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The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002

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Background: Defining the primary characteristics of persons infected with hepatitis C virus (HCV) enables physicians to more easily identify persons who are most likely to benefit from testing for the disease.

Objective: To describe the HCV-infected population in the United States.

Design: Nationally representative household survey.

Setting: U.S. civilian, noninstitutionalized population.

Participants: 15 079 participants in the National Health and Nutrition Examination Survey between 1999 and 2002.

Measurements: All participants provided medical histories, and those who were 20 to 59 years of age provided histories of drug use and sexual practices. Participants were tested for antibodies to HCV (anti-HCV) and HCV RNA, and their serum alanine aminotransferase (ALT) levels were measured.

Results: The prevalence of anti-HCV in the United States was 1.6% (95% CI, 1.3% to 1.9%), equating to an estimated 4.1 million (CI, 3.4 million to 4.9 million) anti-HCV–positive persons nationwide; 1.3% or 3.2 million (CI, 2.7 million to 3.9 million) persons had chronic HCV infection. Peak prevalence of anti-HCV (4.3%) was observed among persons 40 to 49 years of age. A total of 48.4% of anti-HCV–positive persons between 20 and 59 years of age reported a history of injection drug use, the strongest risk factor for HCV infection. Of all persons reporting such a history, 83.3% had not used injection drugs for at least 1 year before the survey. Other significant risk factors included 20 or more lifetime sex partners and blood transfusion before 1992. Abnormal serum ALT levels were found in 58.7% of HCV RNA–positive persons. Three characteristics (abnormal serum ALT level, any history of injection drug use, and history of blood transfusion before 1992) identified 85.1% of HCV RNA–positive participants between 20 and 59 years of age.

Limitations: Incarcerated and homeless persons were not included in the survey.

Conclusions: Many Americans are infected with HCV. Most were born between 1945 and 1964 and can be identified with current screening criteria. History of injection drug use is the strongest risk factor for infection.

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A decade ago, the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) showed hepatitis C virus (HCV) to be the most common chronic bloodborne infection in the United States (1). An estimated 3.9 million people (1.8% of the population) tested positive for antibody to HCV (anti-HCV), and 2.7 million had chronic infection. Most (65%) anti-HCV–positive persons were 30 to 49 years of age and had been infected for fewer than 20 years. The genetic diversity of HCV circulating in the United States (2) and the pattern of age-specific prevalence (3, 4) both suggest that the incidence of infection increased substantially in the 1960s and 1970s and peaked in the 1980s.

Identification of HCV-positive persons for appropriate counseling and management is the major focus of a national prevention program, and routine testing is recommended for persons most likely to have HCV infection (5). To determine the characteristics of HCV-infected persons in the general United States population today and to monitor trends in prevalence, we analyzed data on HCV infection from the most recent NHANES.

Methods

The National Center for Health Statistics has conducted NHANES periodically to compile nationally representative statistics on the health of the U.S. population (6). The most recent series was begun in 1999 and is designed to run continuously; data are released every 2 years. Our analysis includes data collected from 1999 through 2002.

Participants were chosen according to a stratified, multistage algorithm to produce a representative sample of the civilian, noninstitutionalized population of all 50 states and the District of Columbia. Extensive efforts were made to ensure high participation rates, and all respondents were reimbursed for time and travel expenses (6).

Initially, a questionnaire covering only nonsensitive topics was used to interview participants in person at home. Information on potentially sensitive subjects, such as sexual practices and illicit drug use, was obtained later at a mobile examination center by means of computer-assisted interviewing technology. The ethnicity of each par-

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Context

The Third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994, indicated that 1.8% of people in the United States had been infected with hepatitis C virus (HCV), 70% of whom had chronic infection. Most anti-HCV–positive individuals were between 30 and 49 years of age.

Contribution

Data from the recent NHANES (1999–2002) show little change in anti-HCV prevalence, but peak prevalence has shifted to individuals between 40 and 49 years of age. More than 85% of HCV RNA–positive individuals may be identified through targeted testing of 18% of adults between 20 and 59 years of age: persons with abnormal serum alanine aminotransferase levels, those who have used injection drugs, and those who received blood transfusions before 1992.

Cautions

Incarcerated and homeless people were not included in the survey.

Implications

Despite a decrease in new HCV infections, aging of chronically infected individuals may presage an imminent increase in complications.

—The Editors

ticipant was categorized as non-Hispanic white, non-Hispanic black, and Mexican American. Persons not fitting these categories were classified as "other" and were included in the total population. Blood samples were obtained at the mobile examination center (7). Only participants who were 6 years of age or older were eligible for HCV testing because of low sample volume in younger children.

Laboratory Methods

Serum specimens were sent to the Centers for Disease Control and Prevention, where they were tested for anti-HCV by using Ortho HCV enzyme-linked immunosorbent assay (ELISA), version 3.0 (Ortho-Clinical Diagnostics, Raritan, New Jersey). Supplemental recombinant immunoblot assays (RIBA) (Chiron RIBA HCV Strip Immunoblot Assay, version 3.0, Chiron Corp., Emeryville, California) were performed on all specimens that were repeatedly reactive by ELISA testing. For those specimens classified as positive or indeterminate by RIBA, separate, archived aliquots stored at −70 °C and suitable for nucleic acid amplification testing were submitted for quantitative HCV RNA testing using Cobas Amplicor HCV Monitor Test, version 2.0 (Roche Molecular Diagnostics, Pleasanton, California). If that result was below the level of detection, a qualitative assay (Amplicor HCV Test, version 2.0, Roche Molecular Diagnostics) was performed. Samples found to be reactive by enzyme immunoassay and confirmed by RIBA or Amplicor were considered to be anti-HCV–positive. Alanine aminotransferase (ALT) levels (reference range, 0 to 39 U/L) were measured in specimens that had been stored and shipped under appropriate refrigeration conditions (4 °C to 8 °C).

Statistical Analysis

All statistical analyses were performed with SUDAAN software (RTI International, Research Triangle Park, North Carolina) according to National Center for Health Statistics guidelines. We used appropriate study design variables and published weights that were further adjusted to compensate for missing anti-HCV values (8). These weights accounted for oversampling of certain demographic groups (6) and for nonparticipation such that the sum of the weights for persons with anti-HCV results equaled the U.S. civilian, noninstitutionalized population 6 years of age and older. To estimate the number of HCV RNA–positive persons, these weights were further adjusted to compensate for the RIBA-positive and RIBA-indeterminate specimens that were unavailable for RNA testing because of inadequate specimen volumes.

Proportions from univariable analyses were compared by using chi-square tests (as implemented in SUDAAN). The P values presented were not corrected for multiple comparisons; P values less than 0.05 were considered statistically significant. Two logistic regression models were used for multivariable analysis; 1 model was used for persons 20 to 59 years of age whose drug use and sexual practices data were available, and the other model was used for persons 60 years of age or older. Two variables, history of blood transfusion (both models) and injection drug use (persons 20 to 59 years of age), were forced into the models on the basis of substantial published data that has established them as risk factors for HCV infection. We sought the most parsimonious model by using these and all other variables that were significant at a P value less than 0.20 on univariable analysis. With the resulting model, we then examined the effect of adding other variables of interest, including those variables that had been excluded at earlier steps in the modeling process. In the final models, all first-order interactions were examined for statistical significance, epidemiologic plausibility, and the impact of their inclusion on the other model parameters.

Role of the Funding Source

No external funding was received for this study.

RESULTS

Of 21 509 participants 6 years of age or older, 17 548 were interviewed and 15 079 gave a blood sample suitable for anti-HCV testing (final response rate for testing, 70.1%). Among those who completed home interviews, participation rates did not differ significantly between those with and without risk factors for HCV infection.

Table 1. **Prevalence of Antibody to Hepatitis C Virus by Demographic Characteristics and Potential Risk Factors**

Characteristic	Participants Tested, *n*	Prevalence of Antibodies to Hepatitis C Virus (95% CI), %	Estimated Persons with Characteristic Nationwide, *n*	Estimated Persons Ever Infected Nationwide (95% CI), *n*
All participants	15 079	1.6 (1.3–1.9)	255 400 000	4 060 000 (3 410 000–4 850 000)
Sex				
Male	7307	2.1 (1.8–2.5)	123 900 000	2 570 000 (2 140 000–3 090 000)
Female	7772	1.1 (0.8–1.7)*	131 500 000	1 490 000 (1 010 000–2 200 000)
Ethnicity				
Non-Hispanic white	5991	1.5 (1.1–1.9)	176 500 000	2 610 000 (2 020 000–3 380 000)
Non-Hispanic black	3530	3.0 (2.4–3.9)†	30 100 000	920 000 (720 000–1 170 000)
Mexican American	4422	1.3 (0.8–2.1)	20 500 000	260 000 (150 000–430 000)
Birthplace				
United States	12 107	1.8 (1.4–2.1)	220 400 000	3 870 000 (3 190 000–4 680 000)
Mexico	1854	0.5 (0.3–0.9)†‡	9 900 000	50 000 (30 000–90 000)
Elsewhere	1059	0.6 (0.2–1.6)*‡	24 400 000	150 000 (60 000–400 000)
Education (participants age ≥20 y)				
>12 y	5036	1.3 (0.9–1.8)	104 300 000	1 370 000 (980 000–1 910 000)
≤12 y	3810	2.8 (2.3–3.6)†	93 700 000	2 670 000 (2 120 000–3 350 000)
Family income				
≥2 times poverty threshold	6665	1.0 (0.7–1.4)	145 000 000	1 410 000 (960 000–2 060 000)
1–1.9 times poverty threshold	3634	2.3 (1.7–3.1)†	51 200 000	1 170 000 (850 000–1 600 000)
Below poverty threshold	3341	3.2 (2.5–4.1)†	35 600 000	1 240 000 (970 000–1 570 000)
Service in U.S. armed forces (men age ≥20 y)				
No	2894	2.7 (2.1–3.3)	66 800 000	1 770 000 (1 410 000–2 220 000)
Yes	1283	2.8 (1.9–4.2)	27 900 000	790 000 (530 000–1 190 000)
Blood transfusion before 1992				
Participants age 20–59 y				
No	5477	2.0 (1.6–2.5)	143 100 000	2 900 000 (2 340 000–3 610 000)
Yes	316	5.8 (3.7–9.0)†	8 800 000	510 000 (330 000–790 000)
Participants age ≥60 y				
No	2458	0.5 (0.3–0.9)	35 500 000	190 000 (110 000–320 000)
Yes	458	3.2 (1.5–6.8)	7 400 000	240 000 (110 000–500 000)
Lifetime drug use (participants age 20–59 y)				
No drug use or only marijuana	4330	0.7 (0.4–1.1)	112 300 000	770 000 (490 000–1 210 000)
Other drug use (except marijuana)	949	3.5 (2.4–4.9)†	27 600 000	960 000 (680 000–1 360 000)
Injection drug use	89	57.5 (44.1–69.9)†	2 800 000	1 620 000 (1 240 000–1 970 000)
Lifetime number of sexual partners (participants age 20–59 y)				
0–1	1202	0.5 (0.2–1.4)‡	29 800 000	140 000 (50 000–420 000)
2–9	2596	1.1 (0.5–2.1)‡	69 500 000	740 000 (370 000–1 470 000)
10–19	763	2.6 (1.5–4.6)*	21 500 000	560 000 (310 000–1 000 000)
20–49	559	7.5 (5.3–10.6)†	15 600 000	1 180 000 (840 000–1 650 000)
≥50	237	12.0 (8.5–16.7)†	6 400 000	770 000 (550 000–1 070 000)
Age at first sexual intercourse (participants age 20–59 y)				
≥18 y	2109	0.9 (0.5–1.7)‡	59 200 000	540 000 (290 000–1 020 000)
16–17 y	1489	2.3 (1.4–3.7)*	40 600 000	930 000 (570 000–1 510 000)
12–15 y	1318	4.5 (3.5–5.8)†	33 400 000	1 510 000 (1 170 000–1 940 000)
≤11 y	138	10.1 (5.8–17.0)*	3 300 000	330 000 (190 000–560 000)
Antibody to herpes simplex virus type 2 (participants age 18–49 y)				
Negative	4522	1.7 (1.3–2.2)	103 100 000	1 750 000 (1 360 000–2 260 000)
Positive	1088	5.2 (3.9–6.9)†	24 500 000	1 280 000 (960 000–1 690 000)

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Table 1—Continued

Characteristic	Participants Tested, *n*	Prevalence of Antibodies to Hepatitis C Virus (95% CI), %	Estimated Persons with Characteristic Nationwide, *n*	Estimated Persons Infected Nationwide (95% CI), *n*
Antibody to HIV type 1 (participants age 18–49 y)				
Negative	5650	2.3 (1.9–2.8)	128 800 000	3 020 000 (2 500 000–3 650 000)
Positive	31	13.8 (5.3–31.3)‡	600 000	80 000 (30 000–180 000)
Serum alanine aminotransferase level§				
<40 U/L	11 983	0.9 (0.7–1.1)	207 400 000	1 860 000 (1 460 000–2 350 000)
40–79 U/L	930	8.4 (5.4–12.7)†	18 300 000	1 530 000 (990 000–2 320 000)
80–119 U/L	125	12.7 (6.1–24.8)*‡	2 300 000	290 000 (140 000–560 000)
≥120 U/L	75	24.0 (12.0–42.3)*‡	1 400 000	340 000 (170 000–600 000)

* $P < 0.05$ for comparison with referent group (the first listed category of the variable).
† $P < 0.005$ for comparison with referent group (the first listed category of the variable).
‡ Because of the small number of survey participants in these subgroups, the estimates and 95% CIs are unstable and may not accurately reflect the true proportion.
§ Reference range, 0–39 U/L.

The weighted prevalence of anti-HCV in the United States was 1.6% (95% CI, 1.3% to 1.9%), corresponding to 4.1 million (CI, 3.4 million to 4.9 million) anti-HCV–positive persons (**Table 1**). Of anti-HCV–positive participants, 78.8% had specimens suitable for HCV RNA testing; 79.7% (CI, 70.4% to 86.6%) of these tested positive for HCV RNA. After we accounted for untested specimens, the nationwide prevalence of HCV RNA among all participants was 1.3% (CI, 1.0% to 1.5%), equating to 3.2 million (CI, 2.7 million to 3.9 million) HCV RNA–positive persons.

Demographic Characteristics Associated with HCV Infection

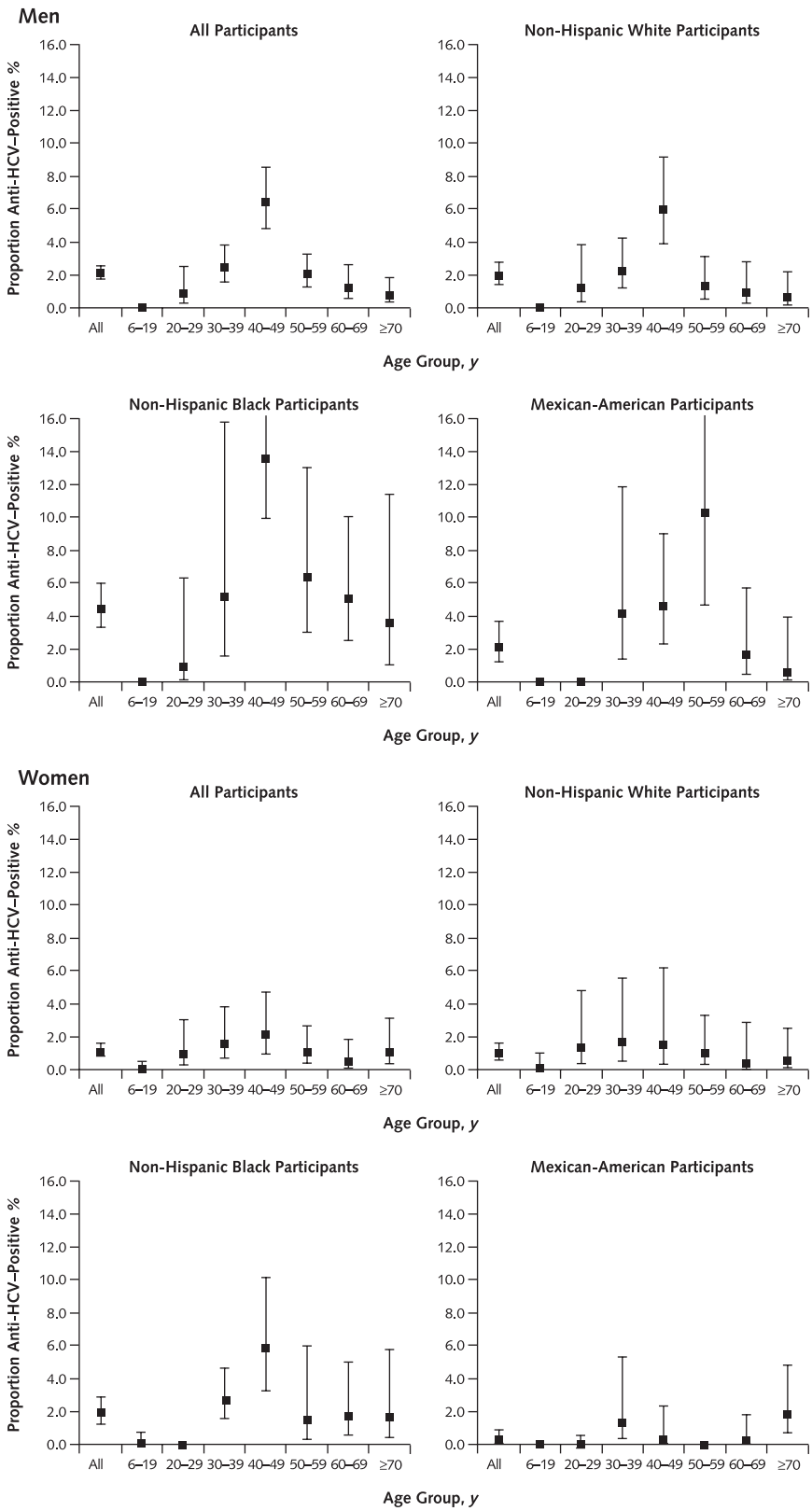
Anti-HCV prevalence was significantly higher in men than in women (**Table 1**). Prevalence was also higher in non-Hispanic black participants than in either of the other 2 ethnic groups. Among persons younger than 50 years of age, prevalence of anti-HCV increased with age from 1.0% in those 20 to 29 years of age to a peak of 4.3% in those 40 to 49 years of age (**Figure 1**). Among older persons, anti-HCV prevalence decreased to 1.6% in persons 50 to 59 years of age and to 0.9% in persons 60 years of age and older. Prevalence was higher in men than in women in most age groups (**Figure 1**). The higher overall prevalence among non-Hispanic black persons compared with non-Hispanic white persons was almost entirely attributable to differences among older participants. Among participants 40 to 49 years of age, 9.4% of non-Hispanic black persons had positive results for anti-HCV compared with 3.8% of non-Hispanic white persons ($P < 0.001$); of participants 50 years of age or older, 3.3% of non-Hispanic black persons had positive results compared with 0.9% of non-Hispanic white persons ($P = 0.002$). The demographic group with the highest prevalence was non-Hispanic black men between 40 and 49 years of age (13.6% [CI, 10.0% to 18.2%]). Prevalence was not significantly different between non-Hispanic black and non-Hispanic white persons who were younger than 40 years of age (1.2% vs. 1.1%; $P = 0.73$). Participants who were born in the United States had a higher prevalence of anti-HCV than those who were not, and prevalence increased with decreasing family income and level of education (**Table 1**). Among men, prevalence did not vary according to service in the military (**Table 1**). The sample of women who had served in the military was too small to analyze.

The overall prevalence of anti-HCV in the current survey was similar to that observed in NHANES III, but the peak in age-specific prevalence moved from persons 30 to 39 years of age to those 40 to 49 years of age (**Figure 2**). When participants in both surveys were categorized according to approximate birth year, there was little difference in prevalence (**Figure 2**). Most anti-HCV–positive participants identified in both surveys (68.7% in NHANES III and 65.6% in the current survey) were born between 1945 and 1964.

Risk Factors for HCV Infection

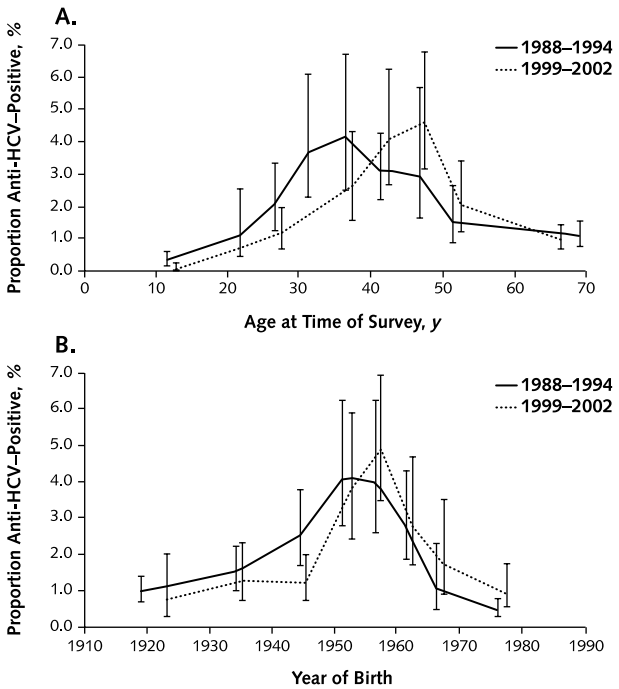
Risk factor analysis was restricted to adults 20 years of age or older because of the limited risk factor data and the small number of anti-HCV–positive persons ($n = 3$) among younger participants. Among persons 20 to 59 years of age, 21.3% (CI, 19.4% to 23.4%) had ever used illicit drugs (injection or noninjection drugs, excluding marijuana) and 2.0% (CI, 1.6% to 2.7%) had ever injected illicit drugs. Among persons 20 to 39 years of age, lifetime history of injection drug use was more common in non-Hispanic white persons (2.4%) than in non-Hispanic black persons (0.6%) ($P = 0.024$ for the difference). However, among persons 40 to 59 years of age, history of injection drug use was more common among non-Hispanic black persons (5.3%) than among non-Hispanic white persons (2.0%) ($P = 0.016$ for the difference). Of all those who acknowledged ever injecting drugs, regardless of age, most (83.3%) had not done so for at least 1 year before the survey. Injection drug use correlated with such demographic factors as low family income and little education

Figure 1. **Prevalence of antibodies to hepatitis C virus (*HCV*) by ethnicity, age, and sex.**



The vertical bars represent 95% CIs. The upper 95% CIs are not shown for 2 groups: 40- to 49-year-old non-Hispanic black men (18.2%) and 50- to 59-year-old Mexican-American men (20.0%).

Figure 2. **Prevalence of antibodies to hepatitis C virus (*HCV*) by age group (*A*) and year of birth (*B*) in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) and the current NHANES (1999–2002).**



The vertical bars represent 95% CIs.

and with such risk factors as high numbers of sex partners and noninjection drug use.

Among adults who had ever injected illicit drugs, prevalence of anti-HCV was 48.4% in those between 20 and 59 years of age. Overall prevalence of anti-HCV was 57.5% and was higher among non-Hispanic black persons (88.5%) than among non-Hispanic white persons (51.7%) ($P = 0.034$). Anti-HCV prevalence was significantly higher among those who had ever injected drugs than among those who had ever used noninjection illicit drugs (other than marijuana); both of these groups had a significantly higher prevalence than persons who had never used illicit drugs or had only used marijuana (**Table 1**). Anti-HCV prevalence was also significantly correlated with a history of receiving a blood transfusion before 1992, increasing lifetime number of sexual partners, decreasing age at first sexual intercourse, and positive results on herpes simplex virus type 2 antibody testing (**Table 1**). Among men, anti-HCV was not associated with ever having had sex with another man (data not shown).

In a logistic regression model that included data from participants between 20 and 59 years of age and controlled for age and sex, anti-HCV was most strongly associated with injection drug use. Anti-HCV was also associated with Mexican-American ethnicity, birth in the United States, low family income, noninjection illicit drug use, and a lifetime total of 20 or more sexual partners (**Table 2**). Blood transfusion before 1992 was not significantly associated with anti-HCV after adjustment for other variables but was kept in the model because it is an accepted risk factor for HCV infection. In a separate logistic regression model for participants 60 years of age or older whose drug use and sexual histories had not been collected, anti-HCV was independently associated with non-Hispanic black ethnicity and a history of blood transfusion before 1992 (**Table 3**).

Characteristics of Participants with Chronic Infection

Among anti-HCV–positive participants whose serum specimens were sent for HCV RNA determination, more men (89.0%) than women (63.4%) had positive results ($P = 0.017$), and more persons who were 40 years of age or older (89.6%) had positive results than did persons who were 6 to 39 years of age (60.2%) ($P = 0.023$). Rates of HCV RNA positivity were similar among non-Hispanic white persons (77.3%) and non-Hispanic black persons (79.7%).

Participants who had positive results for HCV RNA were significantly more likely to have abnormal serum ALT levels (58.7%) than were anti-HCV–positive, HCV RNA–

Table 2. **Adjusted Relative Odds of the Presence of Antibody to Hepatitis C Virus among Participants 20 to 59 Years of Age**

Variable	Adjusted Odds Ratio (95% CI)*
Ethnicity	
Non-Hispanic white	1.0
Non-Hispanic black	1.9 (0.9–3.8)
Mexican American	2.6 (1.2–5.8)
Place of birth	
Within United States	1.0
Outside of United States	0.2 (0.08–0.7)
Ratio of family income to poverty threshold	
≥2.0	1.0
1.0–1.9	3.5 (1.9–6.4)
0.0–0.9	9.1 (4.5–18.2)
Blood transfusion before 1992	
No	1.0
Yes	2.6 (0.9–7.3)
Illicit drug use (ever)	
Never (or marijuana only)	1.0
Noninjection drug use (except marijuana)	3.7 (1.7–7.9)
Injection drug use	148.9 (44.9–494)
Lifetime number of sexual partners	
0–1	1.0
2–19	1.4 (0.3–6.0)
≥20	5.2 (1.5–18.2)

* The model is adjusted for age (10-year categories), sex, and the interaction of age and sex. Two variables, history of blood transfusion and injection drug use, were forced into the model. See Methods section for further details regarding the modeling strategy.

negative participants (10.3%) or participants with no HCV markers (8.8%). The prevalences in the latter 2 groups were not significantly different from each other.

Adults who had positive results for HCV RNA reported heavier alcohol intake during the previous year than other adults; this group was almost 3 times more likely to consume an average of more than 1 drink per day (35.3% vs. 13.5%; $P = 0.003$) and almost 8 times more likely to consume more than 3 drinks per day (19.2% vs. 2.4%; $P = 0.010$). Adults who were HCV RNA positive were also more likely to have had 5 or more drinks in a single day during the previous year than other adults (47.8% vs. 27.7% per year; $P = 0.002$), and 33.2% had done so on at least 50 days during the previous year. Regardless of HCV status, the proportion of adults with abnormal serum ALT levels was greater among those who reported more than 1 drink per day than in those who reported 1 or fewer drinks per day (**Table 4**). This difference was statistically significant only among anti-HCV–negative persons.

Of HCV RNA–positive adults, 9.8% had received at least 1 dose of hepatitis A vaccine and 14.7% had received at least 1 dose of hepatitis B vaccine. These rates were not significantly different from those of other adults ($P = 0.66$ and $P = 0.132$, respectively).

Evaluation of Screening Criteria for HCV Infection

Among persons 20 to 59 years of age, 7.3% had a history of injection drug use or had received a blood transfusion before 1992; anti-HCV testing of this group would identify 53.1% of HCV RNA–positive persons (**Table 5**). If testing also included those with abnormal serum ALT levels (a common "incidental finding" in medical practice), 85.1% of HCV-infected persons could be identified on the basis of testing 18.1% of the population. Among persons 60 years of age and older, 21.1% had received a blood transfusion before 1992 or had an abnormal serum ALT level; anti-HCV testing of this population segment would identify 87.4% of HCV RNA–positive persons.

DISCUSSION

These results highlight the substantial burden of infection attributable to HCV in the United States. Approximately 3.2 million persons in the general population have chronic infection; however, this figure is probably an underestimate because the sampling frame of NHANES did not include incarcerated or homeless persons, who are known to have high prevalences of HCV infection (5, 9, 10). If the estimated number of HCV infections among incarcerated persons (9) were added to those from NHANES, the total number of persons with chronic infection would increase to an estimated 3.5 million.

It is unknown what proportion of HCV-positive persons in the United States are aware of their infection; however, the high rates of alcohol use (a co-factor known to accelerate HCV-related chronic liver disease) and low rates of hepatitis A and hepatitis B immunization noted in our study suggest that many of the HCV-positive persons we identified have not been tested, have not received appropriate counseling, or have disregarded that counseling. Most HCV-infected persons are only now reaching an age when complications of liver disease may start to develop, and multiple studies have predicted a rise in future HCV-related morbidity and mortality rates (3, 4, 11, 12). To characterize the type of care and counseling that HCV-infected persons receive in the United States, researchers are performing a follow-up survey of anti-HCV–positive participants who were identified in NHANES.

Most HCV-infected Americans were born between 1945 and 1964, and most have engaged in high-risk drug

Table 3. **Adjusted Relative Odds of the Presence of Antibody to Hepatitis C Virus among Participants 60 Years of Age and Older**

Variable	Adjusted Odds Ratio (95% CI)*
Ethnicity	
Non-Hispanic white	1.0
Non-Hispanic black	4.3 (1.9–9.6)
Mexican American	1.6 (0.6–4.0)
Blood transfusion before 1992	
No	1.0
Yes	4.9 (1.7–14.1)

* The final model included only ethnicity and history of blood transfusion. Age, sex, birthplace, and family income were not statistically significant in this model and were not included. Questions about drug use and sexual activity were not administered to participants who were 60 years of age or older, and therefore these data were not available for analysis.

Table 4. **Relationship between Alcohol Use and Abnormal Serum Alanine Aminotransferase Level***

HCV Status†	Participants with Abnormal Serum ALT Levels			
	0–1 Drinks per Day (95% CI), %	>1 Drink per Day (95% CI), %	Difference, *percentage points*‡	*P* Value
Anti-HCV negative ($n = 8095$)	8.5 (7.8–9.3)	17.8 (15.5–20.4)	9.3	<0.001
HCV RNA positive ($n = 117$)	54.6 (40.2–68.3)	69.5 (47.5–85.1)	14.9	0.2

* ALT = alanine aminotransferase; HCV = hepatitis C virus.
† Because of small sample sizes, participants who were anti-HCV positive but HCV RNA negative were excluded from this table.
‡ Difference in prevalence of abnormal serum ALT levels among participants who consumed more than 1 drink per day and those who drank 1 or fewer drinks per day.

Table 5. **Evaluation of Potential Screening Criteria for Hepatitis C Virus Infection***

Screening Criteria*	Participants with Criteria, %	
	General Population	HCV RNA–Positive Population
Persons age 20–59 y†		
Risk factor history		
Injection drug use	1.9	46.6
Injection drug use or transfusion before 1992	7.3	53.1
Injection drug use or transfusion before 1992 or ≥20 lifetime sex partners	21.0	76.1
Any illicit drug use‡ or transfusion before 1992 or ≥20 lifetime sex partners	33.2	89.7
Risk factor history and ALT level		
Abnormal ALT level	12.0	62.6
Abnormal ALT level or injection drug use	13.3	82.8
Abnormal ALT level or injection drug use or transfusion before 1992	18.1	85.1
Abnormal ALT level or injection drug use or transfusion before 1992 or ≥20 lifetime sex partners	30.0	93.5
Abnormal ALT level or any illicit drug use‡ or transfusion before 1992 or ≥20 lifetime sex partners	40.7	98.6
Persons age ≥60 y		
Risk factor history		
Transfusion before 1992	17.2	60.1
Risk factor history and ALT level		
Abnormal ALT level	5.1	56.7
Abnormal ALT level or transfusion before 1992	21.1	87.4

* ALT = alanine aminotransferase; HCV = hepatitis C virus.
† The analysis of persons 20 to 59 years of age included only those for whom all 4 variables (drug use history, sexual history, transfusion history, and ALT level) were not missing. The analysis of persons ≥60 years of age included only those for whom both transfusion history and ALT level were not missing. For this reason, the estimates may vary slightly from estimates elsewhere in the text.
‡ Includes drug use by injection or otherwise, except marijuana.

and sexual behaviors at some point in their lives. Many with such histories may not recognize that transient behavior decades earlier has put them at risk for a potentially lifelong infection. Of those who ever injected drugs, for example, more than 8 out of 10 had not done so in the past year and may not have injected drugs for many years.

High-risk behavior does not account for all HCV infections in the United States. Among HCV-positive survey participants 60 years of age or older, more than half reported receiving blood transfusions before 1992. Among younger participants, blood transfusion probably accounted for a relatively smaller proportion of HCV infections. This trend reflects public health interventions during the 1980s and 1990s that led to a progressive reduction in the risk for post-transfusion HCV infection (5, 13, 14). Other well-known risk factors, such as long-term hemodialysis and health care work involving frequent exposure to blood (5), could not be evaluated in NHANES because of their low frequency or lack of availability in the NHANES data set. These risk factors generally account for fewer than 10% of infections (15, 16).

The lower prevalence of anti-HCV among adolescents and young adults (<30 years of age) compared with that among older adults is encouraging. The similarity of the prevalences among young non-Hispanic black and white adults, as well as the lower prevalence of injection drug use among young non-Hispanic black persons, is consistent with that of another national survey (17); this finding suggests that younger non-Hispanic black persons may not be subject to the disproportionately high burden of disease that was seen in the previous generation. However, the small number of younger anti-HCV–positive participants limits definitive conclusions.

The prevalence of chronic infection did not vary significantly by race. In the previous NHANES, non-Hispanic black persons were more likely to have chronic infection than non-Hispanic white persons (1). This difference could represent a loss of HCV markers as the cohort aged; a real change in prevalence of chronic infection; or a chance observation, particularly because of the smaller numbers of HCV-positive participants in the current survey.

There are limitations to NHANES, a survey with a broad scope of which HCV is but one of many components. In addition to excluding certain high-risk populations, the survey allowed only self-reporting of such risk factors as injection drug use; the limitation of this format may result in an underestimation of the prevalence of these factors and the strength of association with HCV. In 1 longitudinal study, 7.4% of persons who had acknowledged a history of cocaine use on at least 2 previous surveys did not do so when responding to subsequent surveys (18). Studies of volunteer blood donors found that 30% to 50% of those whose donations were rejected because of a positive HCV test result admitted to a history of injection drug use after being presented with their result (19–21). None of these donors had reported this risk factor at the time of

donation. Because injection drug use is an overwhelmingly strong risk factor for HCV infection, small amounts of unacknowledged injection drug use can confound any cross-sectional survey (22). In our study, for example, injection drug use correlated with such variables as low family income, high numbers of sex partners, and noninjection drug use. Unacknowledged injection drug use may account for at least part of the association observed between these variables and HCV infection. Finally, sources of HCV infection for individual participants cannot be definitively determined in a cross-sectional study.

The lack of change in HCV prevalence between the 1988 to 1994 NHANES and the 1999 to 2002 NHANES is consistent with the 5- to 10-fold decrease in incidence of acute hepatitis C that was observed in the early 1990s (3, 15). However, there is no guarantee that the incidence of acute infection will remain low. Among young injection drug users, the annual incidence of HCV infection ranges from 10% to 36% (23–27). Furthermore, the stabilization of HCV prevalence will not prevent the increase in cirrhosis and liver cancer that is projected to result from HCV infections acquired in previous decades (11, 12, 28). Therefore, prevention of HCV-related liver disease should remain a key focus of clinical and public health interventions, which rely on the identification of persons with chronic HCV infection (5). Although there has been insufficient time to demonstrate that antiviral therapies and other interventions directly reduce HCV-related morbidity and mortality rates, we cannot ignore the potential benefits of reducing liver injury by eradicating the virus or by eliminating other hepatotoxic agents (for example, infections and alcohol) in the interim (29, 30).

There may be concern regarding the feasibility of ascertaining risk factor histories during routine patient visits, but the data in this report demonstrate that about 85% of HCV-positive persons can be identified on the basis of 1 of 2 risk factors, history of injection drug use or receipt of a blood transfusion before 1992, or 1 laboratory result showing an abnormal serum ALT level. Of particular importance to clinicians is that most HCV-infected persons who acknowledge a history of injection drug use have not used these drugs recently and may not fit conventional stereotypes of injection drug users. All patients should be asked about their history of injection drug use, and those who report such a history, no matter how transient or remote, should be tested for HCV.

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References

1. **Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al.** The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999;341:556-62. [PMID: 10451460]
2. **Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, et al.** Inaugural article: a comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci U S A. 2002;99:15584-9. [PMID: 12438687]
3. **Armstrong GL, Alter MJ, McQuillan GM, Margolis HS.** The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology. 2000;31:777-82. [PMID: 10706572]
4. **Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ.** Empirically calibrated model of hepatitis C virus infection in the United States. Am J Epidemiol. 2002; 156:761-73. [PMID: 12370165]
5. **Centers for Disease Control and Prevention.** Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep. 1998;47(RR-19):1-39. [PMID: 9790221]
6. **Centers for Disease Control and Prevention.** NHANES 2001-2002 Public Data General Release File Documentation. Accessed at www.cdc.gov/nchs/data/nhanes/nhanes_01_02/general_data_release_doc.pdf on 1 July 2004.
7. **Centers for Disease Control and Prevention.** General Information about NHANES Interview Data. Accessed at www.cdc.gov/nchs/data/nhanes/nhanes_01_02/questdoc_b.pdf on 1 July 2004.
8. **Centers for Disease Control and Prevention.** NHANES Analytic Guidelines. Accessed at www.cdc.gov/nchs/data/nhanes/nhanes_general_guidelines_june_04.pdf on 1 July 2004.
9. **Weinbaum C, Lyerla R, Margolis HS.** Prevention and control of infections with hepatitis viruses in correctional settings. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2003;52(RR-1):1-36. [PMID: 12562146]
10. **Cheung RC, Hanson AK, Maganti K, Keeffe EB, Matsui SM.** Viral hepatitis and other infectious diseases in a homeless population. J Clin Gastroenterol. 2002;34:476-80. [PMID: 11907367]
11. **Wong JB, McQuillan GM, McHutchison JG, Poynard T.** Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health. 2000;90:1562-9. [PMID: 11029989]
12. **Davis GL, Albright JE, Cook SF, Rosenberg DM.** Projecting future complications of chronic hepatitis C in the United States. Liver Transpl. 2003;9: 331-8. [PMID: 12682882]
13. **Alter HJ, Houghton M.** Clinical Medical Research Award. Hepatitis C virus and eliminating post-transfusion hepatitis. Nat Med. 2000;6:1082-6. [PMID: 11017126]
14. **Donahue JG, Muñoz A, Ness PM, Brown DE Jr, Yawn DH, McAllister HA Jr, et al.** The declining risk of post-transfusion hepatitis C virus infection. N Engl J Med. 1992;327:369-73. [PMID: 1320736]
15. **Centers for Disease Control and Prevention.** Hepatitis Surveillance Report Number 58. Accessed at www.cdc.gov/ncidod/diseases/hepatitis/biblio/CDC_2003_Surveill58.pdf on 1 July 2004.
16. **Alter MJ, Hadler SC, Judson FN, Mares A, Alexander WJ, Hu PY, et al.** Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. JAMA. 1990;264:2231-5. [PMID: 2170702]
17. **Armstrong GL.** Trends in self-reported injection drug use (IDU) in the United States. In: Proceedings of the 42nd Annual Meeting of the Infectious Diseases Society of America. Boston: Infectious Diseases Society of America; 2004:191. Abstract no. 860.
18. **Johnston LD, O'Malley PM.** The recanting of earlier reported drug use by young adults. NIDA Res Monogr. 1997;167:59-80. [PMID: 9243557]
19. **Conry-Cantilena C, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L, et al.** Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med. 1996;334:1691-6. [PMID: 8637513]
20. **Murphy EL, Bryzman SM, Glynn SA, Ameti DI, Thomson RA, Williams**

AE, et al. Risk factors for hepatitis C virus infection in United States blood donors. NHLBI Retrovirus Epidemiology Donor Study (REDS). Hepatology. 2000;31:756-62. [PMID: 10706569]
21. **Orton SL, Stramer SL, Dodd RY, Alter MJ.** Risk factors for HCV infection among blood donors confirmed to be positive for the presence of HCV RNA and not reactive for the presence of anti-HCV. Transfusion. 2004;44:275-81. [PMID: 14962320]
22. **Thomas DL.** Hepatitis C epidemiology: injecting new tools in the field [Editorial]. Hepatology. 2000;31:790-1. [PMID: 10706576]
23. **Thorpe LE, Ouellet LJ, Hershow R, Bailey SL, Williams IT, Williamson J, et al.** Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. Am J Epidemiol. 2002;155:645-53. [PMID: 11914192]
24. **Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, et al.** Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis. 2002;186:1558-64. [PMID: 12447730]
25. **Des Jarlais DC, Diaz T, Perlis T, Vlahov D, Maslow C, Latka M, et al.** Variability in the incidence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection among young injecting drug users in New York City. Am J Epidemiol. 2003;157:467-71. [PMID: 12615611]
26. **Fuller CM, Ompad DC, Galea S, Wu Y, Koblin B, Vlahov D.** Hepatitis C incidence—a comparison between injection and noninjection drug users in New York City. J Urban Health. 2004;81:20-4. [PMID: 15047780]
27. **Hagan H, Thiede H, Des Jarlais DC.** Hepatitis C virus infection among injection drug users: survival analysis of time to seroconversion. Epidemiology. 2004;15:543-9. [PMID: 15308953]
28. **El-Serag HB, Davila JA, Petersen NJ, McGlynn KA.** The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med. 2003;139:817-23. [PMID: 14623619]
29. **Alter MJ, Seeff LB, Bacon BR, Thomas DL, Rigsby MO, Di Bisceglie AM.** Testing for hepatitis C virus infection should be routine for persons at increased risk for infection. Ann Intern Med. 2004;141:715-7. [PMID: 15520428]
30. **Strader DB, Wright T, Thomas DL, Seeff LB.** Diagnosis, management, and treatment of hepatitis C. Hepatology. 2004;39:1147-71. [PMID: 15057920]

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