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Evaluation of the Virological Status of the Family Members of Chronic HBV Patients and Possible Vaccination

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Abstract:

Introduction: Hepatitis B virus (HBV) is the most common chronic viral infection in the world and represents a major global healthcare challenge with significant morbidity and mortality. The Hepatitis B vaccine (HepB) has been available since the early 1980s and is considered a breakthrough in the global effort to eradicate the virus. It is highly immunogenic and reduces morbidity and mortality related to HBV.

Aim of the work: To assess the virologic status of the family members and householders of chronic HBV patients, b) assess immunological response after various durations of hepatitis B vaccination, c) vaccinating of the non-immune family members and d) to identify causes of decreased immunogenicity of HBV vaccination.

Subjects and methods: This is a cross-sectional study on 104 chronic hepatitis B (CHB) cases recorded at the Unit of National Committee for Control of Viral Hepatitis (NCCVH) in Fayoum General Hospital and managed according to Egyptian guidelines for HBV treatment and 455 of their family members were **categorized to vaccinated and non-vaccinated groups and tested for hepatitis B virologic status.**

Results: Regarding the immunogenicity of the HepB vaccine our study estimated 72.9% seropositive results among vaccinated participants with a significant reduction of the titer with increasing the age and the time since the last vaccination dose. The overall prevalence rate of HBsAg among household / close contacts was 10.65% (47/445) of the examined participants and interfamilial spread was detected in (27.8%) of the families included.

Conclusion: The low rate of infection transmission among children reveals the effectiveness of the universal vaccination programs but the presence of non-immune subjects after vaccination spots to the importance of post-vaccination tests to ensure the response to the vaccine and the introduction of booster vaccination if needed especially in high-risk groups.

Keywords: chronic hepatitis B; hepatitis B vaccine; anti-HBs titer.

1. Introduction

Hepatitis B virus (HBV) is the most common chronic viral infection in the world and represents a major global healthcare challenge with significant morbidity and mortality [1]. World Health Organization (WHO) announced that chronic hepatitis B (CHB) affects more than 296 million individuals worldwide [2]. An estimated 887.000 people die yearly from the complications of HBV as persistent infection, liver cirrhosis and hepatocellular carcinoma (HCC) [3].

CHB is highly endemic in Africa, Asia, in addition parts of Central and Eastern Europe [4]. Egypt lies in the zone of low prevalence and genotype D is the most prevalent [1].

HBV is highly infectious and can be transmitted in the absence of visible blood [5]. Persons with chronic infection are considered the main reservoir for HBV transmission [6]. There are three major modes of HBV infection: perinatal "mother-to-child transmission" (MTCT), sexual transmission and unsafe injections [7]. In addition to these modes of transmission, horizontal transmission through household/close contact which causes "intra-family clustering" also plays a crucial role in spreading HBV [8].

Antiviral drugs are not curative and treatment is lifelong and expensive [9]. So, it is very important to identify persons with chronic infections, testing and vaccinating their contacts and household members [10].

Hepatitis B vaccination (HepB vaccine) is now obligatory in the immunization schedule at birth and is also indicated for persons at increased risk of getting the infection because of ongoing intimate contact with a chronically infected case [11].

HepB vaccine has been available since the early 1980s and is considered a breakthrough in the global effort to eradicate the virus [12]. It is highly immunogenic and decreases morbidity and mortality related to HBV.

In Egypt; yeast-dependent recombinant vaccine “Recombivax HB (Merck)” has been a part of the routine national immunization program since 1992 and it is given in 3 doses scheduled at 2, 4 and 6 months of age [13]. According to the National Demographic and Health Survey (NDHS), the coverage rate of the vaccine is about 97% [14].

Since 2019, hospitals have been introducing the “birth dose” and delivering the first dose of the vaccine within 24 hours

after birth [15]. Testing for verification of protective immunity to the HBV vaccine is required as some people do not develop adequate levels of antibodies against HBsAg (anti-HBs) [16].

2. Subjects and Methods

2.1.Subjects

We performed a cross-sectional study on 104 CHB cases recorded at the Unit of the National Committee for Control of Viral Hepatitis (NCCVH) in Fayoum General Hospital and managed according to Egyptian guidelines for HBV treatment and 455 of their family members

Eligibility criteria

CHB patients and their household members were enrolled in this study unless refused by the patient or his/her relative (s).

2.2.Methods and data gathering

All included family members were subjected to face-to-face interviews and self-administered questionnaires including demographic data, history of HepB vaccination, family relationship with CHB patients, occupation and co-morbidity. Under strict aseptic precautions, 3 ml of venous blood was collected from all participants in a vacutainer containing a clot activator. Serum separation was performed.

Then they were categorized into vaccinated and non-vaccinated participants.

1) All vaccinated participants were subjected to do Anti-HBs titer. The quantification of serum anti-HBs level was done by ELISA technique using a commercially available kit. According to the results:
   - A titer less than 10 mIU/ml was regarded as non-protective immunity and the subjects tested were eligible to receive a full dose vaccination if HBsAg and anti-HBc were negative.
   - Titers between 10 and 100 mIU/ml were considered hypo-responsive and needed to be evaluated on a case-by-case basis.
   - A titer of more than 100 mIU/ml was considered a high level of immunity.
2) All non-vaccinated participants were subjected to HBsAg and anti-HBc (total). According to the results:
   - If both HBsAg and anti-hepatitis B core (HBc) were negative, patients were considered not-immune, had not been infected but were still at risk of possible

future infection and were obtained to get the vaccine.

- Samples that were (+ve) for either anti-HBc or HBsAg were subjected to quantification of the HBV genome by real-time polymerase chain reaction (PCR) to determine if the patient had an acute, chronic or occult infection.

All Subjects need vaccination were referred to NCCVH in El-Fayoum governorate to receive the HepB vaccine "Recombivax HB (Merck)", given by injection into a muscle in 3 doses scheduled at 0, 1 and 6 months.

- Children and Adolescents dose: 5 mcg (0.5 mL).
- Adult dose: 10 mcg (1.0 mL).

3. Results

The present study recruited 455 family members of 104 HBsAg-positive patients.

As regards demographic characteristics of the household/ close contacts of HBV patients; 216 individuals (47.5%) were male and 239 (52.5%) were females with a mean age of 16.65±13.21 years. Most of the participants 68.90% (292/455) were students and according to their relation to patients, they were 45 husbands, 55 wives, 161 sons, 162 daughters, 5 mothers, 14 brothers, 5 sisters, 3 nieces and 2 nephews. 7.5% (34/455) of the participants were smokers.

Regarding the medical history of the participants, nine were hypertensive (9/455), four had diabetes mellitus (DM) (4/455), only one patient had chronic disease (bronchial asthma) and was on steroids and none of them was on immunosuppression drugs rather than steroids.

Among the family members evaluated, 395 (86.8%) of them were previously vaccinated during the compulsory vaccination program in Egypt after 1992 or electively received vaccination after discovering a subject with HBsAg positive in the family as shown in **Figure 1.**

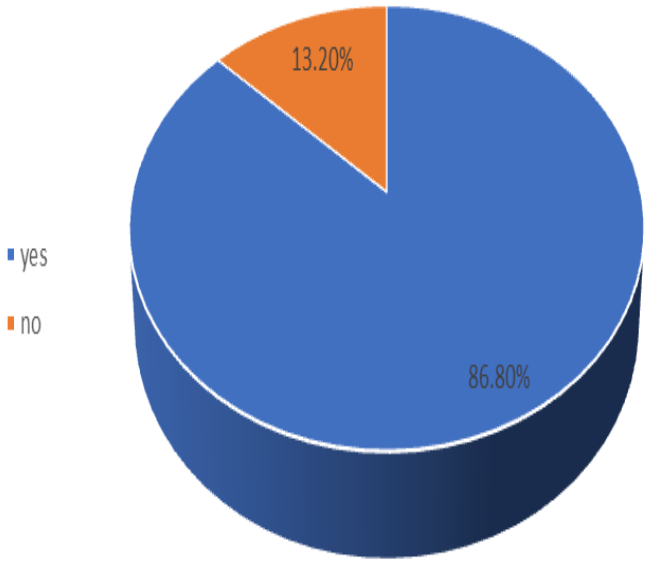

Figure 1: Percentage of vaccinated household / close contacts of HBV patients.

Table 1 showed the percentage of each category among the vaccinated group and revealed that 87.59% of vaccinated group received it among compulsory vaccination program.

Table 1: Vaccination status (compulsory, HBIG and booster) of the vaccinated household / close contacts of HBV patients.

Vaccination status	Count (%) Total number (395)
Compulsory vaccination program	n=298 (75.44%)
Compulsory vaccination program and HBIG	n=21 (5.32%)
Compulsory vaccination and booster vaccination	n=27 (6.84%)
After HCV treatment	n=5 (1.27%)
After discovering a subject with HBsAg positive in the family	n=44 (11.14%)

Anti-HBs test was done and found to be seropositive (above 10 mIU/ml) for 282 (72.9%) out of 387 [from 10-100 mIU/ml 37.7% and > 100 mIU/ml is 35.14%]; as 8 subjects were lost to follow up. Mean titer of (161.71± 268.84 mIU/ml) in the examined vaccinated subjects (**Table 2**).

Table 2: Interpretation of Anti-HBs test among vaccinated household/ close contacts of HBV patients.

Anti-HBs titer	Count (%) Total number (387)
Less than 10 mIU/ml	105 (27.13%)
10-100 mIU/ml	146 (37.73%)
More than 100 mIU/ml	136 (35.14%)

As regards baseline demographic data of the participants with anti-HBs less than 10 mIU/ml. The main gender was female 59.05% (62/105) with a mean age of 12.61 ± 6.57 years.

Most of them were students 83.81% (88/105), non-smokers 99.05% (104/105) and offspring of the index cases 90.48% (95/105). Regarding medical conditions; none of them had hypertension (HTN) or DM and only one had bronchial asthma on steroids.

The mean time since the last vaccination dose was 11.91 ± 6.26 years. Regarding the immunogenicity of the vaccine, anti-HBs mean titer was 3.96 ± 2.75 mIU/ml.

The relation between age, time since the last vaccination dose and anti-HBs titer was examined as factors affecting immunogenicity after the vaccine and is shown in **Table 3** and **Figures 2** and **3**. The younger the patient and the less the duration of vaccination the more the anti-HBs titer with p =0.018 and <0.001 respectively.

Table 3: The demographic characteristics of included participants.

Variables	Anti-HBs titer		*P*-value
	Above 10 mIU/ml	**Below10 mIU/ml**	
Age	13.55 ±11.77	14.47 ±9.55	0.018*
Time of the last vaccine	7.77 ±4.95	11.11 ±5.93	<0.001*

*significant.

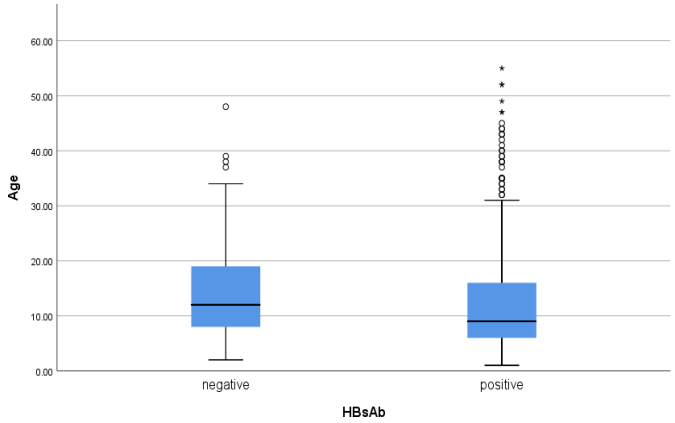

Figure 2: Relation between age and anti-HBs titer among vaccinated households/ close contacts of HBV patients.

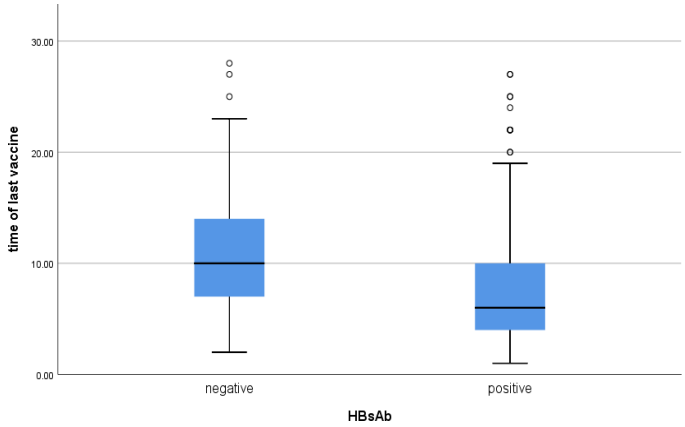

Figure 3: Relation between the time of last vaccination and anti-HBs titer among vaccinated household / close contacts of HBV patients.

Further analysis was performed regarding the immunogenicity of the HepB vaccine denoted by anti-HBs titer and other variables such as gender, HTN, DM, smoking, chronic disease and steroid intake with no statistical significance. Vaccinated participants with anti-HBs less than 10 mIU/ml (n=105/387) were tested for HBsAg and then anti-HBc if HBsAg was negative as shown in **Table 4**. Eighteen participants with HBsAg (+) and one with anti-HBc (+) were for HBV deoxyribonucleic acid (DNA) PCR and treatment if eligible. HBsAg (-) or anti-HBc (-) would obtain a booster dose of HepB vaccination.

Table 4: Virologic status of vaccinated participants with anti-HBs less than 10 mIU/ml.

Virologic status	Number (105)
HBsAg (-) HBcAb (-)	n=86
HBsAg (-) HBcAb (+)	n=1
HBsAg (+)	n=18

Regarding non-vaccinated family members (n=60/452); there were 29 known HBsAg positive on treatment or not eligible for treatment on regular follow up and 2 refused to do labs. The virologic status was tested in HBsAg-negative individuals (n=29/452) as shown in **Table 5.** All HBsAg (-) and HBcAb (-) received full dose vaccination and all anti-HBc (+) were eligible for repeating all virologic markers and HBV PCR to confirm the results and exclude OBI before vaccination.

Table 5: Virologic status of non-vaccinated participants.

Tests	Results	Number (105)
HBsAg: HBcAb total	negative (-): positive (+)	n=13
HBsAg: HBcAb total	negative (-) negative (-)	n=16

Among those 29 families, 9 families showed spread among offspring, 8 of them were offspring of females and 1 family was offspring of male and female which indicates the perinatal transmission. Sexual and horizontal modes of transmission were probably found in 13 and 12 families respectively. The overall HBsAg is positive in our study among household / close contact is 10.56% (n= 47/445) as 10 subjects refused to test as mentioned above.

Among HBsAg positive participants (n =47), eighteen (38.30%) received vaccination and 29 (61.70%) were not previously vaccinated as shown in **Table 6** and **Figure 4** denoting either vaccination of positive HBsAg or non-immunogenic HBV vaccine.

Table 6: vaccination status of HBsAg-positive household / close contacts of HBV patients.

Variables	HBsAg		*P*-value
	Positive	Negative	
Vaccinated	18 (38.30%)	377 (92.85%)	<0.001*
Not	29 (61.70%)	29 (7.14%)	

*significant.

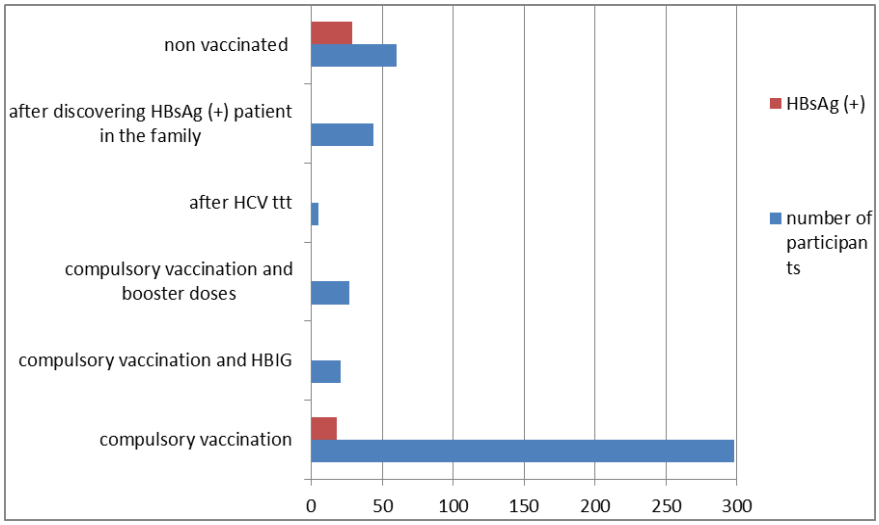

Figure 4: Vaccination and virologic status of household / close contacts of HBV patients.

4. Discussion

Egypt is still fighting against HBV to prevent the impact of this infection on people's health, the long-term morbidity and the long-term treatment burden. So, we need to prioritize and scale up the national control strategy with regular monitoring and surveillance of the high-risk groups for HBV infection, awareness campaigns, enhancement of infection control practices, full vaccination coverage of infants, family members counselling and assessment, proper patients management & follow up, expand subsidized treatment facilities as National Treatment Centers (NTC) & Health Information Organization (HIO) and successful research programming to battle the hepatitis B epidemic [15].

This study aimed to explore the HBV spread problem among one of the major risk groups (family members of CHB patients) and the impact of the vaccination program in controlling the transmission, evaluate the immunogenicity of the vaccine in the long run and discuss the recommendations for booster vaccination.

Our study was a cross-sectional study of 455 family members of 104 HBsAg positive cases 216 individuals (47.5%) were male and 239 (52.5%) were females with a mean age was 16.65 ± 13.21 years. In our study, the vaccination coverage rate was about (86.8%).

Regarding the immunogenicity of the hep B vaccine, our study estimated 72.9% seropositive results among vaccinated participants with a significant reduction of the titer with increasing age or time since the last vaccination dose.

Among vaccinated subjects (27.1%) had non-protective immunity anti-HBs <10, no available data about if those subjects were non-responsive to the vaccine from the start or the immunity of the patients was decreased. Although the World Health Organization (WHO) does not recommend post-vaccination testing, it is important to examine the response at 9-12 months of age in infants born to HBsAg-positive mothers and 1-2 months after the final dose of vaccination especially in high-risk groups for HBV infection to confirm that the subject achieved adequate immune response to the vaccine [5].

The overall prevalence rate of HBsAg among household / close contacts was 10.65% (47/445) and interfamilial spread was detected in (27.8%) of the families included (29/104). Family members of HBV-positive patients are at increased risk of infection and clustering of HBV infection within the family is common.

Clustering of HBV infection was observed in 6 families which have spouses, offspring and/or siblings and parents spread that confirmed the multiple interfamilial routes of transmission.

Among vaccinated participants, there was a significantly lower rate of HBsAg positive 4.65% (18/387) than non-vaccinated participants as the prevalence was 50% (29/58).

The presence of positive cases among vaccinated participants could be explained by acquiring the infection in the period between the birth and the time of the 1st vaccination dose which was at 2 months of age before application of 1st dose of the vaccine within 24 hours after birth “birth dose” since 2019, decrease immunity of the patients, decrease antibodies titers by the time and need booster vaccination and may due to ineffective vaccine as the vaccine is very sensitive to heat and freezing and any change in temperature causes loss the potency of the vaccine.

Positive HBsAg subjects <18 years should be included in NCCVH regular follow-up programs to early catch the children and adolescents who are candidates for treatment.

This result highlights this high-risk group and all efforts must continue to prevent HBV transmission through progress in screening, vaccination and treatment of the chronically infected patients and their families to rid Egypt of HBV.

5. Conclusion

In Egypt, although shifting to a low endemicity area of HBV with HBsAg prevalence (< 2%) due to the rapid expansion of the coverage of hep B vaccinations after their addition to the national immunization program in the 1990s, HBV still considered a disease burden in Egypt [17]. As some people do not develop sufficient levels of anti-HBs, testing for verification of protective immunity to HBV vaccination is required [16].

Our study evaluated the serological markers of HBV infection in the family members of HBsAg-positive patients in Fayoum governorate, Egypt. The low rate of infection transmission among children reveals the effectiveness of the universal vaccination programs but the presence of non-immune subjects after vaccination points to the importance of post-vaccination tests to ensure the response to the vaccine and introduction of booster vaccination if needed especially in high-risk groups.

Ethical approval and consent to participate: The Faculty of Medicine Research Ethical Committee reviewed this study. The participants were informed about the objectives of the study and the investigations that were done by the researcher. Also, the confidentiality of their information and their right not to participate in the study were considered.

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Conflicts of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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