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REVIEW ARTICLE

Hepatitis C virus infection in USA: an estimate of true prevalence

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Abstract

The recent National Health and Nutrition Examination Survey (NHANES) sampled only the civilian, non-institutionalized population of USA and may have underestimated the prevalence of hepatitis C virus (HCV) in this country. We searched the database MEDLINE, the Bureau of Justice Statistics, Center for Medicare and Medicaid and individual states Department of Corrections for all epidemiological studies regarding the prevalence of HCV in populations not sampled by the NHANES survey namely the incarcerated, homeless, nursing home residents, hospitalized and those on active military duty. Because of their relatively low frequency in the NHANES sample, we also expanded our search to include healthcare workers and long-term dialysis patients. Although included in the NHANES sample, we also performed searches on drug users (injection and non-injection) and veterans to confirm the findings of the NHANES study. Based on the prevalence of studies identified meeting our inclusion criteria, our most conservative estimates state that there at least 142 761 homeless persons, 372 754 incarcerated persons and 6805 persons on active military duty unaccounted for in the NHANES survey. While the NHANES estimates of drug users (both injection and non-injection) appear to be reasonable, the survey seems to have underestimated the number of HCV-positive veterans. Our most conservative estimates suggest that there are at least 5.2 million persons living with HCV in USA today, approximately 1.9 million of whom were unaccounted for in the NHANES survey.

Hepatitis C virus (HCV) is the most common blood-borne infection in USA (1) and worldwide (2). Chronic HCV can lead to hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC) and is the leading cause of liver transplantation nationwide (3).

The National Health and Nutrition Examination Surveys (NHANES) is a series of surveys that have periodically collected data on HCV prevalence, allowing clinicians to target at-risk groups with educational services and therapeutic options. According to the most recent NHANES, 1.6% or 4.1 million persons in USA were anti-HCV positive, most of whom were born between 1945 and 1964 (4). With 15 079 total participants, its information is invaluable and easily the largest epidemiological survey of HCV data in existence regarding HCV prevalence in USA. The NHANES study highlights the burden of HCV infection in the aforementioned birth cohort and the need to diagnose these individuals before complications develop.

The survey, however, sampled from a non-institutionalized, civilian population, did not include certain high-risk persons, namely the incarcerated, homeless, nursing homes residents, hospitalized patients, those on active military service and immigrants. Other groups with an expected high prevalence of HCV infection missed by the survey include healthcare workers (HCW) and persons on long-term haemodialysis because of low frequency and lack of availability in the NHANES dataset. As a result, the NHANES has likely underestimated the true prevalence of HCV in USA.

This study will focus on these high-risk groups not captured in the NHANES survey and addresses the true prevalence of HCV in USA. As injection drug use (IDU) and history of military service were captured by the NHANES, we will also systematically review the literature to determine concordance between the NHANES data and the available published data of these high-risk groups.

Methods

Search strategy and identification of studies

We searched the database MEDLINE for all epidemiological studies on HCV prevalence from 1975 when the first cases of hepatitis because of non-hepatitis A, non-hepatitis B were described (5) to the current day. We used a combination of the keywords 'Hepatitis C virus', 'prevalence', 'incarcerated', 'prison', 'homeless', 'intravenous drug use', 'injection drug use', 'non-injection drug use', 'cocaine', 'heroin,' 'tattoo', 'healthcare worker', 'doctor', 'surgeon', 'dentist', 'firefighter', 'police', 'emergency medical technician', emergency medical service', 'hemodialysis', 'blood transfusion', 'hemophiliac', 'military', 'veteran', 'nursing home', 'hospitalized' and 'immigrant'. Bibliographies of all identified studies were searched for relevant articles for additional studies. We also searched additional electronic sources from the United States Census, Center for Medicare and Medicaid, the Bureau of Justice Statistics and individual state Department of Corrections for additional data on HCV prevalence.

Inclusion and exclusion criteria

We included all studies published in scientific journals that provided HCV prevalence data for the aforementioned high-risk groups: incarcerated, homeless, nursing home residents, persons on active military duty, HCWs, persons on long-term haemodialysis, recipients of chronic blood transfusions (i.e. haemophiliacs), injection drug users and veterans. As our study attempted to estimate the prevalence of HCV in USA, only studies whose source populations resided in USA were included; all others were excluded. We used HCV prevalence data taken from prisons in lieu of jail data as persons entering prison are generally incarcerated for longer periods of time and should be considered more representative of the standard incarcerated population. Data from confirmatory tests for HCV infection (i.e. recombinant immunoblot assay) were used in lieu of standard HCV screening tests, if available, although the vast majority of studies only used HCV antibody screening. Data adjusted for confounders were used in lieu of unadjusted data when available. Lastly, studies that focused on the HCV prevalence of a specific subpopulation of each respective high-risk group were collected but not used in prevalence estimates as these subpopulations were not considered representative of the general population of each high-risk group. For example, studies that tested the HCV prevalence of human immunodeficiency virus (HIV)-positive homeless persons were reported in Table 2, but were not used in HCV prevalence estimation as these patients would be at a higher risk for HCV than the general homeless population. Other specific exclusions will be discussed in the 'Prevalence estimates' section of our study.

Prevalence of hepatitis C virus in high-risk populations

Incarcerated

The true prevalence of HCV in the incarcerated population is difficult to obtain as no mandated screening programmes exist and the number of studies that investigated HCV prevalence in this population is limited. Of these studies, the prevalence of HCV ranged from 23.1 to 39.4% (6–12) (Table 1). The most recent data from California correctional system were a cross-sectional study of 469 prisoners from three California State correctional facilities in 2005, which showed a prevalence of 34.3% (6). In an older, but much larger study also set in California, 4513 inmates in six correctional facilities, the overall prevalence was 41.2% (10). Similarly, in a study of 4269 prisoners in Rhode Island, 23.1% of prisoners were HCV antibody positive (8). Another large study from the Maryland correctional system yielded an HCV prevalence of 29.7% (12). In 2004, the Bureau of Justice Statistics published the results of a survey of 1209 of 1584 State public and private correctional facilities nationwide (76% participation). Of 57 018 HCV tests administered, 17 911 were positive (31%) (13). There were no additional data from individual States' Department of Corrections that were identified.

Despite differences in the time of study and region of USA, the prevalence of HCV is relatively uniform among these studies of incarcerated populations. Noticeably missing from these data are seroprevalence studies from other states; hence, any extrapolation from this relatively

Table 1. Prevalence of hepatitis C virus in USA prison population

Reference	Year published	Location	Study design	Number of subjects	Number of HCV positive (%)
Fox *et al*. (6)	2005	California	Cross sectional	467	160 (34.3)
Solomon *et al*. (7)	2004	Maryland	Cross sectional	3661	1089 (29.7)
Macalino *et al*. (8)	2004	Rhode Island	Prospective cohort	4264	983 (23.1)
Baillargeon *et al*. (9)	2003	Texas	Cross sectional	2144	593 (27.7)
Ruiz *et al*. (10)	1999	California	Cross sectional	4513	1859 (41.2)
Spaulding *et al*. (11)	1999	Colorado	Cross sectional	1224	367 (30.0)
Vlahov *et al*. (12)	1993	Maryland	Prospective cohort	265	100 (38.0)

HCV, hepatitis C virus.

Table 2. Prevalence of hepatitis C virus in USA homeless population

Reference	Year published	Location	Study design	Number of subjects	Number of HCV positive (%)
Schwarz *et al.* (15)*	2008	Maryland	Cross sectional	168	32 (19.0)
Riley *et al.* (16)†	2005	California	Prospective cohort	330	212 (64.2)
Hall *et al.* (17)†	2004	California	Prospective cohort	249	172 (69.1)
Stein *et al.* (18)	2004	California	Cross sectional	198	104 (52.5)
Desai *et al.* (19)	2003	Massachusetts	Prospective cohort	418	184 (44.0)
Klinkenberg *et al.* (20)	2003	Missouri	Cross sectional	114	34 (30.0)
Cheung *et al.* (21)	2002	California	Retrospective cohort	597	249 (41.7)
Nyamathi *et al.* (95)	2002	California	Case–control	884	197 (22.2)
Rosenblum *et al.* (23)	2001	New York	Cross sectional	139	45 (32.3)

*Included only homeless care givers, likely not representative of the general homeless population.
†Only HIV-positive homeless persons, likely not representative of the general homeless population.

small dataset would be an estimate. In one study by Spaulding *et al.* (11), a survey was sent to the Department of Corrections for each of the 50 states plus the District of Columbia regarding HCV statistics in their respective prisons. Of the states polled, 36 states and the District of Columbia responded. Of the states that did respond, only California reported a formal seroprevalence study (10), but otherwise stated that prisoners were not routinely screened for HCV. Colorado was the only state that reported routine HCV screening of prisoners and found a prevalence of 30%. Other states that responded to the survey did not report routine screening and not surprisingly reported a wide range of HCV prevalences ranging from 5 to 83%. It is unclear when prisoners who underwent non-routine screening were tested for HCV and this was not defined by any of the states. But as this was non-routine screening, these results are difficult to interpret in this setting and are inherently biased.

Homeless

A homeless person, as defined by the US Department of Housing and Urban Development, is not only an individual who does not have a night-time residence, but can also reside in a homeless shelter, or temporary housing (including welfare hotels, congregate shelters and transitional housing) (14). In studies involving homeless persons, the prevalence of HCV was found to range from 19 to 69.1% (15–23)(Table 2). Two studies that involved homeless veterans found prevalences of 41 and 44% (19,21).

Homeless persons infected with HIV at baseline had the highest prevalences of HCV (65 and 69.1%) (16, 17). Further, in the study where 69.1% prevalence was found, the prevalence increased to 73.1% by the end of the median follow-up period of 39.7 months (17). In their subset of HIV-positive veterans, Cheung *et al.* (21) found that 72.7% were found to be HCV positive. As there are shared routes of transmission, HIV as a risk factor for HCV in the homeless population is biologically plausible (24). Studies have shown that HCV is increased in HIV-positive persons (25–27) and those who are homeless (22, 23), but there is a paucity of data correlating HIV co-infection as a risk factor for HCV in the homeless population. These data strongly suggest, however, that HIV-positive homeless persons are at a particularly high risk for HCV infection. However, as HIV-positive homeless people are not representative of homeless population in general, prevalence data from these studies will not be used to calculate the prevalence of HCV in the homeless population as this would lead to overestimation.

The lowest HCV prevalence in a homeless population was found by Schwarz *et al.* (15) to be 19% among homeless caregivers. A caregiver was defined as a person who functioned as a parent (not necessarily biological) to a child aged 2–18 years. All of the caregivers identified for the study lived in homeless shelters or transitional housing in Baltimore, MD. While this prevalence found is elevated from the general population reported in the NHANES study (4), it is significantly lower than the aforementioned homeless populations. It may be that persons acting as caregivers may be less likely to engage in high-risk activities that would predispose them to HCV, leading to lower rates of infection.

Injection drug users

Injection drug use is now considered the primary cause of HCV in USA today (28). The prevalence of HCV among injectable drug users ranged from 27 to 93% (29–40). This wide range reported in the literature is partially explained by variations in the duration of IDU among subjects. A recent study by Tseng *et al.* (36) showed HCV prevalences of 66.2, 87.6, 97.6 and 98.7% for drug usage durations of < 9, 10–19, 20–29 and >30 years respectively ($P < 0.0001$). Younger age groups also had significantly lower incidences of HCV than older age groups ($P < 0.0001$), although age is likely a surrogate for duration of IDU. Indeed, the studies that showed $< 40\%$ prevalence of HCV only included patients younger than 30 years of age (30, 32, 35). On the opposite end of the spectrum was a large multicity trial (Seattle, Detroit, Newark, San Francisco, Denver and Baltimore) that included patients up to 45 years of age, but not

specific data on duration of use, and had the highest rates of HCV prevalence (69–93%) (34).

Perhaps the greatest contribution to decreased HCV prevalence among injection drug users is outreach and harm reduction programmes implemented nationwide. The Drug User Interventional Trial (DUIT) is a national trial that took place in major cities across USA (Balitmore, Chicago, Los Angeles, New York and Seattle). It is described as a 'small group, cognitive behavioural, peer education intervention designed to reduce injection and sexual risk behaviours for HIV and HCV in young injection drug users' (41). The DUIT observed a 29% decline in overall injection risk and sexual risk behaviours (42). Needle exchange programs have reported similar success in reducing new cases of HCV (36, 39, 43, 44) and increasing access to sterile syringes would likely decrease transmission of HCV as well (45). Thus, a major contributor to the lower HCV prevalences seen in the aforementioned studies has been outreach and harm reduction programmes targeted at this very high-risk population.

The largest study involving injection drug users in USA is the Collaborative Injection Drug User Study (CIDUS), which collected data from 1994 to 1996 (CIDUS I), 1997 to 1999 (CIDUS II) and 2002 to 2004 (CIDUS III/Drug User Intervention Trial) (31). CIDUS collected information from four sites: Baltimore, Chicago, Los Angeles and New York and showed HCV prevalences of 65, 35 and 35% during CIDUS I, II and III respectively. Thus, there appears to be a large decrease in HCV prevalence nationwide among injection drug users over the years, but it is important to realize that the demographics of the study population across the three studies has changed dramatically over time as well. In CIDUS I, the majority were drug users aged 31–40 years old and 44.7% used injection drugs for >10 years. During CIDUS II and III, however, injection drug users were never older than 30 years and only 5.8 and 8.0% used injection drugs for >10 years. Because of this, the CIDUS studies should not be considered a representative sample as older injection drug users were not included in their final analysis.

Emerging evidence suggests that non-injection drug use (NIDU) is also considered a risk factor for the transmission of HCV. Transmission likely requires exposure to HCV RNA in biological fluids and disruptions in mucous membranes that allow the virus to enter the bloodstream (46). Besides blood, HCV RNA has also been detected in the saliva and gingival crevicular fluid of persons with chronic HCV (47, 48). Nasal secretions of intranasal drug users have also been shown to harbour HCV (49). Thus, sharing of drug paraphernalia contaminated with HCV RNA appears to facilitate the transmission of the virus.

A recent systematic review by Scheinmann *et al.* (50) showed that HCV prevalence was increased in non-injection drug users compared with the general population. Among the identified studies, 12 had American source populations, with HCV prevalences ranging from 3.9 to 31.8%. Importance weaknesses to his body of literature, however, must be noted. Nine of the 12 American studies identified in the systematic review were based in New York and may not reflect NIDU usage patterns in other parts of the nation. Also, in many of these studies, NIDU was a secondary outcome to IDU and may be subject to investigator confounding. Further, many of the studies may have been subject to misclassification bias and may not have controlled for drug-related confounders. The authors concluded that studies investigating the relationship between HCV and NIDU are in their early stages and more rigorous studies still need to be performed.

The NHANES study found an HCV prevalence of 57.5% among patients who reported the use of injectable drugs during their lifetime, but did not collect information regarding the duration of drug use or any other demographical information specific to injectable drug users (4). Still, the estimated prevalence by the NHANES appears to be a good estimation of the true HCV prevalence among injection drug users as it falls within the range of the aforementioned studies available in the literature.

The NHANES also collected data coded as 'no drug use or only marijuana' (0.7% HCV prevalence) and 'other drug use (except marijuana) (3.5% HCV prevalence)'. By this classification, NIDU would fall into the latter category. Although the quality of studies investigating the relationship between NIDU and HCV has been called into question, the NHANES result appears to be a reasonable estimate as it nearly equals the most conservative HCV prevalence among non-injection drug users found in the literature.

Healthcare workers

Most HCV transmission to HCW is because of direct percutaneous exposure to blood contaminated with HCV (24). The overall prevalence of HCV infection in HCWs appears to be similar to the general population estimated by NHANES, ranging from 0.7 to 3.2% (51–63) (Table 3). The definition of HCW is broad and seroprevalence studies have generally involved physicians, surgeons, firefighters, paramedics and emergency medical technicians. In seroprevalence studies of medical doctors (specifically surgeons and dentists), the prevalence was found to be 0.9–1.8% (59–63). The vast majority of other seroprevalence studies, however, involve firefighters, emergency medical technicians and paramedics.

Veterans (non-active military personnel)

Two recent nationwide studies have suggested that veterans are at an increased risk for HCV infection. A study by Dominitz *et al.* (64) used a two-stage cluster sample to randomly select 3863 users of the veterans affairs (VA) medical services nationwide. Of these, 1288 veterans

Table 3. Prevalence of hepatitis C virus in USA healthcare workers

Reference	Year published	Location	Study design	HCW studied	Number of subjects	Number of HCV positive (%)
Gershon *et al*. (51)	2007	Rhode Island, Texas, Maryland	Cross sectional	C	310	7 (2.3)
Datta *et al*. (52)	2003	Georgia	Crosssectional	F	437	9 (2.1)
Datta *et al*. (52)	2003	Connecticut	Cross sectional	C, E, F, P	382	5 (1.3)
Datta *et al*. (52)	2003	Pennsylvania	Cross sectional	F	2127	77 (3.6)
Rischetti *et al*. (54)	2002	Oregon	Cross sectional	C, F, P	719	7 (1.0)
Roome *et al*. (55)	2000	Florida	Cross sectional	E, F	3362	70 (2.1)
Peate *et al*. (56)	2001	Arizona	Prospective cohort	E	477	9 (1.9)
Upfal *et al*. (57)	2001	Michigan	Cross sectional	E, F, P	2447	28 (1.1)
Werman and Gwinn (58)	1997	Ohio	Prospective cohort	E	107	1 (0.9)
Thomas *et al*. (59)	1996	Maryland	Cross sectional	D, S	648	9 (1.4)
Panlilio *et al*. (60)	1995	Georgia	Cross sectional	S	770	7 (0.9)
Gerberding (61)	1994	California	Prospective cohort	M, O	815	12 (1.4)
Polish *et al*. (62)	1993	California	Retrospective cohort	M, O	1677	23 (1.4)
Klein *et al*. (63)	1991	New York	Case–control	D	456	8 (1.8)

C, HCW in a correctional setting; D, dentists; E, emergency medical services (includes paramedics and emergency medical technicians); F, firefighters; HCV, hepatitis C virus; HCW, healthcare workers; M, medical doctors; O, other [includes nurses, nurse aides, technicians (electrocardiograms, nuclear medicine), lab personnel, radiologists, respiratory therapists, and pharmacists]; P, police; S, surgeon (includes general, obstetrics and gynaecology and orthopaedics).

responded and the researchers found an overall prevalence of 5.4% after correcting for sociodemographical factors. The authors found that veterans had a higher prevalence because of excess exposure to traditional risk factors (blood transfusions and IDU) compared with the general population. A similar nationwide study of 26 102 veterans undergoing phlebotomy nationwide on National Hepatitis C Surveillance Day showed a prevalence of 6.6% (65).

Conversely, the NHANES study found an overall prevalence of 2.8% (95% confidence interval 1.9–4.2%) and appears to have underestimated the prevalence of HCV in veterans (4). The prevalence of HCV among veterans has been reported to be 5.4–41.7% in large studies over the past decade (19, 21, 64–76) (Table 4). The range of HCV prevalences reported is wide and reflects the varying populations of veterans who reside in USA. The highest prevalences of HCV came from studies involving homeless veterans (19, 21). Other subpopulations of high-risk veterans studied include those with HIV and mental illnesses who also appear to be at an increased risk. Conversely, a study by Seeff *et al*. (77) of young health military recruits in a university setting reported a prevalence lower than the general population, highlighting the importance of veterans' lifetime exposure to risk factors and the development of HCV infection.

Recipients of chronic haemodialysis

Patients on chronic haemodialysis are at increased risk for HCV infection and it appears to be related to time that the patient has been receiving dialysis as well as the number of blood transfusions received (78). Blood transfusions received before second-generation HCV screening assays in 1992 is considered an independent risk factor for HCV transmission (79), but has not, to our knowledge, been specifically studied in the haemodialysis population.

Hepatitis C virus outbreak investigations at dialysis centres have revealed multiple opportunities for cross contamination between infected and non-infected patients including using receiving dialysis immediately after an infected patient, dialysis equipment that is improperly sterilized, use of common medical carts with contaminated surfaces and sharing of multiple dose medication vials and priming buckets (78).

The most recent national surveillance study on dialysis-associated diseases was published in 2002 and represents the most current infection control statistics from dialysis centres nationwide (80). In conjunction with the Centers for Medicare and Medicaid Services (CMS), the Center for Disease Control (CDC) sent out surveys to all 4185 haemodialysis centres licensed by the CMS in USA, with a 96% response rate. The overall prevalence of HCV in this national study was 7.8%, which is decreased from 1995 (10.4%). The authors attributed this decrease, in part, to increased awareness on HCV transmission.

Haemophilia

Patients with haemophilia are blood transfusion dependent and are at an increased risk for HCV infection. Specifically, those who received blood transfusions before 1987, when heat inactivation of factor concentrates dramatically improved blood safety relative to HCV and other viral agents, have been reported to have high prevalences of HCV: 76.3, 98 and 100% (81–83). The advent of the second-generation HCV screening assay in 1992 has nearly eliminated the transmission of HCV

Table 4. Prevalence of hepatitis C virus in USA veterans over the past decade

Reference	Year published	Population	Study design	Number of subjects	Number of HCV positive (%)
Himelhoch *et al*. (67)*	2009	Veterans with schizophrenia or bipolar	Cross sectional	223 137	13 352 (6.0)
Groom *et al*. (68)	2008	Minnesota VA outpatients	Retrospective cohort	12 485	681 (5.4)
Kilbourne *et al*. (69)*	2008	Veterans with schizophrenia, bipolar or depression	Retrospective cohort	18 056	1250 (6.9)
Mallette *et al*. (70)	2008	Rhode Island VA with one traditional risk factor†	Cross sectional	5646	412 (7.3)
Dominitz *et al*. (64)	2005	Randomized national sample	Cross sectional	1288	52 (5.4)‡
Matthews *et al*. (71)*	2008	Veterans with substance abuse and bipolar disorder	Retrospective cohort	130 021	13 531 (10.4)
Goulet *et al*. (72)*	2005	HIV-positive veterans	Case–control	25 116	4489 (17.8)
Desai *et al*. (19)*	2003	Homeless veterans	Cross sectional	418	184 (44.0)
Mishra *et al*. (73)	2003	Florida and Georgia outpatients	Cross sectional	274	27 (9.9)
Brau *et al*. (74)	2002	New York VA in/outpatients	Cross sectional	1098	116 (10.7)
Cheung *et al*. (21)*	2002	Homeless veterans	Retrospective cohort	597	249 (41.7)
Roselle *et al*. (65)	2002	Phlebotomy in/outpatients on 1 day nationwide	Cross sectional	26 102	1724 (6.6)
Briggs *et al*. (75)*	2001	Urban California VA	Cross sectional	1032	185 (17.7)
Austin *et al*. (76)	2000	Georgia VA inpatients	Cross sectional	530	56 (10.6)
Cheung (66)*	2000	VA in/outpatients including psychiatric disease	Cross sectional	8558	2985 (34.8)

*Excluded from prevalence estimate calculation, likely not representative of the general veteran population.

†Risk factors included (i) Vietnam veteran, (ii) blood transfusion before 1992, (iii) injection drug use, (iv) intranasal cocaine use, (v) $\geq$5 drinks/day for $\geq$10 years, (vi) $\geq$10 lifetime sexual partners, (vii) man who has sex with men, (viii) exposure to blood on skin or mucous membranes, (ix) haemodialysis dependent, (x) tattoo or body piercing, (xi) positive HIV or HBV and (xii) unexplained liver disease.

‡Adjusted for non-participation; unadjusted prevalence was 4.0%.

HBV, hepatitis B virus; HIV, human immunodeficiency virus; VA, veterans affairs.

through blood transfusion. The risk is not zero, however, as mathematical modelling has suggested that transfused blood may still transmit HCV in 1:100 000 to 1:200 000 recipients (79). The estimated prevalence of haemophiliacs who have received transfusions and other blood products before the screening era is $< 0.01\%$ of the US population today (28).

Active military duty

Service men and women on active duty would not have been sampled by the NHANES survey because only civilian populations were surveyed. There has only been one study involving HCV prevalence among those on active military duty. Hyams *et al.* (84) surveyed 10 000 active duty personnel in the United States military and found a prevalence of 0.48%. The authors interpreted this as a decreased risk of HCV infection and attributed it to infrequent IDU in the military because of mandatory drug testing throughout military service.

Nursing home residents and hospitalized patients

Nursing home residents would also not have been sampled by the NHANES because only non-institutionalized persons were included. There is only one study that measured the prevalence of HCV in the nursing home population. Chien *et al*. (85) found that 4.5% of residents at three nursing homes in the greater St Louis area were anti-HCV positive. It would be unwise to draw certain conclusions regarding HCV in the nursing home population but it would appear that they are at an increased risk.

Patients hospitalized during the NHANES study would have been missed by the survey. We found seven studies that measured the prevalence of HCV in hospitalized patients, with prevalence ranging from 4 to 20.3% (66, 76, 86–90) (Table 5). Of these, three involved patients in emergency rooms (ERs) (87–89), two collected data from inpatients at VA hospitals (66, 76), one collected data from a large psychiatric hospital (90) and one collected data from inpatients and outpatients in a university hospital (86).

Hepatitis C prevalence data from non-published reports

As discussed in our section on the 'Incarcerated', we located a report by the Bureau of Justice Statistics that approximated the prevalence of HCV to be 31% among incarcerated persons (13). A United States Census report stated that 845 cases of HCV were self-reported in 2007 (91). Clearly, these data from the US census are subject to reporting bias and should not be used to estimate the prevalence of HCV nationwide. Lastly, we were unable to locate any additional data from websites of the Center for

Table 5. Prevalence of hepatitis C virus in hospitalized patients

Reference	Year published	Population	Study design	Number of subjects	Number of HCV positive (%)
Hall *et al.* (89)	2010	Emergency room	Cross sectional	404	16 (4.0)
Meyer (90)	2003	Psychiatric inpatients	Retrospective cohort	535	109 (20.3)
Brillman *et al.* (88)	2002	Emergency room	Cross sectional	223	38 (17.0)
Austin *et al.* (76)	2000	Veteran inpatients only	Cross sectional	530	62 (11.7)
Cheung (66)	2000	Veteran in/outpatients	Cross sectional	8558	2985 (34.8)
Lanphear *et al.* (86)	1994	In/outpatients	Prospective cohort	1387	176 (12.7)
Kelen *et al.* (87)	1992	Emergency room	Cross sectional	2523	454 (18.0)

Table 6. Estimated total prevalence of hepatitis C virus in the USA

Population	Reported prevalence range	Estimated number in US population	Estimated range of HCV cases
Homeless	22.2–52.5%	643 067 (14)	142 761–337 610
Incarcerated	23.1–41.2%	1 613 656 (96)	372 754–664 826
Veterans	5.4–10.7%	22 915 943 (97)	1 237 461–2 452 006
Active military duty	0.48%	1 417 747 (98)	6805
Healthcare workers	0.9–3.6%	7 200 950 (99)	64 809–259 234
Nursing home residents	4.5%	1 413 540 (85)	63 609
Chronic haemodialysis	7.8%	263 820 (80)	20 578
Haemophiliacs with transfusions before 1992	76.3–100%	17 000 (92)	12 971–17 000
		Unaccounted number of HCV positive	1 921 748–3 821 668
		NHANES*	3 270 000
		Total	5 191 748–7 091 668

*Original NHANES estimate minus HCV cases attributed to veterans (4 060 000 total – 790 000 veterans).
HCV, hepatitis C virus; NHANES, National Health and Nutrition Examination Survey.

Medicare and Medicaid or individual States' Department of Corrections.

Prevalence estimates

Our most conservative estimate suggests that 5.2 million persons had HCV infection, approximately 1.1 million that the NHANES did not account for (Table 6). Prevalence estimates were calculated based on the approximate number of persons in each high-risk group and reported as a range based on the seroprevalences of HCV reported in the literature identified after excluding non-representative studies. The approximate number of persons in each high-risk group was found from national statistics published by various United States government agencies (Table 5). These national statistics were chosen over other sources like advocacy groups as these could be biased and tend to overestimate the number of persons in each high-risk group. The number of HCV cases in each respective group was added to the NHANES estimate to estimate the true prevalence of HCV in USA today.

For the prison and HCW populations (Tables 1 and 3), all studies located were used to determine the range of prevalences and therefore the estimated number of HCV cases in each group as these studies were considered representative of their respective populations. Only one was study located for persons living in nursing homes (85) and active military personnel (84). Similarly, one study by Finelli *et al.* (80) was used to estimate the prevalence of HCV in persons undergoing chronic haemodialysis as this was a national poll of all registered dialysis centres with a 96% response rate.

Conversely, all studies identified in hospitalized patients were excluded from our analysis (Table 5). Most patients in the ER setting will be discharged from the ER directly and not admitted and should be considered representative of the general hospitalized population. Other studies either mixed inpatient and outpatient populations or only included high-risk groups (i.e. veterans). The remaining study identified was set in a psychiatric hospital and should also not be considered representative of the general hospitalized population.

Among studies of the homeless population, we excluded three studies from the prevalence estimate because their study populations were not considered representative of the general homeless population (Table 2). Specifically, the studies by Schwarz *et al.* (15) (homeless caregivers), Riley *et al.* (16) and Hall *et al.* (17) (HIV-positive homeless persons) were excluded from the HCV prevalence calculation because these subpopulations would likely be of a lower and a higher risk, respectively, than the general homeless population.

As stated previously, the NHANES appears to have underreported the prevalence of HCV among veterans. Thus, we calculated a new estimate of HCV prevalence based on the epidemiological studies that we identified and subtracted the number of HCV cases attributed to veterans in the NHANES study before adding our estimate to the NHANES estimate to prevent double counting. Over the past decade, we located 15 studies that examined the epidemiology of HCV infection among veterans (Table 4). We did, however, exclude studies whose veterans were HIV positive, homeless and diagnosed with psychiatric disease as these would not be representative of the general veteran population. The study Cheung (66) published in 2000 was also excluded because the study population included a 'large psychiatric and alcohol and drug rehabilitation unit'. Similarly, the Briggs *et al.* (75) study was excluded as it was based in an urban centre and had a disproportionate number of subjects with a history of IDU, incarceration and drug and alcohol rehabilitation. Specifically, the studies by Himeloch *et al.* (67), Kilbourne *et al.* (69), Matthews *et al.* (71), Goulet *et al.* (72), Desai *et al.* (19), Briggs *et al.* (75) and both studies by Cheung *et al.* (21, 66) were excluded.

For the cohort of haemophiliacs receiving blood transfusions before 1992, three studies with HCV prevalences of 76.3, 98 and 100% (81–83) were located. The current HCV prevalence nationwide for haemophiliacs is based on a 1994 estimate of the number haemophiliacs residing in USA by the Center for Disease Control (92). After 1997, the incidence of HCV in USA haemophiliacs for the purposes of this study was considered negligible.

We identified a number of studies regarding IDU and HCV infection. As mentioned previously, we found a prevalence of 27–93% among identified studies, while the NHANES reported an incidence of 57.5%. This appears to be a reasonable estimate of the prevalence among identified studies and there is no indication to provide another estimate of our own.

Discussion

The purpose of our study was to provide an accurate estimate of HCV disease burden in USA, including those in high-risk groups omitted from national surveys. Our results indicate that the infection may be more prevalent than previously thought and underscores the importance of more comprehensive sampling among persons at a high risk for chronic HCV infection. We estimate that the total number of anti-HCV-positive persons in the US population is at least 5.2 million, approximately 1.1 million more persons than estimated by the NHANES study. The NHANES estimate of a 1.6% prevalence of anti-HCV positivity would correlate to a 2% prevalence if our data were used. The upper limit of our estimates is 7.1 million total infected persons; hence, the actual number may be much higher than our conservative estimate.

The most-feared sequelae of chronic HCV infection are decompensated cirrhosis and HCC (3). A prospective study of Americans with HCV cirrhosis found that the cumulative probabilities for each were 22.2 and 10.1%, respectively, and the authors estimated the yearly events of mortality and liver transplantation among these patients to be 3.4 and 9.8% respectively (93). Recently, Davis *et al.* (94) used Markov modelling to estimate that complications of chronic HCV infection would increase drastically over the next 20 years: hepatic decompensation (up 106%), HCC (up 81%) and liver-related deaths (up 180%). These data, along with the results of our study, highlight the burden of HCV infection especially in high-risk populations and underscore the importance of education and prevention programmes targeting these persons before they become infected or before long-term complications develop if already infected.

A number of limitations to our study must be considered. Firstly, our estimates are based mainly on cross-sectional studies that may not be representative of each respective group. We attempted to manage this by excluding studies that focused on subgroups that were at a higher risk than the group as a whole. For example, we only included studies on veterans in general, but did not use prevalences from studies of HIV-positive veterans. Similarly, in some cases, there was clear publication bias as only one epidemiological study for nursing home residents and persons on active military duty was found. Secondly, there is no reliable estimate of homeless persons in USA and our estimate is based on usage of homeless and transitional housing facilities for at least one night's stay. Thirdly, we are unable to draw any conclusions regarding the prevalence of chronic HCV infection because many studies did not include information on HCV RNA levels. Similarly, some studies did not confirm anti-HCV positivity with a confirmatory RIBA test while others did. We used the RIBA data when available; hence, a number of false positives could have been present in our dataset as well. Further, we were unable to identify any viable studies that investigated the prevalence of HCV in hospitalized patients. Lastly, the seroprevalence HCV in Eastern European immigrants to USA is anecdotally high, but no studies have been published to our knowledge to investigate this. Thus, the HCV burden of immigrants has also likely been missed by the NHANES survey and our study as well.

Conclusions

The NHANES survey has provided invaluable information regarding the prevalence of HCV and risk factors for infection, but it has missed certain high-risk groups namely the homeless and incarcerated. Veterans, HCWs and persons on long-term dialysis were also underrepresented in the dataset. Despite the limitations of our study, our findings suggest that the true prevalence of HCV in USA is approximately 2% or 5.2 million persons using the most conservative estimates compared with 1.6% of

4.1 million reported by the NHANES. Our findings underscore the importance of the interventions necessary to decrease new infections in high-risk groups.

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