

# Hepatitis A Vaccine Effectiveness and Seropositivity Among 1- to 18-Year-Old Children: 10-Year Results

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## What is already known on this topic?

- Each year, 1.5 million cases of hepatitis A virus (HAV) infection are reported worldwide.
- HAV disease can be prevented with vaccination.

## What this study adds to this topic?

- This is the most comprehensive report of HAV seropositivity in Turkey.
- Anti-HAV IgM positivity has increased slightly in recent years, which is likely due to the increased number of refugees from the Syrian war in this region of Turkey.

## ABSTRACT

**Objective:** The aim of the study was to examine and compare hepatitis A seropositivity in children.

**Materials and Methods:** The study included patients aged 0–18 years who presented to our hospital and were examined for hepatitis A virus serology between 2009 and 2018. Patients were separated into 2 groups: those who presented before (group I) or after (group II) September 2012, when the mandatory hepatitis A vaccination program came into effect in Turkey.

**Results:** In total, 34 809 patients were evaluated: 20 111 (57.8%) males and 14 698 (42.2%) females, with a mean age of  $8.2 \pm 5.3$  years. Anti-hepatitis A virus immunoglobulin M positivity was observed in 3.3% of patients, most often in January and from January to April when the region experiences more rainfall. Anti-hepatitis A virus immunoglobulin M positivity decreased dramatically in group II compared to group I (0.26% vs. 7.42%,  $P < .001$ ). Anti-hepatitis A virus immunoglobulin G positivity was observed in 53.8% of all patients. A statistically significant increase was determined in anti-hepatitis A virus immunoglobulin G seropositivity in group II compared to group I (81.9% vs. 42.1%,  $P < .001$ ).

**Conclusion:** Hepatitis A virus infection in Turkey decreased dramatically following improvements to infrastructure and sanitation and implementation of the vaccination program. This study is the most comprehensive report of hepatitis A seropositivity in Turkey to date.

**Keywords:** Children, HAV seropositivity, vaccination

## INTRODUCTION

Hepatitis A virus (HAV) infection is a significant public health problem worldwide and is the most frequent acute viral agent in the pediatric age group.<sup>1</sup> Although the disease is observed in all countries, it is more common in developing countries. The incidence varies depending on the socio-economic level of the community, whether living conditions are crowded, accessibility to clean water, and hygiene standards.<sup>2</sup>

Hepatitis A disease can be prevented with vaccination. When the vaccine is administered in 2 doses, it provides close to 100% and long-term protection.<sup>3</sup> The Turkish Ministry of Health added the HAV to the mandatory vaccination calendar for children in September 2012.

The aim of this study was to examine and compare hepatitis A seropositivity in children. We investigated the seropositivity in children of different age groups who presented to our hospital at different times of the year and with different complaints and were tested for acute hepatitis A serology. We compared hepatitis A seropositivity before and after mandatory vaccinations were introduced, between years, with pediatric age groups in different regions of the world. The following discussion presents the results along with relevant literature.

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## MATERIALS AND METHODS

This study was a retrospective evaluation of children aged 0–18 years who presented to the Children's Health and Diseases Polyclinic at our hospital between January 2009 and December 2018 with various complaints and were tested for hepatitis A serology.

### Demographic Characteristics

Data related to the date of birth, sex, age at presentation, season of presentation, antibody levels, and diagnosis were retrieved from the hospital automated records system and patient files. Records of the vaccination status of patients could not be obtained.

### Diagnostic Procedure

Blood samples from patients were examined for the presence of anti-HAV immunoglobulin (Ig) M and anti-HAV IgG using the macro enzyme-linked immunosorbent assay method (Architect, Abbott Diagnostics, Abbott Park, Ill, USA). Test results of  $\geq 1$  signal-to-cutoff (S/CO) were accepted as positive.

### Patient Groups

Patients were separated into 3 age groups: 0–6, 6–12, and 12–18 years. They were also classified into 3 groups based on anti-HAV IgM positivity according to seasons: from January to April, when the region is cold and rainy; September to December, when schools are open together with rainy weather; and May to August, when it is hot and dry.

Finally, patients were also separated into group I, those who presented before September 2012, when the HAV was incorporated into the mandatory vaccination calendar, and group II, those who presented after September 2012. The hepatitis A seropositivity rate was evaluated by examining the anti-HAV IgM and anti-HAV IgG results, and the effects of HAV on these rates were evaluated.

### Statistical Analyses

Statistical analyses were conducted using the Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA). Data with skewness and kurtosis values

between  $-2.58$  and  $+2.58$  were assumed to have normal distribution. It was also evaluated with histograms. Continuous data with a normal distribution are expressed as the mean  $\pm$  standard deviation and non-parametric data as the median (minimum–maximum). The chi-square test was used in the evaluation of categorical variables. The Mann–Whitney *U* test was used to compare independent groups of non-parametric variables. A value of  $P < .05$  was accepted as statistically significant. Using the G-Power computer program, the effect size of the study was calculated as 0.27 and the power of the study was calculated as 99%.

## RESULTS

### Demographic Evaluations

In total, 34 809 patients were evaluated: 20 111 (57.8%) males and 14 698 (42.2%) females, with a mean age of  $8.2 \pm 5.3$  years. Group I included 14 983 (43%) patients and group II included 19 826 (57%) patients.

### Seropositivity of Anti-HAV IgM

Anti-HAV IgM positivity was determined in 1166 (3.3%) patients, most frequently in January (16.4%), followed by March (12.4%), February (10.7%), and December (10.2%). Figure 1 presents the distribution of anti-HAV IgM positivity by months. When the distribution of anti-HAV IgM positivity was examined by year, the results revealed 0 cases after 2012, but the rates have been increased slightly in recent years (Figure 2).

Statistical analyses revealed a significant difference in anti-HAV positivity between age groups and seasons, and no difference with regard to sex ( $P < .05$ ,  $P < .05$ ,  $P = .22$ , respectively). Table 1 lists the distribution and comparisons of anti-HAV IgM positivity according to age groups, seasons, and sex. The median age of patients in group I was significantly lower than that group II and the rate of male patients was greater (6.89 years (1 month to 18 years), 8.19 years (1 month–18 years), and 59.3%, 56.5%,  $P < .001$  and  $P < .001$ , respectively). Anti-HAV IgM positivity was observed in 1113 (7.42%) patients in group I and in 53 (0.26%) patients in group II. The difference between the 2 groups for anti-HAV IgM positivity was highly significant ( $P < .001$ ). Table 2 compares groups I and II.

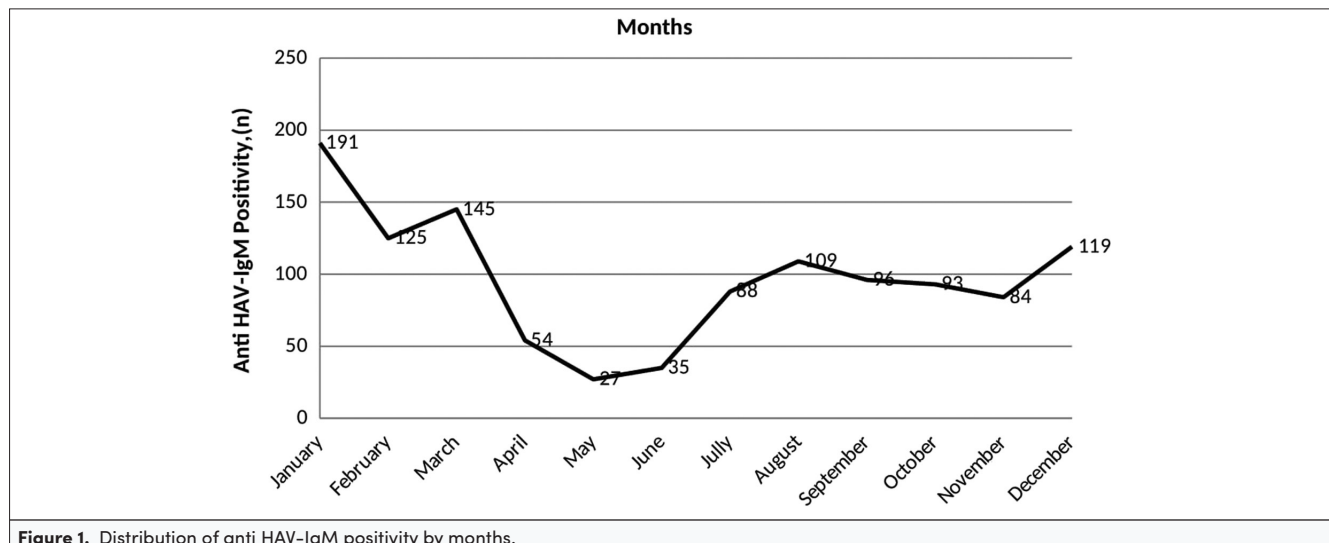
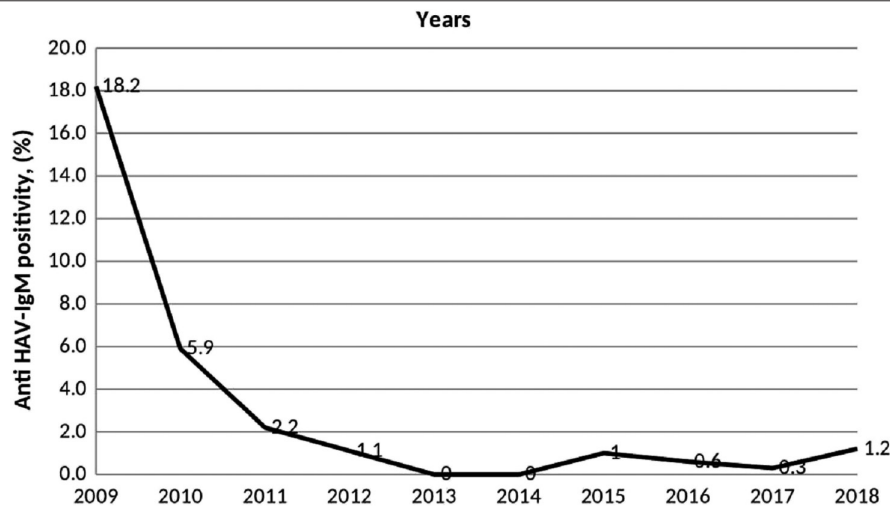


Figure 1. Distribution of anti HAV-IgM positivity by months.



**Figure 2.** The alteration of anti HAV-IgM positivity by year.

### Seropositivity of Anti-HAV IgG

Anti-HAV IgG was assessed in 21 267 patients. Positivity was observed in 11 467 (53.8%) of the patients examined for anti-HAV IgG, who had a mean age of  $7.3 \pm 4.4$  years. The rate of males with anti-HAV IgG positivity was greater (54.5%, 45.5%, respectively,  $P = .029$ ), and no difference was observed between negative and positive patients with regard to mean age ( $7.31 \pm 4.3$ ,  $7.41 \pm 4.5$  years,  $P = .11$ ). Anti HAV-IgG positivity was significantly higher in group II compared to group I (81.9% vs. 41.2%,  $P < .001$ ) (Table 2).

### DISCUSSION

Each year, 1.5 million cases of HAV infection are reported worldwide. However, the actual figure is thought to be approximately 100–120 million per year, considering that asymptomatic infections in children and missing reports constitute a large group.<sup>3</sup> This study was conducted retrospectively to investigate hepatitis A seropositivity in children: it included the largest population studied in Turkey to date. The results revealed that hepatitis

A seropositivity decreased with improved sanitation and the hepatitis A vaccination program. Anti-HAV IgM positivity has increased slightly in recent years, which is likely due to the number of refugees from the Syrian war in this region of Turkey.

Hepatitis A is the most frequent form of acute viral hepatitis worldwide. Generally, as the socio-economic level of a country increases, hepatitis A infection is seen at an older age. In under-developed and developing countries, it continues to be a significant health problem and is associated particularly with insufficient infrastructure. In contrast to developed countries, contact with the virus generally occurs during childhood.<sup>4</sup> In our study, the mean age of patients with anti-HAV IgM was  $6.63 \pm 3.8$  years. When patients were grouped according to age, anti-HAV IgM positivity was found in 5.01% of the 0–6 years age group, and this rate decreased to 0.47% in the 12–18 years age group. These data suggest that the disease is encountered at a young age in Turkey.

Countries may be classified as having high, moderate, and low endemic rates of hepatitis A infection. In countries with poor sanitation conditions, 90% of the population up to the age of 10 years have positive hepatitis A serology, while in developed countries, only 30% of the population up to the age of 30 years have positive serology. Countries classified as the moderately endemic group have seropositivity rates in 90% of the population up to the age of 15 years.<sup>5,6</sup> Turkey is classified as moderately

**Table 1.** Anti-HAV IgM Positivity According to Age Groups, Seasons, And Gender

	Positive	Negative	P
Age (year), median (min-max)	5.1 (1 month-18 years)	7.67 (1 month-18 years)	<b>&lt;.001<sup>a</sup></b>
Age range			
0–6 years, n (%)	699 (5.01)	13 244 (94.99)	<b>&lt;.05<sup>*</sup></b>
7–12 years, n (%)	425 (3.56)	11 505 (96.44)	
13–18 years, n (%)	42 (0.47)	8894 (99.53)	
Gender			
Male, n (%)	694 (3.45)	19 417 (96.55)	.22 <sup>*</sup>
Female, n (%)	472 (3.21)	14 226 (96.79)	
Season			
September to December, n (%)	392 (3.32)	11 389 (96.68)	<b>&lt;.05<sup>*</sup></b>
January–April, n (%)	515 (4.49)	10 946 (95.51)	
May–August, n (%)	259 (2.23)	11 308 (97.77)	

min, minimum; max, maximum; <sup>a</sup>Mann-Whitney U test; <sup>\*</sup>Chi-square test Bonferroni correction. Statistically significant values are indicated in bold.

**Table 2.** Comparison of Group I and Group II

Parameter	Group I	Group II	P
Gender, male/female, %	59.3/40.7	56.5/43.5	<b>&lt;.001<sup>i</sup></b>
Age (year), median (min-max)	6.89 (1 month-18 years)	8.19 (1 month-18 years)	<b>&lt;.001<sup>a</sup></b>
Anti-HAV IgM positivity, %	7.42	0.26	<b>&lt;.001<sup>i</sup></b>
Anti-HAV IgG positivity, %	42.1	81.9	<b>&lt;.001<sup>i</sup></b>

min, minimum; max, maximum; anti-HAV, anti hepatitis A virus;

IgM, immunoglobulin M; IgG, immunoglobulin G; <sup>i</sup>chi-square test;

<sup>a</sup>Mann-Whitney U test. Statistically significant values are indicated in bold.

endemic group.<sup>6</sup> In India and some countries in Africa, almost all children up to the age of 3 years are seropositive for HAV. Although seropositivity rates in some countries in the Far East are similar to those of African countries, positivity rates fall with improvements in socio-economic status.<sup>7,8</sup> Previous studies in Turkey have reported a wide range of anti-HAV IgG positivity of 40%–87.7% because of regional socio-economic differences.<sup>6,9–11</sup> In this study, of the patients whose anti-HAV IgG was examined, the mean age was 7.3 years and the positivity rate was 53.8%, consistent with previous data reported in Turkey.

Some studies have reported no differences between the sexes in hepatitis A seropositivity,<sup>9,12–14</sup> whereas other studies have found higher hepatitis A seroprevalence in males.<sup>6,15</sup> In the present study, anti-HAV IgG positivity was higher in males, but the difference was not statistically significant. Male children having more contact with an outside environment and consuming unhygienic food and drinks may play a role in this difference.

Hepatitis A vaccinations are extremely effective; almost 100% protection has been reported after the administration of a single dose. Although a single dose vaccination provides short-term protection, 2 doses are recommended for long term and effective protection.<sup>16</sup> In Turkey, the hepatitis A vaccination was included in the mandatory routine vaccination program after September 2012. In studies conducted before that date, anti-HAV IgM positivity in the pediatric age group was reported at high rates: 18.1% by Arvas et al.<sup>12</sup> 15.1% by Okur et al.<sup>17</sup> 9.8% by Parlak et al.<sup>15</sup> 5.04% by Tekay et al.<sup>18</sup> and 2.9% by Kalem et al.<sup>19</sup> In studies conducted after September 2012, rates have been reported to be as low as 0.2%.<sup>5</sup> In our study, anti-HAV IgM positivity was found to be 7.42% before the vaccine was included in the mandatory vaccination program and this rate fell to 0.26% after that date. However, a significant decrease in seropositivity was observed between 2009 and 2012, even though hepatitis vaccination had not yet been implemented. This decrease was likely related to improvements in infrastructure and sanitation conditions in Turkey. Vaccination has further contributed to this decline. In studies conducted in Turkey before mandatory vaccination, different rates were reported because of socio-economic differences between regions.<sup>12,14–19</sup> These differences are no longer observed since the mandatory hepatitis A vaccination.

Previous research suggests that HAV infections are observed more often in the rainy periods of autumn and winter, including in Turkey.<sup>20</sup> In our study, anti-HAV IgM positivity was observed most often in January (16.4%), followed by March (12.4%), February (10.7%), and December (10.2%). Seasonally, anti-HAV IgM positivity was observed most often in the period of January to April, followed by September to December, and least often in May to August. The difference between these groups was statistically significant. The greater frequency of anti-HAV IgM seen in the autumn and winter months is associated with more rainy weather; transmission is also more likely during this time of year because of closer contact of people in closed environments due to cold weather, and infection may spread between children because the schools are open.

Turkey has hosted 3.6 million Syrian refugees since the beginning of the civil war in Syria and currently hosted the highest number of Syrian refugees.<sup>20</sup> The adverse conditions associated

with migration, including communal living areas, difficulties in accessing clean water, and inadequate infrastructure, are effective factors in the formation and spread of infectious diseases.<sup>20</sup> While the immunization rate for communicable diseases in Syria was above the 80% threshold in the pre-war period, this decreased to 45% with the war.<sup>20,21</sup> Leishmaniasis, typhoid fever, and hepatitis A diseases are endemic in Syria.<sup>22</sup> In the present study, when anti-HAV IgM positivity was examined by year, rates were as high as 18.2% before 2012 when the vaccine was incorporated into the mandatory vaccination program and cases fell to 0 after that year. There has been a slight increase in recent years. The region where the study was conducted has a high density of refugees, which is likely the reason for this recent increase, but a more comprehensive and controlled investigation will be needed to confirm this.

### Study Limitations

This study was limited by its retrospective nature and also because the study population included only patients admitted to the hospital.

### CONCLUSION

HAV infections can be effectively prevented with vaccinations. These infections were reduced dramatically in Turkey after improvements in infrastructure and sanitation and introduction of the hepatitis A vaccine into the routine childhood vaccination program. This study included the largest population studied in Turkey to date.

**Ethics Committee Approval:** This study was approved by Ethics committee of Health Sciences University, Gazi Yaşargil Training and Research Hospital (Approval No: 2020/574).

**Informed Consent:** Informed consent was not obtained from the parents of patients in this study because of the retrospective nature of the study.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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