MAJOR ARTICLE

Decline in Hepatitis E Virus Antibody Prevalence in the United States From 1988–1994 to 2009–2010

Eyasu H. Teshale, Maxine M. Denniston, Jan Drobeniuc, Saleem Kamili, Chong-Gee Teo, and Scott D. Holmberg

Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Previous population-based estimates in the United States have shown a relatively high prevalence of hepatitis E virus (HEV) antibody. We sought to determine whether changes in the prevalence of HEV antibody have occurred over time.

Methods. We analyzed data from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) and NHANES III (1988–1994). Using the same serologic assay, we compared the estimated anti-HEV immunoglobulin G (IgG) prevalence and risk factors for antibody positivity for the 2 periods.

Results. The prevalence of HEV antibody among those aged ≥6 years declined from 10.2% (95% confidence interval [CI], 9.1%–11.4%) during 1988–1994 to 6.0% (5.2%–6.8%) during 2009–2010, and the prevalence for those of US birth ranged from 9.6% (8.4%–10.9%) to 5.2% (4.4%–6.2%). Among US-born persons, the estimated HEV antibody prevalence declined significantly for all subgroups of age, sex, region of residence, and number of persons per room in the household; significant declines also were observed for persons at or above poverty level and for persons of non-Hispanic white, non-Hispanic black, and Mexican American race/ethnicity. No clear associations with food consumption were found.

Conclusions. The anti-HEV prevalence is declining in the United States. Although the decline suggests a decrease in exposure to HEV over time, the risks associated with exposure remain unknown.

Keywords. Hepatitis E virus; seroprevalence; NHANES; anti-HEV; IgG assay.

Hepatitis E in developed countries is now recognized as a disease with unique clinical and epidemiological characteristics [1, 2]. In contradistinction to developing countries, where both sporadic and epidemic cases of hepatitis E occur from drinking water contaminated by feces of persons infected with hepatitis E virus (HEV) or from person-to-person spread [3, 4], in developed countries it can be a foodborne zoonosis resulting from consumption of raw or undercooked meat and offal of HEV-infected pigs, boars, and deer [5–8]. There is also evidence suggesting that HEV may be transmitted by eating fecally contaminated shellfish [9, 10].

A previous study by Kuniholm et al estimated that the prevalence of immunoglobulin G (IgG) antibody to HEV in the United States was 21% (95% confidence interval [CI], 19%–22.9%), based on testing persons who participated in the Third National Health and Nutrition Examination Survey (NHANES III) during 1988–1994 [11]. Similar high seroprevalences have been documented among blood donors, veterinary workers, persons with chronic liver disease, and injection drug users sampled from different parts of the United States [11–15]. Further, the force of incident infection with HEV in the United States has been estimated to be 7 infections per 1000 susceptible persons per year [16].

However, these study findings do not align with acute hepatitis E encountered in the United States. To date, few cases of locally acquired acute hepatitis E have been documented in the United States [17], even among immunocompromised persons [18], with the exception of recipients of solid-organ transplants [19, 20]

Received 20 May 2014; accepted 12 August 2014; electronically published 21 August 2014.

Correspondence: Eyasu H. Teshale, MD, 1600 Clifton Rd, MS G-37, Atlanta, GA 30333 (eteshale@cdc.gov).

The Journal of Infectious Diseases® 2015;211:366–73

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2014. This work is written by (a) US Government employee(s) and is in the public domain in the US.

DOI: 10.1093/infdis/jiu466

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

and persons with presumed drug-induced liver toxicity [21] or chronic liver disease [22]. Moreover, for persons with a diagnosis of incident hepatitis E, no definitive link with known foods or recreational activities has been established [17–21], unlike cases reported from Japan [5, 6, 8] or France [7].

Another factor confounding the understanding of the epidemiology of hepatitis E in the United States relates to differences in performance characteristics of serologic assays used for detecting anti-HEV antibodies, particularly of the IgG class, whose presence in peripheral blood signifies prior HEV exposure or infection [23–28]. Few studies have compared the prevalence of anti-HEV IgG over time by using the same serologic assay, and none were population based [24]. We report here findings of a study using a single serological assay to determine the prevalence of anti-HEV IgG among NHANES participants and to determine whether changes occurred from 1988–1994 to 2009–2010, and to identify factors associated with seropositivity for both periods, particularly among 2009–2010 participants, from whom information on potential food-associated risks (ie, shellfish consumption) was available.

METHODS

Survey Design

The NHANES, conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), collects nationally representative data on the health and nutritional status of the US noninstitutionalized civilian population. NHANES uses a complex, stratified, multistage probability sampling design and collects information by using standardized interviews, physical examinations, and tests of biologic samples. For NHANES III, data were collected from nearly 30 000 persons from 1988 through 1994; for NHANES 2009–2010, data were collected from approximately 5000 persons per year. Participants were interviewed in their homes by using the Computer-Assisted Personal Interviewing (interviewer-administered) system to ascertain demographic characteristics and in the Mobile Examination Center to ascertain possible risks and exposures for HEV infection. Persons aged ≥16 years and emancipated minors were interviewed directly; an adult proxy provided information for participants aged <16 years and for individuals unable to answer the questions themselves. All participants provided written informed consent. More detailed information on survey design for NHANES, including institutional review board approval is accessible on the NHANES Web site (http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm).

Subsampling of NHANES III Participants

A subset of NHANES III specimens was chosen by selecting a stratified random sample of 6000 participants, using SAS PROC SURVEYSELECT (SAS, version 9.2; SAS Institute, Cary, NC). After consideration of the estimated standard errors and confidence interval (CI) half-widths that might be obtained for variables of interest with sample sizes ranging from 1000 to 6000, a sample size of 6000 was chosen because that was expected to allow estimation of the anti-HEV IgG prevalence, stratified by select demographic characteristics, with a precision comparable to that of the estimates of Kuniholm et al [11]. All NHANES III participants aged ≥6 years who had an anti-HEV antibody result from that study and a positive sampling weight were eligible for sampling. Sampling was stratified on the basis of the test results obtained by Kuniholm et al (positive or negative), to sample specimens with a positive result at a higher rate. Unequal probability of selection was conducted to ensure a sufficient number of positive results for statistical analysis should a lower antibody prevalence be found by means of the serological assay we used. Thus, unweighted prevalence will differ greatly from weighted prevalence estimates.

Laboratory Testing

Serological testing was performed using the anti-HEV IgG assay manufactured by Diagnostic System (DSI, Saronno, Italy). Samples that were initially reactive were retested in duplicate for confirmation. The analytical sensitivity of the DSI assay was 1.6 IU/mL, as determined by using serial dilutions of the World Health Organization Reference Reagent for Hepatitis E Virus Antibody (code 95/584; 100 IU/mL, purchased from the National Institute of Biological Standards and Control, Potters Bar, Hertfordshire, United Kingdom). Specificity was evaluated using a panel consisting of 1008 NHANES sera tested by the DSI assay and an in-house Western blotting assay, which found that among 890 DSI-reactive samples, 863 were reactive by Western blotting, thereby giving a 97% concordance (unpublished data).

Statistical Analysis

SAS-callable SUDAAN (version 11.0), a statistical package designed to analyze complex survey data, was used for analysis. Estimates were weighted to represent the total US noninstitutionalized civilian population and to account for oversampling and nonresponse to the household interview and physical examination. Weights (WTPFEX6) for the subsample of NHANES III participants were adjusted to account for the fact that not all NHANES III participants were tested for HEV antibody by Kuniholm et al [11] and were further adjusted for the unequal selection probabilities for subsampling by multiplying the initially adjusted WTPFEX6 weight by the subsampling weight from SAS ProcSurvey Select. A P value of $< .05$ was considered significant.

We used repeated reactivity by the DSI assay as measure of persons ever exposed to HEV. In addition to demographic characteristics such as age, sex, race/ethnicity, place of birth, and region of residence, our analysis also included risks and exposures

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

Table 1. Prevalence of Anti-Hepatitis E Virus (HEV) Immunoglobulin G Among Individuals Aged ≥6 Years, by Select Demographic Characteristics: National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2009–2010

	NHANES III (1988–1994)[a]			NHANES 2009–2010		
Characteristic	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)
Overall	5966	1000	10.2 (9.1–11.4)	7885	490	6.0 (5.2–6.8)
Age, y						
6–29	2149	130	2.6 (1.8–3.7)[b]	3129	34	1.1 (.7–1.9)[c]
30–39	964	137	9.9 (7.4–13.1)	949	39	4.2 (3.0–5.7)
40–49	736	157	13.5 (10.4–17.4)	1043	68	5.9 (4.1–8.5)
50–59	545	148	21.4 (17.2–26.2)	874	81	8.4 (6.0–11.5)
60–69	677	186	20.8 (17.0–25.3)	901	119	13.0 (10.3–16.3)
≥70	895	242	19.5 (16.9–22.3)	989	149	14.6 (12.3–17.3)
Sex						
Male	2802	520	10.7 (9.2–12.5)	3906	260	6.2 (4.9–7.9)
Female	3164	480	9.7 (8.3–11.3)	3979	230	5.7 (4.9–6.7)
Race/ethnicity						
Non-Hispanic white	2297	456	10.9 (9.4–12.6)[b]	3465	243	6.3 (5.2–7.6)[d]
Non-Hispanic black	1640	142	5.6 (4.5–7.0)	1416	52	3.4 (2.3–4.9)
Mexican American	1774	362	11.2 (9.6–13.1)	1697	114	6.2 (4.7–8.1)
Other	255	40	9.9 (6.8–14.4)	1307	81	6.5 (4.8–8.6)
Country of birth						
United States	4721	653	9.6 (8.4–10.9)[b]	6058	303	5.2 (4.4–6.2)[b]
Mexico	825	270	19.1 (16.4–22.2)	767	89	10.0 (7.7–13.0)
Other	400	76	13.2 (9.9–17.2)	1054	98	9.6 (6.5–14.0)
Region of residence						
South	2487	323	6.9 (5.9–8.2)[b]	2629	107	3.6 (2.7–4.7)[b]
Northeast	766	117	10.4 (8.0–13.5)	1256	82	7.1 (5.2–9.6)
Midwest	1237	249	13.5 (10.8–16.9)	1933	141	7.0 (5.7–8.5)
West	1476	311	11.1 (8.7–14.1)	2067	160	7.1 (5.8–8.5)

Data are based on the DSI anti-HEV test.

Abbreviation: CI, confidence interval.

[a] Results are for a random subsample of NHANES III specimens tested with the DSI assay. Because of unequal probabilities of selection, unweighted prevalences will differ greatly from weighted prevalence estimates.

[b] $P < .01$, by the χ^2 test, within a given period.

[c] $P < .001$, by the χ^2 test, within a given period.

[d] $P < .05$ by the χ^2 test, within a given period.

investigated by Kuniholm et al [11], noting that some risks and exposures included in their analysis were slightly different for NHANES 2009–2010 participants, owing to differences in questionnaire content between the 2 surveys. In particular, more-detailed questions concerning frequency of shellfish consumption were added to the questionnaire for 2009–2010.

Bivariate analyses were used to estimate the anti-HEV IgG prevalence by demographic characteristics, and the prevalence of potential risk factors or exposures among population subgroups. χ^2 tests were used for statistical comparisons between subgroups within a given period. CIs were used to compare prevalence across surveys, with differences being considered significant if the estimate for the later survey was not included in the 95% CI of the corresponding estimate from the earlier survey. Potential risk factors and exposures were investigated only for those who reported having been born in the United States. Simple and multivariate logistic regression models were used to identify factors associated with anti-HEV IgG positivity. Separate logistic analyses controlling for age, sex, race/ethnicity, and region of residence were performed for each risk factor or exposure. Although some variables in our analyses were age dependent (ie, based on the age eligibility for certain tests or questions), we maintained, to the extent possible, consistency with those used in the analysis by Kuniholm et al [11]. Differences in risk factors over time were assessed by comparing the significance of the factor within each survey. Because variables for region of residence and metro/nonmetro residence were not available in the public use data for NHANES 2009–2010,

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

analyses were performed in the NCHS' Restricted Data Center (RDC). To protect participant confidentiality, analyses for small subgroups are not released by the RDC; thus, no results are available for male-to-male sex as a risk factor.

RESULTS

Of the 30 390 persons aged ≥6 years sampled for the NHANES III during 1988–1994, 25 733 (76.4%) were interviewed, and 23 070 of those interviewed (88.3%) were examined. Kuniholm et al [11] performed anti-HEV IgG testing on 18 695 examined participants with available serum specimens; of these, 3963 (21.0%; 95% CI, 19.0%–22.9%) tested positive [11]. Of the randomly selected subset of 6000 NHANES III participants with samples previously tested by Kuniholm et al for anti-HEV IgG, 5966 had serum specimens available for our testing with the DSI assay. Of these, 1000 (10.2%; 95% CI, 9.1%–11.4%) were positive for anti-HEV IgG (Table 1). Of the 11 357 sampled for NHANES 2009–2010 aged ≥6 years, 8814 (77.6%) were interviewed, and 8591 of those interviewed (97.5%) were examined. Serum samples were available for DSI testing for 7885 examined participants (91.8%). Of these, 490 (6.0%; 95% CI, 5.2%–6.8%) tested positive for anti-HEV IgG. The anti-HEV IgG prevalence among US-born participants was 9.6% (95% CI, 8.4%–10.9%) for 1988–1994 and 5.2% (95% CI, 4.4%–6.2%) for 2009–2010 (Table 1). For all participants, anti-HEV prevalence declined in all age groups from 1988–1994 to 2009–2010 (Figure 1).

Among all participants and US-born participants, the estimated anti-HEV IgG prevalence between the 2 study periods declined significantly for all subgroups age group and sex (Tables 1 and 2). Among the US-born participants, declines also were found by region of residence, by number of persons per room in the household, among persons at or above poverty level, for those residing in both metropolitan and nonmetropolitan areas, and for those of non-Hispanic white, non-Hispanic black, or Mexican American race/ethnicity (Table 2). For both surveys, age, race/ethnicity, region of residence, number of persons per room in the household, and income were significantly associated with anti-HEV IgG positivity, with lower prevalence among younger persons, residents of the South, those below the poverty level, and those living in more-crowded conditions and higher prevalence among non-Hispanic whites (Table 2).

For the 1988–1994 participants, risk factors associated with higher antibody prevalence in bivariate (χ^2) analyses were military service, never having used cocaine or crack, less frequent consumption of processed meats, and hepatitis A virus (HAV) antibody positivity. After adjustment for age, sex, race/ethnicity, and region of residence, only anti-HAV positivity remained significantly associated with anti-HEV positivity (Table 3). For the 2009–2010 participants, higher antibody prevalence was significantly associated in bivariate analyses with having a well, cistern, or spring as the source of tap water for drinking; with less frequent consumption of processed meats; and with more-frequent consumption of green leafy vegetables or lettuce salad. Not drinking tap water was significantly associated with a lower antibody prevalence. After adjustment for age, sex, race/ethnicity, and region of residence, the only risk factor significantly associated with seropositivity was more-frequent consumption of processed meats, but this factor was protective (Table 3).

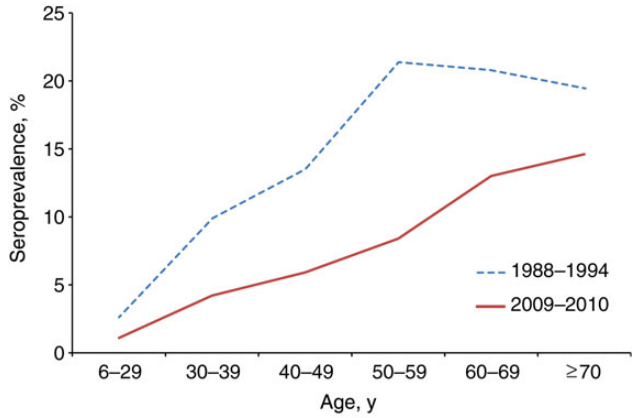

Figure 1. Estimated prevalence of anti-hepatitis E virus immunoglobulin G, by age group, National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2009–2010.

DISCUSSION

The estimated overall anti-HEV IgG prevalence in the United States declined by approximately 40% from 1988–1994 (10.2%) to 2009–2010 (6.0%). The prevalence decreased across age groups, sex, race/ethnicity, country of birth, and region of residence. The higher prevalence among older persons in both periods despite the decline in prevalence for all age groups may indicate that exposures to and infections by HEV are occurring at a lower rate in younger persons. Persons who live in crowded situations and below the poverty line were found to have a significantly lower prevalence than those who live in less crowded situations and lived at or above the poverty line. These findings suggest that HEV infection may be associated with relative affluence. However, the nature of affluent lifestyle or behavior that would lead to HEV infection remains to be identified.

Among NHANES participants from both study periods, less frequent consumption of processed meats was associated with higher seropositivity rates. Such lesser frequency, however, would not mean more-frequent consumption of nonprocessed meats, which would include meats that were eaten raw or inadequately cooked, nor would consumption of meat (whether processed or not) necessarily relate to affluence. Nonetheless, the finding of an association between

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

Table 2. Prevalence of Anti-Hepatitis E Virus (HEV) Immunoglobulin G Among US-Born Individuals Aged ≥6 Years, by Select Demographic Characteristics: National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2009–2010

	NHANES III (1988–1994)[a]			NHANES 2009–2010		
Characteristic	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)
Total	4721	653	9.6 (8.4–10.9)	6058	303	5.2 (4.4–6.2)
Age, y						
6–29	1713	50	1.9 (1.2–3.0)[b]	2655	16	0.5 (.3–.8)[b]
30–39	691	76	9.6 (6.9–13.1)	669	15	2.6 (1.4–4.7)
40–49	542	89	13.2 (9.6–17.8)	685	37	5.0 (3.2–7.6)
50–59	430	109	21.5 (17.1–26.7)	611	49	8.2 (5.5–12.1)
60–69	566	142	20.1 (16.4–24.4)	629	75	12.3 (9.5–15.8)
≥70	779	187	18.0 (15.5–20.7)	809	111	13.8 (11.4–16.5)
Sex						
Male	2176	331	10.0 (8.4–11.9)	3004	152	5.1 (3.9–6.7)
Female	2545	322	9.2 (7.8–10.8)	3054	151	5.3 (4.4–6.3)
Race/ethnicity						
Non-Hispanic white	2183	421	10.6 (9.2–12.4)[b]	3278	214	6.0 (4.8–7.4)[c]
Non-Hispanic black	1533	136	5.7 (4.5–7.2)	1251	47	3.4 (2.2–5.2)
Mexican American	940	91	4.7 (3.4–6.3)	926	24	2.4 (1.4–4.4)
Other	65	5	2.7 (1.0–6.9)[d]	603	18	2.4 (1.2–4.6)[d]
Region of residence						
South	2120	220	6.0 (5.0–7.3)[b]	2184	78	3.3 (2.7–4.0)[c]
Northeast	608	98	10.5 (7.7–14.0)	847	45	5.7 (2.8–11.1)[d]
Midwest	1104	212	13.4 (10.8–16.6)	1717	119	6.8 (5.5–8.3)
West	889	123	9.5 (6.8–13.2)	1310	61	5.3 (4.1–6.8)
No. of persons/room						
<0.8	3380	566	10.8 (9.4–12.4)[b]	4418	281	6.0 (5.0–7.1)[b]
≥0.8	1326	86	5.0 (3.4–7.3)	1604	21	1.5 (.8–2.9)[d]
Residence						
Nonmetropolitan	2576	325	7.9 (6.4–9.8)[e]	1049	68	6.2 (4.7–8.0)
Metropolitan	2145	328	11.6 (9.8–13.7)	5009	235	5.0 (4.0–6.1)
Poverty index						
At or above poverty line	3322	525	10.5 (9.1–12.1)[b]	4334	233	5.5 (4.6–6.6)[e]
Below poverty line	1031	74	3.2 (2.2–4.7)	1303	44	3.3 (2.0–5.5)

Data are based on the DSI anti-HEV test.

Abbreviation: CI, confidence interval.

[a] Results are for a random subsample of NHANES III specimens tested with the DSI assay. Because of unequal probabilities of selection, unweighted prevalences will differ greatly from weighted prevalence estimates.

[b] $P < .001$, by the χ^2 test, within a given period.

[c] $P < .01$, by the χ^2 test, within a given period.

[d] Estimate has a relative standard error (RSE) of >30%. Estimates with a RSE of >30% and estimates based on <10 positive persons may be unstable and should be interpreted with caution.

[e] $P < .05$, by the χ^2 test, within a given period.

more-frequent consumption of green leafy vegetables or lettuce salad and higher rate of anti-HEV prevalence among NHANES 2009–2010 participants might possibly reflect the preference by more-affluent participants for organic food products, but that possibility remains speculative. Detailed inquiry into shellfish consumption habits among the NHANES 2009–2010 participants did not generate significant associations, although the questions did not cover the eating of filter-feeding bivalves other than oysters and clams, such as mussels and cockles, that inhabit shallow water beds or the consumption of raw shellfish [29].

The high anti-HEV prevalence reported from developed countries, where hepatitis E outbreaks are not observed, remains to be explained. One possibility is the poor sensitivity and specificity of anti-HEV IgG assays used in seroprevalence studies of populations at low risk of HEV infection, such as

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

Table 3. Estimated Prevalence of Anti-Hepatitis E Virus (HEV) Immunoglobulin G and Adjusted Odds Ratios (ORs) for Anti-HEV Positivity, Based on DSI Anti-HEV Testing, Among US-Born Individuals, by Select Characteristics: National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2009–2010

	NHANES III (1988–1994)[a]				NHANES 2009–2010			
Characteristic	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)	Adjusted OR[b] (95% CI)	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)	Adjusted OR[b] (95% CI)
Military service[c]								
No (reference)	3175	486	10.8 (9.5–12.2)[d]	1.1 (.8–1.7)	3840	232	6.0 (5.0–7.2)	0.6 (.3–1.03)
Yes	666	155	17.4 (13.2–22.5)		665	63	7.1 (5.0–9.7)	
Source of tap water in house[e]								
Water company (reference)	3688	515	9.2 (8.0–10.5)	1.1 (.7–1.5)	5022	234	4.8 (3.6–6.5)	1.2 (.6–2.2)
Well or spring	564	87	11.6 (7.8–16.9)		870	63	6.9 (4.8–10.0)	
Source of tap water for drinking[e]								
Water company (reference)	. . .	. . .	. . .	. . .	3969	193	5.1 (3.7–7.0)[f]	
Well/cistern/ spring					742	51	7.0 (4.6–10.6)	1.1 (.5–2.4)
Don't drink tap water					945	38	3.3 (2.2–4.8)	0.8 (.5–1.1)
Sex partners in lifetime, no.[g]								
1–10 (reference)	1695	224	10.4 (8.6–12.6)	1.2 (.7–1.9)	1643	60	4.1 (3.0–5.7)	0.8 (.6–1.3)
>10	491	73	11.8 (8.2–16.5)		815	32	3.8 (2.5–5.9)	
Ever used cocaine or crack[g]								
No (reference)	1961	272	11.2 (9.4–13.2)[f]	0.8 (.5–1.3)	2527	135	5.1 (4.3–6.2)	1.1 (.6–1.8)
Yes	301	32	6.8 (4.3–10.7)		629	28	5.0 (3.0–8.2)	
Have any pet[e]								
No (reference)	3016	413	9.9 (8.6–11.3)	1.1 (.8–1.4)	ND	ND	. . .	. . .
Yes	1704	240	9.2 (7.3–11.6)					
Have a dog[e]								
No (reference)	3630	486	9.2 (8.0–10.6)	1.3 (.9–1.8)	ND	ND	. . .	. . .
Yes	1090	167	10.5 (8.0–13.7)					
Have a cat[e]								
No (reference)	3986	553	9.9 (8.8–11.1)	0.9 (.6–1.2)	ND	ND	. . .	. . .
Yes	734	100	8.4 (6.0–11.6)					
Eat bacon, sausage, or processed meats (no. times/mo)[h]								
0–10 (reference)	2830	495	12.5 (10.8–14.3)[f]	0.9 (.6–1.2)	2845	136	5.2 (4.4–6.2)[d]	0.7 (.4–.99)
>10	1024	147	9.7 (7.6–12.4)		1112	38	3.1 (2.1–4.4)	
Eat liver or other organ meats in past 30 d[h]								
No (reference)	2822	479	11.5 (9.9–13.4)	1.1 (.8–1.5)	ND	ND	. . .	. . .
Yes	1031	162	12.7 (10.0–16.1)					
Eat pork or ham (no. of times/month)[h]								
0–5 (reference)	3076	529	12.2 (10.6–14.0)	0.9 (.6–1.3)	ND	ND	. . .	. . .
>5	778	112	10.1 (7.2–14.0)					
Eat green leafy vegetables/lettuce salad (no. of times in past 30 d)[i]								
0–5 (reference)	ND	ND	ND	. . .	2419	67	2.9 (1.8–4.4)[d]	
6–12					1255	45	4.2 (2.6–6.4)	1.1 (.6–2.0)
>12					1200	66	6.4 (4.9–8.2)	1.4 (.8–2.6)
Eat any shellfish in past 30 d[e]								
Yes	2072	341	11.4 (9.5–13.8)	1.3 (.9–1.8)	2883	141	4.9 (3.9–6.3)	0.9 (.6–1.3)
No (reference)	1778	298	12.0 (10.0–14.2)		2980	147	5.3 (4.3–6.5)	
Eat clams in past 30 d[e]								
Yes	ND	ND	. . .	. . .	325	27	7.2 (4.6–11.1)	1.2 (.8–1.9)
No (reference)					5538	261	5.0 (4.2–5.9)	

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

Table 3 continued.

Characteristic	NHANES III (1988–1994)[a]				NHANES 2009–2010			
	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)	Adjusted OR[b] (95% CI)	No. Tested	No. Positive	Weighted Percentage Positive (95% CI)	Adjusted OR[b] (95% CI)
Eat crab in past 30 d[e]								
Yes	ND	ND	. . .	. . .	726	39	4.8 (3.2–7.4)	1.1 (.7–1.8)
No (reference)					5137	249	5.2 (4.3–6.2)	
Eat lobster in past 30 d[e]								
Yes	ND	ND	. . .	. . .	235	16	6.8 (4.2–10.9)	1.1 (.6–1.9)
No (reference)					5628	272	5.0 (4.2–6.0)	
Eat oysters in past 30 d[e]								
Yes	ND	ND	. . .	. . .	273	14	3.3 (1.5–7.3)[j]	0.7 (.3–1.4)
No (reference)					5590	274	5.2 (4.4–6.2)	
Eat scallops in past 30 d[e]								
Yes	ND	ND	. . .	. . .	349	22	6.2 (4.4–8.7)	0.9 (.5–1.7)
No (reference)					5514	266	5.0 (4.1–6.2)	
Eat shrimp (no. of times in past 30 d)[e]								
0 (reference)	ND	ND	. . .	. . .	3439	173	5.4 (4.5–6.4)	
1–2					1744	79	4.5 (3.3–6.2)	0.8 (.5–1.2)
>2					681	36	5.5 (3.6–8.2)	0.9 (.6–1.4)
HCV antibody positive[e]								
No (reference)	4607	642	9.6 (8.4–11.0)	0.6 (.2–1.6)	5967	296	5.1 (4.3–6.2)	1.8 (.5–6.0)
Yes	100	8	5.5 (1.9–14.6)[j]		91	7	10.3 (3.4–27.2)[j]	
HBc antibody positive[e]								
No (reference)	4409	602	9.4 (8.2–10.7)	1.2 (.6–2.2)	5877	287	5.1 (4.3–6.1)	1.1 (.5–2.2)
Yes	309	50	13.6 (8.5–21.1)		181	16	7.6 (4.0–13.8)	
HAV antibody positive[e]								
No (reference)	2786	326	8.8 (7.2–10.6)[f]	0.7 (.5–.9)	3722	188	5.2 (4.2–6.4)	1 (.7–1.4)
Yes	1933	326	11.8 (10.0–13.9)		2132	105	5.3 (4.2–6.7)	

Ages included for each variable will vary depending on age eligibility for a particular question or laboratory test.

Abbreviations: CI, confidence interval; HAV, hepatitis A virus; HBc, hepatitis B virus core antigen; HCV, hepatitis C virus; ND, not determined in the survey.

[a] Results from a random subsample of NHANES III specimens tested with the DSI assay. Because of unequal probabilities of selection, unweighted prevalences will differ greatly from weighted prevalence estimates.

[b] Adjusted for age, sex, race, and region of residence.

[c] Among participants aged >17 years.

[d] $P < .01$, by the χ^2 test, within a given period.

[e] Among participants aged >6 years.

[f] $P < .05$, by the χ^2 test, within a given period.

[g] Among participants aged 20–59 years.

[h] Among NHANES III participants aged >12 years and among NHANES 2009–2010 participants aged 12–69 years.

[i] Among participants aged 12–69 years.

[j] Estimate has a relative standard error (RSE) of >30%. Estimates with a RSE of >30% and estimates based on <10 positive persons may be unstable and should be interpreted with caution.

blood donors and persons drawn from the general community. In such contexts, studies have shown substantial differences in the performance of anti-HEV IgG assays [22, 25, 27, 28]. Our current study, in which we used the DSI assay for analysis of the 1988–1994 NHANES III specimens, showed a prevalence of 10.2%, which is lower than the 21% prevalence reported by Kuniholm et al [11]. This disparity could be due to differences in performances between the assays applied.

This study has the following limitations. First, NHANES data are only generalizable to the US noninstitutionalized civilian population because it excludes homeless individuals, persons living in correctional institutions, and individuals living in other group quarters (eg, students living in dormitories and military recruits). Second, small sample sizes for some of the variables may have limited our power to detect statistically significant differences between subgroups. Third, the self-reported

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018

information is subject to recall bias. Fourth, the level of detail regarding some of the dietary questions was limited to frequency of consumption and lacked important information that may contribute to risk (eg, whether shellfish was consumed cooked or raw), thus limiting our ability to find significant associations even for those dietary sources of infection that are already known. Finally, the duration of IgG anti-HEV after exposure is not well known. In a serological follow up of 320 persons known to have hepatitis E during an outbreak, 50% of the cases still had detectable anti-HEV IgG 14 years later [30]. It remains unknown whether the antibody prevalence in our study populations is a result of recent or remote infection. Nonetheless, given the lower antibody prevalence in younger persons, the higher prevalence in the older population is likely a result of infection that took place in the remote past.

In conclusion, our data show a decline in the seroprevalence of anti-HEV in the United States from 1988–1994 to 2009–2010, but the prevalence is still relatively high, at 6.0%. Whether this decline is a consequence of factors such as a decrease in exposure of susceptible persons due to lifestyle or behavioral changes or a change in the etiologic agent over time remains to be answered.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. This work was supported by the Divisions of Viral Hepatitis at the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Teshale EH, Hu D, Holmberg SD. The two faces of hepatitis E. Clin infect Dis **2010**; 51:328–34.
2. Faber M, Wenzel J, Jilg W, et al. Hepatitis E virus seroprevalence among adults, Germany. Emer Inf Dis **2012**; 10:1654–7.
3. Teshale EH, Howard CM, Grytdal SP, et al. Evidence of person-to-person transmission of hepatitis E virus during large outbreak in Northern Uganda. Clin Infect Dis **2010**; 50:1006–10.
4. Aggarwal R, Jameel S. Hepatitis E. Hepatology **2011**; 54:2218–26.
5. Miyashita K, Kang JH, Saga A, et al. Three cases of acute or fulminant hepatitis E caused by ingestion of pork meat and entrails in Hokkaido, Japan: Zoonotic food-borne transmission of hepatitis E virus and public health concerns. Hepatol Res **2012**; 42:870–8.
6. Teo CG. Much meat, much malady: changing perceptions of the epidemiology of hepatitis E. Clin Microbiol Infect **2010**; 16:24–32.
7. Colson P, Borentain P, Queyriaux B, et al. Pig liver sausage as a source of hepatitis E virus transmission to humans. J Infect Dis **2010**; 202:825–34.
8. Mizuo H, Yakazi Y, Sugawara K, et al. Possible risk factors for the transmission of hepatitis E virus and for the severe form of hepatitis E acquired locally in Hokkaido, Japan. J Med Virol **2005**; 76:341–9.
9. Crossan C, Baker PJ, Craft J, et al. Hepatitis E virus genotype 3 in shellfish, United Kingdom. Emerg Infect Dis **2013**; 18:2085–7.
10. Said B, Ijaz S, Kafatos G, et al. Hepatitis E outbreak on cruise ship. Emerg Infect Dis **2009**; 15:1738–44.
11. Kuniholm MH, Purcell RH, McQuilllan GM, Engle RE, Wasley A, Nelson KE. Epidemiology of hepatitis E virus in the United States: results from the Third National Health and Nutrition Examination Survey, 1988–1994. J Infect Dis **2009**; 200:48–56.
12. Thomas DL, Yarbough PO, Vlahov D, et al. Seroreactivity to hepatitis E virus in areas where the disease is not endemic. J Clin Microbiol **1997**; 35:1244–7.
13. Drobeniuc J, Favorov MO, Shapiro CN, et al. Hepatitis E virus antibody seroprevalence among persons who work with swine. J Infect Dis **2001**; 184:1594–7.
14. Meng XJ, Wiseman B, Elvinger F, et al. Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries. J Clin Microbiol **2002**; 40:117–22.
15. Atiq M, Shire NJ, Barrett A, et al. Hepatitis E virus antibodies in patients with chronic liver disease. Emerg Infect Dis **2009**; 15:479–81.
16. Faramawi MF, Johnson E, Chen S, et al. The incidence of hepatitis E virus infection in the general population of the USA. Epidemiol Infect **2011**; 139:1145–50.
17. Drobeniuc J, Greene-Montfort T, Le NT, et al. Laboratory-based surveillance for hepatitis E virus infection, United States, 2005–2012. Emerg Infect Dis **2013**; 19:218–22.
18. Crum-Cianflone NF, Curry F, Drobeniuc J, et al. Hepatitis E virus infection in HIV-infected persons. Emerg Infect Dis **2012**; 18: 502–6.
19. Davern TJ, Chalsani N, Fontana RJ, et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. Gastroenterology **2011**; 141:1665–72.e1–9.
20. Yoo N, Bernstein J, Caldwell C, et al. Hepatitis E virus infection in a liver transplant recipient: delayed diagnosis due to variable performance of serologic assay. Transpl Infect Dis **2013**; 15:166–9.
21. Te HS, Drobeniuc J, Kamili S, et al. Hepatitis E virus infection in a liver transplant recipient in the United States: a case report. Transplant Proc **2013**; 45:810–3.
22. Mast EE, Alter MJ, Holland PV, et al. Evaluation of assays for antibody to hepatitis E virus by a serum panel. Hepatitis E Virus Antibody Serum Panel Evaluation Group. Hepatology **1998**; 27:857–61.
23. Mansuy JM, Legrand-Abravanel F, Calot JP, et al. High prevalence of anti-hepatitis E virus antibodies in blood donors from South West France. J Med Virol **2008**; 80:289–93.
24. Christensen PB, Engle RE, Hjort C, et al. Time trend of the prevalence of hepatitis E antibodies among farmers and blood donors: a potential zoonosis in Denmark. Clin Infect Dis **2008**; 47:1026–31.
25. Bendall R, Ellis V, Ijaz S, et al. A comparison of two commercially available anti-HEV IgG kits and a re-evaluation of anti-HEV seroprevalence data in developed countries. J Med Virol **2010**; 82:799–805.
26. Drobeniuc J, Meng J, Reuter G, et al. Serologic assays specific to immunoglobulin M antibodies against hepatitis E virus: pangenotypic evaluation of performances. Clin Infect Dis **2010**; 51:e24–7.
27. Verhoef L, Koopmans M, Duizer E, Bakker J, Reimerink J, Van Pelt W. Seroprevalence of hepatitis E antibodies and risk profile of HEV seropositivity in The Netherlands, 2006–2007. Epidemiol Infect **2012**; 140:1838–47.
28. Wenzel JJ, Preiss J, Schemmerer M, et al. Test performance characteristics of anti-HEV IgG assays strongly influence hepatitis E seroprevalence estimates. Clin Infect Dis **2013**; 207:497–500.
29. Ijaz S, Vyse AJ, Morgan D, Pebody RG, Tedder RS, Brown D. Indigenous hepatitis E virus infection in England: more common than it seems. J Clin Virol **2009**; 44:272–6.
30. Khuroo MS, Khuroo MS. Seroepidemiology of a second epidemic of hepatitis E in a population that had recorded first epidemic 30 years before and has been under surveillance since then. Hepatol Int **2010**; 4:494–9.

Downloaded from https://academic.oup.com/jid/article-abstract/211/3/366/2912187
by Stephen B. Thacker CDC Library user
on 28 February 2018