Incidence and Transmission Patterns of Acute Hepatitis C in the United States, 1982-2006

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Background: Monitoring disease incidence and transmission patterns is important to characterize groups at risk for hepatitis C virus (HCV) infection. Clinical cases generally represent about 20% to 30% of all newly acquired infections.

Methods: We used sentinel surveillance to determine incidence and transmission patterns for acute hepatitis C in the United States using data from 25 years of population-based surveillance in the general community. Acute cases of hepatitis C were identified from 1982 through 2006 by a stimulated passive surveillance system in 4 to 6 US counties. Cases were defined by a discrete onset of symptoms, alanine aminotransferase (ALT) levels greater than 2.5 times the upper limit of normal (×ULN), negative findings for serologic markers for acute hepatitis A and B, and positive findings for antibody to HCV or HCV RNA. Incidence and frequency of reported risk factors were the main outcome measures.

Results: Of 2075 patients identified, the median age was 31 years, 91.5% had ALT values greater than 7 × ULN, 77.3% were jaundiced, 22.5% were hospitalized, and 1.2% died. Incidence averaged 7.4 per 100 000 individuals (95% confidence interval [CI], 6.4-8.5 per 100 000) during 1982 to 1989 then declined averaging 0.7 per 100 000 (95% CI, 0.5-1.0 per 100 000) during 1994 to 2006. Among 1748 patients interviewed (84.2%), injection drug use (IDU) was the most commonly reported risk factor. The average number of IDU-related cases declined paralleling the decline in incidence, but the proportion of IDU-related cases rose from 31.8% (402 of 1266) during 1982 to 1989 to 45.6% (103 of 226) during 1994 to 2006. Among IDU-related cases reported during 1994 to 2006, 56 of 61 individuals (91.8%) had been in a drug treatment program and/or incarcerated.

Conclusions: The incidence of acute HCV declined substantially over the 25 years of population-based surveillance. Despite declines, IDU is the most common risk factor for new HCV infection.

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The main focus of clinical research since the identification of the hepatitis C virus (HCV) 20 years ago has been development of effective medical management and treatment for the estimated 3 to 4 million chronically infected persons nationwide to prevent progression and reduce severity of liver disease. Identifying persons at high risk for HCV infection depends on knowledge of the characteristics of HCV-infected persons; these characteristics are a reflection of the past incidence and transmission patterns of acute HCV infection.

Cases of acute disease represent approximately 20% to 30% of all newly acquired infection, and the case-infection ratio does not seem to differ by type of exposure. Collecting information about exposures shortly after onset of illness from persons with acute hepatitis C allows for an examination of possible exposures that may have been the source of infection since the temporal sequence between the exposure and onset of disease is known. Data from the Sentinel Counties (see details in the “Methods” section) have been used to identify risk factors for acquiring infection by comparing the frequency of exposures reported by cases compared with population-based controls. The distribution of risk factors found to be associated with acquiring hepatitis C can then be used to describe cases subsequently identified in the same settings to monitor epidemiological changes. In this analysis, we examined changes in incidence and transmission patterns of acute hepatitis C in the Sentinel Counties during a 25-year period from 1982 to 2006.

Methods

Study Population

In the United States, nationwide surveillance for acute hepatitis C has been conducted by the Centers for Disease Control and Prevention.
We defined acute hepatitis C as (1) the discrete onset of symptoms consistent with acute viral hepatitis, (2) serum alanine aminotransferase levels greater than 2.5 times the upper limit of normal with or without jaundice, (3) IgM antibody to hepatitis A virus negative, (4) IgM antibody to hepatitis B core antigen negative, (5) antibody to HCV (anti-HCV) or HCV RNA positive, and (6) exclusion of other etiologies of liver injury (eg, drug or toxin exposures) as ascertained by interview of the diagnosing physician and review of patient medical records. Particular attention was paid to clinical presentation, history of alcohol use, prescription and nonprescription medications, recent hepatotoxic exposures, and the results of other laboratory testing to exclude other etiologies of liver injury. Serologic specimens were collected from patients within 6 weeks of onset of illness. Patients identified before 1991 met the same clinical case definition with the exception of testing for anti-HCV or HCV RNA because samples from this period were not uniformly available for retrospective testing.

Patients were interviewed by a trained study investigator using a structured questionnaire to obtain clinical, demographic, and epidemiologic data designed to elicit information on both known and potential risk factors for acquiring HCV. Data were also collected on certain behaviors that occurred over the lifetime of the case patient. Beginning in 1990, we expanded our evaluation of potential sources for infection by interviewing and collecting serologic specimens from sexual and household contacts of patients with acute hepatitis C. Beginning in 1991, we collaborated with blood collection facilities to identify and retest the donors of the units of blood received by patients who reported a history of blood transfusion in the 6 months preceding onset of illness. Healthcare-related and dental procedures were evaluated for all patients who denied injection drug use (IDU), occupational exposure to blood, and sexual or household contact with an HCV-positive person. This evaluation included review of available medical records to identify additional incident cases and potential sources of infection (ie, exposure to known HCV-positive health care person nel or patients). Beginning in 1996, patients reporting IDU during their exposure period were asked questions relating to their drug use, including which type of drugs they used and how long they had injected before their illness onset. Beginning in 2001, patients were asked if they had ever been incarcerated or in a substance abuse or drug treatment program to assess the potential for primary prevention services offered to injection drug users in these settings to reduce their risk of HCV infection.

ASSIGNMENT OF RISK FACTORS FOR INFECTION

The exposure period (incubation period) for acute hepatitis C was defined as the 6 weeks to 6 months prior to onset of illness. Based on results of case-control studies of acute disease,6,9 patients were considered to have a known risk factor for acquiring hepatitis C if during their exposure periods they reported having had any of the following: (1) blood transfusion, (2) IDU, (3) occupational exposure to blood, (4) chronic hemodialysis, (5) sexual contact with a person known to be anti-HCV positive, or (6) household contact with a person known to be anti-HCV positive. For patients who reported more than 1 known risk factor during the exposure period, a single category was assigned that represented their more likely source of infection based on the relative efficiency of the transmission route according to the order described herein. To address concerns about underreporting of high-risk drug and sexual behaviors, patients who denied any of the 6 known risk factors were shown a list of these same factors at the end of the interview and asked if any one of them applied without having to specify which one. This “aggregate risk category” was incorporated during 1996 to 2006.

Patients who reported no known risk factors for acquiring hepatitis C during their exposure periods were described according to other high-risk sexual and drug practices that might indicate recent exposures not reported during interview.10 These practices included (1) sexual contact with a person suspected of having hepatitis C during the exposure period, (2) more than 2 heterosexual partners during the exposure period, (3) a lifetime history of IDU, and (4) a lifetime history of ever snorting any illegal drug.

Hepatitis C incidence rates were calculated by using county-specific US Census Bureau data11 with intercensal population estimates. Because census data on Hispanic ethnicity were not available at the county level before 1990, county-specific Hispanic population estimates from 1990 were used for prior time periods. For the purposes of analysis, the study period was divided into 3 intervals based on trends in incidence: 1982 to 1989 (8 years), 1990 to 1993 (4 years), and 1994 to 2006 (13 years). Differences in proportions were compared using a 2-tailed Mantel-Haenszel χ² test. P < .05 was considered statistically significant. This project was reviewed and received human subjects approval from the institutional review boards of the CDC and each participating county health department.

RESULTS

DISEASE INCIDENCE

A total of 2075 patients with acute hepatitis C were identified over the 25-year period. During 1982 to 1989, the incidence of hepatitis C averaged 7.4 cases per 100 000 population (95% confidence interval [CI], 6.4-8.5 per 100 000) and differed between counties. Incidence was higher than average in 2 of the counties (12.2 per 100 000 with a peak of 16.6 per 100 000 in Denver City/Denver
County and 11.1 per 100,000 with a peak of 17.2 per 100,000 in Pierce County) and lower than average in the other 2 (4.9 and 4.1 per 100,000 in Jefferson and Pinellas Counties, respectively) (Figure). After 1989, the overall incidence declined by approximately 90% then stabilized during 1994 to 2006, averaging about 0.7 per
The median age of patients was 31.0 years (range, 1-97 years). Patients were significantly older during the 1994-1989 period compared with the 1982-1989 period (median ages, 36 years and 31 years, respectively) (P < .001). Among patients, 53.4% were male, 67.0% were non-Hispanic white, 12.5% were non-Hispanic black, and 17.6% were Hispanic (Table 2). There were no significant differences in proportions of patients by sex or race/ethnicity over the study periods. Most patients (74.1%) had 12 or fewer years of education.

Approximately 92% (91.9%) of patients had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels 7 or more times the upper limit of normal; 37% had bilirubin levels range (anti–HBc positive) 7.0-15.9 311 (15.2) ≥16.0 1569 (76.7) Bilirubin, mg/dL (n=1822)c <1.5 227 (12.5) 1.5-2.9 172 (9.4) ≥3.0 1423 (73.1) Jaundiced (n=2049)c 1584 (77.3) Hospitalized (n=2049)c 461 (22.5) Died (n=2047)c 24 (1.2) Male sex (n=2073)c 1106 (53.4) Race/ethnicity (n=2075)c White, non-Hispanic 1375 (67.0) Black, non-Hispanic 257 (12.5) Hispanic 360 (17.6) Other 83 (2.9) Educational grade completed (n=1746)c >12 y of education 435 (24.9) 9-12 y of education 1198 (68.6) 1-8 y of education 113 (6.5) Evidence of previous hepatitis A infection, bin range (anti–HAV positive) <20 (n=139) 36 (25.9) 20-29 (n=770) 244 (31.7) 30-39 (n=651) 260 (39.9) 40-49 (n=230) 125 (54.3) ≥50 (n=284) 197 (69.4) Evidence of previous hepatitis B infection, bin range (anti–Hbc positive) <20 (n=139) 27 (19.4) 20-29 (n=770) 151 (19.6) 30-39 (n=651) 173 (26.6) 40-49 (n=230) 62 (27.0) ≥50 (n=284) 59 (20.9) Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBV, hepatitis B virus; ULN, upper limit of normal. a Data are given as number (percentage) except where noted. b Denominators total to less than 2075 owing to missing values. c See the “Methods” section for details about the sentinel counties surveillance project.

The trends in overall incidence for age, sex, and racial/ethnic groups are presented in Table 1. During 1982 to 1989, the highest incidence was among persons 20 to 29 years of age followed by those 30 to 39 years of age. During 1990 to 1993, these age groups exhibited the largest declines (approximately 90%), after which the highest incidence was in persons 30 to 39 years of age. Average incidence rates were similar for males and females during the study period, although there was a slight male predominance (male to female ratio, 1.25:1) before 1990. Among the 3 most common racial/ethnic groups, Hispanics had rates of disease approximately 3 times higher than non-Hispanic whites and blacks in all time intervals.

### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

The median age of patients was 31.0 years (range, 1-97 years). Patients were significantly older during the 1994-2006 period compared with the 1982-1989 period (median ages, 36 years and 31 years, respectively) (P < .001). Among patients, 53.4% were male, 67.0% were non-Hispanic white, 12.5% were non-Hispanic black, and 17.6% were Hispanic (Table 2). There were no significant differences in proportions of patients by sex or race/ethnicity over the study periods. Most patients (74.1%) had 12 or fewer years of education.

Approximately 92% (91.9%) of patients had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels 7 or more times the upper limit of normal; 77.3% had jaundice (Table 2). A total of 22.5% were hospitalized for their hepatitis, and the case fatality rate was 1.2%. Patients 50 years or older had significantly higher hospitalization (47.7% [135 of 283]) and death rates (4.6% [13 of 280]) than patients younger than 50 years (18.3% [326 of 1777]) and 0.6% [11 of 1766], respectively) (P < .001 for both comparisons). Approximately 40% of patients had serologic evidence of past hepatitis A virus infection; the prevalence increased with increasing age. Approximately 20% of patients had serologic evidence of past hepatitis B virus infection, with little variation in prevalence across age groups (Table 2).

### TRANSMISSION PATTERNS

Of the 2075 patients with acute hepatitis C identified during 1982 to 2006, 1748 (84.2%) were interviewed. Risk factor information from these cases was used to evaluate trends in transmission patterns during the study period.
Table 3. Known and Potential Exposures During the 6 Months Prior to Onset of Illness Reported by 270 Patients With Acute Hepatitis C Virus (HCV), Sentinel Counties, \(^4\) United States, 1994-2006\(^5\)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Proportion of Population, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>1.9</td>
</tr>
<tr>
<td>IDU</td>
<td>46.7</td>
</tr>
<tr>
<td>Health care worker with blood exposure</td>
<td>3.3</td>
</tr>
<tr>
<td>HCV-positive sex partner</td>
<td>7.0</td>
</tr>
<tr>
<td>HCV-positive household contact</td>
<td>1.5</td>
</tr>
<tr>
<td>Sex with &gt;2 partners</td>
<td>3.3</td>
</tr>
<tr>
<td>Sex partner with suspected HCV</td>
<td>3.7</td>
</tr>
<tr>
<td>Aggregate risk category</td>
<td>3.7</td>
</tr>
<tr>
<td>No risk factor identified(^6)</td>
<td>29.3</td>
</tr>
</tbody>
</table>

Abbreviation: IDU, injection drug use.
\(^4\)See the “Methods” section for details about the sentinel counties surveillance project.
\(^5\)For patients who reported more than 1 known risk factor during the exposure period, a single category was assigned that represented their more likely source of infection (see the “Methods” section).
\(^6\)But 14.5% who denied IDU during the exposure period reported prior injecting (6.7%) or intranasal (7.8%) drug use.

Injection Drug Use

Injection drug use was the most commonly reported risk factor in all study intervals. The number of IDU-related cases declined after 1989, consistent with the overall decline in incidence. In the 4 counties that participated during the entire 25-year period, there was an 84.3% decrease in the average annual number of cases reporting IDU between the 1982-1989 period and the 1994-2006 period (50.3 vs 7.9), while the proportion of such cases increased, accounting for 31.8% of cases (402 of 1266) during the 1982-1989 period, 33.5% of cases (71 of 212) during the 1990-1993 period, and 45.6% of cases (103 of 226) during the 1994-2006 period. The highest proportion of IDU-related cases was reported by Hispanics (40.2%), followed by non-Hispanic whites (34.1%) and non-Hispanic blacks (27.5%). Among the 109 patients with a history of IDU who reported when they began injecting drugs (data collected during 1996 to 2006), 34.9% reported they had begun injecting in the previous 6 months, 13.3% in the previous 6 to 12 months, 27.4% in the previous 1 to 5 years, and 26.4% more than 5 years previously. Patients who reported IDU were significantly younger than those who denied IDU (mean ages, 32.5 years vs 41.9 years; \(P < .001\)). During this period, the most commonly used drugs included cocaine (72.5%), crack cocaine (47.7%), heroin (46.8%), amphetamines (41.3%), and “speedball” (cocaine and heroin together) (36.7%). During the 2001-2006 period when the question was asked, 56 of 61 of patients reporting IDU (91.8%) had previously been in a substance abuse or drug treatment program (44 [72.1%]) and/or incarcerated (44 [72.1%]).

Blood Transfusion

There was a steady decline over the entire study period in both the number and proportion of persons who reported receiving a blood transfusion during the 6 months prior to illness, with the sharpest declines occurring before 1986 and after 1993. During 1982 to 1985, 15.0% of patients (96 of 638) received a blood transfusion, a proportion that was significantly higher than that during 1986 to 1989 (4.9% [31 of 628 patients]) (\(P < .001\)). This proportion remained steady at 4.2% (9 of 212) during 1990 to 1993 and then declined to 1.9% (5 of 270) thereafter. For the 5 cases identified during 1994 to 2006, investigations did not identify any HCV-infected donors; however, all donors were not located and tested for each of the cases. Two of these patients reported other recognized risk factors for HCV infection. Other iatrogenic sources of infection were not identified for any of the cases.

Distribution of Risk Factors for Infection During 1994 to 2006

Since the incidence was relatively stable during 1994 to 2006 and similar data collection methods were used, we limited the description of risk factor histories for this time period. Of the 352 patients with acute hepatitis C reported during this period, 270 (76.7%) were interviewed. Injection drug use was the most common risk factor during 1994 to 2006, reported by 126 of 270 patients (46.7%) (Table 3). Nineteen patients (7.0%) reported sexual intercourse with an HCV-positive partner as their only risk factor, of these, 14 (73.7%) were female, 15 (78.9%) reported only a single partner during the exposure period, and 7 (36.8%) reported ever being diagnosed with a sexually transmitted disease (STD). An additional 19 patients reported possible sexual exposures during their exposure periods, including sex with a partner they suspected had hepatitis C or who had a history of hepatitis (10 of 270 [3.7%]), and sex with more than 2 partners (9 of 270 [3.3%]). Of these, 9 of 19 (47.4%) were female and 5 of 19 (26.3%) reported a history of an STD. Overall, 38 of 270 of infections (14.1%) potentially could be attributed to sexual transmission. Eighteen of 270 patients (6.7%) denied IDU during the exposure period but reported they had previously injected (ie, > 6 months before illness onset), and 21 of 270 (7.8%) reported ever snorting illegal drugs.

Nine patients (3.3%) reported health care occupations that involved potential exposures to blood. Among the 5 patients identified beginning in 1998 when the question was added, 1 patient reported a sharps injury 8 weeks prior to symptom onset, 2 reported other unspecified work-related exposures to blood, and 2 did not report any specific exposures. Four patients (1.5%) reported having nonsexual household contact with an HCV-positive person as their only risk factor. An additional 10 patients (3.7%) reported an unspecified risk factor as listed in the “aggregate risk category.”

Cosmetic and alternative medical procedures such as tattooing, body piercing, and acupuncture were uncommonly reported during 1994 to 2006. Of 16 patients (5.9%) who reported receiving a tattoo during the exposure period, 8 (50.0%) also reported current IDU, 1 reported having a household member with HCV, and 2 reported previous but not current IDU. Similarly, of 14 patients (5.1%) reporting piercing and 6 (2.2%) reporting acupuncture dur-
ing the exposure period, 8 (57.1%) and 5 (83.3%), respectively, also reported current IDU.

Male homosexual activity during the exposure period was not common among persons identified as having acute hepatitis C. Of the 21 patients (7.8%) who reported such activity during 1994 to 2006, 12 (57.0%) also reported current (n=9) or past (n=3) IDU. Among the remaining 9 patients, 6 reported having 2 or more male partners in the 6 months prior to their illness. Among the 3 patients with a single male partner, 1 reported that the partner had hepatitis C, and 1 reported that his partner had a history of hepatitis.

We report findings of 25 years of continuous, high-quality, population-based surveillance for acute symptomatic hepatitis C in the United States, including dramatic changes in the epidemiologic characteristics of acute hepatitis C. The incidence, which peaked in the 1980s, declined by more than 90% after 1989 and subsequently remained low and remarkably stable. While this decline was observed across all demographic groups, it was most striking in younger adults 20 to 29 years old and those 30 to 39 years old and in the number of patients who reported IDU. Despite this decline, IDU accounted for an increasing proportion of acute hepatitis C during the study period. In contrast, the largest decline in the number of acute cases attributed to blood transfusion occurred before 1989 and was temporally related to changes in donor screening practices to prevent human immunodeficiency virus transmission. The decline in both number and proportion of transfusion-associated cases continued as donors were tested with surrogate and successive generations of HCV assays and following the introduction of a screening assay for anti-HCV in 1992. In the latter years of the study, the number of transfusion-associated cases, if any, was very small, particularly after 1998 when testing for HCV RNA became routine.

The reasons for the decline in the number of IDU-related acute hepatitis C cases are not as clear, but a similar trend was observed for acute hepatitis B. Several factors may have played a role, including the saturation of the IDU community with HCV infection (overall prevalence, >80%) and harm reduction education and programs. Although the incidence of hepatitis C among seronegative injection drug users remains high, they account for a small proportion relative to the population previously infected.

In our study, approximately 14% of infections potentially could be attributed to sexual transmission; these patients, who reported no other risk factors, had sex with an infected or suspected-to-be-infected partner or had more than 2 partners during their exposure period. Case-control studies of persons with acute hepatitis C identified similar risk factors as significantly associated with acquiring disease. However, long-term partners of infected patients have a low prevalence of infection, similar to that of the general population. Although factors that might facilitate HCV transmission between sexual partners are not known, persons with acute HCV infection may be more infectious than those with chronic infection.

About a third of patients ascertained during the most recent surveillance period reported no recognized risk factor during their exposure period. However, most of these patients reported illicit drug use behaviors at some time in the past, suggesting the possibility that current IDU was not reported during the interview. Other studies have shown that IDU is underreported by some persons, including volunteer blood donors. Cosmetic procedures, such as tattooing and body piercing, were uncommonly reported, and previous case-control studies did not find associations between acquiring disease and having these procedures during the incubation period. In addition, HCV prevalence is low among persons who have a history of tattooing or body piercing but deny IDU. While all percutaneous procedures are a potential source for blood-borne infections and should be performed using aseptic technique, routine testing based on histories of cosmetic procedures alone is not warranted.

Investigations of patients in the Sentinel Counties who reported no known risk factors did not find any evidence of iatrogenic transmission. Previous case-control studies did not find associations between acquiring disease and medical, surgical, and dental procedures. Percutaneous procedures are also a source of HCV transmission in health care settings, and an increasing number of outbreaks have been recently reported. Most of these were due to unsafe injection practices or other iatrogenic exposures in outpatient settings. Prevention efforts need to be directed toward ensuring that aseptic techniques are used for preparing and administering therapeutic injectable medications in any setting.

This surveillance system had several limitations. Only patients with symptoms of acute viral hepatitis, which represent a minority of all HCV infections, were included. Hence, the incidence of new HCV infections cannot be directly calculated from these data. Nonetheless, the specific case definition, used consistently over time, allows for monitoring of trends. Furthermore, because route of exposure or the size of inoculum does not seem to affect the likelihood of having symptoms, these cases should represent the broad range of risk settings. There is the potential for ascertainment bias owing to differential reporting by source of infection (eg, a health care worker with hepatitis C may be more likely to be reported than those with drug or sexual risk factors). However, findings from our surveillance study are generally consistent with the characteristics of the current population-based cohort of persons chronically infected with HCV. The overall prevalence in the general population did not change during the past decade as predicted by the low and stable incidence observed during that time. Most chronically infected persons were 40 to 59 years old, a cohort effect resulting from high incidence rates when they were younger, and 40% to 50% reported ever injecting drugs while less than 10% reported receiving a blood transfusion. Our study relied on self-reporting of such risk factors as IDU, which may have resulted in an underestimation of these factors. The use of injection drugs is a socially stigmatized illegal activity that may have resulted in people being unwilling to admit this behavior.
Determining acute disease incidence trends and transmission patterns is necessary to characterize groups at risk for infection, target and evaluate primary prevention activities, and estimate future disease burden. In the absence of effective screening and increases in the proportion of persons in care and treated for HCV infection, morbidity and mortality related to chronic hepatitis C can be expected to continue to rise over the coming decade, primarily among middle-aged adults. Despite declines in the number of cases attributable to IDU, it remains the most common source of infection. More than half of the injection drug users identified in our surveillance system had been injecting for more than a year, suggesting a window of opportunity for interventions to prevent HCV infection among new users of injection drugs and those at risk for starting to inject. 15, 30 Many users of injection drugs had been previously incarcerated or in a drug treatment program, suggesting that providing primary prevention services in correctional and drug treatment settings could be an effective means to further reduce hepatitis C incidence in the United States.

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REFERENCES