

Awareness of chronic viral hepatitis in the United States: An update from the National Health and Nutrition Examination Survey

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Summary

The World Health Organization has set the goal of reducing the hepatitis-related mortality rate by 65% between 2015 and 2030. Diagnosis and awareness of infection is the first essential step towards achieving this goal. Our study examined the current awareness rate of chronic viral hepatitis in the United States and the potentially associated factors. In the National Health Nutrition and Examination Survey 2013-2016, there were 11 488 persons who participated in serology testing for chronic viral hepatitis. We defined chronic hepatitis B virus (HBV) infection by HbsAg, HBV past exposure by anti-HBc and hepatitis C virus (HCV) infection by HCV RNA. At risk for significant fibrosis was determined by AST to Platelet Ratio Index >0.7. Awareness of chronic HBV infection, past HBV exposure and HCV infection were present in 33.9%, 11.7% and 55.6% of participants, respectively. Among HCV-infected baby boomers, the awareness was in 61.5%. The awareness of HBV infection was significantly higher in individuals with high education level. Age group (40-60 years), women, non-Black race/ethnicity and those with high household income who were born in the United States with insurance plans tend to be aware of their infection. For HCV, awareness was the lowest in Hispanics and Asians, foreign-born who lived below the federal poverty level and low education level. Awareness among chronic viral hepatitis patients at risk for significant fibrosis was 62.0% in HBV and 38.2% in HCV infection. In conclusion, current awareness of chronic viral hepatitis in the United States remains suboptimal. Active public health policy to identify persons at risk and provide appropriate management is warranted.

KEYWORDS

awareness, epidemiology, NHANES, viral hepatitis

1 | INTRODUCTION

Chronic viral hepatitis, hepatitis B virus (HBV) or hepatitis C virus (HCV) results in more than 1 million deaths annually worldwide and 20 000 deaths in the United States. Collectively, chronic viral hepatitis accounts for more deaths than that from HIV/AIDS, tuberculosis

or malaria.¹⁻³ In 2014, the World Health Organization (WHO) set a goal to reduce the incidence of chronic viral hepatitis by 90% and reduce the mortality rate by 65% between 2015 and 2030.²

Diagnosis and awareness of infection is the first essential step towards achieving this goal. Using National Health and Nutrition Examination Survey (NHANES) data from 2002 to 2007, Volk

Abbreviations: AASLD, Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HbC, serum antibody to hepatitis B core; HbsAb, serum antibody to hepatitis B surface antigen; HbsAg, serum hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey; WHO, World Health Organization.

et al⁴ found that ~49% of individuals with HCV infection were unaware of their infection. We also reported 26.2% awareness of HBV chronic infection using NHANES 2013-2014 data.⁵ Recently, several national initiatives have focused on enhancing screening and diagnosis of chronic viral hepatitis in the United States.^{6,7} For example, the Centers for Disease Control and Prevention (CDC) set forth the birth cohort screening recommendation in 2012 for HCV infection.⁸ However, the effect of these efforts on the current diagnosis and awareness rate of chronic viral hepatitis in the United States is not fully understood. Lack of these data is one of the key roadblocks in implementing appropriate health policy towards achieving the WHO's goal.⁹

Our study aimed to estimate the current awareness of chronic viral hepatitis and possible factors associated with the awareness, using the nationally representative NHANES data for the most current cycles from 2013 to 2016.

2 | METHODS

2.1 | Data collection

National Health and Nutrition Examination Survey is a series of cross-sectional, population-based surveys conducted every 2 years by the National Center for Health Statistics (NCHS) of the CDC.¹⁰ It collects nationally representative data on the health and nutritional status of the noninstitutionalized, civilian population of the United States in 2-year cycles. This survey is conducted using a complex, stratified and multi-stage probability sampling design and obtains information using standardized household interviews, physical examinations and testing of biologic samples. In the NHANES 2013-2016 survey, 11 488 persons age 20 years and over were sampled, of whom 10 343 (90.0%) were tested for serum antibody to hepatitis B core antigen (anti-HBc), serum antibody to hepatitis B surface antigen (HBsAb), serum hepatitis B surface antigen (HBsAg) and serum antibody to hepatitis C (anti-HCV). Persons with or without available viral hepatitis serologic testing did not substantially differ with respect to age, sex and race/ethnicity. The NHANES study was approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent.¹¹

2.2 | Laboratory data

Collected blood specimens were processed, stored and shipped to the Division of Viral Hepatitis, National Center for Infectious Diseases (Atlanta, GA, USA). Enzyme-linked immunoassays were used to measure HBsAg, HBsAb and anti-HBc (VITROS Immunodiagnostic Products by Ortho-Clinical Diagnostics; Raritan, NJ, USA).¹² Qualitative determination of anti-HCV in blood serum or plasma was measured using the Fujirebio INNO-LIA HCV Score Assay.¹³ For each assay, participants were considered negative if the test was nonreactive and no further testing was performed. All reactive tests underwent repeat testing to confirm reactivity. Serum samples that were confirmed positive

or indeterminate for anti-HCV were further tested for HCV RNA using an in vitro nucleic acid amplification test for the quantitation of HCV RNA in human serum or plasma, using the COBAS AMPLICOR HCV MONITOR Test, version 2.0 (v2.0).¹⁴ Results were expressed qualitatively as positive or negative for anti-HBc, HBsAg and HCV RNA test. As previous studies defined^{15,16}, chronic HBV infection was defined by positive serum HBsAg whereas past exposure was defined by the presence of positive serum anti-HBc. Chronic HCV infection was determined whether test results for anti-HCV were confirmed positive or indeterminate combined with positive results of their HCV RNA test.

2.3 | Study variables

The awareness of chronic viral hepatitis infection was based on the medical questions HEQ010: "Ever told you have Hepatitis B?" and HEQ030: "Ever told you have Hepatitis C?" Similarly, those with HBV past exposure were considered to be aware of their prior infection if they answered "Yes" to the HEQ010 question.¹⁷ We also included the following variables in our analysis: race/ethnicity (non-Hispanic Whites, non-Hispanic Blacks, Hispanics, non-Hispanic Asians, Others), age group (20-39, 40-59, ≥60 years), sex (male, female), household income (below or above the poverty level) and insurance status (private, public [Medicare or Medicaid], other insurance, no insurance). The cut-offs for poverty level, calculated by dividing family income by the poverty guidelines, specific to family size, appropriate year and state, were made according to the commonly used percentages of the poverty guidelines by federal programmes in determining eligibility.¹⁸ We classified subjects as patients with elevated liver enzymes if alanine aminotransferase (ALT) value was >40 IU/L or aspartate aminotransferase (AST) was >37 IU/L in men, and ALT or AST was >31 IU/L in women.¹⁹ We defined persons at a high risk for significant fibrosis based on AST to Platelet Ratio Index (APRI) score >0.7,²⁰ but used a higher cut-off (>1.0) to define risk for significant fibrosis as part of a sensitivity analysis.

2.4 | Statistical analysis

Data were analysed using R software version 3.2.2, Boston, MA, USA using the "survey" package.²¹ We used appropriate analytic methodology and published weights for all analyses.²² Appropriate weights were calculated for the 4-year period by halving the 2-year weights provided for NHANES 2013-2016. Data were age-adjusted using the direct standardization method according to NHANES analysis guidelines.²³ The proportions of participants with awareness of chronic viral hepatitis infection were estimated using published weights to account for oversampling and nonparticipation. Since Asians or non-Hispanic Blacks comprised the majority of those with chronic HBV infection, we combined non-Hispanic Whites and Hispanics as "non-Asians, non-Blacks" for the chronic HBV infection comparison. Similarly, we combined non-Hispanic Asians and other races in one group in HCV infection comparison. We used survey-weighted multivariable logistic

regression analyses to investigate potential demographic factors associated with awareness of the disease, accounting for age, sex and race/ethnicity. In each model, awareness of chronic HBV and

HCV infection, and past exposure to HBV served as the dependent variable. *P*-value <0.05 was considered significant.

TABLE 1 Awareness of chronic hepatitis B virus (HBV) infection

	Awareness rate among people with HBV infection (%; N) N = 21/68 33.9% [95% CI: 16.7-51.1]	Adjusted odds ratio ^a [95% CI]
Age group (y)		
20-40	24.4% (5/19)	REF
40-60	45.3% (14/30)	2.07 [0.44-9.68]
≥60	29.5% (2/19)	0.80 [0.21-3.03]
Gender		
Male	32.9% (14/41)	REF
Female	34.9% (7/27)	1.44 [0.50-4.14]
Race/Ethnicity		
Non-Hispanic Whites	38.2% (2/10) ^b	1.11 [0.11-11.4]
Hispanics		
Other		
Asian	39.1% (17/44)	REF
Non-Hispanic Black	13.9% (2/14)	0.29 [0.05-1.70]
Education		
≤High school	19.7% (7/32)	REF
>High school	44.3% (14/36)	3.24 [1.10-9.54]
Income		
Below poverty level	23.4% (8/30)	REF
Above poverty level ^c	38.0% (10/32)	2.01 [0.47-8.55]
Birthplace		
United States	32.4% (2/15)	REF
Foreign	34.7% (19/53)	0.57 [0.07-4.34]
Insurance		
Without insurance	23.3% (5/18)	REF
Private	39.1% (10/26)	2.71 [0.46-16.1]
Public (medicare or medicaid)	32.6% (2/17)	1.20 [0.26-5.64]
Other insurance	47.2% (4/7)	3.57 [0.36-35.7]
At risk for significant fibrosis ^d : 24.8% (13/67)	62.0% (6/13)	NA

^aEstimated by survey-weighted logistic regression analyses adjusting for age group, gender and race/ethnicity.

^bWe combined non-Hispanic Whites, Hispanics and other races due to small sample size.

^cA ratio of family income to poverty threshold ≤1.3 according to the poverty guidelines used by federal programmes in determining eligibility.

^dOne participant with unavailable liver enzymes.

3 | RESULTS

3.1 | Awareness of hepatitis B virus infection

There were 68 persons with chronic HBV (0.3% [95% confidence interval (CI): 0.2-0.4]) in NHANES 2013-2016 data, corresponding to 0.59 million adults in the United States. The awareness of HBV infection was 33.9% [95% CI: 16.7-51.1], showing that approximately 0.39 million adults with chronic HBV were unaware of their disease (Table 1). HBV awareness was significantly lower in individuals with less than high school education (odds ratio=3.24 [95% CI: 1.10-9.54]). Higher awareness was also observed in persons between 40 and 60 years old, females, non-black race/ethnicity, those with high household income, those who were born in the United States and persons with an insurance plan, although these differences did not reach statistical significance. Similarly, there were 866 persons with HBV past exposure (4.9% [95% CI: 4.2-5.6]), corresponding to 9.6 million adults in the United States. The awareness of HBV past exposure was 11.7% [95% CI: 7.9-15.6] (Table 2). Non-Hispanic White group had significantly higher awareness of past exposure compared to non-White race/ethnicity group. Higher awareness was observed in age group between 40 and 60 years old, males, persons with higher education and those born in the United States than their comparison groups, although these differences did not reach statistical significance. There was no difference in the awareness by household income category and insurance type.

3.2 | Awareness of hepatitis C virus infection

There were 117 persons with HCV infection (0.9% [95% CI: 0.8-1.1]), corresponding to approximately 1.8 million adult patients in the entire United States. The awareness of HCV infection was 55.6% [95% CI: 42.6-68.6]; thus, approximately 0.8 million adults with chronic HCV in the United States were estimated to be unaware of their disease status (Table 3). Among HCV-infected baby boomers (born between 1945 and 1965), awareness was present in 61.5% [95% CI: 46.2-76.7]. Awareness of HCV infection was lowest in Hispanics and Asians/Other race, those with low education level, who live below the federal poverty level and those who were foreign-born, although none of these differences reached statistical significance. There was no difference in the awareness proportions by gender and insurance type.

3.3 | Proportions with awareness in persons with chronic hepatitis B virus or hepatitis C virus at risk for significant fibrosis

In total, 24.8% (13/67) of patients with HBV had elevated liver enzymes and were at risk for significant fibrosis; of these 62.0% were aware of their infection (Tables 1 and 3). Of the 35.6% (45/117) of

persons with chronic HCV infection at risk for advanced fibrosis, only 38.2% were aware of their infection. Using a higher cut-off for APRI (>1.0, 76% sensitivity and 74% specificity for predicting cirrhosis), three participants with HBV infection and 30 participants with HCV infection were at risk for advanced fibrosis or cirrhosis. The awareness of their infection status was higher in these subgroups than the rest, but remained suboptimal at 78.9% [95% CI: 38.6-119.2] for HBV and 57.7% [95% CI: 32.7-82.8] for HCV.

TABLE 2 Awareness among people with hepatitis B virus (HBV) past exposure

	HBV awareness rate among those with HBV past exposure (%) N = 71/866 11.7% [95% CI: 7.9-15.6]	Adjusted odds ratio ^a [95% CI]
Age (mean)		
20-40	9.9% (10/119)	REF
40-60	16.0% (36/331)	1.32 [0.60-2.92]
≥60	8.2% (25/416)	0.53 [0.17-1.66]
Gender		
Male	14.0% (46/494)	REF
Female	8.8% (25/372)	0.68 [0.37-1.23]
Race/Ethnicity		
Whites	20.6% (20/123)	REF
Hispanics	8.0% (9/136)	0.28 [0.11-0.74]
Black	4.6% (13/277)	0.17 [0.06-0.46]
Asian	8.4% (26/304)	0.34 [0.16-0.73]
Other	11.0% (3/26)	0.42 [0.11-1.56]
Education		
≤High school	9.2% (19/264)	REF
>High school	14.3% (41/395)	1.16 [0.66-2.03]
Income		
Below poverty level ^b	10.7% (29/327)	REF
Above poverty level	11.5% (33/451)	0.82 [0.44-1.55]
Birthplace		
United States	15.3% (34/352)	REF
Foreign	7.6% (37/514)	0.55 [0.21-1.45]
Insurance		
Without insurance	10.5% (15/161)	REF
Private	13.7% (25/278)	1.13 [0.47-2.72]
Public (medicare or medicaid)	11.0% (23/346)	1.33 [0.49-3.63]
Other insurance	10.0% (8/81)	1.00 [0.33-3.04]

^aEstimated by survey-weighted logistic regression analyses adjusting for age group, gender and race/ethnicity.

^bA ratio of family income to poverty threshold ≤1.3 according to the poverty guidelines used by federal programmes in determining eligibility.

4 | DISCUSSION

Lack of diagnosis of viral hepatitis is the primary barrier to antiviral treatment in the United States.⁴ Our findings suggest that current awareness of both HBV and HCV infection in the United States remains suboptimal. Using data from the most recent wave of NHANES, we found that 33.9% of persons with HBV infection were aware of their infection status. Although a higher proportion of HCV-infected persons (55.6%) were aware of their HCV status, this estimate was not much higher than the 49% awareness rate in 2007-2008 (only ~13% relative increase).⁴

Our findings suggest that awareness of both HBV and HCV infection tended to be higher in persons with high education and household income, and those who were born in the United States. Low awareness among persons born in a foreign country was prominent in HCV infection. This finding is consistent with the previous studies that showed immigrants were diagnosed with their liver disease after almost 10 years following arrival and at more advanced stage.²⁴⁻²⁸ This may be due to lack of healthcare access and health information, poor knowledge of the disease and asymptomatic disease progression. There was also racial disparity in the awareness; Blacks were less likely to be aware of HBV infection whereas Hispanics and Asians were less likely to be aware of HCV status. However, most of these differences did not reach a statistical significant level, in part due to small sample size despite using the largest available national health survey that included both viral hepatitis serology and awareness information.

In general, our findings demonstrate the widespread and systemic under-diagnosis of viral hepatitis in the United States. The awareness rates were below 50%-60% for most subgroups examined in this study. Of note, we found low awareness rates in patients who may be at risk of advanced fibrosis (APRI score >0.7 and >1.0). Indeed, for HCV, awareness was lower in the group at risk for advanced fibrosis compared with the overall estimate. This may be due to the differences in demographic characteristics between HCV-infected persons (older, more likely to be Hispanics, live under the poverty level and foreign-born; Table S1) with and without significant fibrosis. Additionally, persons with chronic HCV at risk for significant fibrosis who were aware of their infection tended to have a higher education level, higher household income and insurance plans than persons who were at risk but unaware of their infection, although these findings did not reach statistical significance (Table S2).

Our results suggest that broadscale interventions that target all individuals at risk for chronic viral hepatitis simultaneously would be more effective in enhancing viral hepatitis testing and awareness than focused efforts that target specific subgroups. Given the relatively limited impact of top-down mandates, our data underscore the need for grassroots movements, organized by and within communities, to assume responsibility for ensuring that all high-risk individuals are screened for viral hepatitis. These efforts may be the best way to make inroads into the problem of suboptimal testing and awareness.

Benefits of increasing awareness of the disease in individuals with chronic viral hepatitis may extend beyond those related to

antiviral treatment. This is particularly true for patients who may be at a high risk for advanced fibrosis, a subgroup that may benefit surveillance programme of cirrhosis and hepatocellular carcinoma. Current American Association for the Study of Liver Diseases (AASLD) guidelines recommend that those at risk of HCC, including any persons with cirrhosis, Asian men with hepatitis B aged ≥ 50 , Asian women with hepatitis B aged ≥ 40 , African/North American Blacks with hepatitis B aged ≥ 20 , should be routinely screened

by ultrasonography every 6-12 months for progression to cirrhosis and development of HCC.^{29,30} Based on our findings, there are ~0.3 million persons with chronic hepatitis B infection and ~0.4 million persons with chronic HCV infection who are not receiving HCC screening due to lack of knowledge of their infection and the importance of surveillance in the United States.³¹

Although most people with past HBV infection would not experience any liver-related illness, we believe that it is still clinically relevant to estimate their awareness of past exposure. Being unaware of their past exposure to HBV may result in serious reactivation of the virus among persons with HBV past exposure who receive chemotherapy, immunosuppressant drugs or rheumatologic biologic agents.²⁹ Previous studies suggest that HBV reactivation from chemotherapy and anti-rheumatic biologic therapies occurred 8%-18% and 1.7% of patients with HBV past exposure, respectively.^{32,33} However, many studies have reported suboptimal screening for HBV infection before initiation of chemotherapy, biologics or other immunosuppressant drugs.³⁴⁻³⁶ Data from a major US hospital network in Connecticut showed that only 17.1% of people undergoing chemotherapy were screened for HBV infection.²⁴ Furthermore, HBV testing rate prior to anti-TNF inhibitor was 23.7% in a recent US national study of inflammatory bowel disease patients.²⁵

Strengths of our study include the nationally representative data that allowed us to provide the most updated estimates of national awareness rate of chronic viral hepatitis and potentially associated demographic factors. Our findings may have significant implications for the United States as well as global initiatives targeted at eliminating chronic viral hepatitis by 2030. However, there are several limitations in our study. Despite using the largest available U.S representative health survey that includes chronic viral hepatitis awareness information, the number of participants with chronic hepatitis was still small. Many of our statistical analyses could not reach to a significant level in part due to lack of power. Moreover, there can be remaining confounding factors since our analyses were only adjusted for age, sex and race/ethnicity group due to the small sample size. Still, we believe our findings can provide insights on widespread nature of a persistent problem that will need renewed efforts to close the testing gap. In addition, due to a cross-sectional survey data format, there is a risk of recall bias when participants responded to the questionnaire. Furthermore, chronic hepatitis B infection was defined by a single instance of a positive of hepatitis B surface antigen and may reflect acute infection although we believe the number of those with acute HBV infection would be small in this cohort. Lastly, NHANES does not include homeless or incarcerated persons who may be at high risk of chronic viral infection.

In conclusion, our findings suggest that the overall awareness of chronic viral hepatitis was 33.9% in chronic HBV infection, 55.6% in chronic HCV infection and 11.7% in past HBV infection. Awareness levels of chronic viral hepatitis remained suboptimal across demographic subgroups. The awareness rate in baby boomers still leaves significant room for improvement. With these persistent gaps in diagnosis, it would be difficult, if not impossible, to achieve the WHO's

TABLE 3 Awareness of chronic hepatitis C virus (HCV) infection

	Awareness rate among people with HCV infection (%; N) N = 61/117 55.6% [95% CI: 42.6-68.6]	Adjusted odds ratio ^a [95% CI]
Age group (y)		
20-40	49.5% (4/8)	REF
40-60	57.0% (28/56)	1.30 [0.20-8.40]
≥ 60	55.0% (29/53)	1.27 [0.15-10.6]
Gender		
Male	54.9% (41/81)	REF
Female	57.4% (20/36)	1.02 [0.37-2.81]
Race/Ethnicity		
Non-Hispanic Whites	60.9% (29/37)	REF
Hispanics	45.9% (12/27)	0.54 [0.20-1.42]
Asian/Other	30.6% (3/9) ^c	0.29 [0.04-2.16]
Non-Hispanic Black	57.3% (26/44)	0.84 [0.28-2.52]
Education		
\leq High school	51.4% (41/81)	REF
>High school	65.1% (20/36)	1.54 [0.37-6.44]
Income		
Below poverty level ^b	45.2% (31/62)	REF
Above poverty level	64.0% (27/48)	2.40 [0.77-7.41]
Birthplace		
United States	57.8% (57/101)	REF
Foreign	26.4% (4/16)	0.26 [0.08-0.85]
Insurance		
Without insurance	55.0% (13/34)	REF
Private	48.9% (11/24)	0.78 [0.17-3.67]
Public (medicare or medicaid)	62.6% (33/50)	1.37 [0.30-6.26]
Other insurance	52.7% (4/9)	0.91 [0.09-9.70]
At risk for significant fibrosis: 35.6% (45/117)	38.2% (21/45)	NA

^aEstimated by survey-weighted logistic regression analyses adjusting for age group, gender and race/ethnicity.

^bA ratio of family income to poverty threshold ≤ 1.3 according to the poverty guidelines used by federal programmes in determining eligibility.

^cWe combined Asians and other races due to small sample size.

goal of eliminating viral hepatitis by 2030. Active public health policy to identify persons at risk and provide appropriate management is warranted.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

HSK carried out statistical analysis. All authors contributed to study and design; acquisition, analysis or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative, technical or material support; and supervision of the study. Dr. H.S Kim had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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