MAJOR ARTICLE

Emerging Epidemic of Hepatitis C Virus Infections Among Young Nonurban Persons Who Inject Drugs in the United States, 2006–2012

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Background. Reports of acute hepatitis C in young persons in the United States have increased. We examined data from national surveillance and supplemental case follow-up at selected jurisdictions to describe the US epidemiology of hepatitis C virus (HCV) infection among young persons (aged ≤30 years).

Methods. We examined trends in incidence of acute hepatitis C among young persons reported to the Centers for Disease Control and Prevention (CDC) during 2006–2012 by state, county, and urbanicity. Sociodemographic and behavioral characteristics of HCV-infected young persons newly reported from 2011 to 2012 were analyzed from case interviews and provider follow-up at 6 jurisdictions.

Results. From 2006 to 2012, reported incidence of acute hepatitis C increased significantly in young persons—13% annually in nonurban counties ($P = .003$) vs 5% annually in urban counties ($P = .028$). Thirty (88%) of 34 reporting states observed higher incidence in 2012 than 2006, most noticeably in nonurban counties east of the Mississippi River. Of 1202 newly reported HCV-infected young persons, 52% were female and 85% were white. In 635 interviews, 75% of respondents reported injection drug use. Of respondents reporting drug use, 75% had abused prescription opioids, with first use on average 2.0 years before heroin.

Conclusions. These data indicate an emerging US epidemic of HCV infection among young nonurban persons of predominantly white race. Reported incidence was higher in 2012 than 2006 in at least 30 states, with largest increases in nonurban counties east of the Mississippi River. Prescription opioid abuse at an early age was commonly reported and should be a focus for medical and public health intervention.

Keywords. hepatitis C; analgesics; opioid; incidence; young adult.

Hepatitis C virus (HCV) infection is a major public health threat, with mortality nationally surpassing that from human immunodeficiency virus (HIV) infection [1]. National hepatitis surveillance relies upon passive reporting of cases by providers and laboratories to state and local health departments, with the exception of 6 US jurisdictions funded for enhanced surveillance during 2006–2011 [2]. According to these national surveillance data, the number of cases of acute hepatitis C declined rapidly from 1992 to 2003 but has increased since 2006, especially among younger persons who inject drugs (PWID) [2]. This increase has coincided with numerous HCV outbreaks among PWID in nonurban

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communities, frequently associated with injection or prior misuse of prescription opioids [3–6]. Meanwhile, prescription opioid sales quadrupled from 1999 to 2010, and overdose and death have risen dramatically [7].

The elevated risk of HCV infection among young PWID has been widely reported, including in the United States [8–12]. During 2010–2011, investigations in Massachusetts and Wisconsin [3, 4, 13] suggested an emergence of HCV infection, especially among young persons of non-Hispanic white race who reported abuse of prescription opioids at an early age. Although prescription opioid abuse has been associated with elevated HCV risk [6, 14], this association has not been examined across multiple states or amid US trends in HCV incidence among young persons. To better understand HCV infection trends and characteristics in young persons, we examined national surveillance data of acute hepatitis C among persons aged ≤30 years and analyzed risk factors and demographic information from supplemental case follow-up of similarly aged HCV-infected persons newly reported to selected health departments.

METHODS

All analyses focused on HCV-infected persons aged ≤30 years in the United States, hereafter termed "young persons." This report is a compound study, that (1) examined trends in incidence of acute hepatitis C reported in national surveillance and (2) performed supplemental case follow-up in 6 jurisdictions to provide descriptive epidemiology of recently infected young persons.

National Surveillance

Surveillance data reported to CDC during 2006–2012 were examined for trends in the incidence of acute hepatitis C among young persons. Acute hepatitis C was identified according to confirmed case status reported to CDC, which reflects laboratory-confirmed HCV infection for surveillance purposes [2]. From 2006 to 2012, acute hepatitis C was defined for surveillance as laboratory-confirmed infection with acute illness of discreet onset. Acute illness was considered as the presence of any sign or symptom of acute viral hepatitis plus either jaundice or elevated alanine aminotransferase >400 IU/L [2]. In 2012, the surveillance case definition was expanded to include cases with negative HCV antibody followed by positive antibody within 6 months [15]. Most of 55 states or territories voluntarily report cases of acute hepatitis C to CDC through the National Notifiable Disease Surveillance System (NNDSS) [2]. Age at first diagnosis was considered as the age at first report of HCV infection to state or local public health. Location of residence was classified using urbanization schemes described by the National Center for Health Statistics (NCHS) [16]. These include 4 metropolitan county designations with population ≥50 000 ("large metropolitan, central"; "large metropolitan fringe"; "medium metropolitan"; and "small metropolitan") and 2 nonmetro county designations with population <50 000 ("micropolitan" and "noncore") [16]. Collectively, metropolitan designations are termed "urban," whereas nonmetro designations are termed "nonurban" in analysis by urbanicity.

Supplemental Case Follow-up

During 2011–2012, 5 state (Florida, Massachusetts, Michigan, Minnesota, and Wisconsin) and 1 city (Philadelphia) health departments received supplemental CDC funding to investigate newly reported HCV infection in young persons (hereafter termed "supplemental case follow-up"). Newly reported HCV infection was considered as any hepatitis C, past or present, as opposed to just acute hepatitis C, enabling sites to generate more robust descriptive findings. Sites conducted follow-up with clinical providers and interviewed case-patients who could be located and consented. Sites conducted case interviews to obtain behavioral and risk characteristics, including access to care, incarceration history, exposure to drug or alcohol rehabilitation, risk behaviors related to injection drug use (IDU), and recreational patterns of drug use with age of first use. Health departments attempted interviews up to 3 times either by telephone or in-person at health departments, jails, or prisons. Provider follow-up was conducted with a faxed letter and case report form, telephone calls to provider offices, or both. Efforts were made to collect data consistently across sites, although questionnaire content occasionally varied by site according to local needs. De-identified data were sent securely to CDC for analysis.

Data Analysis and Statistical Methods

From national surveillance data, we calculated annual incidence (per 100 000 persons) of reported acute hepatitis C during 2006–2012 in young persons at the national, state, and county level. We examined trends specifically in or nearby Appalachian jurisdictions, as defined by the Appalachian Regional Commission [17], where the greatest increases were reported. In each year, the number of cases reported through NNDSS was used as the numerator and mid-year (July) population estimates for persons aged ≤30 years from US Census Bureau were used as the denominator for incidence estimates [18]. We limited analyses to states that reported in both 2006 and 2012 to better detect changes in trends. We compared the average annual reported incidence of acute hepatitis C from 2006 to 2010 to that from 2011 to 2012 using an unpaired *t*-test for all ages and specifically for young persons. We compared annual US incidence by urban vs nonurban county of residence, using NCHS classifications [16]. For incidence rates, 95% confidence intervals (CIs) were calculated by Poisson distribution [19]. Temporal trends in incidence from 2006 to 2012 were assessed separately among cases of urban and nonurban county of residence using R-squared test and linear trend analysis. Changes in incidence

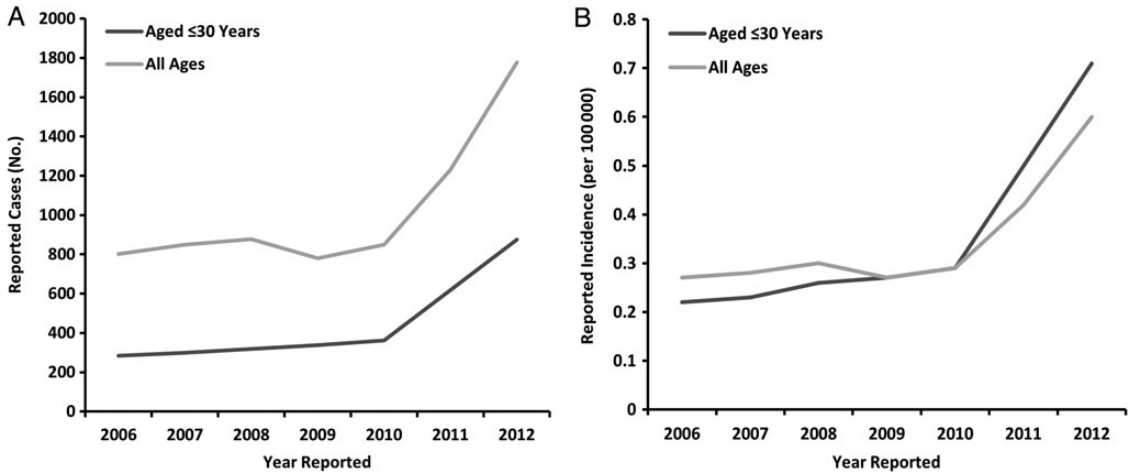

Figure 1. Number of cases (*A*) and incidence (*B*) of acute hepatitis C reported to CDC by year among young persons and all persons, United States, 2006–2012. Abbreviation: CDC, Centers for Disease Control and Prevention.

over time were considered statistically significant at $P < .05$. Using 2006–2011 data, estimates of average annual incidence from national surveillance were compared to estimates from enhanced surveillance [20] to verify that differences in incidence by urbanicity were reproducible in enhanced surveillance sites.

From supplemental case follow-up, sociodemographic characteristics were quantified among cases receiving provider follow-up or case interview. Information on access to care, risk behaviors, and drug use patterns were analyzed from case interview data. Mean and range of age of first use of each drug were calculated among those reporting any drug use.

Analyses were conducted using SAS Version 9.3 (SAS Institute, Cary, North Carolina). Incidence by county and state of residence from national surveillance data was mapped using Geographic Information System software (Esri ArcGIS, Redlands, California) to assess changes between 2006 and 2012, allowing comparison of the most recently available data to the year when increases were initially noted.

RESULTS

National Trends in Incidence

During 2006–2012, 7169 cases of acute hepatitis C were reported to CDC. Of 7077 cases with reported age, 44% were aged ≤30 years. Of these, approximately 1% were aged ≤5 years. In 2012, 49% of all US cases were aged ≤30 years, vs 36% in 2006. From 2006 to 2012, reported cases in young persons were predominantly white (93%) and non-Hispanic (92%), and as likely to be female (50%) as male. Among all ages and specifically among ages ≤30 years, the average annual incidence was significantly greater in 2011–2012 than in 2006–2010 (all ages: $P = .0054$, ages ≤30 years: $P = .002$; Figure 1).

Geographic Variation of Incidence by State

Of 34 US states and territories reporting to CDC in both 2006 and 2012, 30 (88%) reported higher incidence of acute hepatitis C in 2012 compared to 2006 among young persons. Of these states, 15% had increases of 100%–199%, whereas 50% had increases of ≥200% (Figure 2*A* and Supplementary Table). Twenty-five reported ≥10 cases in 2012 compared to only 12 in 2006. The 5 states with the most cases in 2012 were Kentucky (85), Tennessee (60), Georgia (58), Indiana (50), and Florida (47)—all situated east of the Mississippi River, in or nearby Appalachian jurisdictions.

Geographic Variation of Incidence by County

In 34 states reporting to CDC in 2006 and 2012, 451 counties reported ≥1 cases of acute hepatitis C in 2012, in contrast to 194 counties in 2006. In 2012, 102 counties in 34 states observed an incidence of reported acute hepatitis C of >10 cases per 100 000, vs only 36 counties in 2006. Of 102 counties reporting >10 cases per 100 000 in 2012, 89% were east of the Mississippi River, most commonly in Appalachian jurisdictions. Figure 2 shows 2006 (2B) and 2012 (2C) incidence by county in the eastern United States illustrating the increasing frequency and geographic clustering of counties with high reported incidence in or nearby Appalachian jurisdictions.

HCV Incidence Rates and Trends by Urbanicity

Among young persons reported with acute hepatitis C, 31% resided in nonurban counties and 67% in urban counties. The incidence of reported acute hepatitis C significantly increased 13% per year with an overall 170% increase from 2006 to 2012 in nonurban counties ($P = .003$) (Figure 3). Incidence significantly increased among urban counties, as well, by 5% per year

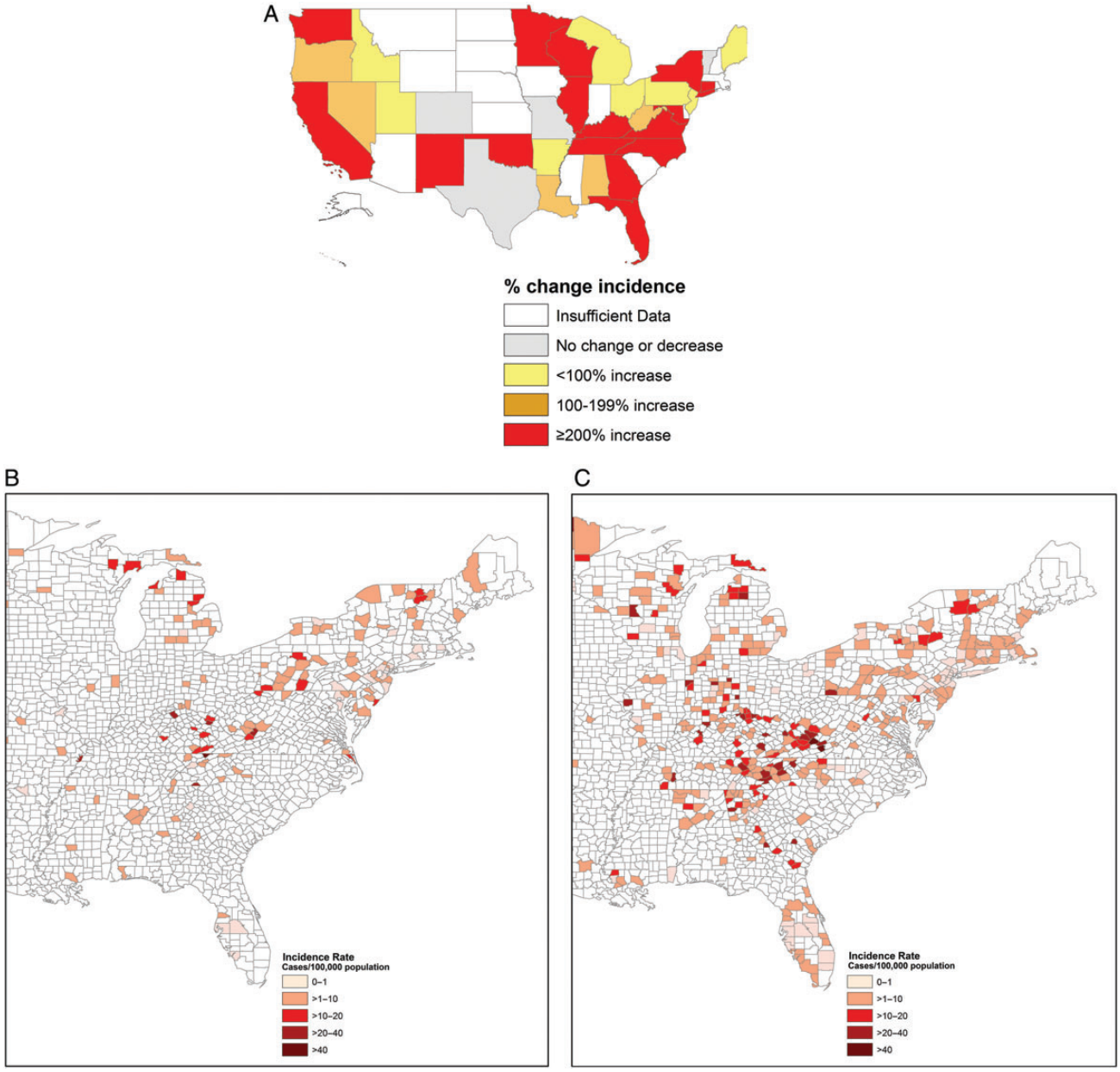

Figure 2. Maps of incidence of acute hepatitis C among young persons reported to CDC, indicating changes by state, United States, 2006 vs 2012 (*A*), and by county, Eastern United States, 2006 (*B*) vs 2012 (*C*). Abbreviation: CDC, Centers for Disease Control and Prevention.

($P = .028$). During 2006–2012, the highest annual incidence occurred in 2012 for both nonurban (1.22 cases per 100 000, 95% CI, 1.07–1.38) and urban (0.55 cases per 100 000, 95% CI, .51–.59) jurisdictions. The greatest year-to-year increase occurred from 2010 to 2011 with an increase of 38% in nonurban and 85% in urban counties. The rate ratio (RR) of nonurban to urban incidence was 2.7 (nonurban: 0.60 per 100 000; urban: 0.22 per 100 000). In six jurisdictions conducting enhanced surveillance [20], we observed a similar RR of nonurban to urban incidence (nonurban: 0.93 per 100 000; urban: 0.30 per 100 000, RR: 3.1).

Selected Characteristics From Supplemental Case Follow-up

For 1202 cases in 6 jurisdictions with provider follow-up or case interviews during 2011–2012 (Table 1), 52% of respondents were female, 56% resided outside central large metropolitan areas, 44% were aged 20–24 years, and 85% were white. Most respondents (73%) were insured and underwent alcohol or drug treatment in their lifetime (76%). One-third (34%) reported being incarcerated in the year preceding HCV diagnosis. In total, 77% reported ever injecting drugs; among them, 57% reported sharing needles or syringes, and

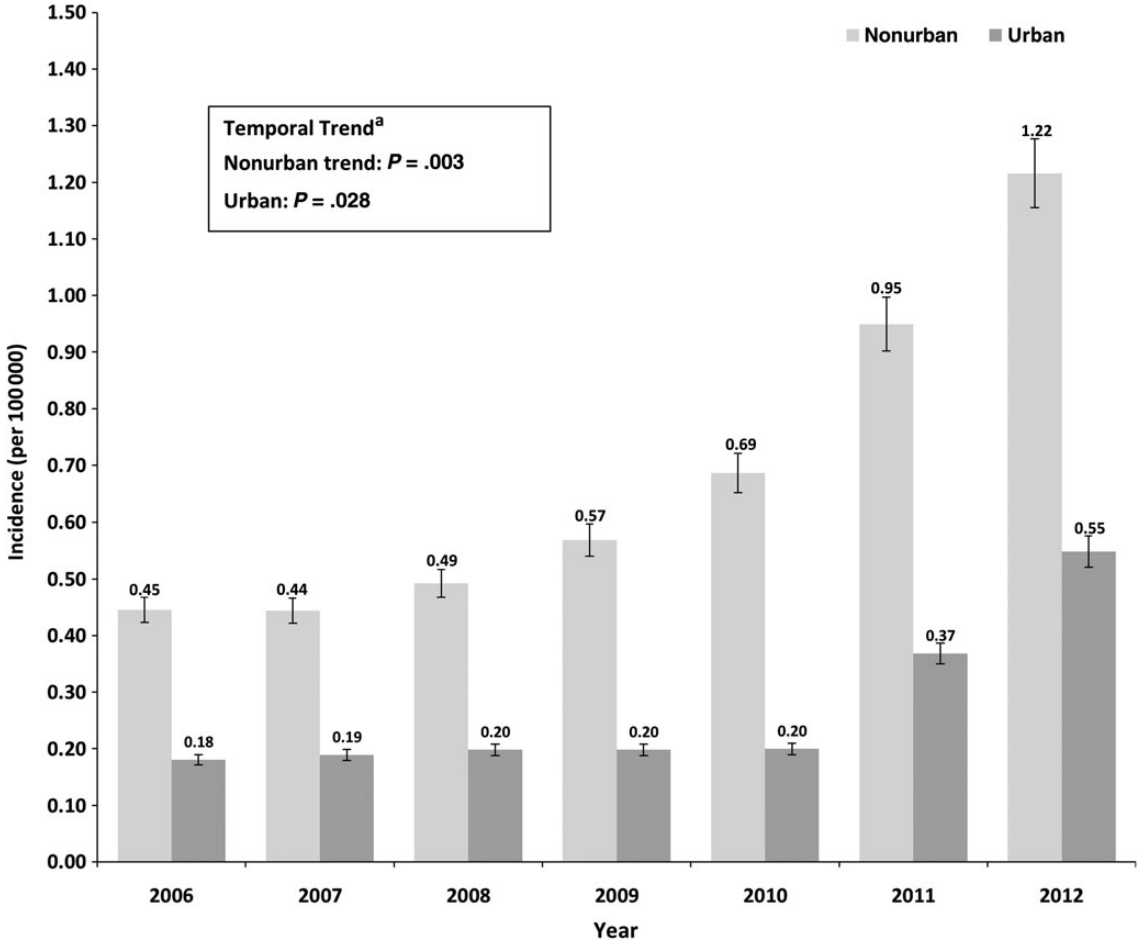

Figure 3. Trends in incidence of acute hepatitis C among young persons reported to CDC, by Urbanicity, 2006–2012. [a]Temporal trends in incidence from 2006 to 2012 were assessed separately among cases of urban and nonurban county of residence using R-squared test and linear trend analysis. Trend was considered statistically significant at $P < .05$. Abbreviation: CDC, Centers for Disease Control and Prevention.

82% reported sharing other drug preparation equipment (Table 2).

Drug Use Patterns From Supplemental Case Follow-up

Among interviewed case-patients aged ≤30 years, 456 (84%) reported having ever used drugs, including alcohol, recreationally (Table 3)—initiated nearly always before 20 years of age (97%). Marijuana (91%) and alcohol (83%) were most commonly abused, followed by any prescription opioids (76%), oxycodone specifically (74%), powder cocaine (71%), and heroin (61%). On average, respondents reported earliest first use of marijuana (age 14.1 years, range 7–26 years) and alcohol (age 15.3 years, range 6–25 years), followed by powder cocaine (age 17.4 years, range 7–29 years), any prescription opioid (age 17.7 years, range 10–28 years), and oxycodone (age 17.9 years, range 10–28 years). For potentially injectable drugs, on average, initial use of heroin (age 19.7 years, range 12–29 years) was 2.3, 2.0, and 1.8 years after that of powder cocaine, any prescription opioid, and oxycodone, respectively. Overall, 54% reported using both heroin and prescription opioids; among them, heroin was used on average 2.4 years after first use of prescription opioids.

DISCUSSION

These data indicate a worrisome increase in HCV infection among young PWID in the United States. The incidence of reported acute hepatitis C among young persons has significantly increased during 2006–2012, with annual increases >2 times greater in nonurban compared to urban jurisdictions. Reported incidence was greater in 2012 than 2006 in at least 30 states, most notably in nonurban jurisdictions east of the Mississippi River in or nearby Appalachian counties. Persons characterized in supplemental case follow-up were predominantly of white race, as likely to be female as male, and frequently resided outside large urban centers. Prescription opioids and powder

Table 1. Demographic Characteristics of 1202 Young Persons[a] With Newly Reported Hepatitis C Virus Infection in 6 Jurisdictions, 2011–2012

Demographic Characteristics	n (%)[b]
Sites[c] (n = 1202)	
Florida	258 (21)
Massachusetts	89 (7)
Michigan	152 (13)
Minnesota	113 (9)
Philadelphia	244 (20)
Wisconsin	346 (29)
Location by MSA[d] (population) (n = 1186)	
Large metropolitan, central	516 (44)
Large metropolitan, fringe	182 (15)
Medium metropolitan	182 (15)
Small metropolitan	124 (10)
Micropolitan	99 (8)
Noncore	83 (7)
Gender (n = 1199)	
Male	571 (48)
Female	628 (52)
Age at diagnosis (years) (n = 1151)	
0–19	131 (11)
20–24	502 (44)
25–30	518 (45)
Race (n = 1030)	
White	878 (85)
Black	81 (8)
Asian or Pacific Islander	9 (1)
American Indian or Alaska Native	27 (3)
Other	42 (4)
Ethnicity (n = 835)	
Hispanic	84 (10)
Non-Hispanic	751 (90)

Abbreviations: CDC, Centers for Disease Control and Prevention; ELC, Epidemiology and Laboratory Capacity; MSA, Metropolitan Statistical Area.

[a] The total number of young persons included for demographic description includes all young persons with acute hepatitis C for whom either a case interview, provider follow-up, or both were conducted.

[b] Denoted as n/N if records were missing responses. Sum of percentages may not equal 100 due to rounding.

[c] Sites include 6 state or city health departments awarded funding from CDC through the Fiscal Year 2012 ELC Cooperative Agreement.

[d] MSA classification adopted from scheme used by the National Center for Health Statistics.

Table 2. Behavioral and Risk Characteristics Among Young Persons With Newly Reported Hepatitis C Virus Infection Interviewed[a] by 6 Jurisdictions, 2011–2012

Characteristic or Risk Behavior	n/N (%)[b]
Currently have health insurance	381/522 (73)
History of alcohol or drug treatment	272/359 (76)
Incarcerated in last year	96/283 (34)
Ever used drugs recreationally	456/543 (84)
Initiation of recreational drug use before age 20	386/398 (97)
Ever injected drugs	367/477 (77)
Injected drugs in past 6 mo	160/398 (40)
Share needles or syringes	76/133 (57)
Share other drug preparation equipment[c]	117/142 (82)

[a] Interviews respondents (635) by state include: Florida (258), Massachusetts (63), Michigan (68), Minnesota (13), Philadelphia (148), and Wisconsin (85).

[b] Denominators in calculations per variable include missing or unknown values which are not presented. Sum of percentages for subcategories of each variable may not equal 100%.

[c] Other drug equipment includes cookers, filters, ties, water, spoon, caps, and glass pipes.

cocaine were commonly abused and first used on average 2.0 and 2.3 years prior to heroin.

These observed increases in reported acute hepatitis C among young persons most likely reflect truly increasing incidence. In 2006–2012, CDC did not fund nor foster any large increase in HCV testing. In fact, data from US opioid treatment programs—a major venue for HCV testing—do not suggest significant changes in the proportion of US programs offering testing during our study period [21]. Moreover, our data predate the policy changes and clinical developments that might explain improved awareness and testing [22–24].

Table 3. Drugs Used and First Use Among Young Persons With Newly Reported Hepatitis C Virus Infection Interviewed by Six Jurisdictions, 2011–2012

	Age Started (Years)		
Drug Used[a]	N (%)	Mean	Range
Marijuana	413 (91)	14.1	7–26
Inhalants	81 (18)	15.2	11–26
Alcohol	379 (83)	15.3	6–25
Tranquilizers	248 (54)	16.4	8–27
Hallucinogens	247 (54)	16.7	11–27
Powder cocaine	324 (71)	17.4	7–29
Any prescription opioid drugs[b]	345 (76)	17.7	10–28
Oxycontin or oxycodone	337 (74)	17.9	10–28
Methamphetamines	134 (29)	18.7	11–27
Crack cocaine	245 (54)	18.8	12–29
Methadone	161 (35)	19.3	12–29
Heroin	280 (61)	19.7	12–29

[a] Percentages of drugs used were calculated using the number of persons reporting recreational drug use (456) as the denominator. Recreational drug use was considered to be use of any street or prescription drug, including alcohol.

[b] Any prescription opioid drugs defined as oxycontin, oxycodone, methadone, or other prescription opioids mentioned in response to use of "other drugs." Other drugs reported include: oxymorphone ("Opana"), hydromorphone ("Dilaudid"), hydrocodone/acetaminophen ("Vicodin," "Lortab"), roxycodone, morphine, and fentanyl.

Finally, although increases might partially reflect improvements in case-finding, the majority of increases were observed across several midwestern and eastern states, in or nearby Appalachia, where minimal changes in funding for hepatitis surveillance occurred.

A Massachusetts report of increases in HCV infection from 2002 to 2009 in young persons across the state was a sentinel signal of a growing national problem [13]. Since 2008, multiple HCV outbreaks among PWID in nonurban settings have been reported to CDC, including one in the Northern Plains among American Indians and Alaska Native populations and others in upstate New York, Indiana, Massachusetts, Wisconsin, and Virginia, primarily among non-Hispanic white populations [3–5, 13]. Prescription opioid abuse was commonly reported—with shared crushing, cooking, and injection of prescription opioids—along with shared injection paraphernalia.

Notably, the highest opioid prescribing rates in the United States were described in states where we observed substantial increases in acute hepatitis C reports, including Appalachian, southern and western states [25]. For example, in Appalachian Kentucky, frequent and early abuse of prescription opioids was associated with HCV infection [6, 26–27]. In supplemental case follow-up, the abuse of prescription opioids was especially common among recently infected PWID and coincided with a dramatic rise in related US overdose deaths and emergency room visits [7, 28–31]. All available information indicates that early prescription opioid abuse and addiction, followed by initiation to IDU, is fueling increases in HCV infection among young persons, especially in nonurban settings, in or nearby Appalachia.

These reports grossly underestimate HCV incidence in young persons for many reasons but mainly because most acute infections are asymptomatic and cannot be detected. Further, classification of HCV infection as acute or chronic and deduplication and transmittal of hepatitis C reports in surveillance are challenged by limited resources [20]. The incidence of HCV infection is also likely to be underestimated due to the disparate access to diagnosis and care in these at-risk populations and their reluctance to seek care due to the associated stigma associated with IDU. Although cases reported to CDC substantially underestimate actual acute infection, they are still useful metrics for evaluating important HCV trends. Accordingly, CDC and the Council of State and Territoral Epidemiologists use a relatively narrow surveillance case definition for "acute hepatitis C," which provides a consistent index of cases, to more reliably estimate trends [15].

As many providers lack knowledge of the disease and awareness of testing recommendations [32], persons with symptoms for HCV infection might not be tested, even in high-risk settings, such as corrections or drug and alcohol treatment. Consequently, these incidence rates and geographic trends undoubtedly miss multiple jurisdictions with unreported acute hepatitis C. Using modeling, CDC estimated that 12.3 HCV infections occur for every acute case in national surveillance, which would indicate that >88 000 actual acute infections occurred among young persons during 2006–2012 [33].

Multiple limitations warrant mention. First, case follow-up data are not necessarily generalizable to all young HCV-infected persons. Case follow-up was limited to the eastern United States and among persons with some access to care. High-risk populations with limited or no care are likely underrepresented, such as incarcerated, homeless, or uninsured persons. Second, risk factors for HCV acquisition from case follow-up should be interpreted with caution since all newly reported cases of hepatitis C, past or present, in young persons were considered. Nevertheless, these likely represent recent infections given their young age, making the association between risk behaviors and HCV transmission more likely. Third, supplemental case follow-up data were subject to recall bias, as with all survey-based studies. Fourth, the frequency of prescription opioid abuse might be underestimated in case interviews since several commonly-abused prescription opioids were not asked about specifically. Fifth, questionnaire instruments used at the 6 supplemental case follow-up sites occasionally varied to meet local needs, which limited the uniformity of aggregate data. Sixth, comparisons of incidence of acute hepatitis C by state and county from national surveillance data were not intended to be precise estimates given the underreporting and year-to-year potential fluctuations in passive surveillance. Finally, certain minorities might be underrepresented in national surveillance given challenges of racial misclassification in public health surveillance [34].

A comprehensive approach is needed to address the increases in HCV infection among young persons. The early abuse of prescription opioids presents an opportunity to mitigate high-risk behaviors. Possible interventions include provider education to reduce opioid misuse, treatment of drug abuse and addiction, national prescription opioid monitoring, and aggressive early education to mitigate evolution to IDU. HCV surveillance, particularly among young persons, should be strengthened to better characterize transmission patterns. Strengthening surveillance and prevention depends upon improvements in HCV testing and provider education. Both CDC and the United States Preventive Services Task Force recommend HCV testing for persons with a history of IDU [22, 23]. The majority of young persons with recent HCV infection in supplemental case follow-up interacted with clinical providers, drug or alcohol rehabilitation, or prison systems—venues where HCV testing and prevention can be focused. Additionally, improved access to syringe exchange programs, behavioral interventions, and opioid agonist therapy is needed in remote, nonurban settings. Together these strategies were shown to reduce HCV seroconversion by 75% [35]. Finally, highly effective direct-acting

antivirals to treat HCV infection offer promise for "treatment as prevention" in young HCV-infected populations who transmit over a lifetime [36]. Models suggest that even modest increases in HCV treatment among PWID can reduce prevalence [37].

A Health and Human Services multi-agency technical consultation was convened in 2013 to address the emerging epidemic of HCV infection among young persons, especially those residing in nonurban areas, and the concurrent problem of prescription opioid abuse with transition to IDU [38–40]. Reducing HCV incidence among young persons is achievable but requires a comprehensive, integrative strategy in response to this emerging threat.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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