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The chronological changes in the seroprevalence of anti-hepatitis A virus IgG from 2005 to 2019

Experience at four centers in the capital area of South Korea

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Abstract

Although universal vaccination has been administered to toddlers, South Korea has had periodic nationwide outbreaks of acute hepatitis A since the late 2000s. We examined the chronological changes in the seroprevalence of anti-hepatitis A virus (HAV) immunoglobulin G (IgG) over the past 15 years (2005–2019). We retrospectively collected data from 45,632 subjects who underwent anti-HAV IgG testing without evidence of acute HAV infection at four centers in the capital area of South Korea between January 2005 and December 2019. The seroprevalence of anti-HAV IgG was analyzed according to age and compared among seven age groups and five time periods. Additionally, age-period-cohort analyses were used to identify the age, period, and cohort effects of the seroprevalence of anti-HAV IgG. The mean age of the enrolled subjects was 39.2 ± 19.2 years, and the average anti-HAV IgG positivity rate was 66.4%. During the 15 years, the seroprevalence of anti-HAV IgG in people aged 0 to 19 years significantly increased over time ($P < .001$). In people aged 20 to 29 years, the seroprevalence slightly decreased to that of the early 2010s (31.3% in 2005–2007 to 19.7% in 2011–2013) but rebounded to 39.5% in 2017 to 2019. In contrast, the seroprevalence of anti-HAV IgG in those aged 30 to 49 years decreased over time ($P < .001$). The seroprevalence of anti-HAV IgG in those aged 20 to 39 years in 2017 to 2019 was still less than 40%. In addition, the seroprevalence of anti-HAV IgG in people aged 50 to 59 years has recently decreased. Since the introduction of the universal vaccination, the seroprevalence of anti-HAV IgG in children and young adults has gradually increased. However, the seroprevalence of anti-HAV IgG in people in their 20s remains low, and the seroprevalence of anti-HAV IgG in people in their 30s and 40s is gradually decreasing. Therefore, a new strategy for HAV vaccination is needed for those in their 20s to 40s.

Abbreviations: APC = age-period-cohort, HAV = hepatitis A virus, IgG = immunoglobulin G.

Keywords: hepatitis A virus, seroprevalence, vaccination

1. Introduction

Hepatitis A virus (HAV) is an RNA virus that causes acute hepatitis by fecal-to-oral transmission through contaminated food or water or by direct contact with patients.[1,2] In the clinical course of HAV, most children are asymptomatic, whereas adolescents and adults are more severely affected. The incidence of acute hepatitis A is associated with seroprevalence of anti-HAV Immunoglobulin G (IgG). Additionally, the seroprevalence of hepatitis A is affected by hygiene, sanitary conditions, and socioeconomic status.[3] In developing countries, the incidence of acute HAV infection is high in children and adolescents.[4] Conversely, in developed countries, the incidence is higher in adults.[5] As seroprevalence decreases in adults, appropriate vaccination is the most effective way to prevent hepatitis A infection.

South Korea is a developing country that has experienced dramatic improvements in sanitation over the last 40 years.

DHL and WS contributed equally to this article.

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Since the late 1990s, the incidence of acute hepatitis A at 10 to 20 years of age has gradually increased. As the peak age of infection increased, 15,231 cases of acute hepatitis A occurred in 2009, resulting in an outbreak.[6] By 2013, the incidence of acute hepatitis A gradually decreased. However, in 2019, 17,363 new cases of acute hepatitis A outbreak occurred, mainly in the 30s and 40s age groups.[7] This phenomenon is associated with low seroprevalence of anti-HAV IgG in a specific age group.[8,9]

To prevent hepatitis A infection in South Korea, national vaccination programs have been implemented in the military since 2012 and in toddlers since 2015.[10,11] However, there are insufficient preventive measures for people in their 20s, 30s, and 40s, and they are the main age group for recent outbreaks.[12] According to a 2008 to 2013 report, the seroprevalence in children and adolescents fell to <30%.[13] As a result, periodic hepatitis A outbreaks occurred until 2019. Data on the seroprevalence of anti-HAV IgG between age groups and by era are lacking. To establish a public health strategy to prevent hepatitis A infection, it is necessary to identify a population susceptible to infection owing to a low IgG anti-HAV positivity rate. Additionally, it is important to understand the changing trends in seroprevalence according to age.

This study aimed to investigate the seroprevalence of anti-HAV IgG in all age groups at four centers in the capital area of South Korea and compare the seroprevalence among specific periods. We attempted to identify susceptible age groups and to establish an appropriate public vaccination policy to prevent hepatitis A infection.

2. Materials and methods

2.1. Study population

We retrospectively reviewed data from four academic hospitals in the capital area of South Korea (National Medical Center, Kangbuk Samsung Hospital, Sanggye Paik Hospital, and Hanyang University Guri Hospital). We analyzed the HAV seroprevalence data collected between January 2005 and December 2019. Subjects aged 0 to 79 years who underwent tests for serum anti-HAV IgG were included in this study. Patients who were positive for serum anti-HAV immunoglobulin M, indicating acute hepatitis A, were excluded from the study. Serum samples were collected for anti-HAV IgG analysis. Serum anti-HAV IgG levels were measured using radioimmunoassay.

2.2. Seroprevalence of IgG anti-HAV

The seroprevalence of anti-HAV IgG was analyzed according to age, sex, and time period. The study population was categorized into seven age groups based on 10-year intervals: 0 to 9 years, 10 to 19 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, and ≥60 years. Time periods were divided into seven: 2005 to 2007, 2008 to 2010, 2011 to 2013, 2014 to 2016, and 2017 to 2019. We analyzed the trend in anti-HAV IgG seroprevalence between 2005 and 2019. We also compared the seroprevalence according to age, sex, and time.

2.3. Statistical analysis

The chi-square test for trends and linear-by-linear association tests were used for statistical analysis. Statistical significance was set at $P < .05$. Age-period-cohort (APC) analyses were used to identify whether the change in seroprevalence of anti-HAV IgG was due to age, period, and cohort effects. The patients were divided into seven age groups, as mentioned above. Additionally, the study period was divided into five time periods. The total number of birth cohorts derived based on the age groups and periods from 1911 to 2019 was 107. Furthermore, it was hypothesized that the seroprevalence rate of anti-HAV IgG followed a Poisson distribution, and the Akaike information criterion was used for optimal model selection for the APC analyses. All statistical analyses were performed using a commercially available statistical software (SPSS Statistics version 26.0; IBM Corp., Armonk, NY and R version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria).

2.4. Ethics

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. All data were reviewed retrospectively, and the institutional review board approved the waiver of informed consent. The study protocol was approved by the institutional review boards of all the participating institutions (IRB number: NMC-2006-017).

3. Results

3.1. Seroprevalence of anti-HAV IgG

A total of 45,632 patients were enrolled between 2005 to 2019. The mean age was 39.2 ± 19.2 years, and the male-to-female ratio was 1:0.71. The average anti-HAV IgG positivity rate was 66.4% (male vs female, 65.9 vs 67.1%, respectively). The seroprevalence of anti-HAV IgG for each hospital is described in Table 1, Supplemental Digital Content, http://links.lww.com/MD/H858, and the number of subjects analyzed during the study period between 2005 and 2019 is described in Table 1.

3.2. Changing patterns of anti-HAV IgG seroprevalence by age and time periods

Table 2 shows the change in anti-HAV IgG seroprevalence according to age and study period. The seroprevalence of all age groups decreased in the late 2000s and the early 2010s (60.6% in 2008–2010 and 61.8% in 2011–2013) but has increased since then. The seroprevalence of all age groups in 2017 to 2019 was 69%, which did not improve compared to 73.8% in 2005 to 2007. We analyzed changes in seroprevalence according to age. In 2005 to 2007, the seroprevalence rate at 0 to 9 years was only 46.1%. This gradually increased to 93.3% during 2017 to 2019. However, the seroprevalence rate among people in their 20s was still low, ranging from 31.3% in 2005 to 2007 to 39.5% in 2017 to 2019. In particular, the seroprevalence rate among people in

Table 1

Number of subjects analyzed during the investigation period (2005–2019) and positive anti-hepatitis A virus immunoglobulin G rate.

	Analysis period															
IgG anti-HAV	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
Total, n	688	787	692	1187	4237	4246	3528	3163	3720	4653	4405	3772	3344	3516	3694	45,632
Positive, n	495	571	534	797	2387	2676	2201	1980	2256	3221	3235	2665	2335	2403	2542	30,298
%	71.9	72.6	77.2	67.1	56.3	63.0	62.4	62.6	60.6	69.2	73.4	70.7	69.8	68.3	68.8	66.4

HAV = hepatitis A virus, IgG = immunoglobulin G, n = number.

Table 2

Comparison of anti-hepatitis A immunoglobulin G virus rates between 2005–2007, 2008–2010, 2011–2013, 2014–2016, and 2017–2019 according to age group.

	Analysis period					
Age (yr)	2005–2007	2008–2010	2011–2013	2014–2016	2017–2019	*P* value
0–9	46.1% (147/319)	53.3% (161/302)	64.8% (291/449)	89.7% (1251/1394)	93.3% (957/1026)	<.001
10–19	13.0% (24/184)	20.4% (102/500)	30.0% (175/584)	59.5% (664/1116)	65.2% (533/817)	<.001
20–29	31.3% (65/208)	20.0% (427/2134)	19.7% (378/1917)	28.7% (555/1936)	39.5% (658/1666)	<.001
30–39	74.0% (222/300)	52.3% (1474/2819)	38.7% (942/2435)	33.6% (629/1872)	32.6% (515/1582)	<.001
40–49	97.0% (350/361)	89.5% (1628/1818)	84.0% (1762/2098)	78.4% (1626/2075)	67.4% (1533/2274)	<.001
50–59	99.6% (265/266)	98.1% (1044/1064)	98.2% (1514/1541)	98.1% (1997/2036)	94.6% (1779/1880)	<.001
60–	99.6% (527/529)	99.1% (1024/1033)	99.1% (1375/1387)	99.9% (2399/2401)	99.7% (1305/1309)	.014
Total	73.8% (1600/2167)	60.6% (5860/9670)	61.8% (6437/10,411)	71.1% (9121/12830)	69.0% (7280/10,554)	<.001

their 30s gradually decreased from 74% in 2005 to 2007 to 32.6% in 2017 to 2019. Even among those in their 40s, the seroprevalence rate gradually decreased (97% in 2005–2007 to 67.4% in 2017–2019). In people over 50 years of age, an almost 100% seroprevalence rate was observed during the study period. However, the seroprevalence of anti-HAV IgG in people 50 to 59 years old has recently decreased (94.6% in 2017–2019). Figure 1 shows the change in seroprevalence according to age and specific time periods. The seroprevalence rate increased significantly in the 0 to 9 years and 10 to 19 years but decreased with time in the 30 to 49 years, especially in the 30 to 39 years ($P < .001$). In 2017 to 2019, the seroprevalence rate among those in their 20s and 30s was <40%, showing the lowest results compared to other age groups (39.5% in 20–29 years and 32.6% in 30–39 years).

Figure 2 shows the age-specific seroprevalence according to time period. The graph shifted to the right as the seroprevalence of the younger age group (0–19 years) increased, whereas the seroprevalence of those in their 30s and 40s decreased.

3.3. Comparison of anti-HAV IgG seroprevalence by sex

We compared the seroprevalence according to sex (Table 3). When comparing 2005 to 2007 and 2017 to 2019, the seroprevalence of the 0 to 9 years, 10 to 19 years, and 20 to 29 years groups increased over time for men and women. However, the seroprevalence decreased in men and women aged 30 to 39 and 40 to 49 years. The seroprevalence decreased more in men than in women aged 30 to 39 years (77.9 to 26.5% in men, 58.1 to 42.9% in women). In other age groups, the difference in seroprevalence between men and women was not remarkable; however, the difference between men and women was noticeable in the 10s to 30s.

3.4. Age-period-cohort analyses

The APC analyses revealed that the APC model was the optimal model with the least Akaike information criterion considering all APC variables simultaneously (Table 4). The effects of age, adjusted for period and birth cohort effects, on the seroprevalence rate of anti-HAV IgG gradually increased from 0 to 9 years to 40 to 49 years old; however, there was no significant change afterward. Cohort effects adjusted for age and period effects were analyzed based on the birth cohort in 1964. When the birth year 1970 was chosen as the reference cohort, there was hardly any change in the seroprevalence rate of anti-HAV IgG of the birth cohorts from 1911 to 1964. However, it decreased until the birth cohort in 1980 and then sharply increased afterward. Period effects adjusted for age and cohort effects decreased from 2005 to 2007 until 2011 to 2013, increased in 2014 to 2016, and then decreased again in 2017 to 2019; period effects on the seroprevalence rate of anti-HAV IgG were weak compared to cohort effects (Fig. 3).

4. Discussion

This study analyzed the changing patterns of anti-HAV IgG seroprevalence from 2005 to 2019 according to age and sex at four centers in the capital area of South Korea. In particular, seroprevalence across age groups showed dynamic changes. The seroprevalence rate of 0 to 19 years has continuously increased due to vaccination during the last 15 years (from 46.1% to 93.3% in 0–9 years, and from 13.0% to 65.2% in 10–19 years). On the other hand, the seroprevalence rate in people in their 20s was still low (<40%), and the seroprevalence rate in those aged 30 to 39 years gradually decreased (from 74.0% to 32.6% in 30–39 years, and from 97.0% to 67.4% in 40–49 years).

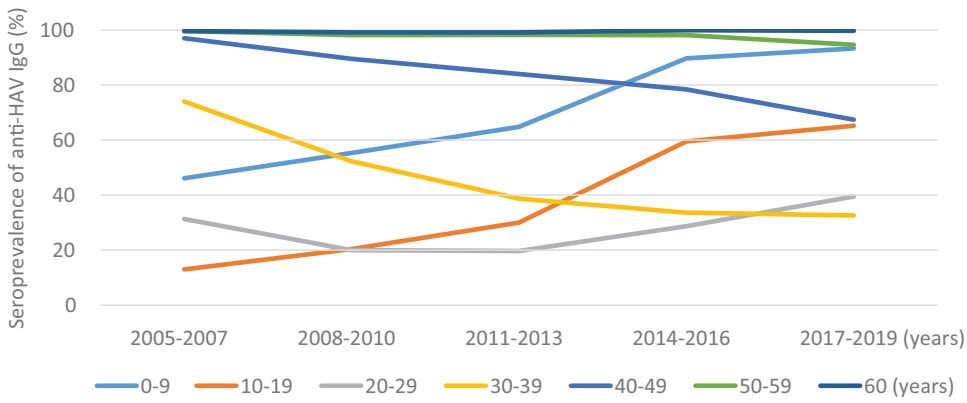

Figure 1. Change of seroprevalence of anti-hepatitis A virus immunoglobulin G according to age group from 2005 to 2014. HAV = hepatitis A virus, IgG = immunoglobulin G

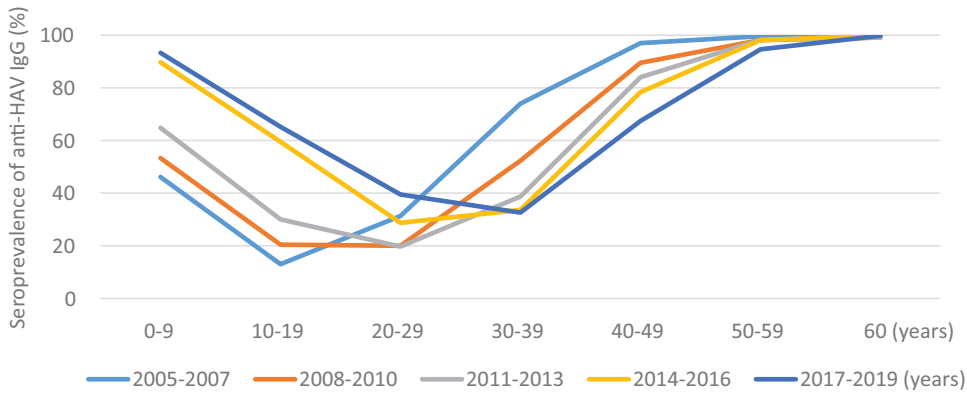

Figure 2. Age-specific seroprevalence of anti-hepatitis A virus immunoglobulin G from 2005 to 2019. HAV = hepatitis A virus, IgG = immunoglobulin G

Table 3

Seroprevalence of anti-hepatitis A immunoglobulin G virus by sex.

		Analysis period				
Age (yr)	**Sex**	**2005–2007**	**2008–2010**	**2011–2013**	**2014–2016**	**2017–2019**
0–9	M	44.3% (82/185)	51.1% (93/182)	61.7% (137/222)	87.8% (640/729)	92.1% (499/542)
	F	48.5% (65/134)	56.7% (68/120)	67.8% (154/227)	91.9% (611/665)	94.6% (458/484)
10–19	M	13.8% (17/123)	20.6% (65/316)	28.7% (102/355)	57.1% (465/639)	61.4% (293/477)
	F	11.5% (7/61)	20.1% (37/184)	31.9% (73/229)	62.7% (299/477)	70.6% (240/340)
20–29	M	29.8% (36/121)	22.5% (210/934)	19.5% (204/1047)	25.5% (273/1070)	35.3% (322/913)
	F	33.3% (29/87)	18.1% (217/1200)	20.0% (174/870)	32.6% (282/866)	44.6% (336/753)
30–39	M	77.9% (134/172)	52.2% (873/1671)	37.8% (615/1629)	31.5% (371/1179)	26.5% (263/994)
	F	58.1% (88/128)	52.4% (601/1148)	40.6% (327/806)	37.2% (258/693)	42.9% (252/588)
40–49	M	96.53% (195/202)	89.2% (1062/1190)	82.9% (1128/1361)	77.8% (909/1168)	68.7% (1021/1486)
	F	97.5% (155/159)	90.1% (566/628)	86.0% (634/737)	79.1% (717/907)	65.0% (512/788)
50–59	M	99.2% (117/118)	98.5% (642/652)	98.3% (918/934)	98.3% (1135/1155)	94.9% (1116/1176)
	F	100.0% (148/148)	97.6% (402/412)	98.2% (596/607)	97.8% (862/881)	94.2% (663/704)
60–	M	99.4% (361/363)	99.2% (644/649)	99.3% (821/827)	99.9% (1222/1223)	99.7% (726/728)
	F	100.0% (166/166)	99.0% (380/384)	98.9% (554/560)	99.9% (1177/1178)	99.7% (579/581)

Table 4

Model fitness for age-period-cohort analyses of seroprevalence rate of anti-hepatitis A virus immunoglobulin G.

Model	**AIC**	**df**	***P* value**
Age	1311	30	Reference
Age-drift	1313	29	.993
Age-cohort	696	26	<.001
Age-period-cohort	682	24	<.001
Age-period	1307	27	<.001
Age-drift	1313	29	.007

AIC = Akaike information criterion, df = degrees of freedom.

In South Korea, the "all-patient report" for acute hepatitis A has been operating since 2011.[13] The number of patients with acute hepatitis A gradually decreased to 867 cases from the year 2011 to 2013. However, it has increased since 2013, reaching 17,598 cases in 2019. In particular, the reported number of acute hepatitis A cases in 2019 was more prevalent in individuals in their 20s to 40s, constituting 86.6% (15,244 cases) of the total cases.[7] Considering the occurrence of a large outbreak every 10 years, the vulnerability of these age groups to hepatitis A can be a significant socioeconomic burden because they have been reported to have the highest total cost of a single acute hepatitis A case.[14]

All men in South Korea undergo compulsory military service, and 95% of those eligible for military service are in their early 20s. The HAV vaccination was initiated in the military in 2012.[10] Our results show that IgG anti-HAV seroprevalence among 20 to 29 years of age is gradually increasing. In addition, universal vaccination was initiated for toddlers aged 12 to 23 months in 2015. It can also be seen that seroprevalence at 0 to 9 years was improving. In the late 1990s, the seroprevalence in the 0- to 9-year-old group was only 2%. However, in the late 2000s, this rate approached 70%.[13,15] In our study, more than 90% of the patients were positive for anti-HAV IgG in late 2010. This result can be considered the impact of childhood vaccination and the HAV vaccination campaign. This value is expected to reach approximately 100% in the future.

Although universal vaccination was introduced, overall seroprevalence did not improve significantly. This was due to a decrease in seroprevalence in the 30 to 49 age group, especially in the 30 to 39 age group. Socioeconomic conditions have

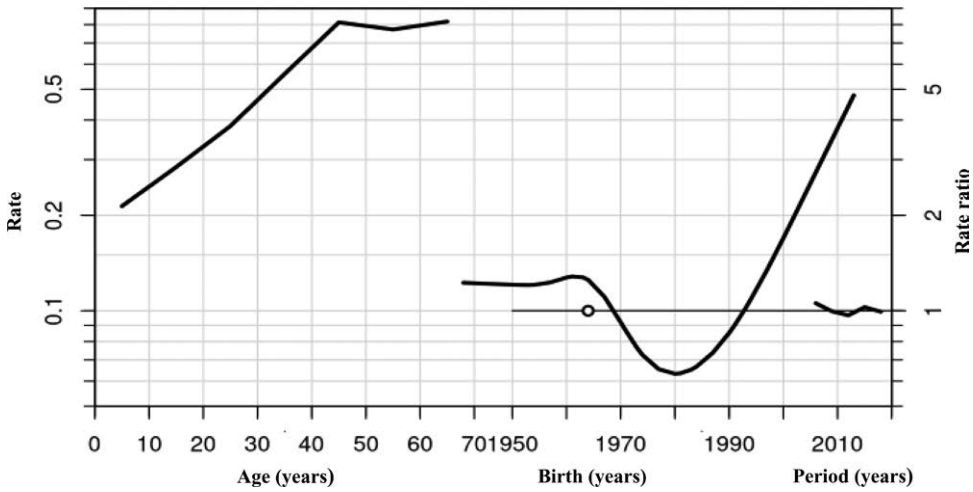

Figure 3. Age-period-cohort analyses of the seroprevalence rate of anti-hepatitis A virus immunoglobulin G.

gradually improved, but these age groups have not received the HAV vaccination. In addition, the seroprevalence of those in their 20s and 30s was <40% (39.5% and 32.6%, respectively), which is a major risk group for HAV outbreaks.

These results are an extension of those of a nationwide study of HAV seroprevalence from 2005 to 2014. The seroprevalence rate in younger age groups increased due to universal vaccination in toddlers, while the seroprevalence gradually decreased in those in their 30s and older due to the cohort effect, and this trend continued.[16] Another study that analyzed seroprevalence from 2001 to 2013 showed that seroprevalence at 25 to 44 years decreased from early 2000 to late 2000.[17] In 2019, more than 17,000 cases of acute hepatitis A infection occurred because of this, and 72.6% were in their 30s and 40s. Therefore, active catch-up immunization without antibody checks may be recommended for these age groups.[18]

We also analyzed the sex differences in seroprevalence according to age. Compared to other age groups, the differences between men and women in the young age group (10–19, 20–29, 30–39) were striking. The seroprevalence of men aged 20–29 years increased, but that of women also increased, and a gap between men and women still existed. In the 30s age group, the difference in seroprevalence between men and women was significant. A possible reason for this finding is vaccination in women with childbearing potential after prenatal testing; however, further studies are required to clarify this hypothesis. Another important finding related to sex differences is that the difference in seroprevalence in the 0- to 9-year-old group gradually decreased since the 2010s. This can be considered the effect of universal vaccination for toddlers, and is consistent with previous studies.[19]

To our knowledge, this is the first study to analyze the seroprevalence of anti-HAV IgG using APC analyses in Korea. In the APC analyses, the age effects gradually increased until 40 years old and reached a plateau afterward. This showed that improved public hygiene due to improved socioeconomic status kept people in their 20s to 40s from reaching higher seroprevalence rates.[15,20] Regarding cohort effects, the seroprevalence of anti-HAV IgG gradually decreased from the birth cohorts in the mid-1960s to 1980; this appeared to be related to socioeconomic development and improvements in public sanitation and personal hygiene in South Korea.[20,21] However, the sharp increase in the seroprevalence from the 1980 birth cohort seems to be related to improved HAV vaccination awareness and national immunization programs.[22] Period effects during the study period did not show many differences with time. Although there was not enough time (15 years) to assess a period effect; hence, warranting the need for further observation periods.

This study had several limitations. First, the participants in this study were those who visited four centers in the capital area of South Korea, and there was a risk of selection bias. Therefore, these results cannot be generalized to all populations in South Korea. These results may reflect the changing trends of IgG anti-HAV in this population rather than presenting the actual prevalence of IgG anti-HAV and are not different from previous studies that have analyzed the seroprevalence trends.[16] Second, this study did not consider the socioeconomic status of the study population. We conducted the study using data from four institutions in the metropolitan area and did not consider the difference in socioeconomic level by region. Regional differences may exist because HAV infection is highly related to socioeconomic status and hygiene levels. Finally, as a retrospective study, our study was limited by the ability to obtain data on seroprevalence. In particular, information on individual vaccination histories was not available. However, this study enrolled all patients tested for serum anti-HAV IgG at the four referral centers. This study was conducted on a very large population of more than 40,000 people, and almost all age groups were included. The results of our study may not be representative of the general population but may provide insight into the current situation and trends in hepatitis A.

Since the introduction of the universal vaccination, the seroprevalence of HAV in children and young adults has gradually increased. However, the seroprevalence of HAV in individuals in their 20s remains low, and the seroprevalence of HAV in individuals in their 30s and 40s gradually decreases. Therefore, a new strategy for HAV vaccination is needed for those in their 20s to 40s.

Author contributions

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Supervision: Seung Woo Nam, Joo Hyun Sohn.
Writing – original draft: Dae Hyun Lim.
Writing – review & editing: Jae Yoon Jeong, Won Sohn.

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