Annals of Medical Research
DOI: 10.5455/annalsmedres.2020.12.810 2020;27(3):743-8

Original Article

Changes in seroprevalence and acute infection rates after vaccination and herd immunity in a pediatric hospital in the Southeastern Anatolia region of Turkey: Effects of adding hepatitis a vaccine to the Extended National Immunization Program

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Abstract

Aim: This study was designed to compare rates of acute HAV infection and HAV seroprevalence in patients aged 0-6 years and 7-15 years in a pediatric hospital before and after the HAV vaccine was added to the national immunization program in 2012.

Material and Methods: A total of 16,917 serum samples were evaluated in the study. Sera of the 5520 patients (3,208 of 0-6 years, 2,312 of 7-15 years) were collected during 2011 and analyzed for anti-HAV IgM and anti-HAV IgG with chemiluminescent assay (period 1). After that a total of 11,397 sera of the patients (5,473 of 0-6 years and 5,924 of 7-15 years) were collected between 1 July 2014 and 31 December 2016 and analyzed for anti-HAV IgM and anti-HAV total (period 2).

Results: In period 1, rates of acute HAV infection and seropositivity were 26.87% and 19.25% in the 0-6 years , and 42.39% and 41.52% in the 7-15 years. Prior to routine vaccination, 54.03% of patients in the 0-6 age group and 16.08% of patients in the 7-15 age groups were susceptible to HAV infection.In period 2, Anti-HAV IgM positivity rates in 2014, 2015, and 2016 were 14.06%, 3.92%, and 2.46% in the 0-6 age group and 16.85%, 6.80%, and 4.48% in the 7-15 age group, respectively. Seropositivity rates were 43.66%, 59.55%, and 66.09% in the 0-6 age group and 45.67%, 55.41%, and 54.04% in the 7-15 age group, respectively. After routine vaccination, rates of children who were susceptible to HAV infection decreased from 42.28% and 36.52 % to 31.45% in the 0-6 years and increased from 37.48%, 37.79% to 41.48% in the 7-15 years. Considering the data as a whole, the most striking finding was that the acute infection rate in the 0-6 years was decreased firstly by 47.67% and then by 85.42% and 90.85% compared to the pre-vaccination period. However, a progressive decline was also observed in the 7-15 years compared to the pre-vaccination period; the rate decreased by 60.25%, 83.96%, and 89.43%, respectively in period 2. This fall in infection rates among a non-target group of HAV vaccination can be attributed to the effect of the vaccine on "herd immunity".

Conclusion: Adding HAV vaccine to the routine immunization program effectively reduced rates of acute infection, demonstrating the contribution of vaccination to herd immunity. Studies showing the efficacy of vaccination programs are essential for raising public awareness.

Keywords: Hepatitis A vaccine; extended national immunization program; herd immunity

INTRODUCTION

Hepatitis A is an infectious disease caused by the hepatitis A virus (HAV). It occurs worldwide, with a higher prevalence in developing countries. Approximately one million new HAV infections are reported annually worldwide; however, the true prevalence of infection is estimated to be higher (1). The exact prevalence remains obscure due to underreporting of the disease and the high incidence of asymptomatic infections.

Studies conducted in Turkey have shown that rates of anti-HAV positivity in adults increase with age, despite minor differences in age at first encounter (2,3). The

Received: 10.12.2019 **Accepted:** 29.02.2020 **Available online:** 10.03.2020
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prevalence of hepatitis A varies over time from country to country, or even regionally within the same country, in relation to hygienic and sanitary conditions and age groups. Therefore, tracking age-specific and temporal changes in seroprevalence is of great importance (4).

HAV is a non-enveloped RNA virus belonging to the genus Hepatovirus of the family Picornaviridae. The very stable structure of this high-yielding virus plays an important role in its transmission and epidemiology. Transmission of the virus occurs via fecal-oral route, direct contact, or exposure to contaminated water or food, and both sporadic cases and outbreaks are seen. A person can be contagious for two weeks before the onset of clinical symptoms, and the infection follows an asymptomatic but productive course in approximately 90% of infected children. These factors promote the spread of the virus. HAV infection remains an important problem due to potential hospitalization, serious complications, and financial burden (5-7).

The Western and Central Anatolia regions of Turkey have intermediate endemicity for HAV, while the Eastern Anatolia region is considered a region of high endemicity. Endemicity of HAV infection varies between countries according to health and hygienic conditions, and also shows regional variations within countries due to socioeconomic differences. Hepatitis A can be prevented worldwide by vaccination. Most countries have an immunization policy established according to the endemic features of the disease and which reflects its endemicity in the entire population (8)

HAV vaccine was added to the national immunization program of Turkey in 2012, under the "Extended National Immunization Program". Nationwide vaccination was initiated in September 2012. Evaluating the epidemiological profile of hepatitis A is critical to gather data necessary to establish policies regarding the prevention and control of the disease.

This study was designed to determine and compare rates of acute HAV infection and HAV seroprevalence in patients in two age groups (0-6 years and 7-15 years) in a pediatric hospital of the Southeastern Anatolia region, before the addition of HAV vaccine to the Extended National Immunization Program and after routine vaccination.

MATERIAL and METHODS

Patients who presented to the emergency department and outpatient clinic of Gaziantep Pediatric Hospital with nonspecific complaints such as malaise, nausea, vomiting, and abdominal pain were included in this study.

Period 1

A total of 3208 samples from patients aged 0-6 years and 2,312 samples from patients aged 7-15 years collected between January 1, and December 31, 2011 were analyzed for anti-HAV IgM and anti-HAV IgG with chemiluminescent assay in an Abbott Architect i2000 (Abbott Laboratories, Illinois, USA). For anti-HAV IgM and anti-HAV IgG, signal-to-cutoff (S/CO) values of >1.20 and >0.99 were considered positive values respectively.

Period 2

Serological markers for HAV (anti-HAV IgM and anti-HAV total) were measured in serum samples collected from patients who presented to the Gaziantep Children's Hospital between July 1, 2014 and December 31, 2016 by electrochemiluminescence assay using a Roche Cobas e601 device (Roche Diagnostics, Indianapolis, IN, USA). The data were analyzed in the last 6 months of 2014, during 2015, and 2016. Anti-HAV IgM and total anti-HAV assays were performed on 1017, 2141, and 2315 serum samples from the 0-6 age group and 1110, 2514, and 2300 samples from the 7-15 age group, respectively, in 2014 (last 6 months), 2015, and 2016.

For anti-HAV IgM, S/CO values of ≥1.00 and anti-HAV total ≥20 IU/L were considered positive values. The anti-HAV IgM and anti-HAV IgG/anti-HAV total test results of all patients were evaluated retrospectively for both periods.

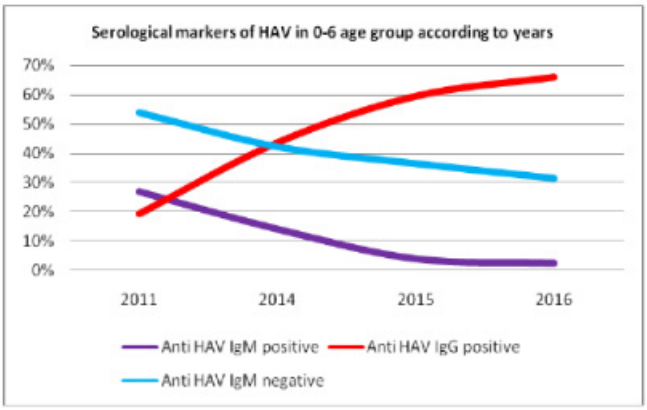
Statistical analysis

Descriptive statistical methods were used for statistical analysis. Categorical variables were expressed as percentage (%). For both periods and both age groups (0-6 and 7-15 years), the chi-square ($\chi 2$) test was used to determine whether there were significant differences in prevalence among those with acute infection, acquired immunity via previous infection or vaccination, and those who were unvaccinated/uninfected. P values <0.01 were considered statistically significant.

RESULTS

Period 1

In the 0-6 age group, 857 of 3208 patients (26.87%) were positive for anti-HAV IgM and were diagnosed with acute HAV infection. Another 1733 (54.03%) had no previous infection, while 618 (19.25%) were seropositive (acquired immunity via previous infection/vaccination). In the 7-15 age group, acute HAV infection was detected as anti-HAV IgM positivity in 980 of 2312 patients (42.39%). Another 372 (16.08%) had no previous infection, and the acquired immunity rate was 41.52% (n=960).



Figur 1. Serological Markers of HAV in 0-6 Age Group According to Years

Table 1. Serological Markers of HAV in 0-6 Age Group According to Years

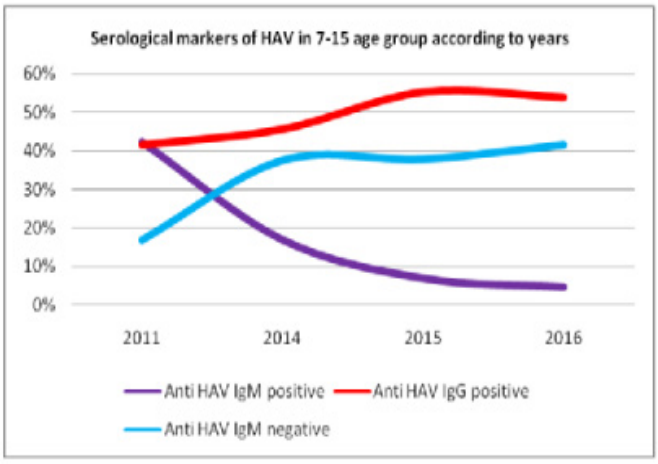
Period	Year	Anti HAV IgM positive	Anti HAV IgG positive	Anti HAV IgG negative	TOTAL
Period 1	2011	857 (%26.87)	618 (%19.25)	1733 (%54.03)	3208 (%100)
	2014 (Last 6 months)	143 (%14.06)	444 (%43.66)	430 (%42.28)	1017(%100)
Period 2	2015	84 (%3.92)	1275 (%59.55)	782 (%36.52)	2141 (%100)
	2016	57 (%2.46)	1530 (%66.09)	728 (%31.45)	2315 (%100)

Period 2

Anti-HAV IgM positivity rates in 2014, 2015, and 2016 were 14.06%, 3.92%, and 2.46% in the 0-6 age group and 16.85%, 6.80%, and 4.48% in the 7-15 age group, respectively. Seropositivity rates (acquired immunity via previous infection/vaccination) were 43.66%, 59.55%, and 66.09% in the 0-6 age group and 45.67%, 55.41%, and 54.04% in the 7-15 age group, respectively. The proportions of children uninfected/unvaccinated in 2014, 2015, and 2016 were 42.28%, 36.52%, and 31.45% in the 0-6 age group and 37.48%, 37.79%, and 41.48% in the 7-15 age group. All results are presented in Table 1 and 2 and Figur 1 and 2.

Statistical analysis

There were statistically significant differences between time periods for both age groups (0-6 and 7-15 years) in rates of acute infection, acquired immunity, and proportion of unvaccinated/uninfected children ($p<0.01$).



Figur 2. Serological Markers of HAV in 7-15 Age Group According to Years

Table 2. Serological Markers of HAV in 7-15 Age Group According to Years

Period	Year	Anti HAV IgM positive	Anti HAV IgG positive	Anti HAV IgG negative	TOTAL
Period 1	2011	980 (%42.39)	960 (%41.52)	372 (%16.08)	2312 (%100)
	2014 (Last 6 months)	187 (%16.85)	507 (%45.67)	416 (%37.48)	1110 (%100)
Period 2	2015	171 (%6.80)	1393 (%55.41)	950 (%37.79)	2514 (%100)
	2016	103 (%4.48)	1243 (%54.04)	954 (%41.48)	2300 (%100)

DISCUSSION

This study demonstrates a changing trend in acute HAV infection and seroprevalence before and after mass administration of hepatitis A vaccine in a subset of the population.

Viral hepatitis is the primary cause of acute hepatitis in children, and HAV-related acute viral hepatitis A is common worldwide. Intermediate to high endemicity levels for hepatitis A have been reported in many countries in the Middle East, Eastern Europe, Southeast Asia, and Latin America, and Turkey (8-12)

The seroprevalence of HAV infection varies according to the socioeconomic and geographic features of countries. Studies from Turkey have shown that the seroprevalence of infection is similar to that of other developing countries. However, this rate may vary between different geographical regions of the same country, depending on the urbanity and hygienic conditions. For example, reported seropositivity rates in the Eastern Anatolia and Southeastern Anatolia regions are above the average for Turkey (13-16). Some studies have reported seropositivity below 40% for the 0-10 years age over 90% for the >15 years. (16-18). In developing countries, contaminated water is a substantial transmission route of HAV infection due to inadequate or inefficient sewage and water supply systems. In contrast, lower HAV incidence in developed countries can be attributed to high water quality, good hand hygiene, and proper human waste disposal (19).

In studies performed in different regions of Turkey, the seroprevalence in 0-10 age group has been reported to be below 40% (19). Çopur et al. reported that the seroprevalence of anti-HAV IgG in children was 29.5% (20). In another study using data obtained between 2015 and 2016, the rate of children was found to be 66.7% (21). In our study the HAV seroprevalence rate of children was 66.09% in 2016. The seroprevalence in children has increased over the years as a result of vaccination. These findings may be considered as the result of routine immunization. Compared to the regions with low viral contamination rates, regions with high viral contamination rates have lower morbidity and mortality rates, because adults in areas with high infection rates are less susceptible to HAV infection. As a result of advances in sanitation and hygiene practices, the epidemiological level of HAV circulation has shifted from high to intermediate. As a paradoxical consequence of this shift, the population has become more susceptible to infection due to reduced immunity, and symptomatic infections have become more common due to delayed age at first encounter. Therefore, the effects of immunization can be confirmed by evaluating acute HAV infections, changes in HAV seroprevalence, reported symptomatic cases, cases of fulminant hepatitis, and liver transplants (22-24).

The prevention of diseases is always more effective and less costly than treatment, and vaccinations are clearly one of the most basic tools in this regard. The CDC (United States Centers for Disease Control and Prevention) recommends immunization for all children between 12-23 months of age, children (between 2-18 ages) and adults who will travel to countries with intermediate or high prevalence, homosexuals, drug addicts, individuals using clotting factor concentrates, individuals with chronic liver disease, and individuals working in child care facilities (25).

The World Health Organization (WHO) states that HAV vaccine can be integrated into the national immunization program for all children over the age of 1 year in countries with intermediate endemicity because increasing socioeconomic status in these countries will shift age of infection to the older age group, thus increasing the risk of more severe disease and mortality. However, in countries with high endemicity, almost all individuals become infected in early childhood, and the infection is either asymptomatic or manifests as mild disease. Therefore, considering the cost of vaccination, large-scale immunization programs are not recommended for these countries (26).

Vaccination is one of the most effective ways to prevent HAV infection. In the past, protective vaccination with immune serum globulin (ISG) administration was recommended for selected groups. However, active immunization with inactivated vaccines replaced ISG for individuals at risk for HAV infection. Passive immunization is currently recommended together with vaccination for people over 40 years of age, immunosuppressed patients, and those with concomitant diseases (2,5). Similarly, the HAV vaccine was added to the Extended National Immunization Program of Turkey in 2012 in order to “prevent the incidence of infection from shifting from childhood to older ages". The vaccine is administered to children aged 15-18 months and older, because 70-100% of the maternal antibodies disappear around this time and children become more susceptible to HAV infection. The HAV vaccine given in our country is an inactivated virus vaccine, administrated as two doses of 0.5 ml at 18 and 24 months of age.

According to our findings, seroprevalence was 19.25% in the 0-6 age group in period 1, and showed an increasing trend in period 2 from 43.66% in 2014 (last 6 months) to 59.55% in 2015 and 66.09% in 2016. In period 1, seroprevalence was 41.52% in the 7-15 age group and increased in period 2 to 45.67%, 55.41%, and 54.04, respectively. The seroprevalence in the 0-6 age group has increased over the years as a result of vaccination. In addition, the rate of children in 0-6 age group with no encounter with the virus decreased after vaccination; this rate was 54.03% in the pre-vaccination period and decreased to 42.28%, 36.52%, and finally to 31.45% by 2016. In contrast, in the 7-15 age group, which is not the target group of the routine vaccination program, the rate was 16.08% in period 1, and increased in period 2 to 37.48%, 37.79%, and finally to 41.48% in 2016.

The addition of HAV vaccine to the Expanded National Immunization Program appears to have a significant effect on reducing acute HAV infection. In 2011, the acute HAV infection rate for children aged 0-6 years was 26.87%. This rate then decreased to 14.06%, 3.92%, and 2.46% respectively in 2014, 2015, and 2016. In the 7-15 years who were not included in the vaccination program, the acute HAV infection rate was 42.39% in 2011, and then fell to 16.85%, 6.80%, and 4.48% respectively in 2014, 2015, and 2016. Considering the data as a whole, the most striking finding is that the acute infection rate in the 0-6 years was decreased firstly by 47.67% and then by 85.42% and 90.85% compared to the pre-vaccination period. However, a progressive decline was also observed in the 7-15 years compared to the pre-vaccination period; the rate decreased by 60.25%, 83.96%, and 89.43%, respectively in period 2. This fall in infection rates among a non-target group of HAV vaccination can be attributed to the effect of the vaccine on "herd immunity". When vaccines are observed to reduce infection rates among unimmunized individuals in addition to immunized individuals, this can be regarded as an indication that the vaccine also provides "herd immunity" (27). In the vaccination target group (0-6 age group), seropositivity rates increased gradually following immunization. In contrast, seropositivity rates decreased in the 7-15 age group, which was not a direct target group of vaccination, due to herd immunity.

Since children are a source of infection for other age groups, preventing the spread of the virus in this group will

contribute to “herd immunity” and protect unvaccinated persons. In Israel, routine hepatitis A vaccination was initiated in children aged 1-4 years in 1999, and the incidence of hepatitis A in the vaccine group decreased by 98%. Similarly, there was a significant reduction in age groups without routine vaccination. Significant decrease in incidence also shows that hepatitis A vaccine provides “herd immunity” in age groups without vaccination (28).

CONCLUSION

In conclusion, with the integration of hepatitis A vaccine into the extended immunization program of Turkey, it has been added to the current vaccination schedule for all children in the 15-18 months age group. Because our country has intermediate endemicity and considering the ongoing infrastructural improvements, the incidence of infection is expected to shift from childhood to older age groups. In terms of cost-effectiveness, inclusion of the vaccine in the routine immunization program will certainly reduce costs and loss of labor, and will also have a positive impact on social immunity. Based on our findings, prior to its addition to the routine vaccination program, a substantial proportion of the child and adolescent population was susceptible to HAV infection. Following its addition to the vaccination program, there was an effective decline in rates of acute infection, which demonstrates the contribution of the vaccine to herd immunity. In addition to raising awareness of the routes of HAV transmission, encouraging routine HAV vaccination is as important as improving hygienic conditions. Presenting the results of studies demonstrating the success of vaccination programs is essential for effectively raising public awareness.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by the Sanko University Ethics Committee of Clinical Research (Date: 31.01.2019, Session No: 2019/01, Decision No: 01).

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