UNIVERSITY OF CALIFORNIA SAN DIEGO

Prevalence and Correlates of Methicillin-Resistant *Staphylococcus aureus* Colonization Among People Who Inject Drugs in San Diego and Tijuana

A Thesis submitted in partial satisfaction of the requirements
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by

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The Thesis of Erin Natale is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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Dedication

To my parents:

I was blessed to get the best of both worlds growing up with Dad in Medicine and Mom as a teacher. I had Dad to help me with everything STEM-related and Mom to make sure everything was done creatively and written properly. You've both inspired me my entire life to pursue my goals and I cannot thank you enough for all of your support.

To Jon and Laura:

You are both my greatest inspirations and best friends. I've been so lucky to have the best brother and sister I could ever ask for. Thank you for always being there to offer advice and to cheer me on.

To Michael:

I am so blessed to have you. You are my best friend and you inspire me daily to work harder and achieve my goals. Thank you for being the best support system and for keeping me company on FaceTime even from across the country while I worked. I love you.

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List of Abbreviations

PWID.....People Who Inject Drugs

MRSA..... Methicillin-resistant *Staphylococcus aureus*

SSTIs.....Skin and Soft Tissue Infections

CVD.....Chronic Venous Disorders

PEH..... People Experiencing Homelessness

AMR..... Antimicrobial Resistant

SIFs.....Supervised Injection Facilities

ABSTRACT OF THE THESIS

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by

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The opioid epidemic in the United States has contributed to a rise in drug injection-related disease transmission and infection. People who inject drugs (PWID) are at an increased risk of developing bacterial infections such as Methicillin-resistant *Staphylococcus aureus* (MRSA). This study examines the prevalence and correlates of MRSA infections and related abscesses amongst PWID in San Diego, California, and Tijuana, Mexico, to better inform harm reduction practices. This is a cross-sectional study conducted from June 2022 until November 2022 in which PWID (N = 187) participating in an ongoing cohort study completed interviewer-administered questionnaires and MRSA swabs nasally and at abscess sites (if present). Chi-Square Tests of Independence, Fisher's Exact Tests, and Wilcoxon Rank Sum Tests

were used to identify potential risk factors. Analysis revealed significant associations between injection practices, structural factors (e.g. homelessness), and prevalent MRSA infections. These positive associations between arm injections, homelessness, and MRSA infections emphasize the need for structural interventions that reduce the barriers PWID face when accessing resources that would improve their health outcomes.

Chapter I:

Introduction

Description of the Public Health Problem

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of infection and subsequent hospitalization amongst people who inject drugs (PWID). In its pathogenic form, it can result in painful skin and soft tissue infections, and sometimes bloodstream infections. It can also colonize nasal passageways, existing commensally. Various studies have been conducted worldwide to determine its prevalence within certain populations, as well as its association with possible risk factors. However, very little of this research has focused on marginalized populations like PWID. One study of PWID in Boston, Massachusetts found that MRSA nasal colonization was associated with sleeping in homeless shelters, using public showers, and sharing bedding[1]. Another study of adult patients with cellulitis in Honolulu, Hawai‘i showed that abscesses were significantly associated with a higher risk of MRSA infections[2]. The literature on variables of injection drug use that predispose an individual to a subsequent infection is limited. Therefore, further research is needed on correlates of MRSA infections to improve preventative medicine strategies within vulnerable populations of PWID.

Description of the Research Question

It is important to understand how lifestyle factors and injection-related behaviors can influence the risk of an outcome because they may potentially be modifiable through interventions. Thus, the overall aims of this study are to establish and characterize MRSA prevalence among PWID in San Diego, California and Tijuana, Baja California, Mexico, and determine what lifestyle and injection-related variables are associated with MRSA colonization. Previous studies from England and the United States have shown that PWID are more likely to

have a skin infection if they utilized their legs, groin, or hands as injection sites [3,4]. Therefore, we hypothesized that there will be a significant association between most commonly injecting in one of these three locations and being colonized with MRSA and/or having a recent abscess. Furthermore, as the circumstances in which someone lives can impact their risk of a MRSA infection [1], it is hypothesized that there will be a significant association between being colonized with MRSA and recent housing instability (i.e. living in transitional housing, staying in a shelter, or experiencing homelessness within the last 6 months).

A Brief History of Methicillin-resistant Staphylococcus aureus

Staphylococcus is a genus of Gram-positive bacteria that was first identified in the 1880s from the pus of a surgical abscess [5]. *Staphylococcus aureus* is a species of *Staphylococcus* that was differentiated from other species based on the golden color of its colonies [5]. Staph bacteria usually exist commensally on the surface of the skin or in the nasal cavity and do not cause any serious problems, but in some cases they can lead to a range of mild to serious infections [6].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a group of *S. aureus* bacteria that have acquired resistance to the antibiotic methicillin which was developed in 1959 to treat infections that had developed resistance to penicillin [7]. However, in 1961, research in the United Kingdom reported that certain isolates of *S. aureus* were no longer susceptible to methicillin [7]. Shortly after that, similar reports arose from other countries such as Japan and the United States [7]. MRSA has spread globally and is now a major problem in hospitals and vulnerable communities as many variants have developed over time. MRSA can cause severe skin and soft tissue infections (SSTIs) and, if left untreated, can lead to more serious, potentially fatal infections of the bloodstream (i.e., bacteremia) or heart valves (i.e., endocarditis). These infections often require hospitalization and have profound economic implications as the price for

treating invasive infections is costly and a strain on the United States healthcare system. For example, one U.S. study reported that the yearly economic burden of MRSA is $478 million to $2.2 billion on third-party payers and $1.4-$13.8 billion on society [8]. Given these public health implications, further research on its sources and modes of transmission within vulnerable, high-risk populations is needed.

Skin and Soft Tissue Infections: The Impact of Drug Injection Behaviors

SSTIs occur when microbes invade the skin and underlying soft tissues. Although the skin serves as the first line of defense against pathogenic microbes, penetration with an object like a needle breaks this protective barrier, allowing for possible infections to develop as a result. SSTIs are a major problem in the United States, with one recent article reporting that 14 million outpatient visits each year are due to SSTIs [9].

Due to the frequent puncture of the skin, PWID are at an increased risk of contracting an SSTI. One study from Australia found that global estimates of SSTIs among PWID is 31.7% [10]. Bacteria flourish on the skin due to inadequate hygiene, unsanitary environments, and contaminated drugs or drug injection preparation equipment. Following the introduction of foreign bodies into the skin and underlying tissues, there is often a delayed immune response due to weakened blood and lymphatic drainage that can make PWID more susceptible to infection [11]. Additionally, there is increasing evidence suggesting that the way in which certain drugs are manufactured or adulterated can encourage the survival of *Staphylococcus aureus* within the equipment used to inject (i.e. needles and syringes) [11]. For example, one study found that Hydromorphone-CR, an opioid pain reliever, extends the survival period of MRSA in injection paraphernalia (e.g., cookers and filters) [12]. These issues emphasize the need to characterize

potential risk factors for MRSA colonization among PWID in order to better inform harm reduction strategies.

MRSA and Injection Drug Use

MRSA can be transmitted through non-sterile needles, skin-to-skin contact, or shared surfaces such as public showers [13]. With its notable resistance to methicillin and presence amongst the regular skin flora, MRSA has become one of the leading causes of SSTIs in the United States. In fact, a 2021 article noted that 59% of SSTIs treated in the emergency departments could be attributed to MRSA,[9] which is associated with abscesses and cellulitis in PWID.

PWID are especially susceptible to MRSA which could be due to their injection behaviors, lifestyle, living conditions, and limited healthcare access. One study conducted in the United States estimated that PWID are approximately 16 times more likely to develop a MRSA infection when compared to the rest of the general population [14]. Another U.S. study from 2021 found that one in every ten invasive staphylococcal infections is related to injection drug use [15]. These data are not surprising given that the U.S. Centers for Disease Control and Prevention (CDC) has reported that 32% of PWID in 23 U.S. cities share needles [16, 17].

Given that there are an estimated 25,000 to 28,000 PWID in San Diego County [18] and approximately 10,000 PWID in Tijuana [19], it is important to establish and characterize the prevalence of MRSA and associated correlates so that PWID, policy makers, and program planners are better informed about what aspects of injection behaviors and high risk environments are more likely to cause harm in order to improve prevention methods. This thesis

project aims to test the two hypotheses that injection site specificity and housing instability will be associated with MRSA colonization/infection.

Injection Site Specificity

Injection site specificity refers to where on the body a person is most likely to inject drugs. Areas of injection include feet, forearm, hands, legs, groin, or neck, with the most common being the arm. Most PWID start out with injecting in the arm because it is a feasible intravenous access point. However, collapsed veins from prolonged injection drug use, specific types of drugs [20], and the stigma associated with having track marks, [21] may influence a person to shift to a different injection site. Unfortunately, literature is scant on which of these sites is more likely to lead to a skin infection like MRSA. One study did note that the lower limbs are the most frequent site of SSTIs based on the presence of *Staphylococcus aureus* in this region [22]. Other studies in the United States and England determined that PWID are at a higher risk of skin infections if they inject drugs in their legs, groin, or hands [3,4].

Research in Scotland has identified high rates of leg ulcerations within populations of PWID [23, 24]. Injection into the legs and groin often requires puncturing the femoral vein which can cause significant damage to the lower venous system, increasing the risk of developing leg ulcers [25] that are then prone to recurrent infections and may eventually lead to further skin infections like abscesses. Given that leg ulceration is considered an end-stage venous disease and commonly results in bacterial infections like MRSA, the implications of leg and groin injections are incredibly important to consider. Deep vein thrombosis can physically impair individuals for many years which, consequently, burdens the healthcare system [24]. Treatment of leg ulceration can be quite costly due to their persistent recurrence as well as their severity, which greatly

impedes quality of life. Furthermore, if the ulcer was to get infected with a pathogenic microbe like MRSA, there are a host of other problems to consider such as treatment/access to treatment, transmission prevention, and harm reduction to avoid recurrence.

One U.S. study that examined chronic venous disorders (CVD) in PWID found a strong association between CVD and injection site. More specifically, this study determined that people who injected in the legs and/or arms were more likely to develop an ulcer, were at a higher risk of venous disease, and ultimately had a high prevalence of severe CVD when compared to those who did not inject [26]. This emphasizes the need to better inform PWID about safe injecting practices, such as injection site rotations, so that they are at less of a risk of developing bacterial infections or chronic venous disorders. In this project, we set out to determine which injection sites predispose PWID to bacterial infections to better inform public health approaches such as education on safe injecting practices and other interventions that could reduce incidence of MRSA (and other SSTIs) within the PWID population.

In the case of hand injections, one significant consequence that can arise is hand edema or "puffy-hand syndrome [27]." As the name suggests, repeated injection of drugs in or around the veins in the hands can cause severe damage to the lymphatics, resulting in noticeable swelling in the area [28]. This accumulation of fluid can make the skin and surrounding soft tissues more vulnerable to pathogenic microbes. Importantly, lymphatic dysfunction in each of the aforementioned regions can undermine the immune system, making someone predisposed to a multitude of infections like MRSA. Ultimately, more research needs to be done to better understand if the chosen injection sites of the legs, groin, or hands predispose a person to a skin infection. Such data could be used to inform public health interventions to improve vein care for PWID.

Housing Instability

Another important variable to consider when analyzing drug injection behaviors is housing instability. The safety and sanitation of where a person lives or injects can be instrumental in determining their individual risk level. People experiencing homelessness (PEH) who also inject drugs, are more likely to spend time in crowded communal facilities such as homeless shelters or day cares where infectious microbes such as MRSA are easily transmissible. One vital aspect of homelessness is reduced access to clean water, sanitation, and personal hygiene facilities [29]. People experiencing housing instability may be unable to shower or maintain dental and hand hygiene, may use public showers, or may not have access to safe water to clean injection sites and syringes. All of these factors increase exposure to skin infections like MRSA. Therefore, one of the likely implications of homelessness or housing instability is increased vulnerability to a pathogenic microbe like MRSA, and consequently, the uncontrolled spread of infection.

Although there is more published literature on the association between housing instability and ensuing bacterial infections like MRSA, very little of it focuses on PWID. Previous research has shown that housing instability is independently associated with all-cause mortality [30], whereas supportive housing placement leads to decreases in substance use-related hospitalizations and emergency department visits [31]. If this project's hypothesis is supported, these detrimental effects of unstable housing will be further shown through its association with MRSA colonization or related skin infections. This project has the potential to increase emphasis on the need for accessible safe water, public hygiene facilities, and the consistent decontamination and maintenance of these resources for PWID. It can also serve as a call to action for public health professionals and policymakers to provide better long-term housing

options for vulnerable communities. Better housing, safe water, and hygiene facilities could ultimately lead to the reduced incidence of MRSA and possibly other bacterial infections.

Chapter II:

Manuscript

Abstract

Background: The opioid epidemic in the United States has contributed to a rise in drug injection-related disease transmission and infection. People who inject drugs (PWID) are at an increased risk of developing bacterial infections such as Methicillin-resistant *Staphylococcus aureus* (MRSA). This study examines the prevalence and correlates of MRSA infections and related abscesses amongst PWID in San Diego, California, and Tijuana, Mexico, to better inform harm reduction practices. *Methods*: A cross-sectional study was conducted from June 2022 until November 2022 in which PWID (N = 187) participating in an ongoing cohort study completed interviewer-administered questionnaires and MRSA swabs nasally and at abscess sites (if present). Chi-Square Tests of Independence, Fisher's Exact Tests, and Wilcoxon Rank Sum Tests were used to identify potential risk factors. *Results*: Analysis revealed significant associations between injection practices, structural factors (e.g. homelessness), and prevalent MRSA infections. *Conclusions*: The significant positive associations between arm injections, homelessness, and MRSA infections emphasize the need for structural interventions that reduce the barriers PWID face when accessing resources that would improve their health outcomes.

Introduction

In recent years, the opioid epidemic in the United States has created a dire public health crisis of disease transmission and infection. Due to frequent puncture of the skin, PWID are at an increased risk of developing wounds that can get severely infected. Pathogenic bacteria flourish on the skin as a result of limited access to soap and water, unsanitary living environments, and contaminated drugs or injection drug preparation equipment. Skin and soft tissue infections

(SSTIs) can then occur when these microbes invade the skin and underlying soft tissues. Although the skin serves as the first line of defense against pathogenic microbes, skin penetration with an object like a needle breaks this protective barrier, allowing for possible infections to develop as a result. This is especially true of opportunistic pathogens like Methicillin-resistant *Staphylococcus aureus* (MRSA).

Staphylococcus aureus is a bacterium that usually exists commensally on the skin or in nasal cavities. MRSA is a group of *S. aureus* bacteria that has acquired resistance to methicillin and can cause severe skin infections such as ulcers, abscesses, cellulitis, endocarditis, and bacteremia which result in considerable morbidity and mortality and place a high burden on the health care system. MRSA is especially concerning because its emergence and global spread is an example of how quickly antimicrobial resistant (AMR) genes can be transmitted. AMR genes caused approximately 4.95 million deaths in 2019, of which over 100,000 were attributable to MRSA [32]. Pathogenic bacteria such as MRSA can greatly impact PWID given insufficient skin disinfection prior to injection and a limited access to healthcare making them especially vulnerable to pathogenic microbes [33]. Importantly, a study of AMR bacteria in Guatemala found that improvement in hygiene was significantly associated with a reduction in the detection of resistant bacteria [34]. This shows that antibiotic stewardship efforts, such as better regulation of antibiotic use, may not be effective without additional efforts to improve access to hygiene resources and education on safe injection practices for PWID. Additionally, global estimates of homelessness and unstable housing within populations of PWID are estimated to be 24.8% [10]. Given that homelessness can be associated with high risk injection behaviors [35], it is important to establish whether housing instability places PWID at a higher risk of developing MRSA infections and related abscesses. Therefore, this study aims to determine the prevalence and

correlates of MRSA infections and related abscesses amongst PWID in San Diego, California, and Tijuana, Mexico, to better inform harm reduction practices and reduce the expansion of AMR bacteria.

Methods

Participant Recruitment and Eligibility

This cross-sectional study draws from semi-annual follow-up visits from a 2020 prospective cohort study engaging PWID in San Diego, California, USA or Tijuana, Baja California, Mexico. To be eligible for enrollment, individuals were aged 18 or older, had injected drugs within the last month, and resided in either San Diego County or Tijuana [36]. For follow-up visits, participants were recontacted between June 2022 and November 2022 by trained interviewers using street outreach and mobile vans to undergo follow-up interviews and specimen collection.

Ethical Considerations

Data collection was conducted by a field team trained to work with populations of PWID as well as people experiencing homelessness (PEH). All data was kept confidential by using a subject identification number. Contact information with participant names was recorded in a separate file and encrypted. Participation in this cross-sectional study was entirely voluntary and had no effect on whether or not a person would receive medical care or other help from the field team.

The protocol for this study had IRB approval from both the University of California, San Diego, and the Xochicalco University Campus, Tijuana and included the MPH candidate as a team member.

Swab Collection for MRSA Detection

Swabs were provided to all participants who were instructed on how to collect the sample themselves from their nasal cavity. Those with abscesses were then instructed to collect an additional sample by swabbing their abscess site. This was done in the presence of a field team member. At the end of every day, swabs were transported in a cooler to the Center for Advanced Laboratory Medicine (CALM) at the University of California, San Diego, and stored in a refrigerator at 4 °C until being tested for MRSA (always within 48 hours of sampling to ensure optimal bacterial survival). At the time of testing, the swabs were vortexed briefly and then plated using a four-quadrant streak plate procedure with a sterilized inoculation loop on Chromogenic agar media, a selective medium for the isolation of MRSA, which grows as a denim blue color. Any colonies that grew as denim blue were then identified using Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry which allows for a quick and accurate determination of the bacterial species. Participants whose swabs returned MRSA-positive were informed of their status by the field team and referred for medical attention.

Interviewer-Administered Questionnaires and Variables of Interest

Participants completed an interviewer-administered questionnaire in English or Spanish at this semi-annual follow-up visit to obtain quantitative data regarding their injecting behaviors and living conditions. These questions pertained to their lifetime experiences and behaviors within the last 6 months. Participants were also asked to report if they had an abscess at any point since their last visit. Interviewers were trained on how to properly conduct the examination to ensure accuracy of the results, and interviews were conducted outside on a laptop computer.

Participants and interviewers followed an approved COVID-19 protocol (i.e., maintaining social distance and wearing personal protective equipment). Participants were given $20 compensation for their time answering questions, and additional $5 compensation if they agreed to be swabbed for MRSA.

The dependent variables of interest were (1) MRSA present either in nares or at an abscess and (2) presence of an abscess. The primary independent variables of interest for this study were (1) injection site specificity (with a focus on injections in the arms, legs, hands, groin, or neck), and (2) housing instability, defined as living in transitional housing, staying in a shelter, living on the street for 24 hours per day, or experiencing homelessness within the last 6 months. These data were obtained from the participant questionnaires and compared to the participant's MRSA and abscess status to determine if the variables were significantly associated with the independent variables of interest.

Variable Definitions

Dependent Variables

This study focused on the two primary outcomes of MRSA and recent or current presence of an abscess for associations with potential risk factors. Due to limited statistical power, these two variables were also combined into a third "Skin Infection" variable given that abscesses are often caused by MRSA. Therefore, the independent variables of interest were analyzed for associations with three potential outcome variables: (1) MRSA, (2) Abscesses, and (3) Skin infection (i.e., MRSA and/or Abscess).

Independent Variables

Literature on which injection sites are most associated with bacterial skin infections is rather limited, but a previous study suggests that the arm may be safer for intravenous injection due to lower incidence of thrombosis when compared to the lower extremities [37]. Meanwhile, the legs, hands, and neck regions are considered higher risk sites for various reasons such as poor circulation, increased likelihood of clots, and proximity to the femoral and carotid arteries [38]. Because of this, participants who reported use of their legs, hands, or neck as their most common injection sites were placed into a "high risk" category following the assumption that problems that arose from these sites would be more likely to result in an infection. Participants who utilized their arms the most were placed into a "low risk" category. No participants reported utilizing their groin region the most, so this site could not be analyzed.

Housing was operationalized in two ways for analysis. First, we created a dichotomous variable for "experiencing homelessness" (yes/no) based on questions assessing living in transitional housing, staying in a shelter, living on the street for 24 hours per day, or having experienced homelessness within the last 6 months. Second, participants were asked how many people they currently live with, which was treated as a continuous variable to determine if a participant was more likely to report an abscess or test positive for MRSA if they were exposed to a large number of people at their residence or shelter.

Data Analysis

The demographic characteristics as well as the most common injection sites and housing insecurity status of the sample were summarized using descriptive statistics. Given the binomial distribution of the data, a binomial test was used in the analysis of MRSA prevalence within the sample. In order to analyze the associations between the variables of interest and a positive

MRSA result or report of an abscess, Chi-Square Tests of Independence were used for categorical variables with expected cell frequencies greater than 5, and Fisher's Exact Tests were used for those with expected cell frequencies less than 5. For continuous variables, Wilcoxon Rank Sum Tests were used due to the non-normal distribution of the data. This yielded 95% confidence intervals based on a binomial distribution as well as computed odds ratios. All of the analysis was performed using *R* [39].

Results

Study Participants

The analytic sample for this cross-sectional study consisted of 187 participants from either San Diego County in California (N = 37), or Tijuana, Baja California, Mexico (N = 150). Of these participants, 137 (73.3%) were male and the average age was 45 years old (IQR: 39-53) (Table 1). The majority of participants (63.1%) were single. In regard to education level, 17.6% of participants stated that they had attended school up to 8th grade or less, while 80.2% attended high school or had some higher education. Of the 184 participants who answered the questions regarding homelessness, 53 (28.8%) reported that they have experienced some form of housing insecurity within the past 6 months.

Table 1: Participant Demographic Information

Variable	**MRSA +** (N=11)	**MRSA -** (N=176)	**Total #** (N = 187)	***p***
Age, median (IQR)	38.5 (37.25-46)	45.5 (39-53.75)	45 (39-53)	0.17
Sex - Male (%)	7 (63.6)	130 (73.9)	137 (73.3)	0.72
Race - Hispanic or Latino	3 (27.3)	149 (84.7)	152 (81.3)	< 0.001
Marital Status, N (%)				
Single	7 (63.6)	111 (63.1)	118 (63.1)	1.0
Married	3 (27.3)	62 (35.2)	65 (34.76)	
Education Level, N (%)				
Middle School or less	3 (27.3)	30 (17.0)	33 (17.6)	0.39
Some High School and Above	7 (63.6)	143 (81.3)	150 (80.2)	

MRSA Results

From the 187 participants, a total of 200 swabs were collected: all 187 were swabbed nasally, and 13 were also swabbed at a current abscess site. There were 11 participants (9 from San Diego and 2 from Tijuana) that tested positive for MRSA either nasally (N = 9) or at the site of an abscess (N = 2), meaning the prevalence was 5.88% (Table 2). A binomial test was run using *R* code which provided a 95% confidence interval of (3.0%, 10.3%). Of those testing positive for MRSA, two (18.2%) tested MRSA-positive at an abscess site while the rest tested positive nasally (81.8%). This suggests that the majority of these participants were colonized with MRSA versus having an active MRSA infection at the time of the specimen collection.

Injection Site Specificity

Within the sample, there were 4 injection sites that were reported as the most often used (Table 3). The most common was the arms, with 63.6% of MRSA-negative participants and 63.6% of MRSA-positive participants reporting using this site. The second most common site was the neck, with 22.2% of MRSA-negative participants but 0% of MRSA-positive participants. The third site was the hands with 3.98% of MRSA-negative participants and 9.1% of MRSA-positive participants. Lastly, the legs were reported as the most common site of injection for 5.7% of MRSA-negative participants, but no MRSA-positive participants. There was no significant association between higher risk injection sites and presence of a MRSA infection (OR: 3.48, 95% CI: 0.43 - 160.4, p = 0.44).

Table 2: MRSA Status by Swab Site From 200 Total Swabs Collected

Swab Site	**MRSA +** (N = 11)	**MRSA-** (N = 189)	***p***
Abscess (%)	2 (18.2)	11 (5.82)	0.154
Nasal (%)	9 (81.8)	178 (94.2)	

Table 3: Injection Site Specificity and MRSA Status Among 187 PWID

Injection Site	**MRSA +** (N = 11)	**MRSA -** (N= 176)	***p***
Lower Risk (%) *Arms*	7 (63.6)	112 (63.6)	0.44
Higher Risk (%) *Hands, Legs, and Neck*	1 (9.1)	56 (31.8)	

Statistical Analysis

The Association of Abscesses and Injection Site Risk

It was originally hypothesized that injection at higher risk sites would be associated with increased odds of MRSA or abscesses when compared to other, safer regions. Overall, there were 17 (9.1%) participants who reported abscesses in the last 6 months, of whom 14 (82.4%) stated that they utilized their arms the most. Ultimately, only one of the participants in this sample who reported having an abscess within the last 6 months, reported a "high risk" site as their most common region of injection (hands). One of the other two participants was not asked for this information because they had not injected for over a year, and the last participant did not complete the questionnaire. A Fisher's Exact test was used to compare the association between having an abscess and injection site specificity risk. This resulted in a significant positive relationship between using the arm as a common site and having an abscess (OR: 7.41; 95% CI: 1.07- 320.81, $p = 0.039$), but the wide confidence interval reveals uncertainty in the estimate. These results are summarized in Table 4.

The Association of MRSA and Injection Site Risk

The various high and low risk injection sites were also analyzed in comparison to the obtained MRSA results. These data were acquired for 8 of the 11 MRSA-positive participants, with 7 reporting use of the low risk site, and 1 reporting use of a higher risk site (hands). A Fisher's Exact test revealed no significant association between MRSA prevalence and injection risk (OR: 3.48; 95% CI: 0.43-160.4, $p = 0.44$) (Table 4).

The Association of MRSA + Abscess Infections and Injection Site Risk

Since abscesses are often caused by MRSA, those that tested positive for MRSA and those that reported having a recent abscess were combined into a single "Skin Infection" variable to determine if there was an association between injection sites and a subsequent infection. This analysis did show a significant positive association (OR: 4.87; 95% CI: 1.099 - 44.82) but, again, the confidence interval was wide.

The Association of Housing Instability and Abscesses or MRSA

It was originally hypothesized that unstable housing would increase susceptibility to skin infections due to factors such as inadequate hygiene and crowded sleeping arrangements. A Chi-Square test revealed a positive association between housing instability and having an abscess (OR: 7.21; 95% CI: 2.42-24.73, $p<0.001$), while a Fisher's Exact test revealed a positive association between housing instability and testing positive for MRSA (OR: 26.89; 95% CI: 3.55-1202.74, $p<0.001$). Additionally, a Chi-Square test determined a positive association between housing instability and having either an abscess or MRSA (OR: 9.06; 95% CI: 3.42 - 27.29, $p<0.001$).

Housing instability was also evaluated based on the number of people a participant reported living with. It was hypothesized that a greater number of people would mean an increase in vectors of exposure, leading to a higher risk of infection. There was a great degree of variance across this variable, with the amount of people ranging from 1 (the participant lives alone) to 400 (the participant lives in a shelter). Wilcoxon Rank Sum tests revealed a significant positive association between the number of people in a participant's home and having had a recent abscess ($p = 0.024$), and the number of people in the home and having either an abscess or

MRSA ($p = 0.030$). However, there was no association between the number of people in a participant's home and MRSA only ($p = 0.21$) (Table 4).

The Association of Age, Sex, and Race with Injection Site Risk and Housing Instability

The demographic factors age and sex were also analyzed for associations with the main outcome variables of interest. However, neither of these variables showed any significant associations with housing instability, abscesses, MRSA, or injection site specificity (Table 4). Interestingly, despite the majority of the participants (81.3%) identifying as being either Hispanic, Mexican, or Latinx, 8 out of the 11 people who tested positive for MRSA were Non-Hispanic/Latinx. A Fisher's Exact test showed a significant negative association between being either Hispanic or Latinx, and having an abscess (OR: 0.096; 95% CI: 0.026 - 0.326, $p = p<0.001$), or testing positive for MRSA (OR: 0.070; 95% CI: 0.011 - 0.312, $p<0.001$) (Table 4).

Table 4: Factors Associated with MRSA and Abscesses Among PWID in San Diego, CA and Tijuana, Mexico

Variable	MRSA (N=11)		Abscess (N=17)		MRSA +Abscess (N=24)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Injection Site Specificity*	3.48 (0.43, 160.4)	0.44	7.41 (1.07, 320.81)	0.039	4.87 (1.099, 44.82)	0.023
Housing Instability**	26.89 (3.55, 1202.74)	<0.001	7.21 (2.42, 24.73)	<0.001	9.06 (3.42, 27.29)	<0.001
Number of People In the Home, median (IQR)	1.5 (1 - 6)	0.21	2 (1 - 3.5)	0.023	2 (1 - 4.5)	0.029
Demographic Variables						
Age, median (IQR)	38.5 (37.25-46)	0.913	45.5 (37.25-52)	0.168	44 (37.25-50)	0.438
Sex at Birth, *male*	1.26 (0.202, 5.840)	0.717	2.61 (0.770, 8.50)	0.074	2.25 (0.783, 6.21)	0.115
Race, *Hispanic/Latinx*	0.070 (0.011, 0.312)	<0.001	0.096 (0.026, 0.326)	<0.001	0.86 (0.279, 3.175)	0.781

*Injection Site Specificity refers to injections at a low risk site (arms) compared to higher risk sites (legs, hands, neck).

**Housing Instability is defined as living in transitional housing, staying in a shelter, living on the street for 24 hours per day, or experiencing homelessness within the last 6 months.

Discussion

In this cross-sectional study of PWID in San Diego, CA and Tijuana, Mexico, the prevalence of MRSA was 5.88% and 9.1% of participants reported having a recent abscess. The prevalence of MRSA was much higher within the San Diego cohort with 9 out of 37 participants testing positive, but there is also a higher prevalence of homelessness in this sample which may explain the disparity. The high prevalence of homelessness in San Diego could also explain why the number of participants recruited from Tijuana (N = 150) was much higher than that of San Diego (N = 37), given that unhoused participants were more difficult to contact for follow-up interviews.

The findings regarding housing instability and skin infections are noteworthy given that the odds ratios suggest a person experiencing homelessness is 7.21 times more likely to develop an abscess, 26.89 times more likely to test positive for MRSA, and 9.06 times more likely to have either of these conditions when compared to someone who is housing stable. However, the wide confidence intervals must also be taken into consideration, as they suggest uncertainty in this analysis. Nevertheless, these data suggest a need for harm reduction services to focus on how to improve housing options as well as proper hygiene resources and education.

Interestingly, the prevalence of MRSA in this study was much lower than what was reported in a similar study conducted in Boston[1]. However, the number of disclosed abscesses in this study was relatively similar to a prior publication out of Baltimore, Maryland in which researchers found that approximately 11% of PWID had at least one abscess within the last 6 months [40]. It was observed that the risk factors of housing instability, arm injections, the number of people in a home, and race were significantly associated with higher odds of having abscesses. Additionally, a significant positive association was found between housing instability and MRSA

presence, and a significant negative association was found between race and MRSA presence. Arm injections, housing instability, and the number of people in the home was also found to be associated with a combined variable of MRSA-positive and/or Abscess-positive.

Although the association between arm injections and an abscess was not consistent with the original hypothesis, it is an important finding regarding safe injection practices. The current literature suggests that the arm is the safest site for injection in regards to venous health and welfare [38], but these data imply that the arm may be more susceptible to infections when compared to other regions of the body. This could be due to the fact that arm abrasions or scabs from injections may be more consistently picked at and touched by unwashed, contaminated hands when compared to the lower extremities that are often covered by clothing, and the neck which is not looked at regularly throughout the day. Alternatively, repeated injections into the arms for many years likely damaged the veins in this region, emphasizing a need for harm reduction programs to promote better vein care and injection site rotations. In order to study this association further, it would be necessary to control for the duration of an individual's injection career as well as their injection frequency.

The positive relationship between housing instability and subsequent skin infections is consistent with previous literature that also found that increased person-to-person contact and overcrowded, unhygienic living situations facilitated the transmission of pathogenic microbes like MRSA [1]. This highlights the urgent need to make hygiene facilities more accessible so that PEH can properly maintain their welfare. Additionally, these findings underscore the exigencies of the homelessness problem in San Diego. Over 8,000 people are currently experiencing homelessness in San Diego County, a number that has risen by at least 10% since 2020 and was likely exacerbated by the Covid-19 pandemic [41]. While there are many interdisciplinary

challenges in addressing homelessness, it is evident from the results of this study that solutions such as permanent supportive housing could significantly improve health outcomes and achieve better health equity for PWID.

Study Limitations

The ability to identify significant associations between variables was limited due to the relatively low prevalence of MRSA and abscesses meaning there was low statistical power to test the hypotheses. Therefore, MRSA results were analyzed as a single variable rather than separate categories that reflected the location of the infection. This means that we could not determine if the presence of MRSA was associated with injection drug use specifically versus other factors such as general hygiene practices. Additionally, the low prevalence meant we were unable to control for potential confounders (e.g., frequency of injection, duration of injection career) or stratify the data based on location (Tijuana or San Diego).

The self-administration of the MRSA swabs may have introduced a level of variability in the way the swabs were collected. It is possible this could have resulted in some false negative results which would have under-estimated MRSA prevalence within the sample. Other study limitations include the potential for misclassification and reporting bias based on the nature of the questionnaire (it was long and there could have been a lack of trust due to fear of discrimination) and the fact that all behaviors were self-reported. The cross-sectional nature of this study also limited our ability to assess temporality which precluded our ability to make causal inferences about what risk factors lead to MRSA exposure and abscesses.

It should be noted that the confidence intervals for several associations were rather wide, likely due to higher variability within the sample as well as smaller frequencies in certain categories. This indicates a greater uncertainty of the strength of associations between variables.

Future research

Analysis was limited due to the small sample size and low MRSA prevalence. Therefore, future research would benefit from a larger sample in which MRSA results could be separated based on if an individual tests positive nasally versus at an abscess site. Additionally, a larger sample from San Diego would have enabled comparisons by city.

Now that it is suggested that arm injections may contribute to the risk of infections, future research could analyze whether or not specific regions of the arm are riskier than others. In other words, it would be interesting to determine if forearm injections are more susceptible to infection than upper arm injections or vice versa. It was originally hypothesized that groin injections would be a high risk region, but none of the participants in this study reported this. Therefore, future research could focus on the potential negative outcomes associated with groin injections. This research should also be conducted on other populations of PWID in cities throughout the United States where homelessness remains a significant problem.

Conclusions

Overall, the findings of this research demonstrate that housing instability and injection behaviors impact the health outcomes of PWID and increase their risk of developing certain bacterial infections. Structural interventions are warranted in order to reduce the barriers PWID and PEH face when attempting to access resources such as healthcare services, safe injection equipment, or stable housing. Policymakers, health clinics, and other harm reduction services

may be able to alleviate some of these concerns through better education of safe injection practices as well as an improvement in proper housing options.

Additional recommendations are warranted to reduce the spread of antimicrobial resistant (AMR) genes in bacteria. Resistance to antibacterial agents is a global public health crisis mostly attributable to the overuse and misuse of antibiotics in healthcare settings as well as the agricultural industry [42]. The consequences of this are considerable with detrimental effects on healthcare costs, increased lengths of hospitalization, and serious illnesses that will result in an estimated 4.95 million deaths globally [32]. Currently, this crisis is being addressed through antibiotic stewardship which involves better training and education of clinicians and other healthcare professionals on properly measuring antibiotic prescriptions to improve patient safety and promote positive health outcomes [43]. This would have a positive impact on vulnerable populations like PWID because it would improve the effectiveness of treatments and shorten the length of hospitalizations. However, as mentioned previously, these efforts may be hindered by unsanitary environments [34], further highlighting the need to promote better hygiene facilities and education on sanitary injection practices. Combatting the issues faced by PWID requires a multifaceted approach involving the cooperation of healthcare providers, public health professionals, and policymakers.

Chapter III:

Dissertation Discussion

Interpretation of Results

Infections and Injection Site Specificity

Although the research is limited, some previous studies out of England, Scotland, and the United States found that PWID are at a higher risk of skin infections and ulcerations if they inject drugs in their legs, groin, or hands [3,4]. It was originally hypothesized that the participants of this cross-sectional study would be more likely to report a recent abscess or test positive for MRSA if they utilized any of these 3 sites as their most common choice for injection when compared to those who use their arms the most. However, even though the arm is generally considered a safer injection site, almost all of the participants who reported an abscess also reported using their arms the most. Analysis revealed that the association between these two variables was statistically significant, meaning that PWID into their arms may be more susceptible to infections than those who do not. Additionally, 7 of the 11 participants who tested positive for MRSA also stated that they inject most frequently into their arms. Although this particular relationship was not statistically significant, it is still important to note that a majority of those who were colonized with MRSA did use their arms for injections.

The question of why arm injections would make PWID more susceptible to infections remains to be answered, but possibly relates to the microbial pathology as well as the physiology of this region of the body. A study of the skin's microbiome revealed that the forearm harbors a greater diversity of microorganisms, resulting in the group and structure of microbes being less stable than other areas of the body [44]. This could indicate a higher likelihood that opportunistic pathogens like MRSA would take advantage of an abnormal situation in which the immune

system is compromised, such as the case of drug injections [11, 45]. Furthermore, the physiology of the arm differs from other injection site regions in terms of the density distribution of sweat glands. One study out of the United Kingdom and another from the European Union's Research and Innovation Program found that there is a greater density of sweat glands on the forearms and upper arms when compared to the upper legs and neck [46, 47]. Abscesses may occur when skin is not kept clean and sweat glands become inflamed due to an accumulation of dead skin cells, oil, and dirt [48]. Therefore, an increased number of sweat glands in a certain area of the body may lead to a higher risk of developing injection-related infections that can lead to abscesses. For example, one participant tested positive for MRSA at an abscess/injection site located near their armpit. The constant friction and higher density of sweat glands in this region may have exacerbated this person's risk of developing an infection. This line of thinking is consistent with the one person who reported an abscess and also uses their hands to inject, given that the hands have one of the highest concentrations of sweat glands on the body [46] . Furthermore, when analyzing the association between arm injections and subsequent infections it is important to consider that most PWID begin using drugs by injecting into this part of the body [20]. They will then move to other regions once they lose access to functioning veins in the arm [49]. It is this sclerosis of the vein that often results in a multitude of consequences such as skin infections and abscesses [49]. Having trouble accessing a vein often forces PWID to poke their skin over 3 times in attempts to hit a vein, increasing the likelihood of a SSTI [49]. Therefore, it is possible that the participants who reported arm injections were more susceptible to infections due to the more extensive damage of their venous systems in this location.

It should be mentioned that the majority of participants (67.6%) who answered the question about injection site specificity stated that they use their arms more frequently. This is

consistent with previous literature that also found the arms to be the most common site of injection [37]. If the results of increased bacterial infection susceptibility in the arms were to hold over other populations of PWID, it could influence where harm reduction efforts are primarily focused in order to address the public health crisis of pathogenic transmission through injection drugs. In other words, education and outreach work could place more emphasis on site rotations to prevent vein collapse and reduce the risk of infection [50]. There should also be efforts to discourage multiple attempts to access a vein using the same needle in the same location. If a vein cannot be accessed the first time, PWID should be urged to use a different needle - or to sterilize their original needle - and rotate to a different site to inject.

Infections and Housing Instability

The proportion of participants experiencing housing instability in the last 6 months (28.3%) was lower than the 40-61% that was reported as the national average of PWID experiencing homelessness in the United States [51], but is consistent with a global estimate of 22% [52]. For the purposes of this study, housing instability was defined as anyone living in transitional housing, staying in a shelter, or experiencing homelessness by spending 24 hours per day on the street. The results of this study demonstrated a significant, positive association between abscess prevalence, MRSA colonization, and housing instability. More specifically, it was determined that PEH are 7.33 times more likely to develop an abscess and 26.89 times more likely to be colonized with MRSA than those who are not experiencing homelessness. These data are consistent with a previous study from Boston, Massachusetts and another from Canada in which researchers found that PEH were more likely to be colonized with MRSA and experience

bacterial infections [1, 53] than those who were not. This is indicative of the poor living conditions and personal hygiene habits often faced by PEH [29].

The role of housing as a social determinant of health is indisputable given the various negative health outcomes experienced by those who do not have safe, stable housing [54]. More specifically, there are many factors in the daily life of a PEH that influence their risk of exposure to infectious diseases. For example, homeless services are often overcrowded facilities in which PEH are forced to come into close contact with numerous other patrons [54]. This increases their likelihood of contracting a communicable disease due to a greater exposure to pathogens and an increase in contact transmission [55]. Additionally, inadequate access to personal hygiene resources such as clean water for bathing, the ability to do laundry, and handwashing and toilet facilities all make PEH more susceptible to illnesses [55]. In fact, it has even been shown that poor hygiene options can exacerbate minor wounds due to insufficient skin care [55]. All of these variables allow bacteria and other pathogens to thrive and spread, making it understandable that PEH would be more likely to be colonized with MRSA or develop an abscess.

Study Limitations

This cross-sectional study had several limitations. First, its cross-sectional nature meant that we could not infer causality. Second, the statistical power of the test was low due to small numbers in some cells and the relatively low prevalence of MRSA. Given that this is a study on injection drug use, it is possible that there was reporting bias to some degree due to a lack of trust or a fear of discrimination. Additionally, we did not have information on the other sites a participant may choose to inject in, but instead just focused on their most common site. Therefore, it is unknown whether they most often develop abscesses/infections at this common

site, or another site they utilize less frequently. Lastly, this study was conducted on a specific cohort in Tijuana and San Diego, and the findings may not be generalizable to other populations or regions.

Current Policy Analysis and Recommendations

Practicing safe injection is key to reducing disease spread and improving health outcomes for PWID. The idea of supervised injection facilities (SIF) has been proposed many times over the past few years in the California legislature. Just recently, in August of 2022, the California Senate passed SB-57, a landmark bill intended to prevent overdoses [56]. If approved, the bill would authorize the counties of San Francisco, Los Angeles, and Oakland to establish supervised injection facilities where PWID would be provided with sterile supplies, treatment resources, and a hygienic space in which to inject safely [56]. While the bill did pass in the Senate, it was shortly after vetoed by Governor Newsom who stated that these sites cannot be implemented without first establishing, "strong, engaged local leadership and well-documented…sustainability plans" [56]. While the vetoing of this bill is discouraging, it will hopefully motivate city and county officials to delineate the minimum standards that should be met in order to provide PWID with more safe and hygienic environments. SIFs have been in place in Europe, Canada, and Australia since 1986 [57], yet the United States Department of Justice (DOJ) continues to criminalize the idea. In fact, in 2019 the DOJ threatened to prosecute anyone who established, worked at, or patronized a facility that offered these services [58]. This is especially disheartening given that previous research has already shown that they have the ability to improve the health outcomes of PWID. For example, one study from Canada reported that, before the opening of an SIF, 15% of PWID were admitted to the hospital for injection-related skin infections compared to 9%

admitted over 4 years after the opening of an SIF [59]. It is evident that these sites would most importantly save lives, but also greatly reduce disease transmission and the economic burden on the United States healthcare system. As evidenced from this study, hygienic environments and education on safe injection practices could play an important role in significantly reducing the risk of infections.

A major contributor of healthcare disparities for PWID is the stigma associated with injection drug use. PWID seeking medical treatment often report feeling discriminated against and looked down upon by the workers at healthcare clinics [21], leaving them discouraged from ever returning for help in the future. However, various research studies out of Australia and New York report the positive experiences of PWID at syringe service programs [21, 60]. PWID describe high levels of trust in these services, stating that the workers are non-judgmental, helpful, and make them feel like any other person [21, 60]. This positive engagement is invigorating, as it suggests that similar methods of the training and education of these service providers could be adapted to the employees of SIFs, should they be made legal. Therefore, it is recommended that policymakers implement a social empathy model when setting the standards for facilities that offer services to PWID. The model promotes individual empathy, contextual understanding, and social responsibility in order to better serve vulnerable populations by being more sensitive towards their lived experiences [61]. An endorsement of funds for instruction and training programs designed to reduce the stigma associated with drug use would be beneficial for encouraging PWID to seek care without fear of discrimination.

Policymakers and healthcare providers can also reduce infectious disease spread and improve health outcomes for PWID by targeting the increasing AMR bacteria crisis. Currently, the United States government has implemented a National Action Plan for fighting

antibiotic-resistant bacteria [62]. This plan focuses on interagency collaboration that promotes the research of bacterial and fungal pathogens, improves diagnostic tests, and encourages organizations across the globe to commit to slowing the expansion of AMR [62]. Furthermore, the plan intends to improve critical hygiene, water, and sanitation facilities in households and communities across the country. As the study from Guatemala showed [34], strengthening hygiene efforts is crucial for reducing AMR bacteria, especially for impoverished individuals. Government agencies should collaborate to evaluate and improve the accessibility of these resources for PWID and PEH.

Suggestions for Future Research

Future research should be centered around determining which interventions have an impact on the prevalence and incidence of MRSA or other skin infections within populations of PWID. For instance, a retrospective cohort study of the health outcomes of PWID who were also experiencing homelessness before and after receiving stable housing would offer insight into how beneficial housing is for reducing the risk of disease.

Given that this study only examined associations with the most common site of injections, other research should be conducted on all of the sites a PWID chooses to inject in. For instance, it is possible that a participant tested positive for MRSA and listed their arm as their most common site, but developed the MRSA infection at a site less frequently used. Additional research could focus on associations between SSTIs and the type of drug injected, like the recent study from Pennsylvania which found an association between the use of Xylazine and skin ulcers and abscesses [63].

Conclusions

Overall, this study observed that PWID are more susceptible to bacterial infections like MRSA if they inject into their arms, or if they are experiencing homelessness or an unstable living situation. However, our inability to control for confounders means it is possible that these are spurious associations. While it is still unknown what exactly would make the arm a riskier site when it comes to infections, there are several possibilities. First, the arms may come into contact with the hands way more frequently than the hands come into contact with other regions such as the legs, groin, or neck. For example, if a person were to develop a scab or a wound on their arms, they are likely to mindlessly scratch at it or touch it throughout the day because it is constantly within their line of sight. This may introduce bacteria in the wound, causing it to become infected. It is important to consider why there were no significant associations between hand injections and subsequent infections. The answer likely relates to the size of the subsample of participants that reported hand injections as their most common site. Out of 187 participants, only 8 (4.28%) stated that they use their hands the most, with 1 out of 8 testing positive for MRSA and 1 confirming an abscess within the last 6 months. Low statistical power reduced the probability of detecting a true effect. Other potential reasons for the relationship between arm injections and infections relate to the microbial diversity as well as the anatomy of the arm. A disparate bacterial flora combined with a weakened immune system allows opportunistic pathogens like MRSA to become virulent. Lastly, the physiology of the arms in regards to sweat gland density distributions as well as damage to the venous system may increase the risk of infections. Inadequate hygiene along with repeated punctures to impaired veins make it more likely that pathogenic bacteria will be introduced to a vulnerable area in which they can thrive.

In regards to the relationship between injecting drugs and housing instability, it is important to take into consideration the daily standards of living that PEH are faced with. This study found a significant association between the number of people someone lives with, and a recent skin infection. In other words, the more people living in the same house or shelter is associated with an increased odds of an SSTI. People living on the streets or in homeless shelters are less likely to be able to practice adequate hygiene due to a lack of publicly available resources, or because the resources that are accessible are not kept clean and sanitized. Sharing facilities or homes with a lot of people, or having to live on the street introduces a greater number of vectors that result in communicable diseases. In fact, in 2019, California public health officials described the crisis of "medieval" diseases plaguing the homeless population due to sidewalks soiled with human feces, poor immune systems, and crowded living situations [64]. All of these factors are then intensified by limited access to medical care [64]. Clearly, safe and stable housing is a necessity when it comes to reducing disease transmission amongst PWID and PEH.

PWID and PEH face unique challenges each day that must be addressed without judgment and with knowledge of what would produce the best health outcomes. The promotion of a social empathy model would encourage service providers to empathize with a patient's lived experiences in order to better understand the best and most feasible ways to help. For instance, adapting a community-based approach in which members of this population are able to voice their thoughts, concerns, and recommendations would help to establish trust as well as provide first-hand insight into what needs should be addressed the most. Additionally, supplying sterile injection equipment or a facility where someone may inject safely has the potential to greatly improve health outcomes for PWID, prevent overdose deaths, and reduce the spread of bacterial infections. The findings of this study emphasize the importance of promoting safe, hygienic

injection practices, and providing better resources for stable housing to reduce the negative health consequences associated with MRSA and other SSTIs among PWID.

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