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Recurring Severe Injection-Related Infections in People Who Inject Drugs and the Need for Safe Injection Sites in Madrid, Spain

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Background. An estimated 58 749 people with opioid use disorder engaged in opioid agonist therapy (OAT) in 1132 centers in Spain during 2017. We aimed to calculate the incidence of severe injection-related infections in people who inject drugs (PWID) engaged in OAT in harm reduction settings without a safe consumption space.

Methods. A retrospective cohort study was performed in PWID engaged in OAT and in a mobile harm reduction unit to quantify admissions to a referral hospital for any severe injection-related infections between 1 January 2016 and 31 December 2019. A Cox proportional hazard regression analysis was used to assess factors associated with any severe injection-related infection.

Results. Two hundred thirty-seven PWID who engaged in OAT were included in the study. After a median follow-up of 5.5 months (interquartile range [IQR], 1.3–22.7 months), a total of 104 episodes of severe injection-related infections occurred among 56 individuals, and admission due to a second event occurred in 35.7% of this same group. The incidence density of any type of severe injection-related infection was 26.8 (95% confidence interval [CI], 20.2–34.8) episodes per 100 person-years, and the incidence density of complicated skin and soft tissue infections that required hospital admission was 20.4 (95% CI, 15.0–27.3) episodes per 100 person-years. Fifty-six (53.8%) of all the episodes were patient-directed discharge (PDD), and people who had 2 or more hospital admissions had a higher PDD frequency.

Conclusions. Severe injection-related infections remain highly prevalent among PWID cared for in a harm reduction setting without a safe consumption space. PDD was more frequent among higher-risk individuals who presented 2 or more hospital readmissions.

Keywords. harm reduction; opioid agonist therapy; safe injection sites; severe injection-related infections; skin and soft tissue infections.

People who inject drugs (PWID) present at hospital emergency departments more often than the general population [1, 2]. Sharing of equipment causes a substantial disease burden in PWID, and bacterial and viral infections are largely responsible for the significant mortality and morbidity of PWID presenting to secondary care [3]. Among those with skin and soft tissue infections (SSTIs), delays in seeking health care, barriers to accessing care, and interruptions of treatment and the subsequent systemic progression may increase treatment costs and mortality in PWID.

PWID with injection-related infections also have a high frequency of patient-directed discharge (PDD) prior to treatment completion [4]. Additionally, a recent study revealed that those who did not receive oral antibiotics upon PDD had a 90-day readmission rate, which is more than double the rate of those with PDD who did have antibiotics prescribed [5]. Another recent study reported that opioid/stimulant use was associated with a higher risk of PDD and in-hospital mortality compared to opioid-only use [6].

Current data suggest that the number of hospital admissions for injecting-related bacterial infections is increasing in some regions [7, 8]. In this sense, safe consumption spaces (SCSs) have been proven to increase access to safer injection conditions, reduce drug use in public spaces, lower overdose rates, link users to health care, and reduce fear and stigmatization [9–12]. Also, SCSs have been shown to be a cost-effective public health strategy that reduces treatment costs associated with new human immunodeficiency virus (HIV) and hepatitis C virus

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(HCV) infections, wound care, and overdose-related services [13, 14].

Harm reduction services in Spain are provided in the different autonomous communities by a large network of public facilities, including social emergency centers, mobile units, pharmacies, and prisons, and are available throughout the country. In addition, drug use for personal consumption is not criminalized in Spain and 13 facilities for supervised drug consumption are available in the autonomous communities of Catalonia and the Basque Country [15]. However, Madrid withdrew a van that offered a drug consumption mobile space integrated into a mobile harm reduction unit in 2009, and currently this mobile unit works but does not provide safe injection facilities.

There are few real-world studies with standardized definitions and documented clinical events calculating the incidence and predictors for hospital admissions for severe bacterial infections among PWID without access to safe injection facilities [16]. Thus, our objective was to estimate the incidence of severe injection-related infections among PWID on opioid agonist therapy (OAT) attending a harm reduction setting in Spain. We hypothesized that hospitalizations for severe injection-related infections and frequency of noncomplicated SSTI in PWID on OAT would be high because this mobile harm reduction unit lacks safe spaces for drug consumption.

METHODS

Study Population

This retrospective, observational study is based on data from a follow-up cohort of people engaged in OAT who actively inject cocaine and heroin at least once daily and who were attending a mobile harm reduction unit located in the outskirts of Madrid between 1 January 2016 and 30 December 2019. This specific group of PWID is characterized by frequent relapses, few or shorter periods of abstinence, impaired physical conditions, poor access to standard medical care, and social exclusion and marginalization. Also, many often suffer from poor mental health and many of them have benzodiazepine dependence, suffer homelessness or unstable housing, and have frequent criminal records and behaviors. The prevalence of alcohol use disorder and use of drugs other than heroin and cocaine is very low.

Study Setting

This study was conducted in a mobile harm reduction unit, where a comprehensive, multidisciplinary team actively cared for and followed PWID with limited access to standard health care. This mobile unit is based on a low-threshold approach consisting of no entry requirements, no appointments, a nonjudgmental nature, flexibility, and on-site health care on demand. Several services were offered from 5 mobile units and included needle-exchange programs (NEPs) consisting of safe disposal for used needles, distributing naloxone, OAT, frequent testing for infectious diseases, dispensing treatment for chronic diseases, harm reduction education, and counseling and social support. All services and access to health care and medications are free of charge in this unit. Despite these provisions, due to the absence of mobile safe injection rooms, people inject alone, in pairs, or in groups in the street, cars, parks, tents or other accomodations, or in their houses. All patients on OAT in the unit, who had any hospital admission, were derived to a unique referral hospital for stay due to the geographic proximity and established protocols of conventional derivation in the health system in Madrid, and, therefore, this hospital serves the majority of the PWID in this setting.

In Madrid, people with opioid use disorder engaged in harm reduction services are dispensed liquid formulations of methadone hydrochloride; no other opiate substitutes are allowed in this setting in order to avoid illegal sale or misuse of opiate pills. However, when individuals are in inpatient hospital care, they all continue methadone treatment and doses are increased to overcome opiate cravings.

Methodology

Registered clinical data at the mobile harm reduction unit were reviewed to identify cases of severe bacterial injection-related infections that required hospital admission in people on OAT. Information related to demographic data, retention in OAT, and type of SSTI was collected from medical records, as well as local electronic data systems at the mobile harm reduction unit. The clinical information and outcomes of each event were collected from the electronic medical records at the hospital.

Healthcare personnel at the mobile harm reduction unit interviewed each participant with a short questionnaire when they commenced OAT and recorded their drug use and clinical data. Information regarding self-reported type of drug use and route of use was collected.

Case Definitions

Severe injection-related infections were defined as the presence of any of the following types of injection drug use (IDU)–related infections that required hospital admission and occurred during follow-up: complicated SSTI, bacterial isolates from blood (bacteremia), infective endocarditis (IE), or bacteremia with spread to other noncardiac locations.

Complicated SSTIs were defined as cases of skin abscesses or ulcers, extended cellulitis, myositis, or fasciitis at the injecting site. An episode of IE diagnosed at the hospital was defined as definite or possible according to the modified Duke criteria [17]. Bacteremia was defined as an isolation of any bacteria from the bloodstream obtained through blood culture systems in conjunction with fever and other symptoms of infection without conclusive evidence of disseminated infection to other organs. Bacteremia with spread to other noncardiac locations

was defined by an isolate of any bacteria considered clinical and microbiologic, related to IDU, with hematogenous spread to other noncardiac organs, such as discitis, arthritis, septic emboli, osteomyelitis, or spondylitis.

Hospital readmissions that occurred within 90 days from the discharge date were considered as relapses and not as new episodes of an SSTI. However, if the readmission occurred within the first 90 days from discharge and the microorganism in the blood culture was different from the previous episode, it was classified as a new event. All of the readmissions for the same individual following 90 days after hospital discharge were considered new episodes of SSTI and recorded as separate events.

Discharges from the hospital were classified as medical advice or PDD, and no data were available to describe how many days of antibiotics were missed by PDD. Because "against medical advice discharge" is not a patient-centered term and can further stigmatize PWID, we use "patient-directed discharge."

For this analysis, the identification of pathogens was verified by bloodstream culture results identified from at least 1 sterile site culture or obtained through a surgical procedure. The events of severe injection-related infections with the isolation of *Staphylococcus aureus* were classified as methicillin sensitive or methicillin resistant.

To calculate the length of stay in hospital, we considered the admission date for any severe injection-related infections and the discharge date for planned discharges or PDD, or the death date in those cases with a fatal outcome. If readmissions due to a relapse occurred, only the first hospital admission was considered.

Statistical Analysis

Categorical variables were compared using the Pearson χ^2 test or Fisher exact test. Continuous variables were compared using the Wilcoxon rank-sum test for independent variables. The Kaplan-Meier method was used to estimate the overall incidence density and incidence density of severe injection-related infections according to the types of infections. The time at risk for any severe injection-related infection was calculated from the date of initiation in OAT at the mobile harm reduction unit to the date of hospital admission for any severe injection-related infections or the date last in OAT. Participants remaining persistently free of severe injection-related infections were censored at the time of their last day in OAT prior to 30 December 2019.

Cox proportional hazard regression analysis was used to assess factors associated with time to event of severe injection-related infection. In the unadjusted analyses, potential predictors were determined according to previous reports and included age (per year), sex, nationality, mental illness, HIV infection, and HCV infection. All variables with $P < .05$ in the univariate analysis were included in the multivariate regression models, and retention within the model was based on their effect on other variables and the Akaike information criterion. Statistical significance was set at $P < .05$; P values were 2-sided.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Asociación Ideas for Health [18]. REDCap is a web-based software platform designed to support data capture for research studies. Analyses were performed using R software (R Foundation, Vienna, Austria).

Ethical Considerations

The Institutional Investigation and Ethics Review Board of Infanta Leonor University Hospital (CEI-ILUH), Madrid, Spain, approved the study (code ILUH R 038-20) on 23 April 2020. The database of low threshold mobile harm reduction unit (LTMHRU) was anonymized with an alphanumeric code that was unique for each individual so that the participant could not be identified and linked to the registered information. As a routine procedure, all people who use drugs who are admitted at the LTMHRU for OAT sign various documents, including informed consent for blood tests, forms for standard follow-up at the unit, and the use of clinical and sociodemographic data in an electronic clinical record tool.

RESULTS

A total of 479 PWID engaged on OAT were followed between 1 January 2016 and 30 December 2019 at the mobile harm reduction unit. Of those, 237 injected drugs at least once daily and were included in the study for calculating the incidence density of severe injection-related infections (Figure 1). All 237 individuals self-reported use of injected heroin and cocaine mixed in different nonquantified proportions (stimulant-only use was not reported). The demographic characteristics are outlined in Table 1.

Overall, we found that 160 (67.5%) individuals included in the study period presented in follow-up with at least 1 (median, 4.5 [range, 1–8]) noncomplicated SSTI that did not require

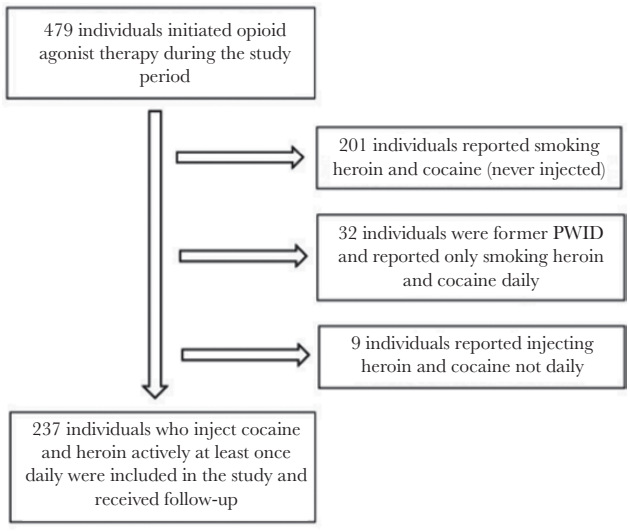

Figure 1. Study flowchart. Abbreviation: PWID, people who inject drugs.

Table 1. Baseline Characteristics of the Overall Cohort (N = 237)

Characteristic	No. (%)
Age, y, mean (SD)	41.8 (7.8)
Sex, male	186 (78.5)
Spanish nationality	137 (57.8)
Mental disorder	27 (11.4)
Dose of methadone, mg, mean (SD)	40 (25)
Time of drug consumption, y, mean (SD)	20 (10)
HIV status, positive	76 (32.3)
HCV antibodies, positive[a]	201 (85.5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

[a]No data were available for HCV RNA at the moment of initiation of the study.

hospitalization, and they were treated with oral antibiotics at the mobile harm reduction unit. Severe injection-related infections were registered in 56 individuals and accounted for 104 episodes. Therefore, the global incidence density for any severe injection-related infection was 26.8 (95% confidence interval, 20.2–34.8) episodes per 100 person-years. The global incidence density according to the type of severe injection-related infection is shown in Table 2. The Kaplan-Meier graphs of time to a severe injection-related infection and stratified by type of infection are shown in Figures 2 and 3.

The recurrence of a new event of severe injection-related infection occurred in 20 of the 56 (35.7%) individuals who had had a previous severe infection, 8 (44.6%) of them with at least 3 episodes and 4 individuals in the entire cohort with 4 or more episodes of severe injection-related infections during follow-up. Episodes of relapses with readmissions to hospital occurred in 11 (19.6%) individuals during follow-up.

All episodes of IE met the Duke criteria and were caused by gram-positive bacteria. The most frequent sites of SSTIs and the microorganisms responsible for severe injection-related infections are outlined in Table 3.

The median hospital length of stay was 6 days (interquartile range [IQR], 2.0–11.0 days); however, 56 (53.8%) of all episodes of severe injection-related infections were subject to PDD and did not complete antibiotic therapy. People who had 2 or more

Table 2. Incidence Density for Injection Drug Use–Related Infections Requiring Hospital Admission

Type of Infection	No. of Episodes	Incidence Density (95% CI), Episodes per 100 PY
Global severe injection-related infection	104	26.8 (20.2–34.8)
Bacteriemia	11	3.0 (1.3–6.0)
Infective endocarditis	8	2.3 (0.8–5.0)
Bacteremia plus any infection with a noncardiac location	21	7.7 (4.6–12.0)
Complicated SSTI	64	20.4 (15.0–27.3)

Abbreviations: CI, confidence interval; PY, person-years; SSTI, skin and soft tissue infection.

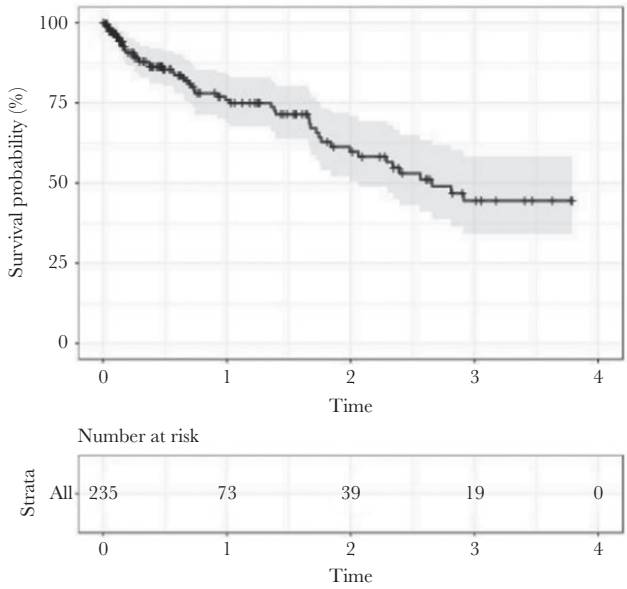

Figure 2. Kaplan-Meier curve estimating survival (free of any severe injection-related infections) of all patients in the cohort.

hospital admissions for IDU-related bacterial infections had more frequency of PDD ($P < .001$) in comparison to people who had a unique hospital admission.

In relation to sociodemographic variables, history of mental illness and HIV and HCV status were not associated with time to a new event of any severe injection-related infection in both the adjusted and unadjusted analysis.

During a median follow-up of 5.5 months (IQR, 1.3–22.7 months), there was only 1 in-hospital death caused by cardiac failure, in the context of an IE.; however, 5 additional deaths occurred during follow-up. Among these, 2 deaths were due to a drug overdose, 2 were traffic or domestic accidents, both in the context of drug use, and 1 person died from respiratory failure due to chronic lung disease.

DISCUSSION

Our findings demonstrate that complicated SSTIs and other severe injection-related infections remain highly prevalent and recurrent among people injecting stimulants/opiates who are actively cared for in a harm reduction setting. Our results show that despite engagement in OAT and NEPs, these incidence rates are even higher than those reported in previous studies of opiate-related, severe bacterial infections in this population [19–22] when harm reduction services did not offer SCSs.

Notably, at follow-up, around a quarter of the cohort required a hospital admission for any severe injection-related infection that occurred during their remaining time on OAT at the mobile harm reduction unit. Recurrences of new events of severe injection-related infection occurred in more than a third of individuals who had a first hospital admission related to any

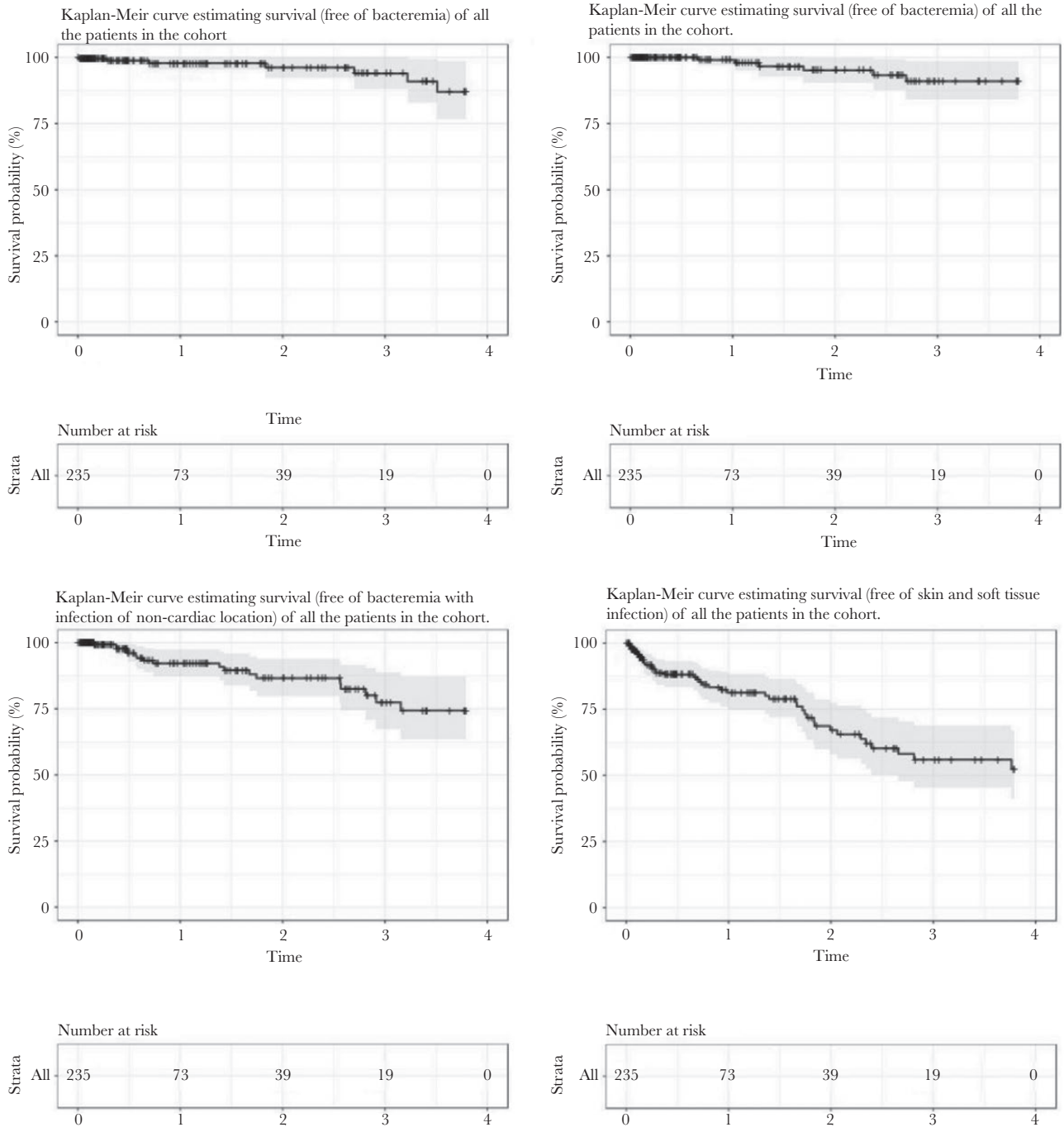

Figure 3. Kaplan-Meier curves stratified by type of severe injection-related infection of all patients in the cohort.

severe injection-related infection. Furthermore, a small subgroup of them had 3 or more recurring episodes of hospital admissions. The IDU-related infections may be explained by daily injecting and engaging in unsafe injecting practices [3, 23], which can contribute to new or repetitive episodes of severe injection-related infections in PWID [3, 24]. We also found that people who had 2 or more hospital admissions for IDU-related bacterial infections had a higher frequency of PDD, and we hypothesized that there is a subgroup of individuals who have higher-risk behaviors, greater severe dependence to stimulant drugs than opiate drugs, and intense craving symptoms, which could explain the recurring events of severe injection-related infections with hospital admissions. Unfortunately, we did not collect data on IDU practices to explore these findings in detail.

In addition, many studies demonstrate that SSTIs are one of the most common reasons for emergency department admissions and hospitalizations in PWID [3, 25], with *Staphylococcus aureus* as a leading cause of complicated SSTIs in PWID [26].

Table 3. Microbiologic Results

Characteristics	No. (%)
Site of SSTI	
Limbs	29 (45.3)
Arms	18 (28.1)
Groin	10 (15.6)
Hands	4 (6.3)
Neck	3 (4.7)
Microorganisms identified	
Staphylococcus aureus	32 (55.2)
MSSA[a]	30 (93.7)
MRSA[a]	2 (6.3)
β-hemolytic streptococci	24 (41.4)
Other *Staphylococcus* species	2 (3.4)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SSTI, skin and soft tissue infection.

[a]Percentages calculated of *Staphylococcus aureus*.

However, there are few current and non-cross-sectional studies that investigate the incidence for such severe bacterial infections among PWID [16]. Indeed, our data show that complicated SSTIs were the most frequent cause of admission for severe injection-related infections and occurred in a fifth of participants during their follow-up. Strikingly, these rates are higher compared to previous studies carried out among PWID who attended drug treatment services, outreach programs, and prison and probation services [19, 21, 22]. Also, we found that these rates are similar to a previously published report of the incidence of visits to the emergency department for SSTIs among PWID attending a SCS, which reported a incidence density of 23.8 per 100 person-years among females and 19.2 per 100 person-years among males [27]; However, this cohort reported all admissions to the emergency department and it remains unknown what proportion of them were admitted to hospital; therefore, we can assume that the rate of hospitalization is lower than that reported by the authors in people who are receiving care in a safe injection setting.

This study also highlights that more than two-thirds of the individuals who presented for follow-up had at least 1 noncomplicated SSTI diagnosed and treatment at the mobile harm reduction unit, which did not require hospitalization. Additionally, their recurrence was very frequent, with individuals having up to 8 episodes of noncomplicated SSTIs during their follow-up. These rates are about twice as high as those reported in previous studies examining SSTIs in NEPs [19, 28]. This variation is likely due to differing aspects, including demographic characteristics and higher-risk injecting behaviors, but we speculate that the absence of SCSs could partially explain these high rates. SCSs have been shown to increase timely access to care for injection-related injuries and infections and increase education with positive changes in injecting practices [9, 29], especially in PWID who are socially disadvantaged [30, 31]. However, no current reports calculating the incidence of SSTI and other injection-related infections, hospital admissions, and attending SCSs have been published in the literature. In the last years, a few studies, carried out in settings other than SCSs such as ours, show similar rates of noncomplicated SSTIs [3, 32]. However, these studies were based on self-reported SSTIs or conducted by qualitative interviews and not clinically documented, resulting in potential bias. Additionally, a study carried out in an SCS demonstrated that 27% of participants received SSTI care within the SCS, and the same study reported a 47% decrease in surgical service hospital admissions [31], but proportion of hospitalizations was not reported. In any case, these rates are lower than the data presented in this cohort (67.5%) who received SSTI care in the mobile unit, and therefore we can hypothesize regarding the positive effect of SCSs in the incidence of noncomplicated SSTI among PWID.

High frequencies of PDD and the use of illicit substances while hospitalized have been reported in previous studies [4, 33]. In our study, we found that at least half of hospital discharges due to severe injection-related infections were PDD. As a probable direct consequence, almost 20% of individuals who had a hospital admission presented with episodes of relapse with readmission to the hospital. These rates of PDD are higher than in other studies examining people who inject opiates/stimulants or opiates only [6]. This can be partially explained by the lack of highly effective medication for stimulant use disorder, which does exist for opioid use disorder, the limited expertise in management of stimulant use disorder by doctors in hospital, and by not using a low-threshold approach during hospitalization.

The strengths of our study include that we had a homogenous sample of PWID actively using drugs, that infections were clinically documented and registered during follow-up in OAT, and that we had complete data on hospitalizations and deaths. In comparison, clinical data resources for calculating the incidence of IDU-related bacterial infections among PWID in traditional, previous cohort studies include large-scale databases or regional or national registers using *International Classification of Diseases* codes or based on self-reports. The former has inherent limitations: there is no code specifically for IDU, no high validity, and no reliable samples that include former IDU and different injected substances, and this population is not exclusively cared for in harm reduction services.

This study is also subject to several limitations. First, this study had a short-term follow-up and it is possible that unsafe injection behaviors decreased over time; therefore, we could be overestimating the incidence of severe injection-related infections. Second, we defined relapses as happening within 90 days of a previous episode of severe injection-related infection (36), which could cause us to underestimate the number of new events of severe injection-related infections. Third, this is a retrospective study carried out using data from a unique hospital, and it is possible that some of the PWID attended other

hospitals in the region or in other regions of Spain. However, since all cases of severe injection-related infections found at our mobile harm reduction unit were derived from this referral hospital due to the geographic location of the health system in Madrid, the likelihood of cases of missed infections is small. Fourth, IDU data were initially collected by self-reporting at the moment of initiating OAT, meaning that it could be affected by self-reporting bias, although this information was confirmed through a medical record review and checking of NEPs. Finally, retention in OAT was not continuous in several cases due to voluntary discontinuations and subsequent restarts; this fact could be the result of bias when assessing the influence of methadone on the incidence of IDU-related infections.

In conclusion, the incidence of severe injection-related infections that occurred among PWID on OAT in a harm reduction setting without a safe injection site was very high and the recurrence of noncomplicated SSTIs was highly prevalent in this setting. Hospital readmissions for a new event of severe injection-related infection were frequent in a subgroup of higher-risk individuals who also presented more frequency of PDD.

Notes

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Data availability. Datasets used and analyzed during the current study may be available from the Subdireccion General de Adicciones (Madrid, Spain) Institutional Data Access for researchers who meet the criteria for confidential data.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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.

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