The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

National Public Health Burden Estimates of Endocarditis and Skin and Soft-Tissue Infections Related to Injection Drug Use: A Review

Isaac See,[1] Runa H. Gokhale,[1] Andrew Geller,[1] Maribeth Lovegrove,[1] Asher Schranz,[2] Aaron Fleischauer,[3,4] Natalie McCarthy,[1] James Baggs,[1] and Anthony Fiore[1]

[1]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [2]Institute for Global Health and Infectious Diseases, University of North Carolina, Chapel Hill, North Carolina, USA, [3]North Carolina Department of Health, Raleigh, North Carolina, USA, and [4]Career Epidemiology Field Officer, Centers for Disease Control and Prevention, Atlanta, Georgia, UA,

Background. Despite concerns about the burden of the bacterial and fungal infection syndromes related to injection drug use (IDU), robust estimates of the public health burden of these conditions are lacking. The current article reviews and compares data sources and national burden estimates for infective endocarditis (IE) and skin and soft-tissue infections related to IDU in the United States.

Methods. A literature review was conducted for estimates of skin and soft-tissue infection and endocarditis disease burden with related IDU or substance use disorder terms since 2011. A range of the burden is presented, based on different methods of obtaining national projections from available data sources or published data.

Results. Estimates using available data suggest the number of hospital admissions for IE related to IDU ranged from 2900 admissions in 2013 to more than 20 000 in 2017. The only source of data available to estimate the annual number of hospitalizations and emergency department visits for skin and soft-tissue infections related to IDU yielded a crude estimate of 98 000 such visits. Including people who are not hospitalized, a crude calculation suggests that 155 000–540 000 skin infections related to IDU occur annually.

Discussion. These estimates carry significant limitations. However, regardless of the source or method, the burden of disease appears substantial, with estimates of thousands of episodes of IE among persons with IDU and at least 100 000 persons who inject drugs (PWID) with skin and soft-tissue infections annually in the United States. Given the importance of these types of infections, more robust and reliable estimates are needed to better quantitate the occurrence and understand the impact of interventions.

The United States is in the midst of a multifaceted drug crisis that has been well described to have profoundly increased rates of drug overdose deaths, as well as infections from hepatitis C and HIV that have been historically linked to injection drug use (IDU) [1–9]. In addition to infections from bloodborne viral pathogens transmitted through IDU, bacterial and fungal infection syndromes, such as infective endocarditis (IE), have also presented concern. The proportion of invasive infections from organisms such as *Candida* spp. and methicillin-resistant *Staphylococcus aureus* that occurs among PWID has been increasing in recent years [10, 11], and public health investigations in some locales have been conducted in response to these concerns [12–14]. Hospitalizations for some of these infection syndromes cost the healthcare system, particularly the Medicaid program, millions of dollars [15]. However, the actual number of such infections is unknown [16].

The current article will review literature and public health surveillance data sources that can describe the burden of bacterial and fungal infections related to IDU in the United States. In addition, we will provide commentary on the limitations of data sources and published estimates, give a range of potential national estimates based on available data, and discuss possible ways to improve confidence in burden estimates. The review will focus on skin and soft-tissue infections and IE, which account for the majority of severe bacterial and fungal infection syndromes related to IDU [14]. IE has been reported to be the second most common type of syndrome related to IDU, and because IE requires prolonged antibiotic treatment and sometimes surgical valve repair or replacement it has been the primary focus of attention for the clinical community [14, 16]. We also review reported mortality rates for IE related to IDU.

METHODS

The ideal data source for estimating national burden of disease would identify infection syndromes of interest using validated

Correspondence: Isaac See, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS H16-3, Atlanta, GA 30329 (isee@cdc.gov).

The Journal of Infectious Diseases® 2020;222(S5):S429–36

DOI: 10.1093/infdis/jiaa149

criteria and delineate specifically which occur in PWID, and would either be designed to create national burden estimates or have a validated method for producing such estimates. Such a data source does not currently exist, and characteristics of existing data sources available to public health are described below and in Table 1.

Administrative Data

Administrative data sets are the most widely accessible source of data for infection syndromes among hospitalized patients and include the National Inpatient Sample (NIS) and state-based hospital discharge databases. Diagnoses and procedures in these data sources are based on *International Classification of Disease*, *Clinical Modification* (*ICD-CM*), codes. In addition, commercial vendors, such as IBM Truven Health Analytics, Premier, and Cerner, also distribute data sets containing administrative data in addition to charges and extracts from electronic health records (eg, microbiology data from laboratories). Administrative data sets with outpatient claims include the Nationwide Emergency Department Sample, Medicaid data, and those distributed by commercial vendors.

The use of administrative data for determining the burden of bacterial and fungal infection syndromes related to IDU has major limitations. First, there is no *ICD-9CM* or *ICD-10-CM* code for IDU. Algorithms to validate surrogate codes have been described in other countries but not in the United States, where drivers for coding and even in some instances codes themselves may be different [17, 18].

Second, there is no standard approach to defining *ICD-9-CM* or *ICD-10-CM* codes for skin and soft-tissue infections. For example, it is unknown whether or not the optimal approach is to include secondary diagnosis codes when looking at hospital discharge data. Validation studies of *ICD-9-CM* codes for skin and soft-tissue infections in the United States have been limited to primary diagnosis codes for hospitalizations or outpatient visits [19, 20] and have not assessed the sensitivity of using primary diagnosis codes, or the positive predictive value of using both primary and secondary diagnosis codes. In contrast, a validation of *ICD-9-CM* codes for IE was conducted as part of an epidemiologic analysis, reporting sensitivity, specificity, and positive predictive value >90% when using a set of codes (421.0, 421.1, 421.9, 036.42, 098.84, 112.81, 115.04, 115.14, and 115.94) to identify confirmed or possible IE using modified Duke criteria as a reference standard (Toyoda et al [21]). However, validation efforts for corresponding *ICD-10-CM* codes have not been published; this is relevant because performance characteristics of administrative codes for other infections have varied over time [22, 23] and might not be the same as for *ICD-9-CM*.

Syndromic Surveillance Data

The National Syndromic Surveillance Program collects data daily from emergency departments (EDs) in the United States. Participating states obtain electronic data feeds of ED visits from the previous day. Standard data elements transmitted include *ICD-10-CM* codes and chief complaint text fields. Currently data are reported from approximately 65% of EDs nationally. A major advantage is timeliness; in addition, the information from the chief complaint text fields can provide additional specificity regarding the presence of IDU; however, the sensitivity and specificity of using such data to identify bacterial and fungal infections and to identify IDU is not known. In addition, it is unclear whether ED data can accurately identify infection syndromes that most typically are diagnosed during a hospitalization (ie, after the end of an ED visit), such as IE.

Emerging infections Program

The Emerging Infections Program (EIP) is a cooperative agreement between the Center for Disease Control and Prevention and a network of state health departments and their collaborating institutions, conducts active, population- and laboratory-based surveillance in selected counties within participating states, and has been described in detail in other articles [24].

Table 1. US Public Health Data Sources for Bacterial and Fungal Infection Syndromes Related to Injection Drug Use

Data Source	Description	Designed for National Estimates?	Primary Means to Identify Infection Syndromes	Specifically Identifies PWID
Administrative, eg, National Inpatient Sample	Data collected through billing records from primarily hospital and ED visits	Yes for some databases	Via *ICD* codes	No
Emerging Infections Program	Laboratory-based surveillance for infection syndromes caused by selected organisms	No	Currently via microbiology results	Yes, through review of medical records
National Syndromic Surveillance Program	*ICD* codes and chief complaint text fields from EDs	No	Via *ICD* codes	Yes but sensitivity/specificity compared with complete medical record unknown
NEISS-CADES	Data abstracted from medical records to find clinician-defined adverse events attributed to medications	Yes	Record review	Yes

Abbreviations: ED, emergency department; *ICD, International Classification of Diseases*; NEISS-CADES, National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance; PWID, persons who inject drugs.

The EIP conducts surveillance for infections due to specific pathogens that are of particular concern to the health of PWID: invasive infections (ie, the organism is isolated from a normally sterile body site, such as blood or cerebrospinal fluid) caused by *S. aureus* or group A *Streptococcus*, and *Candida* spp. bloodstream infections [10–14]. Case finding for these infections occurs through queries for corresponding clinical microbiology results. In general, data collected through the EIP for these pathogens are obtained through medical record review by trained medical record abstractors. In this way, diagnoses of infectious diseases that are recorded in the medical record can be tracked, as can documentation of a patient history of IDU. However, pathogen-independent surveillance for infection syndromes related to IDU is not currently conducted within the EIP.

National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance

The National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project is an active public health surveillance system based on a nationally representative, size-stratified probability sample of hospitals with ≥6 beds and a 24-hour ED in the United States and its territories. As described elsewhere [25], trained NEISS-CADES data abstractors review clinical records of every ED visit to identify clinician-diagnosed adverse events attributed to medications. Beginning in 2016, this system data capture expanded to include adverse events due to medications used for any reason, including cases of acute injection-related complications or infections [26, 27]. However, because NEISS-CADES data are based on clinical assessments in the ED setting, specific pathogens are often not identified. Moreover, NEISS-CADES data likely underestimate the overall burden of IDU-related infections in EDs because ED clinicians may not identify infections that require extensive evaluation or testing to diagnose (eg, IE). In addition, ED visits attributed to illicit substances alone are not included. Strengths of NEISS-CADES includes national representativeness, identification of specific active ingredients and products, and attribution of infection to injection based on retrospective medical record review, rather than billing codes or chief complaints.

Approaches for Estimating Burden Based on Existing Data

We used 3 approaches for estimating national burden of infections related to IDU. We produced these estimates to illustrate the range of burden estimates generated from using different approaches and data sources rather than to produce definitive estimates. Our first approach involved using administrative data sources designed to produce, or validated for making, national projections.

For our second approach, we used internal data sources that provide information about the incidence of infections at a subnational level, and we projected what the burden would be if that incidence were representative of the United States. The principal advantage of this approach is that these data sources, which generally come from medical record review, provide more specific ascertainment of IDU. Incidence projections use US Census data (population denominators) as well as American Hospital Association data (hospital admission denominators). PWID sometimes attempt to self-treat mild skin infections and abscesses rather than access medical care, so reliance on healthcare utilization data underestimates the burden of skin infections [28].

In our third approach, we combined prevalence estimates of infections among a defined population of PWID with previously reported estimates of PWID population size [29]. The source literature describes these infections with various terms such as "drug use–associated"; in the current review, we will call such estimates "IDU-associated" infections. In addition, we reviewed mortality rates reported for IE related to IDU.

Literature Review

We conducted a literature search for articles published or available online before publication during 2011–2019 describing infections in the United States as of October 1, 2019. We limited our search to articles in which infections occurred in 2011 or later to correspond to the reported rises in illicit opioid-involved overdose death rates in the United States. A PubMed search was conducted for articles that had terms for infection types of interest as well as substance use terms. Infection terms included *endocarditis, abscess, cellulitis, skin infection, skin infections, soft-tissue infection,* and *soft-tissue infections*. Substance use was queried using the MeSH term *intravenous substance abuse* or the PubMed terms *injection drug use, intravenous drug use, PWID,* and *IVDU*. Articles useful for this summary either (1) provided the incidence or burden of disease ostensibly related to drug use in a specific institution or population area or (2) provided prevalence of a specific infection type within a population of PWID. Articles describing microbiologic findings in a cohort of patients with IE were also reviewed. Data on burden of disease or infection prevalence were not used if <20 infection events were reported in the article. Articles were also excluded if insufficient data were reported to determine the incidence.

RESULTS

Infective Endocarditis

Five articles in the published literature estimated the number of IDU-associated IE hospitalizations nationally. All of these defined IDU-associated IE as a hospitalization in which discharge codes included both an *ICD-9-CM* code for IE and IDU surrogate codes. These included codes for poisoning, withdrawal and drug dependence, history of hepatitis C, and homelessness (Table 2). Most studies did not report whether or not hospitalizations were restricted to those with a primary diagnosis code

Table 2. Summary of Studies Reporting Incidence of Injection Drug Use–Associated Infective Endocarditis Hospitalizations from Administrative Data Sets

Authors	Data Source	Method of Identifying IE	Injection Drug Use Surrogate	Other Restrictions	Year of Most Recent Results: No. of Hospitalizations That Year[a]; Inpatient Mortality Rate
Collier et al [30]	National Inpatient Sample	Primary *ICD-9-CM* diagnosis codes for IE (421.0, 421.1, 421.9)	Substance abuse/dependence/poisoning, drug counseling codes, codes indicating effects of drugs or withdrawal of newborns	None	2013: 2923; 5.2%
Deo et al [31]	National Inpatient Sample	IE codes, no other details specified	"Intravenous drug use codes" (not specified)	Only patients aged 16–65 y	2014: 3981 ± 119; 4.8%–4.9%
Ronan and Herzig [32]	National Inpatient Sample	Primary or secondary *ICD-9-CM* diagnosis codes for IE (036.42, 098.84, 112.81, 115.04, 115.14, 421.0, 421.1, 421.9)	Opioid abuse/dependence (including in remission) codes, heroin poisoning and adverse effects codes	None	2012: 3035; no endocarditis-specific mortality data provided
Wurcel et al [33]	National Inpatient Sample	Position not specified *ICD-9-CM* IE codes (421.0, 421.9, 424.90, 424.91, 424.99)	Dependence, use, poisoning or accidental death codes for cocaine, heroin, or amphetamine; drug addiction counseling, detoxification, and rehabilitation codes; or hepatitis C codes	Only patients aged 15–64 y	2013: 8530; no mortality data provided
Rudasil et al [34]	National Readmissions Database	Followed methods of Wurcel et al [33]	Followed methods of Wurcel et al [33]	Excluding congenital and rheumatic heart disease; only patients aged 16–64 y	2015: ~5000 (based on figure); 6.8%
Schranz et al [15]	North Carolina State Hospital discharge data	Primary or secondary codes for IE (*ICD-9-CM* codes 112.81, 421.0, 421.1, 421.9, 424.90, 424.91, 424.99; *ICD-10-CM* codes A32.82, B37.6, I33.0, I33.9, I38, I39)	Codes for dependence, poisoning, or withdrawal associated with opioid, other narcotics, benzodiazepine, barbiturate, cocaine, amphetamine, other stimulant, hallucinogen, sedative, anesthetic, or other analgesic; or history of hepatitis C if born after 1965	Only patients aged ≥18 y	2016–2017: 27 570; 8% inpatient (2007–2017)
Fleischauer et al [35]	North Carolina State Hospital discharge data	Primary or secondary codes for IE (*ICD-9-CM,* 421.0, 421.1, 421.9, 424.9; *ICD-10-CM,* I33.0, I33.9, I38, I39)	Opioid, cocaine, amphetamine/stimulant, hallucinogen dependence codes; drug withdrawal	Only patients aged ≥18 y	2015: 6672; no mortality data provided

Abbreviations: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification*; IE, infective endocarditis.

[a]Estimated number of hospitalizations or number projected from subnational data.

for IE. In addition, the surrogate codes used for IDU varied across almost all studies. The most recent estimate came from a study using the National Readmissions Database, estimating approximately 5000 hospitalizations for IDU-associated IE in 2015 [34]. The largest estimate was 8530 hospitalizations in 2013 using NIS [33], although another article estimated 2923 hospitalizations for IDU-associated IE in that same year from NIS [30].

Articles describing local burden or incidence included 2 reports from North Carolina. One showed a rate of IDU-associated IE hospitalizations of 10.95 per 100 000 North Carolina residents aged ≥18 years in 2016–2017, which would translate to 27 570 IE hospitalizations nationally [15]. In that article, a case was defined as IE with a code relating to illicit drug use, or a diagnosis of hepatitis C in a person born after 1965. Another article described incidence as 2.7 cases per 100 000 in 2015, which would project to 6672 cases nationally [35].

Finally, within the 7 EIP sites conducting surveillance for invasive *S. aureus* infections in 2017, an incidence of 1.87 *S. aureus* IDU-associated IE cases per 100 000 residents occurred. That would translate to 6000 cases nationally. Given that *S. aureus* is reported to cause anywhere from 52% to 62% of IDU-associated IE in case series [36, 37], the total estimate of IDU-associated IE cases using EIP data would range from 9700 to 11 500 in 2017. Inpatient mortality rates for IDU-associated IE cases ranged from 4.8% to 8% in the administrative databases.

Skin and Soft-Tissue Infections

No published literature provided a national estimate for skin and soft-tissue infections related to IDU. One article provided data on the number of skin and soft-tissue infections related to IDU that were identified through medical record review of ED visits and hospitalizations in 5 Western New York hospitals over 3 months during 2017 [14]. Based on the number of admissions at these 5 hospitals, the incidence derived from that article would project to 98 000 visits to hospitals nationally for skin and soft-tissue infections related to IDU during 2017. Note that these data are derived from an urgent public health investigation of bacterial and fungal infection syndromes related to IDU and therefore might not be representative of the United States as a whole.

Two articles provided data on the prevalence of skin and soft-tissue infections in the prior year among clients of a syringe service program. Notably, one article reported very different prevalences depending on local patterns of drug usage: in the city where primarily black tar heroin was the primary drug injected, 70% of clients had experienced a skin or soft-tissue infection in the prior year, versus 20% of those from a city where people primarily used powdered heroin [38]. The other article reported a prevalence of 29% [39]. Using the 2011 estimate of number of those who had injected drugs in the past year [29] nationally yielded an estimate of 155 000–540 000 PWID with a skin or soft-tissue infections in the past year.

DISCUSSION

The burden of endocarditis and skin and soft-tissue infections related to IDU in the United States varies widely in the published literature and differs based on the estimation method and data source. However, regardless of the source or method, the burden of disease appears substantial, with estimates of thousands of episodes of IE among persons with IDU and ≥100 000 PWID with skin and soft-tissue infections annually in the United States. Having more accurate and precise national estimates would better define the scope of the problem, measure the impact of efforts to prevent the occurrence of these infections, inform programs and resource estimates needed to address the problem, and provide a basis for comparison with local data to determine which areas are more heavily affected by the epidemic of IE and other infections related to IDU.

Several different strategies could improve our assessment of the burden of these infections. For example, a valid, standardized approach to analyzing data from administrative sources would be a productive first step. Published articles using the same data sets reported very different estimates, on both the national and state levels. The approach to identify IE varied across studies, and none used the set of *ICD-9-CM* codes previously validated [21]. Moreover, there was wide diversity in how the studies used *ICD-9-CM* codes to identify IDU, ranging including from only opioid-related diagnosis codes [32] to including codes for several illicit drugs and hepatitis C diagnosis as a criterion [33, 34]. In addition, 2 articles reporting using the same approach to *ICD-9-CM* codes reported markedly different burden estimates [33, 34] (Table 2). There is clearly an opportunity to improve use of validated codes to identify IDU. Alternatively, instituting a new *ICD-10-CM* code for IDU and incentivizing its use could greatly increase confidence in estimates of IDU-related disease burden gleaned from administrative data.

Another approach would be to update population estimates of the number of PWID and obtain more representative data describing the prevalence of infections among PWIDs. Given reports of outbreaks of infectious diseases in PWID and increases in acute hepatitis C infection incidence that have occurred in recent years [2–9], it is likely that the number of PWID is larger than in 2011, although the possibility that increases in infection incidence are primarily related to changes in injection practices cannot be ruled out. Data on prevalence of infections among PWID might be possible to obtain through ongoing surveys of PWID and syringe service programs.

A final option would be to develop a new approach specifically designed to meet this need. This would likely be based on reporting from clinical providers or otherwise using data from medical records on infection types and IDU in a multisite project that could be generalized to the United States.

A different paradigm is to focus on reliably tracking increases or decreases in the incidence of specific subsets of infections or

outcomes rather than on pinpointing the overall number of infections. For example, a North Carolina study included in this review focused on hospitalizations where valve surgery was performed for IE, because such operations are likely to be billed and hence could be a consistent surrogate for IE [15]. Although less sensitive, such studies of surgically treated infections might represent a lower bound for estimates of the burden.

The inpatient mortality rates seen in administrative data were surprisingly low, especially when compared with findings of a study looking at the IE mortality rate overall (90-day mortality rate, 24%) [21]. It is unclear to what extent this may be because of the relatively high rate of patients leaving the hospital against medical advice or because of the generally younger age of PWID presenting with IE compared with others hospitalized with IE.

The estimates presented here are primarily intended to illustrate possible ways that burden estimates could be obtained and the wide degree of variation that could result from using different data sources. We also limited our search to published literature that has undergone peer or editorial review. Additional data might be available in reports that were not peer reviewed, or in conference abstracts. In addition, the estimates of population size of people who had injected drugs during the past year and populations from which prevalence of infections are derived might not be comparable.

The data we have reviewed illustrate that bacterial and fungal infection syndromes resulting from IDU, such as skin and soft-tissue infections and endocarditis, are a major public health problem. Preventing IDU use, treating substance use disorder (such as medication-assisted treatment for opioid use disorder), and encouraging safer injection practices for those who continue to inject are key strategies in the fight against infectious complications of the ongoing opioid crisis [10, 14]. Better estimates of the burden of infections would provide critical information needed to allocate resources and effectively mobilize public health responses and clinical interventions.

Notes

Acknowledgments. We thank Emerging Infections Program surveillance staff at sites for their work with data collection.

***Disclaimer*:** The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names is for identification only and does not imply endorsement by the Public Health Service or by the US Department of Health and Human Services.

Financial support. Dr Schranz was supposed by NIAID (grant 5T32AI070114-12).

Supplement sponsorship. This supplement is sponsored by the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. NCHS data brief no. 329. Hyattsville, MD: National Center for Health Statistics, **2018**.
2. Zibbell JE, Asher AK, Patel RC, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. Am J Public Health **2018**; 108:175–81.
3. Liang TJ, Ward JW. Hepatitis C in injection-drug users—a hidden danger of the opioid epidemic. N Engl J Med **2018**; 378:1169–71.
4. Peters PJ, Pontones P, Hoover KW, et al; Indiana HIV Outbreak Investigation Team. HIV infection linked to injection use of oxymorphone in Indiana, 2014-2015. N Engl J Med **2016**; 375:229–39.
5. Golden MR, Lechtenberg R, Glick SN, et al. Outbreak of human immunodeficiency virus infection among heterosexual persons who are living homeless and inject drugs—Seattle, Washington, 2018. MMWR Morb Mortal Wkly Rep **2019**; 68:344–9.
6. The Commonwealth of Massachusetts, Department of Public Health, Bureau of Infectious Disease and Laboratory Sciences. Statewide outbreak of HIV infection in persons who inject drugs. 5 February **2019**. https://cfar.globalhealth.harvard.edu/files/cfar/files/statewide_advisory_hiv_in_pwid_2_5_19_0.pdf. Accessed 22 August 2019.
7. Oregon Health Authority. HIV infection among people who use drugs. 20 June **2019**. https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/DISEASESURVEILLANCEDATA/HIVDATA/Pages/HIV_Cluster.aspx. Accessed 22 August 2019.
8. West Virginia Department of Health and Human Resources, Bureau for Public Health. Health advisory #155: increase in new HIV infections among persons who inject drugs. 22 March **2019**. https://oeps.wv.gov/healthalerts/documents/wv/WVHAN_155.pdf. Accessed 22 August 2019.
9. Cincinnati Enquirer. CDC called in to investigate HIV surges in the Cincinnati region. 24 October **2018**. https://www.cincinnati.com/story/news/2018/10/24/ohio-kentucky-ask-cdc-help-hiv-cases-linked-injected-drugs-rise-cincinnati/1684956002/. Accessed 22 August 2019.
10. Jackson KA, Bohm MK, Brooks JT, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections among persons who inject drugs—six sites, 2005–2016. MMWR Morb Mortal Wkly Rep **2018**; 67:625–8.
11. Poowanawittayakom N, Dutta A, Stock S, Touray S, Ellison RT, Levitz SM. Reemergence of intravenous drug use as risk factor for candidemia, Massachusetts, USA. Emerg Infect Dis **2018**; 24:631–637.
12. Valenciano SJ, McMullen C, Torres S, Smelser C, Matanock A, Van Beneden C. Notes from the field:

identifying risk behaviors for invasive group a streptococcus infections among persons who inject drugs and persons experiencing homelessness—New Mexico, May 2018. MMWR Morb Mortal Wkly Rep **2019**; 68:205–6.
13. Barter DM, Johnston HL, Williams SR, Tsay SV, Vallabhaneni S, Bamberg WM. Candida bloodstream infections among persons who inject drugs—Denver metropolitan area, Colorado, 2017-2018. MMWR Morb Mortal Wkly Rep **2019**; 68:285–8.
14. Hartnett KP, Jackson KA, Felsen C, et al. Bacterial and fungal infections in persons who inject drugs—Western New York, 2017. MMWR Morb Mortal Wkly Rep **2019**; 68:583–6.
15. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. Ann Intern Med **2019**; 170:31–40.
16. Infectious Diseases Society of America, HIV Medicine Association, and Pediatric Infectious Disease Society. Infectious diseases and opioid use disorder: policy issues and recommendations. March **2018**. https://www.idsociety.org/globalassets/idsa/topics-of-interest/opioid/id-and-the-opioid-epidemic-policy-brief_3-19-2018-updated.pdf?_ga=2.193293550.21244946.1521734567-1708005240.1512422793. Accessed 22 August 2019.
17. Janjua NZ, Islam N, Kuo M, et al; BC Hepatitis Testers Cohort Team. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. Int J Drug Policy **2018**; 55:31–9.
18. Ball LJ, Sherazi A, Laczko D, et al. Validation of an algorithm to identify infective endocarditis in people who inject drugs. Med Care **2018**; 56:e70–5.
19. Levine PJ, Elman MR, Kullar R, et al. Use of electronic health record data to identify skin and soft tissue infections in primary care settings: a validation study. BMC Infect Dis **2013**; 13:171.
20. Wiese AD, Griffin MR, Stein CM, et al. Validation of discharge diagnosis codes to identify serious infections among middle age and older adults. BMJ Open **2018**; 8:e020857.
21. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York State, 1998–2018. JAMA **2017**; 317:1652–60.
22. Rhee C, Dantes R, Epstein L, et al; CDC Prevention Epicenter Program. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA **2017**; 318:1241–9.
23. Lindenauer PK, Lagu T, Shieh MS, Pekow PS, Rothberg MB. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003-2009. JAMA **2012**; 307:1405–13.
24. Pinner RW, Lynfield R, Hadler JL, et al. Cultivation of an adaptive domestic network for surveillance and evaluation of emerging infections. Emerg Infect Dis **2015**; 21:1499–509.
25. Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). Med Care **2007**; 45:S96–102.
26. Geller AI, Dowell D, Lovegrove MC, et al. U.S. emergency department visits resulting from nonmedical use of pharmaceuticals, 2016. Am J Prev Med **2019**; 56:639–47.
27. Lovegrove MC, Dowell D, Geller AI, et al. US emergency department visits for acute harms from prescription opioid use, 2016–2017. Am J Public Health **2019**; 109:784–791.
28. Harris RE, Richardson J, Frasso R, Anderson ED. Experiences with skin and soft tissue infections among people who inject drugs in Philadelphia: a qualitative study. Drug Alcohol Depend **2018**; 187:8–12.
29. Lansky A, Finlayson T, Johnson C, et al. Estimating the number of persons who inject drugs in the United States by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. PLoS One **2014**; 9:e97596.
30. Collier MG, Doshani M, Asher A. Using population based hospitalization data to monitor increases in conditions causing morbidity among persons who inject drugs. J Community Health **2018**; 43:598–603.
31. Deo SV, Raza S, Kalra A, et al. Admissions for infective endocarditis in intravenous drug users. J Am Coll Cardiol **2018**; 71:1596–7.
32. Ronan MV, Herzig SJ. Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002-12. Health Aff (Millwood) **2016**; 35:832–7.
33. Wurcel AG, Anderson JE, Chui KK, et al. Increasing infectious endocarditis admissions among young people who inject drugs. Open Forum Infect Dis **2016**; 3:ofw157.
34. Rudasil SE, Sanaiha Y, Mardock AL, et al. Clinical outcomes of infective endocarditis in injection drug users. J Am Coll Cardiol **2019**; 73:559–70.
35. Fleischauer AT, Ruhl L, Rhea S, Barnes E. Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug dependence—North Carolina, 2010–2015. MMWR Morb Mortal Wkly Rep **2017**; 66:569–73.
36. Hartman L, Barnes E, Bachmann L, Schafer K, Lovato J, Files DC. Opiate injection-associated infective endocarditis in the Southeastern United States. Am J Med Sci **2016**; 352:603–8.
37. Lorson WC, Heidel RE, Shorman MA. Microbial epidemiology of infectious endocarditis in the intravenous drug abuse population: a retrospective study. Infect Dis Ther **2019**; 8:113–8.

38. Summers PJ, Struve IA, Wilkes MS, Rees VW. Injection-site vein loss and soft tissue abscesses associated with black tar heroin injection: a cross-sectional study of two distinct populations in USA. Int J Drug Policy **2017**; 39:21–7.

39. Dahlman D, Håkansson A, Kral AH, Wenger L, Ball EL, Novak SP. Behavioral characteristics and injection practices associated with skin and soft tissue infections among people who inject drugs: a community-based observational study. Subst Abus **2017**; 38:105–12.