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The changing epidemiology of hepatitis C virus infection in the United States: National health and nutrition examination survey 2001 through 2010

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Background & Aims: In light of the dramatically changing hepatitis C therapeutic landscape, knowledge of the current burden of HCV infection in the general population of the United States is critical.

Methods: The National Health and Nutrition Examination survey collects nationally representative data on HCV infection in the civilian population of the United States. Data from 2001 to 2010 were combined for this study. HCV testing was completed in 38,025 participants.

Results: The prevalence of anti-HCV in the United Sates decreased from 1.9% (95% CI 1.5%–2.5%) in 2001–2002 to 1.3% (95% CI 0.9%–1.8%) in 2005–2006, and remained stable up to 2010. About 67% of all infected persons were positive for HCV RNA, indicating 2.3 million people with chronic HCV infection, of whom 68% have genotype 1. Seventy percent of infected persons were born between 1945 and 1965, with prevalence of 3.5% (95% CI 2.2%–4.8%). The stable rate since 2006 is mostly related to prevalent cases and foreign born persons migrating into US. Other important risk factors include less education and low economic status. Race, HIV status, number of sexual partners, and blood transfusions are no longer associated with HCV infection.

Conclusions: As of 2010, approximately 2.3 million persons were chronically infected with Hepatitis C in the US. Most of those infected are prevalent, rather than incident cases. The prevalence of HCV was on the decline, but has stabilized since 2006. Future studies should explore reasons for no decline in HCV prevalence since 2006.

Keywords: NHANES; Hepatitis C infection; Prevalence; Trends; Risk factors.
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Introduction

Hepatitis C virus (HCV) is the most common blood-borne infection in the USA [1] and worldwide [2]. It is the leading cause of chronic liver disease, hepatocellular carcinoma, and is the most common indication for liver transplantation in North America and Western Europe [3–5]. The number of individuals with chronic hepatitis C virus (HCV) infection in the US increased from 2.7 million during 1988–1994 [1] to 3.9 million during 1999–2002 [6]. Approximately 65–75% of patients with acute HCV develop a chronic infection. Incidence of HCV increased markedly in the 1970s and 1980s, with an average of 230,000 new infections each year [7]. The incidence declined dramatically in the 1990s following the implementation of effective screening of blood product donors. With HCV largely eradicated from the blood product supply, new infections have been largely limited to persons who inject or snort drugs. In 2010, only 17,000 persons were estimated to have acquired new HCV infections [7]. A majority of the pool of individuals currently with HCV is believed to have acquired infection in the remote past, and is at increased risk for time dependent HCV-related morbidity and mortality [8,9].

Identification of HCV-positive persons for appropriate counseling and management is a public health priority. The Center for Diseases Control and US Preventive Services Task Force recommend testing for persons most likely to be infected, including people born between 1945 and 1964 [10,11]. Other risk groups include persons with a history of ever injecting drugs, long term hemodialysis, blood transfusions or organ transplants before 1992 and people with persistent biochemical evidence of liver injury [10]. Screening is also recommended for persons with recognized blood exposure, including health care, emergency and public safety workers, mucosal exposure, children of HCV-infected mothers and HIV infected [12].

Unfortunately, many HCV infected persons are asymptomatic, have not been tested for HCV and only present to care providers when complications occur [4]. A majority of infected persons do not receive antiviral treatment [13,14] because they are unaware of their infection [15,14]. It is estimated that about 45% to 85% of

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US adults who are chronically infected with HCV continue to be undiagnosed [14,16–18].

The National Health and Nutrition Examination Survey (NHANES) periodically collects data on HCV infection, allowing clinicians to target at-risk groups with educational services and therapeutic interventions. The last report on the epidemiology of HCV infection in the US population was between 1999 and 2002 [6]. NHANES has since collected and reported data on HCV up to the year 2010. Management for hepatitis C is evolving rapidly, with increasingly available effective and safe therapies. Knowledge of the current burden and at risk groups for HCV infection nationwide is critical. The main purpose of this study was to describe the current epidemiology of HCV infection in the United States general population. Specifically, we aimed to (1) estimate the national prevalence of Hepatitis C virus infection (2) analyze trends in HCV infection and (3) identify at risk populations for HCV infection among US adults aged 6 years and older.

Patients and methods

Survey

The NHANES is conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). It collates nationally representative data on the health and nutritional status of the non-institutionalized, civilian population of the United States. The NHANES uses a stratified and multistage probability sampling design and collects information from persons using standardized household interviews, physical examinations, and testing of biologic samples. More detailed information on the survey design for the NHANES, including approval from the institutional review board for data collection and analysis, is available from the survey documentation [19].

Initially, a questionnaire covering only non-sensitive topics is used to interview participants at home. Here, demographic data on age, sex ethnicity, country of birth, etc. is collected. Information on potentially sensitive subjects, such as sexual practices and illicit drug use, is obtained later at a mobile examination center by means of a computer-assisted personal interviewing technique. The poverty index was calculated by dividing the total family income by the poverty threshold, as defined by the U.S. Census, with adjustment for family size at the time of the interview. Questions about years of education, marital status, occupation, military service, sexual behavior and illegal drug use including injection drug use were asked of participants 17 years of age or older.

Laboratory testing

Serum specimens are processed, stored, and sent to the Centers for Disease Control and Prevention. Qualitative determination of anti-HCV in blood serum or plasma was measured using an anti-HCV screening enzyme-linked immunosorbent assay (ELISA) (Ortho CD VITROS Anti-HCV Immunodiagnostic System; Ortho Clinical Diagnostics, Raritan, NJ). Supplemental recombinant immunoblot assays (RIBA) (Chiron RIBA HCV Strip Immunoblot Assay, Chiron Corp., Emeryville, California) were performed on all specimens that were repeatedly reactive by ELISA testing. RIBA-positive samples were reported as confirmed positive for anti-HCV, RIBA-negative samples were reported as negative for anti-HCV, and indeterminate results were reported as indeterminate. Beginning in 2005–2006, positive and indeterminate samples were further tested for HCV-RNA using the COBAS AMPLICOR HCV Test (version 2.0; Roche Diagnostics Corp., Indianapolis, IN), an *in vitro* nucleic acid amplification test for the quantitation of HCV-RNA in human serum or plasma. HCV genotypes are identified using the VERSANT® HCV Genotype 2.0 Assay (LiPA), a line probe assay designed to identify hepatitis C virus (HCV) genotypes 1 to 6 in human serum or EDTA plasma samples. Genotypes are reported as genotype 1, other than genotype 1 or undetermined. Alanine aminotransferase (ALT) levels (normal range 0 to 39 U/L) were measured in specimens that had been stored and shipped under appropriate refrigeration conditions (4 °C to 8 °C). Participants 6 years or older are tested for HCV.

Statistical analyses

Data from the 2009–2010 survey cycle were used to describe the current epidemiology of HCV infection in the United States. All analyses were performed using Stata version 11, Tx Inc. software according to the NCHS guidelines. We used appropriate study design variables and published weights that were further adjusted to compensate for missing anti-HCV values. Estimates of prevalence were weighted so as to represent the total U.S. population 6 years and older, and to account for oversampling and for non-participation in the household interview and physical examination. To estimate the number of HCV RNA–positive persons, these weights were further adjusted to compensate for the RIBA-positive and RIBA-indeterminate specimens that were unavailable for RNA testing because of inadequate specimen volumes.

Prevalence of HCV is presented by various demographic factors. Data from 2001 to 2010 of the NHANES survey were combined to evaluate trends and risk factors associated with HCV infection. Only individuals 17 years and older were included in the risk factor analysis. Positive predictive values for an abnormal ALT were calculated for individuals <70 years old and for the 1945–1965 birth cohort. Proportions from univariate analyses were compared using the Chi-square test, with actors having p <0.2 included in the multivariate analyses. p values <0.05 were considered significant in the multivariate model.

Results

Characteristics of study participants

A total of 52,195 individuals participated in the NHANES survey from 2001 to 2010. Of these, 43,179 (82.7%) persons were 6 years and older. Adequate serum samples were available for testing in 38,025 persons (88.1% of >6 years). The median age of study participants was 32 years (IQR 16 to 56 years). About 51.3% were women.

Prevalence of antibodies to HCV in US as of 2010

Based on RIBA testing, the prevalence of anti-HCV positivity in the United States was 1.3% (0.9–1.8%), which translates into approximately 3.5 million persons in the US general population as of 2010. A total of 7764 (98.4%) and 14 (0.3%) samples were RIBA negative and indeterminate respectively. Of all anti-HCV positive individuals, 90.6% had specimens for HCV-RNA testing, with 66.4% (2.3 million) having detectable virus levels. As of 2010, 67.9% and 22.1% cases were genotypes 1 and 2 respectively. Ten percent of cases had indeterminate genotype. Table 1 shows the prevalence of anti-HCV by various characteristics of the study population and gender as of 2010. The prevalence was higher in men than women (1.9% *vs.* 1.1%, p <0.001). By age, greater than two-thirds (70.1%) of those infected were in the 45 years to 65 years old group, corresponding to the 1945 to 1965 birth cohort in 2010. The prevalence in this age group was 3.5% (95% CI 2.2%–4.8%). Fig. 1 shows the burden of anti-HCV by age group as of 2010. The prevalence was noted to be highest among male non-Hispanic Blacks (2.2%) compared to non-Hispanic whites (1.3%). Supplementary Fig. 1 shows the prevalence by race and age group in 2010.

Trends in prevalence of antibodies to HCV infection from 2001 to 2010

Overall, there was a trend for decreasing prevalence of anti-HCV over time; from 1.9% (95% CI 1.5%–2.5%) in 2001–2002 to 1.3% (95% CI 1.0%–1.8%) in 2005–2006 cycles. However, since 2006, the prevalence of anti-HCV has remained stable at 1.3% as of April

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Table 1. Baseline characteristics of study participants and prevalence of antibodies to HCV in 2010.

Characteristic	Number tested	Prevalence		
	N (%)	All % (95% CI)	Male, % (95% CI)	Female, % (95% CI)
All participants	7871 (100)	1.3 (0.9, 1.7)	1.9 (1.2, 2.7)	0.7 (0.4, 1.0)
Age groups (yr)				
<18	2015 (25.6)	n.a.	n.a.	n.a.
19 to 29	1111 (14.1)	0.2 (0, 0.5)	0.3 (0.1, 0.7)	0.1 (0-0.4)
30 to 39	948 (12.0)	0.4 (0.0, 0.8)	0.6 (0.1, 1.3)	0.2 (0.1, 0.6)
40 to 44	530 (6.7)	1.4 (0.6, 2.2)	2.6 (1.3, 3.9)	0.3 (0.2, 0.8)
45 to 65	1983 (25.2)	3.5 (2.2, 4.8)	5.0 (2.7, 7.3)	2.0 (0.9, 3.0)
66+	1284 (16.3)	0.3 (0.2, 0.5)	0.5 (0.1, 0.9)	0.2 (0.1, 0.6)
Race/ethnicity				
Hispanic	2539 (32.3)	1.0 (0.6, 1.5)	1.4 (0.6, 2.2)	0.7 (0.4, 0.9)
Non-Hispanic white	3456 (43.9)	1.3 (1.6, 1.9)	1.9 (1.0, 2.8)	0.6 (0.2, 1.1)
Non-Hispanic black	1415 (18.0)	2.2 (1.6, 2.9)	2.9 (0.8, 5.1)	1.7 (0.5, 2.9)
Birthplace				
USA	6049 (76.8)	1.4 (0.9, 1.8)	2.0 (1.2, 2.9)	0.7 (0.4, 1.1)
Outside USA	1822 (23.2)	1.0 (0.4, 1.6)	1.5 (0.1, 2.9)	0.5 (0.0, 1.0)
Marital status				
Never married	3418 (59.9)	1.3 (0.8, 1.8)	1.9 (1.1, 2.8)	0.6 (0.1, 1.2)
Widow/divorced	1305 (22.9)	2.8 (1.5, 4.1)	4.9 (1.5, 8.4)	1.6 (1.0, 2.2)
Couple	983 (17.2)	1.5 (0.5, 2.6)	2.3 (0.4, 4.2)	0.7 (0.2, 1.2)
Level of education				
Above High School	2940 (51.5)	2.0 (1.3, 2.8)	2.8 (1.6, 4.0)	1.3 (0.6, 1.9)
Below High School	2758 (48.3)	1.3 (0.7, 1.9)	2.1 (1.1, 3.1)	0.5 (0.0, 1.0)
Antibody to Human Immunodeficiency Virus type 1 (HIV1)				
Yes	21 (0.5)	25 (6.4, 56.4)	35 (4.4, 74.5)	n.a.
No	4022 (99.5)	1.7 (1.0, 2.4)	2.5 (1.3, 3.6)	1.0 (0.4, 1.5)
Antibody to Herpes Simplex Virus type 2 (HSV-2)				
No	634 (19.91)	3.2 (0.9, 5.6)	6.3 (1.4, 11.2)	1.7 (0.2, 3.2)
Yes	2546 (80)	0.7 (0.4, 0.9)	0.9 (0.5, 1.3)	0.5 (0.1, 0.8)
Lifetime No. sexual partners				
0 to 1	854 (19.7)	2.4 (0.1, 0.5)	0.4 (0.2, 1.0)	0.1 (0.1, 0.3)
2 to 9	2047 (47.2)	0.7 (0.4, 1.1)	0.6 (0.1, 1.2)	0.8 (0.2, 1.3)
10 to 19	660 (15.2)	2.4 (0.9, 3.9)	3.4 (0.8, 6.0)	1.1 (0.3, 2.5)
20 to 49	519 (12.0)	4.0 (1.3, 6.8)	5.1 (1.4, 8.8)	1.5 (0.4, 2.5)
50 and above	259 (6.0)	6.2 (2.5, 9.9)	7.4 (2.6, 12.2)	2.4 (0.6, 5.4)
Age (yr) at first sexual intercouse				
<11	117 (2.8)	5.6 (1.3, 9.8)	9.1 (2.3, 1.6)	n.a.
12 to 15	1094 (26.5)	4.4 (3.1, 5.8)	6.3 (4.0, 8.6)	2.1 (1.1, 3.1)
16 to 17	1234 (29.9)	1.3 (0.3, 2.4)	1.7 (0.1, 3.4)	0.9 (0.1, 1.9)
>18	1685 (40.8)	0.2 (0.0, 0.3)	0.2 (0.0, 0.4)	0.1 (0.0, 0.3)
Family PIR				
Above	6064 (85.1)	0.9 (0.1, 1.6)	1.3 (0.0, 2.5)	0.4 (0.4, 1.2)
Below	1064 (14.9)	1.5 (0.9, 2.0)	2.2 (1.1, 3.2)	0.8 (0.5, 1.2)
Service in US military service				
Yes	715 (11.6)	1.5 (0.1, 2.9)	0.9 (0.0, 1.8)	8.4 (3.1, 19.9)
No	5453 (88.4)	1.5 (1.0, 2.1)	2.6 (1.5, 3.7)	0.7 (0.4, 1.0)
History of blood transfusion				
Yes	812 (9.2)	2.9 (1.4, 4.5)	4.3 (0.4, 8.3)	2.1 (0.5, 3.7)
No	7.899 (89.8)	1.1 (0.7, 1.6)	1.7 (0.9, 2.5)	0.5 (0.3, 0.8)
ALT levels (IU/L)				
0-39	6170 (90.1)	0.7 (0.4, 1.1)	1.1 (0.6, 1.7)	0.4 (0.1, 0.7)
>39	676 (9.9)	7.0 (4.4, 9.6)	7.1 (4.1, 10.1)	6.6 (1.7, 11.5)
Lifetime drug use				
Yes	79 (1.8)	37.5 (23.2, 52)	50.8 (29.8, 71.9)	20.2 (9.2, 31.2)
No	4290 (98.0)	0.9 (0.5, 1.3)	1.3 (0.6, 2.0)	0.5 (0.2, 0.7)

Characteristics of study participants only for the 2009–2010 cycle are shown, representing the most current data on people with antibodies to HCV. Also shows prevalence of anti-HCV by sex. Totals in strata for each characteristic may not add up to the total number tested due to missing responses.
PIR, poverty index ratio; USA, United States of America; ALT, alanine amino transferase; n.a., not available.

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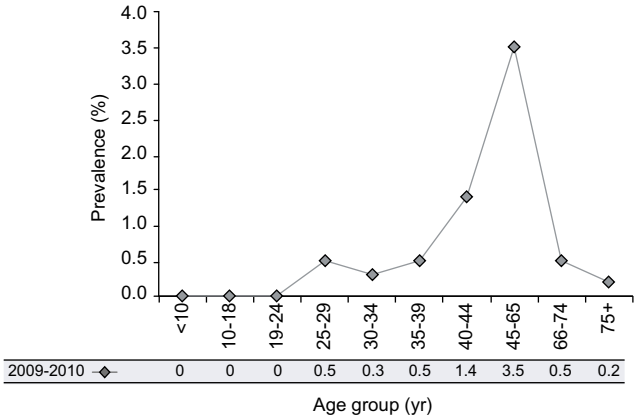

Fig. 1. Prevalence of Anti-HCV by age group in the United States in 2010. Figure shows most infected persons were aged 45, corresponding to the 1945 to 1965 birth cohort.

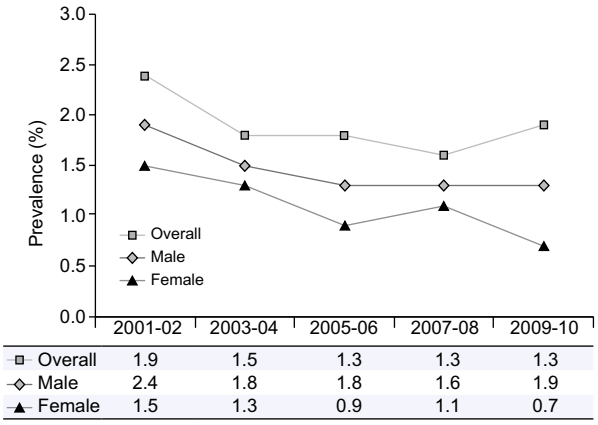

Fig. 2. Trends in prevalence of anti-HCV by gender from 2001 to 2010. The overall prevalence decreased rapidly until 2005, and has since stabilized. Prevalence continues to decrease in women, but increase seen among men.

1, 2010. Fig. 2 shows the trend of anti-HCV by gender. The prevalence decreased similarly in both men and women until 2006. However, the prevalence has continued to decrease among women but an upward trend was noted in men.

An age-cohort effect was observed throughout the study period. In the 2001–2002 cycle, the greatest proportion of anti-HCV persons were the 45–65 (3.5%) year olds, corresponding to the 1945 to 1965 birth cohort (Fig. 3).

An overall decreasing trend was observed by race. Supplementary Fig. 2 shows that while there was a decreasing trend among all races throughout the study period, non-Hispanic blacks bore the greatest burden of HCV infection in the United States.

In 2001–2002, most of the persons with anti-HCV were born in the USA (2.2% *vs.* 0.3%). The prevalence of anti-HCV decreased significantly among US born persons throughout the study period to about 1.4% in 2009–2010. Overall, there was a trend toward increase in the prevalence of anti-HCV among persons born outside of the USA. The prevalence increased from 0.3% to 0.8% between 2001 and 2006. However, it decreased to 0.4% in 2007

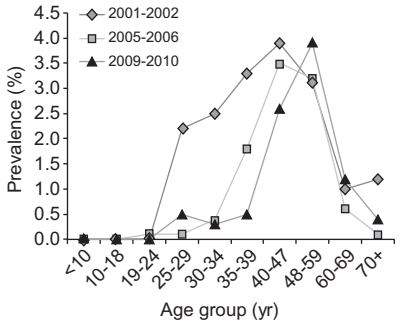

Fig. 3. Prevalence of Anti-HCV by age group from 2001 to 2010: Cohort effect. Figure shows cohort effect of the prevalent cases of anti-HCV in study participants. Shown only for three survey cycles since participants were grouped and back-back years will not show shifting effect.

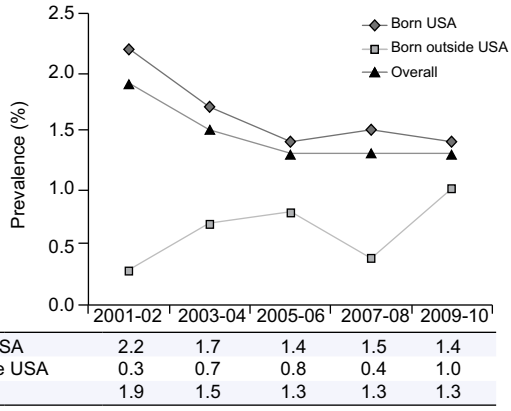

Fig. 4. Trends in prevalence of Anti-HCV by birthplace from 2001 to 2010. Figure shows that prevalence of anti-HCV continues to decrease among US born individuals. However, there is an overall trend towards increase among people migrating in to the US.

but as of 2010, it was up to 1.0%. Fig. 4 shows trends in the prevalence of anti-HCV by place of birth.

Factors associated with presence of antibodies to HCV in the US from 2001 to 2010

Table 2 shows factors associated with having antibodies to HCV. The significant limit for a factor to be included in the multivariate model was set at p <0.2. The strongest risk factors for having anti-HCV included people aged 45 to 65 years old, being born in the United States, less than high school education, lifetime drug use, abnormal alanine aminotransferase levels (ALT >39 U/L) and having antibodies to herpes simplex virus type 2. The positive predictive value for ALT for persons less than 70 years old and for the 1945–1965 birth cohort were 5.14% and 6.7% respectively. Race, HIV status, service in US military and gender were not predictive after adjustment.

Discussion

In this work we analyzed the most recent data from the NHANES survey. The NHANES survey is important as it provides a uniquely

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Table 2. Risk factors for having antibodies to HCV combining NHANES 2001–2010 data.

Characteristic	Univariable analyses			Multivariable analyses		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Sex						
Female	Reference					
Male	1.8	1.4-2.3	<0.001	0.9	0.6-1.3	>0.05
Age groups (yr)						
17 to 29	Reference		<0.001+			
30 to 39	4.9	1.9-12.6	0.001	6.2	1.3-29.4	0.02
40 to 44	9.3	3.3-26.4	<0.001	13.0	2.4-70.1	0.003
45 to 65	11.4	4.6-28.3	<0.001	27.5	5.6-134.9	<0.001
66+	1.9	0.6-5.7	0.25	n.a.		
Birthplace						
USA	Reference					
Outside USA	0.4	0.2-0.5	<0.001	0.2	0.1-0.4	<0.001
Family PIR						
Above	Reference					
Below	2.5	1.7-3.7	<0.001	3.3	1.3-8.5	0.013
Race						
Hispanic	Reference					
Non-Hispanic white	1.1	0.8-1.6	0.42	0.6	0.3-1.0	0.05
Non-Hispanic black	2.2	1.6-3.1	<0.001	0.5	0.3-0.9	0.01
ALT levels (IU/L)						
0-39	Reference					
>39	8.8	7.0-11.1	<0.001	7.2	4.6-11.3	<0.001
Marital status						
Married/cohabits	Reference					
Widow/divorced	1.9	1.4-2.4	<0.001	1.4	0.8-2.5	>0.05
Never married	1.1	0.8-1.4	0.136	2.5	1.4-4.7	0.004
Level of education						
Above High School	Reference					
Below High School	2.1	1.6-2.8	<0.001	2.5	1.6-3.8	<0.001
Antibody to Human Immunodeficiency Virus type 1 (HIV1)						
No	Reference					
Yes	7.1	2.9-17.2	<0.001	0.4	0.01-10.6	>0.05
Lifetime IDU drug use						
No	Reference					
Yes	57.0	41.1-79.0	<0.001	28.3	16.4-48.8	<0.001
Service in US military service						
No	Reference					
Yes	1.4	1.0-1.9	0.07	1.2	0.6-2.7	>0.05
History of blood transfusion						
No	Reference					
Yes	2.1	1.5-2.8	<0.001	1.3	0.7-2.3	>0.05
Antibody to Herpes Simplex Virus type 2 (HSV-2)						
No	Reference					
Yes	4.1	3.1-5.4	<0.001	2.3	1.3-3.8	0.004
Age (years) at first intercourse						
<11	Reference					
12 to 15	2.6	1.6-4.2	<0.001	1.2	0.5-2.6	>0.05
16 to 17	5.4	3.7-7.8	<0.001	2.0	1.1-3.5	0.02
>18	7.3	4.2-12.8	<0.001	1.7	0.6-4.6	>0.05
Lifetime No. of sexual partners						
0 to 1	Reference					
2 to 9	3.6	1.6-8.2	0.003	1.2	0.3-4.2	>0.05
10 to 19	9.0	3.9-20.6	<0.001	1.7	0.4-6.8	>0.05
20 to 49	17.2	7.2-40.9	<0.001	1.5	0.4-6.7	>0.05
50 and above	23.6	10.1-55.1	<0.001	1.4	0.3-5.8	>0.05

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detailed nationally representative dataset of the US non-institutionalized population. The standardization of its methods allows for consistent and good quality data gathering. There are several important findings in this analysis of the NHANES survey. The primary observation of this study is that the prevalence of antibodies to HCV in the non-institutionalized United States population is 1.3% and has not declined since 2006 [1,6]. This corresponds to an estimated 3.5 million people in the United States who are 6 years and older. This prevalence is almost certainly an underestimate as NHANES does not include some high risk populations, including the incarcerated, hemodialysis patients and the homeless. Of all persons with anti-HCV, 2.3 million had evidence of chronic infection as suggested by a positive HCV-RNA. Because HCV-RNA testing is performed only on a single sample, it is possible that some cases with chronic infection are being missed given that viremia can be transient [20].

The prevalence of anti-HCV is at its lowest ever in the United States. However, since 2006, the prevalence has not declined any further. A recent study, however, has reported an increasing trend in HCV prevalence worldwide between 1990 and 2005 [21]. The decline in the anti-HCV prevalence in the US since the 1990s is largely attributed to the decline of illicit drug use, institution of strict policies regarding unsafe medical practices and testing of all blood donors [10]. Over the last decade, IVDU has decreased significantly in the USA [22,23]. Globally, frequencies of HCV transmission by various routes differ and major differences have occurred in some regions of the world [24]. We believe that the decline in HCV prevalence in the US is a validation of the effectiveness of the 1998 recommendations [10].

This study suggests that a majority of the people with positive anti-HCV are on the basis of prevalent rather than incident infections. Greater than two-thirds (70.1%) of all seroprevalent cases were in the 45–65 years old age group (1945–1965 birth cohort). The Centers for Disease Control and US Preventive Services Task Force recommend HCV screening in people born between 1945 and 1965, which corresponds to persons aged 48 to 68 years in 2013 [11,23]. From 2001 to 2010, we were able to show a birth cohort effect with respect to prevalent infection. Fig. 3 clearly shows that the 1945–1965 birth cohort accounts for most of the prevalent cases at each time point. It is anticipated that, as this cohort ages, we will see more HCV related complications such as liver cirrhosis and hepatocellular cancer secondary to HCV acquired several decades ago [25,8]. Furthermore, in light of dramatically changing hepatitis C therapeutic landscape with highly effective and well tolerated pangenomic HCV treatment regimens [26–28], timely diagnosis becomes even more important. Early identification of infected individuals could curb HCV-related morbidity and mortality.

It is encouraging to note that the prevalence of anti-HCV among those less than 30 years old has remained very low. The risk of acquiring HCV infection in the US is at its lowest since the 1990s. In fact, the CDC estimates that only about 17,000 new infections were acquired in the whole country in 2010 [23].

Knowledge of risk factors for HCV infection is crucial in resource allocation for prevention measures. The large numbers in this study have permitted us to pinpoint with confidence the most important risk factors at which our limited resources can be directed with the highest yield from a public health perspective. We were able to show that some factors which have previously been noted as predisposing to HCV transmission (e.g., number of sexual partners, age at first sexual intercourse) may not be as strong as previously thought. Risk-based strategies may fail for a multitude of reasons, including patient denial of risk factor presence [29] or due to providers not eliciting complete risk-factor histories [30]. A recent study found that the current risk-based screening strategy for HCV infection is not being implemented for a large proportion of patients during medical evaluations [15].

Injection drug use remains the strongest risk factor for HCV infection [31–33]. The CDC estimates that most new cases of HCV infection occur in IDU individuals and this group is partially responsible for the non-decline in HCV prevalence since 2006. Annual HCV incidence rates ranging from 8 to 25% have been reported in young adult injectors [34]. The highest incidence rates occur early after initiation of injection drug use [35,36,34], and prevention strategies targeting new injectors or persons at risk of starting should help avert this trend [37]. Early identification of this high risk population provides unique opportunity for interventions aimed at breaking the chain of transmission as well articulated by Page *et al.* [38]. This group is the basis of the ongoing prospective UFO study to inform comprehensive prevention among IDUs [39]. Unfortunately, because of confidentiality issues, NHANES does not routinely collect information on IDU among individuals who are less than 17 years old and therefore, we were unable to explore this group in detail. Low socioeconomic status and less education were associated to anti-HCV. These latter factors are often associated with high risk behaviors, including IDU and thus higher risk of infection.

Abnormal ALT was very strongly associated with anti-HCV presence. However, the positive predictive value of ALT as a screening tool for HCV remains very low even among the 1945–1965 birth cohort. Unfortunately, abnormal ALT remains the main indication for HCV screening in community practices [40]. Studies from other settings have also found elevated ALT not to be predictive of HCV infection [41–43].

Interestingly, as opposed to previous reports [1,6], lifetime number of sexual partners and age at first sexual intercourse were not predictive of anti-HCV. The reason for this difference is probably related to failure of these studies to adjust for several confounders and relative small numbers. Our study is the largest so far and the multivariate model included most established confounders. Although sexual transmission of HCV is well documented among HIV infected men who have sex with men, the risk of transmission among non-HIV infected heterosexual partners, as found in this study, is almost non-existent [44].

Previous blood transfusions are no longer associated with being anti-HCV positive. This finding is likely the result of the public health drive in the 1990s towards reducing the risk of transfusion related HCV infection [45,46]. The associations between blood transfusion and HCV infection in the US have

All analyses were limited to individuals 17 years and older. The NHANES survey policy limits collection of information on most of the risk factors including illegal drug use only to people 17 years and older. All factors reaching a p <0.2 in the univariate analyses were included in the multivariate analyses.
ALT, alanine aminotransferase; USA, United States of America; IDU, injection drug use, n.a., not available.
[+]p, trend for age.

typically been reported prior to 1992 [6]. Our study included blood transfusions at all periods, including the period during which universal screening of blood products for HCV was implemented.

NHANES remains the only nationally representative database in the United States that allows for such a study in the general population. Furthermore, combining data over 10 years provided a large study population, allowing for the calculation of robust and reliable estimates of associations. This study also has some limitations. NHANES is a cross-sectional survey and thus incidence of HCV infection cannot be estimated from this study. We can only infer from the stable prevalence that the rate of new infections is probably very low. Temporal sequence between risk factor(s) exposure and HCV infection cannot be ascertained. Results from NHANES data are only applicable to the non-institutionalized civilian population in the US, which represents only a portion of all HCV infected persons. These results cannot be extrapolated to some high risk groups such as the homeless or incarcerated, for whom the prevalence is likely to be higher than that of the general population. Our study relied on self-reporting and thus subject to recall bias. The use of IDUs is a socially stigmatized illegal activity that can result in people being unwilling to admit to this behavior. The latter may have resulted in an underestimation of these factors. The NHANES 3 step testing process is certainly more costly and time consuming. We think that simple EIA III with reflex to PCR without the RIBA step would have been less costly. RIBA did not, however, detract from the accuracy of our results.

Conclusions

We describe the current epidemiology of hepatitis C in the non-institutionalized civilian US population as of 2010. About 2.2 million persons are chronically infected with Hepatitis C in the US. Most of those infected are prevalent (born between 1945 and 1965), rather than incident cases. The prevalence of hepatitis C infection, which was on the decline in the US, has stabilized since 2006. With an anticipated increase in HCV-related complications as the 1945–1965 birth cohort ages, there is an increased need to identify and treat infected persons, especially in light of the advent of more effective and tolerable HCV therapies. The results of this NHANES survey suggest that screening for HCV should also be considered in persons migrating into the US. Future studies should explore reasons for no further decline in HCV prevalence since 2006.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contribution

Ivo Ditah, Pardha Devaki, Fausta Ditah: Involved in study conception and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript.

Oforbuike Ewelukwa, Henry Luma, Chobufo Ditah and Njei Basile: Involved in acquisition of data; revision of manuscript.

Michael Charlton: Involved in conception, design and critical revision of the manuscript for important intellectual content, study supervision.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2013.11.014.

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