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BRIEF REPORT

Prevalence of Hepatitis B and Hepatitis D Virus Infections in the United States, 2011–2016

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Among adults in the 2011-2016 National Health and Nutrition Examination Survey (NHANES), the estimated prevalence of hepatitis B surface antigen (HBsAg) was 0.36% overall and 3.4% in non-Hispanic Asians. Among adult HBsAg carriers, 42% had antibodies to hepatitis delta virus (anti-HDV). Routine anti-HDV testing should be considered for HBsAg carriers.

Keywords. HBV; HDV; National Health and Nutrition Examination Survey; NHANES.

Hepatitis delta virus (HDV) is a defective human RNA virus that requires the presence of hepatitis B surface antigen (HBsAg) for transmission and persistence [1]. Acute hepatitis D infection occurs following simultaneous acquisition of HDV and hepatitis B virus (HBV) or via HDV superinfection of HBsAg carriers. Simultaneous acquisition of both viruses is often self-limiting in adults and rarely leads to chronic HDV infection (approximately 2%), while HDV superinfection of HBsAg carriers results in chronic HDV infection in nearly all cases (approximately 90%) [1, 2]. In comparison to HBV infection alone, HBV/HDV coinfection is associated with increased progression to cirrhosis, hepatocellular carcinoma, end-stage liver disease, and death [1, 3, 4].

The global burden of HDV infection is unknown. However, Chen et al recently estimated that more than 60 million individuals worldwide have been exposed to HDV [5]. HDV epidemiology varies substantially by geographic region and is also changing over time, partially due to dynamic migration patterns and the scale-up of prophylactic HBV vaccination. HDV prevalence is primarily monitored by the detection of total antibodies to HDV (anti-HDV) among HBsAg carriers [6]. Detectable anti-HDV indicates prior HDV exposure or ongoing HDV infection. Ideally, HDV RNA is measured in anti-HDV–positive individuals to confirm the presence of ongoing HDV infection; however, commercial HDV RNA assays are not widely available.

In the United States, HDV infection is believed to be rare, but surveillance data are limited. Unlike HBV infection, HDV infection is not nationally notifiable. Anti-HDV testing is rarely conducted in the United States [7, 8], thereby limiting the validity of prevalence estimates calculated using electronic medical records. Even systematic anti-HDV testing of HBsAg carriers in clinical cohorts can yield biased estimates [9], as these studies may exclude high-risk HBsAg carriers who are unaware of their HBV infection and/or not engaged in care. HDV serosurveys have been conducted in community-recruited samples, but these studies have predominantly been limited to persons who inject drugs [10].

In this study, population-based data from the National Health and Nutrition Examination Survey (NHANES) were used to estimate the prevalence of ongoing HBV infection and seroprevalence of HDV infection in the US household population.

METHODS

NHANES is a cross-sectional survey continuously conducted by the National Center for Health Statistics (NCHS). NHANES uses a stratified, multistage probability cluster sampling scheme and is designed to be representative of the noninstitutionalized US civilian resident population. Certain minority subpopulations are sampled at higher proportions in order to obtain more reliable and precise estimates among these subgroups (eg, non-Hispanic Asians were oversampled beginning in 2011). Each year, data are obtained from 15 US counties; pooling data from multiple years is recommended to achieve a more representative sample. NHANES consists of a household interview and a follow-up medical examination, where a blood sample is collected for laboratory testing. Data were deidentified and made publicly available in adjacent 2-year cycles. This analysis was waived from review by the Johns Hopkins University School of Medicine Institutional Review Board.

This study was conducted using pooled data from the 2011–2016 NHANES. Examination response rates for persons aged ≥6 years were 67.9% in 2011–2012, 67.3% in 2013–2014, and 57.6% in 2015–2016, yielding 24 133 respondents. The analytic sample was restricted to 21 832 (90.5%) participants who had complete data on demographic characteristics (age, sex, race/ethnicity, and birthplace), HBV core antibody status, HBsAg status, and anti-HDV status. Anti-HDV status was determined using the DiaSorin anti-HDV enzyme-linked immunosorbent assay (ELISA) kit (ETI-AB-DELTAK-2).

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Data are provided for the overall population aged ≥6 years; however, the primary analysis was restricted to adults aged ≥18 years. The prevalence of HBsAg and anti-HDV in the adult population was compared by demographic characteristics using Wald χ^2 tests. The prevalence of anti-HDV among adult HBsAg carriers was examined using descriptive statistics, owing to relatively small sample sizes. As a supplemental analysis, we also examined serologic markers of liver function (eg, FIB-4 index) and awareness of liver disease by HBsAg and anti-HDV status. In 2013–2016, participants were questioned if they were ever diagnosed with hepatitis B. Thus, we also estimated the proportion of adult HBsAg carriers who were aware of their HBV infection.

All analyses used survey weights to adjust for differential sampling probabilities (eg, oversampling of non-Hispanic Asians), unit nonresponse, and noncoverage of the noninstitutionalized US civilian population. To additionally account for excluded examinees, NCHS medical examination weights for each cycle were post-stratified to US population totals by age–sex–race strata. Taylor series linearization was used to calculate standard errors; logit-transformed 95% confidence intervals (CIs) were calculated for prevalence estimates. The analysis was conducted using *svy* commands in Stata SE, version 14.2 (StataCorp).

RESULTS

Among persons aged ≥6 years (n = 21 832), prevalence of HBsAg was 0.28% (95% CI, 0.22%–0.35%), corresponding to approximately 862 000 (95% CI, 668 000–1 056 000) persons with ongoing HBV infection. Prevalence of anti-HDV among persons aged ≥6 years was 0.11% (95% CI, 0.08%–0.17%), corresponding to approximately 357 000 (95% CI, 210 000–503 000) persons with past or ongoing HDV infection.

Among children aged 6–17 years (n = 5689), HBsAg was only detected in 1 participant—a foreign-born, Asian male who was anti–HDV-negative. Among adults aged ≥18 years (n = 16 143), prevalence of HBsAg was 0.36% and prevalence of anti-HDV was 0.15% (Table 1). Asian and foreign-born adults had the highest prevalence of HBsAg and anti-HDV (Table 1).

All anti–HDV-positive adults were HBsAg positive (n = 43). Among HBsAg-positive adults (n = 113), 42% were anti–HDV-positive, with a prevalence of 33% and 46% in HBsAg-positive US-born and foreign-born adults, respectively (Table 1). Anti-HDV prevalence was 45% in Asian HBsAg-positive adults and 39% in HBsAg-positive adults of all other races/ethnicities.

Several serological markers associated with liver disease were higher among HBsAg-positive/anti–HDV-positive adults, especially compared to HBsAg-negative/anti–HDV-negative adults (Supplementary Table S1). Among HBsAg-positive adults, a higher proportion of anti–HDV-positive individuals reported being diagnosed with liver disease (30% [95% CI, 17%–46%]) in comparison to anti–HDV-negative individuals (9% [95% CI, 5%–16%]). In a separate analysis of HBsAg-positive adults in 2013–2016, only 33% (95% CI, 18%–51%) were aware of their HBV infection. Awareness of HBV infection among

Table 1. Prevalence of Ongoing Hepatitis B Virus Infection and Seroprevalence of Hepatitis D Virus Infection in the Noninstitutionalized US Civilian Population Aged ≥18 Years—National Health and Nutrition Examination Survey, 2011–2016

		Overall Adult Population						Anti-HDV Among Adult HBsAg Carriers
		HBsAg			Anti-HDV			
Characteristic	No. Tested	No. Positive	% (95% CI)	*P* Value	No. Positive	% (95% CI)	*P* Value	% (95% CI)
Total	16 143	113	0.36 (0.29–0.46)		43	0.15 (0.10–0.23)		42 (29–56)
Age group, y				.604			.441	
18–49	8690	59	0.34 (0.25–0.47)		21	0.13 (0.08–0.22)		38 (24–54)
≥50	7453	54	0.39 (0.27–0.56)		22	0.18 (0.10–0.33)[a]		46 (27–66)
Sex				.333			.998	
Female	8310	47	0.32 (0.24–0.43)		21	0.15 (0.08–0.28)[a]		47 (27–68)
Male	7833	66	0.41 (0.28–0.58)		22	0.15 (0.09–0.25)		37 (26–50)
Race/ethnicity[b]				<.001			<.001	
Asian, non-Hispanic	1964	70	3.37 (2.62–4.32)		29	1.51 (1.03–2.20)		45 (30–60)
Other races/ethnicities	14 179	43	0.19 (0.14–0.25)		14	0.07 (0.03–0.16)[a]		39 (19–63)
Birthplace				<.001			<.001	
US born	11 227	33	0.16 (0.10–0.24)		9	0.05 (0.02–0.15)[c]		33 (13–63)[a]
Foreign born	4916	80	1.30 (0.96–1.76)		34	0.60 (0.40–0.90)		46 (33–60)

Data are unweighted sample sizes and weighted prevalence estimates with corresponding logit-transformed 95% confidence intervals. *P* values were determined using design-adjusted Wald χ^2 tests. Statistical tests were not performed when comparing anti-HDV prevalence among HBsAg carriers due to low sample sizes.

Abbreviations: anti-HDV, hepatitis D antibody; CI, confidence interval; HBsAg, hepatitis B surface antigen.

[a]Estimate is potentially unstable (relative standard error, ≥30% and <40%).

[b]Race/ethnicity was collapsed into categories that maximized the stability of the prevalence estimates. The "Other races/ethnicities" group includes racial groups precoded by the National Center for Health Statistics: non-Hispanic whites, non-Hispanic blacks, Hispanics, and other/multiracial persons.

[c]Estimate is potentially unstable (relative standard error, 51%).

HBsAg-positive adults was higher in those with anti-HDV (47% [95% CI, 27%–68%]) than in those without anti-HDV (15% [95% CI, 6%–32%]).

DISCUSSION

This population-based study suggests that HDV seroprevalence is significantly higher in the United States than formerly acknowledged. These new data indicate that the population-level prevalence of ongoing HBV infection and anti-HDV in the adult US household population is disproportionately higher among Asians and persons born outside the United States. To the best of our knowledge, this is the first study to estimate HDV seroprevalence among HBsAg carriers in the US household population; more than one-third of adult HBsAg carriers in this study were anti-HDV positive.

As previously noted, the presence of anti-HDV is evidence of past or ongoing HDV infection [6]. Since HDV RNA data were not available, it is unclear what proportion of anti–HDV-positive/HBsAg-positive cases observed in this study had ongoing HDV infection. Given that 90% of HDV superinfections progress into chronicity and that anti-HDV titers decline over time in resolved HBV/HDV coinfections, the majority of the anti–HDV-positive/HBsAg-positive cases in this study likely reflect ongoing HDV infections [1, 6]. This hypothesis is supported by the finding that HBsAg carriers with HDV antibodies were most likely to be diagnosed with liver disease (and HBV infection) and exhibit higher liver enzyme levels. Nonetheless, the prevalence of ongoing (chronic) HDV infection in the United States should be examined in future studies.

The need for population-based designs to study HBV and HDV epidemiology is underscored by the fact that the majority of HBsAg carriers were not aware of their HBV infection. This is the first NHANES analysis of HBsAg and anti-HDV to use 6 years of data during which Asians were oversampled, providing the most representative national sample of Asians. HBV and HDV infections are endemic in several Asian countries [5, 6, 11], thus it is unsurprising that prevalence of HBsAg and anti-HDV was highest in the foreign-born and Asian populations. For example, in a national sample of HBsAg carriers in Mongolia, nearly 60% were anti–HDV-positive [11].

This study has limitations. Since there was a relatively small number of individuals who were anti-HDV positive, additional NHANES cycles will be needed to improve the precision of estimates and examine associations with additional characteristics that are also relatively uncommon (eg, injection drug use). The systematic exclusion of high-risk populations (eg, homeless and incarcerated persons) from the NHANES sampling frame suggests these data may not be generalizable to the entire United States and may potentially underestimate the true seroprevalence of HDV infection in the United States. This study may have also overestimated the seroprevalence of HDV infection. Although the DiaSorin anti-HDV ELISA kit has been shown to have 100% sensitivity and 100% specificity compared to antibody-based methods used in US reference laboratories [12], one study in Mongolia suggests the DiaSorin anti-HDV ELISA kit may have lower specificity in comparison to a novel antibody capture assay [11].

Currently, the American Association for the Study of Liver Disease recommends anti-HDV testing for HBsAg carriers who are at high risk of HDV infection. In contrast, the European and Asian Associations for the Study of the Liver both recommend routine anti-HDV testing among all HBsAg carriers. Given the high prevalence of anti-HDV among HBsAg carriers in this national population-based study, adopting a similar testing strategy in the United States should be considered. Prospects of new HDV treatment strategies underscore the need to identify patients living with chronic HDV infection [13–15]. In addition, HBsAg carriers without prior HDV exposure should be counseled on their risk for HDV superinfection. Increasing equitable coverage of prophylactic HBV vaccination also remains critical for the elimination of HBV and HDV.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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