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Evaluation of Hepatitis B Vaccination Status Among Medical and Paramedical Staff at the University Hospital Center (CHU) of Constantine

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Abstract - Hepatitis B virus (HBV) infection remains a major occupational hazard for healthcare workers. This prospective study aimed to evaluate hepatitis B vaccination coverage, post-vaccination immune response, and factors associated with vaccine non-response among medical and paramedical staff at the University Hospital Center of Constantine (Algeria) between January 2019 and March 2022. A total of 746 healthcare workers were included. Serological testing included HBsAg, anti-HBc, and quantitative anti-HBs antibodies. Protective immunity (anti-HBs ≥ 10 IU/L) was observed in 95.58% of participants, while 4.42% were non-responders. Strong immune response (anti-HBs > 100 IU/L) was found in 66.6% of cases. Non-response was significantly associated with advanced age (≥ 50 years, p = 0.002), obesity (BMI ≥ 30 kg/m², p = 0.001), smoking (p = 0.001), diabetes mellitus (p = 0.001), and autoimmune diseases (p = 0.004). Vaccine response also decreased with increasing time since vaccination, particularly beyond 15 years. Gender and occupational exposure to blood were not significantly associated with non-response. These findings emphasize the importance of post-vaccination serological monitoring and individualized booster strategies for healthcare workers at risk of inadequate immune protection.

Keywords - Hepatitis B virus; Vaccination; Anti-HBs antibodies; Healthcare workers; Vaccine non-response; Risk factors; Obesity; Smoking; Diabetes; Algeria

1 INTRODUCTION

More than 2 billion people worldwide carry markers of exposure to the Hepatitis B Virus (HBV). The World Health Organization (WHO) estimates that 296 million people were living with chronic Hepatitis B in 2019 (representing 3.5% of the global population) and records 1.5 million new infections annually. Hepatitis B resulted in approximately 820,000 deaths, primarily due to complications, notably cirrhosis and hepatocellular carcinoma [1].

The prevalence of HBV is highest in the Western Pacific Region and the African Region, where 116 million and 81 million people, respectively, are chronically infected. There are 60 million infected individuals in the Eastern Mediterranean Region, 18 million in the South-East Asia Region, 14 million in the European Region, and 5 million in the Region of the Americas.

Algeria is a country of intermediate endemicity (prevalence of 2–8%) with approx- imately 700,000 people infected by the Hepatitis B virus, constituting a significant reservoir favoring the transmission of this virus [2].

Hepatitis B is most commonly transmitted from mother to child at birth (perinatal transmission) or through horizontal transmission (exposure to infected blood). It is also transmitted via percutaneous exposure to infected blood and various body fluids, notably saliva, menstrual, vaginal, and seminal fluids, to varying degrees. These modes of transmission have helped define populations at risk for HBV [1]. However, there exist factors in our country different from those described elsewhere (e.g., *Hijama* or cupping therapy) which need to be identified [2].

Public health officials have ranked the reduction of vaccine-preventable diseases among the ten greatest achievements of the 21st century, of which the Hepatitis B vaccine is an integral part. Vaccination against Hepatitis B is indicated to prevent active infection by the virus, which can lead to chronic liver failure and hepatocellular carcinoma (HCC) [3].

The HBV vaccine is the first vaccine capable of reducing cancer incidence. In 1992, the WHO recommended universal vaccination against HBV. It should be possible to eradicate the disease by applying this recommendation on a global scale [4].

The first licensed Hepatitis B vaccine was developed through the purification of the hepatitis B surface antigen (HBsAg) from the plasma of chronic HBsAg carriers. Subse- quently, recombinant DNA technology allowed for the development of a recombinant Hepatitis B vaccine. A series of three vaccine doses can confer long-term protection, exceeding 30 years according to some authors [5].

In Algeria, Hepatitis B vaccination has been included in the national immunization program for newborns since 2000. The vaccine induces the formation of protective antibodies. Its efficacy against the disease and chronic infection is 90% [6].

Approximately 5 to 10% of vaccinated subjects are non-responders (anti-HBs an- tibodies < 10 IU/L) or weak responders (anti-HBs antibodies < 100 IU/L). An insufficient immune response is associated with several factors. The duration of vac- cine protection is not definitively established. Epidemiological and immunological data indicate that it is long-lasting and could even last a lifetime in good responders (anti-HBs greater than 100 IU/L) [7].

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Study Objectives

1. Evaluate the immune response following HBV vaccination among medical and paramedical personnel.
2. Analyze the influence of different factors on the vaccine response.
3. Study the individual diversity of post-vaccination immune responses, as each per- son possesses a unique "immune identity" that may explain significant variations in response to the vaccine.

The Issue of Non-Responders

The question of "non-responders" arises solely in populations exposed to a risk of infection or those susceptible to not responding to the vaccine. For these populations, the quantification of anti-HBs antibodies must be performed at the conclusion of the complete vaccination schedule.

2 MATERIALS AND METHODS

This was a prospective study conducted according to the following protocol:

1. Completion of a self-administered questionnaire.
2. Systematic blood testing: Hepatitis B surface antigen (HBsAg), anti-HBc antibod- ies, and anti-HBs antibodies for non-vaccinated personnel; and quantification of anti-HBs antibodies for subjects who had already received the vaccine.
3. Administration of the Hepatitis B vaccine according to the standard vaccination schedule if the results warranted it.
4. Quantification of anti-HBs antibodies performed 4 weeks after the last vaccine injection.

The study was conducted at the Occupational Medicine Department and the Microbiology Department of the University Hospital Center (CHU) of Constantine, from January 1, 2021, to March 31, 2024. The study population comprised the entire medical and paramedical personnel of the CHU of Constantine.

Every member of the medical or paramedical staff was included upon acceptance to undergo blood testing and complete the Data collection form. Recruitment was consecutive, non-probabilistic, and voluntary, following awareness campaigns across all Departments.

The Data collection form included socio-demographic parameters (identity, gender, age, profession). Blood samples were collected by laboratory personnel under adequate aseptic and safety conditions and collected in sterile EDTA tubes.

The data collection form consisted of five sections (Appendix 1):

- Subject identification.
- Medical and surgical history.
- Serological data.
- Information relative to vaccination.
- Other data: professional, academic, or related to hemodialysis.

Variables Studied

After data collection, the following variables were analyzed:

- **Epidemiological variables:** Gender, age.
- **Clinical variables:** Medical and surgical history (diabetes, arterial hypertension, anemia, immunodepression, etc.).
- **Virological variables:** Serological status (HBsAg, HCV Ab, HIV).
- **Vaccination variables:** Date and number of doses administered, route of admin- istration, anti-HBs antibody levels, and nature of the vaccine response.

Specific characteristics unique to each sub-population were taken into account based on factors influencing the vaccine response.

Assay Technique

An enzyme-linked immunosorbent assay (ELISA) (Bio-Rad) was used for the detection of HBsAg, anti-HBc antibodies, and anti-HBs antibodies.

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Data Collection and Management

All data were entered into an Excel database and analyzed using SPSS software, version 21. Statistical analysis included a univariate approach to describe participant characteristics and a bivariate approach to study associations between variables.

For categorical variables, absolute and relative frequencies were calculated. Quanti- tative variables that were normally distributed were summarized by their mean and standard deviation. Comparisons between categorical variables were performed using the Chi-square test. A p-value < 0.05 was considered statistically significant.

Ethical Aspects

Biological results were communicated to the participants by the Occupational Medicine Department, according to a predefined order. Participants presenting a negative HBsAg result were invited to get vaccinated against Hepatitis B. All participants provided written informed consent prior to inclusion, in accordance with the ethical principles of biomedical research.

3 Results

A total of 746 participants were included in the study. Hepatitis B vaccination coverage was 95.58%, and HBsAg was negative in all participants. The sociodemographic characteristics of the participants are presented in Table 1.

Sociodemographic Characteristics of Participants

Table 1: Sociodemographic characteristics of the participants

Variable	Categories	Count (n)	Percentage
Total		**746**	**100%**
Gender	Male	295	39.5%
	Female	451	60.5%
Age	19–30 years	201	27.5%
	31–40 years	220	26.4%
	41–50 years	187	27.5%
	51–60 years	95	14.3%
	61–70 years	43	5.8%
Profession	Medical	355	47.6%
	Paramedical	305	40.8%
	Administration / Support Staff	86	11.6%
Department	Medical	238	31.9%
	Surgical	277	37.1%
	Biology	206	27.6%
	Others	25	3.4%
BMI	< 18.5	22	2.9%
	18.5–24.9	231	31.0%
	25–29.5	236	31.7%
	> 30	257	34.4%
Smoking	Yes	131	17.6%
OEB (Occupational Exposure to Blood)	Yes	29	3.9%
Comorbidities (Diabetes)	Yes	127	17.0%
Serological Status			

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Table 2: Serological Status of the Study Population

Parameter	Negative	Positive
HBsAg	746 (100%)	0 (0%)
HCV	741 (99.3%)	5 (0.7%)
HIV	745 (99.9%)	1 (0.1%)

Vaccine Response (Anti-HBs Antibody Levels)

Table 3: Vaccine Response (Anti-HBs antibody titers)

Titer (IU/L)	Count	Percentage
0–10	33	4.42%
> 10	713	95.58%
Total	**746**	**100%**

Table 4: Distribution of Anti-HBs Antibody Titers

Titer (IU/L)	Count	Percentage
0–10	33	4.4%
> 10–100	216	28.9%
> 100	497	66.6%
Total	**746**	**100%**

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Data Analysis

Table 5: Analysis of factors associated with non-response (N=33 non-responders)

Category	Number	Percentage	P Value
Gender			
Male	17	51.52%	P=0.437
Female	16	48.48%	
Age			
19–30 years	0	0%	P=0.002
31–40 years	0	0%	
41–50 years	4	12.12%	
51–60 years	9	27.27%	
61–70 years	20	60.61%	
Job Category			
Medical	16	48.48%	P=0.005
Paramedical	12	36.36%	
Administration and others	5	15.2%	
Specialty			
Medical	17	51.5%	
Surgical	15	45.5%	
Biology	1	3.0%	
Others	0	0%	
BMI			
< 18.5	0	0%	P=0.001
18.5–24.9	1	3.03%	
25–29.5	2	6.06%	
> 30	30	90.91%	
Smoking			
Smokers	21	63.64%	P=0.001
Non-smokers	12	36.36%	
Occupational Exposure to Blood (OEB)			
Cases	0	0%	
Non-cases	33	100%	
Diabetes			
Patients	23	69.70%	P=0.001
Non-patients	10	30.30%	
Autoimmune Diseases			
Patients	16	48.48%	P=0.004
Non-patients	17	51.52%	

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Calculation of Percentages - Vaccine Response

1. Vaccine response according to HBsAg, HCV, HIV

Table 6: Vaccine response according to viral markers

Marker	Status	Responder (n=713)	Non-Responder (n=33)	Total	% Responder	% Non-Responder
HBsAg	Negative	713	33	746	100%	100%
HBsAg	Positive	0	0	0	0%	0%
HCV	Negative	712	29	741	99.3%	100%
HCV	Positive	1	4	5	0.7%	0%
HIV	Negative	712	33	745	99.9%	100%
HIV	Positive	1	0	1	0.1%	0%

2. Vaccine response according to the number of vaccine doses

Table 7: Distribution of antibody titers for 2 and 3 doses

Anti-HBs Titer (IU/L)	2 doses (n=746)	%	3 doses (n=616)	%
0–10	349	46.8%	116	18.8%
10–100	267	35.8%	326	52.9%
> 100	130	17.4%	174	28.3%
Total	**746**	**100%**	**616**	**100%**

Table 8: Distribution of antibody titers for 4, 5, and 6 doses

Anti-HBs Titer (IU/L)	4 doses (n=116)	%	5 doses (n=58)	%	6 doses (n=40)	%
0–10	58	50.0%	40	69.0%	33	82.5%
10–100	9	7.8%	4	6.9%	7	17.5%
> 100	49	42.2%	14	24.1%	0	0.0%

3. Vaccine response according to the time since vaccination

Table 9: Vaccine response according to the time elapsed since vaccination

Time elapsed	0–10 IU/L	%	10–100 IU/L	%	> 100 IU/L	%	Total
< 5 years	3	0.6%	149	28.7%	367	70.7%	519
5–10 years	7	5.6%	32	25.4%	87	69.0%	126
> 10–15 years	9	12.3%	27	37.0%	37	50.7%	73
> 15 years	14	50.0%	8	28.6%	6	21.4%	28
Total	**33**	**100%**	**216**	**100%**	**497**	**100%**	**746**

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4 DISCUSSION

The objective of this study was to evaluate the post-vaccination immunity induced against the Hepatitis B virus (HBV) (anti-HBs antibody titer) in the study population and to identify the factors influencing the vaccine response.

An anti-HBs antibody titer > 10 IU/L, measured 4 to 8 weeks after the third dose of the primary vaccination series (or after the booster in the case of an accelerated schedule), is internationally accepted as the threshold for immunization. It is achieved in approximately 95% of immunocompetent adults and is considered protective [8, 9]. Vaccine responders are divided into two categories: those who are strongly immu- nized, with anti-HBs antibodies greater than 100 IU/L, and those who are moderately immunized, with antibodies between > 10 and 100 IU/L [8,9].

Non-response to HBV vaccination is defined by an anti-HBs antibody level of less than 10 IU/L, 4 to 8 weeks after the last injection of the complete vaccination schedule [10].

No study regarding vaccination status has been conducted previously in Algeria. There is no data available regarding the response to Hepatitis B vaccination in Algeria. Our study found that anti-HBV vaccination conferred protective immunity in 95.58% of the recruited subjects, compared to 4.42% who were non-immunized (anti-HBs antibody levels < 10 IU/L).

Our study evaluated the HBV vaccination status in a population of 746 health pro- fessionals, associated with a quantitative assessment of anti-HBs antibodies (markers of immunization against HBV) and anti-HBc antibodies (markers of natural contact with the virus). This marker allows for the differentiation between vaccine-induced immunization and natural immunization through contact with the virus.

Healthcare personnel are considered immunized against Hepatitis B if they provide a medical certificate, even a dated one, indicating the presence of anti-HBs antibodies in the serum at a concentration greater than 100 IU/L [11].

The risk of contact with HBV is higher for health professionals, being 3 to 5 times greater than that of the general population [8].

The quantification of anti-HBs antibodies showed that 33 subjects (4.42%) have an anti-HBs antibody level < 10 IU/L (non-immunized), 216 (28.96%) have a level between 10 and 100 IU/L (moderately immunized), and 497 (66.62%) have a level > 100 IU/L (strongly immunized).

HBV vaccination coverage rates among healthcare workers vary from one country to another. Indeed, studies conducted in France and the United States report high rates, even though these countries are in low endemicity zones. Conversely, in countries with intermediate to high endemicity (e.g., Africa), vaccination coverage among healthcare personnel remains insufficient [8].

The immunization rate via Hepatitis B vaccination among medical personnel in our study is 95.58%. This high rate is similar to a study conducted in **France** in 2009 (97.0%) [12] and close to the rate found in a study conducted in six cities in **China** (86.4%) [13]. It is also close to that of other countries: **Brazil** 2009 (82.4%) [14], **Belgium** 2004 (84.9%) [15], **Italy** 2006 (85.3%) [16], and **Japan** 2016 (83.7%) [17].

Very different results are found in **Ethiopia** [18] and **Côte d'Ivoire** [19], which reported very low rates: 30.30% and 47.42%, respectively.

The age of the subjects in our study ranges from 19 to 70 years, with a mean of 39.3 ±12.5 years. These results are close to those obtained by Ouédraogo H et al. (37.9 ±10 years) [20]. They approximate those obtained in **Cameroon** by D. Noah et al. with 40.69 ±9.29 years [21], and results obtained by K. Djeriri et al. with 41.4 ±7 years [22]. However, they are lower than those of F. Barka et al. with 45.7 ±8 years [23]. The major age group of vaccinated subjects is 31–40 years, followed by the 41–50 years age group. These results differ from those reported by the study of D. Noah et al., where the majority age group was 41–50 years, followed by 31–40 years [21], but are similar to the results of H. Ouédraogo et al. [20] and O. Aydemir et al. [24], where the majority age group was 20–30 years.

The mean age is related to the nature of the study and the recruitment age of the majority of subjects in our population, who are university hospital practitioners.

The low vaccination coverage among healthcare workers aged over 40 is, in part, attributed to the reluctance of senior staff to receive the Hepatitis B vaccine before 1992. Since that date, vaccination has been more widely accepted. However, this delay in administering the vaccine influenced the vaccine response; among the 33 non-responders, 20 subjects were aged 61–70 years (60.61%) and 09 were aged 51–60 years (27.27%). There is, therefore, a significant relationship between advanced age and non-response or poor vaccine response ($P = 0.002$).

These results are similar to those obtained in **China** by Q. Yuan et al. [25] and close to those of H. Tatsilong et al. in **Cameroon** ($P = 0.004$) [26]. They do not agree with the study by O. Aydemir et al. in **Turkey** [24], which found no relationship between advanced age and vaccine response ($P = 0.880$).

A study conducted in **Portugal** by C. Osti and J. Marcondes-Machado reported that older personnel also showed a higher rate of non-response: the mean age of workers with anti-HBs of 0 U/L was 52.3 years, and

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those with anti-HBs > 100 IU/L was 38.4 years, $P < 0.02$ [27]. A study conducted in **Iraq** by H. Sagvan et al. reported that a good vaccine response is correlated with age under 40 years ($P = 0.03$) [28].

regarding gender, the population of our study is predominantly female with 451
cases (60.5%). This can be explained by the high proportion of women in the medical and paramedical professions. These results are similar to those of D. Noah et al. (69%) and close to those of F. Braka et al., who found a proportion of female personnel of 57% in **Uganda** [21, 23], and also those of H. Ouédraogo et al., who found a female proportion of 59.80% in **Burkina Faso** [20].

Among the 33 non-responders, 16 (48.48%) are female and 17 (51.52%) are male, representing a sex ratio of 0.85, with a $P = 0.437$.

The sample consisted mainly of medical personnel (47.6%, 355 cases) and paramed-
ical personnel (40.8%, 305 cases), and to a lesser degree administrators and support staff (11.6%, 86 cases). The importance of the number of vaccinated individuals can be explained by the fact that in recent years, young medical personnel (medical residents) recognize the occupational risks of contracting Hepatitis B in the hospital environment better and have a good tendency to get vaccinated against Hepatitis B after proof of its safety and efficacy.

Medical personnel had significantly higher vaccination rates ($p = 0.005$) than other professional categories, namely nurses, nursing assistants, laboratory technicians, and support staff. This result could be explained by a higher level of knowledge among medical personnel regarding Hepatitis B and the necessity of adhering to the vaccination schedule. Some authors had already reported similar results, notably in **Pakistan** [29], in **Senegal** [30], and in **South Africa** [31].

These results are also similar to results reported by P.J. Lu et al. in the **United States** [32] and by H. Ouédraogo et al. [20] in **Burkina Faso**, and are different from results obtained by G. Abeje and M. Azage in **Ethiopia** [33] and D. Noah et al. in **Cameroon** [21], who reported that nurses represent the majority of vaccinated individuals (61.9%).

In our study, we found a close relationship between obesity and vaccine non- response: 30 of the 33 non-responders were obese (90.91%), $P = 0.001$. Our result is close to that reported in the study by Z. Karacaer et al. in **Turkey** with a $P = 0.003$ [34]. Overweight, expressed in most studies as body mass index (body weight in kilograms/height in meters squared), has been suggested as a risk factor for vaccine failure. This phenomenon is mainly observed in very obese individuals [35].

Obesity is generally associated with forms of chronic inflammation; systemic and intrinsic inflammation of B lymphocytes induced by leptin produced by adipose cells can modulate innate and adaptive immune responses. The incubation of B cells from lean individuals with leptin increased the phospho-AMP signal transducer and the activation of transcription factor (STAT)-3, crucial for TNF-a production, and decreased phospho-AMP-activated protein kinase, the energy-sensing enzyme that could influence immune responses to viral infections or vaccines [36].

Researchers thus estimate that the abundance of adipose tissue weakens and disrupts the functioning of leukocytes, cells involved in the immune response. Conse- quently, overweight individuals are more easily affected by bacteria and viruses and have impaired wound healing. But this also affects their capacity to develop antibodies, notably when they get vaccinated [36, 37].

In our study, among the 33 non-responders, 21 (63.64%) were smokers ($P = 0.001$).

Several studies have shown the influence of smoking on the immune system. A study
done in **Bangladesh** by M. Shaha et al. reported results similar to ours [38].

The alteration of anti-HBs antibody formation proved to be significantly elevated among smokers. The frequency of developing protective anti-HBs antibodies (≥ 10 IU/L) among a vaccinated population was almost nine times lower in smokers. These data suggest that the development of anti-HBs antibodies, whether naturally after infection or after vaccination, is significantly lower in smokers. It is necessary to verify the anti-HBs status in smokers after vaccination; a booster vaccination should be administered if the anti-HBs antibody titer falls below the protective level (10 IU/L) [38].

Smoking impacts both innate and adaptive immunity and plays a dual role in regulating immunity, either by exacerbating pathogenic immune responses or by attenuating defensive immunity. Adaptive immune cells affected by smoking mainly include T helper cells (Th1/Th2/Th17), regulatory T cells (CD4+ and CD25+), CD8+ T cells, B cells, and memory T/B lymphocytes, while innate immune cells affected by smoking are mainly DCs, macrophages, and Natural Killer (NK) cells [39].

In our study, the 33 non-responders had no history of blood exposure, and the 29 exposed subjects were responders. This status can be explained by better management of exposed persons. Sukriti et al. reported in an **Indian study** that 30 personnel having suffered an occupational exposure to blood out of 150 did not respond to Hepatitis B vaccination [40].

Furthermore, the risk of contracting HBV for health personnel is four times higher than in the general population [8]. For a non-immunized person, the transmission rate of HBV after a needlestick injury varies from 6 to 30% depending on the viremia of the source patient. On the other hand, HBV treatment, currently very advanced in Western countries, combines antivirals and immunomodulators. It is not always accessible in all countries. That is why the WHO recommends vaccination against Hepatitis B as the only effective means of fighting this disease, associated with hospital hygiene measures [8].

In our study, diabetes is significantly linked to a poor response to vaccination; 69.70% (23 cases) of non-responders are diabetics with a $P = 0.001$, close to a study conducted in Dhaka, **Bangladesh** by M. Shaha et al. [38]. Conversely, W. Qiang He et al. in the **United States** found no significant relationship between diabetes and poor vaccine response [41].

The vaccine response is linked to an effective immune response characterized by the activation of NK lymphocytes, a subtype of lymphocytes involved in the elimination of infectious agents and tumor cells through the activation of T and B lymphocytes, similar to cases of natural infection [42].

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To clarify this link, a research team led by J. Berrou et al. focused on NK cells [42]. The study compared blood samples from 51 diabetics and controls. They found that two subtypes of NK cells (NKG2D+ and NKp46+) were under-represented in the blood of diabetic patients. They were also less functional: "Degranulation does not occur correctly. This means that these NK cells release fewer enzymes intended to eliminate target cells." Furthermore, it appeared that the higher the blood glucose, the more the quantity of NKG2D+ cells decreased, suggesting a cause-and-effect link between the disease and the alteration of the immune system. This could also explain why septic risk is higher in cases of unbalanced diabetes or acute hyperglycemia [42].

Subsequently, a study conducted in murine models (2018) showed that NK cells played a role in controlling the antibody response. This regulatory role of NK cells not having been studied in humans, researchers at the Duke Human Vaccine Institute sought to answer this question. Their analyses clearly show that human NK cells have the capacity to control the number of T helper lymphocytes as well as the antibody response [43].

Autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis (MS), lupus, and immune-mediated renal diseases are not contraindications to anti-Hepatitis B vaccination. The efficacy of vaccination in these patients has been demonstrated, but much less so than that observed in healthy persons [44]. 16 subjects among the 33 non-responders have an autoimmune disease with a significant relationship

$P = 0.004$, similar to results obtained in the study carried out by Q. Yuan et al. in

China, $P < 0.05$ [25].

Several studies have also demonstrated the good tolerance of vaccination in pa- tients suffering from autoimmune diseases. To date, no data indicates that primary vaccination or boosters increase the risk of relapses or the development of *de novo* autoimmune diseases. In particular, in the case of multiple sclerosis, several studies have demonstrated that vaccination does not induce a risk of MS flare-ups. It should be noted that other studies aiming to demonstrate the efficacy and safety of vaccines for persons suffering from autoimmune diseases are ongoing [45].

While studies demonstrate that patients suffering from chronic inflammatory dis- eases and undergoing low immunosuppressive treatments have a satisfactory post- vaccination immune response, there is nonetheless a risk of poor or non-response for patients suffering from autoimmune diseases and receiving strong immunosuppressive treatment of the anti-CD20 or anti-metabolite type, or Rituximab. A recent study esti- mates that nearly one in 10 people suffering from an immune-mediated inflammatory autoimmune disease would not develop a satisfactory response to anti-Hepatitis B vaccination [46].

Among the 33 non-responders, 04 patients had a positive HCV serology. Several studies have shown that cirrhotic patients or those with hepatitis C may benefit from a double-dose vaccination regimen (40 µg administered twice in adults) to achieve seroconversion, due to a poor response to standard vaccination. [47].

Liver damage leads to an immune deficit depending on the age of infection and the severity of progressive lesions linked to this infection. Patients suffering from chronic liver disease have a compromised cellular and humoral immune system. Furthermore, cirrhotic patients have reduced hepatocellular function [48].

However, the immunogenicity of vaccination in healthy persons (such as the ability to obtain an antibody response above a value considered as a cutoff) is not the same as that of immunodepressed patients. This concept is important because the efficacy of immunization is still high at the beginning of liver disease, when the immune system is not yet compromised. Later, with the progression of the disease, the seroconversion rate lowers progressively [49].

Several factors can explain reduced immune response in the patient suffering from cirrhosis, such as lymphopenia, an alteration of T lymphocyte subpopulations, an alteration of the interaction between antigens and T cells, and finally an abnormal proliferation of activated T lymphocytes.

From our results, it emerges that 267 cases (35.79%) received only 02 doses. A study shows a similar rate of 32% in **Iran** conducted by M. Moghadami et al. [50]. This satisfactory anti-HBs antibody rate after 02 doses is related to the nature of the Hepatitis B vaccine, which is highly immunogenic.

We noted that 267 persons (35.79%) are well immunized with a level > 100 IU/L
after 2 vaccine doses, and 130 cases (17.43%) are moderately immunized with a level between 10 and 100 IU/L. Furthermore, 349 cases (46.78%) are not immunized with a level < 10 IU/L after the 02-dose vaccine schedule.

After injection of 03 doses, 116 (24.22%) persons are not immunized; conversely, 136 (28.39%) are moderately immunized and 227 (47.39%) are strongly immunized.

The administration of one to three additional doses of vaccine allowed obtaining a response in 50% of cases after one dose (58 cases) and in 71.55% (83 cases) of cases after 3 doses. These results agree with those of a study in **South East Asia** conducted by L. Childs et al. with 68% response after 03 doses [51]; and are far from those of the study by H. Tatsilong et al. in **Cameroon** who reported an immunization rate of 24% after 03 doses [26].

The three doses (or more) of the vaccine should all be administered in order to achieve optimal protection of vaccinated personnel, because antibody production induced after vaccination depends in part on the vaccination schedule. Indeed, the strong immunogenicity of the anti-HBV vaccine is well known, but it manifests less when the vaccine is administered in adulthood.

In order to allow exposed professionals to benefit from additional doses in case of non-response to vaccination, a post-vaccination anti-HBs antibody check is thus recommended. This check has a second interest: it allows for the screening of chronic HBV carriers. Indeed, during its reflection on the prevention of caregiver-to-patient transmission, the WHO report [8] highlighted that among caregivers involved in caregiver-to-patient HBV transmissions, some had been vaccinated while they were carriers of a

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chronic infection.

This report led to a modification of regulations, which now imposes the verification of immunization and the absence of HBV infection for all students and health personnel subject to mandatory vaccination against HBV. In practice, a subject having an anti-HBs antibody level greater than 100 IU/L is considered immunized and not a carrier of the virus, even in the absence of documentation of prior vaccination. When the antibody titer is between 10 and 100 IU/L, it is possible, though exceptional, that the person has a high viral load of HBsAg.. This hypothesis must be eliminated by screening for anti-HBc antibodies. If it is negative, the person is considered immunized provided the vaccination schedule is complete; it will thus be completed if incomplete [8]. When the antibody titer is less than 10 IU/L, vaccination must be performed or completed. If negativity persists after a 3-dose schedule, additional doses are possible. An anti-HBs antibody quantification will be performed one to two months after each injection.

HBV could be eliminated by the implementation of universal vaccination, with the advantage of eliminating the main cause of hepatocellular carcinoma (HCC). The success of vaccination programs is documented in high endemicity countries such as Taiwan and The Gambia where HBV prevalence dropped from 10 to 1.1% and 0.6% respectively after the introduction of vaccination programs [8].

The highest number of non-responders is found among subjects whose vaccination dates back more than 15 years (14 cases), followed by those whose date is between 10-15 years (09 cases), ($P = 0.001$).

According to literature data, it is evident that antibody levels decrease with time:
reaching the maximal antibody titer generally occurs about one month after the last vaccine dose. A progressive drop in antibody titer occurs over the months, but the downward trend of antibody concentration slows over time [8].

A prospective study conducted among vaccinated health personnel by S. Heidari et al. demonstrated that the anti-HBs antibody rate decreased significantly since the last vaccination [52]. Furthermore, the response rate to the Hepatitis B vaccine is significantly higher in persons having a short duration between the vaccination date and the serological test compared to personnel vaccinated more than 15 years ago.

The study showed that anti-HBs antibody rates decrease according to a geometric mean, from 516 IU/L after vaccination to 24 IU/L 18 years later. Persons vaccinated 18 years ago have the lowest rate of anti-HBs antibodies [52].

Another Japanese study [17] reported that anti-HBs antibody levels decrease after 10 to 31 years and fall below a level considered protective in about 25% of cases.

Finally, the rapid and strong response to a booster vaccine suggests a long-lasting amnestic response. Vaccination against Hepatitis B offers long-term protection against

Hepatitis B [53].

Additional long-term follow-up studies are necessary to explore longer protection conferred by the Hepatitis B vaccine; furthermore, the necessity of a booster after a certain number of years must also be evaluated.

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Appendices

Appendix 1: Data Collection Form – Medical Personnel

BENBADIS UNIVERSITY HOSPITAL CENTER – CONSTANTINE
DEPARTMENT OF MICROBIOLOGY – PR. K. BENLABED
Tel/Fax : 031- 88- 64- 99

Patient No: _____ **Date:** _____/ _____/ 20_____

Surname: _____**First Name:** _____**Gender:** F □ M □

Age: _____**Date of Birth:** _____

Address: _____ **Professional Status:**

_____ **Department :** _

BMI: _____

Smoker: □ Yes □ No

Substance Abuse: _____

History

Medical: _____**Diabetes:** □ Yes □ No

Anemia: □ Yes □ No **Hypertension:** □ Yes □ No

Autoimmune Disease: □ Yes □ No **Hemodialysis:** □ Yes □ No

Occupational Exposure to Blood (OEB): □ Yes □ No

OTHERS: . . . . . .

Surgical: . . . . . .
. . . . . .

Serology

HBsAg: _____ **HCV:** _____ **HIV:** _____

Anti-HBc: _____ **CMV:** _____ **EBV:** _____

TPHA: _____

Mother HBsAg+: _____ **Contact HBsAg+:** _____

OTHERS: . . . . . .

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Medical Treatments

Anemia Treatment: .....

Immunosuppressive Treatment: .....

Others: .....

HBV Vaccination

Vaccination: □ Yes □

No **Date:** _____

Schedule: 3 doses: _____ 4 doses: _____

No. of Doses	Vaccine Brand	Route of Admin.	Dose Administered	Date
1st Dose				
2nd Dose				
3rd Dose				
4th Dose				
Supp. Dose 1				
Supp. Dose 2				
Supp. Dose 3				

Mode of administration: IM □ ID □ S/C □

Booster: .....

Lot Number : .....

Anti-HBs: Done □ Not Done □

Titer: _____

PRESCRIBING PHYSICIAN