original article

Hepatitis A virus infection and seroprevalence, Istanbul, Turkey, 2020-2023

Mehmet Karabey,[a] Sema Alacam,[a] Nuran Karabulut,[a] Hayriye Uysal,[b] Alper Gunduz,[a] Ozlem Altuntas Aydin[a]

From the [a]Department of Virology, Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey, [b]Department of Microbiology, Istanbul University Faculty of Medicine, Istanbul, Turkey

Correspondence: Dr. Mehmet Karabey · Department of Virology, Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey · karamehmetbey@gmail.com · ORCID: https://orcid.org/0000-0002-7394-186X

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BACKGROUND: Hepatitis A infections continue to be a major global public health problem. The epidemiology and seroprevalence of hepatitis A virus (HAV) have important public health implications. This study aimed to retrospectively examine the hepatitis A cases and hepatitis A seroprevalence in our region in our hospital with the highest number of inpatient and outpatient cases in Istanbul.

OBJECTIVE: Determination of hepatitis A cases and seroprevalence.

DESIGN: Cross-sectional.

SETTING: Tertiary care.

PATIENTS AND METHODS: A total of 39 385 individuals who were tested for Anti-HAV IgM and Anti-HAV Total (IgM+IgG) antibodies between May 2020 and September 2023 and were included in this study. Hepatitis A specific IgM and Total (IgM+IgG) antibodies were determined using the enzyme-linked immunosorbent assay method.

MAIN OUTCOME MEASURE: Hepatitis A seroprevalence.

SAMPLE SIZE: 46 721

RESULTS: The study included a total of 46 721 samples from 39 385 individuals who were tested for hepatitis A serology. The median age of the 39385 individuals included in the study was 28 (interquartile range [IQR]; 22-46), with 58.74% being female and 4.07% (n=1163) being foreign nationals. Reactivity was detected in 91 of the 25 442 patients tested for HAV-IgM. Among these patients, 33 (0.13%) had acute hepatitis A infection, while 58 (0.23%) were considered false positives. Of the acute hepatitis A patients, 13 (0.09%) were women, and 22 (0.80%) were children. Acute hepatitis A was most commonly observed in the 6-9 and 15-18 age groups, with 7 cases each. The seroprevalence rate of hepatitis A was 67.23% among 33 683 individuals. Of those tested for HAV-Total, 13 132 (64.92%) were women, and 2533 (64.88%) were children. The lowest seroprevalence rate among age groups (35.91%) was in the 15-18 age year range, while the highest seroprevalence (98.34%) was detected in individuals aged 60 years and above.

CONCLUSION: With a seroprevalence rate of 67.23%, our region is still considered a medium-endemic area for hepatitis A, and it is crucial to continue administering the HAV vaccine as currently included in the childhood vaccination schedule in our country. Additionally, the significantly low hepatitis A seropositivity, particularly in the 15-18 and 19-24 age groups, indicates the need to promote catch-up vaccination for young adults. Since our study covers a large population, it can serve as a guide regarding the serological status of hepatitis A in Istanbul.

LIMITATIONS: Since vaccination information for the study population was not available, it was not possible to distinguish between seroposi-

tivity due to vaccination or natural immunity. Despite being conducted in Istanbul, a cosmopolitan city, and in the largest city hospital, the results may not be representative of the entire country.

CONFLICT OF INTEREST: None.

Hepatitis A virus (HAV) infection is a vaccine-preventable infectious disease that is seen worldwide, particularly prevalent in underdeveloped and developing countries.[1] HAV is an enveloped, single-stranded, positive-sense RNA virus that belongs to the Hepatovirus genus of the Picornaviridae family.[2] HAV has seven genotypes (I [A, B], II, III [A, B], IV, V, VI, and VII), of which genotypes I, II, III, and VII cause infections in humans.[3] HAV transmission primarily occurs via the fecal-oral route. Its incidence and clinical course vary with age and are strongly associated with socioeconomic and hygiene conditions.[4]

HAV generally causes a self-limiting liver infection and does not become chronic, but it can sometimes progress to severe disease and fulminant liver failure. The severity of the disease is related to age.[5] The infection is common in low- and middle-income countries where health conditions and hygiene practices are poor. Most children (90%) are infected before the age of 10, usually asymptomatically.[6] However, in adults, the clinical presentation can be severe and prolonged.[7] The mortality rate from HAV infection is 0.1% in individuals under 15 years old but increases to 2.1% in those over 40 years old.[5]

According to World Health Organization (WHO) reports, HAV caused 11 000 deaths in 2015 and 7314 deaths in 2016, accounting for 0.8% and 0.5% of viral hepatitis deaths in those years, respectively.[8] Hepatitis A occurs sporadically and in outbreaks worldwide, with a tendency for cyclical recurrence. Serious outbreaks have been linked to food or water contaminated with HAV. One such outbreak in Shanghai in 1988 affected approximately 300 000 people.[6]

In underdeveloped and developing countries, the disease usually occurs in early childhood, conferring lifelong immunity after infection. In recent years, improvements in hygienic conditions have shifted the usual age of HAV infection from early childhood to adolescence or adulthood.[9] A safe and effective vaccine against HAV has been available in Europe since 1991 and in the USA since 1996. The WHO advocates two approaches for measuring HAV seroprevalence to determine HAV endemicity in countries where unvaccinated individuals are the majority, based on the detection of anti-HAV IgG antibodies. The first approach relies on determining seroprevalence in the entire population, classifying endemicity as high if seroprevalence is >50%, moderate if 15-50%, and low if <15%. The second approach uses age-specific seroprevalence, classifying endemicity as high (≥90% by age 10), moderate (≥50% by age 15, <90% by age 10), low (≥50% by age 30, <50% by age 15), and very low (<50% by age 30). The age-related approach is thought to provide more accurate and precise estimate.[10]

The WHO recommends universal vaccination for countries with moderate endemicity and vaccination only for at-risk groups in countries with low and very low endemicity.[11] Turkey is classified as a country with moderate endemicity for hepatitis A infection. The HAV vaccine was included in the childhood vaccination schedule in Turkey at the end of 2012, administered in two doses at 18 and 24 months of age to children born as of March 2011.[12] This study aimed to determine and examine hepatitis A cases and the seroprevalence of hepatitis A in our region at the hospital in Istanbul with the highest number of inpatients and outpatients.

PATIENTS AND METHODS

This retrospective study included cases analyzed for Anti-HAV IgM and Anti-HAV Total (IgM+IgG) antibodies at our hospital's Medical Virology Laboratory between May 2020 and September 2023. This study was approved by the Başakşehir Çam and Sakura City Hospital Ethics Committee (Reference No: 559).

Hepatitis A specific IgM and total antibodies were analyzed using the Elecsys Anti-HAV IgM (clinical sensitivity: 100%, The 95% CI for the sensitivity was 98.3-100%; clinical specificity: 100%, The 95% CI was 99.7-100%) and Elecsys Anti-HAV II (clinical sensitivity: 100%, The 95% CI for the sensitivity was 98.57-100%; clinical specificity: 99-66%, The 95% CI for the sensitivity is 99.00-99.93%). (Roche Diagnostics, Germany) commercial kits with the Roche Cobas e 801 (Roche, Germany) device, employing the Electro chemiluminescence immunoassay (ECLIA) method. Internal quality controls were included in each assay. Samples with a cut-off index of ≥1.0 for the Anti-HAV IgM test and ≤1.0 for the Anti-HAV total test were considered positive. Samples that tested positive for HAV IgM were re-analyzed. Samples from patients with HAV IgM posi-

tivity but with clinical and other laboratory findings inconsistent with acute hepatitis A were considered false positives.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (Armonk, NY: IBM Corp). The normality of the variables was assessed using visual methods (histograms and probability plots) as well as the Kolmogorov-Smirnov test. Age and laboratory parameters that did not follow a normal distribution were compared between groups using the Mann-Whitney U test, while those with a normal distribution were analyzed using the *t* test. Categorical variables such as sex, nationality, age group (child/adult), and years were compared using Pearson's Chi-Square or Fisher's Exact tests, as appropriate. Odds ratio (OR) and 95% confidence intervals confidence intervals were calculated to assess the associations between categorical variables. A *P* value of less than .05 was considered statistically significant.

RESULTS

This study included a total of 46721 samples from 39385 individuals who were tested for hepatitis A serology. The median age of the 39 385 individuals included in the study was 28 (interquartile range [IQR]; 22-46), with 58.74% being female and 4.07% (n=1163) being foreign nationals.

Table 1. Demographic, laboratory and clinical data of the study population for HAV IgM.

	Total n (%)	HAV-IgM			*p*
		Positive n (%)	OR (95% CI)	False Positive n (%)	
Number	25442	33 (0.13)		58 (0.23)	
Age, median (interquartile range)		15 (8.50-21.50)		34.50 (24-55.25)	
Sex					
Male	10850 (42.6)	20 (0.18)	2.07 (0.51- 3.25)	23 (0.21)	.102
Female	14592 (57.4)	13 (0.09)		35 (0.24)	
Child	2752 (10.8)	22 (0.80)	16.62 (5.83-47.32)	6 (0.22)	**<.001**
Adult	22690 (89.2)	11 (0.05)		52 (0.23)	
Nationality					
Turkish	24279 (95.4)	27 (0.11)	0.22 (0.08-0.56)	55 (0.23)	**<.001**
Foreigner	1163 (4.6)	6 (0.52)		3 (0.26)	
Years					
2020	1377	3 (0.22)			
2021	8718	9 (0.10)	0.47 (0.13-1.75)		**.041**
2022	9115	10 (0.11)	0.50 (0.20-1.83)		
2023	6232	11 (0-18)	0.81 (0.23-3.01)		
Laboratory data					
HAV IgM, COI, median (IQR)	91	11.5 (8.7-13.6)			
AST(U/L), mean	32	1673.56 (168.60)			
ALT(U/L), mean	32	1087.75 (145.16)		1.4 (1.1-1.9)	**.001**
GGT(U/L), mean	31	146.23 (13.79)			
Total bilirubin (mg/dL), median, (IQR)	31	474.00 (228-759)			
Direct bilirubin (mg/dL), median, (IQR)	31	366.00 (119-525)			

COI: cutoff index.

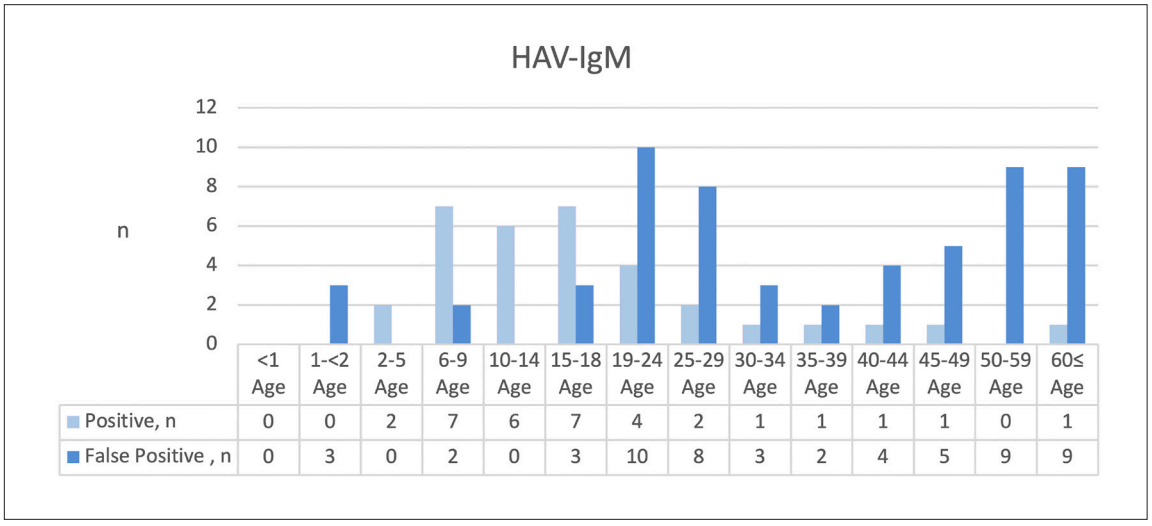


Figure 1. HAV IgM positivity and false positivity by age groups.

Table 2. Demographic and laboratory data of the study population for HAV total.

	Total n (%)	HAV-Total		OR (95% CI)	*p*
		Positive n (%)	Negative n (%)		
Number	33683	22644 (67.23)	11039 (32.77)		
Age. median (interquartile range)		33 (23-51)	23 (20-27)		**<.001**
Sex					
Male	13456 (39.9)	9512 (70.69)	3944 (29.31)	1.30 (1.24-1.37)	**<.001**
Female	20227 (60.1)	13132 (64.92)	7095 (35.05)		
Child	3904 (11.6)	2533 (64.88)	1371 (35.12)	0.89 (0.83-0.96)	**<.01**
Adult	29779 (88.4)	20111 (67.53)	9668 (32.47)		
Nationality					
Turkish	32379 (99.1)	21636 (68.82)	10743 (33.18)	0.59 (0.52.-0.67)	**<.001**
Foreigner	1304(0.9)	1008 (77.30)	296 (22.70)		
Years					
2020	2746	1597 (58.16)	1149 (41.84)		
2021	10570	7424 (70.24)	3146 (29.76)	1.70 (1.56-1.85)	
2022	10776	7374 (68.43)	3402 (31.57)	1.56 (1.43-1.70)	
2023	9591	6249 (65.15)	3342 (34.85)	1.35 (1.23-1.47)	

The HAV-IgM test was performed on 25 442 individuals, and 91 tested positive for HAV IgM. Among these cases, 33 (0.13%) were diagnosed with acute hepatitis A infection, and 6 (0.52%, 6/1163) were foreign nationals. HAV IgM; 95% CI prevalence: 0.0857%-0.1743%. Acute hepatitis A was significantly higher in foreign nationals (*P*=.001). Twenty (60.61%) of the acute hepatitis A cases were male, with no significant difference between genders (*P*=.102). Hepatitis A infection was detected in 66.67% (n=22) of the children, which was statistically higher compared to adults (*P*<.001) (**Table 1**). The highest number of acute hepatitis A cases was found in the 6-9 and 15-18 age groups (**Figure 1**). The number of cases was higher in 2020 compared to other years (*P*=.041) (**Table 1**).

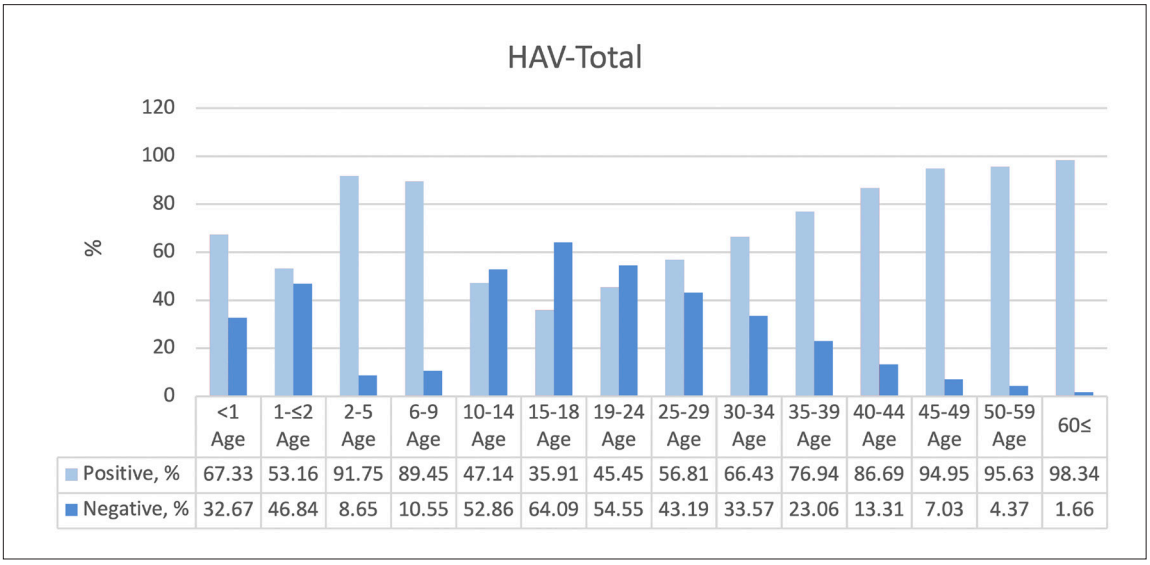
Of the 91 cases that tested positive for HAV IgM, 58 (63.74%) were considered false positives due to the lack of clinical and laboratory consistency with hepatitis A infection. Thirty-five (60.34%) of these false positives were female, with no significant difference between genders (*P*=.102). The rate of false positivity was significantly higher in adults (n=52, 89.66%) (*P*<.001). False positivity was most common in the 19-24 age group (**Figure 1**). Co-infections were investigated in the 58 patients with false positive results, revealing four acute hepatitis B, one acute lymphoblastic leukemia (ALL), one kidney stone, two COVID-19, one biliary atresia, and one case of false positivity due to HAV vaccination.

The HAV-total test was performed on 33 683 individuals, with a seropositivity rate of 67.23%. HAV Total; 95% CI: 66.73%-67.73%. Hepatitis A seropositivity was significantly higher in foreign nationals (77.30%, 1008/1304) (*P*<.001). Hepatitis A seropositivity was also significantly higher in males (70.69%) compared to females (64.92%), and in adults (67.53%) compared to children (64.88%) (*P*<.001 and *P*<.001, respectively) (**Table 2**).

Hepatitis A seropositivity was 82.79% (n=2167) up to 10 years of age, 72.26% (n=3075) up to 15 years, and 52.61% (n=19 273) up to 30 years. The lowest seropositivity was observed in the 15-18 age group (35.91%), while the highest was in the ≥60 age group (98.34%) (**Figure 2**). The median age of hepatitis A seropositive individuals was significantly higher than that of seronegative individuals (*P*<.001) (**Table 2**).

DISCUSSION

Currently, the incidence of HAV infection is decreasing, and the age of exposure to the virus is shifting to older age groups due to improved hygiene and sanitation conditions.1 In our hospital, among the 39 385 individuals included in the study between May 2020 and September 2023, the HAV-IgM test was performed on 25 442 individuals, with 33 (0.13%) being evaluated as having acute hepatitis A. Of the acute hepatitis A patients, 22 (0.80%) were children. In a study conducted in Turkey, similar to our study, the anti-HAV IgM positivity rate was 0.2%.1 In another study conducted in Somalia, the anti-HAV IgM positivity rate was reported as 33.8% (390/1153).[13] In another study conducted in Serbia, between 2008 and 2017, a total of 765 patients and 28 hepatitis A outbreaks were reported, and the



	<1 Age	1-≤2 Age	2-5 Age	6-9 Age	10-14 Age	15-18 Age	19-24 Age	25-29 Age	30-34 Age	35-39 Age	40-44 Age	45-49 Age	50-59 Age	60≤
Positive, %	67.33	53.16	91.75	89.45	47.14	35.91	45.45	56.81	66.43	76.94	86.69	94.95	95.63	98.34
Negative, %	32.67	46.84	8.65	10.55	52.86	64.09	54.55	43.19	33.57	23.06	13.31	7.03	4.37	1.66

Figure 2. HAV-total positivity by age groups .

incidence rate during these years was characterized by an average of 4.0/100 000 (range: 0.9-11.2/100 000).[14] Hepatitis A infection was statistically higher in children compared to adults. Similar to this study, another study conducted in Libya found that 92.6% of acute hepatitis A cases were seen in children aged 5 to 20 years.[15] In almost all laboratory data of acute hepatitis A cases, levels of AST, ALT, GGT, total, and direct bilirubin were elevated. In a study conducted by Rycroft et al, peak ALT and bilirubin values in confirmed acute hepatitis A cases were 13 times and 6.5 times higher, respectively.[16] These results highlight the importance of evaluating serum biochemistry in conjunction with the clinical picture when interpreting HAV IgM results in the diagnosis of acute hepatitis A patients.

Of the 1163 foreign nationals tested for HAV-IgM, 6 (0.52%) were diagnosed with acute hepatitis A. The diagnosis of acute hepatitis A was significantly higher in foreign nationals (*P*=.001). A study conducted in Syria in 2000 reported a hepatitis A seroprevalence of 89%.[17] Another study conducted in Syria in 2018 reported a total of 638 suspected acute hepatitis infection cases.[18] This situation cannot be explained solely by hygiene and sanitation under the same country conditions, but there is a strong correlation between socioeconomic status and HAV. This relationship can be explained by higher income, higher education levels, smaller family sizes, less crowding in homes, and other indicators related to lower socioeconomic status.

When evaluating acute hepatitis A cases by age group, the highest incidence was in the 6-9 and 15-18 age ranges, with 7 cases each. False positives were observed in 10 cases in the 19-24 age range and 9 cases each in the 50-59 and 60+ age ranges. In a study conducted in Turkey, similar to our study, the highest number of acute hepatitis A cases was in the 10-14 age group (12 cases) and the 15-19 age group (19 cases).[1] A study conducted in the United States reported that the rate of HAV infection cases per 100 000 population decreased 17.3 times, from 10.4 in 1990-1998 to 0.6 in 2007-2015, and then increased to 2.8 in 2016-2020. Between 1990 and 1998, the highest incidence rates were reported in individuals under 40 years of age. Throughout the analysis period, the highest age-specific HAV infection rates per 100 000 population occurred in increasingly older age groups; as of 2016-2020, the highest rates (7.0 and 5.0) were seen among individuals aged 30-39 and 40-49, respectively.[19] Another study conducted in Somalia reported that acute hepatitis A infection was most common in the first five years of life (46.8% of all positive cases).[13] This early age infection can be explained by direct contact with unsafe water and food due to inadequate hygiene and sanitation in underdeveloped and developing countries.

Of the 25 442 individuals tested for HAV-IgM, 58 (0.23%) were evaluated as false positives. Among the false positive individuals, 6 (0.22%) were children. False positivity was significantly higher in adults (*P*<.001). The higher incidence of false positivity in adults or individuals from developing countries may be due to their higher likelihood of having had hepatitis A during childhood. When comorbidities were examined in the patients identified as false positives, 9 individuals had comorbidities, and one case was attributed to false reactivity due to the hepatitis A vaccine. Although rare, vaccine-induced IgM positivity can occur in preventable viral infections. In these cases, the lack of clinical evidence and laboratory consistency for acute hepatitis A suggests that false positivity may result from comorbid conditions.

In this study, conducted at the largest city hospital in Istanbul with a sample size of 33 683 individuals, the HAV seroprevalence rate was 67.23%. Several studies conducted in Turkey have reported varying HAV seroprevalence rates: 79.1% in Yozgat in 2019 (n=1473),[9] 87.3% in Erzurum in 2020 (n=25 007),1 74% in İzmir in 2019 (n=989),[20] and 58.9% in Samsun in 2019 (n=2510).[21] The prevalence of hepatitis A is fundamentally linked to socioeconomic status, and HAV is endemic particularly in countries with lower socioeconomic status. We believe that the main reason for the variation in HAV seroprevalence rates across different provinces in Turkey is the differing socioeconomic conditions. Improving socioeconomic levels, raising educational standards, ensuring the widespread availability of safe drinking water, addressing infrastructure and sanitation issues, and emphasizing the importance of hygiene and vaccination could help reduce HAV seroprevalence.

According to WHO's endemicity classification, our country is in the intermediate endemic region. In our study, HAV seropositivity was 82.79% up to 10 years of age, 72.26% up to 15 years of age, and 52.61% up to 30 years of age, which is consistent with WHO's intermediate endemicity classification. WHO recommends universal childhood vaccination against hepatitis A in regions with intermediate endemicity, while targeted vaccination is suggested in regions with low endemicity. In Turkey, the HAV vaccine was included in the childhood vaccination schedule at the end of 2012, administered in two doses at 18 and 24 months of age, in accordance with WHO recommendations.

When examining HAV seroprevalence by age groups, a study by Akbulut UE et al in 2022 the lowest

seroprevalence was in the 1-2 age year group (29.4%) and the highest in those over 41 years old (88.9%).[13] In another study by Çalık Ş et al in 2019, seropositivity was 20.8% in the 10-14 age group, 28.9% in the 15-19 age group, 87.5% in the 0-4 age group, 97.6% in the 45-54 age group, and 95.8% in those aged ≥55 years.[20] In a study conducted in Erzurum, HAV seropositivity was 87.5% in the 0-4 age group, 89.8% in the 25-29 age group, 96.1% in the 30-39 age group, and highest at 99.3% in those over 60 years old.[1]

In our study, the distribution of HAV seropositivity rates by age groups showed the lowest immunity rates in the 15-18 (35.91%) and 19-24 (45.45%) age groups. We believe the low immunity in these age groups is due to the fact that these groups were not yet included in the routine HAV vaccination program in our country during their vaccination age. In this study, seroprevalence was over 94% after the age of 45, with the highest seroprevalence observed in the ≥60 age group at 98.34%. HAV seroprevalence shows a gradual increase with age. In the 2-5 age group, a high immunity rate of 91.75% was observed following vaccination. The relatively high immunity of 67.33% in the <1 age group indicates the presence of maternal antibodies. When examining HAV seropositivity in children and adults, it was significantly higher in adults. This higher rate in adults is due to their higher likelihood of encountering HAV during childhood and the vaccination age being during childhood.

In our study, HAV seroprevalence was significantly higher in males (70.69%). Many studies have examined the impact of gender differences on HAV seroprevalence. In a study by Çeviker et al, HAV seropositivity was 75.3% in females and 33.1% in males.[21] In another study by Gözü Pirinççioğlu et al, seropositivity was 49.8% in females and 41.2% in males.[4] In a study by Yilmaz et al, HAV seropositivity was 86.4% in females and 88.5% in males.[1] In a study conducted in Tunisia, there was no statistically significant difference in HAV seropositivity between males and females, with rates of 84.2% and 85.2%, respectively.[5] The relationship between gender and hepatitis A infection may be explained by regional behavioral differences and gender-specific differences in hygiene and dietary habits. Acute hepatitis A infection and HAV seroprevalence were significantly higher in foreign nationals. Most of the foreign nationals in Turkey, especially those who came from Syria in 2011, come from countries with poor socio-economic conditions and limited access to clean water and hygienic food. Additionally, crowded living conditions, such as multiple people sharing the same home, facilitate the spread of hepatitis A.

This study has some limitations. Firstly, since vaccination information for the study population was not available, it was not possible to distinguish between seropositivity due to vaccination or natural immunity. Secondly, despite being conducted in Istanbul, a cosmopolitan city, and in the largest city hospital, the results may not be representative of the entire country.

In conclusion, with a seroprevalence rate of 67.23%, our region is still considered to have intermediate endemicity for hepatitis A. Therefore, it is crucial to maintain the current implementation of the HAV vaccine in the childhood vaccination schedule in our country. The significantly low incidence of acute hepatitis A cases in children under 5 years old is a result of Turkey's childhood HAV vaccination policy. Additionally, the notably low hepatitis A seropositivity in the 15-18 and 19-24 age groups indicates that the hepatitis A vaccine should also be administered to young adults. Determining seroprevalence is valuable for preventing outbreaks, developing protection policies such as sanitation and hygiene, and particularly for establishing vaccination programs.

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