

## The Efficacy of Hepatitis B Virus Vaccine among Children in Baquba-Diyala Province

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### Abstract:

**Background:** Hepatitis B virus (HBV) vaccination was one of the success stories of the 20<sup>th</sup> century. It is highly effective and safe and was incorporated into national immunization programs of countries worldwide.

**Objectives:** To evaluate the efficacy of HBV vaccine among children 1-14 years old in Baquba city Diyala province.

**Subjects and methods:** This cross sectional study was conducted in Baquba City, the center of Diyala province for the period 20 July/ 2016 to 20 March /2017. A total of 452 children were enrolled, 247 were males and 205 were females, with an age range of 1- 14 years. All were previously immunized with genetically engineered HBV vaccine (Euvax B, Korea), with a dose of 10 micrograms of HBsAg/ 0.5 milliliter (children vial) intramuscularly. Venous blood samples were collected aseptically; sera were separated and subjected for the detection of HBsAg, anti-HBs antibody titer, HBe Ag and total antibody and anti-HBc total antibody using Enzyme Linked Immunosorbant Assay (ACON, Foresight-USA). A pre-constructed questionnaire form was prepared including information of socio-demographic, health, and vaccination status. The human privacy was respected by taken the participants or their parents consent. However 34 of them were refused participation. Statistical analysis was done using the Statistical Package for Social Science (SPSS), Version 23. P values < 0.05 were considered significant.

**Results:** The overall anti-HBs Ab positivity rate was 75.66% (95% CI for prevalence of anti-HBs Ab = 71.5% to 79.6%), with a range of anti-HBs Ab titers (10.1 – 673.4 mIU/ml). However, the anti-HBs Ab titer was failed to reach the protective level ( $\geq 10.0$  mIU/ml) in 110 vaccinees (24.34%). The significantly highest positivity rate (89.2%) was found among 12-17 months old children ( $p < 0.001$ ). Furthermore, significantly higher positivity rate among participants received 3 vaccine doses ( $P < 0.001$ ). The past history of hospitalization of vaccinees has significantly increase the positivity rate ( $P = 0.028$ ). The results also found that among participants administered 4 vaccine doses, highly significant positivity rate was arise after less than one year of vaccination ( $P = 0.004$ ).

**Conclusion:** Implementation of HB vaccine among children in Baquba city is efficacious as it yielded high anti-HBs Ab positivity rate with a protective titer of anti-HBs Ab in the majority of vaccinees.

**Keywords:** HBV infection, HBV vaccine, anti-HBs Ab.

### Introduction;

Hepatitis B virus infection constitutes a major economic and public health problem throughout the world, particularly in the developing countries including the Middle East, where it is responsible for considerable morbidity and mortality and the development of a chronic carrier state, liver cirrhosis that may progress to hepatocellular carcinoma [1]. The HBsAg seroprevalence was 3.61% worldwide with highest endemicity in countries of African, West Pacific and South America regions [2]. Infection in infancy and early childhood is strongly associated with progression to chronic HBV infection, contributing to a significant proportion of chronic liver diseases [3]. More than one third of the World's population was infected with HBV leading to the deaths of 1 - 2 million people annually, and there are nearly more than 350 million chronic carriers of hepatitis B virus [4].

The HBV vaccine is the first anti-cancer vaccine because it helps reduce HCC, which is the second most common cause of cancer death worldwide [5]. The world's first recombinant HBV vaccine was invented in 1986 and still in use today [6,7]. Different studies conducted to determine the efficacy of HBV vaccine had yielded variable protection rates [8-11]. In a previous study in Baghdad to evaluate HBV vaccine among children 1-10 years, found that 77.2 % of children received 3 primary vaccine doses had protective level of anti-HBs Ab [12].

Acute and chronic of HBV infections are a common health problem in Iraq. The prevalence of HBsAg in the pre- and post vaccine era was putting Iraq among the countries of intermediate zone of

endemicity [13-15]. In Diyala province, the first seroepidemiological study of HBV infection from 1989 to 2002, found that the grand prevalence of HBsAg positivity rate was 1.5 [16]. The high rate of intrafamilial clustering beside the relatively high rate of occult HBV infection in Diyala, suggesting that may contribute for maintaining the endemicity of the disease in the community [17,18]. Moreover, even an outbreak of HBV infection was reported in this province [19]. Although, the universal vaccination of infants with HBV vaccine was implemented in Diyala province since 1994 following the schedule recommended by the WHO, the last comprehensive population survey found that the overall HBsAg positivity rate among general population was 0.65, while the anti-HBc IgM and total antibody positivity rates were 3.67% and 9.56% respectively [20].

### Subjects and methods:

This cross sectional study was conducted in Baquba City, the center of Diyala province for the period from 20 July/ 2016 to 20 March /2017, to evaluate the efficacy of HBV universal vaccination program after 10 years post-vaccine implementation.

A total of 452 children were enrolled, 247 were males and 205 were females, with an age range of 1-14 years. All were previously immunized with HBV vaccine (Euvax B, Korea), with a dose of 10 micrograms of HBsAg/ 0.5 milliliter (children vial) intramuscularly. Participants were received different number of vaccine doses at different vaccination schedules. Venous blood sample was collected aseptically; sera were separated and subjected for the detection of HBsAg, anti-HBs antibody titer, HBe

Ag, anti-HBe total antibody and anti-HBc total antibody using Enzyme Linked Immunosorbant Assay (ACON, Foresight-USA). A pre-constructed questionnaire form was prepared including information of socio-economic status, health status, and vaccine status. The enrollment criteria are all participants should be negative for HBs Ag, HBe Ag, and anti-HBc total Ab. The human privacy was respected by taken the participants or their parents consent. However 34 of them were refused enrolment. Statistical analysis was done using the Statistical Package for Social Science (SPSS), Version 23. P values < 0.05 were considered significant.

**Results:**

Out of 452 vaccinated children, 342 were anti-HBs Ab positive with an overall positivity rate 75.66% (95% CI for prevalence of anti-HBs Ab = 71.5% to 79.6%). the range of anti-HBs Ab titers among these participants was (10.1 – 678.4 mIU/ml), table (1). The anti-HBs Ab positivity rates was

significantly higher (p < 0.001) among those participants 12-17 months old, table (2). Table (3) showed that the highest positivity rate was among those participants received 3 vaccine doses, while the lowest positivity rate was among those participants received only one dose of vaccine. The difference was statistically significant (P < 0.001). Socio-demographic factors including , sex, residence, educational levels, type of feeding ( for those < 2years) as well as health status factors including; past histories of jaundice, blood transfusion, chronic diseases had insignificant effect on the anti-HBs Ab positivity rate. However, participants with past history of hospitalization has significantly higher positivity rate compared to their counterpart (82.6 % vs 72.8 %), table (3). The results also found that among participants administered 4 vaccine doses, the highest positivity rate was among those after less than one year, and the lowest positivity rate was among those after 4 years or more duration (duration is time elapsed since last vaccine dose). The difference was statistically significant (P = 0.004), table (5).

**Table (1): Distribution of anti-HBs Ab positivity rate and titer.**

category	Log serum HBs Ab				Anti-log values	
	Mean	SD	SE	No. (%)	Range	Mean
Subjects with positive Ab (≥10 mIU/ml)	1.88	0.53	0.03	342 (75.66)	(10.1 to 673.4 mIU/ml)	75.3

**Table (2): Anti-HBs Ab positivity rate according to age groups.**

Age groups	Total No.	Positive anti-HBs Ab	
		No.	%
12-17 months	65	58	89.2
18-23 months	63	56	88.9
Under 5 years (24-59 months)	218	164	75.2
5-9 years	85	57	67.1
10-14 years	21	7	33.3

$\chi^2 = 36.35$  P < 0.001 [S]

**Table (3): HBs Ab positivity rate according to the number of vaccine doses administered.**

No. vaccine doses administered	Total No.	Positive anti-HBs Ab	
		No.	%
One	16	4	25.0
Two	25	20	80.0
Three	146	122	83.6
Four	200	152	76.0
Five	65	44	67.7

$\chi^2 = 29.76$  P < 0.001 [S]

**Table (4): HBs Ab positivity rate according to the past history of hospitalization.**

Past history of hospitalization	Total No.	Positive anti-HBs Ab	
		No.	%
Negative	320	233	72.8
Positive	132	109	82.6

$\chi^2 = 4.84$  P = 0.028 [S]

**Table (5): Anti-HBs Ab positivity rate after 4 vaccine doses by duration.**

Duration (year)	Total No.	Positive anti-HBs Ab	
		No.	%
Less than one year	69	62	89.9
1-3 years	106	73	68.9
Four and more years	25	17	68.0

$\chi = 11.09$  P = 0.004 [S]

**Discussion:**

Undoubtedly, the importance of the present study was streaming from two aspects; firstly, the relatively high prevalence of HBV infection in Diyala province, particularly the occult infection, as reported by the last epidemiological survey [20]. Secondly, the urgent need for evaluation of HBV vaccination program as it is universally implemented in this province since 12 years ago. The study design was arranged in such a way to include as much as possible of vaccinees of both sexes and wide age range (1-14 years) from different localities of Baquba city (center of Diyala province). Additionally, the study was succeeded to include vaccinated children who followed different vaccination schedules with different number of vaccine doses. More importantly, the study strictly adopted that all participants should be negative for HBsAg, HBeAg, anti-HBc total antibodies, and anti-HBe total antibodies, to exclude the breakthrough as well as occult HBV infection and to be absolutely sure that the detected anti-HBs Ab titer was merely a response to HBV vaccination [21,22]. Of note, the word efficacy, for clinical purposes is synonymous with effectiveness which denotes the maximum response achievable from applying a drug or vaccine in clinical settings.

The present study found that the overall anti-HBs Ab positivity rate among vaccinated children in Baquba city was 75.66% (95% CI for prevalence of anti-HBs Ab = 71.5% to 79.6%). This result is much closer to that found in the lonely previous study conducted in Baghdad to evaluate the HBV vaccine among children 1-10 years, which reported that 77.2 % of children received 3 primary vaccine doses had protective level of anti-HBs Ab [12]. The result is also consistent with other studies from surrounding countries [8,9,11,23]. Moreover, the protection rate obtained in this study is within the range of HBV vaccine protection rate worldwide, since upon reviewing meta-analytic studies published between 1987 and 2015 assessed the seroprotection from recombinant HBV vaccine among healthy newborns, children, adolescents and adults, the overall median seroprotection rate was 98% (range 52%-100%) [24-26]. Therefore, our study

thought that there is a universal consensus of the efficacious role of HBV vaccine in protection against HBV infection.

Basically the recognition of anti-HBs Ab positive vaccinees was followed the WHO recommendation (those who had a protective anti-HBs Ab titer of  $\geq 10$  mIU/ml). It is worth to mention that anti-HBs Ab positive vaccinees in this study had a range of anti-HBs Ab titers (10.1 – 673.4 mIU/ml). So, the present study is consistent with numerous studies worldwide [23,25,27,28]. Logically, as the protection rate increased in the community, the infection rate should be dropdown, and this is what actually evident from cumulative studies elsewhere [27-29]. Therefore, a similar study to figure out the reduction in HBV infection in our community is highly recommended. On the other hand, the 24.34% vaccinees children who failed to have protective levels of anti-HBs Ab were considered low responders as their mean  $\pm$  SD of anti-HBs Ab titer was  $6.3 \pm 1.9$  mIU/ml. Similar results have been reported by other studies suggesting that those low responders may become susceptible again to HBV infection and probably may required a booster dose of the vaccine [30-32]. The reason behind that may be multifactorial; In Iraq, specifically speaking about Diyala province which is one of the hot spots that witnesses military conflicts, resulting in frequent population displacement, deterioration of the health services and retardation of health projects [33]. Certainly, these events hamper the children from reaching the healthcare center to get their vaccine dose and thus disruption of vaccination schedule that in turn may contribute in lowering levels of anti-HBs Ab titer, of note, 70% of low responders in this study were irregularly administered their vaccine doses. On the other hand, it has been found that transplacental transfer of anti-HBsAb occurs and high titres of maternal anti-HBs Ab may suppress the immune response of infants to the standard HBV vaccination, suggesting that the standard vaccination schedule may not be the optimal choice of infants with anti-HBV positive mothers [34]. The duration since last vaccine dose is unlikely to be one of the causes behind the low levels of anti-HBs Ab titer, since 50% of low responder in the present study were tested after 1 – 3 years of the last vaccine dose, which is quite short period. In this regards most of studies demonstrated the presence

of immune memory and protection 5-15 years after the initial course of newborn immunization with recombinant HBV vaccines [35-37], or even in adult healthcare workers, affirming that 10 years after vaccination, anti-HBs antibody levels were significantly inversely related to age at vaccination [38].

Another important result streamed out of this study is the significantly higher anti-HBs Ab positivity rate among those participants 12-17 months old (89.2%,  $p < 0.001$ ). Thereafter, the positivity rate continues declining till it reached 33.3% among those 10-14 years old. This result is concordant with other studies [23,24,39,40]. These results may point out to an interpretation that newborn and infant HBV vaccination programs should be considered the preferred strategy, capable of providing adequate protection up to 14 years of age, and that the annual decay rate of anti-HBs Ab positivity was 10.2% in children who did not receive a booster dose. [41,42]. Additionally, a significantly higher positivity rate was found among those received 3 vaccine doses (83.6%,  $p < 0.001$ ). This result is in agreement with most previous studies affirming that the primary HBV vaccination induces good seroprotection [12,24, 27,28]. Actually, these results raise a question about the need for booster vaccine dose especially among immunocompetent children; however, the answer is still controversial [33,40,42,43].

The results also found that those vaccinees with past history of hospitalization showed significantly higher rate of anti-HBs Ab (82.6%,  $p=0.028$ ). The most eligible explanation is that the children may frequently exposed to nosocomial pathogens during hospitalization, these pathogens are non-specifically act as a boosting agent for stimulation and upregulation of the immune response against these pathogens and also against already existing agents inside the body including the HBsAg of the HBV vaccine [44]. Alternatively, these vaccinated children may exposed to HBs Ag from healthcare workers during hospitalization, and similarly the HBs Ag act as a booster dose and specifically induce an anamnestic anti-HBs Ab response [45,46]. It is worth to mention that high rate of HBV infection was reported among healthcare workers in our health care settings [47].

Regarding the effect of duration on the anti-HBs Ab positivity rate after the booster dose, the present result found that the highest positivity rate was among those after less than one year (89.9%,  $p=0.004$ ). It is worth to mention that similar result seems to be universal among studies included a booster vaccine dose [30, 32,36,37]. This result actually reflect two outcomes; firstly, the induction of anamnestic anti-HBs Ab response after booster vaccination as indicated by high positivity rate after less than one year duration, and secondly, the fading down of the anti-HBs Ab titer by time.

[26,46,48]. In conclusion, the current study found that the implementation of genetically engineered HBV vaccine was highly efficacious as it induced good and durable protection in the community against HBV infection as reflected by high anti-HBs Ab protective titers.

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