



Evaluation of Anti-HBs Antibody Immune Response against Hepatitis B virus in Vaccinated People in a North-eastern Bulgaria Region

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Abstract

Introduction: Hepatitis B virus (HBV) is one of the most significant human pathogens responsible for a huge number of acute and chronic liver infectious diseases worldwide.

Aim: To find the duration of post-vaccination immune response in individuals allocated to five age groups from 6 months to 20 years.

Materials and methods: All tested subjects were born between 1999 and 2018 and therefore covered by the compulsory vaccination program against hepatitis B. For the serological marker anti-HBs Ab we investigated 449 serum samples taken from ambulatory people and patients of St Marina University Hospital in Varna.

Results: A positive antibody response (anti-HBs Ab > 10 mIU/ml) was reported in 79.7% (n = 51) of the group of subjects up to one year old, in 70.0% (n = 196) of the subjects in the age range 1 year/1 month to 15 years, and in 39.3% (n = 33) of the subjects 15 years/1 month to 20 years old. Female sex had a better post-vaccination response than male sex with statistically significant relationship between sex and anti-HBs Ab titer ($\chi^2 = 24.76$, $p < 0.01$).

Conclusions: Regardless of the mass immunization against HBV in Bulgaria, the relative share of chronic HBV infections does not show a downward trend. Therefore, it is very important to study the duration of the post-vaccination immune response by demonstrating the anti-HBs antibodies and to apply a booster dose from the vaccine if needed.

Keywords

anti-HBs Ab, HBV, HBV vaccination

INTRODUCTION

Hepatitis B virus is one of the most significant human pathogens, responsible for a huge number of acute and chronic liver diseases. Complications of HBV infection have 66% relative share of all reported death cases from viral hepatitis worldwide.¹ Bulgaria is in the intermediate endemic area, where 2% (3%–5%) of the population are carriers of HBsAg, ranging from 1.9% to 5.3% for different regions across the country.² Markers for HBV infection can be found in 20% - 60% of the people.³ A survey conducted in Eastern Bulgaria reported the presence of 548 new cases of HBV between 2008 and 2014 as there has been at least a 3-fold decline in the prevalence of HBV incidence in these regions. The age structure of HBV infection in Bulgaria shows markedly higher relative share in the age groups 19 - 29 - 39 years. Young people around the age of 20 are the most vulnerable group, as only a part of them are included in the compulsory vaccination program.⁴ HBV is an etiological agent of 30% of chronic hepatitis in North-eastern Bulgaria and about 15% of all acute viral hepatitis.⁵

HBV infection is a vaccine-preventable anthroponosis and as for its clinical and social significance, in 1991 the WHO appealed for vaccination of all healthy newborn children.⁶ Vaccination against HBV is a highly effective measure for disease prevention and control, although we still cannot talk about global virus eradication. By the end of 2017, vaccines had been administered in 187 countries, with a global coverage of 84%.¹ Most of the countries use mainly recombinant vaccines. The vaccine against HBV is used in 20 of the 27 countries in the European Union.⁷ Compulsory vaccination of new-borns in Bulgaria was carried out from 1991 on with recombinant HBV vaccines. Yet, there are only a few studies evaluating the protection after the vaccination against hepatitis B, especially in children.⁸ According to national statistics, the scope of hepatitis B vaccine among Bulgarian infants in 1992 and 2001 was 71% and 93%, respectively.⁹ The aim of our study was to find the duration of post-vaccination immune response in vaccinated individuals allocated into five age groups (range 6 months to 20 years). All included subjects were born between 1999 and 2018 and therefore were covered by the compulsory vaccination program against hepatitis B applied in Bulgaria.

MATERIALS AND METHODS

STUDY POPULATION

As many as 449 serum samples were investigated in a retrospective study - 58.8% of them (95% CI: 54.1% -63.4%, $n = 264$) were ambulatory patients and 41.2% (95% CI: 36.6% -45.9%, $n = 185$) - patients treated in St Marina University Hospital in Varna. The serum samples were tested in the hospital's laboratory of clinical virology and in Status diagnostic laboratory in Varna. Inclusion criteria: the included

subjects were primarily from ambulatory population covered by the compulsory vaccination against HBV with all the data necessary for the statistical processing. Anti-HBs Ab titres were measured after the full course of mandatory vaccination against HBV in Bulgaria. The analysis excluded subjects positive for HBsAg and anti-HBc total Ab markers without data allowing statistical interpretation, as well as people with a booster dose of the HBV vaccine. The study excluded subjects that were hospitalised in infectious clinics for acute viral hepatitis.

The subjects were divided into 5 age groups: Group 1 (6 months - 1 year) - 14.3% (95% CI: 11.2% -17.8%, $n = 64$); group 2 (1 year/1 month - 5 years) - 20.0% (95% CI: 16.4% -24.1%, $n = 90$); group 3 (5 year/1 month to 10 years) - 24.5% (95% CI: 20.6% - 28.7%, $n = 110$); group 4 (10 years/1 month to 15 years) - 21.6% (95% CI: 17.9% - 25.7%, $n = 97$); and group 5 (15 years/1 month to 20 years) - 19.6% (95% CI: 15.9% -23.3%, $n = 88$).

The relative share of investigated females - 52.8% (95% CI: 48.0% - 57.5%, $n = 237$) was higher than the relative share of the investigated males - 47.2% (95% CI: 42.5% - 52.0%).

We used EIAs- ELISA and CLIA (chemiluminescent immunoassay technology) to detect anti-HBs Ab. ELISA test (anti HBs Ab Dia.PRO, Milano, Italy) is an enzyme sandwich ELISA test for quantification of antibodies to the surface antigen of hepatitis B virus in human plasma and/or serum. Serum samples with concentration greater than 10 mIU/ml were considered positive. A value of specificity of 100% was assessed and a diagnostic sensitivity of 99.7% was found for the test. The LIAISON® XL MUREX anti-HBs (DiaSorin) test was done via CLIA technology in order to quantify anti-HBs antibodies in human serum or plasma samples. The principle of this test of quantifying anti-HBs is a direct, sandwich-chemiluminescent immunoassay. A value of specificity of 100% was assessed and a diagnostic sensitivity of 100.0% was found for the test. Both types of tests were performed according to manufacturer's recommendations. An adequate protective immune response was provided when anti-HBs Ab titer was greater than 100 mIU/ml, one month after administration of the last dose of the vaccine.

ETHICS STATEMENT

The conducted studies and the corresponding results were coordinated and approved by the Ethics Committee at the Medical University, Varna.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS v.23. Results were expressed as mean \pm SD or median (range) as appropriate and confidence intervals (95% CI) were determined. Data were analyzed with t-test, Pearson's χ^2 test, and Spearman rank correlation (r). Cramer (V) test was used to search for associations in the category data and values from 0 to +1. Two-sided p -values < 0.05 were considered statistically significant.

RESULTS

Positive immune response (anti-HBs Ab > 10 mIU/ml) was found in individuals from all five age groups. The highest relative share of positive subjects was found in the range from 6 months to 15 years (**Table 1**). The difference in the relative shares of the positive individuals with the best immune response between the first and the last age groups was statistically significant ($\chi^2 = 81.98$; $p < 0.01$). Spearman rank correlation test showed a significant association but an inverse relationship between age and the immune response ($r = -0.337$, $p = 0.001$). This demonstrated that with age the post-vaccination immune response decreased or became undetectable with the available serological tests. The distribution of investigated people by age group and titre of anti-HBs Ab is presented in **Fig. 1**.

Individuals were allocated according to the titre of anti-HBs Ab (graph abscissa) in 4 groups. Individuals with an immune response of 10 mIU/ml (group 1), with an immune response of 10-50 mIU/ml (group 2), with an immune response of 50-100 mIU/ml (group 3) with an immune response of 100 mIU/ml (group 4). The age code 1 is for persons aged from 6 months to 1 year, code 2 - for those in the range 1 year/1 month - 5 years, code 3 - in the range 5 years/1 month - 10 years, code 4 for those in the range of 10 years/1 month - 15 years and code 5 for people in the range of 15 years/1 month - 20 years old.

As per the results above, we can summarize that a positive immune response up to 1 year old was found in 79.7% of the subjects ($n = 51$), in the age range of 1 year/1 month - 15 years anti-HBs positive were 65.1% ($n = 196$) and in the range 15-years/1 month - 20 years the relative share of

anti-HBs positive people was 39.3% ($n = 33$).

The distribution of anti-HBs antibody immune response by gender is presented in **Table 2**.

The chi-square analysis results for the entire observation period showed that differences in the anti-HBs Ab immune response by gender were significant. Female subjects had a better post-vaccination response than men, with the relationship between sex and anti-HBs Ab being statistically significant ($\chi^2 = 24.76$, $p < 0.01$).

The distribution of the people according to the titre of anti-HBs Ab and sex are presented in **Fig. 2**, where men are marked with code 1 and women with code 2. Absence of immune response (≤ 10 mIU/ml) was indicated via code 1, from 10 mIU/ml to 50 mIU/ml - with code 2, immune response from 50 mIU/ml to 100 mIU/ml - with code 3, and immune response higher than 100 mIU/ml - with code 4.

DISCUSSION

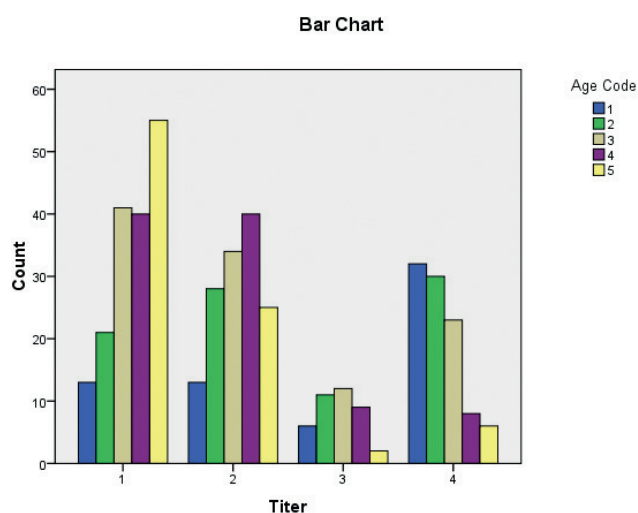
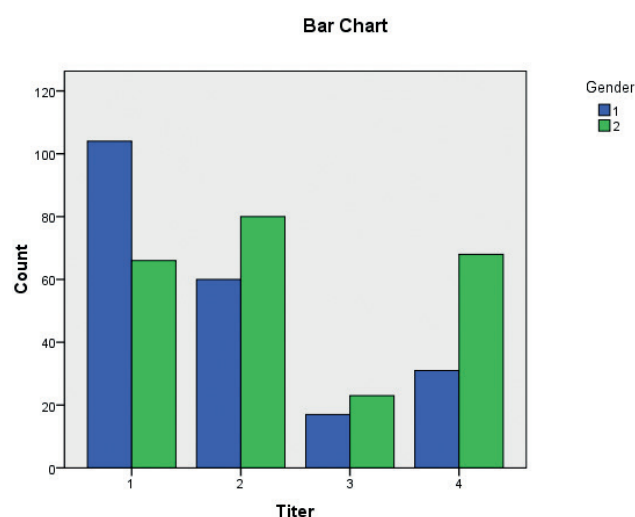
In 2009, a report on the HBV epidemiology in 10 European countries was published in relation to the application of the vaccination policies. At the time of publication of this report, HBV universal vaccination programs recommended by the WHO were in progress in different countries of eastern Europe (the Czech Republic, Romania, and Slovakia), but coverage differed between countries, most probably reflecting the difficulty to reach people living in rural areas in some countries such as Romania and Slovakia.¹⁰ In Poland, HBV vaccination of newborn babies is active and no new HBV cases in childhood and adolescence have been registered, whereas non-vaccinated subjects still show a high

Table 1. Distribution of people by age and anti-HBs antibody titre

			Age					Total	95% CI	p value
			6m/1yr	1 yr/ 1m-5 yrs	5 yrs/ 1m-10 yrs	10 yrs/ 1m-15 yrs	15 yrs/ 1m-20 yrs			
Anti - HBs Ab	<10 mIU/ml	N	13	21	41	40	55	170		<0.001
		%	20.3%	23.3%	37.3%	41.2%	62.5%	37.9%	33.4%–42.5%	
	10-50 mIU/ml	N	13	28	34	40	25	140		
		%	20.3%	31.1%	30.9%	41.2%	28.4%	31.2%	26.9%–35.7%	
	50-100 mIU/ml	N	6	11	12	9	2	40		
		%	9.4%	12.0%	10.9%	9.3%	2.3%	8.9%	6.4%–11.9%	
	>100 mIU/ml	N	32	30	23	8	6	99		
		%	50.0%	33.3%	20.9%	8.2%	6.8%	22.0%	18.3%–26.2%	
	Total	N	64	90	110	97	88	449		
		%								

Table 2. Distribution of tested subjects by gender and anti-HBs Ab immune response

Immune response			Gender		Total	95% CI	p value
			Male	Female			
Anti-HBs Ab	<10 mIU/ml	N	104	66	170		<0.001
		%	49.1%	27.8%	37.9%	33.4%–42.5%	
	10-50 mIU/ml	N	60	80	140		
		%	28.3%	33.8%	31.2%	26.9%–35.7%	
	50-100 mIU/ml	N	17	23	40		
		%	8.0%	9.7%	8.9%	6.4%–11.9%	
	>100 mIU/ml	N	31	68	99		
		%	14.6%	28.7%	22.0%	18.3%–26.2%	
Total		N	212	237	449		

**Figure 1.** Age distribution of study participants by their anti-HBs Ab titer.**Figure 2.** Gender and anti-HBs Ab titer.

rate of acute HBV infection.¹¹ The seroprofile for Romania, in this survey, demonstrates that although the reported coverage of infants with HBV vaccination was high (>95%), a large percentage of children had no markers of vaccination - only 63% of children aged 3–4 years had serological evidence of vaccination. For Slovak children of 1 year of age the results showed that 85% were anti-HBs Ab positive (>10 mIU/ml), for Italy - more than 80%, for Belgium nearly 80%.¹⁰

Our data confirmed the European trends in anti-HBs Ab seroconversion as we have reported an immune response in children up 1 year of age to be nearly 80%. Recombinant vaccines cannot treat already established chronic hepatitis B but are effective and result in seroconversion (appear-

ance of anti-HBs Ab) in children and adults, decreasing the incidence of HBV infection in the general population.¹² Limitations of our research can be different risk factors for inadequate anti-HBs response such as injection not in the deltoid muscle, male gender, obesity, smoking, immunosuppression and specific HLA haplotypes. Additional studies are needed to determine the duration of immunological memory as well as the appropriate time to apply a booster dose of the vaccine.⁵

Due to immunization, as well as overall improvement in preventive measures, Bulgaria has changed its status from high endemic area (with annual incidence rates of approx. 25-35%000 in the 1980s) to moderate endemic area (with only 302 newly reported cases and annual incidence rate of

4.1% 000 in 2013).⁴ According to a recent study conducted in Bulgaria, the prevalence of HBsAg positive individuals up to 19 years vaccinated against HBV is significantly lower, compared with non-vaccinated ones above 20 years old (1% vs. 4.8%).¹³

Our data shows a significant reduction in the number of HBV positive individuals after 15 years of age. Despite recommendations, serological testing of individuals for the presence of anti-HBs antibodies 1 to 2 months after the completion of the main vaccination regimen is not routinely performed.⁵ According to the literature, between 5% and 14% of the adults in the general population do not form anti-HBs Ab after the standard HBV vaccination scheme.¹⁴ It has been demonstrated a possible genetic predisposition to vaccine non-responsiveness likely due to the presence of specific human leukocyte antigen (HLA) haplotypes and specific single nucleotide polymorphism (rs497916, rs3922, rs676925 and rs355687) in genes of cytokine/cytokine receptors and toll-like receptors.¹⁵

The antibody concentration to HBsAg is estimated to be >10 mIU/ml (IU/L) to >100 mIU/ml (IU/L).¹⁶ Some authors assume the value of 10 mIU/ml as positive and protective according to European recommendations.¹⁷ Other authors assume a higher reference level of 100 mIU/ml and more than 100 mIU/ml,¹⁸ especially when the vaccine is used to protect from occupational risk of contamination with blood and blood products¹⁹. Individuals with anti-HBs Ab <10 mIU/ml are considered non-responders. There have been studies demonstrating that postvaccinal immunity against hepatitis B is not only humoral, but it has been detected that immunologic memory determined by HBsAg – specific T-lymphocytes persists long time after vaccination in recipients with serum antibodies <10 mIU/ml.²⁰

We have found better immune response after application of hepatitis B vaccine among female gender compared to male gender, as per most of the authors. Men have a reduced response to conventional hepatitis B vaccines.²¹ There are various mechanisms that explain the more adequate immune response in women. Men and women have different levels of hormones that change over time, further affecting the ability of a person to respond to vaccination.²² There is a hypothesis that immunological differences between sexes are due to steroids, especially testosterone, estradiol and progesterone, which affect the functioning of immune cells.²³ In addition to hormonal influences, genetic and epigenetic factors contribute to differences in the immune response to hepatitis B vaccination based on sex.²⁴

CONCLUSIONS

According to our data post-vaccination immune response is registered in almost 80% of the investigated children from 6 months to one year old. These results confirm the effectiveness of the vaccine against hepatitis B. The post-vaccination immune response is maintained in 67.7% of

the participants up to 15 years and dropped to nearly 40% after this age. Around 60% of the vaccinated individuals after 15 years of age have no protective anti-HBs antibody level with unknown post-vaccination immune response. We found that female gender have stronger and prolonged immune response compared to male gender as this can be due to hormonal influences and genetic and epigenetic factors, as well. We recommend an application of a booster dose of HBV vaccine after 15 years of age. For determination of anti-HBs Ab titer, it is advisable to test the anti-HBs Ab levels 1 month after application of the booster dose, especially in people working with biological materials. In spite of the mass immunization against HBV in Bulgaria, the relative share of chronic HBV infection does not show a downward trend. Therefore it is very important to study the duration of post-vaccination immune response.

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Оценка иммунного ответа анти-HBs-антител против вируса гепатита В у вакцинированных людей из региона северо-восточной Болгарии

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Абстракт

Введение: Гепатит В является одним из наиболее значительных патогенов человека, ответственных за большое количество острых и хронических инфекционных заболеваний во всём мире.

Цель: Определить длительность поствакцинального иммунного ответа у лиц, разделённых на пять возрастных групп от 6 месяцев до 20 лет.

Материал и методы: Все обследованные субъекты родились в период между 1999 и 2018 годами и в связи с этим были включены в программу обязательной вакцинации против гепатита В. Для определения серологического маркера anti-HBs Ab мы исследовали 499 образцов сыворотки, взятых у амбулаторных пациентов и пациентов в Университетской клинике «Св. Марина» в Варне.

Результаты: Положительный ответ антител (анти-HBs Ab > 10 мМЕ / мл) был обнаружен у 79,7% (n = 51) в возрастной группе до одного года, у 70,0% (n = 196) субъектов в возрасте от 1 года / 1 месяца до 15 лет и у 39,3% (n = 33) субъектов в группе в возрасте от 15 лет / 1 месяца до 20 лет. У женщин был лучший ответ после вакцинации, чем у мужчин со статистически значимым различием между полом и титром anti-HBs Ab ($\chi^2 = 24,76$, $p < 0,01$).

Выводы: Несмотря на массовую иммунизацию против гепатита В в Болгарии, относительная доля хронических инфекций HBV не имеет тенденции к снижению. Поэтому очень важно изучить поствакцинальный иммунный ответ, демонстрируя anti-HBs антитела и применять бустерную дозу вакцины по мере необходимости.

Ключевые слова

anti-HBs Ab, HBV, HBV вакцинация
