ORIGINAL ARTICLE

IMMUNE RESPONSE AND ANAMNESTIC IMMUNE RESPONSE IN CHILDREN AFTER A 3-DOSE PRIMARY HEPATITIS B VACCINATION

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Background: Diseases caused by Hepatitis B virus (HBV) have a worldwide distribution. Pakistan adopted the recommendations of World Health Organization (WHO) for routine universal infant vaccination against hepatitis B in 2002, currently being administered at 6, 10, and 14 weeks of age in a combination vaccine. This study was conducted to determine the immune response & anamnestic immune response in children, 9 months–10 years of age, after a 3-dose primary Hepatitis B vaccination. **Methods:** This cross sectional study was conducted in the Department of Paediatrics, King Edward Medical University/Mayo Hospital, Lahore, Pakistan, from January to June, 2014. A total of 200 children of either sex between the ages of 9 months to 10 years, docu-mented to have received 3 doses of hepatitis B vaccines according to Expanded Program of Immunization (6,10,14 weeks) schedule in infancy, were recruited by consecutive sampling. The level of serum anti-HBsAb by ELIZA was measured. Children with anti-HBs titers ≥10 mIU/mL were considered to be immune. Those with anti-HBsAb levels <10 mIU/mL were offered a booster dose of infant recombinant hepatitis B vaccine. The second serum sample was obtained 21–28 days following the administration of the booster dose and the anamnestic immune response was measured. Data was analysed using SPSS 17 to determine the relation between time interval since last vaccination and antibody titer. Chi square test was applied. **Results:** Of the 200 children, protective antibody response was found in 58%. Median serological response was 18.60 (range 2.82–65.15). Antibody levels were found to have a statistically significant (*p*-value 0.019) negative correlation with the time since last administration of vaccine. A booster dose of Hepatitis B vaccine was administered to all non-responders, with each registering a statistically significant (*p*-value 0.00) anamnestic response. **Conclusion:** The vaccination schedule with short dosage interval was unable to provide protection to 42% of the study population. Introduction of birth dose of Hepatitis B vaccine to the existing schedule is recommended.

Keywords: Primary Hepatitis B vaccination; Children; Immune response; Anamnestic immune response

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INTRODUCTION

Hepatitis B virus (HBV) has worldwide distribution, leading to global morbidity in >2 billion people.[1] Sero-prevalence of Hepatitis B surface antigen (HBsAg) in general Pakistani population is reported at 2.6%[2] while it is 1.7–5.5% in paediatric population in Pakistan.[3] Pakistan falls in the intermediate to high endemicity zone of hepatitis prevalence.[4] As of 2008, 177 countries have included hepatitis B vaccine as an integral part of their national immunization programs. There are different schedules being used for Hepatitis B immunization in national programs, depending on the programmatic reasons and local epidemiology.[5]

The sero-protection rate for vaccination is influenced by a number of factors. Important factors are: age, schedule, and interval between the vaccine administration.[6] The available vaccines have safety and efficacy but literature reports falling titres over some period. After primary series, immune response may persist up to 20 years but it is found that with passage of time, immunized children may lose detectable antibody to the level to show the immune response.[7,8] Pakistan is among those countries which adopted World Health Organization (WHO)'s recommendations for routine universal infant vaccination against Hepatitis B in 2002, currently being administered at 6, 10, and 14 weeks of age in a combination vaccine.[9]

So far, we could not find any study, conducted in this country, on the efficacy of Hepatitis B vaccination, given at above schedule. Therefore, considering the schedule and interval of Hepatitis B vaccination and endemicity of Hepatitis B in Pakistan, this study was planned to determine the immune response and anamnestic immune response in children, 9 months–10 years of age, after a 3-dose primary Hepatitis B vaccination.

MATERIAL AND METHODS

This cross sectional study was conducted in the Department of Paediatrics, King Edward Medical University/Mayo Hospital, Lahore, Pakistan, from January to June, 2014. Informed consent was obtained from parents before enrolment. A total of 200 children of either sex between the ages of 9 months to 10 years, documented to have received 3 doses of Hepatitis B vaccines (as part of combination vaccine) according to Expanded Program on Immunization (6,10,14

weeks) schedule in infancy, were recruited by consecutive sampling. The children were recruited from the well child clinic of the hospital. The different age groups selected were 9 months–12 months, 1–1.9 year, 2–2.9 year, 3–3.9 year, 4–4.9 year, 5–5.9 year, 6–6.9 year, 7–7.9 year, 8–8.9 year, 9–10 year. The groups were formed to see the age wise immune response whereas selection of the patients between the groups was random. The data was collected for name, age, sex, residence, and vaccination for the last dose of HBV vaccine and was recorded on a structured questionnaire.

A non-heparanized 1cc venous blood sample was drawn by aseptic measures and sample was sent to reference laboratory. The level of serum anti-HBsAb by ELISA was measured. The children having anti-HBs titers of ≥10 mIU/mL were labelled as "immune". The children having anti-HBs levels less than 10 mIU/mL were administered a booster dose of infant recombinant Hepatitis B vaccine. Subsequently, after 21–28 days, serum sample was obtained to measure the anamnestic immune response. Data was analysed using SPSS-17 to determine the relation between time interval since last vaccination and antibody titres. Chi square test was applied at 5% level of significance.

RESULTS

Of the 200 children, protective antibody response was found in 58%, while 42% were non-responders (anti-HBs levels <10 mIU/mL). Median serological response was 18.60 (range 2.82–65.15). Antibody levels were found to have a statistically significant (*p*-value 0.019) negative correlation with the time since last administration of vaccine. (Table-1 and Figure-1) A booster dose of Hepatitis B vaccine was administered to all non-responders, with each registering a statistically significant (*p*-value 0.00) anamnestic response.

Table-1: Interval between the last vaccination & Immune response among vaccinated children (n=200)

Age group	Non-responders (<10 mIU/ml)	Responders (≥10IU/ml)
9 months	3	17
1–1.9 year	10	10
2–2.9 year	7	13
3–3.9 year	10	10
4–4.9 year	15	05
5–5.9 year	8	12
6–6.9 year	5	15
7–7.9 year	7	13
8–8.9 year	9	11
9–10 year	10	10
Total	84 (42%)	116 (58%)

(*p*-value 0.019 - statistically significant negative correlation with the time since last administration of vaccine)

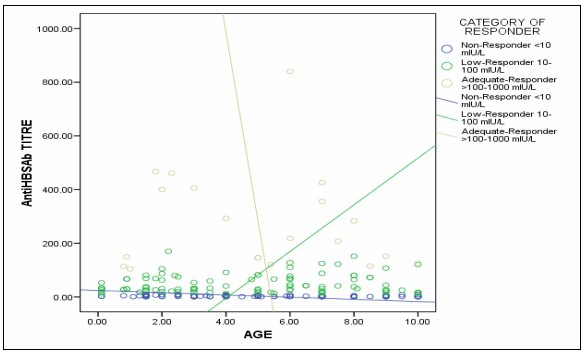

Figure-1: Age related immune response in children (n=200)

DISCUSSION

The study findings showed that 42% of the study population had level <10 mIU/ml which is non-protective. Host factors which can affect the decline in immunity can be dosing interval and, age. We studied the schedule used. Different researchers have studied this factor. Al-Shamahy *et al*[6] evaluated the immune response to the HB vaccine and found 54.8% protective immune response. The sero-protection rate is similar to ours and is low and a major factor contributing to this could be that nearly two thirds of the study group had received vaccine at shorter interval as that of us. In our study, all non-responders were offered the administration of booster dose of Hepatitis B vaccine, with each registering a statistically significant (*p*-value 0.00) anamnestic response. Our results are comparable to Teoharov *et al*[1] from Bulgaria who demonstrated 100% anamnestic immune response. Previous studies on immune response reported 92–100% anamnestic immune response in those children who were offered booster dose, 5–15 years after their primary vaccination series.[11]

Antibody levels were found to have a statistically significant (*p*-value 0.019) negative correlation with the time since last administration of vaccine. Teoharov *et al*[1] from Bulgaria reported the findings comparable to ours. Leuridan *et al*[7] also reported fall in anti-HBs levels with increase in age and timing since primary immunization. Capending *et al*[10], in a multicentre trial, also reported similar findings. Girisha *et al*[12] studied two different schedules and reported higher antibody level with 0, 1, 6 months schedule compared with 0, 1, 2 months. This fact has been studied by other authors and longer interval between the doses has been found better.[13,14]

In countries where a high proportion of HBV infections are reported to be acquired prenatally, WHO has recommended the administration of the first dose of hepatitis B vaccine as early within 24 hours after birth.[5] WHO

recommends two options. One is the primary hepatitis B immunization series (One monovalent birth dose followed by 2 monovalent or combined vaccine doses at the time of DTP_1 and DTP_3 vaccine doses). However, WHO also recommends 4 doses for programmatic reasons of the country (e.g. One monovalent birth-dose followed by 3 monovalent or combined vaccine doses with DTP vaccine doses), as per policy of concerned immunization program.[15] Centre for disease control and prevention (CDC) has also recommended the administration of birth dose of hepatitis B, followed by 2nd and 3rd doses with minimum of 4 and 8 weeks respectively.[8]

This study has the limitation of small sample size as this size makes it difficult to conclude definitively about level of protection. This emphasizes on the necessity of more studies with larger sample size and consideration of possible factors such as age, sex, nutritional status, and vaccine brand.

CONCLUSION

The study demonstrates that the vaccination schedule with short dosage interval was unable to provide protection to 42% of the study population.

Recommendation: We intend to recommend that to improve the immune response as well as to prevent perinatal transmission, a birth dose of Hepatitis B vaccine shall be added to the existing schedule. Thereafter, either administer 2 doses at 6 weeks and 14 weeks with DPT_1 & DPT_2 or for programmatic reason, administer 3 doses with DPT_1, DPT_2 & DPT_3.

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AUTHORS' CONTRIBUTION

All authors have substantially contributed to conception, design, acquisition of data, data analysis &interpretation, drafting article, and revising it for important intellectual concepts.

REFERENCES

1. Teoharov P, Kevorkyan A, Petrova N, Baltadzhiev I, Van Damme P. Immune Memory and Immune Response in Children From Bulgaria 5–15 Years After Primary Hepatitis B Vaccination. Pediatr Infect Dis J 2013;32(1):51–3.
2. Bosan A, Qureshi H, Bile KM, Ahmad I, Hafiz R. A review of hepatitis viral infection in Pakistan. J Pak Med Assoc 2010;60(12):1045–58.
3. Ali SA, Donahue RM, Qureshi H, Vermund SH. Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. Int J Infect Dis 2009:13(1):9–19.
4. WHO. Hepatitis B. World Health Organization. [Internet]. [cited 2014 Dec. 10]. Available from: http://www.who.int/mediacentre/factsheets/fs204/en/
5. WHO. Hepatitis B vaccines, WHO position paper. Weekly epidemiological record Releve epidemiologique hebdomadaire 2009;84:405. [Internet]. [cited 2014 Dec 10]. Available from: http://www.who.int/wer/2009/wer8440.pdf?ua=1
6. Al-Shamahy HA, Hanash SH, Rabbad IA, Al-Madhaji NM, Naser SM. Hepatitis B vaccine coverage and the immune response in children under ten years old in Sana'a, Yemen. Sultan Qaboos Univ Med J 2011;11(1):78–82.
7. Leuridan E, Van Damme P. Hepatitis B and the need for a booster dose. Clin Infect Dis 2011;53(1):68–75.
8. Centre for disease control and prevention. General recommendations on immunization recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 2011;60(2):1–64.
9. WHO. Pakistan, Expanded Program for immunization. World Health Organization. [Internet]. [cited 2014 Dec 15]. Available from: http://www.emro.who.int/pak/programmes/expanded-programme-on-immunization.html
10. Capending MR, Cadorna-Carlos J, Book-Montellanoc M, Ortiz E. Immunogenicity and safety of a DTaP–IPV//PRP~T combination vaccine given with hepatitis B vaccine: a randomized open label trial. Bull World Health Organ 2008;86(6):443–51.
11. Fitzsimons D, François G, Hall A, McMahon B, Meheus A, Zanetti A, *et al*. Long-term efficacy of hepatitis B vaccine, booster policy, and impact of hepatitis B virus mutants. Vaccine 2005;23(32):4158–66.
12. Girisha KM, Kamat JR, Nataraj G. Immunological response to two hepatitis B vaccines administered in two different schedules. Indian J Pediatr 2006;73(6):489–91.
13. Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. J Infect Dis 1989;160(5):766–9.
14. Halsey NA, Moulton LH, O'Donovan JC, Walcher JR, Thoms ML, Margolis HS, *et al.* Hepatitis B vaccine administered to children and adolescents at yearly intervals. Pediatrics 1999;103(6 Pt 1):1243–7.
15. WHO. Summary of WHO position papers-Recommendation for routine immunization. [Internet]. [cited 2016 Oct 2]. Available from: http://www.who.int/immunization/policy/Immunization_routine_table1.pdf?ua=1

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