Immune response to Hepatitis B vaccine among children in Yemen

Talal A. Sallam, MSc, PhD, Haifa M. Alghshm, BSc, Arwa A. Ablohom, BSc, Mona S. Alarosi, BSc, Rasha E. Almotawakel, BSc, Nasrah H. Farea, BSc, Abdo A. Mosleh, BSc.

ABSTRACT

Objective: This study looks into the immune response to hepatitis B vaccine (HBV) among children who completed the 3 doses of vaccine 7-years after inclusion of HBV vaccination to the National Extended Program for Immunizations (EPI) in Yemen.

Methods: Between March 2002 and October 2002, a total of 170 children, aged 13-73 months with a mean age of 43.64 ± 17.42 SD months; and have completed the 3 HBV vaccine doses were investigated for immune response to HBV vaccine by quantifying anti-HBs. Past infection was investigated by testing children to total anti-HBc.

Results: Of all children, 49.4% were males and 50.6% were females. One hundred and forty-two (83.5%) responded to the vaccine (antibody level ≥ 10mIU/ml). Only 3 children of 153 (2%) were reactive to anti-HBc indicating that the response was due to vaccination rather than combined effect of vaccine and HBV past-infections. There was a trend of decreasing antibody level with an increasing age. However, the difference in antibody levels between age groups was not statistically significant (p=0.40). Significantly lower antibody level (p=0.02) was found among children with a low economic status.

Conclusion: This study has revealed a high response rate to HBV vaccine. However, a considerable proportion (32.4%) of vaccinated children remains to be reconsidered for either revaccination or booster doses due to lack, inadequate or low response. The trend of decreasing antibody level with increasing age suggests a need of careful monitoring of HBV vaccine efficacy in Yemen. Demographic factors such as gender number of inhabitants per room and educational level of father did not significantly affect the immune response to HBV vaccine.

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There are 350 million hepatitis B virus (HBV) chronic carriers worldwide.[1] The highest carrier rate is in Asia and Africa.[2] Chronic infection develops among 90% of newborns, 29-40% of children and 5-10% of adults.[3] Patients with long-standing active liver disease are at high risk of developing liver cirrhosis and hepatocellular carcinoma.[4] Hepatitis B virus is responsible for 80% of liver cancer cases in the world.[5] Therefore, prevention of HBV infections has become increasingly important. After an effective and low-cost HBV vaccine became available vaccine prevention of HBV infections became an achievable goal. Aside from selective vaccination of high -risk groups, the Word Health Organization (WHO) recommended inclusion of the HBV vaccine in the expanded program of immunization in countries with intermediate and high HBV endemicity. The vaccination policies have been evaluated in a number of countries. Hepatitis B virus vaccine has

From the Department of Microbiology (Sallam), Faculty of Medicine and Health Sciences, Department of Laboratory (Alghshm), Military Hospital, Ministry of Defense, and the Department of Medical Laboratory Science (Ablohom, Alarosi, Almotawakel, Farea, Mosleh), High Institute of Health Sciences, Ministry of Public Health and Populations, Sana'a, *Yemen*.

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Address correspondence and reprint request to: Dr. Talal A. Sallam, Associate Professor, Department of Microbiology, Faculty of Medicine and Health Sciences, Sana'a University, PO Box 12586, Sana'a, *Yemen*. Tel. +967 (1) 224777/256739. Fax. +967 (1) 256740. E-mail: talalsallam2000@yahoo.com

been reported to have an excellent protective efficacy against hepatitis B surface antigen (HBsAg) carriage in healthy infants, children, and in neonates with protective efficacy of 95-99%.[6] Despite its proven immunogenicity, HBV vaccine remain unable to induce an adequate immune response in 5-10% of healthy adults.[7,8] The response rates of HBV vaccine among children of 83.5%[9] have been reported from Palestine and 90.1%[10] from Egypt. A protective rate of HBV vaccine of 78.4-85.2% has been reported in China with decrease of HBsAg carriage from 2.82% to 0.60%.[11]

In Yemen, the HBV vaccine was included to the EPI in 1995 adopting the policy of 3 HBV vaccine doses given to all babies starting at one month of age. The first and second doses are to be given at one month interval whereas the third dose is given 5 months after the second dose. In general, the HBV vaccination coverage in Yemen reached up to 20.7% and in Sana'a, the governorate and the capital, reached 16.4% in the year 2001.[12] Ever since, this policy has not been evaluated. This study looks into the rate of immune response to HBV vaccine among children who completed the 3 doses of vaccine 7 years after the inclusion of HBV vaccination to the National Extended Program for Immunizations (EPI) in Yemen. It also examines the demographic factors that may affect the level of immune response.

Methods. In an informed consent, a total of 170 children who have completed the 3 HBV vaccine doses according to the vaccination policy implemented by the Yemeni Ministry of Health in several areas of the Capital city of Sana'a were enrolled in this study. Demographic data including age, gender, economic status and level of education of the father were gathered from each child. Venous blood was collected; sera were separated and frozen at –20°C until they were tested. Anti-HBs antibodies were quantified using enzyme-linked immunosorbent assay (ELISA) Axyme (Abbott, USA). Due to lack of volume of sera only 153/170 sera were further tested for total anti-HBc using the commercial ELISA (Human Germany). Data were analyzed using Statistical Package for Social Sciences computer program.

Results. Of 170 HBV vaccinated children enrolled in this study, 84 (49.4%) were males and 86 (50.6%) were females. All children aged 13-73 months with a mean age of 43.64 ±17.42 SD months were included. Of all children, 142 (83.5%) were responders (antibody level ≥ 10mIU/ml) whereas 28 (16.5%) were either weak responders or non-responders (antibody level of zero to below 10mIU/ml). The antibody levels varied in different children according to age. Therefore, children were divided into 5 categories. These were non-responders with no detectable antibody level, inadequate responders with antibody level of <10 mIU/ml, low responders with antibody level of 10-100mIU/ml, adequate responders with antibody level of >100 to <1000 mIU/ml and high responders with antibody level of >1000mIU/ml (**Table 1**). Of 153 samples, that were tested further for anti-HBc, 3 (2%) had an anti-HBc antibody with past HBV infection. The mean antibody levels were compared in various age groups and were found to decrease with the increasing age (**Table 2**). However, the difference in antibody levels was not statistically significant (p=0.393). The level of antibody in female children was higher compared to males (**Table 2**) but this difference was not statistically significant (p=0.102). Significantly, lower antibody level (p=0.02) was found among children whose father had a low economic status. Other demographic factors such as overcrowding and educational level did not significantly affect the antibody level (**Table 2**).

Table 1 - Hepatitis B virus antibody levels among different age groups of children.

Ab level	Children n (%)
Non-responders (zero level)	24 (14.1)
Inadequate responders (<10 mIU/ml)	4 (2.4)
Low responders (10-100 mIU/ml)	27 (15.9)
Adequate responders (>100-1000 mIU/ml)	68 (40)
High responders (>1000 mIU/ml)	47 (29.6)

Discussion. In Yemen, immunization programs against childhood infections in general and against hepatitis B virus infections in particular have not been evaluated before. This is one of the leading studies that evaluate an immunization program in Yemen. The finding of this study showed a high response rate to HBV vaccine as 83.5% of all vaccinated children produced anti-HBV antibodies. Similar findings were reported from Palestine[9] where response rate of 83.3% was found and Egypt[10] of 91.1%. In our study, the antibody response was solely due to vaccination rather than past-infection as indicated by the lack of anti-HBc in 98.1% of anti-HBc tested children. Despite the high response rate, a considerable proportion (32.4%) of vaccinated children remain to be reconsidered for either

Table 2 - Hepatitis B virus antibody levels in relation to demographic factors.

Variables	Children n (%)	Mean Ab level±SD	*p* value	F value
Ab levels in various age groups			0.398	0.767
12-24 month	26 (15.3)	317.9 ± 7.5 mIU/ml		
25-48 month	81 (47.6)	166.8 ± 1.0 mIU/ml		
49-73 month	63 (37.1)	98.1 ± 13.4 mIU/ml		
Ab levels in relation to sex			0.102	2.313
Male	84 (49.4)	138.1 ± 10.2 mIU/ml		
Female	86 (50.6)	165.2 ± 12.7 mIU/ml		
Ab levels in relation to overcrowding (household/room)			0.107	
≥3 people/ room	23 (13.6)	59.4 ± 119.5 mIU/ml		
<3 people/ room	146 (86.4)	175.0 ± 10.1 mIU/ml		
Ab level in relation to father's level of education			0.052	3.842
≥ secondary school	126 (78.2)	202.3 ± 9.8 mIU/ml		
< secondary school	44 (21.8)	65.7 ± 14.4 mIU/ml		
Ab level in relation to father's economic status			0.02	5.507
Medium to High	133 (78.2)	194.1 ± 9.7 mIU/ml		
Low	37 (21.8)	61.6 ± 16.0 mIU/ml		

revaccination or booster doses. These consisted of non-responders, inadequate responders and low responders children. Apart from economic status of father, none of the demographic factors such as age, gender, number of inhabitants per room and father's educational level was found to have statistically significant effect on the antibody level. A larger sample size seems necessary to draw a clear conclusion on the effect of these factors on the antibody level. Although statistically insignificant, a trend of decreasing antibody level with increasing age was observed. Perhaps this trend may have become significant had older age groups of vaccinated children been included in this study. However, inclusion of older age groups was not possible as the HBV vaccination program in Yemen started in 1995 and thus, the oldest child who received the vaccine at the time of the sample collection was 6-years-old. To verify this, another study that includes older age groups should be conducted. The mean antibody level in the age group of 49-73 months was <100 mIU/ml, a level at which a boost is recommended. A steady decline in anti-HBV titers over time after routine vaccination against HBV has also been reported elsewhere.[13] The low prevalence of anti-HBc among our subjects indicate that the response was due to the HBV vaccine and not due to past-HBV infection or due to the combined effect of vaccine and HBV past-infections. This low prevalence of anti-HBc also reflects the role HBV vaccine as an effective measure in controlling HBV infection. A significantly lower rate of HBsAg positivity among vaccinated children compared to the rate among the non-vaccinated in other studies was attributed to the preventive effect of the vaccine.[14,15] The other possible reason of lack of anti-HBc among our subjects could be the lack of mother-to-baby transmission of HBV. In Yemen, the mother-to-baby transmission has been proposed to be uncommon.[16]

In this study, anti-HBs antibody response rate was high among studied children. However, a considerable proportion of vaccinated children remain to be reconsidered for either revaccination or booster doses. The trend of decreasing antibody level with increasing age and the low response among the older age groups of subjects require further investigation.

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