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ORIGINAL ARTICLE

Estimating hepatitis C prevalence in the United States, 2017–2020

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Abstract

Background and Aims: The National Health and Nutrition Examination Survey (NHANES) underestimates the true prevalence of HCV infection. By accounting for populations inadequately represented in NHANES, we created 2 models to estimate the national hepatitis C prevalence among US adults during 2017–2020.

Approach and Results: The first approach (NHANES+) replicated previous methodology by supplementing hepatitis C prevalence estimates among the US noninstitutionalized civilian population with a literature review and meta-analysis of hepatitis C prevalence among populations not included in the NHANES sampling frame. In the second approach (persons who injected drugs [PWID] adjustment), we developed a model to account for the underrepresentation of PWID in NHANES by incorporating the estimated number of adult PWID in the United States and applying PWID-specific hepatitis C prevalence estimates. Using the NHANES+ model, we estimated HCV RNA prevalence of 1.0% (95% CI: 0.5%–1.4%) among US adults in 2017–2020, corresponding to 2,463,700 (95% CI: 1,321,700–3,629,400) current HCV infections. Using the PWID adjustment model, we estimated HCV RNA prevalence of 1.6% (95% CI: 0.9%–2.2%), corresponding to 4,043,200 (95% CI: 2,401,800–5,607,100) current HCV infections.

Conclusions: Despite years of an effective cure, the estimated prevalence of hepatitis C in 2017–2020 remains unchanged from 2013 to 2016 when using a comparable methodology. When accounting for increased injection drug use, the estimated prevalence of hepatitis C is substantially higher than previously reported. National action is urgently needed to expand testing, increase access to treatment, and improve surveillance, especially among medically underserved populations, to support hepatitis C elimination goals.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PWID, people who injected drugs; MEC, Mobile Examination Center; NNDSS, National Notifiable Disease Surveillance System.

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INTRODUCTION

HCV infection is the most commonly reported bloodborne infection in the United States, with an estimated 69,800 new acute HCV infections occurring in 2021.[1] Although curative treatment is available, HCV infection still contributes to liver cancer and death from liver-related disease, and progress toward hepatitis C elimination has been a challenge. It is estimated that only 68% of currently infected persons are aware of their infection,[2] and there were 14,000 hepatitis C-associated deaths in 2021 alone.[1] The Viral Hepatitis National Strategic Plan for the United States calls for at least 80% of persons with HCV infection to achieve viral clearance by 2030.[3] The first step in monitoring and evaluating progress toward hepatitis C elimination is to understand the current burden of disease.

Prevalence of HCV infection is often summarized with 2 measures: prevalence of HCV RNA, indicative of current HCV infection, and prevalence of HCV antibody, indicative of prior infection with HCV. Historically, national hepatitis C prevalence estimates used data from the National Health and Nutrition Examination Survey (NHANES), which measures HCV antibody and HCV RNA using laboratory testing data.[2,4–6] The most recent NHANES report estimated that 2.2 million adults had current HCV infection during 2017 to March 2020,[2] which indicates a lack of progress toward hepatitis C elimination compared to 2013–2016 NHANES data (2.1 million adults with current HCV infection[6]). The NHANES survey is designed to be nationally representative of the noninstitutionalized civilian population of the United States, but the sampling frame excludes key populations known to have high hepatitis C prevalence. To account for this, modeling approaches have been used to supplement NHANES data to estimate the number of additional infections in population groups inadequately represented.[5,6] Members of our team estimated that there were an additional 258,600 current HCV infections that were not captured by the NHANES sample frame in 2013–2016.[6]

While these previous methodologies account for infections among persons excluded from the NHANES sampling frame, they still may underestimate the true number of HCV infections in the United States. People who injected drugs (PWID) have a substantially higher hepatitis C prevalence than the general US population. While PWID are included in the NHANES sampling frame, an evaluation of several population-based surveys (including NHANES) concluded that these surveys underrepresent PWID and yield biased estimates of injection drug use prevalence.[7] Although NHANES uses tested protocols to encourage participation in the survey and medical examination, sampled persons may choose not to participate in NHANES at all, may choose not to participate in the medical examination component, or may choose not to provide a blood sample for HCV testing. PWID may elect not to participate in population-based surveys for many reasons, including stigma, distrust in government, and fear of criminalization. If people who choose not to participate are disproportionately PWID, NHANES may underestimate the prevalence of HCV infection among the noninstitutionalized civilian population.[6]

We aimed to provide 2017–2020 estimates of hepatitis C prevalence among adults aged ≥ 18 years in the United States through 2 approaches. First, to facilitate comparison to previous estimates, we used a published methodology that accounts for key populations excluded from the NHANES sampling frame.[6] Second, we developed a new hepatitis C prevalence estimation methodology that aims to account for the underrepresentation of PWID in the NHANES sampling frame due to nonparticipation. In this paper, we present both approaches and outline the strengths and limitations of each.

METHODS

In this analysis, we estimated the national prevalence of HCV antibody and HCV RNA among adults ≥ 18 years of age during 2017–2020. The first approach replicated the methodology outlined by Hofmeister et al[6] with more recent data sources (hereafter referred to as the NHANES+ model). Briefly, we used NHANES data to estimate the number of persons with HCV antibody or HCV RNA among the US noninstitutionalized population and added literature-based prevalence estimates for 4 key populations that were not part of the NHANES sampling frame. NHANES samples from the noninstitutionalized civilian population living in households and excludes persons living in group quarters, persons experiencing unsheltered homelessness, or those on active military duty.[8] To better reflect the US HCV burden, we computed prevalence estimates for the following additional populations not included in the NHANES sampling frame: incarcerated persons, unsheltered and unhoused persons, active duty military personnel, and nursing home residents. Our second approach extended the NHANES+ model to better account for the underrepresentation of PWID in NHANES (hereafter referred to as the PWID adjustment model).[7] The full methodology for each approach is described in detail below and represented in Figure 1.

Hepatitis C prevalence in the noninstitutionalized adult population

We used data from the pre-pandemic NHANES cycle (January 2017–March 2020). NHANES is a complex, stratified, multistage probability survey that collects

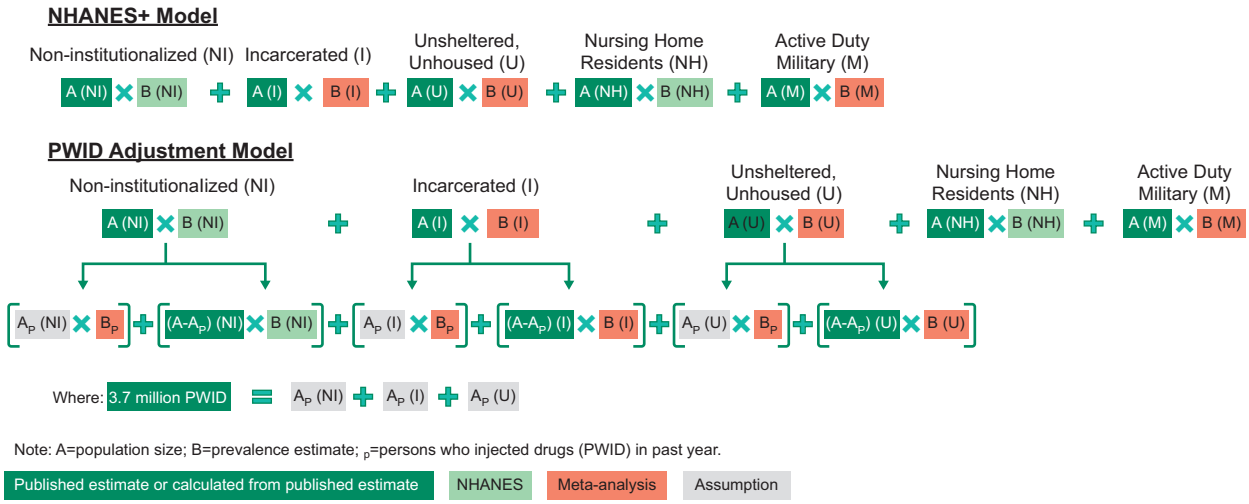

FIGURE 1 Formulas for estimating hepatitis C prevalence, United States. Abbreviations: NHANES, National Health and Nutrition Examination Survey; PWID, persons who injected drugs.

information from ~10,000 residents every 2 years and is designed to provide nationally representative health estimates. The COVID-19 pandemic interrupted field operations for the 2019–2020 NHANES cycle, so the partial 2019–2020 data were combined with the complete 2017–2018 cycle to yield a nationally representative pre-pandemic dataset.[8] In addition to the interview data, participants provided blood samples that were screened for HCV antibody. Antibody-reactive samples were tested for HCV RNA, and HCV antibody confirmation testing was conducted on those samples that were HCV RNA negative.[9]

NHANES provides Mobile Examination Center (MEC) survey weights that account for sampling design and participation in the examination component. Using the previously developed methodology,[6] we adjusted the MEC weights to account for missing HCV test results. First, we multiplied the weights by the ratio of the sum of all MEC weights among participants eligible for HCV testing to the sum of MEC weights for those with valid HCV RNA test results within strata of gender (male and female), race/ethnicity (Mexican American and other Hispanic, non-Hispanic Black, non-Hispanic White, and non-Hispanic Asian and other race identities) and age-group (0–5, 6–11, 12–19, 20–29, 30–39, 40–49, 50–59, 60–69, and $\geq$ 70 y). Second, we multiplied the weights by the ratio of the sum of MEC weights for all participants eligible for antibody confirmation testing to the sum of the MEC weights among those with valid antibody confirmation test results. To estimate the national number of noninstitutionalized adults with HCV antibody and HCV RNA, we multiplied the weighted prevalence estimates by the estimated total number of noninstitutionalized adults in the US population from the 2018 American Community Survey.[10] All NHANES data management and analysis were conducted using SUDAAN and SAS 9.4 Survey Procedures.

Hepatitis C prevalence in additional adult populations

Population size estimates

To estimate the population size for each of the 4 additional populations, we identified published data sources that reflected the most recent time point before March 2020. For the incarcerated population estimate, we used data from the Bureau of Justice Statistics, which includes prison counts from December 31, 2019 and jail counts that reflect the last week in June 2019.[11] For the number of unsheltered and unhoused persons, we used data from the US Department of Housing and Urban Development that reflects a point in time during a night in January 2020.[12] We used data from the US Department of Defense for the active duty military population size.[13] Finally, we used data from the 2018 National Survey of Long-Term Care Providers for the population estimate of nursing home residents.[14] We adjusted this estimate for population growth to 2020 by using a ratio of 2020 to 2018 population sizes in American Community Survey data within 3 age groups (50–64, 65–74, and 75+ years of age).

Literature review and data extraction

We conducted a literature review in January 2023 to identify published studies that reported hepatitis C prevalence within the 4 additional populations described above. We searched PubMed for articles published in English on or after January 1, 2017. All search terms are listed in Table 1. Studies were included if they were conducted in the United States and reported quantitative data on HCV antibody or HCV RNA prevalence among general samples of the

TABLE 1 Search terms and results of literature search for articles with hepatitis C prevalence data

Population	Search terms	Title/abstracts screened	Full Text screened	Articles included
Incarcerated	("hepatitis C" or "HCV") and ("prison" OR "jail" OR "correctional" OR "incarcerated" OR "houses of correction" OR "justice-involved" OR "inmate" OR "detention")	5793	47	15
Unsheltered and unhoused	("hepatitis C" or "HCV") and ("homeless" OR "houseless" OR "homeless persons" OR "housing unstable" OR "housing insecure" OR "unsheltered" OR "experiencing homelessness")	1170	35	8
Active duty military	("hepatitis C" or "HCV") and ("military" OR "armed forces" OR "air force" OR "army" OR "coast guard" OR "marines" OR "navy")	26,472	12	2
Nursing home residents	("hepatitis C" or "HCV") and ("nursing home" OR "nursing facility" OR "long-term care facility" OR "skilled nursing facility")	1827	0	0

population of interest. Studies that intentionally sampled subpopulations at higher risk for HCV infection (eg, people living with HIV and people who inject drugs) were excluded. We excluded any studies in which most data were collected before 2010. If we identified reviews that cited relevant data points, we identified the original source publication for the primary data. For the incarcerated population, we also reviewed citations for data published on hepcorrections.org as of February 1, 2023 to determine if any of those studies met our inclusion criteria.

A single reviewer (Megan G. Hofmeister or Jalissa Shealey) performed a title and abstract review on all literature search results. Two reviewers (Megan G. Hofmeister, Jalissa Shealey, or Eric W. Hall) independently reviewed each full-text article to determine final eligibility for inclusion. Any differences in opinion were discussed and resolved by the 2 reviewers. We extracted dates of testing, the number of persons tested for HCV antibody and HCV RNA, and the number of persons that tested positive for HCV antibody and HCV RNA.

Analysis of prevalence estimates

We did not identify any studies that measured hepatitis C prevalence in nursing home residents. Given that there is insufficient evidence to suggest that this population is at increased risk of HCV infection, we applied age-group–specific (50–64 y, 65–74 y, and 75+ years) NHANES prevalence estimates for this population.[6] For the other 3 populations that had published studies of hepatitis C prevalence estimates, we conducted a meta-analysis to estimate the mean prevalence of both HCV antibody and HCV RNA within each population. For literature sources that provided counts of the number of participants with detectable HCV RNA, current HCV infection prevalence was calculated as RNA-detected among persons who were HCV antibody-reactive, multiplied by the prevalence of HCV antibody among the study population. For studies that only reported the prevalence of HCV antibodies, we estimated the prevalence of current HCV infection by multiplying the HCV antibody prevalence by the proportion of HCV antibody-reactive persons with detectable HCV RNA using 2017–March 2020 NHANES data (43.9%) (Table 2).

Using the meta package (version 6.2-1) in R, we conducted a meta-analysis of single proportions to estimate the overall prevalence of HCV antibody and HCV RNA in each population. Due to the heterogeneity in settings and estimates, we used random effects models[38] for estimates from studies of incarcerated, unsheltered and unhoused populations. Because the active duty military studies had considerably less heterogeneity, we used common effects models weighted by study sample size.

TABLE 2 Included studies and results from a literature search for articles with hepatitis C prevalence data, published between January 2017 and January 2023, United States

Reference	Location	Years	Total # tested for HCV antibody	# HCV Ab reactive	HCV Ab prevalence (%)	# HCV RNA detected	HCV RNA (%)
Incarcerated							
Abe et al[15]	Dallas County, TX	2017	4089	708	17.3	413	12.4[a]
Akiyama et al[16]	New York, NY	2013–2014	10,790	2221	20.6	NA	9.0[b]
Assoumou et al[17]	Washington	2012–2016	24,567	4921	20.0	1727	14.4[a]
Beckwith et al[18]	Rhode Island	2012–2014	249	25	10.0	15	6.5[a]
Chan et al[19]	New York, NY	2014–2018	40,219	NA	26.4[c]	4665	11.6[d]
Chandra Deb et al[20]	North Dakota	2009–2018	8836	1337	15.1	NA	6.6[b]
Cocoros et al[21]	Barnstable County, MA	2009–2011	596	122	20.5	NA	9.0[b]
de la Flor et al[22]	Dallas County, TX	2015-2016	3042	500	16.4	NA	7.2[b]
Hochstatter et al[23]	Wisconsin	2011–2015	22,918	NA	31.1[c]	3126	13.6[d]
Kuncio et al[24]	Philadelphia, PA	2012	1289	154	11.9	NA	5.2[b]
Qureshi et al[25]	Los Angeles County, CA	2019	6231	1623	26.0	NA	11.4[b]
Schoenbachler et al[26]	Durham County, NC	2012–2014	669	88	13.2	66	10.7[a]
Spaulding et al[27]	New Mexico	2018	3295	1688	51.2	1405	42.6[d]
Spaulding et al[27]	Georgia	2016–2018	494	48	9.7	30	6.1[d]
Wynn et al[28]	San Diego, CA	2018	8793	2018	23.0	NA	10.1[b]
Unsheltered and unhoused							
Akiyama et al[16]	New York, NY	2013–2014	998	298	29.9	NA	13.1[b]
Benitez et al[29]	Los Angeles, CA	2016–2019	6767	769	11.4	443	6.6[a]
Cironi et al[30]	New Orleans, LA	2020	102	25	24.5	12	22.6[a]
Coyle et al[31]	Philadelphia, PA	2012–2016	2491	374	15.0	276	11.4[a]
Khalili et al[32]	San Francisco, CA & Minneapolis, MN	2018–2021	766	162	21.1	107	13.9[a]
Leach et al[33]	Philadelphia, PA	2017–2019	306	14	4.6	NA	2.0[b]
Noska et al[34]	Veterans Affairs Medical Centers, USA	2015	189,508	NA	35.2[c]	29,311	15.5[d]
Seaman et al[35]	Portland, OR	2017–2020	1320	NA	62.6[c]	363	27.5[d]
Active duty military							
Kasper et al[36]	Joint Base San Antonio-Lackland, TX	2017–2020	29,615	85	0.29	6	0.02[d]
Taylor et al[37]	Joint Base San Antonio-Lackland, TX	2013–2016	30,660	39	0.13	2	0.01[a]

Note: In some studies, not all persons that were HCV antibody-reactive were tested for HCV RNA. Please see the superscripts and corresponding notes for the calculation of each HCV antibody prevalence and each HCV RNA prevalence.

[a]Calculated HCV RNA prevalence as (number HCV RNA-detected/number tested HCV RNA) × (reported HCV antibody prevalence).

[b]Calculated HCV RNA prevalence as (reported HCV antibody prevalence) × (NHANES 2017–2020 HCV RNA prevalence among HCV antibody-reactive), where NHANES 2017–2020 HCV RNA prevalence among HCV antibody-reactive = 0.439.

[c]Calculated HCV antibody prevalence as (number HCV RNA-detected/NHANES 2017–2020 HCV RNA prevalence among HCV antibody-reactive)/(total number tested) ×100, where NHANES 2017–2020 HCV RNA prevalence among HCV antibody-reactive = 0.439.

[d]Calculated HCV RNA prevalence as (number HCV RNA-detected/total number tested) ×100.

TABLE 3 Population sizes and hepatitis C prevalence estimates, by population, United States, 2017–2020

Population	Estimated adult population size	HCV antibody prevalence			HCV RNA prevalence			Source
	N (95% CI)	%	95% CI		%	95% CI		
Noninstitutionalized[10]	249,177,857	2.04	1.36	3.06	0.89	0.55	1.45	[8]
Unsheltered and unhoused[12]	212,090	22.04	10.53	40.44	11.10	5.94	19.78	Meta-analysis
Incarcerated[11]	2,086,600	19.60	14.98	25.23	9.72	7.10	13.18	Meta-analysis
Active duty military[13]	1,326,200	0.22	0.19	0.26	0.02	0.01	0.03	Meta-analysis
Nursing home residents[14]	1,404,421	1.47	0.94	2.01	0.57	0.30	0.85	[8] (age-adjusted)
Persons who injected drugs in past year[39]	3,694,500 (1,872,700–7,273,300)	53.50	47.00	59.90	43.70	40.70	46.70	[43]

Adjustment for persons who inject drugs

We developed a second model, the PWID adjustment model, to account for the underrepresentation of PWID in NHANES. This model is based upon a recent estimate of 3.7 million adults in the United States in 2018 who injected drugs in the last year (n = 3,694,500; 95% CI: 1,872,700–7,273,300).[39] We assumed that these 3.7 million current PWID were part of 3 populations: incarcerated, unsheltered and unhoused, and non-institutionalized. To determine the percent of incarcerated persons with current injection drug use, we multiplied a published estimate of the percentage of persons in prison who met the criteria for a substance use disorder within the 12 months before incarceration (47.1%)[40] by the percent of persons entering treatment for any substance use disorders in 2020 that reported injection drug use as the route of administration for one of their 3 most used substances (22.6%),[41] resulting in an estimated 10.6% of the incarcerated population with current injection drug use. Similarly, we estimated that 7.4% of the unsheltered and unhoused population had current injection drug use by multiplying the percent of unsheltered and unhoused persons that are estimated to have a non-alcohol substance use disorder (26.0%)[42] by the percent of persons entering treatment for a non-alcohol substance use disorder and reporting injection drug use as the route of administration for one of their 3 most used substances (28.4%).[41] We multiplied these percentages by the population size estimate for each respective population to calculate the number of current PWIDs among the incarcerated population and the unsheltered and unhoused population. Finally, we assumed the remainder of the total adult current PWID population was part of the noninstitutionalized population.

To estimate hepatitis C prevalence in each population, we stratified the incarcerated, unsheltered/unhoused, and noninstitutionalized populations into current PWID and noncurrent PWID. We defined current PWID as persons who injected drugs in the last year and noncurrent PWID as persons who did not inject drugs in the last year (eg, either persons with a history of injection drug use (>1 y ago) or no history of injection drug use). All current PWID in these 3 populations were estimated to have HCV antibody prevalence of 53.5% (95% CI: 47.0%–59.9%) and HCV RNA prevalence of 43.7% (95% CI: 40.7%–46.7%) based on a recently published analysis.[43] We assumed that hepatitis C prevalence among noncurrent PWID incarcerated persons and noncurrent PWID unsheltered and unhoused persons was equal to the values calculated from the literature search and meta-analysis among the general incarcerated and general unsheltered and unhoused populations described above. For the noncurrent PWID in the noninstitutionalized population, we assumed hepatitis C prevalence was equal to the estimate among the general population in the NHANES 2017–March 2020 survey.

The hepatitis C prevalence inputs for each population are reported in Table 3. The estimates and interim calculations for each of these populations are reported in Supplemental Table S1, http://links.lww.com/HEP/I452. In sensitivity analyses, we explored the assumptions that 10.6% of incarcerated persons and 7.4% of unsheltered and unhoused persons are current PWID by generating results with combinations of the most extreme assumptions (ie, 0% or 100% are current PWID) for both populations and examining the impact on national hepatitis C prevalence.

Combined hepatitis C prevalence among US adults and uncertainty intervals

We multiplied the population totals by the respective prevalence estimates (Table 3) and summed across all populations to estimate the total number of US adults with HCV antibody and HCV RNA (Figure 1). We estimated 95% CIs to account for the combined statistical uncertainty in all hepatitis C prevalence estimates (ie, NHANES-based estimates, results from our meta-analyses of prevalence in additional populations, and reported meta-analysis results from Degenhardt el al[43]) and the total number of current PWID in the United States. For each input, we defined normal distributions using the reported or calculated point estimate and SEs. Using a Monte Carlo simulation process (10,000 iterations), we resampled parameter estimates from each distribution and recalculated the results. The 95% CI was defined using the 2.5th and 97.5th percentile from the resulting distribution of results. We present results from both the NHANES+ model and the PWID adjustment model.

RESULTS

The literature search of hepatitis C prevalence among populations not included in the sampling frame identified 37,272 unique papers, of which 25 met the inclusion criteria (Supplemental Figures S1-4, http://links.lww.com/HEP/I452; included papers listed in Table 2). Fifteen studies measured hepatitis C prevalence among people in incarcerated settings, resulting in an estimated mean HCV RNA prevalence of 9.7% (95% CI: 7.1%–13.2%) (Table 3). Eight studies measured HCV RNA prevalence among unsheltered and unhoused persons, resulting in an estimated mean HCV RNA prevalence of 11.1% (95% CI: 5.9%–19.8%). The population size estimates for incarcerated persons and unsheltered and unhoused persons were 2,086,600 and 212,090, respectively.

Using the NHANES+ model, we estimated an HCV RNA prevalence of 0.97% (95% CI: 0.52%–1.43%) among US adults in 2017–2020, corresponding to 2,463,700 (95% CI: 1,321,700–3,629,400) current HCV infections (Table 4). Using the PWID adjustment model, we estimated an HCV RNA prevalence of 1.6% (95% CI: 0.9%–2.2%), corresponding to 4,043,200 (95% CI: 2,401,800–5,607,100) current HCV infections. Using the NHANES+ model, we estimated an HCV antibody prevalence of 2.2% (95% CI: 1.4%–3.0%), corresponding to 5,556,400 (95% CI: 3,519,100–7,688,100) persons. This estimate was lower than the PWID adjustment model, which estimated an HCV antibody prevalence of 2.9% (95% CI: 1.9%–3.9%), corresponding to 7,411,300 (95% CI: 4,917,200–9,979,700) persons. All estimated hepatitis C prevalence results, stratified by population of interest, are reported in Supplemental Table S2, http://links.lww.com/HEP/I452 (NHANES+ model) and Supplemental Table S3, http://links.lww.com/HEP/I452 (PWID adjustment model).

For the PWID adjustment model, we conducted a sensitivity analysis of the percentage of the incarcerated and unsheltered and unhoused populations unsampled by NHANES that were PWID to determine the potential impact these assumptions had on the total estimated number of infections. For example, by evaluating extreme assumptions, we estimated the number of possible current HCV infections ranged from

TABLE 4 Estimated hepatitis C prevalence among adults ≥ 18 years of age, United States

Model	Years	N	n	95% CI		%	95% CI	
					HCV Antibody			
Hofmeister et al 2018[6]	2013–2016	244,869,800	4,101,200	3,357,700	4,861,100	1.7	1.4	2.0
NHANES+	2017–2020	254,207,169	5,556,400	3,519,100	7,688,100	2.19	1.38	3.02
PWID adjustment	2017–2020	254,207,169	7,411,300	4,917,200	9,979,700	2.92	1.93	3.93
					HCV RNA			
Hofmeister et al 2018[6]	2013–2016	244,869,800	2,386,100	1,983,900	2,807,800	1.0	0.8	1.1
NHANES+	2017–2020	254,207,169	2,463,700	1,321,700	3,629,400	0.97	0.52	1.43
PWID adjustment	2017–2020	254,207,169	4,043,200	2,401,800	5,607,100	1.59	0.94	2.21

Note: PWID adjustment results assume 10.6% of incarcerated and 7.4% of unsheltered and unhoused are people who inject drugs.
Abbreviation: PWID, persons who injected drugs (in the past year).

3,839,500 (assuming 100% of incarcerated and 100% of unsheltered and unhoused are current PWID) to 4,047,300 (assuming 0% of incarcerated and 0% of unsheltered and unhoused are current PWID; Table 5).

DISCUSSION

This paper builds upon recently released estimates of hepatitis C prevalence among the noninstitutionalized civilian adult US population[2] by including previously excluded groups that are known to have high hepatitis C prevalence. We sought to update the estimate of hepatitis C prevalence among adults in the United States using 2 methodological approaches: first, by including populations that are not part of the NHANES sampling frame, and second, by further adjusting the prevalence estimate to more accurately account for inadequate representation of current PWID in NHANES. We estimate that during 2017–2020 in the United States, between 2.2% and 2.9% of all adults, or ~5.6–7.4 million persons, had prior infection with HCV (HCV antibody-reactive) and that between 1.0% and 1.6% of all adults, or ~2.5–4.0 million persons, had current HCV infection (HCV RNA-detected). Our findings demonstrate that the hepatitis C burden in the United States is substantial and that the 2017–March 2020 estimate derived from NHANES alone underestimates the actual number of persons with prior HCV infection by ~0.47–2.33 million persons and the number of persons with current HCV infection by ~0.25–1.83 million persons.

Our NHANES+ model aligns with the methodology used to generate the previous national estimate of hepatitis C prevalence in 2013–2016,[6] which allows for a comparison of hepatitis C prevalence estimates between 2013–2016 and 2017–2020. Our results demonstrate that the number of adults with current HCV infection during 2017–2020 has not changed appreciably from 2013 to 2016 (2.4 million infections), highlighting the continued challenge of identifying and treating HCV-infected persons in a timely manner.[2] Additionally, the NHANES+ model estimated that 5.6 million US adults had HCV antibodies during 2017–2020, which is a noticeable increase from the 2013–2016 estimate (4.1 million). This increase reflects the steady rise in the number of acute hepatitis C cases reported to the National Notifiable Diseases Surveillance System (NNDSS) each year since 2013, primarily attributed to injection drug use;[1] overall, the annual number of incident hepatitis C cases reported to NNDSS increased 49.2% during the 2017–2020 analysis period.[1] Teshale et al estimated that 1.2 million people were treated for hepatitis C in the United States during 2014 to 2020.[44] Combined, the trends in HCV antibody and HCV RNA prevalence indicate that although more than 1 million people have been treated for hepatitis C, diagnosis, linkage to care, and treatment are not occurring at a rate sufficient to offset the increase of new HCV infections.

The PWID adjustment model estimated ~1.6 million additional current HCV infections during 2017–2020, compared to the NHANES+ model. The primary difference between the 2 approaches is that the PWID adjustment model uses an estimate of the number of adult PWID in 2018 and assumes all PWID[39] have a higher prevalence of HCV RNA (43.7%) and HCV antibody (53.5%), as reported by meta-analysis[43] (Supplemental Table S1, http://links.lww.com/HEP/I452). This directly addresses one of the stated limitations[6] and published critiques[45] of the previous approach by

TABLE 5 Sensitivity analysis of PWID assumptions among incarcerated and unsheltered and unhoused

% of incarcerated	% of unsheltered and unhoused	n	Lower estimate	Upper estimate	%	Lower estimate	Upper estimate
PWID assumption				HCV antibody			
10.6% (primary results)	7.4% (primary results)	7,411,300	4,917,200	9,979,700	2.92	1.93	3.93
0%	0%	7,466,200	5,451,700	9,581,200	2.94	2.14	3.77
0%	100%	7,420,500	5,409,600	9,541,700	2.92	2.13	3.75
100%	0%	7,098,100	5,069,400	9,235,700	2.79	1.99	3.63
100%	100%	7,055,700	5,022,900	9,198,700	2.78	1.98	3.62
				HCV RNA			
10.6% (primary results)	7.4% (primary results)	4,043,200	2,401,800	5,607,100	1.59	0.94	2.21
0%	0%	4,047,300	2,909,700	5,194,900	1.59	1.14	2.04
0%	100%	4,025,200	2,887,700	5,176,900	1.58	1.14	2.04
100%	0%	3,861,700	2,710,900	5,021,300	1.52	1.07	1.98
100%	100%	3,839,500	2,690,500	5,001,700	1.51	1.06	1.97

Abbreviation: PWID, persons who injected drugs (in the past year).

Hofmeister et al, which noted that if nonresponse in the NHANES sampling frame differs by hepatitis C prevalence, then utilizing NHANES data alone for a hepatitis C prevalence estimate among the US noninstitutionalized population would be biased. Additionally, having a more accurate count of HCV infections among all PWID reduces the potential impact of bias from prevalence estimates or population size estimates for the additional populations not included in the NHANES sampling frame. As a comparison point, a recent paper published after the completion of our literature search estimated there were 91,090 persons with an HCV infection in state prison populations at the end of 2021.[46] Considering the state prison population accounted for ~47% of the total incarcerated population in 2020,[11] this estimate is consistent with our results of 277,300 current HCV infections (from the PWID adjustment model) among persons in prison and jails at a given point in time.

Although NHANES is an important nationwide survey that has generated robust estimates for a variety of chronic health conditions, our analysis indicates that NHANES alone is insufficient for measuring disease burden for conditions that disproportionately occur among persons who may be less likely to participate in a national survey. In both models, a substantial number of current HCV infections were estimated among persons outside the NHANES sampling frame during 2017–2020. This highlights the need to use modeling approaches to generate prevalence estimates that more accurately characterize the hepatitis C burden in the United States than can be achieved through surveillance systems, such as NNDSS or NHANES, alone.[47]

Furthermore, differences between our 2 methodologic approaches highlight that surveillance is challenging for a highly stigmatized disease.[7] Hepatitis C is reportable to the NNDSS, but most infections remain unreported due to the asymptomatic nature of many acute HCV infections and differences in surveillance capacity to identify and investigate potential cases across jurisdictions.[48] In addition, many health departments do not have the capacity to follow persons with HCV infection longitudinally, making it difficult to monitor hepatitis C prevalence over time. In 2022, 83% of state and local jurisdictions produced estimates for the number of HCV cases reported through case surveillance. However, only 20% produced estimates of hepatitis C prevalence, which requires matching HCV case data to deaths in vital statistics and an assessment of how many infections were cleared or cured.[49] Furthermore, one-third of jurisdictions did not produce a surveillance report providing core epidemiologic data on the burden of HCV disease. One-fifth did not have even one full-time employee dedicated to HCV surveillance, while jurisdictions indicated they needed 3–5 employees to perform core surveillance activities.[49] Increased surveillance capacity at state and local levels will be required to produce national and local estimates of hepatitis C prevalence grounded in case-based data.

There are several limitations to our models. First, the small number of persons in NHANES with HCV infection impacts the statistical reliability of estimates. Second, the literature search did not generate nationally representative estimates of hepatitis C prevalence in incarcerated or unsheltered and unhoused populations. However, we excluded studies that intentionally sampled higher-risk groups (eg, people who inject drugs) to reduce potential bias. Although the PWID adjustment model aims to address several of the previously noted limitations of the NHANES+ approach, it introduces new data points and additional assumptions; the validity of these results is contingent on the validity of these additional inputs. First, the results of the PWID adjustment model rely on the validity of the estimated number of current PWIDs in the United States (3.7 million).[39] While the estimate includes a CI of statistical uncertainty that was incorporated into this analysis, it is also contingent on assumptions that could potentially introduce bias. Bradley et al used a hybrid multiplier methodology that used mortality data from the National Vital Statistics System, substance use admission treatment data from the Treatment Episode Data Set-Admissions, a literature-based ratio of fatal overdose to nonfatal overdose, and probability of overdose among PWID in the National HIV Behavioral Surveillance system.[39] In their paper, the authors discuss the potential impact of several assumptions on the PWID population size estimate. If any of those assumptions led to overestimating the adult PWID population size, this could result in overestimating hepatitis C prevalence in our PWID adjustment model.

Similarly, the validity of our PWID adjustment model results is dependent on the validity of the hepatitis C prevalence estimates among PWID as reported in a recent systematic review (HCV RNA = 43.7%; HCV antibody = 53.5%).[43] The systematic review by Degenhardt et al incorporated data from 22 HCV antibody prevalence estimates during 2015 to 2020 and 4 HCV RNA prevalence estimates during 2013 to 2018. All 4 estimates that contributed to the US HCV RNA prevalence estimate were subnational in scale; consequently, the estimate might not be representative of the HCV RNA prevalence among all PWID in the United States. Notably, one of the estimates was restricted to young PWID aged 18–29 years.[50] Despite the limitations of the individual estimates incorporated into the random effects model, the HCV RNA prevalence estimates coalesced into a similar range (40.7%–46.7%) and represent the most relevant hepatitis C prevalence estimates available among PWID for our analysis period.

Finally, for the PWID adjustment model, we were unable to generate hepatitis C prevalence estimates for noncurrent PWID (ie, persons who did not inject drugs

in the last year) among the additional key populations. Therefore, we assumed noncurrent PWID members (which includes people who have a history of injection drug use [> 1 y ago] and those that have never injected) of the key additional populations have a hepatitis C prevalence equal to the overall prevalence estimates from each meta-analysis, which might overestimate the number of infections among noncurrent PWID in each key additional population. Similarly, we were unable to remove current PWID from the NHANES data, so for the non-PWID noninstitutionalized population, we assumed a hepatitis C prevalence equal to the prevalence of HCV infection among all adults in NHANES. Considering that the NHANES sampling frame does capture some PWID, this approach could result in an overestimation of the number of infections in this population. Additionally, based on our literature search, we apportioned the hepatitis C prevalence estimates among PWID (as reported in the Degenhardt et al systematic review[43]) to the incarcerated, unsheltered and unhoused, and noninstitutionalized populations, but not to the active duty military and nursing home resident populations, which might have impacted the overall estimated number of infections. Future characterization of the prevalence of active injection drug use in active duty military and nursing home resident populations would be required to determine the magnitude and direction of the impact.

Despite these limitations, we estimate that during 2017–2020 in the United States, 5.6–7.4 million adults had evidence of past or current HCV infection, of whom 2.5–4.0 million were currently infected with HCV. Although there has been an effective cure for years, the estimated prevalence of current HCV infection in 2017–2020 remains unchanged from 2013 to 2016 when using a comparable methodology. When accounting for increased injection drug use in the United States, the estimated prevalence of hepatitis C is substantially higher than previously reported. National action is urgently needed to expand testing, increase access to treatment, and improve surveillance among people who are medically underserved to support hepatitis C elimination goals.

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CONFLICTS OF INTEREST

Heather Bradley and Eric W.Hall consults for Merck. Patrick Sullivan consults and received grants from Merck. He is on the speakers' bureau and received grants from Gilead and received grants from Viiv. The remaining authors have no conflicts to report.

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