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Hepatitis B Vaccine Coverage and the Immune Response in Children under ten years old in Sana'a, Yemen

*Hassan A Al-Shamahy,[1] Samira H Hanash,[2] Iqbal A Rabbad,[3] Nameem M Al-Madhaji,[1] Samarih M Naser[1]

تغطية التطعيم ضد التهاب الكبد الفيروسي البائي والاستجابة المناعية له عند الاطفال تحت سن العاشرة بمدينة صنعاء (اليمن)

حسن عبد الوهاب الشماحي، سميرة حنش، إقبال رباد، نميم المذحجي، سميرة ناصر

الملخص: الهدف: تحديد مدى تغطية لقاح فيروس الكيد البائي بين الأطفال تحت سن العاشرة، وكذلك تقييم مدى الاستجابة المناعية للأطفال الذين أخذوا الجرعات الثلاث للقاح بواسطة قياس مستوى المُسْتَضِدِّ السَّطْحِيِّ لالْتهاب الكَبِد البائيّ. **الطريقة** :أولا: تم عشوائيا اختيار 840 طفلا من أربع مناطق اختيرت عشوائيا أيضا بمدينة صنعاء لدراسة مَعدل التغطية للَقاح. ثم تَم دراسة جميع الأطفال الذين أخذوا الجرعات الثلاث للقاح (504) طفلا (56% ذكورا و44% إناثا) من ناحية الاستجابة المناعية للقاح عبر قياس مستوى المُسْتَضِدِّ السَّطْحِيِّ لإلْتهاب الكَبِد البائيّ بواسطة التقنية العددية للطريقة الإنزيمية ألارتباطية. تم إملاء استبيان معياري احتوى على المعلومات عن تاريخ التطعيم والجنس والعمر ووقت الدراسة. **النتيجة** : كان معدل تغطية التطعيم ضد فيروس الكبدي البائي (69.9%) فقط وكان مرتفعا قليلا بين الأطفال الذكور (72.1%) مقارنة مع (66.8%) للإناث. أما الاستجابة المناعية للقاح فكانت ايجابية عند 276 طفلا من المجموع الكلي (504) أي بنسبة (54.8%)، إذ كان مستوى المُسْتَضِدِّ السَّطْحِيِّ لالْتهاب الكَبِد البائيّ يساوي 10 ملي وحدة دولية / ملي لتر أو أكثر، بينما كان المستوى أقل من ذلك أو لم يكن هناك مستضد سَطحي في (228) منَ مجمَوع (504) أي (45.2%) من الأطفال. كان أعلى معدل للاستجابة للفئة العمرية من 3–5 سنوات حيث كانت 63.6% والأقل كانت للفئة العمرية من 9–10 سنوات. **الخلاصة**: أظهرت هذه الدراسة معدلا منخفضا في كلا من تغطية اللقاح ومعدل الاستجابة . ويجب إعادة النظر إما في إعادة التطعيم الأطفال أو إعطاء جرعة تنشيطية للأطفال غير الحاملين لكمية كافية من الأجسام المستضدة. وكذلك يجب رفع مستوى التغطية لهذا اللقاح بين الأطفال في صنعاء.

مفتاح الكلمات : التهاب الكبدي البائي ، لقاح ، أطفال ، اليمن ، صنعاء.

ABSTRACT: ***Objectives:*** The study was undertaken, first, to determine the coverage rate of hepatitis B (HB) vaccine and second to evaluate the immune response to HB vaccine among children under 10 years old by measuring the level of circulating anti-HB surface antigen (anti-HBs) antibodies after immunisation with three doses. ***Methods:*** First, 840 children were randomly selected from 4 randomly selected sites in Sana'a city to study the coverage rate of the vaccine; of these, 504 children vaccinated against HBV prior to the study, were tested (56% males and 44% females). Sera were tested for anti-HBs antibodies by ELISA quantitative technique. Each individual's data was collected in a pre-designed questionnaire including: vaccination date, sex, and age at the time of the study. ***Results:*** The coverage rate of HBV vaccine was only 69.9%, being slightly higher among male children (72.1%) than female children (66.8%). A total of 276 (54.8%) of the 504 children responded to the vaccine with anti-HBs antibody level ≥ 10 mIU/ml, while 228 (45.2%) of the 504 children had non-protective anti-HBs antibodies levels (<10IU/ml). Children of ages 3–5 years had the highest protective rate (63.6%), and the lowest protective rate was in the 9–10 years age group. ***Conclusion:*** This study revealed a low coverage rate of HBV vaccine and a low protective rate against HBV infection. A considerable proportion of vaccinated children should be considered for either revaccination or booster doses. There is also the need to complete HBV vaccine coverage among the child population in San'a, Yemen.

Keywords: Hepatitis B; Vaccine; Children; Yemen; Sana'a

Advances in Knowledge

1. *There is a low coverage rate of hepatitis B (HB) vaccine in Sana'a, Yemen (70% of children) as well as a low protective rate against HB infection. This is despite the existence of an official vaccine supply since 2000.*

[1]Department of Medical Microbiology, Faculty of Medicine & Health Sciences, Sana'a University, Yemen; [2]Department of Medical Microbiology, Faculty of Medicine & Health Sciences, Taiz University, Yemen; [3]Department of Medical Microbiology, Faculty of Medical Sciences, University of Sciences & Technology, Sana'a, Yemen.

**Corresponding Author email: shmahe@yemen.net.ye*

Application to Patient Care

1. *Health care centres need to pay more attention to boosting HB vaccine coverage among children.*
2. *The role of vaccine in HB protection is fundamentally important as HB is endemic in Sana'a.*

Hepatitis B (HB) is a human disease caused by a virus that attacks the liver. The hepatitis B virus (HBV) can cause lifelong infection, cirrhosis of the liver, liver cancer, liver failure and death.[1] HB infection is one of the world's most common and serious infectious diseases. It is estimated that more than one third of the world's population has been infected with HBV.[2] About 5% of the population are chronic carriers of HBV, and nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis and primary heptocellular carcinoma (HCC).[3] HBV infection causes more than one million deaths every year.[4]

For long-term protection against HBV, there are two types of vaccines: plasma-derived HB surface antigen (HBsAg) vaccine, and yeast-derived HBsAg vaccine.[5] HB immunisation, using either type of vaccine, has been shown to eliminate HBV transmission and prevent HBV-related chronic liver disease.[6] HBV vaccine can be routinely given to children and individuals at risk, along with other commonly used vaccines in a variety of schedules that results in excellent immunogenicity and do not interfere with the immunogenicity of other vaccines.[7] The sero-conversion rate for vaccination is influenced by a number of factors, the most important ones being age and sex. Rates in excess of 95% are seen in young women, whereas the rate may drop to 80% in older men. Immunosuppressed patients, smokers, and obese individuals show even lower rates.[8]

According to the Yemeni National Infectious Viral Hepatitis Control Programme, Yemen was recognised as HBV-endemic area.[9] In 1998, the World Health Organization (WHO) recommended the inclusion of HB vaccine in the national immunisation programme of Yemen, particularly among neonates, where vertical transmission is common, regardless of the prevalence of HBsAg. In Sana'a city, the HB antigen carrier rate is classified as intermediate, rather than high. The incidence of acute HBV has declined dramatically in the past decade since the start of the vaccination programme, especially among young people, although it may still take several decades until the effect of vaccination is translated into reduced transmission and morbidity.[10]

The aims of this study were first to determine the coverage rate of HBV among children and second to evaluate the immune response to HBV vaccine among vaccinated children with the three doses of HBV vaccine by measuring the level of circulating anti-HB surface antibodies.

Methods

This cross sectional study was carried out from January to March 2010. The study proposal was approved by the Department of Medical Microbiology, Faculty of Medicine & Health Sciences, Sana'a University, Yemen. First, 840 children, aged <1–10 years, (470 males and 370 females) were randomly selected by a systematic random sampling of every fifth child attending randomly selected health centres or from the lists of randomly selected primary schools in Sana'a city. The histories of all 540 children who had received three doses of HBV vaccine were investigated. A total of 81.9% of them had received yeast-derived vaccine and 18.1% plasma-derived vaccin; 62.2% of the children had been vaccinated at a dose interval of 0, 1, 2 months and 37.8% at a dose interval of 0, 1, 6 months The immune response to the HBV vaccine of these 504 vaccinated children was then evaluated. A consent form was completed by the parents for each participant.

A full history was taken from each individual studied and the findings recorded in a pre-designed questionnaire. The data collected included name, age at the time of the study, sex, residence, and vaccination date according to the last dose of HBV vaccine, number of doses, intervals between the three doses and type of vaccine. A full history of vaccinations against other diseases was also taken.

Four millilitres of whole blood were collected from each subject. Then the sera were separated and frozen at -20 °C until tested. Anti-HBs antibodies were determined by an enzyme-linked immunosorbent assay (ELISA) using a

Table 1: The coverage rate of hepatitis B vaccine (HBV) among randomly selected male and female children under ten years old in Sana'a, Yemen

Status	Male (n = 470)		Female (n =370)		Total (n =840)		X2	*P* value
	No.	%	No.	%	No.	%		
Vaccinated for HBV	339	72.1	247	66.8	586	69.9	2.83	0.09
Non-vaccinated for HBV	131	27.9	123	33.2	254	30.2		
Total	**470**	**56**	**370**	**44**	**810**	**100**		

commercially available kit (Biokit, S.A., Barcelona, Spain). Bio-ELISA anti-HB is a direct immuno-enzymatic method of the "sandwich" type in which the samples to be analysed are incubated in wells of micro-plate that are coated with highly purified HB antigens.

In order to differentiate naturally occurring immunity to HBV infection, total anti-HB core antibodies were measured; all individuals with anti-HB core antibody positive were excluded from the evaluation of HBV vaccine group.

The data and results were analysed by using EPI-Info Version 6, Centers for Disease Control (CDC, Atlanta, GA, USA).

Results

The coverage rate of HBV vaccine was only 69.9%, slightly higher among male children (72.1%) than females (66.8%) [Table 1].

Table 2 shows the immune response to HBV vaccine by quantifying anti-HB antibody levels among males and females. A total of 276 (54.8%) of the 504 children responded to the vaccine with anti-HBs antibody levels ≥10 mIU/ml, while 228 (45.2%) had non-protective anti-HBs antibodies level (<10 IU/ml). The average protective rate in both sexes was 54.8%, but higher among males (57.4%) than females (51.4%). There was no statistically significant variation between both sexes. Table 3 shows the protective rate among different age groups, the rate being higher in younger compared to older age groups. Children aged 3–5 years had the highest protective rate (63.6%); the lowest protective rate was in the 9–10 year old age group (32.4%) [Table 3].

Table 4 shows the protection by yearly intervals after primary immunisation against HBV. Children immunised one year or less prior to the study had a higher protective rate (66.7%), than those immunised 4 years prior (44.2%).

In this study, different HBV-markers were obtained from the whole 504 group of vaccinated children. It was found that the frequency of HBsAg positivity among these children was 1.8%.

Table 2: The immune response to hepatitis B vaccine by quantifying anti-HBs antibody levels and protective and non-protective levels among males and females

Antibody levels	Male	%	Female	%	Total	%	χ2	*P* value*
Non-responders (<10 mIU/ml)	120	42.6	108	48.6	228	54.1	1.8	0.17
Low-responders (10–100 mIU/ml)	87	30.9	45	20.3	132	26.2	7.2	0.007
Adequate responders (>100–1000 mIU/ml)	45	16	45	20.3	90	17.6	1.6	0.2
High-responders (>1000 mIU/ml)	30	10.6	24	10.8	54	10.7	0.0	0.95
Immune response								
Protective anti-HBs	162	57.4	114	51.4	276	54.8	1.9	0.17
Non-protective anti-HBs	120	42.6	108	48.6	228	45.2		

*Notes: * χ2≥ 3.84, P <0.05 (significant); Protective anti-HBs ≥10 mIU/ml; Non-protective anti-HBs <10 mIU/ml.*

Table 3: Immune response among vaccinated children in different age groups

Age groups	Protected		Non-protected		X2	*P* value
	No.	%	No.	%		
1–2 years (n = 72)	39	54.2	33	45.8	0.01	0.91
3–5years (n = 165)	105	63.6	60	36.4	7.8	0.005
6–8years (n = 165)	99	60	66	40	2.7	0.09
9–10 years (n = 102)	33	32.4	69	67.6	25.9	0.0000004
Total	**276**	**54.8**	**228**	**45.2**		

Notes: Protected (anti-HBs ≥10 mIU/ml); Non-protected (anti-HBs <10 mIU/ml).

Discussion

Since the 1980s, there has been an increasing body of information on viral hepatitis in Yemen, which is a major public health problem affecting thousands of people throughout the country.[10] Viral hepatitis is a major cause of morbidity and mortality in humans in Yemen, both from acute infection and its chronic sequelae which include hepatitis B and hepatitis C infection, chronic hepatitis cirrhosis and primary liver cancer.[11] The endemic rate of hepatitis B virus infection is considered high in Yemen, where the prevalence of the positive (HBsAg) ranges from 8–20%, and up to 50% of the general population have serological evidence of previous HBV infection.[12]

Yemen introduced a universal immunisation programme against HBV for infants and high risk groups in early 2000, but feed-back on the coverage rate of vaccination and its efficacy in the community have been ignored for a long period. In addition, there has been inadequate information on the prevalence and risk determinants of viral hepatitis as well as on vaccination coverage rate among children in Yemen. This study was carried out in response to this information gap.

One of the aims of this study was to determine the coverage rate of HBV vaccine among children. The study findings showed that the vaccination coverage rate was 69.9%. This result is lower than findings in other HBV endemic countries, where HBV vaccine coverage rates among children range from 90–98%.[13-15]

Also the study findings showed that only 54.8% of all vaccinated individuals were regarded as protected (≥10 mIU/ml), and that the protective rate of HBs antibody was higher in males (57.4%), than in females (51.3%). Different findings were reported elsewhere among children, where a high protective anti-HB response rate was found among vaccinated children (97.4%), and the rate for females was also higher than that for males.[16,17] This difference in the findings could be attributed to a different response in the primary course of vaccination, different age groups, to the different degrees of exposure to natural boosters, or to differences in nutritional status and socioeconomic factors, race factors, or the type of vaccines used.[18]

Concerning the rest of the study group, 45.2% developed a low antibody level (<10 mIU/ml), indicating a poor anti-HBs response after receiving

Table 4: Protected and non-protected vaccinated individuals according to period since vaccination

Year intervals	Protected (n = 276)		Non-protected (n = 228)		X2	*P* value
	No.	%	No.	%		
1 year or less prior to study (n = 72)	48	66.7	24	33.3	4.8	0.02
2 years prior to study (n = 125)	78	62.4	47	37.6	3.9	0.04
3 years prior to study (n = 119)	69	57.9	50	42.1	0.65	0.41
4 years prior to study (n = 86)	38	44.2	48	55.8	4.7	0.03
5 years or more prior to study (n = 102)	48	47.1	54	52.9	3.1	0.08
Total no. = 504						

Notes: Protected ≥10 mIU/ml; Non protected <10 mIU/ml.

a full course of vaccine, as shown in Table 2. It can be deduced from this finding either that these vaccinated individuals were hypo-responsive to the immunisation and that their antibodies may have waned rapidly over time, or that the vaccine was of poor quality. Even in these instances, loss of antibodies does not necessarily imply loss of protection.[19] Considering that anti-HBs may disappear in a substantial proportion of vaccinees after initially successful vaccination, a booster dose of vaccine, following the administration of the primary course, is recommended by most national bodies. However, the results of long-term follow-up studies, together with assessment of the role of immunological memory among vaccinees, now call into question the necessity of providing booster doses following successful course of primary immunisation.[19] Other studies showed that protection is still maintained among vaccinees, even in HBV-endemic countries, despite waning or undetectable anti-HBs levels.[20-23]

In this study, different HBV-markers were obtained from all the vaccinated children studied. However, due to the lack of serological data, either before or after vaccination, it was impossible to conclude whether these children were already infected at the time of vaccination or had been infected subsequently. In the present study, it was found that the frequency of HBsAg positivity among the whole group of children was 1.8%, which was lower than the rate of the non-vaccinated children (2.8%) in Sana'a city in 2001.[11] This indicates the efficacy of HBV vaccine in preventing chronic carriage of infection. In a long-term follow-up study (over c. 16 years) on HB vaccine immune efficacy in China, the positive rate of HBsAg for children born after the introduction of the immunisation programme was much lower than those of the background group before vaccination.[24,25] Also our result were similar to that found in Egypt among children, where HBsAg positivity was 0.8% in vaccinated children compared to 2.2% for non-vaccinated children.[26] No clinically overt hepatitis has been reported so far among the studied vaccinated individuals. This was similar to findings reported elsewhere.[27,28]

Host factors, such as age, may influence the immune response to the vaccine.[29] Increasing age was shown to be correlated with a decreasing level of protection rate [Table 3]. The response rate of anti-HBs declined from 63.6% in the 3–5 years age group to 32.4% in the 9–10 years age group. Similar findings were reported from Saudi Arabia, showing that being in the >10 years age group correlated with a decreasing protection rate.[27] In another study conducted in European countries, the main age for children who had non-protected levels against HBV was 9.5 years, while the main age for those who responded and had protected levels of antibodies was 5.7 years.[30]

In this study, there was a difference in protection rate at the various annual intervals (1–5 years) since vaccination [Table 4]. Zhou *et al.* reported that protective levels of antibodies decrease with time;[25] however, they can remain sufficient in healthy individuals for at least 10 years after primary immunisation.[31]

Conclusion

This study revealed a low coverage rate of HBV vaccine, and a low protective rate against HBV infection. A considerable proportion of vaccinated children should be considered for either revaccination or booster doses due to a non-existent, inadequate, or low response. An effort to complete HBV vaccine coverage to 100% among the Yemeni child population is recommended, especially among newborns.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

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