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Assessment of immune responses to hepatitis A vaccination in children aged 1 and 2 years

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Aim: Hepatitis A can be prevented by vaccination. The aim of this study was to determine seropositivity for hepatitis A before vaccination in healthy children 12 and 24 months of age and compare seroconversion rates after vaccination between these 2 groups.

Materials and methods: Forty-nine children aged 1 year (Group 1) and 51 children aged 2 years (Group 2) were included in the study. Inactive hepatitis A vaccine (Avaxim, 80 antigenic subtypes, 0.5 mL) were administered to every child in 2 doses, 6 months apart. Anti-hepatitis A virus (HAV) IgG and IgM antibodies were detected by Architect HAVAb-IgG and HAVAb-IgM (Abbott, Wiesbaden, Germany) test kits.

Results: Nine percent of the children were seropositive for anti-HAV IgG before vaccination. The seroconversion rate at 2 weeks was 34% and 44% in Group 1 and Group 2, respectively. At 4 weeks the seroconversion rate was 87.7% and 90.1% in Group 1 and Group 2, respectively. All of the children who completed the vaccination program were seropositive at 28 weeks (after the second dose). No serious adverse reaction was observed in any of the children.

Conclusion: It was determined that Avaxim, including 80 antigen units, is safe and immunogenic in healthy children 12 and 24 months of age.

Key words: Hepatitis A vaccine, seroprevalence, safety, immunogenicity, children

1. Introduction

Hepatitis A is an acute, usually self-limiting infection of the liver caused by the hepatitis A virus (HAV). HAV is transmitted from person to person, primarily by the fecal–oral route. The severity of illness varies with age, being more symptomatic in older children and adults. The prevalence of HAV infection is associated with the socioeconomic status of the country and the region (1,2). HAV has one serotype, so immunity by IgG remains for life after infection. Detection of the anti-HAV IgG antibody can be used in seroprevalence investigations (1). In Turkey, the seroprevalence of antibodies to HAV in the general population shows geographic and age-related differences most likely associated with socioeconomic and cultural conditions. A recent study showed that the rate of seropositivity for anti-HAV IgG was over 80% in the age group of 5–9 years old and more than 90% after 14 years of age in the southeastern and eastern regions. The seropositivity rate was lower than 50% in the age group of 5–9 years old and under 80% after 14 years of age in the central and western regions of Turkey (2). In a study by Alabaz et al. (3), maternal hepatitis A antibodies in infants born to hepatitis A antibody-positive mothers were detected in 93.9%, 36.1%, 13.6%, and 6.1% at birth and at 12, 18, and 21 months of age, respectively. Additionally, two-thirds of infants over the age of 12 months were at high risk of acquiring hepatitis A infection. Several studies indicated that passively acquired anti-HAV antibodies interfere with the immune response to hepatitis A vaccine (4,5). Letson et al. (6) reported that infants born to mothers who were anti-HAV–positive had a poorer response to the vaccine series. In a recent study by Shapapov et al. (7), 197 infants and young children were randomized by maternal anti-HAV status into 3 groups to receive a 2-dose hepatitis A vaccine: group 1 at 6 and 12 months, group 2 at 12 and 18 months, and group 3 at 15 and 21 months of age. Anti-HAV levels were measured at 1 and 6 months and at 3, 5, 7, and 10 years after the second dose of hepatitis A vaccination. The results from this study suggest that the seropositivity induced by hepatitis A vaccine given to children of <2 years of age persists for at least 10 years regardless of the presence of maternal anti-HAV (7). After

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the introduction of hepatitis A vaccine in 1995, it became a vaccine-preventable disease. The American Academy of Pediatrics recommends hepatitis A vaccination after 1 year of age (8). The highest incidence rates of HAV infection have previously been reported to occur in developing countries; these data suggest that hepatitis A vaccine should be included in these countries' national immunization schedule (9,10). Hepatitis A vaccine was included in the Turkish National Immunization Program for use in children aged 18 months or older in September 2012.

The aim of this study was to determine seropositivity for hepatitis A before vaccination in healthy children 12 and 24 months of age and to compare seroconversion rates after vaccination between these 2 groups.

2. Materials and methods

This was a prospective study conducted at the Uludağ University Hospital in Bursa, Turkey. The study included healthy children who were admitted for a routine vaccination program at the Well Baby Clinic. This study was conducted in the western regions of Turkey, which have intermediate endemicity. The children were grouped as 1 year old (Group 1: G1) and 2 years old (Group 2: G2). The Uludağ University Medical School Ethics Committee approved the study, which was conducted in accordance with the Declaration of Helsinki and its amendments, and Good Clinical Practice guidelines were followed throughout. Written informed consent was obtained from the parents of each child prior to study enrollment. Children were excluded if they had an acute febrile illness, a chronic immunocompromising disease (e.g., leukemia, cancer, AIDS), immunosuppressive treatment (e.g., chemotherapy, systemic corticosteroid for at least 2 weeks), a previous hepatitis A vaccination, or a history of hepatitis A.

Avaxim (80 U) was obtained from Sanofi Pasteur (Lyon, France), which supported this study. Avaxim 80 U Pediatric was prepared from the HAV strain GBM, inactivated with formaldehyde, and contained 80 antigen units of hepatitis A antigen protein per 0.5 mL dose, adsorbed onto 0.15 mg of aluminum hydroxide. Vaccines were stored between 2 °C and 8 °C throughout the study. Avaxim was administered by intramuscular injection into the deltoid region using a 16-mm 25-gauge needle in 2 doses, 6 months apart. The children were followed for 30 min after vaccination for early adverse reactions. The patients were informed about late adverse reactions and were called by telephone on the 1st, 3rd, and 5th days after vaccination. Local adverse reactions were pain, redness, edema, and hematoma; systemic adverse reactions included fever (axillary temperature of >37.5 °C), headache, and abdominal discomfort.

After physical examination, blood samples for anti-HAV antibodies were obtained by venipuncture before the first dose of vaccine (S0; serum 0), 2 weeks after the first injection (S1; serum 1), at 24 weeks (S2; serum 2) before the second dose, and at 28 weeks after the second dose of vaccination (S3; serum 3). After serum samples were centrifuged at 5000 rpm for 3 min, sera were stored at –70 °C until tested.

Anti-HAV IgG and IgM antibody levels were measured at the Microbiology Laboratory of the university by the Architect system of Abbott study kits (11). Anti-HAV IgG values were measured for each serum sample (4 serum samples for every child) and anti-HAV IgM values were measured only from samples taken before vaccination and at 4 weeks after the first dose. An anti-HAV IgG S/CO [serum sample result/cut-off relative light unit (RLU)] of <1 was considered negative, and >1 was considered positive. The cut-off RLU was calculated by multiplying the medium calibrator RLU value by 0.29. The sensitivity of the test for measuring antibodies was >98% and the specificity was >99.17% (12). S/CO ratios were compared before the first dose of the vaccination, at 2 weeks and at 4 weeks after the first dose, and at 28 weeks after the second dose.

Statistical analysis was performed using SPSS (SPSS, Inc., Chicago, IL, USA). Descriptive statistics [means and standard deviations (SDs) for continuous variables and counts and percentages for categorical variables] were used to describe the results. The results of the data were statistically assessed by the Shapiro–Wilk test, chi-square test, Mann–Whitney U test, and Wilcoxon tests. A P-value of less than 0.05 was considered significant.

3. Results

A total of 100 children, of whom 49 were in G1 and 51 were in G2, were enrolled in the study. In G1 45 children and in G2 49 children completed the study. The S1 samples of 2 children in G1 and the S1 sample of 1 child in G2 were hemolyzed and could not be tested. The G1 group was composed of 19 females (38.7%) and 30 males (61.3%). The G2 group was composed of 19 females (37.2%) and 32 males (62.8%). There was no significant difference between the 2 groups in terms of sex.

The seropositivity of anti-HAV IgG before vaccination was 10.2% for G1 and 7.8% for G2 (Table 1). The seropositivity of anti-HAV IgG before vaccination was not statistically significant between the 2 groups (P = 0.74).

The seroconversion rates are given in Table 1. There were no significant differences between the 2 groups in terms of seroconversion rates. The seroconversion rates for S1, S2, and S3 were 39%, 89%, and 100% (respectively) for all children in the study.

None of the children in G1 and G2 before vaccination had clinical signs of active hepatitis A infection. In

Table 1. Efficiency of vaccination according to serology of anti-HAV before vaccination in G1 and G2.

	Anti-HAV IgG (+) positivity			
	S0 n/N (%)	S1 n/N (%)	S2 n/N (%)	S3 n/N (%)
G1				
Seronegative children before vaccination (n = 44)	44/49 (89.8)	12/43 (27.9)	38/44 (86.3)	41/41 (100)
Seropositive children before vaccination (n = 5)[a]	5/49 (10.2)	4/4 (100)	5/5 (100)	4/4 (100)
Total (n = 49)	49/49 (100)	16/47 (34)	43/49 (87.7)	45/45 (100)
G2				
Seronegative children before vaccination (n = 47)	47/51 (92.2)	19/47 (40.4)	42/47 (89.3)	46/46 (100)
Seropositive children before vaccination (n = 4)	4/51 (7.8)	3/3 (100)	4/4 (100)	3/3 (100)
Total (n = 51)	51/51 (100)	22/50 (44)	46/51 (90.1)	49/49 (100)
P				
Seronegative children before vaccination (n = 91)	P = 0.70	P = 0.37	P = 0.69	P = *
Seropositive before vaccination (n = 9)	P = 0.74	P = *	P = *	P = *
Total (n = 100)	P = *	P = 0.55	P = 0.70	P = *

a: Serum of one subject in S1 and in S2 could not be tested because it was hemolyzed.
*Not applicable.
S0: Serum samples before first dose of vaccination; S1: serum samples 15 days after first dose of vaccination; S2: serum samples 30 days after first dose and before second dose of vaccination; S3: serum samples 30 days after second dose of vaccination.

addition, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels were not high, and anti-HAV IgM tests were negative. Only 6 children (6%) had borderline positive anti-HAV IgM levels in S2 (the limit of positivity S/CO was 0.7–1.0).

The S/CO ± SD ratios of S0, S1, S2, and S3 in G1 and G2 are shown in Tables 2 and 3. There were statistically significant differences between seronegative children in G1 and seropositive ones in G1 with respect to the S/CO ratio in S1; however, no significant differences were seen between S2 and S3 in these groups. The S/CO ratios were not statistically significant between S2 and S3 in seronegative children in G2 and seropositive ones in G2. A significant difference was seen in S1 in seronegative and seropositive children in G2.

The mean S/CO ± SD ratios and seroconversion rates in G1 and G2 are shown in Table 4. No significant difference was found among S1, S2, and S3 in G1 and G2. The mean S/CO ± SD ratios in S0, S1, S2, and S3 are shown in Table 5. There were statistically significant differences between S0 and S1 in seronegative and seropositive children. No difference was found between S2 and S3 in these 2 groups.

The S/CO ratios of S1, S2, and S3 in G1 (n = 49) and G2 (n = 51) increased 2.7, 8.5, and 29 times and 2.9, 11.2, and 35 times, respectively. There was no significant difference between the percentage changes of S/CO ratio in S1, S2, and S3 in G1 and G2 compared with the prevaccination values. The S/CO ratios of S1, S2, and S3 in seronegative (n = 91) and seropositive (n = 9) children increased 4.2, 16.4, and 55.2 times and 1.5, 2.3, and 5.3 times, respectively. No difference was seen between the percentage changes of S/CO ratio in S1 of seronegative and seropositive children compared with the prevaccination values. The increase in the percentage changes of the S/CO ratio was significant between S2 and S3 in seronegative and seropositive children (16.4 vs. 2.3 times, $P < 0.001$; 55.2 vs. 5.3 times, $P < 0.001$) compared with the prevaccination values.

The local and systemic adverse reactions of hepatitis A vaccination are shown in Table 6. No immediate systemic adverse reaction occurring within 30 min of vaccination was noted in any of the children. Local adverse reactions consisted of mild pain and redness at the injection site that resolved spontaneously. The rate of systemic adverse reactions after the administration of the first dose of vaccine, such as myalgia, arthralgia, gastrointestinal symptoms, and headache, was 6.1%, 7.8%, and 7% in G1, G2, and all children in the study group (n = 100), respectively. After the second dose of vaccine, the rate of systemic adverse reactions was 6.1% in G2 while no reaction occurred in G1. After the first dose of vaccination, no significant differences were found between G1 and G2 with regard to the rates of the local and systemic adverse reactions and local and/or systemic adverse reactions (P = 0.71, P = 099, and P = 0.63, respectively). After the second dose of vaccination, no significant differences were found between G1 and G2 with regard to the rates of local and systemic adverse reactions (P = 0.11 and P = 0.24, respectively); however, a significant difference was found with regard to the rates of local and/or systemic reactions (P = 0.013).

Table 2. S/CO levels and seroconversion rates according to anti-HAV IgM serology in G1 and G2.

	S2 Anti-HAV IgM serology n/N (%)	Anti HAV IgG S/CO ± SD values S/CO ≥ 1/N (%)			
		S0	S1	S2	S3
G1, n = 49	Anti-HAV IgM (+) 2/49 (4.1)	0.47 ± 0.07[a] 0/2 (0)	0.47 ± 0.02[b] 0/2 (0)	2.21 ± 1.60[c] 2/2 (100)	13.14 ± 4.21[d] 2/2 (100)
	Anti-HAV IgM (-) 47/49 (95.9)	0.50 ± 0.67[e] 5/47 (10.6)	1.43 ± 1.85[f] 16/45 (35.5)	4.37 ± 3.31[g] 41/47 (87.2)	14.58 ± 2.21[h] 43/43 (100)
G2, n = 51	Anti-HAV IgM (+) 4/51 (7.8)	0.18 ± 0.05[a] 0/4 (0)	0.70 ± 0.53[b] 2/4 (50)	2.65 ± 1.50[c] 4/4 (100)	14.46 ± 0.69[d] 4/4 (100)
	Anti-HAV IgM (-) 47/51 (92.2)	0.40 ± 0.79[e] 4/47 (8.5)	1.22 ± 1.51[f] 20/46 (43.4)	4.66 ± 3.47[g] 42/47 (89.3)	14.13 ± 2.98[h] 45/45 (100)
Total, n = 100	Anti-HAV IgM (+) 6/100 (6)	0.28 ± 0.16[i] 0/6 (0)	0.62 ± 0.43[j] 2/6 (33.3)	2.51 ± 1.38[k] 6/6 (100)	14.02 ± 2.07[l] 6/6 (100)
	Anti-HAV IgM (-) 94/100 (94)	0.46 ± 0.75[i] 9/94 (9.5)	1.33 ± 1.68[j] 36/91 (39.5)	4.52 ± 3.37[k] 83/94 (88.2)	14.35 ± 2.63[l] 88/88 (100)

S0: Serum samples before first dose of vaccination; S1: serum samples 15 days after first dose of vaccination; S2: serum samples 30 days after first dose and before second dose of vaccination; S3: serum samples 30 days after second dose of vaccination.
For a, P = 0.66; b, P = 0.99; c, P = 0.66; d, P = 0.33; e, P = 0.53; f, P = 0.54; g, P = 0.71; h, P = 0.39; i, P = 0.98; j, P = 0.84; k, P = 0.39; l, P = 0.22.

Table 3. Mean values and positivity rates of S/CO* according to vaccination in G1.

		G1			
		S0 (N = 49)	S1 (N = 47)	S2 (N = 49)	S3 (N = 41)
Seronegative children before vaccination (n = 44)	S/CO ± SD	0.33 ± 0.21	1.23 ± 1.73[a]	4.07 ± 3.10[b]	14.50 ± 2.20[c]
	S/CO ≥ 1/N (%)	0/44 (0)	12/43 (27.9)	38/44 (86.3)	41/41 (100)
Seropositive children before vaccination (n = 5)	S/CO ± SD	2.04 ± 1.19	3.07 ± 2.26[a]	6.19 ± 4.54[b]	14.64 ± 3.25[c]
	S/CO ≥ 1/N (%)	5/5 (100)	4/4 (100)	5/5 (100)	4/4 (100)
Total children in G1 (n = 49)	S/CO ± SD	0.50 ± 0.65	1.38 ± 1.83	4.29 ± 3.28	14.51 ± 2.27
	S/CO ≥ 1/N (%)	5/49 (10.2)	16/47 (34)	43/49 (87.7)	45/45 (100)

For a, P = 0.011; for b, P = 0.26; for c, P = 0.47.
S0: Serum samples before first dose of vaccination; S1: serum samples 15 days after first dose of vaccination; S2: serum samples 30 days after first dose and before second dose of vaccination; S3: serum samples 30 days after second dose of vaccination.
*The values above are only S/CO results (serum sample / cutoff RLU) and are not the geometric mean titers of serum antibody concentrations.

4. Discussion

HAV is a common type of infectious hepatitis. The prevalence of anti-HAV antibody varies among different ages, countries, and even different regions of the same country. The decrease in the seroprevalence of anti-HAV antibody is usually explained by the improvement in socioeconomic conditions, access to safe drinking water, improvement of sanitation facilities, and effective vaccination program (12,13). The prevalence of hepatitis A in developed countries varies among age groups, being lower than 20% in subjects of <50 years of age (14). In a study performed in Canada, the prevalence was found to be <20% among children and 40%–60% in adults of >40 years old (15,16). Seroprevalence rates vary among

Table 4. Mean values and positivity rates of S/CO according to vaccination in G2.

		G2			
		S0 (N = 51)	S1 (N = 50)	S2 (N = 51)	S3 (N = 49)
Seronegative children before vaccination (n = 47)	S/CO ± SD	0.20 ± 0.07	1.01 ± 1.27[a]	4.48 ± 3.44[b]	14.23 ± 2.93[c]
	S/CO ≥ 1/N (%)	0/47 (0)	19/47 (40.2)	42/47 (89.3)	46/46 (100)
Seropositive children before vaccination (n = 4)	S/CO ± SD	2.79 ± 1.51	3.94 ± 1.74[a]	4.81 ± 3.06[b]	12.99 ± 1.40[c]
	S/CO ≥ 1/N (%)	4/4 (100)	3/3 (100)	4/4 (100)	3/3 (100)
Total children in G2 (n = 51)	S/CO ± SD	0.40 ± 0.79	1.18 ± 1.46	4.51 ± 3.39	14.15 ± 2.86
	S/CO ≥ 1/N (%)	4/51 (7.8)	22/50 (44)	46/51 (90.1)	49/49 (100)

For a, P = 0.002; for b, P = 0.74; for c, P = 0.18.
S0: Serum samples before first dose of vaccination; S1: serum samples 15 days after first dose of vaccination; S2: serum samples 30 days after first dose and before second dose of vaccination; S3: serum samples 30 days after second dose of vaccination.

European countries, being medium in the eastern and southern regions of Europe, but low in the western and northern regions (13).

The prevalence of hepatitis A is high in Turkey, but it is heterogenic among different regions of the country. In a study conducted in different regions of Turkey, the mean prevalence of HAV infection was 71.3% for all ages, and it was higher in the eastern regions than the western regions of Turkey (2,17). In one study, 14% of subjects between 1 and 4 years of age and 36% between 5 and 9 years of age were found to be HAV-positive in the western provinces (17). In another study in the southern regions of the country, seropositivity was found to be 78.1% and 86.9% in the same age groups, respectively (18). A recent study from Turkey reported that hepatitis A seroprevalence was 23.5% in children at 12 months of age (19). In our study, the seropositivity rate of hepatitis A was 10.2% and 7.8% in children 12 and 24 months of age, respectively. The rate of seropositivity in our study was lower than the rates in some published reports (3,19). Unfortunately, we were unable to determine whether these antibodies in children 12 months of age were of maternal origin or the result of a previous infection. The decrease in the seropositivity of antibodies by 24 months of age and the significant increase in seroconversion rates after vaccination demonstrated that the seropositivity was due to maternal antibodies much more so than to acquired infections.

In a study performed in the United States among infants born to seropositive mothers, seropositivity rates at 6, 12, and 15 months of age were 94%, 15%, and 3%, respectively (20). In a study from Turkey, maternal antibodies were found to be positive in 85% of newborns. In the same

Table 5. S/CO rates of children in the study (1 and 2 years old).

	Total				
	0 (N = 100)	S1 (N = 97)	S2 (N = 100)	S3 (N = 94)	
S/CO of ≥1 / <1 (%)	9/91 (9)	38/59 (39.1)	89/11 (89)	94/0 (100)	
S/CO ± SS in seronegative children before vaccination	0.26 ± 0.17	1.11 ± 1.50	4.28 ± 3.27	14.36 ± 2.60	P = 0.67
	P = 0.001	P = 0.001	P = 0.33		
S/CO ± SS in seropositive children before vaccination	2.37 ± 1.31	3.44 ± 1.94	5.58 ± 3.79	13.93 ± 2.59	
S/CO ± SS in all of the children	0.45 ± 0.73	1.28 ± 1.64	4.40 ± 3.32	14.33 ± 2.59	

S0: Serum samples before first dose of vaccination; S1: serum samples 15 days after first dose of vaccination; S2: serum samples 30 days after first dose and before second dose of vaccination; S3: serum samples 30 days after second dose of vaccination.

Table 6. Local and systemic side effects after vaccination in G1 and G2.

		First dose n/N (%)	Second dose n/N (%)
G1, N = 49	Local n/N (%)	3/49 (6.1)[a]	0/45 (0)[d]
	Systemic n/N (%)	3/49 (6.1)[b]	0/45 (0)[e]
	Local and/or systemic n/N (%)	6/49 (12.2)[c]	0/45 (0)[f]
G2, N = 51	Local n/N (%)	5/51 (9.8)[a]	4/49 (8.1)[d]
	Systemic n/N (%)	4/51 (7.8)[b]	3/49 (6.1)[e]
	Local and/or systemic n/N (%)	9/51 (17.6)[c]	7/49 (14.2)[f]
Total, N = 100	Local n/N (%)	8/100 (8)	4/94 (4.2)
	Systemic n/N (%)	7/100 (7)	3/94 (3.2)
	Local and/or systemic n/N (%)	15/100 (15)	7/94 (7.4)

Local reaction: Pain, hyperemia, and/or induration of injection side. Systemic reaction: Myalgia, arthralgia, abdominal discomfort, and headache.
[a]: Significance of local reaction after first dose of vaccination in G1 and G2; P = 0.71. [b]: Significance of systemic reactions after first dose of vaccination in G1 and G2; P = 0.99. [c]: Significance of local and/or systemic reactions after first dose of vaccination in G1 and G2; P = 0.63. [d]: Significance of local reaction after second dose of vaccination in G1 and G2; P = 0.11. [e]: Significance of systemic reactions after second dose of vaccination in G1 and G2; P = 0.24. [f]: Significance of local and/or systemic reactions after second dose of vaccination in G1 and G2; P = 0.013.

study, 9% of infants at the age of 12 months and 0% at the age of 18 months had remaining maternal antibodies, and so infants over the age of 12 months were found to be at high risk of acquiring HAV infection in Turkey (21).

In a study conducted in the United States to determine the immunogenicity of an inactivated hepatitis A vaccine in infants, 140 infants born to seronegative mothers and 108 infants born to seropositive mothers were randomized into 3 groups, each receiving 2 doses of 720 EL.U. of hepatitis A vaccine (HAVRIX): group 1 at ages 6 and 12 months, group 2 at ages 12 and 18 months, and group 3 at ages 15 and 21 months. In group 1, peak geometric mean concentrations of hepatitis A antibodies between infants born to seropositive mothers (794 mIU/mL) and seronegative mothers (2083 mIU/mL) were significantly different. This study suggests that the hepatitis A vaccine is immunogenic among infants born to seronegative and seropositive mothers if vaccination is applied at ≥12 months of age. The maternal antibody persists for at least 6 months and causes a decrease in the immune response of the hepatitis A vaccine (8).

Similar to previous studies (3,6,20), a significant increase in the percentage changes of the S/CO ratio after vaccination was observed in the seronegative children compared to the seropositive children in our study. The percentage changes of S/CO ratios were not statistically significant between S1, S2, and S3 in G1 and G2. As we could not analyze the geometric mean titer of antibody concentrations, we have no comment on the degree of increase in antibody titers and the duration of the protective period.

In our study, the seroconversion rates in children at 12 and 24 months of age at 2, 4, and 28 weeks were 34%, 87.7%, and 100% and 44%, 90.1%, and 100%, respectively. Unfortunately, we were able to measure only qualitative levels, not the quantitative and medium antibody concentrations. There were no significant differences between the 2 groups in terms of seroconversion rates. Children who completed the vaccination program were seropositive after the second dose. In our study, the seroconversion rates at 2 weeks were lower than in other studies (20,22). However, our seroconversion rates at 4 and 28 weeks were quite comparable to those of previous studies (20,22).

The positivity of anti-HAV IgM in serum samples shortly after the vaccination can cause confusion (23). Only <1% of subjects have anti-HAV IgM positivity 1 month after vaccination (23). In our study, 4 weeks after the first dose of vaccine, the rates of anti-HAV IgM positivity in the serum samples of children at 12 and 24 months of age were 4.1% and 7.8%, respectively. In total, 6% of the children in the study were positive for anti-HAV IgM. Although the total 6% positivity of anti-HAV IgM levels 4 weeks after vaccination does not demonstrate infection, it may be a primary response to vaccination.

The safety of inactive hepatitis A vaccine was demonstrated in several studies (22,24–26). Local adverse reactions after vaccination have been reported to be

between 6.1% and 17.5% and systemic adverse reactions between 6.1% and 19.2% (22,24–26). None of the children in our study experienced sudden allergic reaction. Local adverse reactions occurred in 8% of children after the first dose of vaccine and in 4.2% after the second dose. Systemic adverse reactions occurred in 7% of children after the first dose and in 3.2% after the second dose. Local adverse reactions did not last longer than 3 days. Similar to the previous studies, adverse reactions were mild in this study (22,24).

According to the results of our study, there is no difference between the response rates of vaccination at 12 and 24 months of age, and also there are similar seroconversion rates and no difference for adverse reactions. Based on these results, hepatitis A vaccine can be administered at 12 months of age rather than at 24 months of age. Also, according to the routine vaccination schedule of our country, we can communicate better with the parents of children 12 months of age, and this will increase the vaccination rates.

In conclusion, it was demonstrated that hepatitis A vaccine is immunogenic for 1- and 2-year-old children. We can thus estimate that the vaccine is safe and immunogenic for children 1 year old and older.

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