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Immune Status of Cohort of Children Vaccinated against Hepatitis B Virus in Ekiti State over Ten Years after Incorporation into National Program on Immunization

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hepatitis B vaccine has been introduced in Nigeria for over a decade now, yet, data on sero-conversion status of the immunized cohort in the population are scarce. Such data are important for objective evaluation of the impact and effectiveness of the HBV vaccination program.

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This study therefore aims at determining the sero-conversion status and the prevalence of HBV infection among immunized cohort of children in Ekiti state, Nigeria.

Methodology: This cross-sectional study was conducted across the three senatorial districts of Ekiti state, between October and December, 2017. A total of 441 children consisting of 226 males and 215 females (Male to female ratio= 1.1:1). Immunization was confirmed by immunization cards. Multistage sampling technique was used. Questionaire were administered after caregiver's consent and assent from subjects, 2 to 5 mls of blood samples were then collected and tested for the various hepatitis B viral markers (HBeAg, HBeAb, HBcAb, HBsAb and HBsAg) using Hepatitis B combo kit manufactured by Innovita Biological Technology. Very low levels antibody titres which may not be detectable by qualitative detection method used is a limitation to this study.

Results: Subjects were between 5 to 10 years. All subjects had 3 full doses of hepatitis B vaccination before the age of 1 year and all subjects were negative for HBsAg, HBeAg, HBeAB and HBcAb. However, only 47 (10.7%) had detectable HBsAb. Among HBsAb positive patients 22 were males while 25 were females. Our findings showed zero prevalence of hepatitis B but minimal seroconversion rate among vaccinated children in Ekiti state, Nigeria.

Conclusion: Hepatitis B vaccination protects children against HBV in the study population. However, seroconversion rate showed that majority of the children may be at risk of HBV infection at a later age. We recommend a booster dose of HBV vaccination.

Keywords: Immune status; hepatitis B vaccine; sero-conversion; Ekiti State; Nigeria.

1. INTRODUCTION

Transmission and response to Hepatitis B virus (HBV) infection is dependent on age at infection, with young children infected commonly via contact with contaminated blood while parenteral and sexually transmitted route is commoner in adolescents and adults [1]. The likelihood that hepatitis B will develop from an acute infection into a chronic infection depends on the age of the person infected. The younger a person is when infected with hepatitis B virus, the greater the chance of developing a chronic infection. Approximately 90% of infected infants will develop chronic infection. The risk goes down as a child gets older. Approximately 25%–50% of children infected between the ages of 1 and 5 years will develop chronic hepatitis B. By contrast, about 95% of adults recover completely and do not become chronically infected [2].

Worldwide about 1 million deaths annually are attributed to HBV-related liver disease and hepatocellular carcinoma [1]. It has been reported that approximately 30% of the world's population has serologic evidence of current or past HBV infection with chronic hepatitis B virus carriers worldwide currently estimated at 400 million individuals. This fact and the attendant complications notably liver cirrhosis and hepatocellular carcinoma makes HBV infection a disease of major public health importance worldwide [3,4,5].

The hepatitis B vaccine was included in the immunization schedule in Nigeria in 1995 but the vaccine only became widely available in 2004, when the WHO policy of including HBV vaccination in the routine immunization schedule for children was implemented. The success of the immunization programme can be assessed by the timeliness of receipt of vaccines, the coverage of the vaccine and measurement of morbidity and mortality from the target disease [6]. In a study carried out at the Children Emergency Room of University of Benin Teaching Hospital, 83% of the children admitted within the study period were appropriately vaccinated but despite this high coverage rate in these age group, the study reported a high seroprevalence of HBV infection which was concluded to be due to lack of timeliness in administering the vaccine which rendered the vaccine ineffective [6]. According to the WHO in 2018, HBV vaccine has been introduced in 184 countries in the world with an average global vaccine coverage with 3 doses of hepatitis B vaccine estimated at 84% and as high as 92% in the Western Pacific [7]. In Nigeria however, few studies conducted on estimating vaccination coverage were among Health-care Workers (HCWs) and an average rate of 20% was reported. The risk of occupational exposure of this group of individuals to HBV however remains high [8]. Mortality attributable to this preventable and curable infection is quite high, being a leading cause of death and disability worldwide. The absolute burden and relative rank of viral hepatitis increased between 1990 and 2013 [9]. The availability of effective vaccines and treatments

suggests an important opportunity to improve public health hence, the need to find out the impact of the vaccination among vaccinated individuals.

The aim of this study is therefore to determine the immune-status of cohort of children vaccinated against Hepatitis B Virus in Ekiti State (over ten years after incorporation of HBV vaccination into national program on immunization).

2. METHODOLOGY

This cross-sectional study was conducted in Ekiti State, Southwest zone, Nigeria, between October and December, 2017.

2.1 Study Area and Study Population

Ekiti state has 16 Local Government Areas (LGAs) within three senatorial districts. The current population of Ekiti State based on the projection from 2006 National Population Census and annual growth rate of 3.0% is 3,027,949. Subjects were children between the ages of 5 to 10years the choice of subject is to accommodate children that have been captured in the vaccination program since Hepatitis B vaccine was introduced into routine immunisation.

2.2 Sampling and Sample-size

Multistage sampling technique was used. At the first stage, two LGAs were selected by balloting from each of the three senatorial districts, making a total of 6 LGAs in all. Stage Two involved random selection by balloting for two health facilities from the selected LGAs. The third sampling stage was at the selected health facilities where subjects were selected based on equal allocation of the determined sample size which was determined using the formula:

$$n = Z^2pq/d^2,$$

where n = sample size, Z = Z statistic for a level of confidence (1.96), P = expected prevalence or proportion (in proportion of one; of 50%, P = 0.5), and d = precision (in proportion of one; of 5%, d = 0.05) and 95% confidence intervals (CI) [10].

A sample size of three hundred and eighty-four (384) subjects was calculated, however, to make allowance for attrition, a total of 441 subjects were recruited across the total 12 facilities selected for the study, such that 30 to 42 subjects (children aged 5-10 years) were recruited from each facility.

2.3 Questionnaire

A semi-structured, interviewer-administered questionnaire framed in English and back translated into Yoruba was used. Information was sought from the caregivers on the socio-demographic characteristics and immunisation history of the children using trained research assistants. HBV Immunization status was confirmed using immunization cards of subjects. Survey instrument was pretested in Efon LGA (a LGA outside the study LGA).

2.4 Blood-collection

After caregiver's consent and assent from the children, 2 to 5 mls of blood samples were collected from each subject and tested for hepatitis B viral markers. Serologic testing for hepatitis B was done using rapid test kit searching for HBV markers namely HBeAg, HBeAb, HBcAb, HBsAg and HBsAb using Hepatitis B combo kit manufactured by Innovita Biological Technology (lot:20170101). Manufacturer's instruction was carefully followed in testing procedures and interpretation of results for each subject. The results of the screening were later handed over to each participant's care-giver.

2.5 Study Limitation

Since very low level antibody titres may not be detectable by qualitative detection methods as used in this study, further work using quantitative detection methods is required to confirm total lack of immunoglobulin or otherwise among vaccinated children.

2.6 Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences version 11.0 (SPSS inc, Chicago, USA, 1999). Student T test was used to compare continuous variables while Chi square was used for comparison of categorical variables as well as to evaluate associations between HBV positivity and associated factors. Statistical significance was set at a p-value (probability value) of <0.05.

3. RESULTS

A total of 441 children consisting of 226 (51.2%) males and 215 (48.8%) females between 5 to 10years were recruited into the study given a male to female ratio of 1.1:1. Majority (98.0%) belong to Yoruba ethnic group; 338 (76.6%) of them were in primary schools while only 5 were in secondary schools (Table 1). The highest age number of participants was age 5 years (27%) while the least was 10 years (6.1%). All subjects had 3 doses of hepatitis B vaccination before the age of 1 year. All subjects were negative for HBsAg, HBeAg, HBeAb and HBcAb. A total of 47 (10.7%) subjects had detectable HBsAb. There was zero prevalence of hepatitis B viral infection among the study population as seen by the absence of HBsAg in the serum of all the subjects. Table 2 shows the relationship between respondents' age and sex with the detection of Hepatitis B surface Antibodies. Though a greater proportion of the respondents with positive HBsAb were in the lower age group (12.7%) as against 7.0% in older age group, there was no significant difference in the detection of HBsAb across

Table 1. Socio-demographic characteristics of the respondents

Variables		Frequency, n	Percent (%)
Sex	Female	215	48.8
	Male	226	51.2
Tribe	Yoruba	432	98.0
	Igbo	5	1.1
	Hausa	1	.2
	Others	3	.7
Child's	Pre-Primary	98	22.2
Educational status	Primary	338	76.6
	Secondary	5	1.1
	Total	441	100.0
Age in years	**Frequency, n**		**Percent (%)**
5	119		27.0
6	86		19.5
7	79		17.9
8	68		15.4
9	62		14.1
10	27		6.1
Total	441		100.0

Table 2. Relationship between respondents' age and sex with hepatitis b surface antibodies detection

Age group of respondents	Hepatitis B surface Antibodies (HBsAb)		Total	Statistical test
	Neg	Pos		P=value
5 - 7.4yrs	248 (62.9%)	36 (76.6%)	284 (64.4%)	
7.5 to 10yrs	146 (37.1%)	11 (22.4%)	157 (35.6%)	X^2=3.413
Total	394 (100.0%)	47 (100.0%)	441 (100.0%)	P=0.065
Sex	**Hepatitis B surface Antibodies (HBsAb)**		**Total**	**Statistical test**
	Negative	**Positive**		**P=value**
female	191 (48.5%)	25 (53.2%)	216 (49.0%)	X^2=0.373
male	203 (51.5%)	22 (47.8%)	225 (51.0%)	P=0.541
Total	394 (100%)	47 (100%)	441 (100.0%)	

the various age of individuals in the study population. Furthermore, there was no significant gender difference between the proportion of those with positive Hepatitis B surface antibodies, 11.6% and 9.8% for females and male respectively.

4. DISCUSSION

The coverage rate of HBV vaccine among children in this study was 100%, this is similar to the findings of Patel MK, et al in 2014 where 98% coverage was found following routine infant immunization schedule in French Polynesia [11], and in China where a coverage of 94 percent was found by Xiaofeng Liang et al. when it was found that Hepatitis B vaccine coverage (3 doses) increased from 30.0% for children born in 1992 to 93.4% for children born in 2005 [12]. However coverage rate seen in this study is higher than the coverage rate seen in Yemen by Fuad A. A. Alssamei et al. where a rate of 87.3% was found among children from 6 to 59 months [13]. This Study is comparable with the findings of Bekondi et al. where overall HBV immunization coverage based on immunization cards was 99%, 49% and 100% in Cameroon, Central African Republic (CAR) and Senegal, respectively and that based on maternal recall was 91%, 17% and 88% in Cameroon, CAR and Senegal, respectively [14]. In this study, our assessment of coverage was based on immunization cards. The high coverage rate recorded in this study may be due to the use of immunization cards in assessing immunization coverage rather than just asking from the mothers. Confirming immunization status by maternal recall may not be reliable in the determination of immunization coverage. The coverage rate shows that hepatitis B vaccination has been successfully integrated into routine infant immunization program in most parts of Ekiti state in Nigeria.

There was zero prevalence of hepatitis B among vaccinated children in this study, this is in contrast with the findings of Bekondi et al. where HBsAg positivity prevalence of 0.7%, 5.1%, and 0.2% were seen among children in Cameroon, CAR and Senegal respectively [14]. And in Benin City, Nigeria were Ayebo and Antoinette found a sero-prevalence of 15.4% among individuals after complete HBV vaccination [6]. However, our findings, is similar to that of Patel MK, et al in 2014 among French Polynesia where none of the children were positive for hepatitis B infection [11].

This study showed that only 10.7% of children vaccinated against hepatitis B virus in infancy had detectable antibodies 5 to 10 years after the vaccination. The level of sero-conversion recorded in this study is very low when compared to studies from other countries within and outside Africa. Dassah S et al. found 87.9%, 78.3% and 41.7% seroprotection after 0–6 months, 2-3 years and 3-5 yrs respectively after complete vaccination in Ghana [15], Chakraborty et al found 100% seroprotection (≥ 10 IU/L) in Bangladesh [16], Freitas da Motta et al found a seroconversion rate of 77% in preterm infants and 98% among full term infants 3 months after the third dose among vaccinated children in Brazil [17]. Other findings however shows similarity to ours revealing a decline of HBV vaccine protective levels with time after vaccination. Al-Shamahy et al. in Yemen after 3-5 years had the highest protective rate (63.6%), while the lowest protective rate was found among age group tested 9-10 years after last dose of HBV vaccination [18], and cases of 27.8% of response failure to the vaccine seen by Alsamei et al in Yemen [18]. This may explain the findings of Essam et al. in Saudi Arabia where despite effective vaccine coverage, the rate of infections with HBV increased with age and most infections occurring in persons aged >14 years of age [19] and in Europe in which Nardone et al. found that despite Universal HBV vaccination programmes established seroprevalence of HBsAb was lower than the reported vaccine coverage in three countries [20]. And in China where Jian et al evaluated the impact of the universal infant Hepatitis B vaccination program on hepatitis B virus infection in Hangzhou, China and found among participants aged 0–59years a prevalence of HBsAg and HBsAb of 6.19%, and 45.83% respectively [21]. He et al found a significant reduction in the level of HBsAb among children 1-2 years after when compared to 3–15years [22].

Most HBV vaccines are given in three doses at infancy. A protective response to the vaccine is defined as an HBsAb concentration of at least 10 mIU/ml in the recipient's serum. Lee, Chuanfang [23] postulated that the protection afforded by vaccination is long lasting even after antibody levels fall below 10 mIU/ml [23]. However, other studies has shown HBV prevalence despite the WHO established coverage and have recommended revaccination or booster doses [13-21].

Electric power supply is very poor in Ekiti State and many other states in Nigeria, this may cause broken cold chain of stored vaccine and result in poor sero-conversion in 'vaccinated' children. Other possible causes of low sero-conversion rate include poorly manufactured vaccine, expired vaccine, improper administration and incomplete dosages. However among our study population, these are not likely because of the usual steps taken to ensure potency of vaccines used in the NPI programs.

It has been proposed that Long-term protection is present despite a decrease in anti-hepatitis B surface antibodies [24]. Thus, WHO does not recommend booster vaccination for persons who have completed the 3 dose-vaccination schedule [25]. However, infection rate in vaccinated populations [6,19-21], and sero-epidemiological [13,17,18] studies disagree with such position.

5. CONCLUSION AND RECOMMENDATION

Hepatitis B vaccination protects children against HBV in the study population. However, the sero-conversion rate seen in this study showed that majority of the children may be at risk of HBV infection at a later age. To avert a setback in the goal of hepatitis B viral eradication by year 2030, we recommend booster dose of hepatitis b vaccine at the school age of 6 years to all children in our environment.

CONSENT AND ETHICAL APPROVAL

Prior to data collection, ethical clearance for the study was obtained from the Ethics and Research Committee of Ekiti State University Teaching Hospital, Ado-Ekiti and Ekiti State Ministry of Health. Written consent was obtained from the caregivers of the selected children. Permission to use the Health facilities was obtained from the State Ministry of Health and State Primary Health Care Development Authority. All data were handled in a confidential manner. Pre and post testing counselling was done.

DISCLAIMER

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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