BRIEF ARTICLE

Persistence of anti-HBs and immunologic memory in children immunized with hepatitis B vaccine

Sharif Md Habibur Rahman[1], Md. Rukunuzzaman[2], Rubaiyat Alam[2], Khan Lamia Nahid[2]

[1]Sheikh Russel Gastroliver institute & Hospital, Dhaka, Bangladesh
[2]Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Correspondence to: Dr. Rubaiyat Alam, Email: dr.rubaiyat@yahoo.com

ABSTRACT

Background: We aimed to examine the persistence of anti-HBs in Bangladeshi children aged 5 and 10 years after primary vaccination, and this response to a booster dose.

Methods: A total of 100 children were enrolled who were divided into two groups (A and B). Group A comprised of 50 children vaccinated 5 years ago, and group B had 50 children vaccinated 10 years ago. Hepatitis B surface antibody titer was measured, and a booster dose of the vaccine was administered to those who had anti-HBs less than 10 mIU/ml. Seventeen such children from group A and 27 from group B were vaccinated with a booster dose. After one month, 12 children from group A and 18 children from group B were retested for hepatitis B surface antibody levels.

Results: After 5 and 10 years of primary vaccination, 66.0% and 46.0% children had protective antibody levels. After one month of booster dose, 91.6% children responded to the increased level of anti-HBs in group A. Among them, 66.6% showed an adequate response. In group B, 88.8% had an increased level of anti-HBs antibody where 83.3% had an adequate response. Geometric mean titre of anti-HBs antibody boosted by 35 and 75 times from pre-booster time to post-booster vaccination in group A and B, respectively.

Conclusion: Children had protective levels of anti-HBs antibodies at 5 and 10 years after completion of the primary vaccinations. Anamnestic response to booster vaccination confirmed the persistence of an effective immunological memory in vaccines.

Keywords: anti-HBs antibody, Bangladesh, children, hepatitis B, immunologic memory

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most noteworthy health issues because of its extensive spreading nature. World health organization (WHO) reported that there are more than 350 million carriers of HBV in the world. Approximately 2 million people worldwide die of HBV related diseases including hepatocellular carcinoma (HCC), cirrhosis, chronic hepatitis, and acute hepatitis each year.[1] Prevalence of HBV infection differs markedly among distinct geographical areas. Chronic HBV (CHB) infection can be categorized as high (8%), intermediate (2 to 7%) and low (<2%) endemicity.[2] Most of the chronic infection in infancy and childhood occurs in highly endemic areas, whereas significant numbers of infections occur in adolescents and adults in moderately endemic areas. A community-based study in Bangladesh showed that carrier rate was 5.7% and 9% among urban and rural populations, respectively.[2] Hepatitis B vaccine was introduced to the Expanded Programme on Immunization (EPI) schedule since 2005 in Bangladesh. Neonatal immunization with HBV vaccine has been one of the most competent measures in public health.[3] Long-term reduction of CHB after vaccination is impressive but decreasing antibody titre (anti-HBs) over time against hepatitis B surface antigen is distressing.

In 1992, the global advisory group of EPI at World Health Assembly recommended introduction of HBV vaccine into national immunization programs for countries with a hepatitis B carrier rate of 8% or greater by 1995 and in all countries by 1997.[4] The EPI schedule of vaccines is three doses at 6, 10, and 14 weeks of age in Bangladesh. Vaccine-induced serum concentration of anti-HBs 10 mIU/ml has been considered as protective level in several studies.[5] Undetectable or declining anti-HBs levels are not unusual. Long-term observation of

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HIGHLIGHTS

1. A significant decline of anti-Hbs titer occurs over time.
2. The high anamnestic response rate after the booster dose denotes the existence of immunologic memory.
3. The persistence of immunogenicity of the HBV vaccine is recommended to be studied for more extended periods of time to detect the need for a booster dose in adolescence or early adulthood.

vaccinated newborns revealed that anti-HBs become low or negative in 15%-50% among the vaccine responders within 5 to 10 years.[6] However, long-term protection may exist despite decreasing level of anti-HBs antibodies over time. It is due to the priming of memory cells, which can create a memory (anamnestic) response when challenged.[7] So, the study aimed to evaluate the persistence of anti-HBs five and ten years after primary vaccination by EPI schedule, and also to see anamnestic reaction in those with a declining level of antibody to determine whether or not a booster dose is needed in Bangladeshi Children.

METHODS

This prospective cohort study was operated at the Department of Pediatric Gastroenterology and Nutrition Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) from June 2017 to May 2018. Consecutive 100 hepatitis B vaccinated children attending the in-and out-patient department were included in the study after fulfilling the inclusion criteria. Around 6 and 11 years of either sex children who received 3 doses of hepatitis B vaccine 5 and 10 years ago by EPI schedule were included in the study. They were divided into two groups where group A comprised children vaccinated around 6 years old and group B of around 11 years old (each group contained 50 children).

A structured questionnaire was constructed, and data were collected by the researchers of this study. All ethical issues were discussed with the parents and they were clearly informed in an easily understandable local language about the nature and purpose of the study, procedures followed, risks associated with it, benefits, and their right to participate or withdraw from the study at any time. Then, a written informed was obtained from parents and every caution was taken so that no harm could be caused to the cases. Detailed history regarding age, sex, anthropometry, blood transfusion, history of infected parents, family history of contact with HBV, any surgical or dental procedure, hepatitis B vaccination, and the number of doses were recorded. Anthropometric records, height, and weight were kept for each child. Two ml of venous blood was collected, and samples were tested on the same day for anti-HBs antibody by Chemiluminescent Enzyme Immunoassay method at the virology laboratory of BSMMU. HBsAg was done before vaccination. Those who were HBsAg negative and had declined level of antibodies (<10 mlU/ml), hepatitis B vaccine, genetically engineered recombinant DNA vaccine, Engerix B, manufactured by GlaxoSmithKline, 0.5 ml, intramuscular was given to test for an anamnestic reaction. The antibody level was measured one-month after booster vaccination.

Statistical analysis

Data were analyzed by IBM SPSS version 22.0. Categorical data were expressed by using frequency (percentage) and numeric data were presented as geometric mean (standard deviation). Chi-square test or Fisher's exact test were used to test the association for categorical variables. Paired t-test and Mann-Whitney U test were used to compare numerical values as appropriate. A *P*-value <0.05 was taken as statistically significant.

RESULTS

Thirty (66%) children of group A and 23 (46%) of group B had protective concentration of anti-HBs (anti-HBs >10 mlU/ml) at 5 and 10 years after completion of the primary vaccination course, respectively. A significant decline in anti-HBs titers over time was observed (*P*=0.044). A total of 17 and 27 children from group A and B were administered a booster dose of vaccination, respectively. Following one month after the booster vaccination, blood samples were successfully obtained from 12 children in group A and 18 children in group B. Out of 12 children in group A, 11 (91.6%) responded

with an increased level of anti-HBs. Sixteen (88.8%) children in group B also responded with an increased level of anti-HBs **(TABLE 1)**.

TABLE 1 Distribution of children in Group A and B according to anti -HBs titre (mIU/ml) in pre and post-booster vaccination

Vaccination	Group A* (n= 50)	Group B* (n=50)	*P*
Pre -booster anti HBs titre (mIU/ml)			
<10	17 (34.0%)	27 (54.0%)	0.04
≥10	33 (66.0%)	23 (46.0%)	
Post-booster anti HBs titre (mIU/ml)	(n=12)	(n=18)	
<10	1 (8.3%)	2 (11.1%)	0.31
10-100	3 (25.0%)	1 (5.6%)	
>100	8 (66.6%)	15 (83.3%)	

* Group A and B received primary EPI scheduled vaccinated 5 and 10 years ago respectively

In both groups, children with weight for age percentile (WAP), height for age percentile (HAP) and BMI lie below the 5th percentile had low seroprotection rate than normal children, though findings were not statistically significant **(TABLE 2)**.

TABLE 2 Nutritional status of children in group A and B with different level of anti-HBs

Nutritional indicators	Overall n (%)	Level of anti-HBs		*P**
		<10 mIU/ml n (%)	≥10 mIU/ml n (%)	
Group A (n=50)				
Weight for age percentile, < 5th percentile	9 (18.0)	4 (23.5)	5 (15.1)	0.47
Height for age percentile, < 5th percentile	5 (10.0)	2 (11.8)	3 (9.1)	0.77
Body mass index, < 5th percentile	5 (10.0)	2 (11.8)	3 (9.1)	0.80
Group B (n=50)				
Weight for age percentile, < 5th percentile	4 (8.0)	3 (11.2)	1 (4.4)	0.38
Height for age percentile, < 5th percentile	3 (6.0)	2 (7.5)	1 (4.4)	0.65
Body mass index, < 5th percentile	3 (6.0)	2 (7.5)	1 (4.4)	0.65

*Chi square test was used to assess the association between level of anti HBs titre and different nutritional indicators

The geometric mean titre of anti-HBs increased by 35-fold from 5.9 ± 2.4 mIU/ml at a pre-booster time to 204.6 ±451.6 mIU/ml after booster vaccination in group A and in group B. It increased 75-fold from 4.8 ±1.6 mIU/ml at a pre-booster time to 357.9 ±434.2 mIU/ml after booster vaccination **(FIGURE 1)**.

DISCUSSION

The present study showed that the anti-HBs titer between children tested at 5 and 10 years after primary vaccination had declined with time but they have immunological memory responding to booster doses. A study from Egypt aimed to see long-term protection of hepatitis B vaccination, demonstrated anti-HBs level fall rapidly among all participants. They reported 81% and 48% of all children had HBsAb>10 mIU/ml at 5 and 10 years after vaccination, respectively.[8] Jafarjadeh et al. reported that 81.5% and 47.9% of children had protective antibody levels at 5 and 10 years after completion of the primary vaccination course.[9] The results of the present study revealed that at 5 and 10 years after completion of the primary vaccination course, 33/50 (66%) and 23/50 (46%) of children have protective levels of anti-HBs with geometric mean titre of 35.7 mIU/ml and 16.7 mIU/ml, respectively. The persistence of protective levels of anti-HBs has been attributed to the highest level of antibody titre at one month after fulfillment of the primary vaccination course. Similar results were also reported in other studies.[10-13]

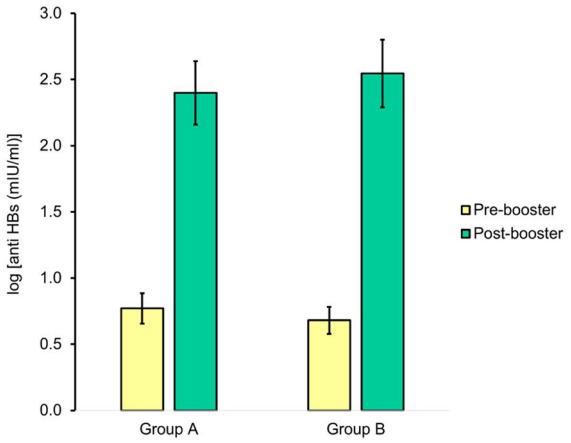

FIGURE 1 Comparison of geometric mean titer of anti-HBs in vaccinees at pre and post-booster vaccination in groups A (n=12) and B (n=18).

In this study, nutritional status of both groups was compared in relation to antibody response. Children with weight for age percentile (WAP), height for age percentile (HAP) and BMI for age lies below the 5th percentile in both groups who had less seroprotection rate than normal children, though findings were not

statistically significant. El sayed et al.[8] and Sami et al.[11] reported no significant difference in seroprotection regarding WAP and HAP percentile.

In the current study, it was found that one month after receiving a booster vaccination, the percentage of individuals with protective levels of anti-HBs at 5 and 10 years after the primary immunization increased to 91.6% and 88.8%, respectively. Furthermore, the geometric mean titer of anti-HBs showed a significant increase of 35 and 75 times. Specifically, the anti-HBs levels rose from 5.89±2.38 mlU/ml and 4.76±1.6 mlU/ml before the booster to 204.6±451.6 mlU/ml and 357.94±434.17 mlU/ml after the booster vaccination in group A and B, respectively. These results clearly represented that the immunological memory remains intact at 5 and 10 years after the completion of primary vaccination with HBV vaccine. The seroprotection rate after booster vaccination is close to the results reported in studies on Chinese neonates (89.6%), Iranian neonates (95.7%) and Egyptian children (94.2%).[14-18]

The present study showed that 17 (34%) and 27 (54%) children lost protective levels of antibodies at 5 and 10 years after primary vaccination, but in majority of them, the immunological memory remained intact. Banatvala et al.[6] reported that those individuals who were vaccinated in the past and whose level of anti-HBs declined to low or undetected levels over time, can climb an anamnestic reaction within a time as short as 4 days of viral exposure.

Conclusion

The study acknowledges certain limitations, with one of them being the reduction in sample size over the course of the follow-up period. An anamnestic response to booster vaccination confirms the persistence of an effective immunological memory in vaccines. A significant decline in anti-HBs titers over time may indicate the necessity of a booster vaccination in adolescence or early adulthood.

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Author Contributions

Conception and design: SMHR, MR, RA. Acquisition, analysis, and interpretation of data: SHMR, RA. Manuscript drafting and revising it critically: SMHR, MR, RA, KLN. Approval of the final version of the manuscript: SMHR, MR, RA, KLN. Guarantor accuracy and integrity of the work: RA, MR, KLN.

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Conflict of Interest

The Authors declare no conflict of interest.

Ethical Approval

Ethical clearance was taken from the IRB of the Bangabandhu Sheikh Mujib Medical University before the initiation of this study. Approval paper was provided after138th IRB meeting which was held on 20th May 2017 (Memo no. BSMMU/2017/5728).

ORCID iD:

Rubaiyat Alam: https://orcid.org/000-0002-6140-7571

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