAg-positive	
		Number	% (95% Confidence interval)
Male	1,078	113	10.5% (8.7; 12.5)
Female	1,097	107	9.8% (8.1; 11.7)
Rural	1,281	132	10.4% (8.8; 12.2)
Urban	1,017	106	10.5% (8.7; 12.6)

age groups is statistically significant ( $\chi^2 = 13.0$ ,  $df = 6$ ,  $P = 0.04$ ). Overall 10.4% (95% CI, 9.2–11.7) of the children were positive for HBsAg. The prevalence of HBsAg was surprisingly high in the two lower-age groups, 0–6 and 7–12 months, at 8.1% (95% CI, 5.5–11.7) and 8.9% (95% CI, 6.1–12.7), respectively. The proportion of HBsAg-positive children increased gradually from 8.1% (95% CI, 5.5–11.7) in the 0–6-month age group to 15.7% (95% CI, 10.7–22.3) in the children aged 61–72 months. This increase is statistically significant ( $\chi^2_{trend} = 5.9$ ,  $df = 1$ ,  $P = 0.02$ ).

HBsAg positivity for the 2,175 children with information on gender and place of residence is shown in Table II. Of the girls, 9.8% (95% CI, 8.1–11.7) were HBsAg-positive compared to 10.5% (95% CI, 8.7–12.5) of the boys. However, this difference is not statistically significant ( $\chi^2 = 0.32$ ,  $df = 1$ ,  $P = 0.57$ ). All but 1 of the 2,299 children had information on the area of residence. Fifty-six percent (1,281/2,298) were from urban areas and 44% (1,017/2,298) were from areas classified as rural. Table II indicates that the proportion of HBsAg-positive children in these two groups was very similar and not statistically different ( $\chi^2 = 0.006$ ,  $df = 1$ ,  $P = 0.94$ ).

## DISCUSSION

This study quantitatively assesses the burden of HBV infection in children between the ages of 0 to 6 years and provides a recent, community-based preimmunization baseline estimate against which to measure the impact of the immunization strategy recently introduced in South Africa.

The average rate of HBsAg positivity of 10.4% in children from the Eastern Cape, as a single indicator of infection with HBV, is similar to previously published data in adult males from this area (9%) [Dusheiko et al., 1989a, 1989b]. This work in adults is the only other study done estimating the burden of HBV infection in

people from the Eastern Cape and was conducted on adult black men employed as gold miners in the Witwatersrand in the 1980s. The older-age groups of children in the present study (49–60 and 61–72 months) show an increase in HBsAg positivity consistent with later acquisition of infection, probably by horizontal routes. However, the peak of HBsAg-positive children in the 61–72-month age group (15.7%) suggests a much higher rate of HBV carriers in adolescents and adults than demonstrated in the earlier published study from the Eastern Cape [Dusheiko et al., 1989a, 1989b]. Therefore, there is a significant burden of HBV infection in this population, which may have been underestimated in the past due to the limited study designs.

We also found that there were no differences in infection with HBV between Eastern Cape children from rural and urban areas, although differences in HBsAg prevalences in South African children from rural and urban environments have previously been demonstrated [Prozesky et al., 1983; Di Bisceglie et al., 1986; Abdool Karim et al., 1988]. The range of HBsAg positivity in these other studies is quite wide, within the rural areas 4.5% [Prozesky et al., 1983] to 18.5% [Abdool Karim et al., 1988] and the urban areas 0.97% [Di Bisceglie et al., 1986] to 10% [Abdool Karim et al., 1988]. The samples for these studies were taken from diversely different parts of the country, thus making it difficult to generalize their results to the whole of South Africa. Moreover, one study clearly showed that socioeconomic disparities per se did not appear to contribute to the differences seen in HBsAg rates, since no obvious differences in HBV infection rates was found between the highest and lowest socioeconomic groups in one area [Di Bisceglie et al., 1986]. However, all these investigations were conducted almost 10 years ago, when the rural/urban divide in South Africa was more obvious. In the past, population movements in South Africa were enforced by racially motivated apartheid laws, which began to collapse in the early 1990s. In the Eastern Cape Province, the rural/urban boundaries have certainly been blurred in recent years due to the mobility and periurban settlement patterns of the population [Pillay, 1996]. This may account for the loss of the strict division of groups as rural vs. urban and explain the similarity in the prevalences of HBV infection found in our study for rural and urban children.

Throughout Africa, lifetime exposure rates to HBV are the same in the two sexes [Kew, 1992]. However, the carrier rate is usually higher in men than in women, with ratios ranging from 1.1:1 and 3.2:1 [Kew, 1992; Abdool Karim et al., 1989; Schoub, 1992]. In South African children, no differences in chronic HBV infection have been shown between children of different sexes [Abdool Karim et al., 1988]. Our findings support this and a difference in HBsAg positivity rates between boys and girls up to the age of 72 months was not found.

The role of vertical transmission from mother to infant has been thought to be less important in South

Africa, with the predominant mode of transmission by undefined horizontal routes in older children (24 to 60 months of age), probably occurring during play activities or ritual scarification [Abdool Karim et al., 1988; Chiaramonte et al., 1991; Kew, 1992; Kire, 1993; Edmund et al., 1996; Martinson et al., 1996]. Also, since the proportion of South African women of child-bearing age that are considered highly infectious carriers (HBsAg- and HBeAg-positive) is relatively low (ranging from 4.6% in urban areas [Guidozzi et al., 1992] to 10.3% in rural areas [Prozesky et al., 1983]), it is thought that vertical transmission is not a major mechanism of HBV infection in South Africa. The high levels of HBsAg in the young-age groups, 0–6 and 7–12 months, of 8.1% and 8.9%, respectively, shown here were therefore not expected. These high levels imply that early HBV transmission is occurring. This transmission may be from mother to infant during the perinatal/neonatal period or via other modes of HBV transmission in this young-age group, such as ritual scarification, ear piercing, and exposure to HBV-infected siblings and family members. Since none of these mechanisms of early infection with HBV were directly measured and because the first age stratification in the our study from 0 to 6 months is relatively crude, we are therefore only able to observe that early transmission is probably occurring and to speculate about the likely mechanisms in South African infants. Further epidemiological studies in the age group below 6 months are needed to clarify this issue.

Hepatitis B infection is a major problem in South African children and may have been underestimated in the past. The recent introduction of universal childhood immunization against HBV in South Africa should be an important step in reducing the long-term sequelae of this disease. The current HBV immunization schedule in South Africa (at 6, 10, and 14 weeks of age) was based on data that showed a predominance of horizontal transmission [Robson et al., 1991, 1992]. This assumption may need to be reevaluated in the light of the high levels of early HBV transmission demonstrated in this study. Preventing perinatal or early neonatal transmission would require changes to the current immunization schedule. It would probably be too expensive for South Africa to provide hepatitis B immune globulin (HBIG) at birth, but it might be feasible to include an additional dose of HBV vaccine at birth. This would be much cheaper than using HBIG and could be included with the oral polio and BCG vaccines currently given at birth. A study to evaluate whether an additional dose of HBV vaccine at birth would reduce the early transmission of HBV in South Africa is an urgent priority.

We described the preimmunization prevalence of HBV infection in a cohort of children from a highly endemic area of South Africa using a single measure of infection, HBsAg. Similar baseline studies in areas of high endemicity for HBV infection have proven extremely valuable to evaluate the impact of HBV immunization strategies [Ruff et al., 1995; Chen et al., 1996].

Although these studies in general are costly in terms of time and resources, they remain the only way to quantify the impact of HBV immunization programs, detect vaccination failures, monitor the level of vaccine coverage in the target age groups, and observe the development of vaccine escape mutants of HBV. This baseline study used in conjunction with follow-up studies of vaccinated children from the Eastern Cape will allow an assessment of the impact of the HBV immunization strategy in South Africa.

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