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SUPPLEMENT ARTICLE

# Not Just Endocarditis: Hospitalizations for Selected Invasive Infections Among Persons With Opioid and Stimulant Use Diagnoses—North Carolina, 2010–2018

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***Background.*** While increases in overdoses, viral hepatitis, and endocarditis associated with drug use have been well-documented in North Carolina, the full scope of invasive drug-related infections (IDRIs) has not. We characterized trends in IDRIs among hospitalized patients in North Carolina.

***Methods.*** We compared invasive infections that were related or not related to drug use among hospitalized patients aged 18–55 years based on retrospective review of administrative records from 2010–2018. Hospitalizations for endocarditis, central nervous system/spine infections, osteomyelitis, and septic arthritis were labeled as IDRIs if discharge codes included opioid and/or amphetamine misuse. Trends, rates, and distributions were calculated.

***Results.*** Among 44 851 hospitalizations for the specified infections, 2830 (6.3%) were IDRIs. The proportion of infections attributable to drug use increased from 1.5% (2010) to 13.1% (2018), and the rate grew from 1.2 to 15.1 per 100 000. Compared with those who had non–drug-related infections, patients with IDRIs were younger (median age, 35 vs 46 years), more likely to be non-Hispanic white (81% vs 56%), and had longer hospitalizations (median, 8 vs 6 days). 43% of hospitalizations for IDRIs involved infective endocarditis.

***Conclusions.*** The rate of IDRIs in North Carolina increased substantially during 2010–2018, indicating an urgent need for enhanced infection prevention, harm reduction, and addiction services aimed at community and inpatient settings.

**Keywords.** people who inject drugs; opioid misuse; amphetamine misuse; injection drug use; drug-related infection

People who inject drugs (PWID) are a vulnerable population facing unique health concerns. In addition to drug overdose, PWID are also at risk for acquiring infectious diseases from nonsterile injection practices. Communicable viral infections have garnered substantial attention due to outbreaks of human immunodeficiency virus (HIV) and rising diagnoses of acute hepatitis C [1–3]. A growing body of evidence has also documented the sharply increasing incidence of hospitalizations for infective endocarditis (IE) in this population [4–6], an infection that can result from nonsterile injection or dissemination from another infection. Bumps in IE incidence may even herald areas potentially experiencing increasingly widespread injection drug use [7].

IE represents only one of the invasive and often-severe infections that can result in hospitalization for PWID. Other invasive infections that can be caused by injection drug use, such as central nervous system (CNS) and spine infections, osteomyelitis, and septic arthritis, may also require similarly complex care resulting in long hospitalizations, prolonged courses of parenteral antibiotics, and surgical treatment [5, 8]. Nationally, hospitalizations for IE, osteomyelitis, epidural abscess, and septic arthritis among people diagnosed with opioid use disorder (OUD) doubled from 2002 to 2012 [8]. More recent studies have noted further increases in IE hospitalizations in more recent years [5, 9], but trends in other invasive drug-related infections (IDRIs) have not been reported. Examining recent trends in multiple types of IDRIs can help elucidate the full burden of drug-related harms impacting PWID and healthcare systems.

North Carolina, like much of the country, has been significantly affected by the opioid crisis. In 2018, there were 6743 emergency department visits for opioid overdose [10]. Diagnoses of acute hepatitis C have risen in NC >400% in recent years, from 36 in 2010 to 186 in 2017 [11]. In North Carolina, incidence of drug-related IE has increased >12-fold from 2007 to 2017, trending with rising opioid use [5].

To estimate the burden of IDRIs, we analyzed statewide hospital discharges for persons with diagnoses of 4 infections that can be caused by injection drug use: IE, septic arthritis, CNS/

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spine infections, and osteomyelitis. We examined annual trends in hospitalizations for these infections and described the characteristics of affected patients.

## METHODS

### Study Design

The North Carolina Hospital Discharge Database includes information on hospitalizations at all nonfederal short-term acute care hospitals in the state. We retrieved deidentified demographic, diagnostic, and billing data for all patients diagnosed with the 4 specified conditions between 1 January 2010 and 31 December 2018. We limited our study to patients aged 18–55 years. The upper age limit was imposed in an effort increase specificity, as an earlier study noted that<20% of drug-related IE cases in 2013 occurred in persons aged 55–64 years, and those persons were largely included based on a diagnosis of hepatitis C rather than drug use [6]. Therefore, we adapted our approach from the general methods of an algorithm for detecting IE among PWID in Canada that restricted assessment of IE in PWID to persons aged 17–55 years [12]. The study was approved by the institutional review board at the University of North Carolina.

### Definitions

Patients were classified as suspected users of injection drugs based on the presence of discharge diagnosis codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) for both (1) an invasive infection that could have been caused by injection drug use and (2) opioid or amphetamine use, dependence, overdose, toxicity, or withdrawal (Supplementary Tables). This proxy measure for injection drug use was used because there is no diagnostic code specific for use of injection drugs. We limited analysis to these 2 drugs given their propensity for being injected and the dynamic use patterns of amphetamines both with and without opioids [13, 14]. In addition, methamphetamine may be the second most common drug injected [15], including in studies of PWID in West Virginia, a nearby state sharing some of the same geographic territory as the hard-hit Appalachian region in Western North Carolina [16, 17]. Infections among suspected users of injection drugs were classified as IDRIs, and infections in those without an opioid or amphetamine code were designated as non–drug related.

### Inclusion Criteria

We examined the following infections: IE, septic arthritis, CNS/spine infections, and osteomyelitis. Owing to the change in coding schema, CNS/spine infections were defined as intraspinal and intracranial abscesses during the *ICD-9-CM* period, but during the *ICD-10-CM* period the category also included vertebral osteomyelitis, diskitis, and infectious vertebral arthritis. Hospitalizations with >1 invasive infection were categorized according to a hierarchy of diagnoses, as follows. Diagnoses of IE were given the highest priority because IE can lead to dissemination resulting in bone, joint, or CNS/spine infections. CNS/spine infections were given second priority because they may require longer courses of antimicrobial treatment and recovery than septic arthritis and nonvertebral osteomyelitis. The remaining hospitalizations were labeled as osteomyelitis or septic arthritis based on whichever diagnosis was listed first in the discharge data record.

Only 9 diagnostic codes were available in patients' records for the years 2010 to 2013; >9 were available beginning in 2014. Because of this limitation, for the years between 2014 and 2018, only those patients whose records had both an invasive infection and a code for drug use listed in the first 9 diagnostic codes were classified as having IDRIs. A total of 195 IDRIs between 2014 and 2018 were excluded based on this limitation.

### Data Analysis

We compared annual rates, demographics, discharge status, and hospital charges between hospitalizations for drug-related and non–drug-related invasive infections. Yearly rates of drug-related and non–drug-related infections (per 100 000 North Carolina residents aged 18–55 years) were calculated using population denominators obtained from the North Carolina Office of State Budget and Management [18]. Hospital charges and length of hospital stay were compared using the Wilcoxon rank sum test. Among IDRIs, hospitalizations related to amphetamines (with or without opioids) were compared with those related to opioid use alone. Differences were considered statistically significant at $P < .05$. To account for the impact of the change in *ICD-9-CM* to *ICD-10-CM,* which occurred in October 2015 [19], we examined trends across 3 periods: (1) the entire study period, (2) the time elapsed since the *ICD-10-CM* transition (13 quarters), and (3) the final 13 quarters of the *ICD-9-CM* period.

## RESULTS

### Annual Trends

There were 44 851 hospitalizations for the specified infections identified during 2010–2018. Of these hospitalizations, 2830 (6.3%) were determined to be IDRIs. The proportion of hospitalizations occurring in suspected users of injection drugs increased nearly 9-fold, from 1.5% of hospitalizations in 2010 to 13.1% in 2018. The rate of IDRIs was >11-fold greater in 2018 (15.1 per 100 000 persons) than in 2010 (1.2 per 100 000), while the rate of non–drug-related infections increased 1.3-fold.

IDRI rates also increased over time when the *ICD-9-CM* and *ICD-10-CM* periods were examined individually. In the last 13 quarters of the *ICD-9-CM* period, the estimated annual rate of IDRI hospitalizations increased from 2.1 per 100 000 persons in 2012 to 5.1 per 100 000 in January–September 2015, a relative

rate of 2.4 (Figure 1). In the 13 quarters since the *ICD-10-CM* transition, the estimated annual rate of IDRI hospitalizations increased from 9.8 per 100 000 persons in 2015 to 15.1 per 100 000 persons in 2018, a relative rate of 1.6.

Changes in disease-specific hospitalization rates across the *ICD-9-CM* to *ICD-10-CM* transition were not consistent between IDRIs and non–drug-related infections. There were substantial increases of 425% and 133%, respectively, in the number of hospitalizations for both drug-related and non–drug-related CNS/spine infections between quarters 3 and 4 of 2015, when *ICD-10-CM* was implemented. In contrast, the number of hospitalizations for IE increased by 103% for drug-related infections but by only 9% for non–drug-related infections. Over the same time period, the number of cases of osteomyelitis increased by 24% for IDRIs but decreased by 32% for non–drug-related infections.

#### Characteristics of Patients and Hospital Visits by Drug Use Status

Twenty percent of hospitalizations for IDRIs resulted in discharge against medical advice (DAMA), compared with only 3% of hospitalizations for non–drug-related infections. Hospitalizations for IDRIs had a longer hospital stays (median, 8 vs 6 days; $P < .01$) and higher hospital charges (median, $41 629 vs $36 856; $P < .01$) than non–drug-related hospitalizations. Total charges for IDRIs during the study period were $182 794 948. Patients hospitalized for IDRIs were younger (median age, 35 vs 46 years), more commonly female (48% vs 34%), primarily non-Hispanic white (81% vs 56%), and more frequently uninsured (38% vs 15%) than those hospitalized for non–drug-related infections (Table 1).

The majority of hospitalizations for IDRIs were in patients who had codes related to opioids (88%); 7% had only amphetamines codes, and 5% were coded for both opioids and amphetamines. Compared with those coded only for opioids, persons coded for amphetamines (alone or in combination) were more frequently white (88% vs 80%) and uninsured (51% vs 37%), more commonly had IE (46% vs 35%), and less commonly had osteomyelitis (14% vs 24%). A high proportion (35%) of hospitalizations among patients suspected of using both opioids and amphetamines resulted in DAMA.

#### Disease-Specific Characteristics of Drug-Related Infections

The most prevalent type of IDRI was IE (43%), followed by osteomyelitis (27%), CNS/spine infections (15%), and septic arthritis (15%) (Table 2). Demographic characteristics of persons hospitalized for IDRIs varied by infection type. The median age for each infection type ranged from 31 years for IE to 41 years for osteomyelitis. Among IDRIs, the median charges per hospitalization ranged from $34 216 for patients osteomyelitis to $54 821 for those with CNS/spine infections.

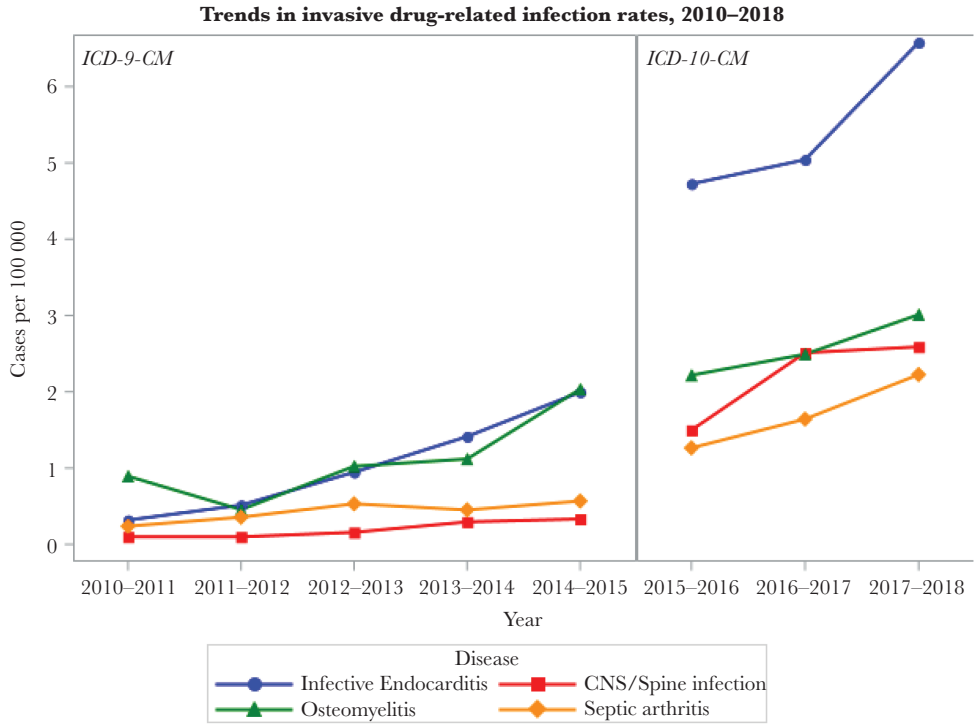


**Figure 1.** Trends in hospitalizations for invasive infections in persons with use of opioids or amphetamines, North Carolina, 2010–2018. Data points were plotted at the beginning of the fourth quarter for each year and reflect the number of cases in the previous 12 months (ie, quarter 4 of the previous year through quarter 3 of the current year). *The International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) transition occurred in quarter 3 of 2015 [19]. Abbreviations: CNS, central nervous system; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; IE, infective endocarditis.

**Table 1. Demographic Characteristics of Patients With Infections Related or Unrelated to the Use of Opioids or Amphetamines, North Carolina, 2010–2018**

| Characteristic | Patients, No. (%)[a] | | |
|---|---|---|---|
| | Total (n = 44 851 [100%]) | IDRIs (n = 2830 [6.3%]) | Non–Drug Related Infections (n = 42 021 [93.7%]) |
| Age, median (IQR), y | 45 (36-15) | 35 (28-44) | 46 (37-51) |
| Sex | | | |
| Male | 29 115 (65) | 1466 (52) | 27 649 (66) |
| Female | 15 736 (35) | 1364 (48) | 14 372 (34) |
| Race/ethnicity | | | |
| Non-Hispanic white | 25 711 (57) | 2281 (81) | 23 430 (56) |
| Non-Hispanic black | 12 623 (29) | 245 (9) | 12 623 (30) |
| Hispanic | 1712 (4) | 51 (2) | 1661 (4) |
| Other/unknown | 4560 (10) | 253 (9) | 4307 (10) |
| Insurance status | | | |
| Medicare | 13 228 (29) | 431 (15) | 12 797 (30) |
| Medicaid | 12 255 (27) | 920 (33) | 11 335 (27) |
| Private | 10 746 (24) | 340 (12) | 10 406 (25) |
| Uninsured | 7487 (16) | 1068 (38) | 6419 (15) |
| Other/unknown | 1135 (3) | 71 (3) | 1064 (3) |
| Disposition | | | |
| Discharge to home | 31 599 (70) | 1550 (55) | 30 049 (72) |
| Transfer | 10 652 (24) | 690 (24) | 9962 (24) |
| Death | 778 (2) | 19 (1) | 759 (2) |
| DAMA | 1634 (4) | 555 (20) | 1079 (3) |
| Other/unknown | 288 (<1) | 16 (1) | 172 (<1) |
| LOS, median (IQR), d | 6 (4-12) | 8 (4-19) | 6 (4-11) |
| Cost, median (IQR), $ | 37 101 (21 876-68 609) | 41 629 (22 353-83 334) | 36 856 (21 850-67 624) |

Abbreviations: DAMA, discharge against medical advice; IDRIs injection drug-related infections; IQR, interquartile range; LOS, length of stay.

[a]Data represent no. (%) of patients unless otherwise specified. Percentages may not add up to 100% owing to rounding.

**Table 2. Disease-Specific Outcomes in Patients With Diagnostic Codes for Both Invasive Infections and Use of Opioids or Amphetamines, North Carolina, 2010–2018[a]**

| Outcome | Patients, No. (%)[a] | | | |
|---|---|---|---|---|
| | IE (n = 1217 [43%]) | Spinal Infection (n = 437 [15%]) | Nonspinal Osteomyelitis (n = 758 [27%]) | Septic Arthritis (n = 418 [15%]) |
| Age, median (IQR), y | 31 (26-38) | 39 (32-47) | 41 (33-48) | 36 (29-45) |
| Cost, median (IQR). $ | 46 305 (21 398-94 128) | 54 821 (27 594-113 757) | 34 216 (20 157-61 845) | 38 694 (23 812-68 916) |
| LOS, median (IQR), d | 10 (4-26) | 11 (5-29) | 6 (4-12) | 6 (4-15) |
| Insurance status | | | | |
| Medicare | 81 (7) | 62 (14) | 225 (30) | 63 (15) |
| Medicaid | 405 (33) | 145 (33) | 266 (35) | 104 (25) |
| Private | 135 (11) | 55 (13) | 95 (13) | 55 (13) |
| Uninsured | 573 (47) | 160 (37) | 151 (20) | 184 (44) |
| Other/unknown | 23 (2) | 15 (3) | 21 (3) | 12 (3) |
| Disposition | | | | |
| Discharge to home | 515 (42) | 242 (55) | 526 (69) | 267 (64) |
| Transfer | 332 (28) | 126 (29) | 162 (21) | 70 (17) |
| Death | 17 (1) | 2 (<1) | 0 (0) | 0 (0) |
| DAMA | 346 (28) | 64 (15) | 67 (9) | 78 (19) |
| Other/unknown | 7 (1) | 3 (1) | 3 (<1) | 3 (1) |

Abbreviations: DAMA, discharge against medical advice; IE, infective endocarditis; IQR, interquartile range; LOS, length of stay.

[a]Data represent no. (%) of patients unless otherwise specified. Percentages may not add up to 100% owing to rounding.

The median length of stay ranged from 6 days for osteomyelitis and septic arthritis to 11 days for CNS/spine infections. The percentage of hospitalizations that resulted in DAMA ranged from 9% in osteomyelitis to 28% in IE, but for all infection types, the proportion of hospitalizations ending in DAMA was greater for IDRIs than for non–drug-related

infections, which ranged from 1.8% for osteomyelitis to 6.1% for IE.

## DISCUSSION

In this population-based analysis, we found that hospitalizations for certain invasive infections among suspected users of injection drugs have increased since 2010 and are continuing on an upward trajectory. The rate of IDRIs increased 11-fold between 2010 and 2018, and the proportion of these infections occurring in suspected users of injection drugs grew by >9-fold. Patients hospitalized for IDRIs are frequently uninsured, compared with those hospitalized for non–drug-related invasive infections, and IDRI hospitalizations commonly result in DAMA. We also found that just 43% of IDRI hospitalizations were for IE. Although IE is generally recognized as the hallmark invasive infection associated with injection drug use, focusing exclusively on IE will markedly underestimate the full spectrum of severe infections.

The increasing incidence of IDRIs is a call to action to ensure that health systems and clinicians have practices in place to screen patients for substance use disorders, provide care and treatment for these disorders, and link patients to harm reduction services, such as syringe exchange programs and overdose prevention. Syringe exchange programs have proliferated in North Carolina in recent years since their legalization in 2016, with 1 587 112 syringes distributed to 5352 participants during the 2017–2018 reporting period [20]. Syringe exchange programs also referred 1014 persons to substance use disorder and mental health services during that same period. Studies from other settings have suggested such programs may be beneficial in mitigating HIV transmission [21]. In addition to improving the safety of injection practices, studies have shown that helping PWID curtail injection frequency may mitigate bacterial infections [22]. Ensuring the availability of medications to treat OUD, as well as the overdose reversal agent naloxone, are also important elements in addressing opioid misuse and drug-related harms. Comparable pharmacotherapeutic options do not yet exist to address methamphetamine use disorder.

In one study, half of PWID who used either heroin or methamphetamine used both, indicating that the true prevalence of polysubstance use may well be higher than captured in our population by discharge codes, and expansion of OUD treatment alone may be inadequate to meet patient needs [15]. Improving inpatient access to OUD treatment is a key component of improving patient outcomes after IDRI [23]. It is conceivable that improved access to OUD treatment in the community setting may stem injection drug use and thus limit new injection-related infections.

The high proportion of IDRI hospitalizations resulting in DAMA presents a major opportunity for further investigation and intervention. The proportion of IDRI hospitalizations resulting in DAMA was large for all infection types, and the rate of DAMA in people who used both opioids and amphetamines was as high as 35%. Studies have demonstrated that substance misuse is a strong predictor of DAMA [24, 25], suggesting that the unique needs of patients hospitalized with substance use disorders are not being met. Our study also noted a greater proportion of women among patients with IDRIs than among those with non–drug-related infections, a trend that has been observed in other studies examining IE associated with injection drug use [4, 26]. Further research is needed to explore the relationship between sex and IDRIs.

The overall trend in IDRI hospitalization rates that we observed is comparable to that seen in a prior study of drug-related IE in North Carolina in 2007–2017 [5], which included the transition from *ICD-9-CM* to *ICD-10-CM*. The present study examined the *ICD-9-CM* and *ICD-10-CM* periods separately. The rates for several diseases showed large changes concurrent with the *ICD-10-CM* transition, resulting in a substantial increase in the rate of IDRIs after 1 October 2015. Therefore, although increases occurred in both the *ICD-9-CM* and *ICD-10-CM* periods, it is likely that the specific coding scheme affected the rate at which these diseases were reported in the discharge data. Because the true incidence of IDRIs is unknown, we are unable to conclude whether infections during the *ICD-9-CM* period represent an underestimate, or if rates observed during the *ICD-10-CM* period are an overestimate. Our results should be cautiously interpreted as capturing 2 distinct periods, during each of which the overall incidence of IDRIs increased.

To our knowledge, there is no validated approach for using *ICD-9-CM* or *ICD-10-CM* codes to reliably identify IDRIs in the United States. One study examined approaches to identifying drug-related IE cases using *ICD-10* codes in Canada [12]. Although our study drew, in part, on the methods of the Canadian approach—specifically, we restricted patient age to <55 years—we do not believe that there is sufficient experience to determine whether the performance characteristics of their algorithm are generalizable to North Carolina hospitals statewide. The previously studied approaches drew on ICD-10 codes from another country and validated them in a small cohort of Canadian hospitals.

In attempts to identify injection drug use in US databases using *ICD-9-CM* or *ICD-10-CM* codes, previous studies in the United States have focused on opioids alone [8] or used combinations of illicit or potentially injectable drugs, or hepatitis C infection in a younger person, as surrogates for injection drug use [4–6, 9]. In our study, we opted to focus on opioids and amphetamines alone. Persons may inject other substances or may be best identified by other means, such as viral hepatitis or HIV diagnoses [12]. As such, there is a need to develop validated approaches that can provide accurate population-based estimates to help public health officials and healthcare systems mobilize the necessary resources to address the needs of patients with or at risk for IDRIs.

Our study examined only certain IDRIs; the full burden of drug-related infections may be significantly larger than could be captured in the scope of our study. Other IDRIs may include severe skin and soft-tissue infections (SSTIs), bacteremia, and other forms of sepsis. Owing to concerns about the performance of ICD codes in evaluating these infections, we elected not to include them. However, these other infections are likely to be more prevalent among PWID than those included in this analysis. In a recent investigation of 111 persons in Western New York treated for injection drug–related infections in a hospital or emergency department, 74% were treated for an SSTI [27]. Although not all SSTIs represent invasive infections, this finding nonetheless suggests that our study may have only captured a subset of drug-related infections occurring in North Carolina; the true burden of drug-related infections might be much greater. Generating a larger, population-based assessment of the incidence and outcomes associated with SSTIs and other drug-related infections is needed to continue to elucidate the infectious diseases toll of injection drug use and understand the scale of resources required to address the needs of patients who use drugs.

This study is subject to several limitations. We used administrative data, rather than medical records or patient report, to determine drug use and infection diagnoses, which introduced the potential for misclassification. Because there is no billing code specific for injection drug use, we used as a proxy diagnostic codes reflecting use, dependence on, or misuse of opioids and/or stimulants. Although these drugs are frequently injected, there is no way to identify solely those users who inject drugs. In addition, our analysis may have included persons using such drugs appropriately as prescribed, rather than misusing them. Consequently, our analysis likely included some users of opioids or amphetamines who do not inject drugs and who may have been infected through other means.

Furthermore, because other drugs can be injected, some of the hospitalizations that were classified as non–drug related might have occurred in persons who injected drugs other than opioids or amphetamines. These issues likely resulted in some degree of misclassification of exposure, which would bias estimates of effect towards the null. In addition, the use of administrative data cannot establish causality or temporality. The presence of drug use codes could reflect past drug use not associated with the current infection.

We did not use individually identifiable data, and therefore we were unable to assess whether hospitalizations represented recurrent or relapsed infections, compared with new, incident infections. DAMA, which was far more common in suspected users of injection drugs than among persons with non–drug-related infections, may conceivably predispose patients to readmission owing to incomplete treatment of the infection, thereby resulting in an overestimate of true incident infections in suspected users of injection drugs. Despite the limitations inherent in administrative data, we believe that they remain a valuable tool for public health research, particularly for sensitive topics such as substance misuse, for which study participation may be low.

In summary, the rate of hospitalizations for certain invasive among people suspected of using injection drugs has increased significantly in the last several years and demonstrates an ongoing upward trajectory. Despite limitations in interpretation across the *ICD-9-CM* and *ICD-10-CM* periods, the current findings nonetheless confirm the ongoing increase in IDRIs. They do not just underscore the urgent need for novel interventions to address substance use disorders in patients with IDRIs, including implementation of existing interventions in the hospital setting, but they also highlight the role for using administrative data sources to monitor the dynamic public health impacts of injection drug use.

## Notes

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