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Long-term immunity to hepatitis B among a sample of fully vaccinated children in Cairo, Egypt

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المناعة الطويلة الأمد لالتهاب الكبد الوبائي في عيِّنة من الأطفال الذين استكملوا تطعيمهم في القاهرة، مصر

فاطمة أحمد شعبان، أمل إبراهيم حسنين، سامية محمد سامي، سمية إبراهيم سلامة، زينب نبيل سعيد

الخلاصة: قيَّم الباحثون المناعة الطويلة الأمد لالتهاب الكبد البائي B لدى 242 من الأطفال المصريِّين الذين تتراوح أعمارهم بين 6–12 عاماً ممَّن استكملوا جدول تطعيمهم في مرحلة طفولتهم الأولى، كما استقصوا العوامل المرتبطة بهذه المناعة. وقد وجدوا أن ما لا يزيد على 39.4٪ من الأطفال لديهم مستويات من الأضداد السطحية لالتهاب الكبد البائي HBsAb (بمقدار يزيد على 10 وحدات دولية/لتر)، وأن هذه المستويات تتناقص مع العمر تناقُصاً لا يُعْتَدُّ به إحصائياً. فقد نقصت المعدلات الوسطية للأضداد السطحية لالتهاب الكبد البائي تناقصاً يُعْتَدُّ به إحصائياً مع تقدُّم العمر، (بقوة احتمال = 0.026)، كما وجدنا ارتباطاً سلبياً يُعْتَدُّ به إحصائياً بين العمر الحالي وبين مستويات الأضداد السطحية لالتهاب الكبد البائي (فقد بلغ معامل الارتباط 0.31 – ، وقوة الاحتمال 0.041)، كما وجدنا أن كلاً من العمر، والوزن منسوباً إلى العمر، هما من العوامل المنبئة التي يُعْتَدُّ بها إحصائياً، على مستويات الأضداد السطحية لالتهاب الكبد البائي غير الواقية.

ABSTRACT We assessed the long-term immunity to hepatitis B among 242 Egyptian children aged 6–12 years who had received a full vaccination course in infancy, and investigated the factors associated with immunity. Only 39.4% of the children had protective (≥ 10 IU/L) hepatitis B surface antibody levels (HBsAb). This proportion decreased with age but the decrease was not statistically significant. The mean level of HBsAb decreased significantly with increasing age ($P = 0.026$). A significant negative correlation was found between current age and HBsAb levels ($r = –0.31$, $P = 0.041$). Age and weight-for-age were found to be significant predictors of non-protective HBsAb levels.

Immunité à long terme contre l'hépatite B après vaccination complète dans un échantillon d'enfants cairotes

RÉSUMÉ Nous avons évalué l'immunité à long terme contre l'hépatite B chez 242 enfants égyptiens âgés de 6 à 12 ans qui, nourrissons, avaient reçu une vaccination complète ; nous avons en outre exploré les facteurs associés à l'immunité. Seuls 39,4 % des enfants présentaient un titre d'anticorps anti-antigène de surface de l'hépatite B (Ac anti-HBs) protecteur (≥ 10 UI/L). Celui-ci diminuait avec l'âge, toutefois de manière non significative. L'avancée en âge de l'enfant s'accompagnait d'une diminution significative du titre moyen d'Ac anti-HBs (p = 0,026). Il est apparu une corrélation négative significative entre l'âge actuel de l'enfant et le titre d'Ac anti-HBs (r = -0,31, p = 0,041). L'âge et le poids en fonction de l'âge s'avèrent être des prédicteurs significatifs d'un titre d'Ac anti-HBs non protecteur.

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Introduction

Hepatitis B virus (HBV) infection is the most prevalent chronic infectious disease and is widespread throughout the world; it is estimated that globally more than 400 million people are infected with the virus [*1*]. The global prevalence of HBV varies widely from low (< 2% as in Western Europe, North America and Japan) to high (> 8% as in Africa, South-east Asia and China) [*2*]. Egypt is considered to be a region of intermediate prevalence for HBV infection with a reported figure of 4.5% [*3*]. The most important epidemiologic factor affecting the chronic carrier rate is age of infection. The earlier in life an infection occurs, the higher the probability that this infection will result in chronic carriage; 90% of infants, 25%–50% of children 1–5 years and > 5% of adults who acquire the infection become chronic carriers [*4*].

Neonatal HBV vaccination is the most effective measure for prevention of HBV infection in countries with intermediate to high levels of HBV endemicity [*5*]. Two types of HBV inactivated vaccines are available, plasma-derived vaccine and recombinant DNA vaccine [*6*]. A compulsory vaccination programme against hepatitis B infection among infants was started in Egypt in 1992 using a yeast recombinant DNA vaccine (10 μg) and with a schedule of 2, 4 and 6 months in age [*7*]. Seroprotection is assured when hepatitis B surface antibody (HBsAb) levels are ≥ 10 IU/L [*8,9*] but more needs to be learned about the duration of protection and indication for booster doses [*10*].

The aim of the present study was to assess the long-term immunity to hepatitis B among Egyptian children vaccinated under the compulsory vaccination programme 6–12 years after receiving the vaccine, and to determine the factors associated with immunity.

Methods

This was a cross-sectional study of children attending the health insurance clinic, for a period of 6 months (October 2003–March 2004). The health insurance clinic is one of the paediatric clinics of the General Institute of Health Insurance of the Ministry of Health and Population. The children were attending the clinic seeking medical advice for illnesses such as anaemia, headache, visual problems and school accidents. Approval was taken from the General Institute of Health Insurance in order to allow the researchers to conduct the study and to collect blood samples from the children. For younger children attending the clinic, their parents were informed about the aim of the study and their consent for their children to be included in the study was taken. For older children both the parents and the child provided consent.

All children consecutively attending the Health Insurance Clinic over the study period and fulfilling the inclusion criteria were included in the study. The inclusion criteria were: age 6–12 years and having received the full course of hepatitis B vaccine as recorded on the back of the child's birth certificate. Thus 242 children (116 males and 126 females) were recruited.

A questionnaire was designed and administered to the parents or caretakers of the children to collect demographic data (age, sex and socioeconomic status) and history of hepatitis B vaccination in infancy. Socioeconomic status was determined according to Fahmy and Sherbiny [*11*]. The children's height and weight were measured at the time of enrolment to determine body mass index (BMI). Anthropometric measurements were converted to standard deviation (SD) scores using the National Center for Health Statistics/Centers for Disease Control and Prevention (NCHS/CDC) standards [*12*]. Nutritional status was assessed by

height-for-age Z score (HAZ) and weight for-age Z score (WAZ). Children, whose WAZ or HAZ scores were below –2 SD from the median of the reference population were classified as underweight or stunted respectively.

Blood was drawn aseptically by venepuncture and serum was separated by centrifugation and stored at –70 °C. The samples were thawed for the quantitative determination of antibody to HBV by competitive enzyme-linked immunosorbent assay (DiaPro, Milan, Italy). Antibody levels were determined quantitatively by means of a standard curve calibrated against the World Health Organization reference preparation.

Data were analysed using *SPSS*, version 9. Descriptive analysis (mean and SD) were performed in order to compare between groups. As the data are not normally distributed, the Mann–Whitney test was used to compare differences between 2 means and the Kruskal–Wallis test was used to compare between more than 2 means. The chi-squared test was performed to compare proportions between 2 categorical variables. To detect the relation between age and antibody titre, a correlation test was used. Multivariate logistic analysis was also carried out to define the independent predictor variables significantly associated with hepatitis B virus seroprotection. Backward Wald analysis was used with > 0.1 removing criteria.

Results

The seroprevalence of HBsAb by titre is shown in Figure 1. Of the 242 children studied, 60.7% had HBsAb titres of < 10 IU/L (no protection) and only 9.9% of them had titres > 100 IU/L. Table 1 shows distribution of the children according to protection status and mean level of HBsAb and age

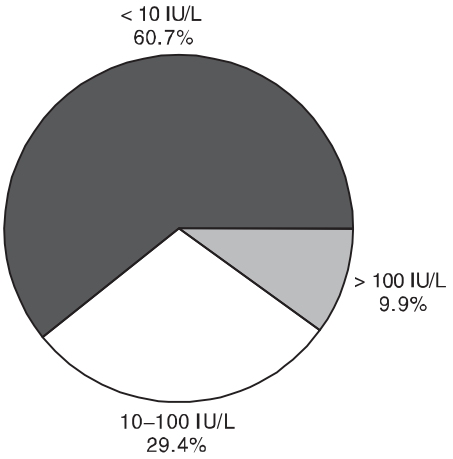

Figure 1 **Distribution of children according to hepatitis B surface antibody level**

and sex. The percentage of children with a titre < 10 IU/L increased with age but the increase was not significant and there was no significant difference between males and females. However, the mean antibody levels decreased significantly with increasing age. Furthermore there was a significant negative correlation between current age and HBsAb levels ($r = –0.31$, $P = 0.041$) (Figure 2).

Although the seroprotection level (≥ 10 IU/L) of HBsAb increased gradually with increase in the socioeconomic status, it was not statistically significant ($P = 0.09$) (Table 2). As regards anthropometric measurements, there was a significantly higher proportion of children with non-protective levels of HBsAb (< 10 IU/L) with WAZ > –2 SD (62.1%, $P = 0.042$). On the other hand, no significant differences were found between the levels of HBsAb and HAZ score and BMI.

By multiple logistic analysis, age and WAZ score were found to be the significant

Table 1 **Distribution of children according to level of hepatitis B surface antibody (HBsAb) and mean level of HBsAb, and age and sex**

Variable	HBsAb level (IU/L)				Total	Mean HBsAb level (SD) (IU/L)
	< 10		≥ 10			
	No.	%	No.	%	No.	
Age (years)						
6–7	42	52.5	38	47.5	80	75. 2 (149.6)
8–9	45	56.2	35	43.8	80	57.1 (127.2)
10–12	60	73.2	22	26.8	82	31.5 (94.6)
P-value		0.09				0.026[a]
Sex						
Male	65	56.0	51	44.0	116	52.9 (119.3)
Female	82	65.1	44	34.9	126	55.7 (133.0)
P-value		0.528				0.134[b]
Total	147	60.6	95	39.4	242	

[a]*Calculated by the Kruskal–Wallis test and significant at* P < *0.05.*
[b]*Calculated by the Mann–Whitney nonparametric test.*
SD = standard deviation.

variables for prediction of HBsAb level < 10 IU/L. For every 1 year increase in age there was a 23% increased risk of becoming non-immune after HBV vaccination. In children with WAZ score > –2 SD, the risk of having non-protective levels of HBsAb was 8 times higher compared to those ≤ –2 SD (Table 3).

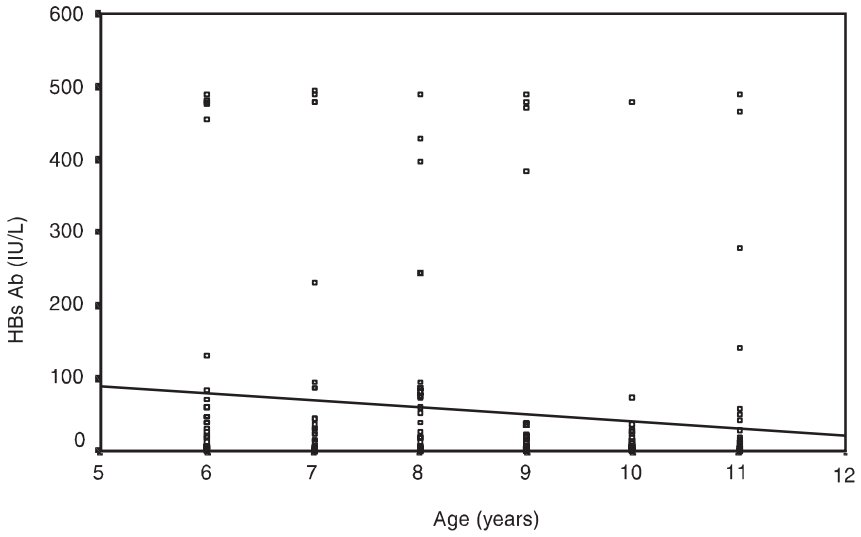

Figure 2 **Correlation between age and hepatitis B surface antibody (HBsAb) level (*r* = –0.31, *P* = 0.041)**

Table 2 **Distribution of children according to level of hepatitis B surface antibody (HBsAb), and socioeconomic status and anthropometric data**

Variable	HBsAb level (IU/L)					*P*-value
	< 10		≥ 10		Total	
	No.	%	No.	%	No.	
Socioeconomic status						0.09
Low	77	64.7	42	35.3	119	
Middle	52	59.8	35	40.2	87	
High	18	50.0	18	50.0	36	
Height-for-age						0.15
≤ –2 SD	7	43.8	9	56.2	16	
> –2 SD	140	61.9	86	38.1	226	
Weight-for-age						0.042*
≤ –2 SD	3	30.0	7	70.0	10	
> –2 SD	144	62.1	88	37.9	232	
Body mass index centile						0.171
≥ 95th	3	37.5	5	62.5	8	
< 95th	144	61.5	90	38.5	234	

**Significant at* P < *0.05.*
SD = standard deviation.

Discussion

Children vaccinated against hepatitis B may show serological evidence of break-through infections, particularly if the level of HBsAb induced by the vaccine is low [*9*]. In the present study, the overall seroprotection 6–12 years after immunization was low (39.3%) and only 9.9% of the children had titres > 100 IU/L. Compared to other studies performed on children within the same age range, considerably greater proportions of children had protective HBsAb levels: ranging from 81.6% to 95% as reported by Yu, Cheung and Keefe, Floreani et al., and Lin et al. [*9,8,13*], and 71.4% to 77% as reported by Al-Faleh et al., Poovarawan et al. and Mariano et al. [*14–16*]. With extension of the age range up to 15 years Ni et al. and Bonanni et al. reported HBsAb seropositivity levels among 75.8% and 79% of their subjects respectively [*17,18*].

On the other hand other studies have reported values similar to our rate of 60.7% with non-protective HBsAb levels. Lu et al. found that 62.6% of the 15-year-olds in their study had non-protective HBsAb levels after primary neonatal immunization with plasma-derived hepatitis B vaccines. Accordingly they recommended one or more booster immunizations [*10*]. In the United States of America, Petersen et al. reported that HBsAb disappeared by 5 years of age in most of the studied children who

Table 3 **Significant risk factors for hepatitis B surface antibody < 10 IU/L as determined by multiple logistic analysis**

Predictive variable	Adjusted odds ratio	95% confidence interval	*P*-value
Age (years)	1.23	1.04–1.5	0.019
Weight-for age > –2 SD[a]	8.3	1.63–42.6	0.01

[a]*compared to ≤ –2 SD.*
SD = standard deviation.

had been vaccinated with hepatitis B vaccine from birth [*19*].

In our study, the seroprotection level (≥ 10 IU/L) was 47.6% 6–7 years after vaccination. Similarly low proportions of children with seroprotective antibody levels (41% at 5 years and 39% at 9 years) were reported by Williams et al. [*20*]. On the other hand, higher rates were reported by Chen et al. in China (65.95%), Garcia et al. in Spain (75%) and Reda et al. in Egypt (67%) 5 years after vaccination [*4,21,22*]. In the older age group, Mariano et al., [*16*] found that 74% of children aged 10–11 years had protective antibody levels compared to 26.9% in our study. In Taiwan, the percentage of children with seroprotective levels of HBsAb gradually decreased from 71.1% at age 7 years to 37.4% at age 12 years [*23*].

In our study there was no significant difference in the frequency of HB seroprotection between males and females. This is in agreement with some studies [*24,25*], while others have found that male sex is a predictor of non-response [*9*].

By multivariate analysis we found age and WAZ to be the only significant predictors of HBsAb level < 10 IU/L. In children with WAZ score > –2 SD, the risk of having a non-protective level of HBsAb was 8 times higher than those with a WAZ score ≤ –2 SD. Although several investigators have reported a strong inverse relation between BMI and final HBsAb titre in children, we did not find such correlation [*9,25,26*]. Yu, Cheung and Keefe reported that the predictors of non-protective levels of HBsAb were: increasing age, male gender and obesity [*9*]. Seroprotection rates and geometric mean titres have been reported to decrease significantly with increasing age possibly reflecting waning HBsAb levels over time [*27,28*].

The low level of HBsAb reported in our study and the diversity of results in the different studies can be attributed to several factors. First, the type of vaccine, whether it is a plasma-derived or yeast-derived vaccine could play a role. Da Villa et al. [*29*] found that the DNA recombinant vaccine gave a higher titre (97.6%) than the plasma-derived vaccine (80.4%), while Floreani et al. [*8*] recorded a slightly higher titre with plasma-derived vaccine than with yeast-derived vaccine (87.8% and 81.6% respectively). Second, the schedule of immunization may also play a role in determining HBsAb level. Da Villa et al. [*30*] found that a higher level of protective HBsAb was achieved when the vaccine doses were administered after the third month of life rather than in the first 3 months, while Williams et al. [*20*] found that persistence of protective levels for a longer period occurred when the vaccine doses were administered soon after birth. According to the Viral Hepatitis Prevention Board, the 2 schedules most widely used for the hepatitis B vaccine are 0, 1, 6 months and 0, 1, 2, 12 months, both of which have been shown to be equally effective and can control perinatal infection [*31*]. Increasing the time between the 1st and 2nd doses and 2nd and 3rd doses appears to increase antibody levels [*25*]. This is in agreement with the findings of previous studies performed in Egypt and accordingly they recommended a new vaccination schedule with an increased interval between the 2nd and 3rd dose [*32,33*]. The third factor is the dose of the vaccine. Zuckerman et al. suggested that increasing the dosage of the vaccine leads to significantly higher levels of HBsAb [*34*].

In conclusion, more than half of the studied children had non-protective levels of HBsAb and this puts them at risk of infection. The failure to achieve satisfactory seroprotection levels by the national immunization programme reflects the need to re-evaluate the current hepatitis B vac-

cination strategy in Egypt. Further studies are needed to explain whether this low seroprotective level is due to waning immunity with time or due to an initial low response. A booster dose is suggested for maintaining a high seroprotective level.

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