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Estimating Prevalence of Hepatitis C Virus Infection in the United States, 2013-2016

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Hepatitis C virus (HCV) infection is the most commonly reported bloodborne infection in the United States, causing substantial morbidity and mortality and costing billions of dollars annually. To update the estimated HCV prevalence among all adults aged ≥18 years in the United States, we analyzed 2013-2016 data from the National Health and Nutrition Examination Survey (NHANES) to estimate the prevalence of HCV in the noninstitutionalized civilian population and used a combination of literature reviews and population size estimation approaches to estimate the HCV prevalence and population sizes for four additional populations: incarcerated people, unsheltered homeless people, active-duty military personnel, and nursing home residents. We estimated that during 2013-2016 1.7% (95% confidence interval [CI], 1.4-2.0%) of all adults in the United States, approximately 4.1 (3.4-4.9) million persons, were HCV antibody-positive (indicating past or current infection) and that 1.0% (95% CI, 0.8-1.1%) of all adults, approximately 2.4 (2.0-2.8) million persons, were HCV RNA–positive (indicating current infection). This includes 3.7 million noninstitutionalized civilian adults in the United States with HCV antibodies and 2.1 million with HCV RNA and an estimated 0.38 million HCV antibody-positive persons and 0.25 million HCV RNA–positive persons not part of the 2013-2016 NHANES sampling frame. *Conclusion:* Over 2 million people in the United States had current HCV infection during 2013-2016; compared to past estimates based on similar methodology, HCV antibody prevalence may have increased, while RNA prevalence may have decreased, likely reflecting the combination of the opioid crisis, curative treatment for HCV infection, and mortality among the HCV-infected population; efforts on multiple fronts are needed to combat the evolving HCV epidemic, including increasing capacity for and access to HCV testing, linkage to care, and cure. (Hepatology 2018;0:1-12).

Hepatitis C virus (HCV) infection is the most commonly reported bloodborne infection in the United States despite being underdiagnosed.[1-3] Highly efficacious, all-oral direct-acting antiviral (DAA) therapy has revolutionized hepatitis C treatment within the past decade, dramatically improving cure rates over previous treatment modalities.[4-6] Access to these therapies, however, is compromised by the high proportion of HCV-infected persons unaware of their status and, for those who have been diagnosed, insurer-implemented treatment restrictions related to concerns regarding the costs of HCV medications. Persons with untreated chronic HCV infection, as well as those who have been cured

but still have advanced HCV-associated disease, are at risk for hepatic fibrosis, cirrhosis, and hepatocellular carcinoma; and HCV infection remains one of the leading causes of liver transplantation in the United States.[7,8] Nationwide, during 2012-2013, the annual number of HCV-related deaths exceeded the total number of deaths reported to the Centers for Disease Control and Prevention associated with the 60 other nationally notifiable infectious diseases combined.[9]

The prevalence of current HCV infection (indicated by HCV antibody positivity and RNA positivity) in a given population at a particular time depends on several factors: the number of people with existing chronic HCV infection (defined as detectable HCV RNA at least 6 months following acute infection), the number of people with incident HCV infection, the number of people cured of HCV infection (through spontaneous clearance or treatment), and the number of deaths among persons with chronic HCV infection, regardless of whether mortality is attributed to complications of HCV infection. An accurate estimate of hepatitis C prevalence can inform public health interventions and resource allocation strategies aimed at reducing the health burden and economic costs caused by hepatitis C in the United States.

The National Health and Nutrition Examination Survey (NHANES) combines interviews and physical examinations to assess the health and nutritional status of adults and children in the United States and to determine the prevalence of major diseases and disease risk factors.[10] A 2014 analysis of NHANES data from 2003-2010 estimated that 3.6 million persons (95% confidence interval [CI], 3.0 million to 4.2 million persons) were HCV antibody–positive, indicating past or current HCV infection; of these, approximately 2.7 million (95% CI, 2.2 million to 3.2 million persons) were HCV RNA–positive, indicating current HCV infection of 1.0% (95% CI, 0.8%-1.2%) among the noninstitutionalized civilian US population aged ≥6 years.[11] A 2015 brief report using NHANES data from 2011-2014 estimated current HCV infection of 0.9% (95% CI, 0.6%-1.2%) among US adults aged ≥18 years but did not report an estimate of HCV antibody positivity.[12]

While the NHANES national probability sample provides the best available measurement of HCV prevalence in the general US population, its sampling frame is the noninstitutionalized, civilian population of the United States; consequently, NHANES underestimates the true prevalence of HCV in the United States because it excludes certain populations known to have high HCV prevalence from its sampling frame. In 2015, researchers estimated that an additional 1.0 million persons (range 0.4 million to 1.8 million) in high-risk population groups unaccounted for by NHANES 2003-2010 data were HCV antibody–positive, of whom 0.8 million (range 0.3 million to 1.5 million) were chronically infected.[13] These estimates suggested that in the United States during 2003-2010 4.6 million persons had HCV antibody and 3.5 million persons were living with current HCV infection. More recent estimates of HCV RNA prevalence are expected to be lower as more people are being cured because of improved HCV treatments; further, because the population in the United States is aging[14] and death rates increase with age, many persons in the age cohort at highest risk for chronic infection, those born during 1945-1965,[15] are dying of HCV-related and other causes. However, incident HCV infections linked to the opioid crisis and other drug use have simultaneously increased the overall prevalence of persons ever infected with HCV in the

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United States,[16] potentially offsetting these expected reductions in HCV prevalence.

To provide an estimate of HCV prevalence among adults aged ≥18 years in the United States, we combined estimates of prevalence in the noninstitutionalized civilian population from NHANES 2013-2016 data with modeled estimates for four additional populations that were not sampled by NHANES.

Materials and Methods

We used NHANES data to estimate HCV prevalence among the US noninstitutionalized civilian population and computed additional prevalence estimates for four populations that were not part of the NHANES sampling frame to provide a more comprehensive estimate of national HCV prevalence among adults aged ≥18 years during 2013-2016. The sampling frame for NHANES is the noninstitutionalized civilian population, which includes all people living in households, excluding institutional group quarters and those persons on active military duty.[17] We used 5-year American Community Survey (ACS) population estimates for 2012-2016 to generate population totals for the noninstitutionalized civilian population. We estimated HCV prevalence and population sizes for each additional population using a combination of literature search and population-size estimation approaches. These were combined to yield an updated estimate that reflects the total number of HCV infections in the United States more accurately than NHANES data alone. Additional enhancements of earlier estimation methods (e.g., refinement of additional populations and expansion of search terms) are described in the accompanying Supporting Information.

HCV PREVALENCE IN THE NONINSTITUTIONALIZED CIVILIAN ADULT POPULATION, 2013-2016

HCV antibody and RNA prevalences were calculated using data from the two most recent NHANES cycles (2013-2016). This complex, stratified, multistage probability survey collected information from approximately 10,000 civilian, noninstitutionalized US residents per 2-year cycle and was designed to provide representative national health estimates for this population.[17] Confirmed antibody data sets used in this analysis were published in January 2018 and accessed through the Research Data Center at the National Center for Health Statistics (NCHS). Survey participants provided blood samples for hepatitis C antibody screening and RNA testing; further antibody confirmation was performed among those participants who tested RNA-negative. In 2013, the NCHS revised its protocol for HCV testing of specimens from NHANES participants to align with updated guidelines for HCV testing published in 2013[18] and replace a laboratory test for HCV antibody confirmation that was removed from the market at the end of 2012 (Chiron RIBA HCV 3.0 SIA; Chiron Corporation, Emeryville, CA).[19-21] Under the protocols used during 1999-2012, antibody screening–reactive participants next received an antibody confirmation test, and confirmed antibody positive participants then received an RNA test.[19] During 2013-2016, NHANES participants first were tested for HCV antibody with a screening test; those with a reactive antibody screening test then received an HCV RNA test, and only RNA-negative participants received an antibody confirmation test using a third-generation line immunoassay (INNO-LIA HCV Score; Fujirebio, Malvern, PA).[20,21] The protocol change complicates formal statistical comparison of data before and after 2013. To estimate the national prevalence of HCV antibody and HCV RNA for 2013-2016 among adults aged ≥18 years, data were weighted to account for sampling design and participation in the examination component using the NCHS-provided Mobile Examination Center (MEC) survey weights. The MEC weights for participants with valid HCV screening and RNA test results were first multiplied by the ratio of the sum of the MEC weights for all participants eligible for HCV testing to the sum of the MEC weights for those with valid HCV test data within the same stratum (defined by sex, age group, and race/ethnicity) and then by the ratio of the sum of the MEC weights for all participants eligible for antibody confirmation testing to the sum of the MEC weights for those with valid antibody confirmation test results. This approach assumes that the prevalence of HCV RNA is the same among those with and without data, within each stratum, and that the prevalence of confirmed antibody is the same among those with and without confirmed antibody

test results. To calculate the number of noninstitutionalized civilians in the United States with HCV antibody and HCV RNA during 2013-2016, prevalence estimates were then multiplied by the estimated total noninstitutionalized civilian adult US population as of December 31, 2016, from the 2012-2016 ACS. Data collection for NHANES was approved by the NCHS Research Ethics Review Board. Analysis of deidentified data from the survey is exempt from the federal regulations for the protection of human research participants. Analysis of restricted data through the NCHS Research Data Center is also approved by the NCHS Ethics Review Board.

HCV PREVALENCE IN FOUR ADDITIONAL ADULT POPULATIONS, 2013-2016

Population-Size Estimates

We used the most recent published data to estimate the size of each of the following populations: incarcerated people, unsheltered homeless people, active-duty military personnel, and nursing home residents (Table 1). When necessary, these estimates

were adjusted for population growth to December 31, 2016, using a ratio of 2016 to 2014 population sizes in six age groups by sex strata, to allow for comparability with the population totals represented in the 2012-2016 ACS. Each additional population nonetheless required slightly different analytic approaches for estimating the 2016 population size and the group-specific HCV prevalence, described in further detail in the accompanying Supporting Information.

Literature Review

SEARCH PROCESS

We performed a literature review using PubMed to search for articles reporting HCV prevalence published in English from January 1, 2013, through December 31, 2017. We restricted the search to this time period in order to yield prevalence estimates reflecting the same period of the 2013-2016 NHANES cycles used for the prevalence estimate calculations. We expanded population-specific search terms from previous methodologies (Table 2).[13] Relevant literature search results were scarce for nursing home and active-duty military; because evidence was insufficient

TABLE 1. Population Inclusion Strategies and Data Sources, Adults Aged ≥18 Years

Population	Population Features Evaluated for Analytic Decisions			Data Sources Used in Analysis	
	Included in NHANES Sampling Frame	Included in ACS Population Size Estimates Used for NHANES Analyses	Evidence of Differential HCV Risk	HCV Prevalence Source	Population-Size Source
Noninstitutionalized civilian population	Yes	Yes	N/A	NHANES	ACS, 2012-2016[22]
Incarcerated	No	No	Yes	Literature	Bureau of Justice Statistics, 2016[23]
Unsheltered homeless	No	No	Yes	Literature	US Department of Housing and Urban Development, 2016[24]
Active-duty military	No	Yes	No	NHANES	US Department of Defense, 2016[25]*
Nursing homes	No	No	No	NHANES	National Survey of Long-Term Care Providers, 2014[26]†
People living in AI/AN areas‡,§	Yes	Yes	Yes	N/A	N/A
Hospitalized§	Yes	Yes	No	N/A	N/A
Other high-risk populations (e.g., people who inject drugs, sheltered homeless)‖	Yes	Yes	Yes	N/A	N/A

*Although this population is represented in the ACS population size estimate used for this NHANES analysis, these supplementary values were used in the adjusted estimate calculation.
†Scaled for population growth to 2016.
‡Residents of Native American reservations and tribal lands and Alaska Native village statistical areas.
§Excluded from analysis due to inclusion in both NHANES (prevalence numerator) and ACS (population size denominator).
‖For people who inject drugs, we assessed likely bias and determined that national NHANES estimates sufficiently represented HCV prevalence in this subpopulation.

TABLE 2. Search Terms and Results of Literature Search for Articles With Hepatitis C Prevalence Data Among Incarcerated Populations and Homeless Populations (January 1, 2013-December 31, 2017)

Population	Search Terms	Unique Articles	Abstracts Screened	Full Text Screened	Articles Included
Incarcerated	("hepatitis C" or "HCV") and ("prison" or "jail" or "correctional")	1,079	56	17	7
Homeless	("hepatitis C" or "HCV") and ("homeless" or "homeless persons" or "housing unstable" or "housing insecure")	1,353	24	9	1
Total		2,432	80	26	8

to suggest that these populations are at increased risk for HCV infection, we applied age-specific and sex-specific NHANES prevalence estimates to these two populations using publicly available data (Table 1); details on the prevalence estimation for these populations are provided in the accompanying Supporting Information.[13,27] Studies were selected for inclusion if they were conducted in the United States and reported quantitative data on HCV prevalence among general samples of incarcerated populations or homeless populations. Those sampling higher-risk subpopulations selectively were excluded (e.g., people living with human immunodeficiency virus or people who inject drugs).

LITERATURE REVIEW AND DATA EXTRACTION

A single reviewer (M.G.H.) performed a title review on all literature search results. Two reviewers (M.G.H. and M.A.B.) independently read abstracts and full-text articles meeting the established criteria to determine final eligibility for inclusion in our analysis; the reviewers discussed and resolved any differences in opinion. Once the list of articles was finalized, one reviewer (M.G.H.) extracted dates of testing, number of persons tested for HCV antibody and HCV RNA, number testing positive for HCV antibody and HCV RNA, and HCV prevalence from each study; this information was then verified by an additional reviewer (M.A.B.). References from the final article set were reviewed for any additional relevant articles.

DATA SYNTHESIS

We calculated the mean prevalence of both HCV antibody and HCV RNA for populations for which multiple published estimates were available (those incarcerated), using a random effects model and study sample size as weights.[28] For literature sources that provided HCV RNA testing data, RNA prevalence was calculated as the RNA test positivity among persons who were HCV antibody–positive and tested, multiplied by the HCV antibody prevalence. For studies that reported prevalence of HCV antibody only, prevalence of current HCV infection was calculated by multiplying the HCV antibody prevalence reported in the study by the proportion of HCV antibody–positive persons with HCV RNA estimated using 2013-2016 NHANES data (57.5%) (Table 3).

COMBINED US HCV PREVALENCE IN ADULTS

We calculated the population-specific number of adults ever infected with HCV (HCV antibody–positive) or currently infected with HCV (HCV antibody–positive and RNA-positive) by multiplying the population size by the respective HCV antibody prevalence and HCV RNA prevalence estimates for each group (Table 4). Because active-duty military are included in the ACS population estimate used in row 1 of Table 4, we subtracted the estimated population size of this group from the ACS population size to estimate the size of the noninstitutionalized civilian US population. We then estimated the number of persons infected with HCV from the adjusted population size and the NHANES HCV antibody prevalence and RNA prevalence. We summed the numbers of infected persons in each population to obtain the overall number of persons in the United States with past and current HCV infection and summed the population sizes to obtain the total US population size. We calculated the final HCV prevalences by dividing the total numbers of infected persons by the total estimated population size.

CONFIDENCE INTERVALS

CIs were used to account for statistical uncertainty in NHANES and additional population prevalence

TABLE 3. Hepatitis C Seroprevalence Studies in Incarcerated Populations and Homeless Populations

Reference	Location	Study Dates	Total No. Tested	No. HCV Antibody–Positive	HCV Antibody Prevalence	No. HCV RNA–Positive	HCV RNA Prevalence
Incarcerated							
Akiyama et al.[29]	New York, NY	2013-2014	10,856	2,234	20.6%	—	11.8%*
Cocoros et al.[30]	Barnstable County, MA	2009-2011	596	122	20.5%	23	15.2%†
de la Flor et al.[31]	Dallas County, TX	2015-2016	3,042	500	16.4%	—	9.5%*
Kuncio et al.[32]	Philadelphia, PA	2012	1,289	154	11.9%	—	6.9%*
Mahowald et al.[33]	Pennsylvania	2004-2012	101,727	18,454	18.1%	5,288	12.6%†
Schoenbachler et al.[34]	Durham County, NC	2012-2014	669	88	13.2%	66	10.7%†
Stockman et al.[35]	Wisconsin	2014-2015	1,239	155	12.5%	110	9.1%†
Mean prevalence:					16.1%		10.7%
Homeless							
Coyle et al.[36]	Philadelphia, PA	2012-2014	1,079	159	14.7%	108	10.8%‡
Mean prevalence:					14.7%		10.8%

*Calculated as (reported HCV antibody prevalence) × (NHANES 2013-2016 HCV RNA prevalence), where NHANES 2013-2016 HCV RNA prevalence among antibody-positives = 0.575.
†Calculated as (number HCV RNA–positive/number tested HCV RNA) × (reported HCV antibody prevalence).
‡Calculated as (reported HCV antibody prevalence) × [number HCV RNA–positive/(0.924 × number HCV antibody–positive)], where the calculation is adjusted by the 92.4% of study participants reported to have received RNA testing.

estimates. For the noninstitutionalized civilian population estimates from NHANES, reported CIs accounted for the multistage, clustered sampling design. For the incarcerated population, the reported CIs were generated from the random effects meta-analysis estimation. The reported CIs for unsheltered homeless persons, active-duty military, nursing home residents, and the combined US HCV prevalence were computed using a Monte Carlo simulation process (10,000 iterations) which resampled parameter estimates from normal distributions defined by the point estimate and standard errors for each population prevalence estimate.

Results

During 2013-2016, the estimated NHANES HCV antibody prevalence among persons aged 18 years or above was 1.5% (95% CI, 1.3%-1.8%), corresponding to approximately 3.7 million persons (95% CI, 3.1 million to 4.4 million persons) with past or current HCV infection in the US noninstitutionalized civilian population. The estimated NHANES HCV RNA prevalence among persons aged 18 years or above was 0.9% (95% CI, 0.7%-1.0%), corresponding to approximately 2.1 million persons (95% CI, 1.8 million to 2.5 million persons) with current HCV infection in the US noninstitutionalized civilian population.

The literature search for hepatitis C prevalence data for incarcerated populations and homeless populations yielded 2,432 unique articles, of which only eight met the inclusion criteria (Table 2). Seven studies of incarcerated persons reported HCV prevalence, with HCV antibody prevalence ranging from 11.9% to 20.6%. Of these, four studies reported HCV RNA prevalence ranging from 9.1% to 15.2%; for the other three studies, HCV RNA prevalence was calculated by multiplying the reported HCV antibody prevalence by the 57.5% of HCV antibody–positive persons with HCV RNA from the 2013-2016 NHANES data (Table 3). The estimated mean HCV antibody prevalence was 16.1%, and the estimated mean HCV RNA prevalence was 10.7%.

One study of homeless persons attending a Federally Qualified Health Center reported an HCV antibody prevalence of 14.7%; HCV RNA prevalence was estimated at 10.8% (Table 3).

The population sizes of the four additional groups ranged from 160,600 for the unsheltered homeless population to 2,131,000 for the incarcerated population (Table 4). We estimated that during 2013-2016 a total of 344,100 incarcerated persons, 23,700 unsheltered homeless persons, 13,500 active-duty military personnel, and 18,900 nursing home residents were HCV antibody–positive, while 227,400 incarcerated persons, 17,400 unsheltered homeless persons, 6,900 active-duty military personnel, and

TABLE 4. Estimated Population Sizes and Hepatitis C Prevalences Among Adults Aged ≥18 Years, United States 2013-2016

| Population | Estimated Adult Population Size* | HCV Antibody Prevalence | | | | HCV RNA Prevalence | | | |
| | | Number of Ever Infected Persons[†] | | Prevalence | | Number of Currently Infected Persons[†] | | Prevalence | |
		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
NHANES[‡]	241,152,600	3,721,000	(3,094,000-4,434,800)	1.5%	(1.3%-1.8%)	2,139,000	(1,794,200-2,529,700)	0.9%	(0.7%-1.0%)
Additional populations									
Incarcerated	2,131,000	344,100	(308,800-382,500)	16.1%	(14.5%-17.9%)	227,400	(201,900-255,600)	10.7%	(9.5%-12.0%)
Unsheltered homeless	160,600	23,700	(20,300-27,100)	14.7%	(12.7%-16.9%)	17,400	(14,400-20,500)	10.8%	(8.9%-12.8%)
Active-duty military	1,288,600	13,500	(8,000-18,100)	1.0%	(0.6%-1.4%)	6,900	(2,700-11,200)	0.5%	(0.2%-0.9%)
Nursing homes	1,425,500	18,900	(11,700-21,000)	1.3%	(0.8%-1.5%)	6,900	(4,600-9,300)	0.5%	(0.3%-0.7%)
Additional populations (subtotal)[§]	5,005,700	400,100				258,600			
NHANES (modified estimate excluding additional populations)[§]	239,864,100	3,701,100	(3,077,500-4,411,100)	1.5%	(1.3%-1.8%)	2,127,600	(1,784,600-2,516,200)	0.9%	(0.7%-1.0%)
Total[§]	244,869,800	4,101,200	(3,357,700-4,861,100)	1.7%	(1.4%-2.0%)	2,386,100	(1,983,900-2,807,800)	1.0%	(0.8%-1.1%)

*Population sizes are estimated as of December 2016 based on the ACS 5-year estimates from 2012–2016.
[†]Number of infected persons is calculated by multiplying the prevalence percentage estimate by the estimated adult population size; values may not multiply due to rounding.
[‡]NHANES prevalence percentage estimates are based on results from 2013–2016 NHANES. Population size includes noninstitutionalized adults eligible for NHANES from the 2012–2016 ACS.
[§]Values may not sum to column subtotal and total due to rounding.

6,900 nursing home residents were living with current HCV infection. The additional populations added approximately 5.0 million persons to the population total, 400,100 persons to the HCV antibody–positive total, and 258,600 to the HCV RNA–positive total. We estimated that overall in the United States 4,101,200 persons had HCV antibody and 2,386,100 persons were currently infected with HCV during 2013-2016.

Discussion

The purpose of our study was to provide an updated estimate of HCV prevalence among adults in the United States that would include persons in high-risk populations not part of the NHANES sampling frame. We estimate that during 2013-2016 in the United States 1.7% of all adults, or approximately 4.1 million persons, were HCV antibody–positive and that 1.0% of all adults, or approximately 2.4 million persons, were HCV RNA–positive. Our findings suggest that the 2013-2016 US HCV prevalence estimate derived from NHANES alone underestimates the actual number of HCV antibody–positive persons by approximately 0.38 million persons and the number of HCV RNA–positive persons by approximately 0.25 million persons.

Our analysis of NHANES data indicates an HCV antibody prevalence of 1.5% (3.7 million persons) during 2013-2016, higher than the previous NHANES estimate of 1.3% (3.6 million persons) during 2003-2010 that was produced using data collected before the 2013 revision of the NHANES HCV protocol.[11] While it is possible that some of this increase is due to the change in the NHANES laboratory protocol, it also likely reflects the changing epidemic of HCV infection in the United States.[1,37,38] From 2006 through 2012, state surveillance data from central Appalachia (Kentucky, Tennessee, Virginia, and West Virginia) demonstrated a 364% increase in the number of acute HCV infections among persons ≤30 years old.[38] Furthermore, from 2011-2014, commercial laboratory data indicated a 22% increase in national rates of HCV detection among women of childbearing age.[39] Overall, the number of incident hepatitis C cases reported in the United States through the National Notifiable Diseases Surveillance System increased 38.8% from 2013 through 2016,

most markedly among those 20-39 years old, although increases occurred among adults of all ages.[1]

Our findings suggest an estimated HCV RNA prevalence in the noninstitutionalized civilian adult US population of 0.9% (2.1 million persons; 95% CI, 1.8 million to 2.5 million persons) during 2013-2016, similar to the NHANES estimate of 0.9% for 2011-2014[12] and lower than the previous NHANES estimate of 1.0% (2.7 million persons; 95% CI, 2.2 million to 3.2 million persons) during 2003-2010.[11] Although the 2013 change in the NHANES HCV protocol may have played a role, the difference in these two estimates of current HCV infection is likely due to a combination of successful HCV treatment through oral DAA therapy and continued mortality (HCV-associated and all-cause).

While current therapies are highly efficacious, many populations have limited access to HCV testing, care, and treatment services. A recent systematic review of the literature indicated that only half of those infected with chronic HCV were diagnosed and aware of their infection, with only a proportion linked to care (43%), prescribed HCV treatment (16%), and achieving cure (9%).[40] In the Chronic Hepatitis Cohort Study, only 5.7% of patients with HCV infection potentially eligible for treatment initiated a DAA regimen prescribed in 2014.[41] Kanwal et al. reported slightly higher treatment rates at the Veterans Administration, where 10.2% of the nearly 150,000 patients with chronic HCV infection seen during the first 16 months of the DAA era received treatment.[42] Encouragingly, oral DAA therapy uptake has increased since the medications were first licensed. At the Veterans Administration specifically, 62,290 veterans completed oral DAA treatment between January 1, 2014, and September 30, 2016; and the Veterans Administration estimates that an additional 59,200 veterans will be cured from 2017 through 2018.[43,44] These data suggest that successful treatment, while contributing to the decline in current HCV infections, does not entirely account for the decrease observed in NHANES-estimated current HCV infection. Unfortunately, continued mortality contributes to the changes in HCV prevalence. During 2016 in the United States, 18,153 hepatitis C–related deaths were reported to the National Vital Statistics System, representing a 6.3% decrease from 2013.[1] A recent analysis demonstrated that HCV is substantially underreported on death certificates (even

when the main cause of death is liver-related), suggesting that the approximately 20,000 death certificates that included documentation of HCV annually during the study period underestimate mortality in chronically HCV-infected persons.[45] Additionally, as the population (adults born during 1945-1965, in particular) ages, deaths from competing, non-HCV-related causes contribute to a decrease in the overall prevalence of HCV infections.

Ultimately, given the rise in the number of persons with serologic evidence of an HCV infection in the past and the decline in the proportion of those persons currently infected with HCV, it is likely that successful treatment played an important role in the decrease in current HCV infection among the US noninstitutionalized civilian population. We estimated that 4.1 million persons were ever infected with HCV and approximately 2.4 million were currently infected, suggesting that about 1.7 million had cleared the infection. These 1.7 million adults either cleared the infection spontaneously or were cured through antiviral treatment. Some 15%-40% of infected persons resolve HCV infection spontaneously; women, younger persons, and those with certain immune response gene variants are more likely than other persons to clear HCV spontaneously.[46,47] Hundreds of thousands have likely been cleared through treatment and cure of their infection. An HCV drug manufacturer estimates that at least 673,000 people in the United States initiated an HCV treatment regimen during 2013-2016 alone.[48]

Compared with a previous estimate of the total US hepatitis C prevalence, our analysis identified lower HCV prevalence and fewer unenumerated HCV infections in populations not part of the NHANES sampling frame.[13] According to our estimates, 0.38 million HCV antibody–positive and 0.25 million HCV RNA–positive persons from populations not part of the NHANES sampling frame should be added to the HCV prevalence estimate generated using 2013-2016 NHANES data alone. Several factors contribute to these differences. The overall additional population size is smaller in our analysis (5.0 million persons) compared with a previously published analysis because we concluded that people living in American Indian/Alaska Native (AI/AN) areas (C. Ogden, personal communication, May 30, 2018), people hospitalized for less than the 8-week duration of the NHANES sampling period, and sheltered homeless people were included in the NHANES sampling frame and therefore did not include them in our analysis of additional populations.[13] This combined with the lower HCV prevalence reported in recent literature for incarcerated populations (16.1% HCV antibody prevalence in recent literature versus 23.1% HCV antibody prevalence in previous literature) and homeless populations (14.7% versus 32.1% HCV antibody prevalence) accounts for the reduction in unenumerated HCV infections in additional populations in our analysis.[13]

Our analysis had several limitations. First, the number of HCV-positive NHANES participants during 2013-2016 is small (n = 185 antibody-positive, n = 117 RNA-positive), even in this large nationally representative sample (n = 12,105 participants aged 18 years and older, of whom n = 10,857 were tested for HCV); although NHANES uses extensively tested protocols to encourage participation even in sensitive aspects of the study, if participants who did not participate in the examination component (n = 446), did not undergo HCV testing or provide a blood sample sufficient to yield conclusive HCV test results (n = 789), or opted not to participate in NHANES at all (n = 6,715, or 37% of, selected participants aged 20 years and above during 2013-2016) were disproportionately persons who had previously or concurrently injected drugs, NHANES may underestimate HCV prevalence even in the noninstitutionalized civilian population. However, one study, based on a dynamic model of HCV infection among the NHANES-eligible population from 2001 and beyond, estimated that 1.84 million noninstitutionalized people were HCV RNA–positive in the United States in 2015.[49] This estimate is only 15% lower than our estimate of HCV RNA prevalence in the noninstitutionalized civilian population during 2013-2016. Second, the effect of the NHANES change in laboratory testing methods on HCV antibody and RNA prevalence estimates before and after 2013 could not be assessed within the NHANES population, and thus any comparison of our current findings with previous estimates should be interpreted with caution. The change in NHANES protocol could potentially be a cause of higher HCV antibody prevalence in the current study; however, a full crossover comparison study using surplus NHANES sera to evaluate the effect of the 2013 change in the NHANES HCV protocol could not be conducted due to ethical considerations of potential

clinically relevant findings from such a study, and lack of availability of RIBA test kits prevented a prospective crossover study among NHANES participants after 2013. Third, none of the studies identified through our literature review were designed to generate nationally representative estimates of HCV prevalence in the additional populations. We excluded studies that selectively sampled higher-risk subpopulations (e.g., people who inject drugs) in an attempt to mitigate the potential lack of representativeness. Furthermore, a recent study published after our literature review was closed estimated that 18% of Americans who are in prison at any given time have antibodies to HCV,[50] slightly above our estimate, suggesting that the studies included in our analysis for the incarcerated population provide a credible HCV prevalence estimate for this additional population. The single study of the homeless population, however, may not be representative of this population nationwide. Fourth, we performed a sensitivity analysis on the homeless population estimates. Had we included the 263,500 sheltered homeless adults in 2016 in our analysis, we would have added 38,900 HCV antibody–positive persons and 28,500 HCV RNA–positive persons to our estimates. Fifth, because the source studies were not conducted for the purpose of synthesis into a national estimate, the application of meta-analytic and other statistical procedures to create CIs for additional populations should be interpreted more cautiously than CIs based on NHANES alone. Sixth, because people living in AI/AN areas could potentially be undersampled by the NHANES sampling frame, we performed a sensitivity analysis, applying a literature-based HCV prevalence estimate specific to people living in AI/AN areas,[51] to determine the HCV prevalence among this population. We estimate that there were approximately 125,000 HCV RNA-positive adults living in AI/AN areas during 2013-2016. This estimate likely represents the upper limit of current HCV infections in AI/AN areas during this time period. Finally, when we applied the 2013-2016 NHANES HCV RNA prevalence to the additional populations, we conferred to them the spontaneous clearance and treatment levels of the noninstitutionalized civilian population. This assumption may not be accurate (i.e., treatment levels are likely to be lower in the additional populations than in the noninstitutionalized civilian population) and could have resulted in underestimation of the prevalence of current HCV infection in the three incarcerated population studies that did not report HCV RNA prevalence; however, HCV antibody prevalence would be unaffected. We performed a sensitivity analysis applying the mean HCV RNA prevalence among those who tested antibody-positive from the four incarcerated population studies that reported HCV RNA prevalence to the three incarcerated population studies that did not report HCV RNA prevalence; the mean HCV RNA prevalence for the incarcerated population increased from 10.7% (when the 2013-2016 NHANES HCV RNA prevalence was applied) to 11.6%, a difference of 20,700 HCV RNA–positive persons overall (data not shown).

In summary, we estimate that during 2013-2016 in the United States approximately 4.1 million adults had evidence of past or current HCV infection, of whom approximately 2.4 million were currently infected with HCV. Compared to past estimates based on similar methodology, HCV antibody prevalence may have increased, while HCV RNA prevalence may have decreased, likely reflecting the impact of the opioid crisis on HCV incidence, use of effective treatment regimens, and continuing mortality among the HCV-infected population. Forthcoming work will include state-level estimates of hepatitis C prevalence using this methodology as well as delve deeper into the NHANES data to examine differences by group and the proportion of those aware of their infection and receiving care. Comprehensive and accurate estimates of HCV prevalence can guide health interventions and resource allocation to link chronically infected persons to care, treatment, and ultimately cure. Continued efforts to reduce the burden of HCV infection will require improved interventions to prevent infections, expanded testing to find undiagnosed persons, and strategies to ensure treatment so that HCV-infected persons are promptly cured.

REFERENCES

1) Centers for Disease Control and Prevention. Viral hepatitis surveillance, United States, 2016. https://www.cdc.gov/hepatitis/statistics/2016surveillance/pdfs/2016HepSurveillanceRpt.pdf. Published April 2018. Accessed April 16, 2018.

2) Centers for Disease Control and Prevention. HIV surveillance report, 2016, vol. 28. https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2017. Accessed February 26, 2018.

3) Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. Hepatology 2012;55:1652-1661.

4) McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593.

5) Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-1898.

6) Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-1992.

7) Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61(Suppl.):S58-S68.

8) Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: liver. Am J Transplant 2018;18(Suppl. 1):172-253.

9) Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003-2013. Clin Infect Dis 2016;62:1287-1288.

10) Centers for Disease Control and Prevention. About the National Health and Nutrition Examination Survey. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed February 26, 2018.

11) Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med 2014;160:293-300.

12) Kruszon-Moran D, Paulose-Ram R, Denniston M, McQuillan G. Viral hepatitis among non-Hispanic Asian adults in the United States, 2011-2014. NCHS data brief, no. 225. Hyattsville, MD: National Center for Health Statistics; 2015.

13) Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. Hepatology 2015;62:1353-1363.

14) US Census Bureau. The nation's older population is still growing, Census Bureau reports. https://www.census.gov/newsroom/press-releases/2017/cb17-100.html. Published June 22, 2017. Accessed March 13, 2018.

15) Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep 2012;61:1-32.

16) Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. Am J Public Health 2018;108:175-181.

17) Johnson CL, Dohrmann SM, Burt VL, Mohadjer LK. National Health and Nutrition Examination Survey: sample design, 2011-2014. Vital Health Stat 2 2014;162:1-33.

18) Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep 2013;62:362-365.

19) Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey: 2007-2012 data documentation, codebook, and frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/SSHCV_E.htm. Published February 2015. Accessed May 1, 2018.

20) Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey: 2013-2014 data documentation, codebook, and frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSHEPC_H.htm. Published January 2018. Accessed May 1, 2018.

21) Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey: 2015-2016 data documentation, codebook, and frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/HEPC_I.htm. Published September 2017. Accessed May 1, 2018.

22) American Community Survey. 2012-2016 ACS 5-year estimates. https://www2.census.gov/programs-surveys/acs/summary_file/2016/data/. Accessed February 1, 2018.

23) Kaeble D, Cowhig M. Correctional populations in the United States, 2016. https://www.bjs.gov/content/pub/pdf/cpus16.pdf. Published April 2018. Accessed May 1, 2018.

24) US Department of Housing and Urban Development. PIT and HIC data since 2007. https://www.hudexchange.info/resource/3031/pit-and-hic-data-since-2007/. Published December 2017. Accessed February 1, 2018.

25) US Department of Defense. 2016 demographics: profile of the military community. https://download.militaryonesource.mil/12038/MOS/Reports/2016-Demographics-Report.pdf. Accessed June 1, 2018.

26) Harris-Kojetin L, Sengupta M, Park-Lee E, Valverde R, Caffrey C, Rome V, et al. Long-term care providers and services users in the United States: data from the National Study of Long-Term Care Providers, 2013-2014. VitalHealth Stat 3 2016;38:x-xii.

27) Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011;31:1090-1101.

28) Borenstein M, Hedges LV, Higgins JPT, Rothstein H. Introduction to Meta-Analysis. 1st edn. Chichester, UK: Wiley; 2009.

29) Akiyama MJ, Kaba F, Rosner Z, Alper H, Holzman RS, MacDonald R. Hepatitis C screening of the "birth cohort" (born 1945-1965) and younger inmates of New York City jails. Am J Public Health 2016;106:1276-1277.

30) Cocoros N, Nettle E, Church D, Bourassa L, Sherwin V, Cranston K, et al. Screening for Hepatitis C as a Prevention Enhancement (SHAPE) for HIV: an integration pilot initiative in a Massachusetts County correctional facility. Public Health Rep 2014;129(Suppl. 1):5-11.

31) de la Flor C, Porsa E, Nijhawan AE. Opt-out HIV and hepatitis C testing at the Dallas County jail: uptake, prevalence, and demographic characteristics of testers. Public Health Rep 2017;132:617-621.

32) Kuncio DE, Newbern EC, Fernandez-Vina MH, Herdman B, Johnson CC, Viner KM. Comparison of risk-based hepatitis C screening and the true seroprevalence in an urban prison system. J Urban Health 2015;92:379-386.

33) Mahowald MK, Larney S, Zaller ND, Scharff N, Taylor LE, Beckwith CG, et al. Characterizing the burden of hepatitis C infection among entrants to Pennsylvania state prisons, 2004 to 2012. J Correct Health Care 2016;22:41-45.

34) Schoenbachler BT, Smith BD, Sena AC, Hilton A, Bachman S, Lunda M, et al. Hepatitis C virus testing and linkage to care in North Carolina and South Carolina jails, 2012-2014. Public Health Rep 2016;131(Suppl. 2):98-104.

35) Stockman LJ, Greer J, Holzmacher R, Dittmann B, Hoftiezer SA, Alsum LE, et al. Performance of risk-based and birth-cohort strategies for identifying hepatitis C virus infection among people entering prison, Wisconsin, 2014. Public Health Rep 2016;131:544-551.

36) Coyle C, Viner K, Hughes E, Kwakwa H, Zibbell JE, Vellozzi C, et al. Identification and linkage to care of HCV-infected persons

in five health centers—Philadelphia, Pennsylvania, 2012-2014. MMWR Morb Mortal Wkly Rep 2015;64:459-463.

37) Suryaprasad AG, White JZ, Xu F, Eichler BA, Hamilton J, Patel A, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006-2012. Clin Infect Dis 2014;59:1411-1419.

38) Zibbell JE, Iqbal K, Patel RC, Suryaprasad A, Sanders KJ, Moore-Moravian L, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years—Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. MMWR Morb Mortal Wkly Rep 2015;64:453-458.

39) Koneru A, Nelson N, Hariri S, Canary L, Sanders KJ, Maxwell JF, et al. Increased hepatitis C virus (HCV) detection in women of childbearing age and potential risk for vertical transmission—United States and Kentucky, 2011-2014. MMWR Morb Mortal Wkly Rep 2016;65:705-710.

40) Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PLoS One 2014;9:e101554.

41) Spradling PR, Xing J, Rupp LB, Moorman AC, Gordon SC, Lu M, et al. Uptake of and factors associated with direct-acting antiviral therapy among patients in the Chronic Hepatitis Cohort Study, 2014 to 2015. J Clin Gastroenterol 2018;52:641-647.

42) Kanwal F, Kramer JR, El-Serag HB, Frayne S, Clark J, Cao Y, et al. Race and gender differences in the use of direct acting antiviral agents for hepatitis C virus. Clin Infect Dis 2016;63:291-299.

43) Belperio PS, Shahoumian TA, Mole LA, Backus LI. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. Hepatology 2017;66:27-36.

44) LaMattina J. The VA will eliminate hepatitis C in veterans by year-end. https://www.forbes.com/sites/johnlamattina/2018/03/01/the-va-will-eliminate-hepatitis-c-in-veterans-by-year-end/#3f4e47dd7d12. Published March 1, 2018. Accessed March 9, 2018.

45) Mahajan R, Xing J, Liu SJ, Ly KN, Moorman AC, Rupp L, et al. Mortality among persons in care with hepatitis C virus infection: the Chronic Hepatitis Cohort Study (CHeCS), 2006–2010. Clin Infect Dis 2014;58:1055-1061.

46) Thomas DL, Seeff LB. Natural history of hepatitis C. Clin Liver Dis 2005;9:383-398.

47) Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.

48) Gilead Sciences, Inc. Q4 2016 earnings results. https://seekingalpha.com/article/4043560-gilead-sciences-inc-2016-q4-results-earnings-call-slides. Published February 7, 2017. Accessed March 29, 2018.

49) Chhatwal J, Chen Q, Aggarwal R. Estimation of hepatitis C disease burden and budget impact of treatment using health economic modeling. Infect Dis Clin North Am 2018;32:461-480.

50) Spaulding AC, Adee MG, Lawrence RT, Chhatwal J, von Oehsen W. Five questions concerning managing hepatitis C in the justice system: finding practical solutions for hepatitis C virus elimination. Infect Dis Clin North Am 2018;32:323-345.

51) Mera J, Vellozzi C, Hariri S, Carabin H, Drevets DA, Miller A, et al. Identification and clinical management of persons with chronic hepatitis C virus infection—Cherokee Nation, 2012-2015. MMWR Morb Mortal Wkly Rep 2016;65:461-466.

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