Evaluation of the Immunological Status to Hepatitis B Vaccine of individuals after 20 years from Receiving Hepatitis B Vaccine in Compulsory Program in Egypt.

Ahmed M.Hassan, Msc [1*], Mohammed A. Arafa MD[1], Mosleh A.Ismail MD[1], Said H Abbadi MD[2]
[1]Family Medicine department, Faculty of Medicine, Suez Canal University
[2]Microbiology Department, Faculty of Medicine, Suez Canal University
[*]Corresponding author

Abstract:

Background: Hepatitis B virus (HBV) is a worldwide public health problem. The prevalence of chronic HBV infection is highly variable. Egypt is considered to be a region of intermediate prevalence for HBV infection with reported figure of 4.5%

In 1991, the World Health Organization (WHO) recommended that hepatitis B vaccination should be included in national vaccination programs in all countries with a hepatitis B carrier prevalence (HBsAg) of ≥ 8% by 1995 and in all countries by 1997.**Objectives:** This study aimed to determine the immunologic status (An anti-HBs level of ≥10 mIU/ml that is protective against HBV infection) among individuals after 20 years from receiving hepatitis B vaccine in compulsory program in Egypt**.**

Methods: It is a cross sectional study. It was carried out on 57 medical students. They are studying in the 2nd year of Faculty of Medicine, Suez Canal University (FOM, SCU). It was conducted at Family Practice clinic affiliated to Suez Canal University Hospital. In the current study a self-administered questionnaire was fulfilled by the studied population. A blood sample was taken to measure serum anti-HBs Ab titre. Individuals with positive protective titre(≥10 mIU/mL) were tested for HBcIgG to determine whether they are positive due to vaccination or old infection, positive HBcIgG individuals were tested for HBsAg to determine if they were still infected or not.

Results: The current study showed that; only 35.1 % of the studied population have got a positive protective HBsAb titre (≥10 mIU/mL). **Conclusion:** The current study concluded that, after 20 years of receiving HBV vaccine in the compulsory vaccination program in Egypt about 2/3 of individuals (64.9%) had anti-HBs titre < 10 mIU/mL. This level of antibodies puts the studied population at an increased risk of acquiring infection with HBV during their future life.

Key Words: Immunological status, Hepatitis B vaccine, duration of protection.

Introduction:

Hepatitis B virus (HBV) is a DNA virus with a human-only reservoir. It is transmitted through parenteral or mucosal exposure to infected blood and body fluids. The mode of transmission is usually vertical or horizontal in highly endemic areas early in life, resulting in a high chronicity rate. In low endemic

countries, transmission is usually in adulthood with self-limiting infection.[1]

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Hepatitis B is a worldwide public health problem. Egypt is considered to be a region of intermediate prevalence for HB infection with reported figure of 4.5%. Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications. The first-generation hepatitis B vaccine, an inactive plasma-derived vaccine, became available in 1982. Consequently, the second generation of HB vaccine, a DNA recombinant HB vaccine was also available for general use in 1986. Both vaccines were proven to be safe and efficacious in preventing HBV infection.[2]

In 1991, the World Health Organization (WHO) recommended that hepatitis B vaccination should be included in national immunization system in all countries with a hepatitis B carrier prevalence (HBsAg) of $\geq$8% by 1995 and in all countries by 1997. By May 2002, 154 countries had routine infant immunization with hepatitis B vaccine.[2]

Three doses are generally required to complete the hepatitis B vaccine series; 1st dose at any given time, 2nd dose at least 1 month after the first dose and 3rd dose 6 months after the first dose. The standard 3-dose schedule induces protective levels of neutralizing antibody against HBV in more than 90–95% of vaccine recipients aged < 40 years.[3,4]

Known factors for poorer response include age of >40 years, smoking, obesity, HIV infection, and some chronic or immune-compromising diseases .Testing for evidence of protective immunity to HBsAg vaccination is essential, as some vaccines do not develop sufficient levels of antibodies against HBsAg (anti-HBs). Anti-HBs levels between 10 and 100 mIU/ml are regarded as hypo-responsiveness and levels >100 mIU/ml are taken as a high level of immunity. An anti-HBs level of $\geq$10 mIU/ml is generally considered as protective against

HBV infection .An anti-HBs titer of < 10 mIU/ml is regarded as non-responsiveness to HBsAg vaccination.[5]

The strategy for the control of HBV infection, as outlined by the WHO and endorsed by the advisory committee on immunization practice (ACIP), is the introduction of hepatitis B immunization at birth .This strategy has dramatically reduced the carrier rate of HBV and significantly decreased the incidence of childhood hepatocellular carcinoma in many areas of the world.[6]

Neonatal HBV vaccination is the most effective measure for the prevention of HBV infection in countries with intermediate to high levels of HBV endemicity. A compulsory vaccination program against hepatitis B infection among infants was started in Egypt in 1992 using a yeast recombinant DNA vaccine (10 mcg) and with a schedule of 2,4 and 6 months of age. Sero-protection is assured when hepatitis B surface antibody (HBsAb) levels are $\geq$ 10 IU/L, but more needs to be learned about the duration of protection and indication for booster doses.[7]

The duration of hepatitis B vaccine protection has not been firmly established. Zanetti et al. suggested the strong immunological memory persists > 10 years after immunization of infants and adolescents with a primary course of vaccination, and a booster dose does not seem necessary.[8] McMahon and colleagues reported that hepatitis B vaccination strongly protects against infection for at least 15 years and a booster dose is not needed before the onset of sexual activity.[9]

According to the above mentioned studies, there is a need to conduct the current study aiming at identifying the immunologic status among individuals who received hepatitis B vaccine in the compulsory vaccination program after 20 years.

Methods:

The present study is a cross sectional study. The study was conducted at family practice outpatient clinic Suez Canal University hospital which is located on Ismailia city-Egypt in the period of January to August 2016. It was carried out on the 57 medical students (calculated sample size). They were studying in the 2nd year of Faculty of Medicine, Suez Canal University (FOM, SCU). They were selected by systematic random method.

Inclusion criteria of the study population included both genders who had received hepatitis B vaccine 20 years ago and those reported receiving 3 vaccinations in compulsory vaccination program in Egypt by reviewing documented vaccination history in birth certificate. On the other hand exclusion criteria included the following; evidence of previous hepatitis B booster vaccination, history of hepatitis B disease, history of immunological disease and administration of immunoglobulin and/or blood products within the last 3 months.

A self administrated questionnaire was used to inquire about socio-demographic data and history of risk factors that might affect the immunological status of individuals received hepatitis B vaccination (immunodeficiency – chronic illness-blood transfusion- dental procedures and family history of hepatitis. Analysis of blood sample for each enrolled student to determine HBs antibody titer using a commercial HBsAb ELISA system and following manufacturer's instruction. Individuals with positive protective titre($\geq$10 mIU/mL) were tested for HBcIgG to determine whether they are positive due to vaccination or old infection, positive HBcIgG individuals were tested for HBsAg to determine if they were still infected or not.

Data were entered and processed using Social sciences (SPSS) software program version 18 software program. The appropriate statistical tests were used (Qualitative data were expressed as number and percentage and Chi-square test to identify the statistically significant difference). The results were

presented in the appropriate tables and figures. The research protocol was approved by Ethical Committee of Faculty of Medicine –Suez Canal University with guarantee obtaining an informed consent from every participant in the study, assuring the confidentiality of the information and test results and the right of each participant to withdraw of the study at any time.

Results:

The present study was conducted on 57 Egyptian 2nd year medical students with mean age of (19.96±0.22) years and nearly equal numbers of males (46%) and females (54%). The majority of the studied population (89%) are residing in urban areas. The study showed that 20 students (35.1 %) of the studied population have got a positive protective HBsAb titer ($\geq$10 mIU/mL). On the other hand, 37 students (64.9%) have got a negative non-protective HBsAb titer (< 10 mIU/ml) as shown in Figure (1).

Out of the 20 students who have positive protective level of HBsAb titer, 3 students (15%) are positive for HBcIgG titer. The positive participants for HBcIgG titer are confirmed to be negative for HBsAg reflecting that those 3 students have got old infection with HBV as shown in Figure(2).

By reviewing the history of exposure to the risk factors, the study found that the majority of the studied population (93%) have negative family history of hepatitis B, while (75%) and (79%) have negative past history of surgical operations and dental procedures respectively. None of the studied population had any exposure to blood transfusion in the past. The difference between HBsAb positive and negative students is statistically insignificant regarding exposure to risk factors of HBV infection (P>0.05%) as shown in Table (1).

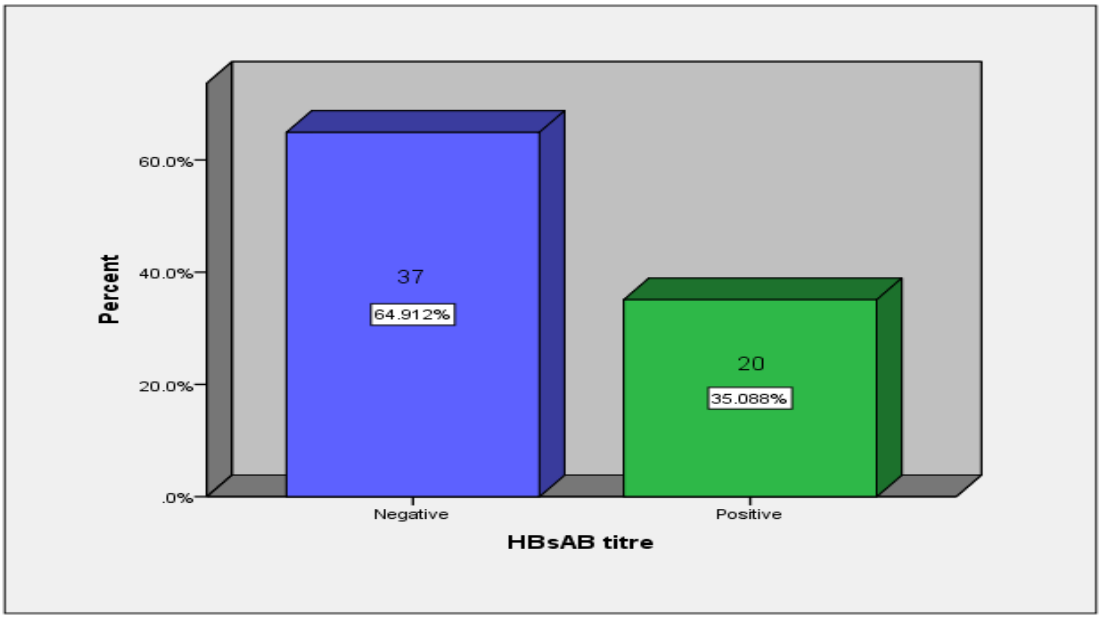

Figure (1): Distribution of the studied population according to the level of HBsAb titer (n= 57)

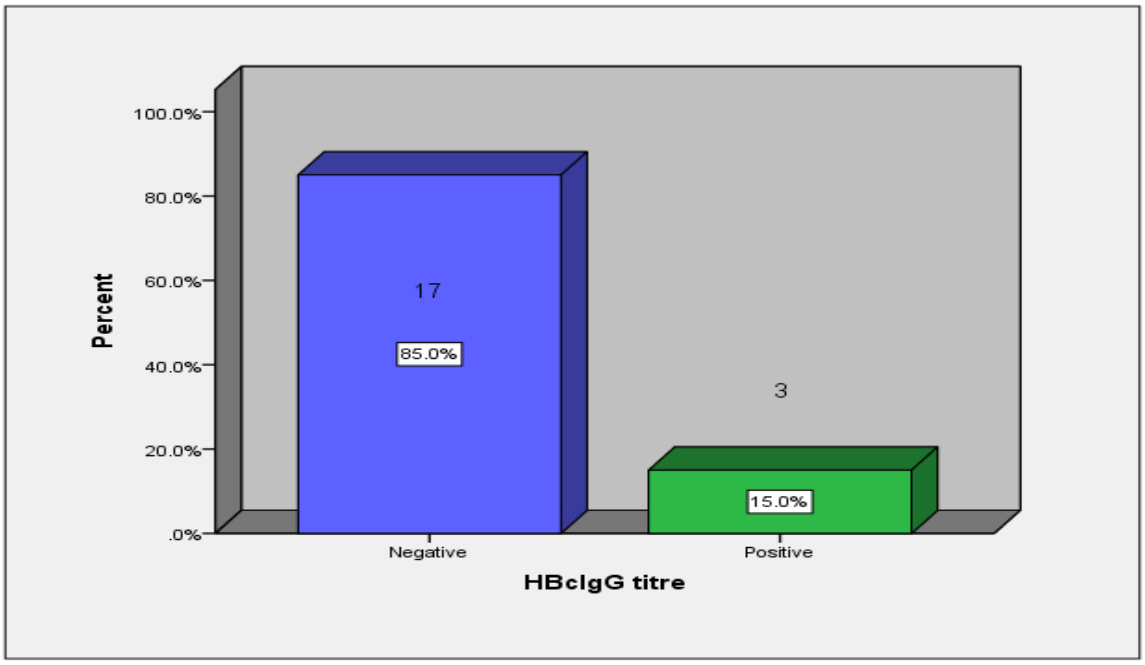

Figure (2): Distribution of the studied population with positive HBsAb titer (≥ 10mIU/ml) according to HBcIgG (N=20)

Table (1): Distribution of the studied population according to their exposure to the risk factors of HBV infection (n=57).

Risk Factor		Positive HBsAb (protected)		Negative HBsAb (non-protected)		χ^2	P value
		No	%	No	%		
Family history of hepatitis B	Positive	2	10%	2	5.4%	0.42	0.517*
	Negative	18	90%	35	94.6%		
Past history of surgical procedure	Positive	4	20%	10	27%	0.346	0.556*
	Negative	16	80%	27	73%		
Past history of dental procedure	Positive	3	15%	9	24%	0.679	0.41*
	Negative	17	85%	28	76%		
Total		20	100%	37	100%		

*= is not significant at the 95 % confidence level (2-tailed) - $\chi 2$ = chi-square.

Discussion:

In this study, the researchers have investigated the immunologic status among individuals who received hepatitis B vaccine after 20 years in compulsory vaccination program in Egypt. A self-administered questionnaire was fulfilled by the studied population. A blood samples were taken to measure serum anti-HBs Ab titre to assess their immunologic protection. Individuals with positive protective titre were tested for HBcIgG to determine whether they are positive due to vaccination or old infection , positive HBcIgG individuals were tested for HBsAg to determine if they were still infected or not.

The results of current study showed that; 20 students (35.1 %) of the studied population got a positive protective HBsAb titre ($\geq$10 mIU/mL). On the other hand, 37 students (64.9%) of the studied population got a negative unproductive HBsAb titre (< 10 mIU/Ml). Among those 20 positive students for HBsAb titer, three students (15 %) were positive for HBcIgG titer. HBsAg had been measured for those positive HBcIgG students and it was negative

denoting that they have got old infection. These results were in consistent with Alfaleha et al., in a study aimed to assess long-term protection of hepatitis B vaccine 18 years after vaccination among Saudi adolescents. A total of 1355 students (689 males and 666 females) were selected randomly from the three areas. No reported cases of positive HBsAg or anti-HBc were detected among the study population. Five hundred and ten students (38%) showed protective anti-HBs titers (≥10 mIU/ml), while 528 (39%) students had undetectable anti-HBs titers (<10 mIU/ml).[10]

These results were in concordance with the reported results by Robert et al., in a study conducted in Alaskan Native population who were vaccinated with the recommended three-dose regimen of plasma-derived hepatitis B vaccine. It was evident that, 94% of the studied population were positive for anti-HBs at levels <10 mIU/mL after 10 years of vaccination. These data suggest that immunization with hepatitis B vaccine continues to provide high levels of protection from clinical disease for at least 10 years.[11]

Additional evidence comes from study done by Lu et al., showed that**,** 243 persons were tested for anti-HBs levels 30 years after receiving HB vaccine. Among 243 persons (56%) who responded to the original primary series but received no subsequent doses during the 30-year period, 125 (51%) had an anti-HBs level ≥10 mIU/mL. This study concluded that, More than 90% of participants had evidence of protection 30 years later.[12] Another study conducted by Michael et al., on 6156 high school students who have vaccinated with plasma-derived hepatitis B vaccine during infancy. They were screened serologically for sustained immunity after 15 to 18 years. Approximately 10 % of the total population had lost their vaccine-conferred immune response.[13]

Such agreement could be explained in the view of similarity of the schedule of compulsory HBV vaccine and the precaution regarding integrity of cold chain of vaccine.

The current study did not consistent with the reported results from a clinical trial in Thailand. It was conducted on subjects born to mothers with positive HB surface antigen and HB e-antigen. They were vaccinated according to a 4-dose schedule at 0, 1, 2 and 12 month of age and a single dose of hepatitis B immunoglobulin concomitantly at birth. All enrolled subjects were followed for 20 years to assess the persistence of antibody to the hepatitis B surface antibody (anti-HBs). At year 20, 64% of subjects had got protective anti-HBs antibody concentrations (≥10 mIU/ml). This study confirms the long-term immunogenicity of the 4-dose regimen of the HBV vaccine eliciting long-term persistence of antibodies and immune memory against hepatitis B for up to at least 20 years after vaccination. [14]

Such disagreement could be explained in the view of difference in the HBV vaccination schedule as in our study we evaluated the immunological status after 20 years from HBV vaccination (3 dose schedule), but in this clinical trial they evaluated the 4-dose HBV vaccination schedule.

Conclusion: The current study concluded that after 20 years from receiving HBV vaccine in the compulsory vaccination program in Egypt more than sixty percent of individuals (64.9%) had got un-protective anti-HBs titre (<10 mIU/mL). Such situation might put them at increased risk of acquiring infection with HBV during their future life.

Study limitation and extrapolation: There was no limitation in the present study and conducting such study in wide scale in different governorates could be considered before going ahead in extrapolation the results.

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الملخص العربى

تقييم الحاله المناعيه للاشخاص بعد 20 عاما من تلقيهم تطعيم الالتهاب الكبدى ب فى البرنامج الاجبارى التابع لوزارة الصحه المصريه

ط.احمد محمد محمود حسن- طبيب مقيم قسم طب الأسره – مستشفيات جامعة قناة السويس
د. مصلح عبد الرحمن – أستاذ طب الأسرة– كلية الطب جامعة قناة السويس
د. محمد عبد الواحد- مدرس طب الأسرة– كلية الطب جامعة قناة السويس
د.سعيد حامد عبادى – استاذ الميكروبيولوجى – كلية الطب – جامعة قناة السويس

ان فيروس ب أحد أنواع الفيروسات المتسببة في حدوث الالتهاب الكبدي ، هو فيروس يحتوي على الحمض النووي منقوص الأكسجين والإنسان هو العائل الوحيد لذلك الفيروس . إن مرض الالتهاب الكبدي الوبائي ب هو مشكلة صحية منتشرة على مستوى العالم . وهذاالمرض ينتقل إما عن طريق تعرض الطبقة المخاطية للإنسان لدم أو أي سائل جسدي أخر ملوث بالفيروس ب أو بأخذ حقن ملوثة بذلك الفيروس. وفي سنة 1991 اعلنت منظمة الصحة العالمية ان التطعيم ضد فيروس ب يجب ان يكون ضمن جدول التطعيمات فى جميع الدول. في عام 2002 أصبح 154 دولة على مستوى العالم تضع التطعيم ضد فيروس ب ضمن جدول تطعيماتها الإجبارية. وهدفت هذه الدرايه الى تحديد الحاله المناعيه للاشخاص بعد 20 عاما من اخذ اللقاح فى برنامج التطعيم الاجبارى بوزارة الصحه المصريه .

وقد اجريت هذه الدراسه الوصفيه المقطعيه على مدار 8 اشهر من يناير حتى اغسطس عام 2016.وقد تم اجراء الدراسه على 57 طالب بكلية الطب البشرى بالصف الثانى بجامعة قناة السويس والذين تلقوا تطعيم الالتهاب الكبدى (ب) منذ 20 عامل وتمت فى عيادة طب الاسره بمستشفى جامعة قناة السويس وتم عمل استمارة استبيان لكل طالب واخذ عينة دم لتحليل نسبة الاجسام المضاده لفيروس (ب) لتقييم الحاله المناعيه لديهم بعد 20 عاما من اخذ التطعيم الاجبارى لفيروس (ب) فى البرنامج الاجبارى التابع لوزارة الصحه المصريه.وقد اوضحت الدراسة ان نسبه1و35% من الطلاب لديهم نسبة اجسام مضاده

للالتهاب الكبدى (ب) الواقيه بعد 20 عاما من تلقى تطعيم الالتهاب الكبدى (ب) فى فى البرنامج الاجبارى التابع لوزارة الصحه المصريه . و ان اكثر من ثلثى العينه من الطلاب لديهم نسبة اجسام مضاده للالتهاب الكبدى (ب) غيرواقيه مما يعرضهم لخطورة الاصابه بالالتهاب الكبدى (ب) فى المستقبل.