



# Hepatitis A virus age-specific seroprevalence after the implementation of a Toddlers' Vaccination in Turkey: Shifting susceptibility to adolescents

Türkiye'de Hepatit A virüsünün aşılama programına alınması sonrasındaki yaşa spesifik seroprevelans değerleri; duyarlılığın ergen yaş grubuna kayması

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## The known about this topic

Hepatitis A virus infection in children is typically asymptomatic or an acute, self-limited disease associated with general, nonspecific symptoms. In 1996, the Advisory Committee on Immunization Practices recommended routine two-dose hepatitis A vaccination for children age under 2 years in countries of intermediate/high endemicity, and Turkey added hepatitis A vaccine to its routine immunization schedule in 2012. Vaccination may reduce the risk of exposure to hepatitis A virus in early life, but may increase the susceptibility of infection in adolescent and adult populations when morbidity and mortality are highest.

## Contribution of the study

This single-center study revealed that hepatitis A virus seropositivity was significantly higher in the preschool age group, but decreased in school-age children and adolescents after vaccination. Hepatitis A vaccination, also covering adolescents and young adults, should be considered among state-sponsored vaccines nationwide.

## Abstract

**Aim:** In Turkey, improvements in sanitation and the implementation of a vaccination program resulted in reduced rates of childhood exposure to hepatitis A virus. The incidence of symptoms and the complications of the disease are known to be increased in later ages. We aimed to describe changes in the seroprevalence of hepatitis A virus from the pre-vaccine era (2012) to the post-vaccine era (2018) in different age groups.

**Material and Methods:** Levels of anti-hepatitis A virus immunoglobulin (Ig)-G of patients with no chronic disease and who were admitted to our hospital between 2013–2018 were obtained retrospectively from a single children's hospital database system.

**Results:** A total of 3238 subjects were enrolled in the study (2820 children, 418 adults). The overall percentage of seropositivity was 60.5% in group 1 (age  $\leq 2$  years), 57.9% in group 2 (age 2–6 years), 31.2% in group 3 (age 7–11 years), 32.7%

## Öz

**Amaç:** Türkiye'de sanitasyon ve aşılama programının uygulanmasında gelişmeler, hepatit A Virüsüne çocuklukta maruz kalma oranlarının düşmesine neden olmuştur. Yaş artışı ile birlikte hastalığın semptom ve komplikasyon sıklığında artış olduğu bilinmektedir. Hepatit A virüsünün, aşı öncesi 2012 döneminden aşı sonrası 2018 yılına kadar olan farklı yaş gruplarındaki seroprevelans değişimlerini sunmayı amaçladık.

**Gereç ve Yöntemler:** Tek merkezli bir çocuk hastanesi veri tabanı sisteminde, 2013–2018 yılları arasında hastanemize başvuran ve kronik hastalığı olmayan çocuk yaş grubu olguların serum Anti-hepatit A Virüs IgG değerleri geriye dönük olarak değerlendirildi.

**Bulgular:** Çalışmaya toplam 3238 alındı (2820 çocuk, 418 yetişkin). Genel seropozitiflik yüzdeleri, grup 1'de ( $\leq 2$  yaş) % 60,5; grup 2'de (0–6 yaş) % 57,9; grup 3'de (7–11 yaş) % 31,2; grup 4'te (12–18 yaş) % 32,7; grup 5'te

Cont. ➔

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in group 4 (age 12–18 years), 44.6% in group 5 (age 19–24 years), and 73.9% in group 6 (age >25 years). Between 2013–2018, the increase in the number of seropositive individuals in group 2 ( $p<0.01$ ), and the decrease in groups 3 and 4 were statistically significant from 2013 to 2018 ( $p=0.028$ ,  $p<0.01$ ).

**Conclusion:** According to the data of this single-center children's hospital in Turkey, hepatitis A virus seropositivity increases significantly in the preschool age group, but decreases in school-age children and adolescents after vaccination.

**Keywords:** Children, hepatitis A virus, seroprevalence, vaccination

(19–24 yaş) % 44,6 ve grup 6'da (> 25 yaş) % 73,9'du. İki bin on üç–2018 yılları arasında grup 2'deki seropozitif olgu sayısındaki artış ( $p<0,01$ ), grup 3 ve 4'teki seropozitif olgu sayısında azalma istatistiksel olarak anlamlıydı ( $p=0,028$ ,  $p<0,01$ ).

**Çıkarımlar:** Türkiye'deki tek merkezli çocuk hastanesi verilerine göre; aşılama sonrası hepatit A Virüsü seropozitifliği okul öncesi çocuklarda anlamlı artmaktadır, fakat okul çağı ve adolesanlarda anlamlı azalma göstermektedir.

**Anahtar sözcükler:** Çocuk, hepatit A virüsü, seroprevelans, aşılama

## Introduction

Hepatitis A virus (HAV) infection in children is typically asymptomatic or an acute, self-limited disease associated with general, nonspecific symptoms. Older children and adults with HAV infection are usually symptomatic for several weeks. Unlike hepatitis B and C, HAV infection does not cause chronic liver disease, but it can cause debilitating symptoms and fulminant hepatitis (acute liver failure) with a reported incidence of 0.015–0.5%. Older children, adolescents, and adults usually present more symptomatic HAV infection and suffer associated morbidity with direct and indirect costs of medical care and school/work loss (1, 2).

The highest incidence rates of HAV infection have previously been reported to occur in developing countries (most of Africa and parts of Asia, South America, and Eastern Europe) (3–5). As individual income increases and access to safe drinking water and improved sanitation conditions increases, the incidence of HAV infection decreases (1, 4, 6, 7). In countries where vaccination programs are applied, it is stated that HAV infection cases have decreased but unpredictable outbreaks have been reported (5, 7–10).

In 1996, the Advisory Committee on Immunization Practices (ACIP) recommended a routine of two doses of hepatitis A vaccination for children aged under 2 years in countries of intermediate or high endemicity. Hepatitis A vaccines are highly immunogenic, and >95% of immunocompetent persons develop protective antibodies within 4 weeks of application of 1 dose of the vaccine (11). As a result of the implementation of a childhood vaccination strategy, symptomatic HAV cases have declined in countries that implement HAV in their routine vaccination program (4, 12–14).

Sero-surveys based on anti-HAV antibody detection represent one of the main sources of information used for estimating the burden of disease associated with HAV infection. The percentage of anti-HAV IgG positivity from various age groups provides information about both recent and past epidemiologic patterns (1, 15). Geographical distribution areas can be classified as having

high, intermediate or low levels of HAV infection. These categories are made based on the prevalence of anti-HAV IgG in human serum and reflect seropositivities of <15%, 15–50%, and >50%, respectively, in the studied populations (4).

Turkey has an intermediate level of anti-HAV seroprevalence with differences among various geographic regions (16). In countries of intermediate endemicity, the World Health Organization (WHO) recommends childhood vaccination and Turkey added the hepatitis A vaccine to its routine immunization schedule in 2012. Studies conducted in different parts of Turkey revealed that the hepatitis A seroprevalence varied by region, ranging from 7.8% to 88%, with lower seroprevalence generally noted where sanitation infrastructure was better (17). Although the incidence rate in Turkey is expected to decrease further as a result of both the vaccination program and ongoing infrastructural development, there might likely be new outbreaks associated with the increasing refugee population and international trade. Most European populations are immunized against vaccine-preventable diseases, but an imminent challenge is introduced with the refugees from Africa and the Middle East spread around in Europe, especially due to the lack of vaccination against expected re-emerging infections; HAV infection is a case in point (9).

Hepatitis A incidence rates in Turkey have declined over the past 15 years (17). Vaccination may reduce the risk of exposure to HAV in early life, but may increase the susceptibility in adolescent and adult populations to HAV infection when morbidity and mortality are highest. Karacaer et al. (18) presented the changes in the viral epidemiology of viral hepatitis in recent years in an adult Turkish population. They determined HAV seropositivity in 37.6% of 852 patients and stressed that larger vaccination programs covering these age groups should be implemented. Age-stratified seroprevalence allows indirect measurement of age-specific HAV infection and is considered to be the best way to evaluate the hepatitis A situation in a country. To our knowledge, there is no information about the results of annual surveillance and seroprevalence alteration rates since the introduction of the routine HAV vaccination program in Turkey.

In this manuscript, we present the current age-stratified seropositivity rates and the simultaneous surveillance results of hepatitis A after the implementation of immunization in the data from a single-center children's hospital in Ankara.

### Material and Methods

This study was performed in a children's hospital in Ankara, the capital of Turkey, between 2013 and 2018. Anti-HAV IgG levels of patients with no chronic disease who were admitted to our hospital between 2013 and 2018 were obtained retrospectively from the hospital database system. The study was approved by the Local Ethics Committee of our hospital (No.: 2018-147). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee (Human Studies Subcommittee at the VA Connecticut Healthcare System) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The data of the 2015 were excluded from the study due to an insufficient number of individuals for comparison. Information regarding sex (biologic), age, diseases, and laboratory results was evaluated retrospectively from the hospital's digital records. Individuals with no chronic disease who were admitted to the outpatient clinics for any reasons were included. Patients diagnosed as having primary immunodeficiency and those who had secondary immunodeficiency due to chemotherapy or other medications (organ transplantation) were excluded.

The subjects were classified into six different age groups:  $\leq 2$  years as group 1, 2–6 years as group 2, 7–11 years as group 3, 12–18 years (adolescence) as group 4, 19–24 years (young adult) as group 5, and 25 years and older (adult) as group 6.

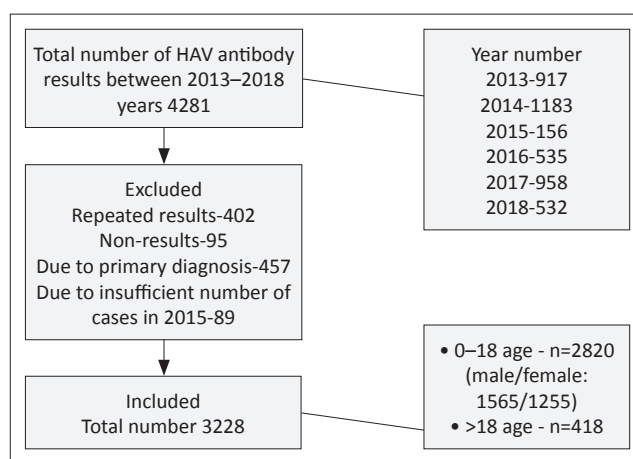
Sera were tested at the time of hospital admission for the presence of IgG against HAV using a microplate-based enzyme-linked immunosorbent assay (Etimax-3000, Diasorin) according to the manufacturer's instructions (19).

### Statistical Analyses

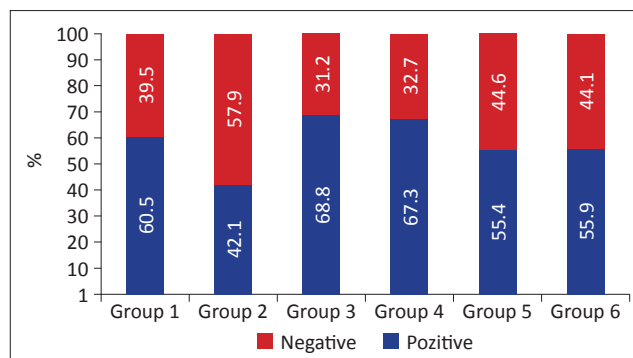
All of the variables were categorical. Therefore, descriptive statistics are expressed as frequency and percentages. Variables were transformed into cross-tabulations and analyzed using Pearson's Chi-square test and Bonferroni correction. All data were statistically analyzed using the IBM SPSS Statistics Version 24 (SPSS Inc., Chicago, IL) and the level of significance was taken as 0.05.

### Results

A total of 3238 subjects were enrolled in the study (children aged 0–18 years,  $n=2820$  and adults aged  $>18$  years,  $n=418$ )



**Figure 1.** Flowchart of the cases included according to the HAV seroprevalence results between the years 2013–2018



**Figure 2.** The overall percent of HAV seropositivity according to age groups

(Fig. 1). In the children group, the percentage of male sex was 55.5% (1565 of 2820). The overall percentage of seropositivity was 40.7% (1147 of 2820) in the children group. The overall percent of seropositivity was 60.5% in group 1 ( $\leq 2$  years), 57.9% in group 2 (2–6 years); 31.2% in group 3 (7–11 years); 32.7% in group 4 (12–18 years); 44.6% in group 5 (19–24 years) and 73.9% in group 6 ( $>25$  years) (Fig. 2).

The percentage of seropositivity from 2013 and 2018 was 60.5% and 71.4% in group 1, 44.4% and 84.6% in group 2, 38% and 39.6% in group 3, 44.3% and 26.5% in group 4, 50% and 55.6% in group 5, and 80.3% and 72.7% in group 6, respectively. Between 2013 and 2018, the increase in the number of seropositive individuals in group 2 ( $p<0.01$ ), and the decrease in groups 3 and 4 were statistically significant ( $p=0.028$ ,  $p<0.01$ ). When the groups with significant differences were compared according to the years, it was found that the percentage of seropositivity in 2018 in group 2 was significantly higher than that of all other years, there was no significant difference between the years for group 3, and group 4 (adolescent age) was significantly lower than 2018 compared to 2013 (Table 1).

**Table 1. The percentage values of hepatitis A seropositivity through 2013-2018 between the age groups**

	≤2 age (Group 1)		2–6 age (Group 2)		7–11 age (Group 3)		12–18 age (Group 4)		19–24 age (Group 5)		>25 age (Group 6)	
	Positive	p	Positive	p	Positive	p	Positive	p	Positive	p	Positive	p
2013												
n	52	0.27	54 <sub>cde</sub> **	<0.001*	60***	0.028*	86 <sub>cde</sub> **	<0.001*	5	0.60	49	0.76
%	60.5		35.3		38.0		44.3		50		80.3	
2014												
n	83		88 <sub>de</sub> **		62***		136 <sub>cd</sub> **		11		54	
%	63.8		49.4		27.0		37.8		50		71.1	
2016												
n	30		34 <sub>ae</sub> **		34***		32 <sub>ab</sub> **		7		36	
%	51.7		72.3		31.2		22.2		38.9		75	
2017												
n	51		83 <sub>abe</sub> **		40***		77 <sub>ab</sub> **		8		62	
%	55.4		74.1		25.5		27.2		33.3		72.10	
2018												
n	25		41 <sub>abcd</sub> **		38***		41 <sub>a</sub> **		10		40	
%	71.4		95.3		39.6		26.5		55.6		72.7	

$\alpha=0.05/10=0.005$ ; \*: Pearson Chi-square Test; \*\*: Post-hoc Bonferroni correction; \*\*\*: No difference; a: Different from the year 2013; b: Different from the year 2014; c: Different from the year 2016; d: Different from the year 2017; e: Different from the year 2018

**Discussion**

Improvements in sanitation, and the development of highly efficacious vaccines and vaccinations programs have markedly reduced the worldwide occurrence of HAV infection over the past quarter-century (4, 13). Besides the decrease in the incidence of HAV infection, the mean age of population immunity is increasing, and the proportion of symptomatic cases is increasing as the average age at infection increases (20). The globalization of trade, and travel refugees from third world countries seeking asylum in developed countries are also important drivers of epidemiologic change for HAV. Different vaccination strategies were developed based on different hypotheses for transmission pathways, timings, and populations at risk using epidemiologic and microbiologic evidence. Background surveillance data are important for the evaluation of the initial hypotheses and choice of different measures of infection control (20).

Countries such as Turkey, that have undergone significant socioeconomic changes in recent decades, could pass a transition from having a high incidence of asymptomatic infections in young children to seeing a growing number of outbreaks resulting in symptomatic cases in adults. Kurugol et al. (21) compared their anti-HAV seroprevalence rates in 2008 with a previous study conducted in 1998 involving the same location in Turkey. Their study was conducted prior to the vaccination program and they

revealed that there was a shift in HAV seroprevalence from younger to older age groups and indicated that HAV infection in childhood was decreasing, and the pool of susceptible adolescents and young adults was increasing. From a public health perspective, it is important to identify such epidemiologic shifts because the severity of HAV disease increases with age (2, 10).

In Turkey, the influx of refugees since 2011 has affected the outcomes of the current vaccination program as a result of the unvaccinated refugee population, possibly causing a suitable environment for epidemics such as viral hepatitis (22). Outbreaks have occurred recently in several refugee camps in Europe that are hosting people who have fled from the conflict in Syria, including camps in Germany and Greece (9). Between September 2015 and March 2016, parallel to peaking numbers of asylum seekers arriving in Germany, notified cases of hepatitis A in Germany increased substantially (10).

This study revealed that the overall HAV seroprevalence in Turkish children (age 0–18 years) was 40.7% and in young adults 44.6% and 73.9% in adults. With the result of the overall seropositivity, Turkey is still in the intermediate zone of endemicity.

In a study from Turkey conducted between 2011–2013, HAV seroprevalence in a total of 3868 patients aged 1–79

years in Istanbul was detected as 64.8%, age-specific prevalence was 55% in children 0–16 years and 47% in those aged 17–30 years (23). One of the studies published in 2002 before the immunization program for HAV with 4462 subjects age under 30 years in nine provinces of Turkey identified an overall HAV seroprevalence rate of 71.3%, and 50% of Turkish children were seropositive for HAV by the age of 10 years (24). In our study, data were evaluated as subgroups within child age groups as preschool, school age, and adolescent. The seroprevalence rates of children who were born before and after the onset of routine vaccination were compared using annual data over a 6-year period after vaccination. The percentages of seropositivity from 2013 to 2018 were significantly increased in group 2 (vaccinated) and were significantly decreased in group 3 and 4 (unvaccinated, age 7–18 years). This can be interpreted as a favorable outcome for the vaccinated population, but decreased seropositivity in later stages of life may also indicate that this age group may be susceptible to infection.

The surveillance results of HAV infection in Turkey between 2012 and 2017 were presented with the permission of the relevant department epidemic diseases affiliated to the Ministry of Health (25). According to the data of the Ministry of Health, the morbidity and mortality rates declined from 2007 through 2017. The disease rate fell from 3624 cases in 2007 with a morbidity rate 5,28/100,000, to 471 cases in 2017, with a morbidity rate of 0.58/100,000.

#### Limitations

We did not give the coverage rate results of HAV vaccination because the Ministry of Health in Turkey has not yet gathered or reported on this data. We presented the number of cases of HAV infections between 2007 and 2017, but we have not yet obtained data of how many cases were adolescents and young adults. The number of patients from the adult age group was insufficient to elaborate on this trend.

The percentage of various age groups of individuals who test positive for anti-HAV IgG provides information about both recent and past epidemiologic patterns. Anti-HAV antibodies cannot explain whether this is natural or vaccine-related immunization.

In the present study, we analyzed the age-specific seropositivity rates of HAV over the past 6 years. As far as we know, this is the first study to explore the age-specific HAV infection seroprevalence among children and adults after the addition of the HAV vaccine to the national vaccination program.

Our research revealed that the decrease of seropositivity in the unvaccinated 7–18 age group was statistically significant and this can be interpreted as the age of encounter with hepatitis shifting towards older ages in Turkey. Implementation of an HAV vaccination covering this age group is required and routine, nationwide, government-sponsored vaccination of adolescents and young adults against HAV could be useful.

**Ethics Committee Approval:** Ethics committee approval was received for this study (No.: 2018-147).

**Informed Consent:** Patient consent was not obtained in the study due to the retrospective design.

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

**Author Contributions:** Concept - A.O.A.; Design - A.O.A., B.B.A.; Supervision - A.K.U., D.T.; Data Collection and/or Processing - A.O.A.; Analysis and/or Interpretation - A.A.A., B.Y.B., A.K.U.; Literature Review - A.O.A.; Writing - A.O.A.; Critical Review - A.K.U., D.T.

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