# Efficacy of hepatitis B vaccination in children under five years of age: a sample from city of Baghdad

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## ABSTRACT

**INTRODUCTION**: Hepatitis B Virus (HBV) is one of the most common chronic viral infections. Universal immunization against HBV is considered to be the best way of prevention of HBV infection. Protection is usually linked to the level of anti-HBs antibodies after primary vaccination. No available documented data about this issue at Ministry of Health.

**OBJECTIVE**: is to evaluate the level of the adequacy of seroconversion when hepatitis B vaccine is given at 0, 1 and 6 months as per WHO schedule among children under age of five years of age in Baghdad, Iraq.

**METHODS**: A total 568 serum samples obtained from healthy children received three doses of recombinant Hepatitis B vaccine from January to November 2016, the serum samples were analysed by VIDAS for the quantitative detection of anti-hepatitis B surface antigens.

**RESULTS**: Results showed that 488 (86%) children had a protective anti-hepatitis B surface antigens (≥ 10 IU/L) and 80 (14%) children had inadequate levels of antibodies (≤10 IU/L), the geometric mean titers for anti-HBs were 208 IU/L with standard deviation of ± 147 IU/L. Karkh district had no significant differences in the mean titer of anti-HBs antibody, females had high titers of HBs against vaccination as compared to that of males ($P \leq 0.05$).

**CONCLUSION**: The vaccination program has been proven efficacy in children under five years of age living in Baghdad, the results showed that anti-HBs antibody titer may decrease over time after vaccination, finally, along with prevention and control strategies, ongoing investigation and monitoring antibodies level against HBV in children and other ranges are recommended.

**Key words**: HBV, vaccine, Immune response, Baghdad.

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## INTRODUCTION

Hepatitis B Virus (HBV) is one of the most common chronic viral infections in the world. WHO estimates that, globally, about 2 billion people have been infected with hepatitis B virus, more than 240 million are chronically infected and nearly 686000 die every year from acute and chronic sequel of primary infection of the disease.[1] HBV is known to be the major cause of liver failure, cirrhosis, and hepatocellular carcinoma.[2] Chronic infection after exposure to (HBV) has been observed in 30% to 90% of children aged less than five years. The prevalence of HBV infection varies markedly among different geographical regions and chronic HBV infection can be categorized as high, intermediate and low endemicity. The age at the time of infection is associated with the endemicity. In highly endemic areas (carriage rate 8% or more), infection in infancy and childhood accounts for most of the chronic carriage, whereas in moderately endemic areas (carriage rate 2-7%), significant number of infections occur in adolescents and adults.[3]

Hepatitis B Virus (HBV) was of moderate endemicity in Iraqi population with a rate of 3%,[4] another study reported 1.6% and was more frequent in age group above 40 years and in males

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more than females.[5]

Hepatitis B vaccines are based on Hepatitis B surface antigen (HBsAg) produced from recombinant yeast strains or recombinant mammalian cells. They are highly immunogenic[6] and available as monovalent formulations or in fixed combination with other vaccines including diphtheria–tetanus–pertussis (DTP), *Haemophilus influenzae* type b, and inactivated polio. The immune responses and safety of these combinations of vaccines are comparable to those observed when the vaccines are administered separately. However, in immunizing a child at birth against HBV only monovalent hepatitis B vaccine should be used.[7] The vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete vaccine series.[8]

Universal immunization against HBV is considered to be the best way of prevention of HBV infection. In Iraq, the National HBV Vaccination Programme has been included in the Ex¬panded Programme on Immunization (EPI) which was started at 1993 by a recombinant vaccine. The schedule of vaccination adopted by Iraqi Ministry of Health was three doses of a recombinant HBV vaccine (Euvax B / LG Life Sciences - Korea) administered to all in¬fants at the ages of (0, 1 and 6 months) to coincide with other compulsory vaccines.[5] At the Vaccine and Biological Products Registration, no study has ever been conducted to measure the response to hepatitis B vaccine in order to detect which one of the vaccinated child according to this programme has a satisfactory immunological response and who is not hence, we can recommend a booster dose at an appropriate interval. So, the aim of this study is to evaluate the effectiveness of recombinant HB vaccine given to Iraqi children below the age of five years after primary immunization by measuring the level of anti HBs antibodies.

## METHODS

**Study design and settings:** A cross sectional study was conducted in Baghdad by the authors from 1st of January 2016 to 31st of December 2016. Baghdad is the capital of Iraq and its biggest city divided into 2 parts by Tigris River; Karkh which is located to the west of the river and Rusafa to its east bank. Each side is served by several primary health care centres.

**Ethical consideration:** The study was approved by the Ministry of Health (MoH) in Iraq, the aim was explained to all participants' parent and a consent was taken from each participant before being enrolled in the study.

**Definition of the participant, inclusion and exclusion criteria:** The children were chosen randomly from 31 primary health care centres representing geographic areas of Baghdad. We have used a convenient sampling in our study to enrol children aged 9-60 months and have completed their immunization series in its three doses at age of 0,1, and 6 months whom attending to the primary health centre for routine immunization programme. Full immunization was documented by checking the records of the child kept at the primary health care centre. Children out of the age range of this study, having unknown or missing vaccination history, being refused to participate by the parents, and having any medical illness that may affect the immunological response like infectious diseases or using immunocompromising drugs were excluded from this study.

**Formulation of the questionnaire:** The questionnaire form; "Research Questionnaire on Immunization Strategy of Hepatitis B" was prepared by the Centre for Control Disease and Prevention at ministry of health. It contains basic demographic criteria of the child like age and gender, in addition to some data about the hepatitis B vaccine like date and interval of vaccination.

**Procedure:** About (5 ml) of venous blood were taken from each child. Then serum samples were extracted, collected and stored at -20˚C. The serum samples were sent to the Centeral Public Health Laboratory (CPHL) /AIDS and Hepatitis References Laboratory in Baghdad. At this reference laboratory a quantitative determination of the anti-HBs was done by VIDAS using commercial test kits (VIDAS Anti-HBs Total II Quick HBST; Biomerieux/ Italy ,10 µg). We categorized the children according to WHO reference value into three groups:[9] non-responders to HB vaccination when the level of HBs antibody is < 10 IU/L, hypo-responder when the level is 10-100 IU/L, and good responders when the level is > 100 IU/L. Level of HBs antibodies of > 10 IU/L is considered adequate immunological response

Table 1: Age related mean titer of Anti- HBs antibody

| Age groups (Month) | No. of vaccinated children | Last dose period (Mean ±SD) Month | Anti-HBsAb<10 IU/L | Anti-HBsAb ≥ 10IU/L | •GMT (Mean±SD) | P-Value |
|---|---|---|---|---|---|---|
| 9 | 58 | 1.9 ± 0.6 | (3) 5.1 % | (55) 94.9% | 341± 195 | |
| 13-24 | 112 | 10.3 ± 0.6 | (65) 5.3% | (106) 94.7% | 199± 198 | 0.002 |
| 25-36 | 112 | 23.3 ± 12.3 | (14) 12.5% | (98) 87.5% | 181± 188 | 0.001 |
| 37-48 | 114 | 45.45 ± 12.7 | (27) 23.6% | (87)76.4% | 127± 171 | 0.001 |
| 49-60 | 172 | 58.2 ± 18.4 | (30) 17.4% | (142) 82.6% | 130 ± 173 | 0.001 |
| Total | 568 | 33.5 ± 10.6 | (139) 14.1% | (429)85.9% | (208) ± 147 | |

•GMTs: Geometric Mean Titer

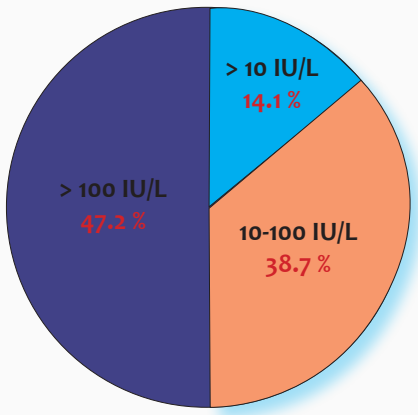


**Figure 1**: Immunological response to HBV vaccination among children participated in the study (n=568)

to the vaccine hence offer a protection.

**Statistical analysis**: t- student test was used for analysis of data. Mean titer was calculated by Microsoft Excel software and P value less than 0.05 was considered as significant.

## RESULTS

**Figure 1** shows the distribution of participants according to the level of HBs antibodies. About half of the participants have shown a good immunological response where the level of HBs antibody is > 100 IU/L. In 80 children (14.1%) the level is < 10 IU/L which is called immunologically non-responders or seronegative. About a third of children were showing a titer of 10-100 IU/L; hypo responders. In general, 80 children (14 %) showed a serum HBsAb level below 10 IU/ml which is not protected, whereas 488 (86.0%) had a protective level of serum HBsAbs.

**Table 1** shows effect of age and mean of period from the last vaccine in months on the response to vaccination. Until age of 24 months with a mean period from last dose of 10.3 ± 0.6, about 95 % of children have a protective level of HBs Ab. It decreases to about 80% in children between age of 49-60 months with a mean period from last dose of 58.2 ± 18.4. This link has shown a statistically significant difference. The geometric mean titer has progressively decreased from 341± 195 to 130 ± 173 as the mean of period from the last dose decreased from 1.9 ± 0.6 month to 58.2 ± 18.4 and this difference was also statistically significant.

**Table 2** shows that the difference in geometric mean titer in the two districts of Baghdad, Karkh and Rusafa and in male and female are statistically non-significant.

**Table 2**: GMT in IU/L of HBsAbs in different age group

| Age group (Month) | Karkh | Rusafa | Male | Female |
|---|---|---|---|---|
| 9 | 332.9 | 419 | 349 | 452 |
| 13-24 | 198.8 | 206 | 212 | 194 |
| 25-36 | 173 | 224 | 181 | 229 |
| 37-48 | 116 | 248 | 214 | 178 |
| 49-60 | 136 | 53 | 67 | 141 |
| Mean | 191 | 241 | 189 | 236 |
| SD | 86 | 174 | 231 | 174 |
| P-Value | | 0.2 | | 0.3 |

## DISCUSSION

HBV infection is a significant health problem around the world. Fortunately, it is one of the oncoviruses that is vaccine preventable. HB vaccine induces anti- HBs response

which can prevent HBV infection. Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications. Studies have shown that childhood vaccination significantly reduced the rate of chronic HBV infection.[10]

Age group (37- 48 months) as shown in **table 1**, was at the lowest level of productivity (76.4 %) with GMT (127± 171). The protection rate and mean level of anti-HBsAb were decreased significantly with increasing age (P = 0.0001). these results were in agreement with two studies conducted in South Africa and Brazil. [11,12]

In the current study, 568 studied children received three doses of HB vaccine during infancy and none of them had an evidence of chronic HBV or breakthrough infection. The overall seroprotection rate among all studied children was 86 %. This rate is closed to that from Red Sea in Egypt where seroprotection rate for children > 5 years was 82.8% [13] and from an Iranian study which in demonstrated 80.7 % of children 6 years after hepatitis B vaccine have antibodies level of > 10 I.U/L.[14] The immune response to the vaccine may be affected by host related or vaccine relate factors.

In our study, seroprotecting rate against HBV was decreasing with age. Non-protection rate was 17.4 % in children aged 49-60 months while it is 5.1% in those below age of 12 months, and this was statistically significant (P<0.05). Yazdanpanah et al[15] has similarly reported that non-protection rate was found in 15.6 % of HBV vaccinated children of 5-7 years. This immune behaviour was seen even after 10 years of follow up, in a study from Iran seroprotective antibody level was seen in 47.9 % of children 10 years after primary vaccination with three doses of HB Vaccine with a geometric mean titer (GMT) of 68.12 IU/ml.[16] Afifi et al[17] has shown a similar trend in a sample of 242 children; seroprotection rate at one year and at 6 - 11 years after vaccination were 84.3% and 39.3%, respectively. And this is clearly demonstrated that vaccine- induced immunity is waning with time after the third dose.

Many other studies worldwide have come to variable results about the extent of immune-protection years after HB vaccination. The variability may occur even in studies from a same country which may argue, if we excluded the effect of sampling on the results, against geographical factors as a cause for this difference. From Iran, a study from Ahvas has reported a positive response rate of 75.4 % among children 5 years after HBV vaccination ,[18] while another study from Isfahan has showed a protective anti-HBs Ab levels in only 29.2 %of children 6 years after vaccination.[19] A study from Taiwan showed the low response to booster among 67% of 5-year-old children.[20] This rate is different to that of a study carried out in Dakahlya Egypt where seroprotection rate was 57.7% with geometric mean titers (GMTs) 68.5±3.5 I.U/L among children below five years.[20] In Turkey, children under three years of age had 66.4% protective level of antibody against HBsAg.[22] A study from Chine[23] has shown that revaccination of non-responders succeeded to enhance the response in 85.3%.

The complete vaccine series induces protective antibody levels in more than 95% of infants, children and young adults. Protection lasts at least 20 years and is probably lifelong. Thus, WHO does not recommend booster vaccination for persons who have completed the 3 dose vaccination schedule.[1] but the booster dose of vaccine is recommended by the National Immunization Technique Advisory Committee (NITAC) in a particular country.

Regarding the females showed more high titers of antiHBs against vaccination as compared to that of males (P>0.05). A study in Iran at 10 years after primary vaccination found that the seroprotection rates and mean titer of antibody similarly expressed in males and females,[16] that means no statistically differences in the immune response for both gender in the community.

The long-term efficacy of Hepatitis B vaccine depends primarily on peak antibody levels after vaccination.[24] It is estimated that about 5-15% of the vaccines may be non-responder.[25]

However, dose, storage, site and route of administration, male sex, genetic factor, obesity, diabetes, and immunosuppression can all adversely affect the immune response. Post vaccination testing for antibody titer within 1 to 6 months after completion of vaccination series is recommended to detect non-responder or hyporesponder.[11] The recommendation of this study, is important to assess antibody titer within 1 to 6 months after complete of the vac-

cine series to detect non-responder or hyporesponder in post-vaccination children.

## CONCLUSION

Immunogenicity of HBV vaccine was 86% in children below 5 years of age, hepatitis booster doses are not currently needed for these age Hence, the complete course of vaccination is sufficient for prevention of HBV and there is no need for booster dose or dose re-administration, however HBsAb should be tested to make sure of immunity.

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**Abbreviation list:** Antibody (**Ab**), Centre Public Health Laboratory (**CPHL**), Diphtheria–tetanus–pertussis (**DTP**), Expanded Programme on Immunization (**EPI**), Hepatitis B Surface Antigen (**HBsAg**), Hepatitis B Virus (**HBV**), International Unit/Liter (**IU/L**), Vitek Immuno Diagnostic Assay System (**VIDAS**), World Health Organization (**WHO**)

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