

# Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014

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**Objectives.** To compare US trends in rates of injection drug use (IDU), specifically opioid injection, with national trends in the incidence of acute HCV infection to assess whether these events correlated over time.

**Methods.** We calculated the annual incidence rate and demographic and risk characteristics of reported cases of acute HCV infection using surveillance data from 2004 to 2014 and the annual percentage of admissions to substance use disorder treatment facilities reporting IDU for the same time period by type of drug injected and demographic characteristics. We then tested for trends.

**Results.** The annual incidence rate of acute HCV infection increased more than 2-fold (from 0.3 to 0.7 cases/100 000) from 2004 to 2014, with significant increases among select demographic subgroups. Admissions for substance use disorder attributed to injection of heroin and prescription opioid analgesics increased significantly, with an almost 4-fold increase in prescription opioid analgesic injection. Significant increases in opioid injection mirrored those for reported cases of acute HCV infection among demographic subgroups.

**Conclusions.** These findings strongly suggest that the national increase in acute HCV infection is related to the country's opioid epidemic and associated increases in IDU. (*Am J Public Health.* 2018;108:175–181. doi:10.2105/AJPH.2017.304132)

 See also Page et al., p. 156; and also Wong, p. 173.

Hepatitis C virus infection is the most common chronic blood-borne infection in the United States and a substantial cause of morbidity and mortality.<sup>1</sup> Injection drug use (IDU) is the primary risk factor for HCV transmission and the leading cause of incidence in the United States.<sup>2</sup> HCV infection can occur rapidly after IDU initiation: A meta-analysis examining the time from onset of injection to incidence of HCV infection found a cumulative incidence of 28% (95% confidence interval = 17%, 42%) at 1 year of drug injection.<sup>3</sup> Consequently, once the virus is introduced into a network of persons who inject drugs (PWID), it can circulate quickly through the reuse of contaminated drug injection equipment—specifically, needles, syringes, cookers, and

filters.<sup>4,5</sup> Other factors associated with increased risk for HCV infection include having a high injection frequency,<sup>6</sup> using high dead-space syringes,<sup>7</sup> and injecting prescription opioid analgesics (POAs).<sup>8,9</sup>

The demographic characteristics and behavioral risk factors associated with the increase in cases of acute HCV infection correspond to the populations and behaviors that characterize the nation's opioid epidemic. State surveillance data indicate a nationwide increase in reported cases of acute HCV infection since 2004, with the largest increases occurring east of the Mississippi River and exceptionally high concentrations in central Appalachia.<sup>10</sup> Findings from an analysis of data of 4 central Appalachian states from 2006 to 2012 showed that 45% of the increases in acute cases of HCV infection were among young persons (aged ≤ 30 years), with nearly three-quarters (196/265) of persons who reported a risk factor citing IDU.<sup>11</sup> Over the same time period, these 4 states also experienced a significant increase in the proportion of young persons admitted to substance use disorder (SUD) treatment who reported injecting opioids, including heroin and POAs. Similar increases in IDU and HCV infection have been documented in Massachusetts,<sup>12</sup> Wisconsin,<sup>13</sup> and New York,<sup>14</sup> and most recently a major HIV outbreak in southeastern Indiana was facilitated by the injection of the prescription opioid

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oxymorphone, with 92% of persons newly identified with HIV coinfecting with HCV.<sup>15</sup> Overall, these reports suggest that national increases in acute HCV infections are being fueled by the nation's opioid epidemic.

To improve our understanding of the relationship between the epidemics of acute HCV infection and opioid use and misuse, we extend our previous 4-state analysis of central Appalachia<sup>11</sup> to the country as a whole. In this work, we examine cases of acute HCV infection reported by US states from 2004 to 2014 in conjunction with analyzing national SUD admissions data from the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Treatment Episode Data Set—Admissions (TEDS) for trends in any opioid injection, heroin injection, POA injection, and other (i.e., nonopioid drug) injection for the same time period. We expected to find concurrent increases in SUD treatment admissions among persons with opioid use disorders who inject drugs and acute HCV infections on a national scale, echoing the dual epidemics previously identified in Appalachia.

## METHODS

We obtained confirmed cases of acute HCV infection and associated demographic and risk characteristics from the National Notifiable Disease Surveillance System (NNDSS) for 2004 to 2014.<sup>16</sup> The surveillance case definition for confirmed acute HCV infection requires satisfying clinical and laboratory criteria as defined by the Council of State and Territorial Epidemiologists. From 2004 to 2014, all cases of acute HCV infection had 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 liver enzyme levels. In 2012, the surveillance case definition was modified to include cases with a documented negative HCV antibody test result followed by a positive result within 6 months. Demographic characteristics included age, gender, race/ethnicity, and state of residence. Of cases that included risk factor

data from 2004 to 2014, we report the proportion indicating IDU.

## National Estimates of Acute Hepatitis C Virus Infection

We used NNDSS data from 2004 to 2014 to assess the annual incidence rate (per 100 000 persons) and demographic and risk characteristics of reported cases of acute HCV infection among persons of all ages. To calculate annual incidence, we stratified cases reported through NNDSS by year, age, gender, and race/ethnicity categories as numerators and midyear (July) population estimates from the US Census Bureau<sup>17</sup> as denominators. Statistical significance of a linear trend in annual incidence of acute HCV infection by year, age, gender, and race/ethnicity was assessed using the Spearman correlation trend test. Changes in incidence over time were considered statistically significant at  $P < .05$ . We conducted analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Treatment Episode Data Set—Admissions

TEDS is a national data system administered by SAMHSA. It collects information on annual admissions to SUD treatment facilities in the United States. TEDS contains data on admissions to publicly funded and state-certified SUD treatment facilities by year and by state of treatment facility for all persons aged 12 years or older. By state law, treatment facilities provide data to TEDS. TEDS is estimated to include 67% of all SUD treatment admissions and 83% of TEDS-eligible admissions in the United States. For each admission, up to 3 substances of abuse with a corresponding route of administration and demographic characteristics may be reported. Reportable substances of abuse, data collection methods, and limitations of TEDS have previously been listed.<sup>18</sup>

TEDS classifies opioids into 3 categories: heroin, nonprescription methadone, and opiates and synthetics. For this analysis, 3 types of opioid drug injection were defined: any opioid injection (includes heroin, nonprescription methadone, and opiates and synthetics), heroin injection, and POA injection (includes nonprescription methadone and opiates and synthetics). We compare the

percentages of the 3 categories of opioid injection with that of a fourth category, nonopioid injection (includes injection of drugs not classified as opioids, e.g., cocaine and methamphetamine).

## National Estimates

We calculated the national annual percentage of admissions reporting any IDU and any opioid injection, heroin injection, POA injection, and nonopioid injection among all admissions in TEDS for 2004 to 2014. Additionally, we calculated the annual percentage of admissions reporting any opioid injection, heroin injection, POA injection, and other injection by age group (12–17, 18–29, 30–39, 40–49, and  $\geq 50$  years), gender (female, male), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic). We report the percentage difference and percentage change from 2004 to 2014 for each indicator. Denominators for all annual percentages are the total number of reported treatment admissions in that year for each respective demographic group. Statistical significance of a linear trend from 2004 to 2014 was assessed using the Mann–Kendall test for trend and was considered significant at  $P < .05$ . We generated all TEDS analyses using R version 3.3.2 (R Foundation for Statistical Learning, Vienna, Austria).

## State-Level Estimates

We also calculated the annual percentage of cases of acute HCV infection by state from 2004 to 2014. Denominators for each year were calculated using midyear (July) population estimates for each state. In addition, we calculated the annual percentage of admissions for any IDU, heroin injection, and POA injection and report the percentage change for these 3 indicators over the 11-year period by state. Some states did not have admissions data available for 2004, 2014, or both years. When 2004 data were missing, we used the next available year (i.e., 2005) to calculate percentage differences and percentage change. When 2014 data were missing, we used the latest year for which data were available (i.e., 2013) to calculate percentage difference and percentage change. Denominators for all annual percentages are the total number of reported treatment admissions within each state in that year. Last,

we examined scatterplots to further gauge the relationship between state-level rates of acute HCV infection and the percentage of treatment admissions reporting the injection of any opioid. Rates of acute HCV infection were plotted on the y-axis and percentage of treatment admissions for any opioid IDU was plotted on the x-axis for 2004, 2009, and 2014. We fit a linear trend line and calculated the  $R^2$ .

## RESULTS

From 2004 to 2014, we found significant concurrent increases in reported cases of acute HCV infection and reported treatment admissions for injection of opioids. These increases were observed for the nation as a whole and among select demographic populations.

### National Notifiable Disease Surveillance System

A total of 12 953 cases of acute HCV infection were reported in the United States from 2004 to 2014. The annual incidence rate of acute HCV infection increased significantly from 0.3 cases per 100 000 in 2004 to 0.7 cases per 100 000 in 2014 ( $P < .001$ ), representing an overall rate increase of 133%

(Figure 1; Table A, available as a supplement to the online version of this article at <http://www.ajph.org>). Annual increases in incidence over the 11-year period were also observed among persons in all age, gender, and race/ethnicity categories. The largest increases ( $> 100\%$ ) were among persons aged 18 to 29 and 30 to 39 years (400% and 325%, respectively), non-Hispanic Whites, and Hispanics. Increases were statistically significant among persons aged 18 to 29 years ( $P < .001$ ) and 30 to 39 years ( $P < .001$ ), for both women and men ( $P < .001$ ) and among non-Hispanic Whites ( $P < .001$ ) and Hispanics ( $P < .001$ ). In almost every year from 2004 to 2014, IDU was reported in 60% or more of cases that included risk factor data, with more than 75% of cases reporting IDU each year from 2011 to 2014 (Table A). Of the 68% (836) of cases that included risk factor data in 2014, 84% (702) indicated IDU.

Of the 40 states with data reported to NNDSS for all years (2004–2014), an increase over time of 500% or higher in the number of cases of acute HCV infection was found in 15 states, with 6 states (Kansas, Maine, New Jersey, Wisconsin, Ohio, and Massachusetts) showing increases of 1000% or higher (Table C, available as a supplement to the online version of this article at <http://www.ajph.org>). Only 7 states (Delaware, North Dakota, Nevada, Texas, Vermont, South

Carolina, and Michigan) saw decreases in reported cases of acute HCV infection over the 11-year period.

### Treatment Episode Data Set-Admissions

Among all admissions reported to TEDS from 2004 to 2014, admissions attributed to any IDU increased 76%, and admissions attributed to heroin injection and POA injection both increased significantly by 85% and 258%, respectively (Figure 2; Table B, available as a supplement to the online version of this article at <http://www.ajph.org>). In 2004, 13% of all admissions reported IDU compared with 22% reporting IDU in 2014. Among all reported admissions, the percentage of those reporting injection of any opioid increased 93% ( $P < .001$ ) from 2004 to 2014 (10% in 2004 to 19% in 2014), whereas admissions for other nonopioid injection showed no significant change over time.

Among persons aged 12 to 17 years, admissions for any opioid injection, heroin injection, and POA injection increased 103% ( $P = .005$ ), 97% ( $P = .008$ ), and 194% ( $P = .020$ ), respectively (Table B; Figure 2). Among persons aged 18 to 29 years, admissions significantly increased for any opioid injection (622%), heroin injection (603%), and POA injection (817%). Among persons aged 30 to 39 years, admissions significantly increased for any opioid injection (83%), heroin injection (77%), and POA injection (169%). We observed no significant increases among persons aged 40 to 49 years for all categories except POA injection. Among persons aged 50 years or older, all injection categories significantly decreased, except POA injection, which showed no significant change over time.

From 2004 to 2014, the percentage of admissions attributed to any opioid injection increased significantly for both women and men (99% and 89%, respectively; Table B; Figure 3). Over this same time period, the percentage of admissions attributed to heroin injection significantly increased for both women and men (89% and 83%, respectively), as did those for POA injection (263% and 249%, respectively). We observed no significant changes over time for nonopioid injection admissions for either women or men.

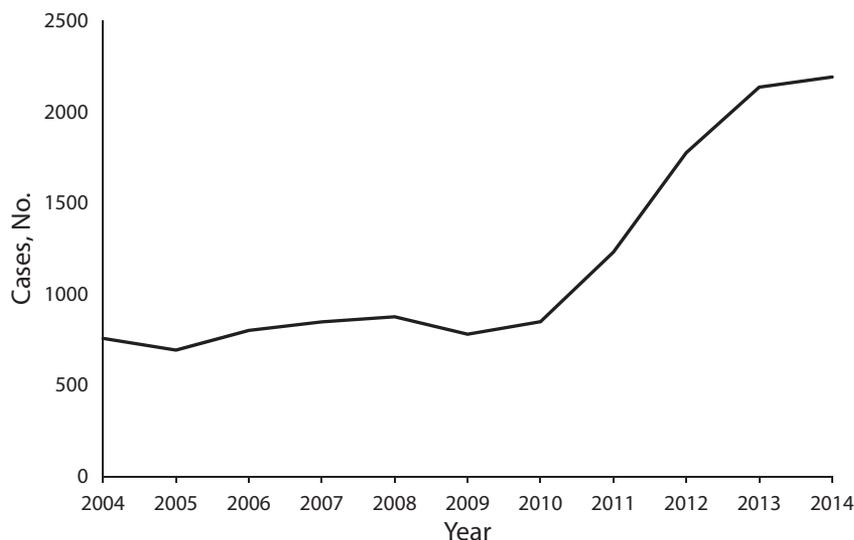
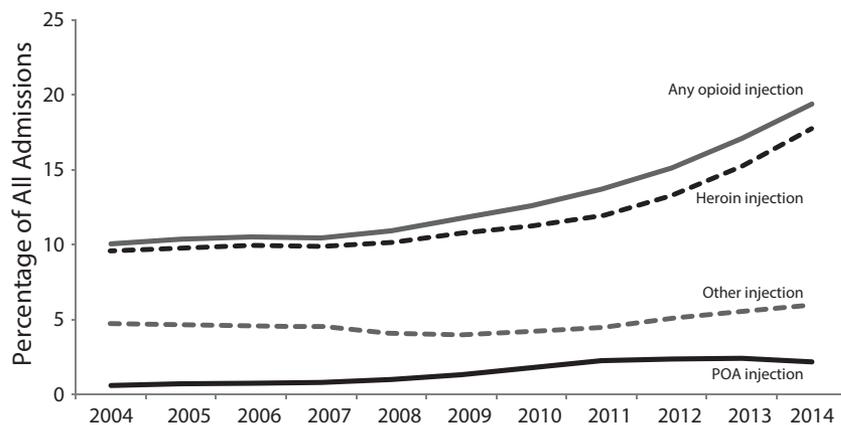


FIGURE 1—Reported Cases of Acute HCV Infection by Year: National Notifiable Disease Surveillance System, United States, 2004–2014



Note. POA = prescription opioid analgesic.

**FIGURE 2—Percentage of All Admissions to Substance Use Disorder Treatment Facilities Attributed to the Injection of Any Opioid, Prescription Opioid Analgesic, Heroin, and All Other Drugs, by Year: Treatment Episode Data Set-Admissions, United States, 2004–2014**

Among non-Hispanic Whites, admissions attributed to any opioid injection significantly increased 134% over the 11-year period, with heroin injection increasing 126% and POA injection increasing 248% (Table B). Among non-Hispanic Blacks and Hispanics, only admissions attributed to POA injection increased significantly (167% and 429%, respectively).

Of the 50 states and the District of Columbia with reported TEDS data each year from 2004 to 2014, we found an increase over time of 500% or higher in the number of admissions for POA injection in 8 states, with 5 states (Arizona, Florida, New Hampshire, New Mexico, and West Virginia) showing increases of 1000% or higher (Table D, available as a supplement to the online version of this article at <http://www.ajph.org>). For heroin injection admissions, 5 states and the District of Columbia saw increases of 500% or higher, and 2 states (Kentucky and West Virginia) and the District of Columbia saw increases of 1000% or higher. No state reported a decrease in admissions for POA injection, although Hawaii reported a decrease in admissions for heroin injection over the 11-year period. Results from the scatterplot showed a positive correlation, which increased in strength over time, between state rates of acute HCV infection and the corresponding state percentage of treatment admissions reporting any opioid IDU (Figure 3).

## DISCUSSION

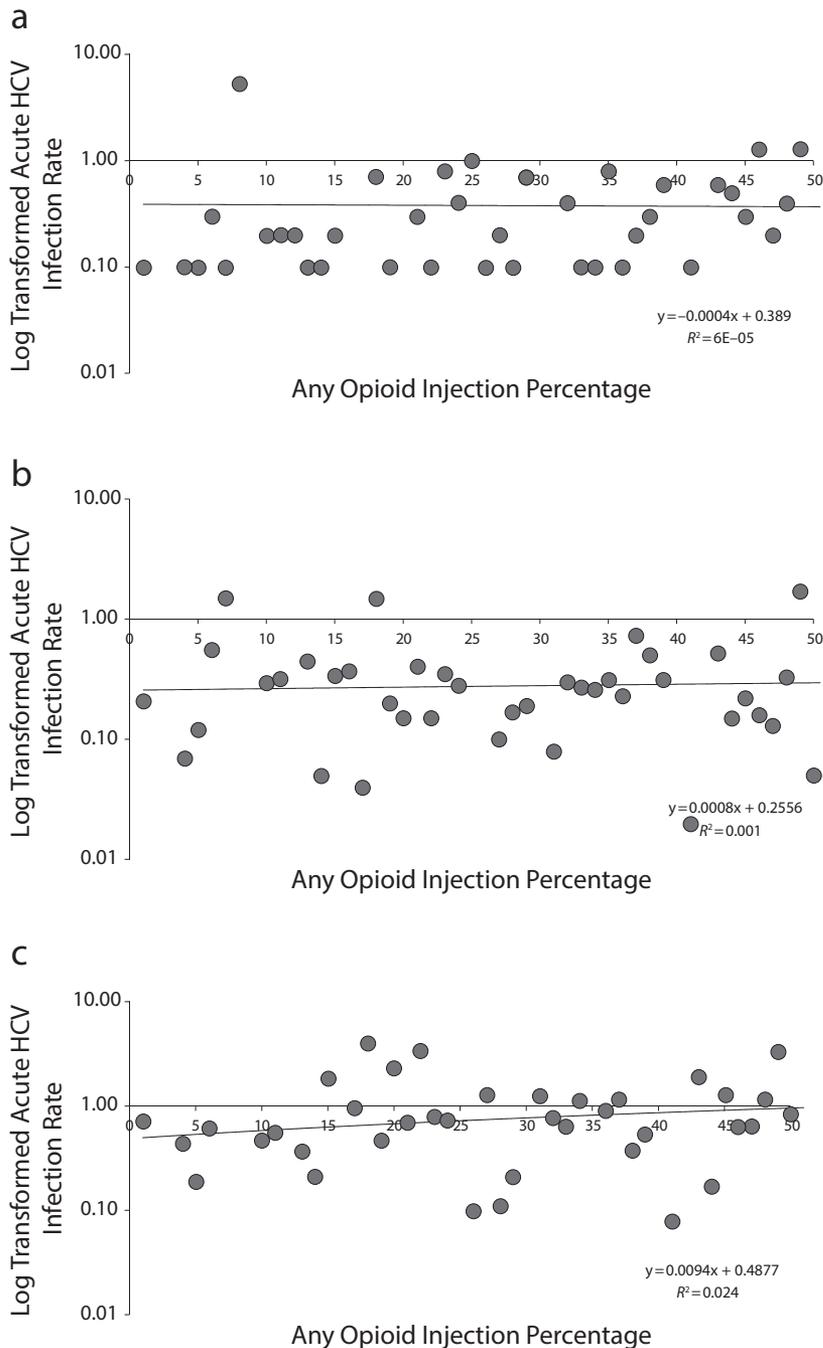
National surveillance data show a substantial increase in the incidence of acute HCV infection throughout the United States from 2004 to 2014. This increase was significant for persons aged 18 to 39 years, women and men, and non-Hispanic Whites and Hispanics, with rates of acute HCV infection increasing almost 4-fold among women and more than 2-fold among men over the 11-year period. IDU was the most frequently cited risk factor, and in the current analysis more than 80% of acute case reports with an identified HCV-related risk indicated IDU in 2014. Consistent with this pattern, the proportion of treatment admissions from 2004 to 2014 that were characterized by injecting any opioid increased significantly over the same 11-year period for persons aged 18 to 39 years, both women and men, and non-Hispanic Whites. Moreover, when we examined the data by state, the results from the scatterplot analysis provided additional support for a positive correlation. Taken together, these increases indicate a striking demographic convergence among opioid use or misuse, IDU, and acute HCV infection.

After years of relatively low and stable incidence, the United States began to witness an increase in reported cases of acute HCV infection in 2004. At the same time, the country started to experience a demographic change in the profile of incident cases of acute HCV infection. TEDS demonstrates that this

increase occurred in tandem with a similar demographic shift in the population of PWID entering treatment for SUD. From 2004 to 2014, a significant increase occurred in the proportion of SUD treatment admissions among persons who reported injecting any opioid. Of these, the number of treatment admissions attributed to POA injection increased at a substantially higher rate over this time period than the number for heroin injection and injection of drugs other than opioids. The concurrent increase in cases of acute HCV infection and SUD treatment admissions attributed to POAs from 2004 to 2014 may be explained by recent studies showing that persons who inject POAs have a higher risk for HCV infection than persons who inject heroin and nonopioid drugs.<sup>9</sup> Our findings, which reveal national increases in both the number of persons injecting POAs and the number of acute HCV infections, indicate a more widespread problem than previous studies have shown.<sup>9,12,13,19</sup>

Although treatment admissions attributed to POA injection represented a higher percentage change than admissions for heroin injection, the latter accounted for an overall greater percentage of the total number of admissions attributed to any opioid injection from 2004 to 2014. For example, admissions attributed to heroin injection constituted 18% of all treatment admissions in 2014, compared with 6% of admissions for POA injection. The steady increase and high percentage of heroin injectors in SUD treatment reported to TEDS from 2004 to 2014 correspond with national survey reports estimating an increase in first-time heroin use from 2006 to 2014 (90 000–198 000) and a doubling of the number of persons reporting heroin dependency (based on *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., criteria), from 214 000 in 2002 to 586 000 in 2014.<sup>20</sup>

By contrast, SUD treatment admissions attributed to nonopioid injection, although comprising a higher proportion of admissions than those attributed to POA injection each year from 2004 to 2014, showed no significant change over the 11-year period, whereas cases of acute HCV infection significantly increased. These findings offer further support that the increase in acute HCV infection is a sequela of the opioid epidemic and



Note. The number of states that reported cases of acute HCV infection to the National Notifiable Disease Surveillance System was 39 in 2004, 40 in 2009, and 37 in 2014.

**FIGURE 3—Percentage of State Admissions to Substance Use Disorder Treatment Facilities Reporting Any Opioid Injection by State Rate of Acute HCV Infection in (a) 2004, (b) 2009, and (c) 2014: National Notifiable Disease Surveillance System and Treatment Episode Data Set—Admissions, Selected US States**

facilitated by an increase in the number of PWID in SUD treatment who report injecting heroin, POA, or both.

Parallel increases in acute HCV infections and treatment admissions attributed to POA injection occurred among women and men

alike, yet both increased at a higher rate for women than for men, with the largest percentage change for both genders occurring among those aged 18 to 39 years. The increase in the number of women of childbearing age with acute HCV infection is consistent with reports showing increases in the number of infants born to HCV-infected mothers (68% increase from 2011 to 2014)<sup>21</sup> and a 4-fold increase in overall incident cases of neonatal abstinence syndrome from 1999 to 2013.<sup>22</sup> The upward trends in infants born to HCV-infected mothers and infants diagnosed with neonatal abstinence syndrome correspond with the time period and risk profiles associated with increases in both acute HCV infections and SUD treatment admissions for persons injecting any opioid. These trends illustrate the extraordinary burden of the opioid epidemic on the health of women and children in the United States.

Although our findings further corroborate those of previous studies identifying a demographic shift in persons affected by acute HCV infection in the United States,<sup>11,19</sup> of particular concern and not previously identified at the national level is the significant increase in both acute HCV infections and treatment admissions attributed to POA injection among Hispanics from 2004 to 2014. Although admissions for POA injection account for less than 1% of total SUD admissions among Hispanics, and heroin admissions comprise the majority of admissions attributed to the injection of any opioid for this population, the increase in the percentage of admissions for POA injection (429%) was significant and substantially higher over time than that for heroin injection (4%). Consistent with these findings are those of studies showing increases in the number of Hispanics dying from opioid-involved overdoses in certain regions of the country<sup>23,24</sup> and IDU prevalence estimates increasing more than 20% in a substantial proportion of metropolitan statistical areas with large Hispanic populations (Las Vegas, NV; New Orleans, LA; Atlanta, GA; St. Louis, MO; Tacoma, WA; Jacksonville, FL; and Detroit, MI, among others).<sup>25</sup>

### Limitations

The findings in this article are subject to some limitations. Because we could not link

cases of acute HCV infection to individual treatment admissions, we conducted an ecological analysis. Consequently, the concomitant increase in cases and treatment admissions attributed to IDU cannot be considered causally related. Underreporting of cases of acute HCV infection is another important limitation of our data. Current US surveillance for viral hepatitis is both passive and voluntary. In addition, most acute HCV infections are asymptomatic, yet the case definition for acute infection captures only persons with signs and symptoms of illness and, since 2012, those who previously tested negative in the past 6 months.<sup>26</sup> Despite this change in the definition during the time period under analysis, we believe it had minimal, if any, effect on the trends we observed, primarily because it occurred near the end of our time period, and changes such as these, particularly on a national scale, typically take several years to become established practice.<sup>27</sup> Moreover, the surveillance data indicate that the upward trend in the number of acute cases began in 2010, 2 years before this change in the case definition.<sup>28</sup> Compounding the underreporting is missing risk information. Nevertheless, even with missing risk information, IDU consistently accounted for a majority of cases with a reported risk factor each year.

The TEDS data also have important limitations. Because treatment is provided to only a fraction of persons with SUD in the United States, TEDS does not capture all persons with these disorders. For example, in 2014 an estimated 80% of persons who reported needing treatment for illicit substance use did not receive it.<sup>20</sup> Accordingly, the actual number of persons with SUD who inject drugs is likely larger than that reported here. Also, multiple treatment admissions by a single individual (i.e., readmissions) might have occurred within and across years, states, or both and could not be excluded from the TEDS analysis. Despite the limitations related to underreporting on which the annual estimates for both acute HCV infection and treatment admissions for SUD are based, we have confidence in the national trends we observed. We do note, however, that our trend tests for acute HCV infection and treatment admissions were based on annual percentages of each and were not adjusted for other potentially relevant variables that might

have been correlated with time. Last, we draw attention to the fact that, for many states, the numbers are quite small in any given year for both reported cases of acute HCV infection and treatment admissions, and because reporting to TEDS also varies by state, we advise the reader to interpret state-specific trends and state-by-state comparisons with considerable caution.

## Public Health Implications

The results of this study strongly suggest that the national increase in acute HCV infection is associated with the nation's opioid epidemic. Substantial increases in the number of persons with opioid use disorders who inject drugs have the potential to thwart the nation's efforts to control morbidity and mortality associated with HCV infection, consequently undermining the National Academies of Sciences, Engineering, and Medicine's national strategy for the elimination of hepatitis B and C.<sup>29</sup> It also challenges the Centers for Disease Control and Prevention's Viral Hepatitis Strategic Plan for 2016 to 2020, which underscores reductions in HCV infections caused by IDU behaviors as a priority area.<sup>30</sup> Integrated health services that include syringe service programs, medication-assisted treatment, and comprehensive HCV testing and linkage to care and treatment of HCV-infected PWID are essential to reduce prevalence and incidence among the population.<sup>29</sup> Increasing access to curative HCV treatment is also a key component of a comprehensive program. These efforts will require evidence-based strategies to effectively recruit and engage PWID into treatment for both SUD and HCV infection. A coordinated response among federal, state, and local health departments is essential to address the syndemic of opioid use and misuse and HCV infection on a national scale. **AJPH**

## CONTRIBUTORS

J. E. Zibbell, R. C. Patel, and D. Holtzman originated the idea and design for this article. R. C. Patel, B. Kupronis, and K. Iqbal analyzed the data and created the figures and tables. J. E. Zibbell, A. K. Asher, J. W. Ward, and D. Holtzman conducted literature searches and wrote the article.

## HUMAN PARTICIPANT PROTECTION

This research did not need institutional review board approval because it used existing de-identified publicly available data.

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