Evaluation of the routine hepatitis B immunization programme in Palestine, 1996

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تقييم برنامج التمنيع الروتيني ضد التهاب الكبد البائي في فلسطين

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خلاصة: تهدف هذه الدراسة إلى تقييم برنامج التمنيع الروتيني ضد التهاب الكبد البائي في فلسطين. فتم تحليل عينات دم أخذت من 119 طفلاً (89 منهم حصلوا على تطعيم كامل و30 لم يحصلوا على أي تطعيم). وتبيَّن أن مستويات الأضداد الواقية بين ذوي التطعيم الكامل كانت أعلى منها بين غير المطعَّمين. وكانت مستويات الأضداد بين الأطفال المطعَّمين أدنى بين الأطفال الأكبر عمراً (أكثر من 36 شهراً)، ولكن لم تظهر أية فروق بين الجنسين في مستوى الأضداد. وهكذا يمكن القول إن التمنيع ضد التهاب الكبد البائي كان له أثر ممتاز في الوقاية من انتقال هذا المرض (نسبة الوقاية 85%). وكانت نسبة عدم المستجيبين 14.6% من أفراد العينة، وهي نسبة أكبر من مثيلاتها في الدراسات الأخرى.

ABSTRACT The objectives of this study were to evaluate routine hepatitis B immunization in Palestine. Blood samples of 119 children (89 fully immunized and 30 non-immunized) were analysed. The protective antibody levels among immunized children were greater than the non-immunized children. Antibody levels among the immunized children were lower in the older age group (> 36 months), but no sex differences in antibody level were apparent. Thus, hepatitis B immunization had an excellent impact on preventing hepatitis B transmission (85% preventive). The non-responders constituted 14.6% of the sample, which is higher than other studies.

Evaluation du programme de vaccination systématique contre l'hépatite B en Palestine, 1996
RESUME Les objectifs de cette étude étaient d'évaluer la vaccination systématique contre l'hépatite B en Palestine. Des prélèvements sanguins effectués sur 119 enfants (89 complètement vaccinés et 30 non vaccinés) ont été analysés. Les niveaux d'anticorps protecteurs chez les enfants vaccinés étaient plus élevés que chez les enfants non vaccinés. Les niveaux d'anticorps chez les enfants vaccinés étaient inférieurs dans le groupe des enfants les plus âgés (> 36 mois), mais aucune différence dans le niveau d'anticorps selon le sexe n'était apparente. La vaccination contre l'hépatite B a donc eu un excellent impact sur la prévention de la transmission de l'hépatite B (préventif à 85%). Les non-répondeurs constituaient 14,6% de l'échantillon, ce qui est plus élevé que dans d'autres études.

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Introduction

Vaccination is the most important tool for hepatitis B prevention. It provides 95% protection to a neonate whose mother is a hepatitis B virus (HBV) carrier when given as soon after delivery as possible [*1*]. In 1991, the Global Advisory Group of the Extended Programme on Immunization (EPI) recommended that the routine immunization of infants and adults should take the highest priority and decided to include HBV immunization in the national universal programme [*2,3*].

According to studies on the response to licensed HBV vaccination, 5%–10% of normal individuals are considered non-responders [*4*]. Non-responders are those whose antibody levels never exceed 10 mIU/mL after hepatitis B immunization [*1*] and poor responders are those individuals with antibody levels less than 100 mIU/mL who should receive a booster dose to be adequately protected [*4*].

Antibodies resulting from immunization decline after 5 years. Tilzey and colleagues [*5*] suggested a booster dose in healthy individuals when the antititre fell below 500 mIU/mL to provide full protection for at least 3 years. This is a good guideline for a booster dose to increase the efficacy of the vaccine. Although the HBV carrier pool will be reduced by the initial 3-dose immunization in infancy, an increasing number of acute hepatitis cases may be expected to occur in later adult life if a booster dose is not administered. Studies show that the antibody level among poor responders and non-responders can be increased up to 1000 mIU/mL after a booster (fourth) dose of hepatitis B immunization [*4,6,7,8*].

The general aim of our study was to evaluate the routine hepatitis B immunization programme in Palestine (Gaza provinces) in 1996, and to study the associated factors affecting immunization efficiency. Specifically we aimed to:

- estimate the hepatitis B antibody levels among immunized children;
- detect and estimate those children who were hepatitis B surface antigen-positive (HBsAg);
- measure the impact of hepatitis B immunization on Palestinian children.

Methods

Blood samples were collected from 89 fully immunized children aged 15–36 months selected from five maternal and child health (MCH) centres from all over Gaza. The MCH centres were selected by a simple random sampling method and the children by systematic sampling from the immunization registry in each centre. The parents were asked to sign a consent form for blood examination.

Because of the high immunization coverage in Gaza, it was difficult to find non-immunized children of the same age. Thus, blood samples were collected from 30 non-immunized schoolchildren aged 7–10 years, to be used as a comparison group.

The blood samples were analysed at the central government laboratory and three tests were performed for each sample.

- Enzyme immunoassay for quantitative determination of HBsAg. The results were interpreted as positive or negative.
- Enzyme immunoassay for quantitative determination of total antibodies to hepatitis B core antigen (anti-HBc) in the sera of samples. The results were interpreted as positive or negative.
- Enzyme immunoassay for quantitative determination of antibodies to HBsAg (anti-HBs) in the sera. Anti-HBs was interpreted as:

- non-responders: those with antibody levels < 10 mIU/mL
- responders: those with antibody levels ≥ 10 mIU/mL.

Table 1 Residence, sex and age of the immunized children

Demographic data	No. (n = 89)	%
Residence		
North	16	18.0
Gaza City	35	39.3
Midzone and Khan Younis	20	22.5
Rafah	8	20.2
Sex		
Male	45	50.6
Female	44	49.4
Age (months)		
≤18	44	49.4
>18	45	50.6

The reference methods for all the above-mentioned tests were performed using Sorin products. Statistical analysis was carried out using *Epi-Info*. Cross-tabulation was made between Anti-HBs and other independent variables.

Results

Table 1 shows the distribution of the study population by residence, sex and age. The mean age (SD) at which hepatitis B immunization was given to the children was:

- First dose: 19 (8) days
- Second dose: 65 (19) days
- Third dose: 9 months and 26 days (19) days.

The relationship between antibody level and age, sex, and residence (Table 2) showed that a greater proportion of the

Table 2 Relationship between antibody level and age, sex and residence

Characteristic	Antibody level			
	0–100 mIU/mL		101–4000 mIU/mL	
	No.	%	No.	%
Age (months)				
≤18	18	40.9	26	59.1
>18	26	57.8	19	42.2
Total	44	49.4	45	50.6
Odds ratio = 0.51 (95% CI: 0.2–1.20, P = 0.11)				
Sex				
Male	22	48.9	23	51.1
Total	44	49.4	45	50.6
Odds ratio = 0.96 (95% CI: 0.38–2.39, P = 0.916)				
Residence				
North	10	62.5	6	37.5
Gaza City	15	42.9	20	57.1
Midzone and Khanyounis	10	50.0	10	50.0
Rafah	9	50.0	9	50.0
Total (P = 0.64)	44	49.4	45	50.6

CI = confidence interval.

younger children had a high antibody titre compared with the older children (59.1% and 42.2% respectively). This difference was not statistically significant ($P = 0.1$). There was no difference in high antibody level between the sexes. There were more non-responders and poor responders in the North area than the other areas. The highest response rate was in the Gaza area. This suggests that the nearer the children to the central stores (where vaccines are stored), the higher the response rate. The response rate to immunization was similar in Rafah, and Midzone and Khan Younis.

In all, 14.6% of the immunized children had antibody levels from 0 to 10 mIU/mL, which is considered a non-responder level, compared to 83.3% of non-immunized children. Also, 34.8% of the immunized children and 6.7% of the non-immunized children had antibody levels in the range 11–100 mIU/mL, 29.2% of the immunized and 6.7% of non-immunized children had antibody levels in the range 101–1000 mIU/mL and 21.3% of the immunized and 3.3% of the non-immunized children had antibody levels in the range 1001–4000 mIU/mL.

Table 3 shows the relationship between the immunization status and antibody levels. There were 13 children (14.6%) among the immunized and 25 children (83.3%) of the non-immunized who had low hepatitis B antibodies (non-protective), and there were 76 children (85.4%) among the immunized and 5 children (16.7%)

Table 3 **Relationship between antibody level and immunization status**

Antibody level (mIU/mL)	Immunized ($n = 89$)		Non-immunized ($n = 30$)		Total no.
	No.	%	No.	%	
0–10	13	14.6	25	83.3	38
11+	76	85.4	5	16.7	81

Odds ratio = 9.2, P = *0.00001.*

Table 4 **Hepatitis B surface antigen (HBsAg) and total anti-HBc (hepatitis B core) among the immunized and non-immunized children**

Variable	Immunized ($n = 89$)		Non-immunized ($n = 30$)	
	No.	%	No.	%
HBsAg				
Negative	87	97.8	29	96.7
Positive	2[a]	2.2	1	3.3
Anti-HBc				
Negative	88	98.9	28	93.3
Positive	1[b]	1.1	2	6.7

[a] *The antibody levels of the two immunized children with positive HBsAg were 3 mIU/mL and 10 mIU/mL, i.e. both were non-responders to immunization.*

[b] *Among the immunized children, the positive case for total anti-HBc was also positive for HBsAg. Thus, the net result is that only two cases were HBV carriers.*

among the non-immunized who had protective antibody levels (odds ratio = 9.2, P = 0.0001).

Table 4 shows that among the immunized children, there were 2 (2.2%) positive for HBsAg (one of them was positive for both HBsAg and total anti-HBc). Among the non-immunized children, 2 of them (6.7%) were positive for total anti-HBc and 1 (3.3%) was positive for HBsAg.

Discussion

Palestine is considered an endemic area for HBV carriers; the prevalence among blood donors is 5%–7%. Cultural and behavioural factors contribute to the viral transmission, including low socioeconomic status, high population density especially in the Gaza Strip, high household crowding and vertical transmission.

Universal hepatitis B immunization was introduced in Palestine on 1 January 1993. Like the other types of universal immunization, it is given free of charge to all children at 0, 2, and 9 months of age. The justification for its introduction was the estimated high prevalence of HBV infection among the population and the availability of a safe vaccine (S. Jamal et al., unpublished data, 1995). The time schedule of HBV immunization was selected to integrate with the EPI schedules so as to avoid extra visits to MCH clinics.

The present policy of the Ministry of Health is to examine routinely blood donors and to give pre-employment examinations in order to detect HBV carriers and those with human immunodeficiency virus. Screening for HBV-positive contacts and immunization of those who are negative is free of charge. The immunization coverage (%) since the introduction of HBV vaccination is shown in Table 5 [*9*].

Table 5 Immunization coverage (%) since the introduction of hepatitis B vaccination

Dose	1993	1994	1995
First dose	88	100	100
Second dose	80	99	97
Third dose	82	96	97

In our study, 14.6% of the immunized children did not produce an antibody response, which is higher than the proportion reported in other studies. The antibody level among the older age group was lower than the younger age group, which can be explained by the decline in antibody levels with increasing age. There is a causal association between immunization and increased antibody levels.

There were 3 (10%) cases among the non-immunized children who were diagnosed as positive for either HBsAg or HBc, two of them had high antibody levels and one had an antibody level of < 10 mIU/mL in response to the natural infection. There were 2 (2.2%) positive HBV carriers among the fully immunized children and they had no antibody response against hepatitis B virus immunization or infection. Among the 13 cases of non-responders to immunization, there were 2 (15.4%) who were HBsAg-positive. So the expected number of HbsAg-positive cases if the children had not been immunized would have been 13 (14.6%). Thus, immunization prevented 11 cases of 13, an estimated impact of 85%.

Conclusion and recommendations

Immunization has a significant impact on hepatitis B transmission (estimated prevented fraction is 85%). In all, 49.4% of

the immunized children had a low response (0–100 mIU/mL), including 14.6% who were non-responders (0–10 mIU/mL). This indicates the need for the introduction of a booster fourth dose of immunization. The following are therefore recommended:

- continue the hepatitis B universal immunization;
- give a fourth booster dose to the children 3–5 years after the third dose;
- implement the immunization policy, which recommends giving hepatitis B immunization immediately after birth;
- continuously monitor the programme and ensure cold chain preservation.

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