Chronic Hepatitis B Prevalence Among Foreign-Born and U.S.-Born Adults in the United States, 1999-2016

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Hepatitis B virus (HBV) infection remains a major global health problem, exacerbated by poor linkage to care. We aimed to determine the prevalence of HBV infection, exposure, self-reported vaccination, vaccine-induced immunity, disease awareness, and treatment in the United States by birthplace and race/ethnicity during 1999-2016. A total of 47,628 adult participants in the National Health and Nutrition Examination Survey who completed HBV core antibody (anti-HBc) and surface antigen (HBsAg) tests and 47,618 adults who completed HBV surface antibody (anti-HBs) and anti-HBc tests were included in the analysis. HBV infection was defined by positive HBsAg and past exposure by positive anti-HBc. Vaccine-mediated immunity was defined by positive anti-HBs and negative anti-HBc. No significant change in the prevalence of HBV infection was observed between 1999 and 2016 (P = 0.442), affecting 0.35% (95% confidence interval [CI], 0.28-0.45) or 0.84 million adults. In contrast, a significant decrease in HBV exposure and increase in vaccine-mediated immunity was observed. U.S.-born persons had significantly lower prevalence of HBV infection and exposure as well as higher prevalence of vaccine-mediated immunity and self-reported vaccination than foreign-born persons. Prevalence of HBV infection was highest in non-Hispanic Asians in both foreign- (3.85%; 95% CI, 2.97-4.97) and U.S.-born (0.79%; 95% CI, 0.17-3.59) persons during 2011-2016. Among infected persons, liver disease awareness was only 15.19%, and treatment rate was only 4.60%. *Conclusion:* This study revealed disparities of HBV infection among ethnic/racial groups and between U.S.-born and foreign-born persons. Awareness of liver disease and treatment rate among infected persons was dismal. (HEPATOLOGY 2020;71:431-443).

Hepatitis B virus (HBV) infection continues to be a global health threat and a leading cause of cirrhosis and primary liver cancer, globally affecting approximately 257 million people according to the World Health Organization in 2015 and 292 million people according to the Polaris Observatory in 2016.[1,2] In the United States, prior analyses of noninstitutionalized persons without adequate sampling of racial/ethnic minorities estimated that there was a total of 847,000 persons with HBV infection in 2011-2012.[3] However, the total burden has been estimated to be as high as 2.2 million in analyses that accounted for HBV prevalence in high-risk U.S.-born and immigrant populations.[4]

Poor disease awareness and linkage to care may contribute to the high disease burden of HBV.[2-4] The Racial and Ethnic Approaches to Community Health study, which surveyed 28 minority communities across the United States, reported poor awareness and linkage to care among ethnic minorities.[5] Studies

from community and academic medical centers have also shown suboptimal evaluation and undertreatment even among those linked to care.[6-9]

Non-Hispanic Asians are an important ethnic minority group with probably the highest disease burden from HBV in the United States, yet prior iterations of one of the largest national programs for the study of the health of adults and children in the United States, the National Health and Nutrition Examination Survey (NHANES), did not adequately sample non-Hispanic Asians. To remedy this deficiency, Asians have been oversampled since 2011 to provide more nationally representative data.[10]

Therefore, we aimed to use the NHANES database from 1999 to 2016 to provide population estimates for HBV infection, exposure, immunity, liver disease awareness, liver disease severity, and treatment rates for all major racial/ethnic groups including Asian Americans and examine the impact of birthplace (U.S. vs. foreign born).

Participants and Methods

DATA SOURCE AND STUDY POPULATION

Our study used data from NHANES 1999-2016. Details of survey design and laboratory methods can be found in Supporting Appendix S1. NHANES has been approved by the National Center for Health Statistics Research Ethics Review Board of the CDC and all participants provided written informed consent before participation in NHANES. To determine the prevalence of HBV exposure and infection, we included adult participants aged 18 years and older who had completed hepatitis B core antibody (anti-HBc) and hepatitis B surface antigen (HBsAg)

testing. For self-reported vaccination history, we included patients who answered questions regarding vaccination history in the NHANES questionnaire. For vaccine-induced immunity, we identified participants who had both hepatitis B surface antibody (anti-HBs) and anti-HBc testing. Participant birthplace was based on self-reporting.

DATA EXTRACTION AND VARIABLE DEFINITION

Analysis of HBV Prevalence, Exposure, Serologic Evidence of Vaccine-Mediated Immunity, and Self-Reported Vaccination History

We defined HBV infection as seropositivity for HBsAg and exposure to HBV as seropositivity for anti-HBc. Serologic evidence of vaccine-mediated immunity was defined as seropositivity for anti-HBs and seronegativity for anti-HBc. Those who were anti-HBs and anti-HBc reactive were considered as having immunity by prior exposure.

For history of self-reported vaccination, we extracted data on participant response to the questionnaire regarding history of vaccination. Participants who responded "yes, all three doses" to the question "have you ever received the 3-dose series of the hepatitis B vaccine?" were defined as having history of vaccination.

Analysis of HBV Disease Severity, Concurrent Fatty Liver, General Health Care Use, Awareness of Liver Disease, and Treatment Rate for HBV Infection

We evaluated liver disease severity by liver enzymes (aspartate aminotransferase [AST]) and alanine

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aminotransferase [ALT]) and Fibrosis-4 (FIB-4) score.[11] The formula for FIB-4 score is (age*AST level)/(platelet count*$ALT^{1/2}$). We also extracted relevant laboratory data to calculate the United States Fatty Liver Index (USFLI) to identify patients with concurrent fatty liver.[12] Participants with a USFLI >30 were considered to have fatty liver.

Awareness of having a liver disease, general health care use, and rate of treatment for HBV infection were assessed through the NHANES questionnaire. To evaluate participant awareness of liver disease, we extracted the response to the survey question "Has a doctor or other health professional ever told you that you had any kind of liver condition?" This question is not specific for HBV infection, but participants who were aware of HBV infection would most likely be aware that they had a liver condition. The answer to this question is binary—either "yes" or "no."

For participant health care use within the past 12 months, we extracted the response to the survey question "During the past 12 months, how many times have you seen a doctor or other health care professional about your health at a doctor's office, a clinic, a hospital emergency room, at home, or some other place?" Finally, we estimated the rate of anti-HBV treatment based on NHANES interviewer review of all prescribed medication containers. If no container was available at the time of interview, the interviewer asked the participant to verbally report the name of the medication. A list of HBV antiviral drugs recorded in NHANES can be found in Supporting Table S1.

Analysis by Race/Ethnicity and Birthplace

Birthplace of each subject was categorized as U.S. born or foreign born. Participants were asked to select one of the six racial/ethnic groups that fits them best: non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, non-Hispanic Asian, and other-multiracial. Data on non-Hispanic Asians were only available for 2011 to 2016 survey. Therefore, race/ethnicity-specific analyses only included data from NHANES 2011-2016.

Analysis for Time Trends

Trends analyses were conducted for 1999-2016. In addition, subgroup analyses were conducted by combining data for three 6-year periods: 1999-2004, 2005-2010, and 2011-2016.

STATISTICAL ANALYSES

Adjusted prevalence estimates of HBV infection, HBV exposure, self-reported vaccination history, and hepatitis B vaccine–mediated immunity were calculated for each NHANES survey cycle, from 1999 to 2016. Trends analyses were conducted using logistic regression, with NHANES survey cycle as the dependent variable. Race/ethnic specific estimates for HBV infection, HBV exposure, self-reported vaccination history, and hepatitis B vaccine–mediated immunity were calculated using data from 2011 to 2016, as NHANES only began oversampling for non-Hispanic Asians from 2011.

Population estimates for HBV infection, exposure, and immunity in the general population were calculated using NHANES data from the most recent cycles 2011-2016, which has adequate sample size for subanalyses on race/ethnicity-specific population estimates. In order to calculate the population estimates, adjusted prevalence estimates were multiplied by population totals from the American Community Survey of the U.S. Census Bureau averaged over their respective time periods.

Univariate and multivariate logistic regression were used to estimate odds ratios relating various participant characteristics to disease awareness, and multinomial logistic regression was used to estimate risk ratios relating participant characteristics to health care use. All variables that had a $P < 0.10$ in stepwise forward logistic regression, or those that were clinically relevant, were included in the model.

A two-tailed P value of < 0.05 was considered to be statistically significant. Weighted analyses were performed using STATA 15.1 (Stata Corporation, College Station, TX), which allows appropriate use of the NHANES survey weights to project the results of the analysis to the noninstitutionalized, general population of the United States.

Results

STUDY POPULATION

As shown in Fig. 1, of the 92,062 participants in NHANES between 1999 and 2016, we excluded

38,714 of those aged younger than 18 years. We then separated the NHANES participants into three groups based on completion of HBsAg, anti-HBc, and both anti-HBc and anti-HBs tests. Among the 53,348 participants aged 18 years or older, 89.31% (n = 47,650) were tested for both HBsAg and anti-HBc; all but 10 of these were also tested for anti-HBs. Twenty-two persons were excluded because of missing birthplace data. In total, we included 35,263 U.S.-born and 12,365 foreign-born persons who completed HBsAg testing and anti-HBc testing and 35,255 U.S.-born and 12,363 foreign-born persons in the study analyses.

PREVALENCE OF HBV INFECTION, EXPOSURE, SELF-REPORTED VACCINATION HISTORY, AND SEROLOGIC EVIDENCE OF VACCINE-MEDIATED IMMUNITY

Overall Analysis and Analysis by Birthplace

Overall, 232 (0.49%) persons included in the study tested HBsAg positive, of whom 88 were U.S. born (37.90%) and 144 were foreign born (62.10%). During 1999-2016, there was no significant change in the prevalence of HBV infection in the general U.S. population, with an adjusted overall prevalence of 0.31% (95% confidence interval [CI], 0.20-0.50) during 1999-2000 and 0.29% (95% CI, 0.18-0.47) during 2015-2016 ($P = 0.442$; Fig. 2A). Since 2011, when oversampling of Asians was initiated, HBV prevalence was higher among foreign-born versus U.S.-born persons. In addition, despite variations in NHANES cycles, there were no statistically significant changes in HBV prevalence for either U.S.-born ($P = 0.347$) or foreign-born ($P = 0.270$) groups (Fig. 2B; Table 1).

We observed a significant decrease in the prevalence of HBV exposure from 5.80% (95% CI, 4.51-7.42) during 1999-2000 to 4.69% (95% CI, 3.89-5.65) during 2015-2016 ($P = 0.014$; Fig. 2C). However, on subanalysis by birthplace, this decrease was observed only in U.S.-born persons from 4.22% (95% CI, 3.31-5.36) in 1999-2000 to 2.66% (95% CI, 2.13-3.30) in 2015-2016 ($P < 0.001$), but not in the foreign-born group ($P = 0.437$; Fig. 2D; Supporting Table S2).

During 1999-2016, the prevalence of vaccine-mediated immunity increased significantly from 10.8% (95% CI, 9.8-12.0) in 1999-2000 to 23.1% (95% CI, 20.8-25.6) in 2015-2016 ($P < 0.001$; Fig. 2A,C) overall, with increases in both the U.S.-born (from 11.3% [95% CI, 10.2-12.6] to 23.6% [95% CI, 21.1-26.4]; $P < 0.001$) and foreign-born groups (from 8.5% [95% CI, 6.26-11.3] to 21.0% [95% CI, 17.9-24.5]; $P < 0.001$).

Out of the whole study population of 47,621, a total of 33,867 participants (71.12%) did not have complete vaccination, with 32,457 participants (67.22%) responding "No" to any vaccination and 1,410 (3.07%) to "less than three doses." We observed a discrepancy in the prevalence of self-reported vaccination history and vaccine-mediated immunity by serologic results (anti-HBs reactive but anti-HBc negative). For example, in 2011-2016, 36.79% (95% CI, 35.56-38.04) of participants reported having completed the three-dose hepatitis B vaccine series, but serologic evidence of vaccine-mediated immunity was observed in only 23.11% (95% CI, 21.96-24.30; Supporting Tables S3 and S4).

Analysis by Age, Race/Ethnicity, and Birthplace Among Cohorts Studied in 2011-2016

The prevalence of HBV infection was lowest among the younger age groups and highest among the older age groups, with the exception of non-Hispanic blacks, whose HBV prevalence did not vary with age (0.54%-0.75%; $P = 0.905$; Fig. 3). Among non-Hispanic blacks, HBV prevalence was generally higher in U.S.-born than in foreign-born persons, except for those in the 18-34 age group (Fig. 3, third panel). In contrast, among non-Hispanic Asians, the vast majority of persons with HBV infection were foreign born, and this was true across all age groups (Fig. 3, sixth panel).

The prevalence of HBV exposure as well as immunity through prior exposure increased with age (Fig. 4). As expected, the prevalence of serologic evidence of vaccine-mediated immunity was highest in young adults and lower in older adults (Fig. 4, gray bar). Additional information on race/ethnicity-specific prevalence of HBV infection, exposure, and vaccine-mediated immunity stratified by various demographic variables in foreign-born and U.S.-born participants can be found in Supporting Tables S5 and S6, respectively.
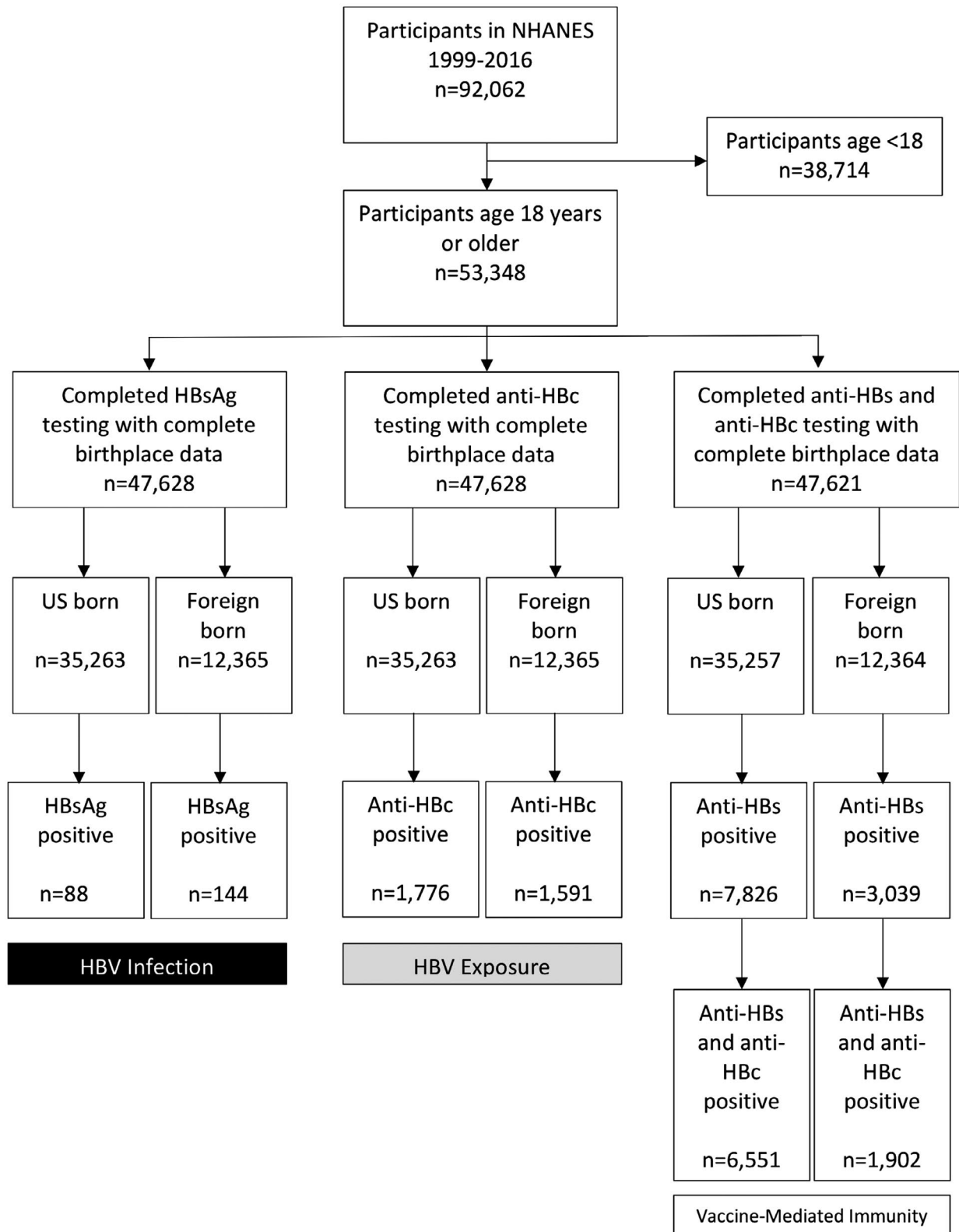
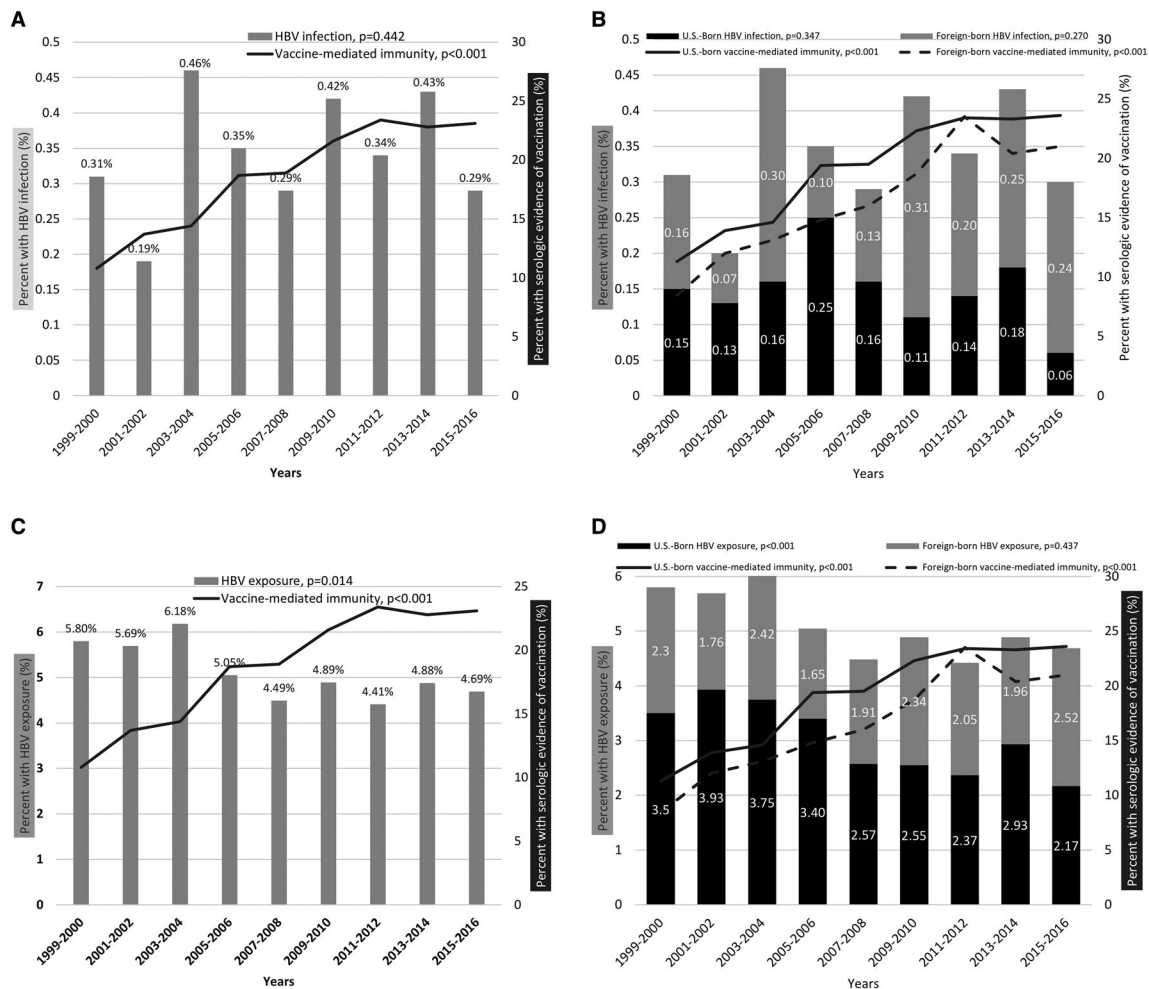**FIG. 1.** Flowchart for cohort selection from NHANES 199-2016.

FIG. 2. (A,B) Trends in HBV infection (positive HBsAg) and vaccine-mediated immunity (positive anti-HBs with negative anti-HBc), 1999-2016. (A) Overall and (B) by birthplace. (C,D) Trends in HBV exposure (positive anti-HBc) and vaccine-mediated immunity (positive anti-HBs with negative anti-HBc), 1999-2016. (C) Overall and (D) by birthplace.

Population Estimates of HBV Infection, Exposure, and Serologic Evidence of Vaccine-Mediated Immunity

Population level analyses for the most recent time period of 2011-2016 estimated a total of 0.84 million (95% CI, 0.67-1.07 million) persons with HBV infection, 11.10 million (95% CI, 9.91-12.44 million) persons with prior exposure to HBV, and 54.98 million (95% CI, 52.19-57.87 million) persons with vaccine-mediated immunity among the general noninstitutionalized U.S. population (Supporting Table S7). Supporting Tables S8, S9, and S10 described the race/ethnicity-specific population estimates for

the overall population, the U.S.-born population, and the foreign-born population, respectively.

Analysis of the HBV-Infected Cohort: Demography, Disease Severity, General Health Care Use, Disease Awareness, and Treatment Rate

Based on data of the 232 persons with HBV infection, population estimates on various demographic and clinical characteristics of the population infected with HBV were calculated and are described in Table 2. The mean age was 46.50 ± 15.9 years, 61.29% were male, and 56.80% were foreign born. Among the

TABLE 1. Prevalence of HBV Infection (Positive HBsAg), 1999-2016

Characteristics	1999-2004		2005-2010		2011-2016		Trends Analysis
	Sample Size	Adjusted % (95% CI)	Sample Size	Adjusted % (95% CI)	Sample Size	Adjusted % (95% CI)	P Value
Overall	14,876	0.32 (0.24-0.43)	16,601	0.35 (0.25-0.50)	16,148	0.35 (0.28-0.45)	0.602
Sex							
Male	7,121	0.40 (0.28-0.58)	8,094	0.51 (0.33-0.78)	7,835	0.40 (0.28-0.57)	0.926
Female	7,758	0.24 (0.14-0.43)	8,094	0.21 (0.13-0.32)	8,507	0.31 (0.23-0.42)	0.408
Age groups (years)							
18-34	5,182	0.35 (0.20-0.64)	5,037	0.29 (0.14-0.58)	4,764	0.30 (0.19-0.47)	0.641
35-49	3,346	0.33 (0.19-0.58)	4,031	0.32 (0.17-0.60)	3,927	0.37 (0.25-0.57)	0.710
50-64	2,804	0.36 (0.20-0.65)	3,731	0.60 (0.39-0.94)	3,981	0.41 (0.26-0.64)	0.898
65+	3,547	0.18 (0.08-0.45)	3,802	0.16 (0.08-0.34)	3,476	0.35 (0.17-0.70)	0.241
Birthplace							
United States	11,528	0.17 (0.12-0.25)	12,503	0.21 (0.13-0.33)	11,232	0.15 (0.10-0.24)	0.706
Foreign	3,351	1.16 (0.75-1.80)	4,098	1.07 (0.62-1.85)	4,916	1.28 (0.95-1.73)	0.675
Race/ethnicity							
NH white	7,162	0.08 (0.04-0.17)	7,894	0.18 (0.11-0.31)	6,060	0.11 (0.05-0.24)	0.633
NH black	2,917	1.05 (0.64-1.72)	3,327	0.78 (0.48-1.24)	3,571	0.69 (0.45-1.04)	0.201
Mexican American	3,596	0.03 (0.01-0.15)	3,204	0.06 (0.02-0.23)	2,298	0.17 (0.06-0.50)	0.092
Hispanic	665	0	1,404	0.24 (0.08-0.70)	1,729	0.06 (0.01-0.37)	0.390
NH Asian	0	N/A	0	N/A	1,964	3.41 (2.64-4.39)	N/A
Other	539	3.17 (1.95-5.12)	772	2.01 (1.06-3.79)	526	0.40 (0.12-1.30)	0.002
Education level (age 20+)							
<High school	4,304	0.59 (0.36-0.98)	4,526	0.36 (0.20-0.64)	3,480	0.49 (0.31-0.80)	0.571
High school	6,555	0.25 (0.17-0.38)	7,934	0.35 (0.22-0.57)	8,008	0.32 (0.24-0.45)	0.331
≥College	2,454	0.28 (0.11-0.68)	3,072	0.37 (0.18-0.75)	3,847	0.32 (0.20-0.52)	0.802
Birthplace and race/ethnicity							
United States	11,528	0.17 (0.12-0.25)	12,503	0.21 (0.13-0.33)	11,232	0.15 (0.10-0.24)	0.706
NH white	6,785	0.06 (0.03-0.15)	7,478	0.14 (0.08-0.24)	5,799	0.08 (0.03-0.22)	0.700
NH black	2,638	0.76 (0.46-1.25)	3,018	0.54 (0.30-0.97)	3,153	0.52 (0.32-0.85)	0.312
Mexican	1,611	0	1,279	0.09 (0.01-0.67)	1,032	0.14 (0.03-0.61)	0.207
Hispanic	227	0	415	0.37 (0.08-1.68)	530	0	0.831
NH Asian	0	N/A	0	N/A	291	0.79 (0.17-3.59)	N/A
Other	267	1.39 (0.35-5.38)	313	0.91 (0.22-3.65)	427	0.46 (0.14-1.54)	0.255
Foreign	3,351	1.16 (0.75-1.80)	4,098	1.07 (0.62-1.85)	4,916	1.28 (0.95-1.73)	0.675
NH white	377	0.38 (0.12-1.17)	416	1.06 (0.35-3.17)	261	0.64 (0.14-2.93)	0.556
NH black	279	3.84 (1.86-7.76)	309	2.95 (1.13-7.46)	418	1.94 (1.13-3.30)	0.138
Mexican	1,985	0.05 (0.01-0.27)	1,925	0.04 (0.01-0.17)	1,266	0.19 (0.04-0.88)	0.247
Hispanic	438	0	989	0.18 (0.03-0.93)	1,199	0.09 (0.01-0.53)	0.349
NH Asian	0	N/A	0	N/A	1,673	3.85 (2.97-4.97)	N/A
Other	272	4.72 (2.59-8.46)	459	2.70 (1.33-5.43)	99	N/A	0.068
Insured	11,596	0.30 (0.20-0.44)	12,542	0.33 (0.22-0.49)	12,737	0.33 (0.26-0.41)	0.699
Private	6,757	0.24 (0.15-0.37)	6,806	0.30 (0.17-0.54)	6,575	0.28 (0.20-0.38)	0.593
Government	4,741	0.40 (0.23-0.71)	5,678	0.38 (0.24-0.61)	6,042	0.41 (0.28-0.61)	0.902
Uninsured	3,100	0.44 (0.28-0.70)	4,041	0.46 (0.24-0.87)	3,386	0.50 (0.29-0.86)	0.758
Pregnant at time of survey	801	0.06 (0.01-0.41)	450	0.82 (0.21-3.21)	169	0	0.527
Poverty-income ratio							
<1	2,778	0.50 (0.24-1.03)	3,289	0.37 (0.17-0.78)	3,509	0.51 (0.32-0.82)	0.896

TABLE 1. *Continued*

| Characteristics | 1999-2004 | | 2005-2010 | | 2011-2016 | | Trends Analysis |
	Sample Size	Adjusted % (95% CI)	Sample Size	Adjusted % (95% CI)	Sample Size	Adjusted % (95% CI)	P Value
≥1	10,835	0.27 (0.19-0.38)	12,024	0.34 (0.23-0.50)	11,248	0.31 (0.22-0.42)	0.575
Military veteran	2,039	0.15 (0.07-0.31)	2,070	0.36 (0.13-0.98)	1,482	0.18 (0.07-0.42)	0.628
Heavy drinker*							
Male	1,946	0.35 (0.16-0.75)	2,443	0.46 (0.21-0.97)	2,455	0.26 (0.16-0.43)	0.516
Female	1,796	0.12 (0.34-0.39)	2,261	0.15 (0.05-0.47)	2,332	0.14 (0.06-0.33)	0.828
FIB-4 score							
<1.45	11,932	0.29 (0.21-0.42)	12,675	0.32 (0.21-0.48)	11,845	0.27 (0.20-0.37)	0.745
1.45-3.25	2,643	0.40 (0.20-0.80)	3,413	0.52 (0.30-0.89)	3,788	0.60 (0.39-0.91)	0.324
>3.25	304	1.11 (0.41-3.01)	513	0.36 (0.05-2.67)	515	0.70 (0.42-1.18)	0.586
ALT or AST >2 × ULN[†]	570	1.54 (0.64-3.65)	621	0.68 (0.13-3.39)	554	2.48 (1.26-4.83)	0.734
NAFLD[‡]	2,202	0.18 (0.06-0.53)	2,583	0.29 90.12-0.66)	2,365	0.34 (0.17-0.69)	0.334

*Heavy drinker defined as >2 drinks/day for men or >1 drink/day for women.
[†]AST ULN: 40 U/L; ALT ULN: 35 U/L for males, 25 U/L for females.[‡]
NAFLD defined by USFLI, USFLI ≥30.
Abbreviations: N/A, not applicable; NAFLD, nonalcoholic fatty liver disease; NH, non-Hispanic; ULN, upper limit of normal.

foreign born persons, non-Hispanic Asian made up the largest group (49.84%), followed by non-Hispanic black (25.55%). Among U.S.-born persons with HBV infection, the non-Hispanic white group made up the largest group (49.15%) followed by non-Hispanic black (45.53%).

Whereas foreign-born persons carried the majority of the HBV disease burden, U.S.-born persons with HBV infection were more likely to have elevated aminotransferases (ALT or AST >2 × upper limit of normal) compared with foreign-born persons (13.20% vs. 3.21%; P = 0.008). There was also a trend for a higher prevalence of advanced liver fibrosis in the U.S.-born group (6.28% FIB-4 >3.25 vs. 3.04%; P = 0.070). U.S.-born persons were also older and had a higher rate of significant alcohol use defined as >1 drink/day for women and >2 drinks/day for men (37.7% vs. 22.7%; P = 0.067). However, there was no significant difference in the prevalence of fatty liver between the U.S.-born and foreign-born groups as assessed by the USFLI (26.72% vs. 20.74%; P = 0.484).

Population estimates for liver disease awareness rates were based on data from the 191 persons who answered the survey question about having been told of a liver condition. Disease awareness rate was very low overall with only 15.19% of persons who tested HBsAg positive reporting having been told they had a liver condition by a doctor or other health

professionals. There were no statistically significant differences in the liver disease awareness rate between U.S.-born and foreign-born persons with HBV infection (P = 0.814; Table 2). In sensitivity analysis for disease awareness by time period, we found that there was no significant difference in the awareness rate among the 71 infected persons in 1999-2006 compared with the 120 persons in 2007-2016 (16.90%, 95% CI, 8.77-30.09 vs. 13.80, 95% CI, 8.39-21.85; P = 0.61). Notably, the majority of both U.S.-born (96.60%) and foreign-born (65.70%) participants with HBV infection reported having received care at least once in the 12 months preceding the survey. In multivariable logistic regression (Supporting Table S12), after controlling for age, sex, insurance status, race/ethnicity, birthplace, poverty, and educational levels, the only independent predictor for increased disease awareness among infected persons was having one or more health care visits (versus none) in the previous 12 months (adjusted odds ratio = 5.22; P = 0.042). In an alternative model controlling for the same variables but with further breakdown of the number of health care visits in 12 months (1, 2-3, 4 or more versus none), we observed that having only one visit per year was not a statistically significant predictor for higher likelihood of disease awareness (adjusted odds ratio = 3.26; P = 0.175), whereas there was a trend with 2-3 visits a year (adjusted odds ratio = 5.24;
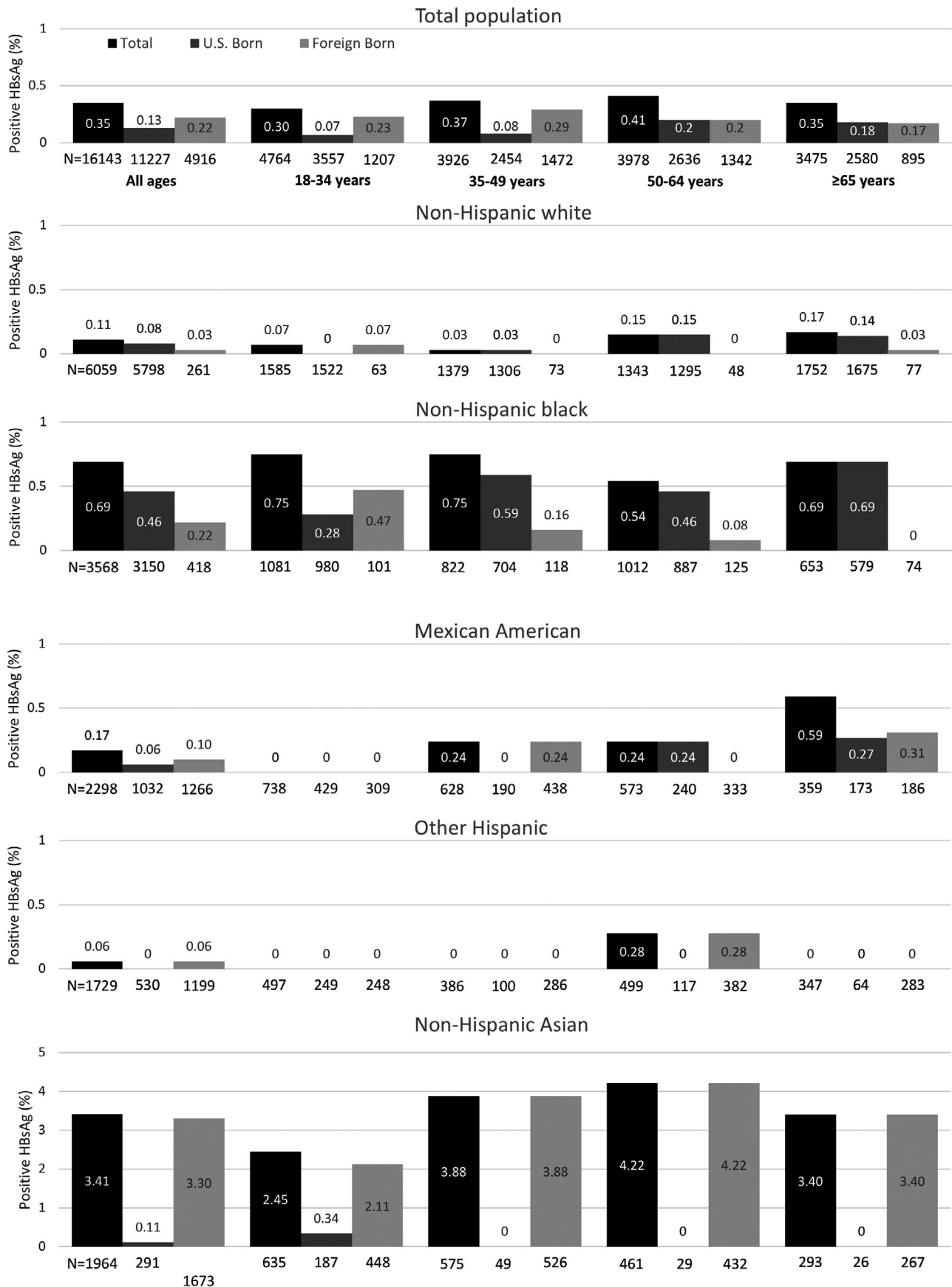
Total population

Non-Hispanic white

Non-Hispanic black

Mexican American

Other Hispanic

Non-Hispanic Asian

FIG. 3. Age- and birthplace-specific prevalence of HBV infection (positive HBsAg) by race/ethnicity, 2011-2016. The scale for non-Hispanic Asian (0-5) is different than those of other racial/ethnic groups (0-1) owing to the high prevalence.

P = 0.109), and having ≥4 health care visits in the past year was a statistically significant predictor (adjusted odds ratio = 19.00; P = 0.004). In multinomial logistic regression, older persons, female, U.S.-born, insured, and more educated persons were more likely to visit a health care facility in the previous 12 months (Supporting Table S11).

Of the 28 participants infected with HBV who were aware of their liver condition, 8 (26.26%) had received or were receiving antiviral treatment, giving an overall treatment rate of roughly 5% among all infected persons. Data for subanalysis by birthplace are shown in Table 2, but the sample sizes for subgroups were very small.

Supporting Fig. S1 shows the population estimates for HBV infection, awareness, overall treatment, and treatment among those aware of infection in this NHANES cohort, 1999-2016.

Discussion

Using the NHANES database, we determined that the prevalence of HBV infection in the general U.S. adult population from 1999 to 2016 remained stable, whereas the prevalence of HBV exposure significantly decreased and the prevalence of vaccine-mediated immunity significantly increased during this period.

Based on the most recent survey in 2015-2016, the prevalence of HBV infection was 0.29%, which equated to 0.71 million persons with HBV infection among the noninstitutionalized, general U.S. population. Overall, U.S.-born and younger persons showed a lower prevalence of HBV infection and exposure as well as a higher prevalence of vaccine-mediated immunity and self-reported vaccination than foreign-born and older persons. There was also a trend for higher rate of advanced fibrosis in U.S.-born HBV-infected persons compared with the foreign-born group, and this could be due to the older age and higher rate of significant alcohol use among the U.S.-born cohort.

A very encouraging finding for the U.S.-born population was the positive effect that the multifaceted efforts to reduce HBV infection (screening of pregnant women, universal infant and catch-up vaccinations, and screening of blood supply)[13-15] had in decreasing HBV exposure. However, despite the progress of vaccination coverage in the U.S., we found that more than 70% of the general adult population did not have serological evidence of vaccine-mediated immunity. Our results are also in line with recent reports that approximately 64 million U.S. persons considered to be high risk by the Centers for Disease Control and Prevention criteria still had undetectable immunity against HBV in 2013-2014 (69.4%),[16] suggesting that although these efforts are
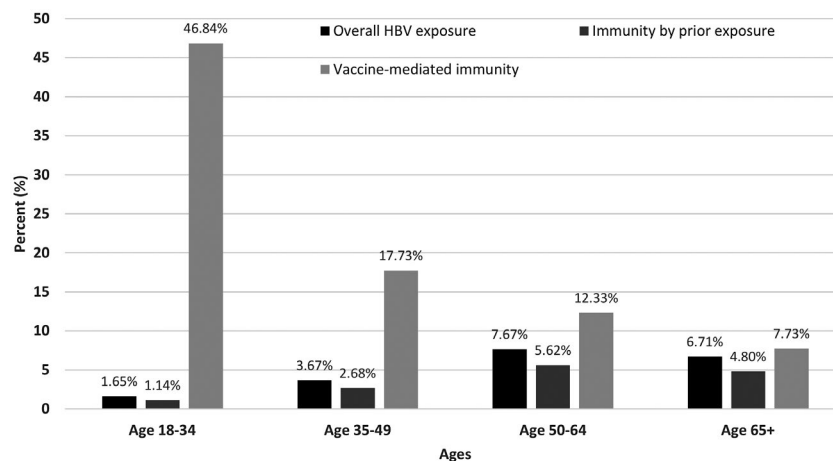

FIG. 4. Age-specific prevalence of overall HBV exposure (positive anti-HBc), immunity by prior exposure (positive anti-HBs and positive anti-HBc), and vaccine-mediated immunity (positive anti-HBs with negative anti-HBc), 2011-2016.

TABLE 2. Characteristics of Persons With HBV Infection (Positive HBsAg)

Variable	Total HBV (n = 232)*	U.S. born (n = 88)*	Foreign born (n = 144)*	P Value[†]
Age in years (mean ± SD)	46.50 ± 15.90	50.82 ± 14.28	43.2 ± 16.29	0.001
Male	61.29 (53.20-68.81)	61.82 (48.54-73.54)	60.90 (50.3-70.6)	0.913
Race/ethnicity				<0.001
NH white	33.96 (24.81-44.50)	49.15 (36.09-62.32)	18.30 (9.60-32.08)	
NH black	35.70 (27.55-44.75)	45.53 (33.05-58.59)	25.55 (17.42-35.83)	
Mexican American	3.06 (1.26-7.27)	2.34 (0.71-7.40)	3.81 (1.17-11.7)	
Other Hispanic	1.90 (0.68-5.16)	1.32 (0.27-6.17)	2.50 (0.66-9.01)	
NH Asian	25.38 (19.03-32.99)	1.66 (0.37-7.20)	49.84 (37.65-62.05)	
Awareness of liver disease	15.19 (10.11-22.19)	14.40 (7.30-26.44)	15.89 (9.44-25.53)	0.814
Treated among aware	26.26 (10.65-51.53)	49.49 (17.76-81.64)	7.68 (2.01-25.28)	0.021
Treated among all infected	4.60 (2.02-10.16)	7.03 (2.43-18.67)	2.54 (0.87-7.20)	0.158
Income-to-poverty ratio >1	79.17 (71.23-85.37)	82.12 (70.28-89.92)	76.67 (65.97-84.79)	0.416
Treated among income-to-poverty ratio >1	4.77 (1.72-12.50)	8.07 (2.44-23.53)	1.40 (0.33-5.84)	0.040
Insurance	75.35 (67.72-81.68)	83.37 (72.22-90.62)	69.25 (57.68-78.82)	0.065
Treated among insured	6.12 (2.69-13.33)	8.39 (2.94-21.70)	3.74 (1.21-10.99)	0.278
FIB-4> 3.25	4.44 (2.51-7.76)	6.28 (2.62-14.32)	3.04 (1.81-5.05)	0.070
% with NAFLD[‡]	23.45 (14.69-35.26)	26.72 (13.16-46.72)	20.74 (12.55-32.30)	0.484
ALT or AST> 2 × ULN[§]	7.54 (4.16-13.29)	13.20 (6.52-24.90)	3.21 (1.30-7.70)	0.008
Times received health care over past year				<0.001
0	21.01 (15.05-28.54)	3.40 (1.34-8.35)	34.30 (24.8-45.18)	
1-3	49.49 (41.95-57.11)	55.44 (41.14-68.89)	45.01 (36.96-53.32)	
4-9	12.84 (9.06-17.89)	14.33 (8.32-23.57)	11.72 (7.50-17.85)	
10+	16.65 (10.46-25.47)	26.83 (15.28-42.72)	8.98 (4.51-17.08)	

Note: Data are presented as proportion (95% CI) unless otherwise indicated.
*Data shown as population estimates derived from 232 infected persons, NHANES 1999-2016.
[†]P value represents the significant level of the comparison between U.S.-born and foreign-born patients with HBV.
[‡]NAFLD defined by USFLI, USFLI ≥30.
[§]AST ULN: 40 U/L; ALT ULN: 35 U/L for males, 25 U/L for females.
Abbreviations: NAFLD, nonalcoholic fatty liver disease; NH, non-Hispanic; ULN, upper limit of normal.

effective, efforts may need to be specifically targeted to those at the highest risk for HBV (foreign born, non-Hispanic Asian, adults with high-risk behaviors) to bring about a substantial decrease in HBV exposure.

Among U.S.-born persons, non-Hispanic blacks who were male, 50-64 years of age, heavy drinkers, and on government health care insurance were found to have the highest prevalence (0.54%) and the highest prevalence of exposure on the population level (8.35%). Such a finding may be due to a lower use of health care and thus a lower chance of HBV vaccination.[17,18] Together, these are important findings because Asians and blacks with chronic hepatitis B are known to have an 11-fold- and 7-fold-higher risk for developing hepatocellular carcinoma (HCC) than whites, respectively.[17] Furthermore, a recent study

found poorer survival of black patients with HCC compared with white patients.[19] Therefore, more efforts are needed to screen these high-risk persons for HBV, to enter them into an HCC surveillance program using culturally appropriate approaches, and to consider them for treatment to prevent long-term complications such as HCC.[18] Such a recommendation would also be in line with the report from a U.S. HBV screening surveillance study sponsored by the Centers for Disease Control and Prevention in which the investigators concluded that persons born in highly-HBV-endemic countries (China, Vietnam, Somalia, Myanmar, and Laos) should be considered high risk for HBV and screened appropriately.[20] Furthermore, we would suggest that both providers and at-risk populations need education and that the use of alerts in electronic health records or a clinical checklist with place

of birth should be used to improve HBV screening/diagnosis and treatment.[19-21]

The current study also noted that, among HBV-infected persons, only 15% of patients were aware of having a liver disease and only 5% received antiviral therapy; however, among those who were aware, almost 25% did receive treatment. We recognize that the survey question was not specific for HBV infection, and it is possible that some participants who did not have symptoms of liver disease might be aware they were infected but did not consider themselves to have a liver disease or did not remember being told (recall bias). We also recognize that because of the lack of HBV DNA and HBeAg data in NHANES, we were not able to identify patients who met indications for antiviral therapy, so the treatment rate must be interpreted with caution and requires further study. In addition, our results may not be generalizable given our small sample size.[4,21]

In addition to the study limitations noted above, we recognize that we could not differentiate between acute and chronic HBV infection because we had HBsAg results from only one time point, although it is likely that the vast majority of persons who tested positive in population surveys have a chronic infection.[22] Moreover, the absence of serologic evidence of vaccine-mediated immunity may not mean lack of immunity, as some might have had prior vaccination with loss of anti-HBs over time, and these persons may remain protected on exposure.[23,24] Additionally, this study likely underestimates the true prevalence of HBV infection in the United States, as NHANES does not sample for several high-risk populations such as the homeless and incarcerated. Finally, treatment options for hepatitis B in earlier years were limited, although disease awareness rates did not improve in recent years.

In conclusion, the prevalence of HBV infection has remained relatively stable during 1999-2016 in the civilian population of the United States at 0.35%, with an estimated 0.84 million infected persons during 2011-2016. There are wide variations in the prevalence of HBV infection and exposure by age, race/ethnicity, and birthplace. The majority of HBV burden occurred in foreign-born persons, with non-Hispanic Asian having the highest prevalence (3.30%). Meanwhile, non-Hispanic blacks had the highest prevalence among U.S.-born persons (0.54%). Among persons with HBV infection, awareness of having a liver condition and treatment rate were low. To achieve the goal of the Department of Health and Human Services to increase the diagnosis rate from one-third to two-thirds of persons with chronic HBV by 2020[25] and the elimination of HBV by 2030, more effort is needed to improve screening and disease awareness among providers and high-risk groups for HBV infection so as to provide vaccination to those who remain unvaccinated and treatment to those who require treatment.[16]

REFERENCES

1) Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018;3:383-403.

2) WHO. Global Hepatitis Report 2017. Geneva, Switzerland: World Health Organization; 2017:2017.

3) Roberts H, Kruszon-Moran D, Ly KN, Hughes E, Iqbal K, Jiles RB, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: National Health and Nutrition Examination Survey (NHANES), 1988–2012. HEPATOLOGY 2016;63:388-397.

4) Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. HEPATOLOGY 2012;56:422-433.

5) Hu DJ, Xing J, Tohme RA, Liao Y, Pollack H, Ward JW, et al. Hepatitis B testing and access to care among racial and ethnic minorities in selected communities across the United States, 2009–2010. HEPATOLOGY 2013;58:856-862.

6) Liou IW, Nguyen MH. The cascade of care in chronic hepatitis B. Curr Hepatol Rep 2016;15:209-219.

7) Ku KC, Li J, Ha NB, Martin M, Nguyen VG, Nguyen MH. Chronic hepatitis B management based on standard guidelines in community primary care and specialty clinics. Dig Dis Sci 2013;58:3626-3633.

8) Kim LH, Nguyen VG, Trinh HN, Li J, Zhang JQ, Nguyen MH. Low treatment rates in patients meeting guideline criteria in diverse practice settings. Dig Dis Sci 2014;59:2091-2099.

9) Nguyen VH, Le AK, Trinh HN, Chung M, Johnson T, Wong C, et al. Poor adherence to guidelines for treatment of chronic hepatitis B virus infection at primary care and referral practices. Clin Gastroenterol Hepatol 2019;17:957-967.e7.

10) Kim HS, Rotundo L, Yang JD, Kim D, Kothari N, Feurdean M, et al. Racial/ethnic disparities in the prevalence and awareness of Hepatitis B virus infection and immunity in the United States. J Viral Hepat 2017;24:1052-1066.

11) Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. HEPATOLOGY 2003;38:518-526.

12) Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther 2015;41:65-76.

13) Hepatitis B. virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 1991;40:1-25.

14) Centers for Disease Control and Prevention. Postexposure prophylaxis of hepatitis B. MMWR Morb Mortal Wkly Rep 1984;33:285-290.

15) The Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP). Diseases and Organisms. In; 2017. https://www.cdc.gov/bloodsafety/bbp/diseases-organisms.html. Accessed March 2019.

16) **Yeo YH**, **Le MH**, Chang ET, Henry L, Nguyen MH. Prevalence of undetectable vaccine-induced immunity against hepatitis B virus in US adults at high risk for infection. HEPATOLOGY 2019;69:1385-1397.

17) Chayanupatkul M, Omino R, Mittal S, Kramer JR, Richardson P, Thrift AP, et al. Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. J Hepatol 2017;66:355-362.

18) Pollack H, Wang S, Wyatt L, Peng CH, Wan K, Trinh-Shevrin C, et al. A comprehensive screening and treatment model for reducing disparities in hepatitis B. Health Aff (Millwood) 2011;30:1974-1983.

19) Estevez J, Yang JD, Leong J, Nguyen P, Giama NH, Zhang N, et al. Clinical features associated with survival outcome in African-American patients with hepatocellular carcinoma. Am J Gastroenterol 2019;114:80-88.

20) Liu SJ, Iqbal K, Shallow S, Speers S, Rizzo E, Gerard K, et al. Characterization of chronic hepatitis B cases among foreign-born persons in six population-based surveillance sites, United States 2001–2010. J Immigr Minor Health 2015;17:7-12.

21) Gish RG, Cohen CA, Block JM, Brosgart CL, Block TM, Clary R, et al. Data supporting updating estimates of the prevalence of chronic hepatitis B and C in the United States. HEPATOLOGY 2015;62:1339-1341.

22) Iqbal K, Klevens RM, Kainer MA, Baumgartner J, Gerard K, Poissant T, et al. Epidemiology of acute hepatitis B in the United States from population-based surveillance, 2006–2011. Clin Infect Dis 2015;61:584-592.

23) Bagheri-Jamebozorgi M, Keshavarz J, Nemati M, Mohammadi-Hossainabad S, Rezayati MT, Nejad-Ghaderi M, et al. The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination with recombinant hepatitis B vaccine at infancy. Hum Vaccin Immunother 2014;10:3731-3736.

24) McMahon BJ, Dentinger CM, Bruden D, Zanis C, Peters H, Hurlburt D, et al. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis 2009;200:1390-1396.

25) Department of Health and Human Services. Action plan for the prevention, care, and treatment of viral hepatitis: 2014–2016; 2015. https://www.hhs.gov/sites/default/files/viral-hepatitis-action-plan.pdf. Accessed March 2019.

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