

**HUMORAL IMMUNE RESPONSE OF HOSPITAL EMPLOYEES  
INDUCED BY A RECOMBINANT HEPATITIS B VACCINE:  
5 YEARS AFTER THE PRIMARY STANDARD IMMUNIZATION**

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**Abstract.** 148 hospital employees were examined at different time periods after immunization with recombinant DNA Hepatitis B vaccine (Engerix-B) according to recommended intramuscular method. 20 (13.5%) hospital employees for whom 5 years have elapsed since first vaccination had insufficient levels of antibody (HBsAb) response, <10 mIU/ml, and considered unprotected. 46 (31.1%) had titers between 11 and 100 mIU/ml indicating feeble protection. 82 (55.4%) were considered sufficiently protected (>100 mIU/ml), and 28 (18.9%) from them had very high levels of HBsAb (>1000 mIU/ml). HBsAg was not detected in any of examined workers. Median concentrations of serum immunoglobulins (IgG, IgM, IgA) were within normal laboratory ranges, but lower among unprotected and feebly protected persons than among those with sufficient protection. Our data demonstrate an association of time lapse between vaccination and the degree of antibody response. They also suggest that immunological host factors influence the outcome of vaccination.

**Key words:** hepatitis B vaccination, hospital employees, and humoral response

**Rezumat.** 148 personal sanitar, imunizați anti-hepatită B cu vaccinul Engerix-B, au fost examinați la diferite perioade de timp. 20 (13,5%) persoane, care aveau 5 ani de la prima vaccinare, au prezentat niveluri reduse (< 10 m/U/ml de AcHBs, fiind considerate ca neprotejate. 46 (31,1%) persoane au avut titruri de 11-100 m/U/ml, ceea ce indică o protecție redusă. 82 (55,4%) persoane au prezentat titruri > 100 m/U/ml, iar 28 (18,9%) au fost cu titruri > 1000 m/U/ml, fiind considerate ca suficient protejate. AgHBs nu a fost pus în evidență la nici o persoană. Concentrațiile imunoglobulinelor serice (IgG, IgM, IgA) au fost mai reduse la persoanele neprotejate și slab protejate comparativ cu cele care au prezentat niveluri ridicate de AcHBs. Datele autorilor demonstrează asocierea dintre timpul de la vaccinare și nivelul răspunsului imun. De asemenea, este subliniată influența factorilor imunitari ai gazdei asupra rezultatelor vaccinării.

**Cuvinte cheie:** personal sanitar, imunizare, vaccin Engenix-B, nivel anticorpi

**INTRODUCTION**

Over two billion people around the world have been infected with hepatitis B virus (HBV), of whom over 350 million are chronic carriers. Some 25% of carriers develop progressive liver disease. The annual

mortality from HBV-infection and its sequels is evaluated to 1-2 million people worldwide (1).

Hepatitis B virus (HBV) infection is today a very important occupational health hazard among medical staff. Hospital care workers are the group at

high HBV infection risk (2-6). Health care workers at risk for HBV infection are recommended to vaccination (7-9). Hepatitis B causes acute and chronic liver disease and may be prevented by vaccination in this risk group (10, 11).

Hepatitis B vaccine in high-risk population is well established as very efficacious, but immune response to the vaccine after primary immunization is highly individual specific (12, 13). HBV vaccination led to a both humoral and cellular immune response and resulted in protected levels of HBs-specific antibodies (14). The immunogenicity of hepatitis B vaccine is insufficiently known for health care workers (15). The present paper summarizes results of vaccine's monitoring during five years after primo-vaccination against hepatitis B.

#### MATERIALS AND METHODS

##### **Vaccine and vaccination procedure**

148 individual employed at Laniado hospital as medical care specialists, along with members of paramedical services or administrations were vaccinated against hepatitis B with a recombinant DNA vaccine (Engerix B). This vaccine contains purified HBV surface antigens; being

administered intramuscularly 20 mcg in 1 ml three times D0, D30, and D180.

For each vaccinee a detailed socio-demographic, occupational and health disease history questionnaire was completed.

##### **Laboratory monitoring**

Laboratory tests conducted included complete blood count, serum levels of HBV surface antigens (HBsAg) and relevant antibodies (HBsAb), along with serum levels of immunoglobulins (IgG, IgM, IgA).

#### RESULTS AND DISCUSSION

We examined 148 Laniado hospital employees to identify their immune protective response to a standard primary hepatitis B immunization series by testing for antibodies to hepatitis B surface antigen (anti – HBsAb) would be obviated following vaccination.

Twenty hospital employees (13.5%) for whom 5 years have elapsed since first vaccination had insufficient of antibody response, i.e. <10 mIU/ml, and are considered unprotected. Forty-six (31.1%) had titers between 11 and 100 mIU/ml indicating feeble protection. Eighty-two (55.4%) were considered sufficiently protected (>100 mIU/ml), and 28 (18.9%) from them had very high (>1000 mIU/ml) levels of HBsAb (Table 1).

**Table 1. Serum concentration of HBsAb (5 years after vaccination)**

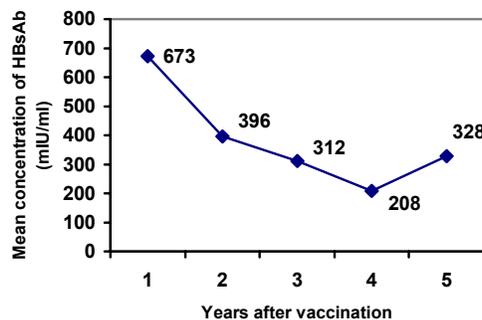
Category	HBsAb level mIU/ml	Number of persons	%
A.	<10	20	13.5
B.	11 – 100	46	31.1
C.	101 – 1000	54	36.5
D.	>1000	28	18.9
Total		148	100.0

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The recombinant hepatitis B vaccine provides immunity in approximately 95% vaccinated health care personnel, but there is a certain percentage that responds insufficiently (16). In health care workers the overall percentage with inadequate levels of anti-HBsAb, less than 10 IU/ml, was 5.2%, and the percentage of individuals with low response (10-100 IU/ml) was 27.5% (17). Among vaccinated emergency physicians after three years titer levels of anti-HBsAb were found to be protective in 81%, at borderline in 5%, and no reactive in 14% (18). Among healthy adult volunteers who received the full vaccination course with a recombinant DNA yeast-derived hepatitis B vaccine, 40% had a blood positive sample taken 8 years after the first vaccination (19). Ten-year period after vaccination against HBV identified that 57% of hospital employees showed protective antibody titers (20).

Hepatitis B surface antigen (HBsAg) was not detected in any of examined hospital workers. In the adult German population the percentage of HBsAg carriers showed a maximum of 1.12% in 41-50-year-old individuals (21). Preventive antibody levels were obtained after HBV vaccination in most of the HBsAg, anti-HBc positive persons (22). A mathematical model predicts anti-hepatitis B virus surface antigen decay after vaccination against hepatitis B (23).

Our data demonstrate an association of time lapse between vaccination and the degree of antibody response: a decrease of the mean HBsAb concentration (Figure 1). The mean titer of HBsAb after three years decreased in 34.5% of subjects who had initially acquired protective antibody titers (24). Long-term protection against hepatitis B disease is dependent on persistence of a strong immune memory (25).



**Fig. 1 Mean concentration of HBsAb and time after vaccination**

Analysis of association between HBs antibody titers, demographic and occupational factors performed to date

does not indicate that these determinants predict immune response (Tables 2-5).



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**Table 2. Serum concentration of HBsAb (mIU/ml) and sex**

Category	HBsAb level mIU/ml	Sex (%)	
		Male	Female
A.	<10	14.3	11.6
B.	11 – 100	47.6	28.3
C.	101 – 1000	33.3	37.4
D.	>1000	4.8	24.2

**Table 3. Serum concentration of HBsAb (mIU/ml) and age of vaccinated persons**

Category	HBsAb level mIU/ml	Age at vaccination (%)	
		20 –40 years	41 –56 years
A.	<10	10.4	11.6
B.	11 – 100	29.9	34.9
C.	101 – 1000	37.7	34.9
D.	>1000	22.0	18.6

**Table 4. Serum concentration of HBsAb (mIU/ml) and place of birth**

Category	HBsAb level mIU/ml	Place of birth (%)		
		Israel	Euro-America	Asia- Africa
A.	<10	11.1	7.4	13.3
B.	11 – 100	36.5	25.9	23.3
C.	101 – 1000	33.3	55.6	26.7
D.	>1000	19.1	11.1	36.7

**Table 5. Serum concentration of HBsAb (mIU/ml) and profession**

Category	HBsAb level mIU/ml	Profession (%)		
		Physician	Nurse	Paramedical
A.	<10	-	12.0	6.2
B.	11 – 100	25.0	30.0	43.8
C.	101 – 1000	75.5	34.0	43.8
D.	>1000	-	24.0	6.2

But hepatitis B vaccines have decreased their immunogenicity associated with increasing age, obesity, smoking, and male gender (26).

Median concentrations of serum immunoglobulins (IgG, IgM, IgA)

were within normal laboratory ranges, but lower among unprotected and feebly protected persons than among those with sufficient protection (Table 6).

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**Table 6. Category and HBsAb level (mIU/ml) and serum concentration of immunoglobulins**

Category and HBsAb level	IgM (mg/ml)		IgG (mg/ml)		IgA (mg/ml)	
	Median quantity	Range	Median quantity	Range	Median quantity	Range
A. <10	1.38	0.10-2.33	10.6	6.1-12.2	1.82	0.17-3.39
B. 11 – 100	1.48	0.40-4.39	11.1	7.5-17.4	1.89	0.13-4.50
C. 101 – 1000	1.68	0.43-4.67	13.2	7.7-28.2	2.35	1.02-5.95
D. >1000	1.85	0.69-4.67	14.8	9.2-23.0	2.76	1.51-4.21

No statistically significant differences regarding the immunoglobulin quantification (IgG, IgA, IgM) were detected in responders and non-responders to hepatitis B vaccine (27). The immunogenicity of the recombinant hepatitis B vaccine is satisfactory, but the lack of immune response to vaccination remains a problem, first of all for health care workers (28, 29, 30).

In adults, nonresponse to hepatitis B vaccine can result from the absence of an immune response gene in the major histocompatibility complex (31). Here the mechanisms that underlie hepatitis B vaccine nonresponse have considered the distribution of HLA alleles, age, sex, height and weight in addition to the T-cell response to hepagene derived antigens (32, 33, 34).

The vaccination route may influence the success of immunization against HBV. Intradermal HbsAg vaccination is more effective even in former “vaccine nonresponders” (35). Intradermal vaccination is efficacious in the majority of health care workers who failed to respond to intramuscular vaccine (36). Another way is using of hepatitis B booster vaccination for health care workers who had not respond and

feeble respond to standard vaccine (37).

#### CONCLUSIONS

Studies of the association between HBsAb titers, occupational and demographic factors performed to date do not indicate that these factors have a predictive value in terms of immune status of health care workers.

Our data also suggest that humoral immunological host factors may influence the outcome of vaccination.

The high prevalence of unprotected individuals, who have received the complete standard vaccination against HBV, is of concern and warrants review of current vaccination strategies.

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