STATUS OF VIRAL HEPATITIS IN UŞAK PROVINCE, TURKEY: A 9-YEAR RETROSPECTIVE ANALYSIS

Serdar Güngör
Department of Clinical Microbiology, Faculty of Medicine, Uşak University, Uşak, Turkey

ABSTRACT

Background*: Viral hepatitis is a significant global health problem. Millions of people are affected by chronic hepatitis, and thousands are lost every year. This study aimed to determine viral hepatitis status in the Uşak Province of Turkey between 2009 and 2017.*

Methods*: The serological data from assays for anti-HAV immunoglobulin (Ig) G, anti-HAV IgM, HBV surface antigen (HBsAg), anti-HBs, anti-HBc (HBV core antigen) IgG, HBV e-antigen (HBeAg), anti-HBe, and anti-HCV were retrospectively analyzed in terms of gender and age distributions.*

Results*: The rates of positivity in assays were as follows: anti-HAV IgG: 73.89%, anti-HAV IgM: 0.77%, HBsAg: 2.51%, anti-HBs: 44.66%, and anti-HCV: 1.37%. Of anti-HBs-positive individuals, 33.33% were also positive for anti-HBc IgG. A significant decreasing trend was observed for anti-HCV positivity. The prevalence of HBsAg did not change significantly over the years, but significantly decreased in males. The anti-HAV IgG positivity and anti-HCV positivity was higher in females. The prevalence of HBsAg was significantly higher in males. The individuals between the ages of 6 and 24 were the most sensitive group for hepatitis A infection. HBsAg positivity was the highest in the 55-64 age group (4.04%), and anti-HCV prevalence was the highest in the over-65 age group (2.89%).*

Conclusion*: These results indicate that the prevalence of anti-HCV is low and decreasing, HBsAg prevalence is at the intermediate level and stable, anti-HAV IgG prevalence is high enough to provide herd immunity for the population in Uşak Province.*

Keywords: *viral hepatitis, hepatitis A, hepatitis B, hepatitis C, epidemiology, Turkey.*

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Introduction

Hepatitis is defined as liver inflammation and is a severe public health problem affecting the global population. Although there are many causes of hepatitis, viruses are among the leading causes. Viruses causing viral hepatitis are generally classified as hepatitis A through E. Hepatitis A and E infections develop as a spontaneous acute infection with the transmission of the virus from contaminated food and water and usually end with clearing the virus from the body by the immune system. However, infections with Hepatitis B, C, and D viruses (HBV, HCV, and HDV, respectively) are considered more critical since they may also cause chronic infections. HBV, HCV, and HDV are transmitted by exposure to infected blood. In addition to blood, HBV and HDV are also spread by contact with other body fluids. HDV infection occurs only in people infected with HBV[1,2].

Acute viral hepatitis is mainly caused by the Hepatitis A virus (HAV). HAV-related hepatitis is a self-limiting disease and does not develop into the chronic stage but has serious public health and socioeconomic consequences, especially when the adult population is infected[3].

Vaccines for HAV were available since 1996 and significantly contributed to a decrease in the incidence of HAV infection worldwide[4,5]. The disease incidence shows a strong relationship with access to clean water resources, socioeconomic indicators, and hygiene standards[6]. The prevalence of HAV infection varies by country, and it is generally categorized as intermediately endemic in Turkey[7].

Chronic viral hepatitis is mainly stemmed from hepatitis B. The clinical course in HBV infection is related to the age of the patient. Generally, it is asymptomatic with a 90% frequency in childhood, while it is symptomatic with a frequency of 20-30% in adults. About 1% of acute hepatitis B in adults has a fulminant course and may require liver transplantation. HBV infection becomes chronic in 90% of the cases if it occurs in the perinatal period, 20-30% if transmitted until the age of five, and 2-5% in adulthood[8]. Hepatitis B is a preventable disease. There are effective HBV vaccines that have been available since 1981, and that had a significant impact on the prevention of HBV transmission worldwide[9,10]. Still, it was estimated that 235 million people were affected, and 877,000 people died from hepatitis B-related liver diseases worldwide in 2015[11]. The global prevalence of HBV was estimated to be 3.9% (3.4%-4.6%) in 2016[12]. In Europe, the prevalence was 1.6%, and in the Eastern Mediterranean region, the prevalence was estimated to be 3.3%[11]. Turkey has a low intermediate endemic profile for hepatitis B, with a prevalence of about 4%[7,13]. One out of every three people over 18 in Turkey has already been exposed to HBV. It is reported that HBV infection is responsible for 30-40% of cirrhosis cases and 40-50% of liver cancer cases in Turkey[8]. Chronic hepatitis C virus infection is endemic, with approximately 71 million infected individuals accounting for 1% of the world population[11]. The prevalence of HCV infection in the Eastern Mediterranean Region and the European Region are 2.3% and 1.5%, respectively[14]. In Turkey, the prevalence of HCV was around 1% in the adult population[14]. While 30% of the infected people recover within six months without any treatment, 55% to 85% may turn into chronic infections. Although a successful vaccine has not been developed to date, the recovery of more than 95% of people with hepatitis C infection is possible thanks to the highly effective pan-genotypic direct-acting antivirals (DAAs)[1]. DAAs also reduce the risk of death from cirrhosis and liver cancer, but access to drugs is limited in developing countries.

It was globally estimated that 1.37 million people died from cirrhosis and hepatocellular carcinoma due to viral hepatitis. The mortality rate is comparable to tuberculosis but above the mortality rate due to AIDS and malaria in 2015[11]. More than half of the cases of liver transplantations performed in Turkey between the years of 2012-2016 were due to viral hepatitis[8].

The global fight against viral hepatitis strictly depends on epidemiological studies for monitoring epidemics' status, estimation of prevalence, decisions for diagnosis, and treatment policies. The status of viral hepatitis epidemics was unknown in Uşak Province, located in the Aegean region of Turkey. This report presents a retrospective analysis of hospital databases between 2009 and 2017 in Uşak Province.

Material and methods

This longitudinal retrospective study was performed in Uşak Province. Uşak has a population of 370,000 and is located in the Aegean region in western Turkey. In the study, patient records of a hospital were analyzed between 2009 and 2017. The test results of anti-HAV immunoglobulin (Ig) G, anti-HAV IgM, HBV surface antigen (HBsAg), anti-HBs, anti-HBc (HBV core antigen) IgG, HBV e-antigen (HBeAg), anti-HBe, and anti-HCV assays were sorted and grouped according to gender and age. Individuals were clustered in eight age groups: 0-5 years, 6-14, 15-34, 35-44, 45-54, 55-64, and 65 age and older. The anti-HBs assay results were only available for 2015, 2016, and 2017. The anti-HAV IgG test results were available between 2011 and 2017.

The study was conducted according to the declaration of Helsinki and approved by the Uşak University Ethics Committee for non-Interventional Clinical Studies (dated 19/06/2019 and numbered 39-03-12).

Statistical analysis

Descriptive statistics were summarized as a mean ± standard deviation for continuous variables depending on the distribution in the data. Categorical variables were summarized as numbers and percentages. The normality of numerical variables was checked with the Kolmogorov-Smirnov test. In comparing two independent groups, the Independent Samples t-test was used when numerical variables showed normal distribution, and the Mann-Whitney

U test was used in cases where there was no normal distribution. In the comparisons between categorical variables, the Pearson chi-square test was used in 2x2 tables. If any of the values observed in 2x2 tables were below 5, Fisher's exact test was used. If any of the values observed in RxC tables was below 5, then the Fisher-Freeman-Halton test was used. The relationship between numerical variables was examined with Spearman's rho correlation coefficient. Statistical analyses were done with the Jamovi Project (version 1.1.9.0) and JASP (version 0.11.1) programs. Trend analysis was performed using time series regression models for anti-HCV, HbsAg, and anti-HAV IgG. The Eviews package program (version 11.0) was used for time series analysis. The statistical significance level (p-value) was considered as 0.05, and Bonferroni correction was applied when appropriate.

Results

A total of 277,832 individual test results were analyzed, of which 173,132 were female (62.32%), and 104,700 were male (37.68%). The female/male ratio has not been stable and decreased over the years (2.1 - 1.3). The number of females was always higher than males throughout the studies period. A total of 148,211 age data were analyzed. While 148,211 age data were available in the database for the 2009-2010 and 2015-2017 periods, only 25 data points were present in 2011-2014. Therefore, data between 2011 and 2014 were not analyzed in terms of age. There were some irregularities discovered in anti-HAV IgG data for 2009 and 2010; therefore, anti-HAV IgG data was not analyzed for that period. The mean age was 39.9 ± 21.8 years. The mean age of males was significantly higher than that of females (40.8 ± 24.6 vs. 39.3 ± 19.8 years, p<0.001).

Hepatitis A

Anti-HAV IgG antibody was detected in 4,111 (73.89%) of 5,564 individuals between 2011 and 2017 (Table 1). The anti-HAV IgG was detected more frequently in females than males (76.26% and 70.06%, respectively, p<0.001). Anti-HAV-IgM antibody was found in 64 (0.77%) out of 8,363 people. There was a significant decrease in the rate of anti-HAV IgG seropositivity between 2011 and 2017. The change of anti-HAV Ig positivity over the years was given in Table 2. Between 2015 and 2017, anti-HAV IgG seropositivity was 78.01% in the 0-5 age group, while it was 26.85% for the 6-24 age group, and 93.45% for the 25-98 age group. The rates of anti-HAV Igs by the age groups were given in Table 3. The mean age in the anti-HAV-IgG-positive group was 45.8 ± 23 years. No significant difference was found between males and females in terms of age (45.6 ± 22.9 vs. 46 ± 23 years, p=0.706). No significant trend pattern was found in the anti-HAV IgG series.

Serological marker	n (%)	N
Anti-HAV IgG	4111 (73.89)	5564
Anti-HAV IgM	64 (0.77)	8363
HBsAg	6637 (2.51)	264309
HBsAg/HBeAg	163 (19.38)	841
HBsAg/Anti-HBe	615 (71.51)	860
Anti-HBs	24174 (44.66)	54130
Anti-HBs/Anti-HBc IgG	217 (33.33)	651
Anti-HCV	3545 (1.37)	258153
Isolated anti-HBc IgG	4 (4.94)	81

Table 1: The prevalence of viral hepatitis serological markers in Uşak Province, Turkey.
N: total test number, n: number of positive tests

Hepatitis B

Anti-HBs antibody test results were available for 2015-2017 in the hospital database. The distributions of assay positivity over the years for hepatitis B were given in Table 2. Overall, 24,174 (44.66%) individuals were anti-HBs positive out of 54,130 individuals (Table 1). The anti-HBs positivity was significantly higher in males than females (48.2% and 41.7%, respectively, p<0.001).

Assay		2009	2010	2011	2012	2013	2014	2015	2016	2017	p
Anti-HAV IgG	Positive (%)	- (-)	- (-)	587 (76.63)	415 (76.15)	547 (71.04)	598 (75.31)	551 (76.32)	625 (75.85)	788 (68.94)	**0.0061**
	Total	-	-	766	545	770	794	722	824	1143	
Anti-HAV IgM	Positive (%)	12 (1.92)	11 (2.89)	15 (1.82)	9 (1.68)	13 (1.5)	1 (0.12)	2 (0.15)	1 (0.08)	0 (0)	**<0.0001**
	Total	624	381	825	537	864	803	1348	1233	1748	
Anti-HBs	Positive (%)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	1964 (42.07)	9671 (44.54)	12539 (45.19)	**0.0003**
	Total	-	-	-	-	-	-	4668	21715	27747	
Anti-HCV	Positive (%)	534 (1.85)	328 (1.35)	398 (1.59)	401 (1.51)	339 (1.35)	309 (1.21)	368 (1.15)	423 (1.26)	445 (1.2)	**<0.0001**
	Total	28856	24364	25039	26635	25136	25517	32020	33567	37019	
HBsAg	Positive (%)	727 (2.4)	659 (2.62)	680 (2.67)	740 (2.74)	700 (2.72)	588 (2.28)	787 (2.41)	810 (2.35)	946 (2.5)	0.0662
	Total	30291	25143	25462	27000	25714	25788	32678	34419	37814	

Table 2: The distribution of HAV, HBV, and HCV assay results between 2009 and 2017.

A total of 217 (33.3%) people were positive for anti-HBc IgG out of 651 anti-HBs positive individuals. Isolated anti-HBc IgG prevalence was 6.2% (35/563). The mean age for the anti-HBs positive group was found to be 28.4 ± 23.7 years. The mean age of females in the group (30.5 ± 22.2 years) was significantly higher than the mean age of males (26.2 ± 25 years) (p<0.001). The prevalence of anti-HBs by age groups was given in Table 3.

Between 2009 and 2017, a total of 264,308 people were screened for HBsAg. The test was

positive in 6,637 (2.51%) individuals (Table 1). Overall, HBsAg reactivity did not fluctuate drastically over the years and did not change significantly (Table 2). HBsAg positivity was found significantly higher in males (3.2%) than females (2.1%) (p<0.001). It was also found that the HBsAg prevalence significantly decreased in males (3.28% - 2.77%, p<0.001). There was no significant change in females (1.99% - 2.99%, p=0.867). The mean age of the HBsAg positive group was 46.6 ± 17 years. The mean age of HBsAg positive males was significantly higher than that of females (48.4 ± 16.8 vs. 44.9 ± 17.1, respectively, p<0.001). The rate of HBsAg positivity increased significantly with age (p<0.001). HBsAg positivity was the highest in the 55-64 age group (4.04%), followed by the 45-54 age group (3.97%) (Table 3). No significant trend pattern was found in the HBsAg series.

In the HBsAg positive group, 799 people were also tested for anti-HBe antibodies and HBeAg antigen. The rate of anti-HBe positivity (71.51%) in this group was higher than the rate of HBeAg positivity (19.38%) (Table 1).

		0-5 age	6-14 age	15-24 age	25-34 age	35-44 age	45-54 age	55-64 age	65+ age	p
Anti-HAV IgG	Positive (%)	110 (78.01)	31 (14.03)	168 (31.28)	219 (70.42)	281 (94.93)	308 (99.68)	264 (100)	470 (100)	<0.001
	Total	141	221	537	311	296	309	264	470	
Anti-HAV IgM	Positive (%)	2 (0.95)	6 (1.97)	6 (0.81)	0 (0)	2 (0.29)	1 (0.17)	0 (0)	0 (0)	< 0.001
	Total	210	304	741	786	694	592	541	918	
Anti-HBs	Positive (%)	4806 (82.66)	2616 (55.46)	6985 (77.97)	1949 (23.6)	1816 (26.6)	1483 (25.94)	1711 (30.42)	2808 (34.18)	<0.001
	Total	5814	4717	8959	8257	6828	5716	5624	8215	
Anti-HCV	Positive (%)	23 (0.43)	12 (0.27)	134 (0.6)	213 (0.8)	185 (0.96)	216 (1.27)	304 (1.96)	694 (2.9)	<0.001
	Total	5355	4394	22512	26600	19190	17040	15473	23966	
HBsAg	Positive (%)	19 (0.33)	22 (0.45)	326 (1.41)	563 (2.06)	629 (3.18)	700 (3.97)	636 (4.03)	528 (2.19)	<0.001
	Total	5727	4938	23050	27349	19753	17645	15764	24161	

Table 3: The distribution of positivity in HAV, HBV, and HCV assays according to age groups.

Hepatitis C

During the study, the anti-HCV test results of 258,152 people were examined. Between 2009 and 2017, the anti-HCV was detected in a total of 3,545 (1.37%) people (Table 1). The change in anti-HCV positivity through this period is given in Table 2. Overall, anti-HCV reactivity has been found to decrease significantly over the years (1.85% - 1.2%, p<0.001). Anti-HCV positivity was higher in females (1.39%) than males (1.34%), but the difference was not significant (p=0.341). The anti-HCV positivity has decreased significantly over the years in females (1.73% - 1.28%, p=0.002) and males (2.1% - 1.1%, p<0.001). The overall mean age of the anti-HCV positive group was 54.4 ± 20.3 years. There was no significant difference between males and females in terms of mean age (54.6 ± 21.3 vs. 54.3 ± 19.7 years, respectively, p=0.776). The anti-HCV positivity significantly increased with age (p<0.001). Anti-HCV prevalence was the highest in those over 65 (2.89%). The distribution of anti-HCV prevalence in age groups was given in Table 3. The trend analysis using the power regression model revealed a decreasing trend in anti-HCV prevalence over the years (p=0.0031) (Figure 1).

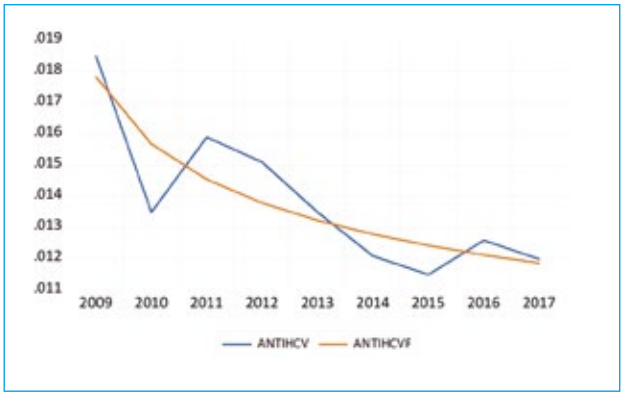

Fig. 1: The change in anti-HCV prevalence and trend model graph through the years. ANTIHCV shows actual data, and ANTIHCVF shows the modeled trend series.

Discussion

In this study, the anti-HAV IgG prevalence was 73.89%, while the prevalence of the anti-HAV IgM antibody was only 0.77% in Uşak Province. As HAV infection usually develops asymptomatically, the investigation of HAV infection's epidemiology is generally based on the prevalence of anti-HAV-IgG antibody, which could be detected throughout the lifetime. The anti-HAV IgM serology test is not sufficient to identify the prevalence of the HAV infection since it could only be caught in a limited time frame during active infection or within 3-6 months after the infection. However, the anti-HAV IgM test can give an idea about the incidence of acute hepatitis A. While the anti-HAV IgM rate was found to be 1.92% in 2009, the rate decreased every year, and anti-HAV IgM was not detected in 2017. Specifically, positive test results decreased ten times in 2014 compared to 2013. This sudden drop may have resulted from the nationwide HAV vaccination, which started at the end of 2012[15]. According to anti-HAV IgM data, it can be concluded that the incidence of acute hepatitis A decreased gradually. The anti-HAV IgG prevalence had also reduced by approximately 7% in Uşak Province in 2017. A decreasing trend in anti-HAV IgG positivity in the population can be attributed to the development of

infrastructure and socioeconomic conditions of the region and the HAV vaccination program[6, 17].

The anti-HAV IgG test results in the 2015-2017 period were also compared by age. It was found that the prevalence of anti-HAV IgG in the 0-5 age group (78.01%) was higher than that in the 6-24 age group (26.25%). The HAV vaccination program is considered to be the main factor for the difference between the two groups. A similar result showing the effect of the vaccination program was demonstrated in a study conducted in İzmir Province in the Aegean region[16]. Low anti-HAV IgG prevalence in school-age children and young adults, but the high prevalence in individuals older than 25 years shows that the incidence of hepatitis A in Uşak Province has decreased in the last two decades[17]. This change can be attributed to the infrastructure improvements, access to clean food and water, and the improvement of socioeconomic status in the last decades[6]. Similar improvements have been reported in other studies conducted in the Aegean region and other parts of Turkey[16,18-20]. With the improvement of sanitation conditions and socioeconomic status, childhood morbidity rate has decreased. Paradoxically, in the following years, the number of symptomatic acute hepatitis A cases has increased among adults[21]. For this reason, an increase in hospitalizations due to hepatitis A should be anticipated in Uşak and similar regions.

Overall, anti-HAV seroprevalence and the hepatitis A incidence have decreased in Uşak Province. These results are also compatible with the general trend of acute Hepatitis A in Turkey[8,17,22]. For a long time, the HAV prevalence was not homogenous in Turkey since HAV was highly endemic in the eastern and southeastern regions[23]. However, in recent years it is observed that there are no significant regional differences in Turkey[8]. The 6-25 age group shows high seronegativity and is at risk for acute hepatitis A. Therefore, it is recommended to apply encouraging programs for catch-up HAV vaccination for young adults and school-age children.

In this study, the prevalence of HBsAg through 2009-2017 was 2.5% in Uşak Province, lower than in other studies conducted in Turkey (13,24,25). Neonatal HBV vaccination, which has been implemented nationwide since 1998, and applying a catch-up vaccination program for risk groups in the following years resulted in a decrease in HBsAg prevalence over the years[25]. However, given that the HBsAg prevalence did not change significantly between 2009 and 2017, it is understood that current vaccination programs would not be sufficient to eliminate the disease, although it restricts the infection by inhibiting the increase of hepatitis B incidence. Also, factors such as improved socioeconomic status, use of disposable medical materials, improved quality and accessibility of health care services, and education could limit the disease[13,24,26]. It was found that the prevalence of HBsAg among males was significantly higher than females, which is compatible with other studies in the literature[13,25-27]. This difference could be attributed to the gender roles in work and social life in the cultural context. Besides, it was observed that the prevalence of HBsAg decreased significantly in males over the years. The decrease of HBsAg prevalence in males could be related to vaccination and increased public awareness, but it could also stem from the sampling method used in the study. Among HBsAg positive groups, the rate of anti-HBe positive individuals (71.2%) was higher than the rate of HBeAg positive individuals (19.4%). Increased frequency of anti-HBe in comparison to low HBeAg positivity in HBsAg positive individuals was reported in other studies conducted in Turkey[13,25]. HBeAg seroconversion is a marker of transition from the active disease to the inactive carrier state, associated with lower rates of disease progression and improved survival rates[28]. These results may also suggest that mutant forms of HBV are circulated in the region[29].

The prevalence of HBsAg was 1.9% in Manisa Province in the Aegean region in 2014[30]. The prevalence of HBsAg reported in the present study (2.5%) is higher, although close to the values found in other studies conducted in the Aegean region (13,30). The higher prevalence of HBsAg is probably related to the utilization of hospital data in this study, which is comparatively more limited than the population-based studies with higher sample volumes and convenient sampling strategies for epidemiological studies[24,25].

The prevalence of anti-HBs (44.66%) in 2015-2017 in Uşak Province was similar to the data (43.6%) derived from a hospital in Ankara in 2000-2010[25]. These results support that the national HBV vaccination program resulted in a stable prevalence of anti-HBs antibodies within the population. However, the current HBV vaccination policy is not sufficient to eradicate the disease. The rate of people who were positive for anti-HBc IgG in the anti-HBs-positive group was found to be 33.3%, which shows

that at least one-third of the population receives immunity by HBV infection[13,25]. Long-term asymptomatic disease, low awareness among those who carry the virus, and vaccination programs that target only newborns and high-risk groups might be the underlying factors for the high rate of horizontal transmission of HBV in the population[13].

The isolated anti-HBc IgG rate was 4.94% (Table 1), which was higher than those previously reported in Turkey[13,31]. Several possible factors might explain the differences, such as infection with the mutated version of the virus, false-negative test results for HBsAg, or false-positive test results for anti-HBc IgG.

In previous studies based on hospital data, anti-HCV prevalence in Turkey ranged from 0.76% to 2.76% (27,32–34). In the current study, the anti-HCV prevalence was found to be 1.37% in Uşak Province. Overall anti-HCV prevalence was found to show a statistically significant downtrend between 2009 and 2017 (1.85% - 1.2%). Such a trend has not been reported for the rate of anti-HCV prevalence in Turkey in the last decade but is compatible with the international trend of hepatitis C[11,35]. The decrease in HCV prevalence is likely related to the treatment with DAAs, the use of disposable medical equipment, increased awareness about risky behaviors and occupations, and the aging population's death. In the last decade, DAAs showed a high treatment success in Turkey due to high antiviral activity that can inhibit different targets in HCV's life cycle[8]. The number of patients treated with DAAs has globally increased since drugs became more available, especially in low-middle income countries[1]. The data in Uşak Province shows that anti-HCV prevalence is within the range of previously reported rates in Turkey and lower than the endemic rate in Europe[11,27,32-34].

A higher anti-HCV prevalence was reported in females than in males in some studies conducted in Turkey[27,33]. Even though anti-HCV prevalence was higher in females than in males in the current study (1.39% vs. 1.34%, respectively), the difference was not statistically significant. Among age groups, the lowest seropositivity rate was in the 6-14 age group (0.27%), and the highest was in those older than 65 years (2.9%) followed by the 55-64 age group (1.96%). Anti-HCV prevalence increased significantly with age in the current study, which is compatible with the worldwide trend[11,36]. Being over 50 was a significant risk factor for hepatitis C in Turkey[13]. Similarly, several previous studies reported that anti-HCV prevalence was higher in those 55 and older compared to other age groups. The high prevalence of anti-HCV in the elderly may be due to factors such as lack of anti-HCV screening in blood transfusion before 1996, absence of effective antiviral therapies, unsafe medical injection practices, and high-risk occupations[13,27,33,34].

Conclusion

In this study, current prevalence data related to hepatitis A, B, and C in Uşak Province between 2009 and 2017 were evaluated. Hepatitis A and C had a decreasing trend, but hepatitis B did not show a significant change. Therefore, the implementation of a vaccination program for those born before 1998 should be considered to eliminate hepatitis B. Programs should be implemented for screening of asymptomatic HBV carriers in the population. It is necessary to develop HAV vaccine programs, especially for school-age children and young adults, to prevent HAV outbreaks that may arise during ongoing global mass migrations between countries. Due to the high prevalence of hepatitis C among the elderly, serological testing programs for elders and activities to increase public awareness should be considered.

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Corresponding Author:
Serdar Güngör, MD, Assistant Professor
Department of Clinical Microbiology
Uşak University Faculty of Medicine
Ankara İzmir Yolu 8.Km Bir Eylül Kampüsü
Merkez / UŞAK
Email: serdar.gungor@usak.edu.tr
(Turkey)