Public Health Res Perspect 2011 2(1), 46—50
doi:10.1016/j.phrp.2011.04.009
pISSN 2210-9099 eISSN 2233-6052

ELSEVIER

ORIGINAL ARTICLE

Seroprevalence of Hepatitis A and E Viruses Based on the Third Korea National Health and Nutrition Survey in Korea

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Received: February 7, 2011
Revised: March 2, 2011
Accepted: March 11, 2011

KEYWORDS:
hepatitis A virus,
hepatitis E virus,
Korea,
seroprevalence

Abstract
Objectives: The purpose of this study was to investigate the seroprevalence of hepatitis A virus (HAV) and hepatitis E virus (HEV) in Korea during 2005.
Methods: Study subjects were selected from across Korea using a stratified multistage probability sampling design, and HAV and HEV seroprevalence was compared on the basis of sex, age, and residency. A total of 497 rural and urban people aged 10—99 years of age (mean ± SD age = 28.87 ± 17.63 years) were selected by two-stage cluster sampling and tested serologically for anti-HAV and anti-HEV IgG using an enzyme-linked immunosorbent assay.
Results: Among this population, the overall seroprevalence of HAV was 63.80% (55.21% aged in their 20s and 95.92% in their 30s, $p < 0.01$) and that of HEV was 9.40% (5.21% aged in their 20s and 7.14% in their 30s, $p < 0.01$). Seroprevalence also varied according to area of residence. HEV prevalence in rural areas was higher than that of urban regions based on the anti-HEV antibody, odds ratio 3.22 (95% confidence interval: 1.46—7.10, $p < 0.01$). There were no significant differences between male and female against anti-HAV/HEV antibodies.
Conclusion: Our study suggested that the seropositive rates of HAV and HEV might be related to age and environmental conditions.

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1. Introduction

Hepatitis A (HAV) and E (HEV) viruses have a global distribution and are transmitted by means of the oral-fecal route by the consumption of contaminated water. Human isolates of HAV are classified only as a single serotype. However, previous studies have indicated that significant nucleic acid heterogeneity exists within isolates, allowing them to be grouped according to geographical origin. HEV-mediated hepatitis is a serious public health problem in the developing countries of Asia, the Middle East, Africa, and Central America [1−3]. The highest incidence of HEV infection occurs in young adults, whereas high rates of fulminant disease are also associated with pregnancy. Waterborne epidemics of this disease have been reported in Southeast and Central Asia, the Middle East, Africa, and North America [4]. Most HEV infections reported in developed countries were identified in travelers who had previously visited HEV endemic countries.

Worldwide epidemiological patterns (low, intermediate, and high) of endemicity are dependent on the age of individuals and hygiene levels [5−7]. Even within a designated country, patterns of infection are variable based on the rate of infection, prevalent age, of a population and modes of transmission [8]. Although seroprevalence is low during childhood in industrialized countries with low endemicity pattern, the age group of the most susceptible population has changed from young children to older children and adults [9] (WHO 2000, WHO/CDS/CSR/EDC/2000-7). Clinically severe cases of HAV infection in non-immune adults have also increased recently.

In developing countries, low economic status, high crowding, and inadequate water treatment contribute to a high endemicity pattern, with more than 90% of the population having acquired natural immunity before 10 years of age and infection often persisting as asymptomatic forms [8,10]. With the implementation of improved standards of hygiene, sanitation, and socioeconomic conditions, the epidemiologic pattern of hepatitis A infection and other infectious diseases is currently changing in many developing countries [7,11,12]. Studies conducted in such emerging countries have reported epidemiologic changes over the last decade. HAV and HEV now appear to affect the population at a later age, with an increased risk of symptomatic infection and potentially more severe forms of this disease [13].

In Korea, epidemiologic-serological prevalence data on HAV and HEV transmitted by means of oral-fecal route are fragmentary, non-systematic and limited to studies on acute symptomatic HAV infection [14−16]. The purpose of this study was to investigate the age-specific epidemiological characteristics of HAV and HEV serology in Korea based on the third National Health and Nutrition Survey.

2. Materials and Methods

2.1. Study design and population

This study was a descriptive, cross-sectional, seroepidemiological investigation of HAV and HEV among 497 people from Korea, who were aged between 10 and 99 (mean age 29.01 years). People were selected from across Korea using a stratified multistage probability sampling design, and constituted a representative sample of the Korean population. The Ethics Committee of the Korea National Institute of Health approved both the study protocol and the statement of informed consent of the third Korea National Health and Nutrition Survey III. Written informed consent was also obtained from all subjects before the start of this study. Our study was conducted between 1 April 2005 and 31 June 2005, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines in force during this time.

2.2. Data collection method

Data collected included general information on participants (sex, age, and residency), who were categorized into six age groups that ranged from 10 to 99 years old. After informed consent was obtained from participants or parents in the case of individuals who were under 16 years old, blood samples were collected for HAV and HEV serology.

2.3. Enzyme-linked immunosorbent assay

To assess seroprevalence, the presence of anti-HAV IgG in human sera was determined using a commercial HAV enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (Diagnostic Automation Inc., Calabasas, CA, USA). Briefly, 50 μL of each test serum sample, and positive and negative controls, were added to the microplate. Horseradish peroxidase-conjugate antibody (50 μL) was then added to each well, except the blank, and the microplate was incubated for 1 hour at 37°C. The microplate was then washed before chromogen solution A and TMB were added. The color-developing reaction was stopped and the absorbance for each well was determined at 450 nm with a Sunrise microplate reader (TECAN Trading AG, Männedorf, Switzerland).

The presence of anti-HEV IgG in human sera was determined using a commercial HEV ELISA kit according to the manufacturer's instructions (Diagnostic Automation, Inc.). Briefly, 10 μL of the serum sample was added to each well containing 100 μL of the diluent, and the microplate was incubated for 30 minutes at 37°C. The microplate was washed before Horseradish peroxidase-conjugated HEV antigen was added. The microplate was further washed and then chromogen solution and TMB were added. The color-developing reaction was stopped and the absorbance was determined as described above.

Table 1. Seroprevalence of anti-HAV antibodies in Korea according to sex, age, and residency

Variables	Total number (%)	Number of anti-HAV IgG positives (%)	Odds ratio (95% CI)[a]	*p*
Sex				
Male	239 (48.88)	145 (60.67)	1	0.1585
Female	250 (51.12)	167 (66.80)	1.30 (0.90, 1.89)	
Age groups				
10−14	118 (24.13)	45 (38.14)	1	<0.0001
15−19	78 (15.95)	22 (28.21)	0.64 (0.34, 1.18)	
20−29	96 (19.63)	53 (55.21)	2.00 (1.16, 3.46)	
30−39	98 (20.04)	94 (95.92)	38.12 (13.11, 110.85)	
40−59	65 (13.29)	65 (100.00)	55.00 (22.10, 115.70)	
≥60	34 (6.95)	33 (97.06)	53.53 (7.07, 405.10)	
Residency				
Urban	201 (41.10)	124 (61.69)	1	0.6183
Suburban	234 (47.85)	151 (64.53)	1.13 (0.76, 1.67)	
Rural	54 (11.04)	37 (68.52)	1.35 (0.71, 2.57)	

[a]*CI = confidence interval; 1 = referent.*

Odds ratio to have HAV antibioses by sex, age group and residency calculated by χ^2 test. HAV = hepatitis A virus.

2.4. Statistical analysis

We compared the seropositivity of HAV and HEV on the basis of sex, age, and residency by administrative district (urban; suburban; rural). Each of these variables was selected as a possible risk factor based on previous studies. If required, χ^2 and Cochran-Mantel-Haenszel (CMH) tests were performed. The level of significance was $p < 0.05$ and all statistical analyses were performed using SAS version 8.0 (SAS Institute Inc., NC, USA).

3. Results

The overall prevalence of HAV was 63.80%, with 60.67% ($n = 145$) of infections in males and 66.80% ($n = 167$) in females. According to age group, a significant increase in prevalence was observed with increasing age. For individuals in their 20s, 30s, and 40s, a prevalence of 55.21% ($n = 53$), 95.92% ($n = 94$) and 100% ($n = 65$) was observed, respectively, compared with that in the 10−14 age group ($p < 0.01$). There were no differences in prevalence based on residency (Table 1). The overall prevalence of HEV was 9.40%, with 10.88% ($n = 26$) in males and 8% ($n = 20$) in females. For individuals in their 20s, 30s and 40s, a prevalence of 5.21% ($n = 5$), 7.14% ($n = 7$), and 23.08% ($n = 15$) was observed, compared with that in the 10−14 age group ($p < 0.01$). Prevalence in people from rural areas was significantly higher than that in people from urban areas ($p = 0.01$) (Table 2).

Based on statistical analysis, no significant difference in overall HAV prevalence was observed between males and females. However, on the basis of age, significant differences were observed between the 31.25% (among individuals in their 10s), 46.81% (20s), 95.92% (30s), and 100% (40s) prevalence rates for males ($p < 0.01$).

Table 2. Seroprevalence of anti-HEV antibodies in Korea according to sex, age, and residency

Variables	Total number (%)	Number of anti-HEV IgG positives (%)	Odds ratio (95% CI)[a]	*p*
Sex				
Male	239 (48.88)	26 (10.88)	1	0.2757
Female	250 (51.12)	20 (8.00)	0.71 (0.39, 1.31)	
Age groups				
10−14	118 (24.13)	1 (0.85)	1	<0.0001
15−19	78 (15.95)	0 (0.00)	−	
20−29	96 (19.63)	5 (5.21)	6.43(0.74, 55.99)	
30−39	98 (20.04)	7 (7.14)	9.00 (1.09, 74.47)	
40−59	65 (13.29)	15 (23.08)	35.10 (4.51, 272.97)	
≥60	34 (6.95)	18 (52.94)	131.63 (16.44, 148.07)	
Residency				
Urban	201 (41.10)	18 (8.96)	1	0.0003
Suburban	234 (47.85)	15 (6.41)	0.70 (0.34, 1.42)	
Rural	54 (11.04)	13 (24.07)	3.22 (1.46, 7.10)	

[a]*CI = confidence interval; 1 = referent.*

Odds ratio to have HEV antibioses by sex, age group and residency Calculated by χ^2 test. HEV = hepatitis E virus.

Table 3. Seroprevalence of antibodies against HAV/HEV in Korea according to age and sex

	Percent positives (number of anti-HAV IgG positive/total number)		Percent positives (number of anti-HEV IgG positive/total number)	
Age groups	Male*	Female*	Male*	Female*
10−14	35.19 (19/54)	40.63 (26/64)	1.85 (1/54)	0.00 (0/64)
15−19	2.16 (11/42)	30.56 (11/36)	0.00 (0/42)	0.00 (0/36)
20−29	46.81 (22/47)	63.27 (31/49)	4.26 (2/47)	6.12 (3/49)
30−39	95.92 (47/49)	95.92 (47/49)	8.16 (4/49)	6.12 (3/49)
40−59	100.00 (32/32)	100.00 (33/33)	31.25 (10/32)	15.15 (5/33)
≥60	93.33 (14/15)	100.00 (19/19)	60.0 (9/15)	47.37 (9/19)
Total	60.67 (145/239)	66.80 (167/250)	10.88 (26/239)	8.00 (20/250)

*A p value <0.0001 by χ^2 test. Calculated by Cochran-Mantel-Haenszel Statistics for sex in HAV IgG(+) χ^2(overall) = 2.6575, p = 0.1031. Calculated by Cochran-Mantel-Haenszel Statistics for sex in HEV IgG(+) χ^2(overall) = 2.2310, p = 0.1353. HAV = hepatitis A virus; HEV = hepatitis E virus.

Likewise, significant differences were also observed among the 37.00% (among individuals in their 10s), 63.27% (20s), 95.92% (30s), and 100% (40s) prevalence rates for females ($p < 0.01$) (Table 3).

No significant difference in the HEV prevalence was revealed between males and females. However, on the basis of age, significant differences were observed between the 1.04% (among individuals in their 10s), 4.26% (20s), 8.16% (30s), and 31.25% (40s) prevalence rates for males ($p < 0.01$). Significant differences were also observed between the 0.00% (among individuals in their 10s), 6.12% (20s), 6.12% (30s), and 15.15% (40s) prevalence rates for females ($p < 0.01$) (Table 3). Prevalence significantly increased with age (Table 4).

4. Discussion

Our study successfully reports the seroprevalence of HAV and HEV in Korea on the basis of age, sex and residency. The overall seroprevalence of HAV among this population was 63.80% (55.21% and 95.92% for people aged in their 20s and 30s, respectively; $p < 0.01$) and that of HEV was 9.40% (5.21% and 7.14% for people aged in their 20s and 30s, respectively; $p < 0.01$) in the same population. The significantly higher HEV positive rate in rural areas compared with urban areas ($p < 0.01$) might be a consequence of the inferior tap water and other sanitary facilities available to people living in rural locations.

HAV was previously endemic in Korea during the 1980s, with most adults acquiring natural immunity through asymptomatic infection [17,18]. Since 2001, Korea has experienced a nationwide outbreak of HAV, as indicated by data from the nationwide surveillance report for acute hepatitis A by the Korea Centers for Disease Control and Prevention (www.cdc.go.kr). The number of annual reported cases of hepatitis A in 2005 was 798, which increased to 2,081 in 2006 and 2,233 in 2007. A further abrupt increase in incidence was observed from 2008 (n = 7,895) to 2009 (n = 15,231), followed by a potential decline in 2010 (n = 6,794 up to October 2010). Since the implementation of improved standards of hygiene and sanitation in Korea, anti-HAV antibody prevalence in the 1−20 years of age group declined from 60% in 1980 to 9% in 1995 [19], and the age group of the most susceptible population has changed from young children to older children and adults [15,16,19,20]. Given that clinically severe cases of HAV infection have also

Table 4. Seroprevalence of antibodies against HAV/HEV according to age and residency

	Percent positives (number of anti-HAV IgG positive/total number)			Percent positives (number of anti-HEV IgG positive/total number)		
Age groups	Urban*	Suburban*	Rural*	Urban*	Suburban*	Rural*
10−14	43.48 (20/46)	35.94 (23/64)	25.00 (2/8)	0.00 (0/46)	1.56 (1/64)	0.00 (0/8)
15−19	20.00 (6/30)	35.14 (13/37)	27.27 (3/11)	0.00 (0/30)	0.00 (0/37)	0.00 (0/11)
20−29	50.00 (23/46)	62.22 (28/45)	40.00 (2/5)	4.35 (2/46)	6.67 (3/45)	0.00 (0/5)
30−39	93.02 (40/43)	97.96 (48/49)	100.00 (6/6)	9.30 (4/43)	6.12 (3/49)	0.00 (0/6)
40−59	100.00 (22/22)	100.00 (30/30)	100.00 (13/13)	18.18 (4/22)	16.67 (5/30)	46.15 (6/13)
≥60	92.86 (13/14)	100.00 (9/9)	100.00 (11/11)	57.14 (8/14)	33.33 (3/9)	63.64 (7/11)
Total	61.69 (124/201)	64.53 (151/234)	68.52 (37/54)	8.96 (18/201)	6.41 (15/234)	24.07 (13/54)

*A p value <0.0001 by χ^2 test. Calculated by Cochran-Mantel-Haenszel Statistics for residency in HAV IgG(+) χ^2(overall) = 0.2991, p = 0.5845. Calculated by Cochran-Mantel-Haenszel Statistics for residency in HEV IgG(+) χ^2(overall) = 0.8436, p = 0.3584. HAV = hepatitis A virus; HEV = hepatitis E virus.

recently increased in Korea, active immunization against this disease should be considered [20,21].

HEV is one of the causative agents of enterically transmitted non-A/non-B hepatitis worldwide. It is responsible for the major outbreaks of acute hepatitis in developing countries, especially in tropical and subtropical regions of the world, where outbreaks are usually associated with fecal contamination of drinking water [1,3,22]. Although the highest prevalence is found mostly in countries where the disease is endemic, such as India, the geographic prevalence of people with ant-HEV antibodies is worldwide [10,23].

Although Korea is not an endemic area of hepatitis E, the human HEV genotype III was previously isolated from Korean population, and also the human HEV genotype IV, which was first isolated by our research team [24,25]. Limited cases of acute viral hepatitis E have been reported, and few studies have been conducted on the epidemiology of this infection in Korea.

Given that the sample size used for our study was relatively small, our data might not be an accurate representation of the entire population. However, this study does provide certain important information concerning the prevalence of HAV and HEV in Korea based on age, sex, and residency. Furthermore efforts are needed to clarify the prevalence in the younger generation (i.e. below 10 years) and the modes of transmission involved.

Acknowledgement

This work was supported by Korea Centers for Disease Control and Prevention, Korea (3300-3338-300, 4800-4863-300).

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