Skin and soft tissue infections among people who inject drugs. Prevalence and correlates of bacterial infections and colonization assessed through clinical and epidemiological studies.

Dahlman, Disa

2017

Document Version:
Publisher's PDF, also known as Version of record

Skin and soft tissue infections among people who inject drugs

Prevalence and correlates of bacterial infections and colonization assessed through clinical and epidemiological studies

DISA DAHLMAN
DEPT. OF CLINICAL SCIENCES, PSYCHIATRY, LUND | LUND UNIVERSITY

Skin and soft tissue infections among people who inject drugs

Skin and soft tissue infections among people who inject drugs

Prevalence and correlates of bacterial infections and colonization assessed through clinical and epidemiological studies

Disa Dahlman

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at CRC, Jan Waldenströms gata 35, Skåne University Hospital, Malmö, June 3rd 2017 at 10.00 AM.

Faculty opponent
Thomas Benfield, PhD, Professor

Department of Infectious Diseases, Hvidovre Hospital, Hvidovre, Denmark

Organization	Document name
LUND UNIVERSITY	DOCTORAL DISSERTATION
Faculty of Medicine Dept. of Clinical Sciences Lund, Psychiatry, Lund, Sweden	Date of issue 2017-06-03
Author Disa Dahlman	Sponsoring organization

Title: Skin and soft tissue infections among people who inject drugs – Prevalence and correlates of bacterial infections and colonization assessed through clinical and epidemiological studies

Abstract

Background: People who inject drugs (PWID) have significant mortality and morbidity, but bacterial infections are sparsely investigated compared to bloodborne viral infections and other drug related harms.

Objective: The general aim of this thesis was to investigate to what extent PWID are subject to bacterial infections and colonization, especially skin and soft tissue infections (SSTI), and identify groups and behaviors associated with increased risk of infection and colonization.

Methods: The study aims were assessed through two interview studies with PWID at Malmö needle exchange program (NEP; paper I) and in San Francisco (paper II); two register studies with data retrieved from the Swedish criminal justice system (paper III), the Causes of Death Register (paper III) and Swedish National Patient Register regarding methicillin-resistant *Staphylococcus aureus* (MRSA; paper IV), SSTI and systemic infections (paper III); and one microbiological study based on bacterial cultures and PCR (paper V).

Results: Self-reported prevalence of SSTI was high (lifetime prevalence 59% in paper I, 70% in paper II), as was incidence rates of registered SSTI diagnosis (28.3 per 1,000 person-years in paper III) among PWID. Risk of SSTI diagnosis was 1.6–2.5 times increased among PWID compared to non-injectors (paper III), and people mainly using heroin were at significantly higher risk of SSTI than people using amphetamine or multiple drugs (paper III). Incidence of systemic bacterial infection, defined as septicemia and infections in heart, bone/joints or central nervous system,was 9.1 per 1,000 person-years among PWID (paper III) and PWID had more than twice as high risk for systemic infection compared to non-PWID. Fatal bacterial infections were rare. MRSA diagnosis (colonization or infection) was significantly associated with dependence of opioids and amphetamine, compared with alcohol dependence (paper IV). Colonization with *Staphylococcus aureus* (*S. aureus*) was detected in 67% of PWID at Malmö NEP, and PWID were significantly more colonized in the perineum than non-injecting controls with substance use disorders (paper V). Several correlates (paper I and II) and risk factors (paper III) of SSTI were identified. Demographic correlates were female sex (paper I), higher age (paper I), previous overdose (paper III), homelessness (paper III), being resident in a large city (paper III) and self-reported hepatitis C (paper III). Behavioral correlates were non-powder injection (paper I), neck injection (paper I) and receptive needle/syringe sharing (paper II).

Conclusions: The results imply certain attention to risk groups of PWID and calls for implementation and evaluation of infection preventive interventions. There is a need for future MRSA surveillance and studies assessing associations of *S. aureus* colonization, SSTI and systemic infections.

Key words People who inject drugs, skin and soft tissue infections, systemic bacterial infections, Staphylococcus aureus, MRSA, epidemiology

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language English
ISSN and key title 1652-8220, Lund University, Faculty of Medicine Doctoral Dissertation Series 2017:91		ISBN 978-91-7619-471-3
Recipient's notes	Number of pages 188	Price
	Security classification	

Signature  Date April 27, 2017

Skin and soft tissue infections among people who inject drugs

Prevalence and correlates of bacterial infections and colonization assessed through clinical and epidemiological studies

Disa Dahlman

LUND
UNIVERSITY

Cover picture by Caroline Mannerfelt

Faculty of Medicine
Department of Clinical Sciences, Lund

ISBN 978-91-7619-471-3
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2017

Content

List of papers

I. **Dahlman D**, Håkansson A, Björkman P, Blomé MA, Kral AH. Correlates of Skin and Soft Tissue Infections in Injection Drug Users in a Syringe-Exchange Program in Malmö, Sweden. Subst Use Misuse 2015;50(12):1529-35.

II. **Dahlman D**, Håkansson A, Kral AH, Wenger L, Ball EK, Novak SP. Behavioral characteristics and injection practices associated with skin and soft tissue infections among people who inject drugs: A community-based observational study. Subst Abus. 2017;38(1):105-12.

III. **Dahlman D**, Berge J, Björkman P, Nilsson AC, Håkansson A. Both localized and systemic bacterial infections are predicted by injection drug use: A prospective follow-up study in Swedish criminal justice clients. Submitted manuscript.

IV. **Dahlman D**, Berge J, Nilsson AC, Kral AH, Björkman P, Håkansson A. Opioid and amphetamine dependence is associated with methicillin-resistant Staphylococcus aureus (MRSA): An epidemiological register study with 73,201 Swedish in- and outpatients 1997-2013. Infect Dis (Lond). 2017;49(2):120-7.

V. **Dahlman D**/Jalalvand F (first authors), Alanko Blomé M, Håkansson A, Janson H, Quick S, Nilsson AC. High perineal and overall frequency of Staphylococcus aureus in people who inject drugs, compared to non-injectors. Curr Microbiol. 2017;74(2):159-67.

Abbreviations

ADHD	Attention deficit and hyperactivity disorder
Anti-HCV	Anti-hepatitis C antibody
AOR	Adjusted odds ratio
ASI	Addiction Severity Index
CDR	The Causes of Death Register
CFU	Colony forming unit
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GEE	Generalized estimating equations
HBV	Hepatitis B virus
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSV-2	Herpes simplex virus type 2
ICD	International Classification of Diseases
IDU	Injection drug user
IQR	Interquartile range
MRSA	Methicillin-resistant *Staphylococcus aureus*
NEP	Needle exchange program
NPR	The National Patient Register

OR	Odds ratio
OST	Opioid substitution treatment
PCR	Polymerase chain reaction
PWID	People who inject drugs
S aureus	*Staphylococcus aureus*
SAMHSA	Substance Abuse and Mental Health Services Administration
SIF	Supervised injection facility
SMI	Swedish Institute for Communicable Disease Control
SSTI	Skin and soft tissue infection
STI	Sexually transmitted infection
UNODC	United Nations Office on Drugs and Crime

Introduction

People who inject drugs (PWID) are the main focus of this thesis. PWID constitute a vulnerable group in society with increased morbidity and mortality, and poorer socioeconomic conditions than the general population. Therefore, the health of PWID is of great importance from a clinical perspective.

PWID do, however, not constitute a homogenous group. Injection drug use includes several different substance syndromes and a wide range of socioeconomic characteristics. It is beyond the aim of this thesis to survey living conditions of PWID. However, a brief introduction of central concepts and research regarding PWID is necessary to lay the ground for a later discussion on behavioral and socioeconomic factors associated with bacterial infections and bacterial colonization.

The Introduction begins with a brief overview of the demographic characteristics of PWID as a group; i.e. prevalence of injection drug use, age, sex, economy and housing, as well as widely prevalent injection drugs. Thereafter follows a summary of previous research regarding comorbidity and bacterial infections in PWID. Finally, harm reduction research aiming to minimize infectious complications from injection drug use is briefly described.

Basic concept definitions: *Drugs*, *people who inject drugs* and *harm reduction*

Drugs will, in this thesis, be used to refer to illicit drugs, and legal drugs used in a nonmedical way. Misuse (previously named nonmedical use) of prescription drugs is defined by Substance Abuse and Mental Health Services Administration (SAMHSA) as use without a doctor's prescription, use in greater amounts, more often, longer, or in any other way different from a doctor's direction (1).

The term *people who inject drugs* (PWID) is defined as anyone who injects drugs nonmedically, no matter the legal status of the drug. In most cases this translates as illicit drug injection, but in some cases the injected drug can be legal, such as oral opioids or internet drugs not yet illegalized (1). PWID are usually but not necessarily substance dependent; also recreational injection drug use and injection of steroids and

appearance-changing drugs are included in the concept. Intravenous as well as intramuscular and subcutaneous injections are included. In the thesis, the term PWID, used in paper II, III, IV and V, is preferred to *injection drug users* (IDU) which was used in paper I. The latter term implies that someone who uses drugs is above all a *drug user* (rather than a person with a range of characteristics, interests and habits – of which drug use is one), and *PWID* is preferred due to it carrying less stereotypical connotations then IDU. Even though PWID is a wide concept that should be used with care, there are occasions when it is relevant to discuss PWID as a certain group or community. When PWID are found to be at statistically increased risk for health hazards, there are clinical implications to further investigate reasons and possible preventive strategies targeting PWID as a group. However, to avoid stigma and exotization, the wide heterogeneity within the epithet PWID should be considered continuously.

Harm reduction is an umbrella term that includes interventions and strategies aiming to improve the health and life quality of people who use drugs, but not necessarily aiming towards drug use cessation. Powelson et al. describe harm reduction as a "framework for public health intervention that focuses on a pragmatic and compassionate approach to reduce harms from unhealthy behaviors" (2). Harm reduction is controversial in Sweden and needle exchange programs (NEPs) are basically the only current form of harm reduction intervention. In many countries, harm reduction strategies are more developed (3–5), and besides NEPs there are supervised injection facilities (SIFs), overdose prevention, low threshold medical and social services. Opioid substitution treatment (OST) is an evidence based treatment of opioid dependence (6,7) that is sometimes also defined as a part of the spectrum of harm reduction interventions.

People who inject drugs

Four of the studies in the thesis concern Swedish people who use or inject drugs and, while one (paper II) includes PWID in San Francisco Bay Area. To be able to compare the results from these different settings, the living conditions and characteristics of PWID in Sweden and the U.S. are briefly sketched. However, it is beyond the scope of this thesis to assess drug use in the U.S. in any greater detail.

Prevalence of injection drug use

Globally, the number of PWID in the year 2014 was estimated to 12 million by United Nations Office on Drugs and Crime (UNODC) (8). The number of PWID in the U.S. year 2002 was estimated to be 1.3–2.6 million, and approximately 1% of U.S. residents aged 15–64 were estimated to inject drugs (9). According to UNODC, there were 2 million PWID in North America in 2014 (8). Based on data from 2008–2011, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has estimated that 1.3/1,000 persons in Sweden, which equals 0.11–0.25% of Swedes aged 15–64, inject drugs (10).

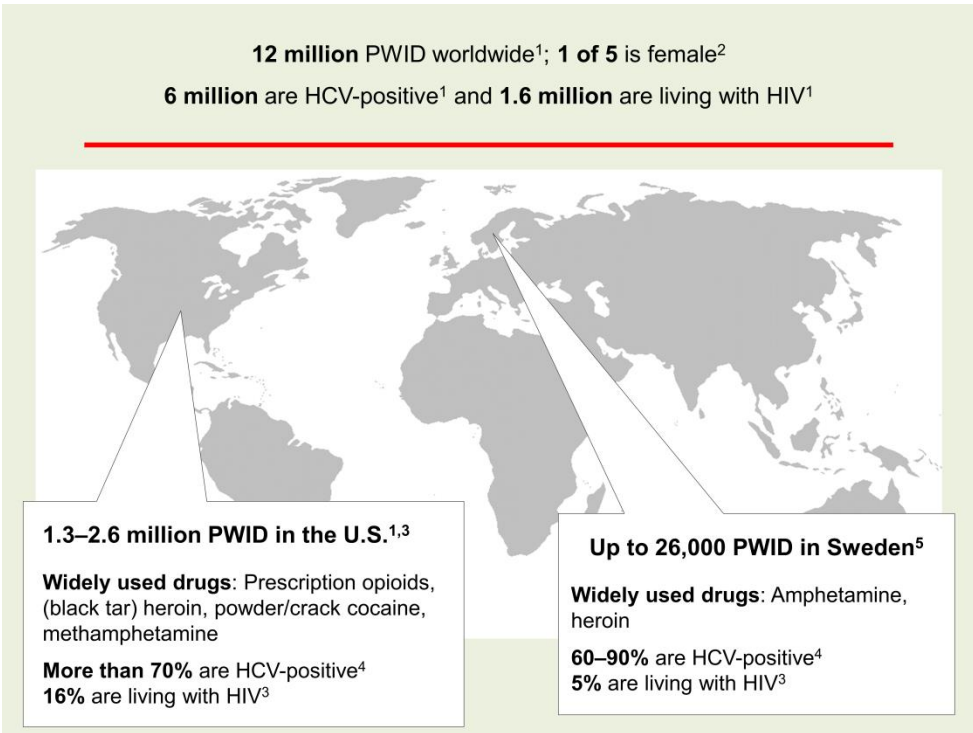

Figure 1. Prevalence of injection drug use and national drug use patterns in Sweden and the U.S.

[1] United Nations Office on Drugs and Crime, World Drug Report 2016. [2] Des Jarlais DC et al., Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas (Drug Alcohol Depend. 2012;124:95-107). [3] Mathers BM et al., Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review (Lancet. 2008;372:1733-45). [4] Nelson PK et al., Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews (Lancet. 2011;378(9791):571–83). [5] Byqvist S, Patterns of drug use among drug misusers in Sweden. Gender differences (Subst Use Misuse. 2006;41(13):1817–35). World map retrieved from Wiki Commons, public domain.

There exists no systematic data collection on the number of PWID in Sweden. According to an estimation from the Swedish Public Health Agency, at least 8,000 people in Sweden are thought to be PWID (11). "Heavy drug use" ("Tungt narkotikamissbruk") has been investigated in national surveillance reports in 1979, 1992 and 1998, based on estimated numbers reported by local informers (social services, healthcare, prison and probation service etc.) (12). "Heavy drug use" was equivalent to drug injection in the last 12 months or daily/almost daily use of illicit drugs in the last 4 weeks. The estimated numbers were 15,000 in 1979, 19,000 in 1992, and 26,000 in 1998 (12). Approximately 90% of these had injected drugs in the past 12 months. Another survey assessing illicit drug use in Sweden was conducted in 2004, and the number of people with "problematic drug use", based on inpatient care records, was still estimated to 26,000 (13). In 2007, "problematic drug use" was estimated to 29,500 persons, based on data from patient registers and the criminal justice system (14). Injection of drugs was not specifically assessed in the survey from 2007. According to the most current estimation of illicit drug use in Sweden, based on a questionnaire and web survey concerning alcohol, narcotics, doping and tobacco in 2013, 55,000 persons had used illicit drugs in the past 12 months (15).

Demographic characteristics of PWID

Male sex is overrepresented in most studies on drug use. Globally, only approximately 22% of PWID are estimated to be women (16). For people using heroin, cocaine and amphetamines, male sex is three times as common as female sex, while female sex is overrepresented for misuse of prescription drugs (8). In the nationwide Swedish surveys from 1979, 1992 and 1998, approximately 23% of people with "heavy drug use" were female, and the mean age was increasing from 27 years in 1979 to 37 years in 1998 (12). 55–60% was residing in the three counties containing Stockholm, Gothenburg and Malmö. At Malmö NEP, the percentage of female persons who frequents the facility has been approximately 25% since the start in 1987 (17).

Economic status and housing among PWID has been assessed in several studies from the U.S., and PWID display low education status, unemployment and poor economy (18). A recent study from California showed self-reported food insecurity in 58% of active PWID in San Francisco and Los Angeles, more prominent in homeless PWID, compared to 14% in the average U.S. population (19). In the said study, 63% reported being currently homeless, and 81% reported an income under USD 1,350/month. Food insecurity has been reported in previous studies on PWID from Canada, where 65% of PWID reported being currently hungry due to lack of money (20), and 55% of PWID reported not having enough to eat because of lack of money (21). In these Canadian studies, 51% of 144 PWID reported that they had slept

outdoors in the last 6 months (21), and unstable housing – but not use of any specific drug – was significantly associated with self-reported hunger (20). Poor nutrition status and nutritional deficits in PWID with HIV has been assessed previously (22).

Homelessness can be defined in several ways. It may be limited to strict lack of housing i.e. living on the streets, in a tent or in a shelter, but also include persons living indoors but not having one's own house or apartment. Unstable housing, defined as living in a single room occupancy hotel, transitional living arrangements, or being homeless, was prevalent in more than 60% of 1,585 PWID in Vancouver (23). Homelessness and food insecurity among Swedish PWID has been scarcely assessed. Twenty-six percent of people with "heavy drug use" in Sweden 1998 had unstable housing situation, and 60% were unemployed (24). In a dissertation including studies from Malmö NEP in the early 2000s, nearly half of the PWID participating in the study reported unstable housing in the past 12 months (25). In contrast, among female PWID participating in Malmö NEP, eleven percent reported being homeless or living in a shelter, while 54% had their own housing (26).

One of the studies in the thesis focuses PWID in the Swedish criminal justice system, which motivates a brief overview of health and injection drug use among incarcerated people. Data on the global percentage of PWID who are convicts is not available, but the numbers are presumably high since almost one of five sentenced prisoners is serving time for a drug offence (8). Previous studies show that a high percentage of people in the criminal justice system use drugs. According to an international review study, 10–48% of men and 30–60% of women in prison were dependent on illicit drugs (27). Data from the Swedish criminal justice system showed that 22% of male and 41% of female incarcerated people had been diagnosed with drug dependence (28). In a review from 2011 of studies on prisoners' health, Fazel and Baillargeon conclude that more than 20% of inmates in many prisons report a history of injection drug use (29). The authors also stress the remarkably high numbers of suicide and psychiatric illness (psychosis 4%, major depression 10–12% and personality syndrome 40–70%) and state that one in seven prisoners have a treatable mental illness (29). Sharing of injection equipment and overrepresentation of bloodborne infections (HIV, hepatitis B, hepatitis C) as well as tuberculosis are also stressed as important challenges for prisoners' health (29).

Common drugs administered through injection

More or less all drugs can be administered through injection. This includes many drugs that are commonly administered in other ways, such as smoking, snorting, inhaling, swallowing or rectal administration is more common. Injection causes a faster and more intense high, and is therefore sometimes preferred to other ways of administration. Most injectable drugs are preferably injected intravenously. Injections

can be located intramuscularly or subcutaneously, by mistake or on purpose. The drug use pattern among illicit drug users in Sweden has traditionally consisted of an, in international comparison, large number of amphetamine users (10,12). In the Swedish national survey from 1998 (24), 32% of persons with "heavy drug use" reported that amphetamine was their main drug, and 28% reported opiates.

In a survey from Malmö NEP, self-reported main drug was amphetamine in 57% and heroin in 42% of cases (30). In studies from Malmö NEP, the numbers of people using amphetamine was 67–75% and heroin 43–45% (25). In Sweden, amphetamine is commonly injected intravenously (12,31), but can also be snorted, orally consumed or inhaled/smoked. Amphetamine is a synthetic stimulant causing alertness, motoric restlessness and hunger suppression. Other stimulants are less common in Sweden. Methamphetamine is uncommon in Sweden but is of clinical importance and undergoing substantial increase since the 1990s in the U.S. (32,33), and has been a major health issue in Australia (34), Japan (35) and Thailand with spreading to other countries in Asia Pacific (36). Methamphetamine can be administered orally, snorted, smoked and inserted rectally, but is injected in approximately 20% of users according to U.S. studies (33,37). Cocaine use is common in the U.S. (38,39) and some European countries such as the U.K. and Spain (40) but relatively uncommon in Sweden (10,40). Cocaine is the most commonly used stimulant drug in Europe (10). In Sweden, cocaine is expensive and is mostly used occasionally for recreational purposes, and administered through snorting. Globally, cocaine can be used in powder form, or as crack cocaine which is cheaper and frequently used in the U.S. population (39).

Heroin is an opioid with depressant effects, derived from the opium poppy plant, that is widely used worldwide through injection or smoking/inhaling (8). Depending on the production area, heroin can have different characteristics in terms of color, physical state, purity and solubility. Heroin from "the Golden Triangle" in Southeast Asia is stereotypically a white powder with high water solubility, while heroin from Southwest Asia is usually a coarser powder with brown color. Black tar heroin is produced in Mexico and is a solid, sticky form of heroin with low purity (41). According to data based on drug seizures, brown heroin is most common in Sweden (13), while black tar heroin is commonly used in Southern and Western U.S. including the San Francisco Bay Area (42). In Sweden, people who use heroin are significantly younger than those using amphetamine (31).

Nonmedical use and injection of prescription drugs is a problem on the rise. Injection is described for opioid analgesics (43–45), methadone and buprenorphine (30,46,47), and methylphenidate (48). Methadone can be injected in its liquid form, and all opioid tablets can be crushed and injected. In the U.S., nonmedical use of prescription opioids is considered an epidemic posing an important threat on public health (8,49,50).

Mortality and morbidity among PWID: Putting bacterial infections in perspective

Infectious diseases are common hazards among PWID that should be understood as part of a larger cluster of somatic comorbidity affected by strictly medical as well as socioeconomic factors. Research on PWID's physical health is sparse, and much of previous studies concern bloodborne infections. Psychiatric comorbidity is also a vast problem among PWID but is beyond the scope of this thesis, as is overdose morbidity and mortality which is treated very briefly.

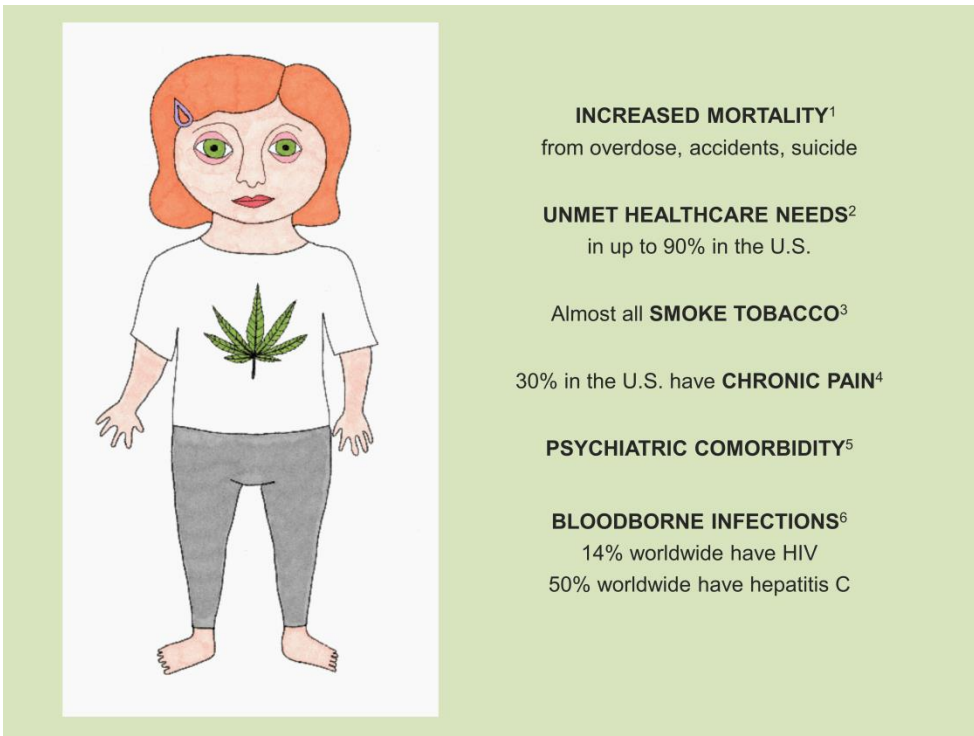

Figure 2. Overview of mortality and morbidity among PWID.

Illustration: Caroline Mannerfelt. [1] Degenhardt L et al., Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies (Addiction. 2011;106:32–51). [2] Chitwood DD et al., Satisfaction with access to health care among injection drug users, other drug users, and nonusers (J Behav Health Serv Res. 2002;29:189–97). [3] Federman AD, Arnsten JH, Primary care affiliations of adults in a methadone program with onsite care (J Addict Dis. 2007;26:27–34). [4] Heimer R et al., Prevalence and experience of chronic pain in suburban drug injectors (Drug Alcohol Depend. 2015;151:92–100). [5] Grant BF et al., Prevalence and Co-occurrence of Substance Use Disorders and Independent Mood and Anxiety Disorders: Results From the National Epidemiologic Survey on Alcohol and Related Conditions (Arch Gen Psychiatry. 2004;61(8):807–16). [6] United Nations Office on Drugs and Crime, World Drug Report 2016.

Mortality: Overdose, violence and accidents

Unnatural causes of death such as unintentional poisoning (overdose), poisoning with unclear intent, accidents, homicide and suicide, are dramatically overrepresented among people who use and inject drugs. UNODC estimated that in year 2014, 207,400 deaths worldwide were drug-related (8). According to Ericsson et al., at least 84% of deaths among clients in the Swedish criminal justice system primarily using amphetamine were violent or drug-related (51). These findings are in line with other Swedish follow-up studies assessing causes of death among criminal justice clients with substance use problems. In a longitudinal study, Chang et al. identified alcohol and drug dependence as factors significantly increasing the risk of death among previously incarcerated people in the Swedish criminal justice system (28). Overall mortality in the study by Chang et al. was 6% after release from prison. Hakansson and Berglund showed that unnatural causes of death were prevalent in 84% of deceased criminal justice clients who used drugs (52). Overdose was the registered cause of death in 27%, and other common causes of death were poisoning/injury with undetermined intent (12%), traffic accidents (13%) and suicide (10%). Heroin use was significantly predicting death in this population (52), and in a more recent study on the same study sample (53) heroin use predicted both fatal accidental intoxication and fatal intoxication/injury with undetermined intent. International meta-analysis data note similar risk increase of unnatural death among people with substance use disorders and people who use opioids (54).

Overdose is the single most common cause of death among people who use heroin (55), and mortality is dramatically increased compared to the general population (6,55,56). People who use opioids including heroin are estimated to have mortality rates 15 times higher than the general population (57). Previous mortality data from Sweden have identified heroin-related fatalities as predominant causes of death not only among people using heroin but also among those mainly using amphetamine and other drugs (58). In Sweden, the number of fatal opioid overdoses have been increasing since the early 1990s, and mortality rates are currently among the highest in Europe (10,59–61). While the European average number of drug related deaths among individuals aged 15–64 is 17 per million individuals, the Swedish number is 70 per million (61,62). Interview studies from Malmö NEP have shown that 50–74% of people who injected heroin had survived at least one overdose (63,64), and 96% of people who used heroin had witnessed someone else having an overdose (63).

Self-perceived health and unmet healthcare needs

Perceived need of healthcare among PWID has been assessed in a number of surveys from the U.S. around year 2000. These studies were comparing healthcare satisfaction in PWID, non-injecting drug users and non-drug users, and showed that almost 90% of PWID in Miami reported a need for healthcare in the past year (65). Among PWID, 76–87% reported unmet healthcare needs in the past year, and injection drug use was significantly associated with higher odds for unmet healthcare needs (65,66). In another U.S. study by Chitwood et al., 43% of 224 PWID in the study reported self-perceived fair/poor health, while only 25% had received primary physical examination in the past 12 months (67). Both people with injection and non-injection drug use had significantly lower odds for having received primary preventive healthcare than non-drug users.

In a recent interview study from San Francisco, women who were using methamphetamine (approximately half of the sample were PWID) had unmet healthcare needs concerning chronic diseases, sexual/gynecological health (92% reported a need for women's preventive healthcare and 46% had an unmet need for care in the last year), and dermatological healthcare (35% reported need for healthcare, and 66% of these had an unmet need for care in the last six months) (2). In the same study, 69% reported a healthcare need for a chronic health condition, and 31% had an unmet need for care in the last six months. Women who had a healthcare provider or a case manager had lower odds for unmet healthcare needs for a chronic health condition/women's preventive healthcare, and dermatologic care, respectively.

Problem areas concerning PWID's health

Non-infectious conditions

Research on chronic medical conditions in PWID is sparse. Chronic diseases that are common in the general Swedish population, such as diabetes mellitus, cardiovascular diseases, musculoskeletal problems and asthma/Chronic Obstructive Pulmonary Disease (COPD) have not been assessed specifically in PWID in Sweden. In a New York based study from 2007, 76% of previous heroin users currently in OST reported one or more chronic conditions (including asthma, COPD, hypertension and diabetes), and 26% had three or more chronic conditions (68). In a review article from 2007, Kaye et al. showed that people using amphetamines have increased risk of cardiovascular pathology, which is suggested to be caused by the toxic effects from stimulant drugs (69).

Previous research has shown that up to nine out of ten patients in OST smoke tobacco (68,70) and it has been suggested that chronic diseases related to smoking

and low socioeconomic status, such as diabetes mellitus, hypertension and asthma/COPD, are likely to be overrepresented. Among Swedish convicts mainly using amphetamine or heroin, 94–96% were daily smokers (52). An American follow-up study of the physical health among aging people who use drugs showed that more than half of the study participants had hypertension, and more than one third suffered from pulmonary dysfunction (71).

There are a small number of studies on physical pain in PWID, suggesting that chronic venous insufficiency, causing chronic leg pain, is common (72,73). In these studies, foot trauma is also suggested to be a common reason for lower extremity pain. One third of PWID in previous studies from the 2010s reported chronic pain (74,75). Among HIV-positive patients, those who inject drugs have been shown to report more pain than those who do not inject drugs (76,77). Other common causes of pain among PWID are dental and oral problems, such as cavities. An interview study with 340 street drug users in San Francisco showed that while 63% of participants experienced need for oral healthcare in the past six months, only 27% of them had actually sought care (78).

Dermatological problems other than bacterial infections have been described among people who use and inject drugs, more specifically if using stimulants such as methamphetamine (79). In addition, injection related injuries and complications may cause dermatological conditions such as scarring, necrosis and ischemia. People living under unstable housing conditions are often subject to diseases carried by lice and scabies, skin infections, trauma, and eczemas (80–82). The feet are particularly vulnerable (80,81), with diabetes neuropathy, trauma, poor hygiene, unfitting shoes all being part of the explanation (81).

Psychiatric comorbidity

Psychiatric comorbidity constitutes a large problem among people with substance use problems. Association between substance use disorders and psychiatric problems are well described in the scientific literature, for mood and anxiety disorders (83), schizophrenia (84), antisocial personality syndrome (85) and Attention Deficit and Hyperactivity Disorder (ADHD) (86). Drug use patterns have also been associated with specific psychiatric comorbidity such as depression and suicide among people who use heroin (87) and psychotic symptoms and schizophrenia among people who use stimulants (88–90) and people with polysubstance use (91). Apart from high overdose mortality, an overrepresentation of suicidal behavior and suicide mortality is described among people with substance use disorders in international (92) and Swedish (51–53) studies. Among people with heroin dependence at Malmö NEP, one out of three reported previous suicide attempt (93). Association between cannabis use and psychosis/schizophrenia is well described in the scientific literature (94–96) but is beyond the scope of this thesis.

Bloodborne and sexually transmitted infections

Chronic or potentially chronic bloodborne viral infections are common among PWID. According to global data from UNODC in 2016, 14% of all PWID worldwide (which equals 1.6 million PWID) are living with HIV and as much as one in two PWID (6 million) have hepatitis C (8).

While the estimated hepatitis C prevalence among PWID varies greatly between geographic regions, the prevalence is estimated to be 40% or more in 61 of 77 countries with accessible data, and in 12 countries at least 80% of PWID are estimated to be infected (97). The prevalence of hepatitis C-antibodies (anti-HCV) is between 62–88% among PWID in Sweden, and 70–77% in the U.S. (97). In a recent Swedish study, Jerkeman et al. showed that 88% of patients in opioid substitution treatment were anti-HCV-positive, 69% were viremic, and two thirds of the viremic patients had significant liver fibrosis (98). In a study assessing attitudes towards hepatitis C among people with heroin dependence in Malmö, 80% reported that they had hepatitis C, while only 23% have had any kind of healthcare contact concerning their hepatitis (99). In an Australian study, 73% of PWID visiting a NEP tested positive for hepatitis C virus (HCV) while only 36% were aware of their HCV status prior to testing (100).

The high hepatitis C prevalence among PWID is of great clinical importance since chronic HCV-infection is the most common cause of end-stage liver disease in North America (101) and Europe (102). Up to 20% of patients with chronic HCV-infection are estimated to develop cirrhosis over 20 years with 1–5% annual risk of liver decompensation and/or hepatocellular carcinoma (103–105). Annual mortality rate is up to 18% in cirrhotic patients with significant liver decompensation (106). In an Australian cohort study from 2011, liver disease, mostly caused by HCV, was the most common cause death among aging people with opioid dependence recruited from OST facilities (107). Liver mortality was 17 times higher among people with opioid dependence than in the general population (107). Similar data were provided by Larney et al. (2013) where liver-related mortality was almost 10 times higher in patients with opioid dependence, and 76% of those with fatal liver disease had HCV (108). Hser et al. showed that 50% of aging people who used drugs had liver dysfunction (71).

HIV-infection poses a great health threat to PWID worldwide. In a study from 2008, approximately one of five PWID was estimated to be HIV-infected, which equals 10% of the 33 million people living with HIV (9). While HIV prevalence rates among PWID varies greatly, average numbers are 12% in China, 16% in the U.S. (9–22%), and 37% in Russia. Nine countries (Thailand, Vietnam, Kenya, Brazil, Nepal, Indonesia, Burma, Estonia and Argentina) have HIV prevalence rates among PWID that exceeds 40% (9). Coinfection of HIV and HCV is common among PWID, with up to 45–90% prevalence (highest prevalence among Indian PWID) in some cohorts

(109). Coinfection HIV/HCV increases the risk of hepatocellular cancer due to HCV and earlier progression to HCC (109). HIV prevalence among PWID in Sweden is low in an international perspective, 5.4% (9), with numbers ranging from less than 1% at Malmö NEP (110) to 7% in Stockholm (111).

Sexually transmitted infections (STI) and unsafe sexual behaviors are common among people who use and inject drugs. A review of 11 studies from the U.S. assessing herpes simplex virus type 2 (HSV-2) in people who used drugs showed HSV-2 seroprevalence in 38–75% (112). Studies from Australia and the U.S. have shown current rates of STI (mainly Chlamydia, but also Gonorrhea and Trichomonas) in 7–8% of PWID (100,113). STI prevalence was higher in PWID who reported that crack cocaine was their drug of choice, and the authors found an association between crack cocaine use and involvement in sex trade (buying or selling) (113). Injection of drugs in the past six months was significantly associated with *N. gonorrhoeae* and *C. trachomatis* in a Canadian study from year 2001 (114).

As part of HIV risk-reduction, previous studies have investigated risk-taking sexual behavior and unprotected sex in communities of PWID. In an interview study assessing high-risk sexual practices among San Francisco based on men who had sex with men and were injecting drugs, 70% of those who reported that they were HIV-positive and practicing intercourse had unprotected sex (115). Inconsistent condom use is described in other studies on PWID in the U.S. (116) and heroin users in Spain (117). High-risk behaviors such as unprotected sex and syringe-sharing were identified among PWID in an Australian study, where 65% had unprotected sex in the past six months (100). Among young PWID in Baltimore, 68% had two or more sex partners in the past three months, and fewer than half of these were consistently using condom (118). In a national survey with 2,400 PWID from England, Wales and Northern Ireland, unprotected sex in the last year was reported by two thirds (59–66%) of both male and female sex workers and non-sex workers (119). Involvement in sex work, i.e. trade of sex in exchange for money, drugs, other goods or favors, is much more common among female PWID than among male PWID. Numbers of female and male PWID, respectively, engaging in sex work are ranging from 31% and 8% in England, Wales and Ireland (119) to 72% and 6% in Estonia (120). STI prevalence among PWID in Sweden has not been systematically investigated. Sex work in the past 14 days was reported by 22% of female PWID at Malmö NEP (26).

Bacterial infections affecting PWID

General aspects

Apart from SSTI, PWID are subject to a variety of bacterial infections (Table 1). Tuberculosis among PWID living under poor socioeconomic conditions (121,122) and incarcerated PWID (29) has been described in the scientific literature. In studies from the U.S., clonal outbreaks of tuberculosis have been noted among people using cannabis, crack cocaine, methamphetamine (123–125). Globally, prevalence rates of active tuberculosis in PWID are widely varying from 0.5% in U.S. samples to 66% in Portugal (121). Tuberculosis among PWID is associated with HIV and HCV co-infection (126). Cluster outbreaks of infections from spore-forming bacteria such as *Clostridia* causing botulism and tetanus, and *Bacillus anthracis* causing anthrax have been described in PWID in the U.S. (127) and Europe (128,129), and the suggested route of infection has been from contaminated heroin batches.

While central nervous system (CNS) infections are usually not considered a consequence of injection drug use, they include abscesses and secondary foci from septicemia that can be injection-related. In previous research, meningitis has been associated with household crowding, low socioeconomic status, smoking, alcohol dependence and sexual habits (130). Meningococcal meningitis has also been described in clusters of people using methamphetamine and cocaine, and the hypothesized route of infection has been bacterial transfer from close contact and cramped living rather than injections themselves (130).

In this thesis, bacterial infections affecting PWID are selected because of their presumed association with injection drug use. SSTI, septicemia, bone and joint infections and cardiac infections can all be caused by bacterial transfer from the skin, from the drug or from drug paraphernalia/drug adulterants, to the tissues or bloodstream. Pulmonary infections including pneumonia and tuberculosis, urinary tract infections and gastrointestinal infections are not considered to be injection-related, and are subsequently not discussed further.

Table 1. Overview of bacterial infections among people who inject drugs (PWID).

Type of infection	Statistical association with injection drug use	Lifetime prevalence among PWID
Skin and soft tissue infection	Unknown	6–69% (131)[2]
Septicemia	Yes[1] (132)	2–10% (131)[3]
Infective endocarditis	Yes (133)	0.5–12% (131)[4]
Bone and joint infection	Unknown	0.5–2% (131)[5]
Necrotizing fasciitis	Yes (134)	3.9% in the U.S. (135)
Central nervous system infection	Unknown	Unknown
Tuberculosis	Unknown	0.5–66% (121)[6]

[1] Assessed for invasive pneumococcal infection (90%< bacteremia) in people with HIV.
[2] Studies from Australia, Taiwan, the U.S., Iran, Scotland, Mexico and Ireland.
[3] Studies from Australia, the U.K. and the U.S.
[4] Studies from Australia, the U.K., the U.S., Iran and Denmark.
[5] Studies from Australia and the U.S.
[6] Studies from Portugal, Hungary, Switzerland, Spain, India, Thailand, Malaysia, Iran, Taiwan, Brazil and the U.S.

Prevalence data on bacterial infections among PWID

Skin and soft tissue infections

Skin and soft tissue infections (SSTI) are infections in the dermis, epidermis or subcutis. In this thesis, SSTI is defined as abscess and cellulitis, in contrast to surgical wound infection, decubitus etc. Bacterial infections affecting skin and soft tissues are common in PWID. In previous research, SSTI lifetime prevalence in PWID range between 6% and 69% (131), with lower prevalence in Australia (136,137) and higher prevalence in Mexico, Canada and the U.S. (135,138,139). SSTI is also the most common cause of hospital admission and emergency department visits among PWID (140–143). Prevalence of SSTI is not previously described among PWID in Sweden.

Systemic bacterial infections

Several systemic bacterial infections are overrepresented in PWID. In a recent review study, Larney et al. reported lifetime prevalence of systemic infections among PWID in 2–10% for sepsis, 0.5–12% for infective endocarditis, and 0.5–2% for bone and joint infections (131). Increased risk of systemic infections among PWID has been shown for endocarditis (133) and necrotizing fasciitis (134), but there is a notable sparsity of large-scale studies comparing morbidity among PWID and non-PWID. Larney et al. found only one study in which older age and injecting career was associated with infective endocarditis (144), but no studies assessing predictors for septicemia, bone/joint infections or other infections among PWID (131).

In a Danish study, Harboe et al. identified injection drug use as significantly associated with increased risk of invasive pneumococcal infection (bacteremia in more than 90%) among individuals with HIV (132). The authors noted that risk of invasive pneumococcal infection remained unchanged over time for PWID while it decreased in the general sample. Infective endocarditis, defined as bacterial or fungal infection in the endocardium, is described as a consequence of injection drug use in clinical reports (145–153). In previous research, drug use has been related to 6–64% of hospitalizations due to infective endocarditis (146,154–157). Spijkerman et al. (1996) showed that endocarditis was independently associated with HIV-infection and previous endocarditis (158). In the study by Spijkerman et al., female sex and SSTI appeared to increase the odds for endocarditis, but it did not reach statistical significance. According to Swedish register data, PWID have been noted to be at 60 times higher risk of infective endocarditis compared to non-PWID of the same age (159). The incidence of endocarditis in Sweden is 6–8/100,000 persons per year and increasing with age (159,160). Swedish incidence rates are within the range of international endocarditis incidence, 3–10/100,000 persons per year (161). It is notable that right-sided endocarditis, affecting the tricuspid valve, is more closely associated with injection drug use (146,152,153). According to Swedish data, 76% of patients with right-sided endocarditis are PWID (159). The suggested route of infection is transfer of bacteria and debris from injection into the right side of the heart from the blood-stream (146). The most common pathogen is *Staphylococcus aureus* (*S. aureus*), followed by streptococci and enterococci (159,161,162).

Bone and joint infections in PWID have been assessed in clinical descriptions and case reports (163–171). While only 4% of patients with hematogenous vertebral osteomyelitis had a history of injection drug use in a U.S. study from 2010 (172), an older (year 2000) study from the U.S. showed that 25% of patients with vertebral osteomyelitis reported drug injection in the month prior to admission (173). Necrotizing fasciitis among PWID is also assessed through case reports, where special attention is given to skin popping and injection of black tar heroin as potential risk factors (174–176). Lifetime prevalence of necrotizing fasciitis among PWID was almost 4% in a U.S. study published in 2010 (135).

Fatal bacterial infections

Fatal bacterial infections in PWID have been sparsely investigated. PWID have been shown to have lower or comparable mortality rates than non-PWID from necrotizing fasciitis (134), infective endocarditis (133) and streptococcal bacteremia (177). In a North American study comparing clinical profile of PWID and non-PWID presenting at an emergency department, PWID had higher rates of SSTI but no significant differences in length of hospital stay or mortality (178). Pedersen et al. conducted a study on outcome of *S. aureus* meningitis, a rare type of meningitis, where PWID – counting for 12 cases of 96 – had significantly lower mortality than

non-PWID in univariate analysis but not in multivariate analysis including age, comorbidity and critical illness as covariates (179). Overall mortality from *S. aureus* meningitis was 56%.

In general, *S. aureus* bacteremia has mortality rates around 20–30% in studies from Denmark (180) and the U.K. (181), but was not assessed specifically in PWID in these studies. Overall mortality after endocarditis was 7% in HIV-negative PWID in studies from the 1990s (148,150), and 4% in PWID with right-sided *S. aureus* endocarditis in a retrospective Spanish study covering 22 years (182). After surgical intervention for infective endocarditis, injection drug use was associated with a 10-fold hazard ratio increase of death or reoperation (183). Complications from and mortality of left-sided endocarditis is higher than mortality of right-sided endocarditis (mortality 38% and 17%, respectively) (182), which can explain the lower mortality among PWID. A Swedish nationwide study showed low 30-day mortality rates (6.5%) due to infective endocarditis among PWID – who were a young subpopulation with a median age of 39 years and were more often diagnosed with right-sided endocarditis – but the long-term standardized mortality ratio was high, 19.2 (160).

Mortality rate is high and sequelae due to necrotizing fasciitis are common. A recent multi-center review study from the U.S. showed mortality rates 9–22% in the general population (184). In a study from 1998, necrotizing soft tissue infections was studied in 30 PWID, with a mortality rate of 20% (185). In a U.S. study from year 2001, 29% did not survive (10% of PWID and 21% of non-PWID), and 29% had >5% of their total body surface debrided (134). The lower mortality rate in PWID was interpreted as a result of the younger age and less comorbidities, such as diabetes mellitus, among PWID.

Association between SSTI and systemic infections

Patients with bacterial SSTI often need medical assistance with drainage and/or antibiotics. The infections can also lead to serious complications, sometimes needing inpatient care. SSTI can lead to spreading of bacteria from the local infection site, to the bloodstream and vital organs, and cause for example sepsis, endocarditis and osteomyelitis (186–188).

Association between SSTI and invasive infections in PWID is scarcely investigated. In a Norwegian study, 179 cases of SSTI in PWID led to complications in only a few cases; two patients had deep venous thrombosis and one needed skin transplant (189). In contrast, a Danish study conducted in the 1980s showed serious complications (amputation, thrombosis, pneumonia, septicemia, compartment syndrome) of acute injection site soft tissue infections needing hospitalization in 17 of 89 cases, including 4 lower-extremity amputations due to arterial lesions (190).

SSTI was the most commonly identified focus of community-acquired *S. aureus* bacteremia in a Danish longitudinal study (180), while 60% of cases did not have an identified infection focus. Methicillin-resistant *S. aureus* (MRSA) bacteremia was significantly associated with SSTI in a British epidemiological study (191). In this study, an increase in the proportion of episodes of MRSA bacteremia associated with SSTI was noted. In an American study assessing hematogenous vertebral osteomyelitis, SSTI in the past 30 days was a predisposing factor (172).

SSTI correlates and suggested etiology

To develop an SSTI, two basic things are necessary (192):

1) Pathogenic microbes and

2) Lesions in the skin barrier.

Most research on predictors for SSTI among PWID focus the latter category, and stress the importance of demographic and behavioral characteristics increasing the risk of SSTI. Several variables have been associated with SSTI, and in review articles the authors stress female sex, skin-popping, frequent injections and the use of certain substances such as speedball and black tar heroin as risk factors of SSTI (131,193,194). Five different categories of predictors are presented in Table 2 below.

Since risk factors associated with SSTI among PWID include demographic, medical, hygiene, drug associated and injection associated factors, the etiology for SSTI is most likely multifactorial, and can be viewed from several perspectives. Here, suggested SSTI etiology is presented from one macro-level *contextual perspective* focusing demographic and lifestyle related correlates of SSTI; one local *injection related perspective* focusing behavioral factors that are likely to facilitate bacterial transfer and bacterial growth; and one micro-level *microbiological perspective*, with specific pathogens and their prevalence in focus.

Table 2. Overview of factors associated with skin and soft tissue infections among people who inject drugs. Independent associations in multivariate analysis, if not stated otherwise.

	Factors associated with skin and soft tissue infections (SSTI)
CONTEXTUAL FACTORS	
Demographic	Female sex (23,138,158,195–198) Homelessness/cramped housing (23,136,197–199) Sex trade (23,138,158) Older age; Age 24< (136,196)
Medical	HIV-status (23,158) Hepatitis C-status (196,199) Recent overdose (199,200)
INJECTION RELATED FACTORS	
Drug related	Use of speedball (heroin + cocaine) (140,158) Methamphetamine smoking (138) Frequent cocaine use (23); crack cocaine injection (196); daily cocaine injection (197) Heroin use[1] (195) Non-powder injection (136) Injection of both opioids and stimulants (198)
Hygiene related	Contaminated/reused needles (140,196,198,199) Injection site cleaning frequency (135,139,140,195,196,200) Hand washing frequency before injecting[2] (136)
Injection related	Injection in the groin[1] (196); injection in the neck[1] (196,198) Multiple site injection (200) Duration of injecting (195,198,199) Being injected by someone else (138,197) Injection frequency (136,158,196,198,200); injection frequency of heroin[1] (135,195) Subcutaneous/intramuscular injection (135,139,140,195) Syringe sharing (197,199)

[1] Bivariate association only.
[2] Association with injection-related injuries and diseases including but not limited to SSTI.

A contextual perspective on SSTI – Demographic and lifestyle factors

Biological sex has been consistently shown to be a strong predictor, with female PWID being at higher risk for SSTI than males (23,138,158,195–198,201). One hypothesized mechanism is that females characteristically have smaller veins and therefore may be more likely to inject extravascularly (202). Gender dynamics within networks of PWID has also been discussed as a possible, however much more complex, reason of this association (197). In qualitative research, female PWID have been previously described to have less control over drug acquisition, preparation and administration – including equipment sharing and assisted injections – than male PWID (203). Other demographic factors that have been found to be associated with

SSTI include unstable housing or homelessness (23,136,197,198). Descriptive studies show that skin infections are common among homeless people living in shelters (82).

Susceptibility to SSTI is also assessed in studies showing association between HIV-infection and SSTI (23,158). Studies regarding HIV and SSTI have, however, yielded diverging findings and other studies did not find an association (140).

An injection related perspective on SSTI – Behavioral factors

Several injection practices have been linked to SSTI. For example, injecting in the femoral vein has been shown to be associated with higher risk for SSTI (196), presumably due to the heavy bacterial load in the groin and genital area (204). Some data suggest that licking the needle before injection increases the risk of infections due to transfer of pharyngeal or oral bacteria to the tissues or bloodstream (202). This route of infection is described for osteomyelitis (170). In a study by Binswanger et al., licking the needle before injection was associated with higher prevalence of SSTI, but the finding did not reach statistical significance (139). Extravasal injection, both intramuscular and subcutaneous ("skin-popping"), can cause tissue irritation and scarring and has been associated with SSTI in several studies (135,139,140,195,201). High injection frequency is a known risk factor for SSTI in PWID (135,136,158,196,198,200).

The physical properties of the drugs themselves may cause tissue damage and promote SSTI. In addition to SSTI, injection of non-powder drugs has been described to cause ischemia and vein damage (46,136,205–209). SSTI have been described after injection of specific substances, such as buprenorphine tablets (210,211) and speedball (mix of heroin and cocaine) (140,158). Even within a given type of illicit drug, there may be differences in SSTI risk depending upon the formulation of the drug. For example, Black tar heroin may be more strongly associated with SSTI than white powder heroin, possibly due to venous inflammation and scarring, which may lead to more frequent intramuscular or subcutaneous injections (212). Rapid vein loss due to drug adulterant acidity has been suggested to be a factor involved in PWID's high prevalence of SSTI (213). Direct and indirect immuno-modulating effects from several drugs (cannabis, opioids including heroin, stimulants such as cocaine and amphetamines) have been suggested to affect PWID's susceptibility to bacterial, viral and fungal infections (194).

Lack of hygiene involving the dermis and the needles appear to be risk factors of SSTI. Infrequent skin cleaning prior to injection (135,139,140,195,196,200) and sharing equipment (197,199) or using contaminated needles (140,196–199) have been identified as factors associated with SSTI.

A microbiological perspective on SSTI – Common pathogens and routes of infection

Most studies conducted among PWID are focusing behavioral and demographic risk factors, and few microbiological studies exist (214,215). Important routes of infection are listed in Figure 3 below.

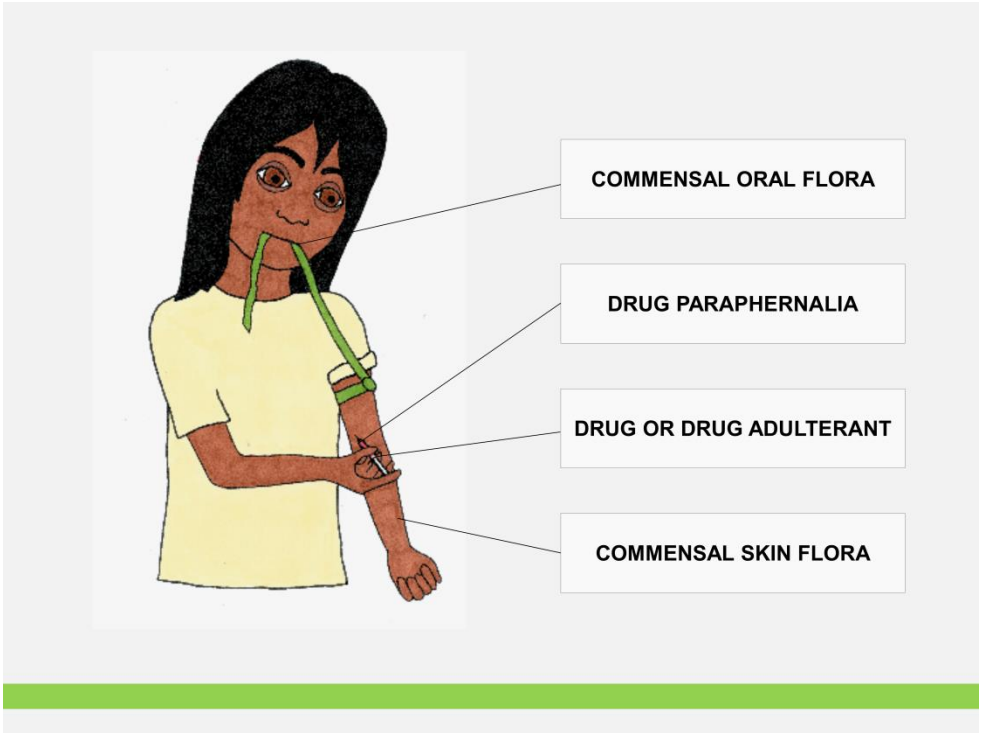

Figure 3. Overview of routes of bacterial infection among people who inject drugs.

Illustration: Caroline Mannerfelt. Information retrieved from Kaushik KS et al., Shooting up: The interface of microbial infections and drug abuse (J Med Microbiol. 2011;60:408–22) and Swisher LA et al., Needle licker's osteomyelitis (Am J Emerg Med. 1994;12:343–6).

The most common pathogen causing SSTI is *S. aureus* (192), a potentially pathogen bacterium that can colonize or infect skin and mucosa. Other pathogens, such as *Clostridia* and other spore-forming bacteria have also been identified as SSTI pathogens (192–194). *S. aureus* is normally not colonizing intact skin. PWID are often affected by superficial and invasive infections with *S. aureus*, which result in increased length and cost of hospitalization (202). Microbiological studies have shown that PWID are more frequently colonized with *S. aureus* than the average population (35% of recent injectors compared to 11% in healthy controls, $p<0.05$)

(216), with nasal colonization in 28-45% (217–219) and overall colonization in 39% (220). Already in the 1930s, association between *S. aureus* nasal colonization and increased risk for infection was reported (221). This finding has been supported by several more recent studies (221–224). *S. aureus* infections have been suggested to originate from endogenous nasal bacteria that spread to the skin, which in turn cause infection when the integrity of the skin is compromised (223). In a study by von Eiff et al., approximately 80% of *S. aureus* bacteremia was caused by a pathogen identical to the *S. aureus* stem colonizing the subject's nose (224).

Another concern regarding *S. aureus* is antibiotic resistance, as in the case of methicillin-resistant *S. aureus* (MRSA). With the increasing spread of antibiotic resistance in general, hospital- and community acquired MRSA has become a major clinical issue globally (215). Sweden is a low prevalence country, with MRSA prevalence in approximately 1% of blood cultures positive for *S. aureus* (225). Injection drug use is associated with MRSA colonization and infection in studies from the U.S., the U.K. and Egypt (226–229). Outbreaks of community-acquired MRSA have been reported in populations of PWID in the U.S. (228) and Switzerland (230). Illicit drug use administered through other routes than injection (smoking, inhaling, snorting, etc.) has been associated with MRSA colonization (226), MRSA bacteremia (231) and MRSA SSTI (232,233).

Single clones or strains of MRSA and *S. aureus* have been identified in PWID communities, implicating spreading through close social contacts. In two Swiss studies from the early 2000s, one single clone of MRSA resulted in an epidemic spread in the PWID community (230,234). The same MRSA clone remained in the PWID community at almost identical prevalence in a follow-up study two years later (235), indicating that close contact between PWID might be part of the explanation for increased MRSA risk. Other studies have supported that similar strains or clones of both MRSA (236) and methicillin susceptible *S. aureus* (218,237) tend to colonize people who use drugs (PWID and non-injectors) within the same community.

Apart from *S. aureus*, pathogens which are supposedly associated with injection drug use due to cluster outbreaks among PWID are spore forming bacteria such as *Clostridia* and *Bacillus* species (127–129) and *Pseudomonas aeruginosa* (194) that may contaminate the drug, the solution water, or the drug adulterant. Bacterial infections after needle licking have also been described, where notified pathogens have been bacteria from the oral flora such as *Streptococcus milleri* (194) and *Eikenella corrodens* (170). Other microorganisms such as fungi and parasites are also identified as important pathogens among PWID in the literature (194), but are beyond the scope of this thesis.

In conclusion, SSTI among PWID is a multifactorial problem requiring both microbiological and behavioral approach. SSTI might be prevented through better knowledge of prevalence and risk factors that can provide evidence based preventive interventions. Thus, clinical as well as epidemiological studies on prevalence and risk factors of SSTI among PWID have significant clinical implications.

Infection prevention research among PWID

Specific research on bacterial infection prevention among PWID is not thoroughly investigated. A few small pilot studies have evaluated injection technique and hygiene education (238,239), and the results were promising in terms of safe injection behaviors as well as the rate of bacterial infections. Decolonization studies to prevent SSTI have been conducted in cohorts consisting of American recruits. Some studies did not find any SSTI preventive effect from skin decolonization with chlorhexidine (240,241), while others have shown association between chlorhexidine body wash and reduced nasal MRSA colonization (242). In dermatological clinical praxis, chlorhexidine body wash is used for treatment of furunculosis (243). Studies evaluating the effects of skin decolonization in PWID are lacking.

Sharing of syringes with high dead-space may increase the risk of bloodborne viral infections since they retain over 1000 times more blood after rinsing than low dead-space syringes (244–246). The importance of syringe dead-space for *bacterial* infections is, however, not investigated. Filters have been experimentally shown to remove large particles and bacteria when injecting crushed tablets (247–249), but their use has not been evaluated as an infection prevention method among PWID.

In a broader sense, other harm reduction facilities may prevent infections in PWID. Previous research has shown review-level evidence for NEPs effect on risk for viral infections (250). NEPs have been proposed as a platform for bacterial infection prevention as well, but this has never been thoroughly evaluated. NEPs are used as harm reduction in both Sweden (Malmö) and the U.S. (San Francisco). Supervised injection facilities (SIFs) are present in Canada, Australia and several European countries including Norway and Denmark (251,252), but not in Sweden. SIFs as a means of reducing SSTI through sufficient time for injection and access to cleaning equipment has been discussed, while the most stressed benefit from SIFs are decreased overdose rates (253,254). To some extent opioid substitution treatment (OST) can be considered as harm reduction, as it aims at making PWID decrease or abandon injection as a route of drug administration. According to previous studies, OST has had an effect on decreasing the risk of HIV and hepatitis C (250), but potential effects on bacterial infections do not seem to have been investigated.

Aims of the thesis

General aim

The main aim of this thesis was to investigate to what extent PWID are subject to bacterial infections, especially SSTI, and identify groups and behaviors associated with increased risk of infection. Four of the five studies were conducted in Sweden, while paper II was conducted in the U.S. (San Francisco Bay Area, California), which allowed analyses of SSTI and its correlates in settings with different drug use patterns, healthcare systems and harm reduction practices.

Study specific aims

(I) To study self-reported SSTI prevalence among PWID at Malmö NEP. A second aim was to identify factors associated with self-reported SSTI.

(II) To study self-reported prevalence of SSTI, and correlates of SSTI, among community PWID in San Francisco Bay Area. The focus in this study was behavioral correlates in terms of injection habits.

(III) To investigate the incidence rates of diagnosed SSTI, systemic bacterial infections, and fatal bacterial infections, among PWID in the Swedish criminal justice system. A second aim was to survey demographic and drug use related factors associated with SSTI and systemic bacterial infection.

(IV) To investigate the number of reported MRSA cases among Swedish subjects with opioid and amphetamine dependence compared with a control group of subjects with alcohol dependence.

(V) To investigate the prevalence of methicillin-sensitive and -resistant *S. aureus* among PWID at Malmö NEP, and compare it to that of non-injectors with substance syndrome. A second aim was to examine the quantitative level and body distribution of *S. aureus* colonization among PWID.

Material and methods

The methods in this thesis include bacterial sampling and laboratory methods, questionnaire-based interviews, and analysis of register data. An overview of the methods is shown in Table 3. A more detailed discussion regarding methodological limitations and strengths follows in the Discussion section.

Study design

Paper I, II and V were clinical studies, and paper III and IV were epidemiological. Paper I and II were questionnaire-based interview studies. Paper III was a prospective register follow-up cohort study. Paper IV was a retrospective register study with longitudinal design. Paper V was a cross-sectional clinical study that used microbiological methods (culture and PCR), and also included a short questionnaire. All studies were observational.

Table 3. Methodological overview of paper I–V.

SSTI, skin and soft tissue infection; *S. aureus*; *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; GEE, generalized estimating equations.

Characteristic	Paper I	Paper II	Paper III	Paper IV	Paper V
STUDY DESIGN					
Type of study	Cross-sectional	Cross-sectional	Longitudinal prospective, cohort	Longitudinal retro-spective	Cross-sectional
Follow-up time	NA	NA	Up to 14 years	17 years	NA
Control subjects	No	No	Yes	Yes	Yes
DATA COLLECTION					
Data type	Interview	Interview	Register	Register	Sampling
Outcome variable(s)	Lifetime SSTI	Past month SSTI	SSTI; systemic infection	MRSA	*S. aureus* detection
Covariate selection	Bivariate analysis	Bivariate analysis	Model selection	Pre-identified	Bivariate analysis
Validated data collection[1]	No	No	Yes	Yes	NA
Reliability tested data collection[2]	No	No	Yes	No	No
STATISTICS					
Multivariate analysis	Logistic regression	Logistic regression	Cox regression	GEE	Logistic regression
Covariates tested for multicollinearity	No	Yes	Yes	Yes	No

[1] Validity, i.e. whether correct data is measured with the instrument used, was evaluated for the National Inpatient Register (255) and the Causes of Death Register (256) used in paper III and IV.

[2] Reliability, i.e. whether the measurements are reliable and reproducible, was evaluated for the Addiction Severity Index questionnaire (257) used in paper III.

Settings

Paper I and V were clinical studies, conducted at Malmö NEP. Paper II was a clinical study as well, conducted in three field sites in San Francisco Bay Area. Paper III and IV were based on register data from The Swedish Prison and Probation Service (Kriminalvården) and The Swedish National Board of Health and Welfare (Socialstyrelsen).

Malmö needle exchange program

Malmö NEP opened in 1987. It is located in the Malmö metropolitan area, which is the third largest city in Sweden with an estimated population of 350,000 inhabitants. A total of 1,130 PWID are estimated to live in Skåne county where Malmö is located (11), and approximately 600 of them are active NEP visitors each year (17). The median age among participants is 44 years, female percentage 25% (17) and amphetamine is the most common drug used (25,30). Prerequisites for NEP enrollment are self-reported injection drug use, age 20 years or older, signs of recent venipuncture, and consent to HIV testing (110).

Malmö NEP is a part of the Department of Infectious Diseases at Skåne University Hospital in Malmö. The NEP offers sterile injection equipment in exchange for used equipment, certain healthcare services, and surveillance and treatment of viral infections.

The Swedish National Patient Register

The Swedish National Patient Register (NPR) for inpatient and outpatient care includes physicians' registration of patients' diagnoses according to International Classification of Diseases (ICD; ICD-10 since 1994). The national inpatient register is of high quality and main diagnosis is registered in 99% of inpatient episodes (258). In a previous validation study, 85–95% of inpatient register diagnoses were valid (255). The outpatient register include data on both outpatient appointments and emergency visits, but no data from primary healthcare.

The Swedish Causes of Death Register

From 1961 to 2011, the Causes of Death Register (CDR) includes data on all deceased individuals who were registered in the Swedish Population Register at the time of death, regardless of the individual's location at the time of death. The register is updated annually. From year 2012 the register includes all individuals who died in Sweden, including persons not registered in the Swedish Population Register in Sweden by the time of death. Causes of death are registered according to ICD. Cause of death is reported by physicians' registration in a death certificate. In some cases, a death certificate is missing, and no cause of death is registered. In the year 2008, less than 1% of all fatalities lacked a death certificate, while 2.7% had a death certificate in which the reported cause of death was insufficiently specified. However, since 1991, all deceased individuals – with or without a death certificate – are included the CDR through the Swedish Population Register data on mortality (259).

The reliability of registered causes of death was validated in year 2009 (256). Causes of death in the CDR from the year 1995 (compared with diagnoses from the NPR for inpatient care) were correct in 77%. Cause of death is more reliable in younger individuals with fewer chronic conditions, and in fatalities due to accidents and rapid disease progress (259).

Addiction Severity Index interview database

Addiction Severity Index (ASI) is a well-documented interview instrument for surveying the level of assistance needed by persons with substance misuse or dependence in clinical settings and in the criminal justice system (260). The Swedish version of ASI has become a standard instrument in Swedish addiction care as well (261), and has been shown to have high reliability in a test-retest study (262). Since year 2001, ASI interviews are routinely conducted by The Swedish Prison and Probation Service as a screening of criminal justice clients' substance use problems. The responses are documented in a database. The ASI database used in paper III consists of results from interviews with 7,085 convicted clients from the Swedish Prison and Probation Service, conducted between 2001 and 2006 according to the modified ASI-X questionnaire (263). This ASI data have been used in several previous Swedish studies after being blinded and delivered to the research group (52,263,264).

Subjects

The study sample in *paper I* consisted of 80 PWID at Malmö NEP. The recruitment was conducted by the thesis author, and assisted by the staff at the NEP. Inclusion criteria were current or previous injection drug use, and participation in Malmö NEP. Patients were excluded from the study if they were unable to provide informed consent or perform the interview due to Swedish language difficulties, psychiatric disability, or intoxication. All visitors to the NEP, who were not obviously intoxicated or in a rush, were approached by the interviewer (Dahlman) or the nurses at the NEP during March and April 2013. Each respondent received a gift card worth a sum equivalent to US$10.

In *paper II*, the study sample consisted of 201 community-based PWID. This sample was part of a larger cohort study of people who use drugs in San Francisco Bay Area. The data were collected from November 2011 through April 2014. Participants were recruited from community settings using targeted sampling methods (265,266). Three community field sites located in neighborhoods in close proximity to large populations of PWID were utilized to conduct the interviews. Inclusion criteria were injection drug use in the past 30 days, age 18 years or older, and being able to provide informed consent. At baseline, injection drug use was confirmed by a research associate through a brief physical exam to identify signs of recent injection. Study participants received US$20 for completing the baseline interview, and US$30 for completing the follow-up interview which included the questions included in paper II. Included in the analyses were subjects from the follow-up interview who reported injection of drugs in the past 30 days.

Baseline data to *paper III* was retrieved from the ASI interview database 2001–2006 (Figure 3). Subjects from the ASI database were included in the study if they either had reported regular injection drug use *and* main drug heroin, amphetamine or polysubstance use (i.e. more than two drugs in the same day, of which at least one illicit substance); or if they had denied regular injection drug use *and* reported alcohol as their main drug. The ASI material consists of interviews with 7,085 individuals. Of these, 50 were excluded due to uncertain or unreliable replies to the ASI interview, resulting in a total sample of 7,035 individuals. Previous studies based on the ASI material have shown that approximately 6% of criminal justice clients refused the interview (263). Mean duration from intake to the criminal justice facility where the interview took place to the interview is 60 days (median 27 days; 98% were interviewed within a year). The number of criminal justice clients who reported lifetime history of injection drug use (minimum 6 months consecutive drug use) and defined their main drug was heroin, amphetamine and polydrug use, respectively, was 378 (heroin), 1,265 (amphetamine) and 812 (polysubstance use). Seven hundred and thirty-five persons reported alcohol as main drug, not in combination with injection

drug use. Three clients were excluded from the analyses in paper III because they had been interviewed according to the adolescent instrument ADAD (267). An opt-out procedure was used in the study, through a presentation of the planned study in a free daily magazine in Stockholm, Gothenburg and Malmö. However, no subjects opted out of the study.

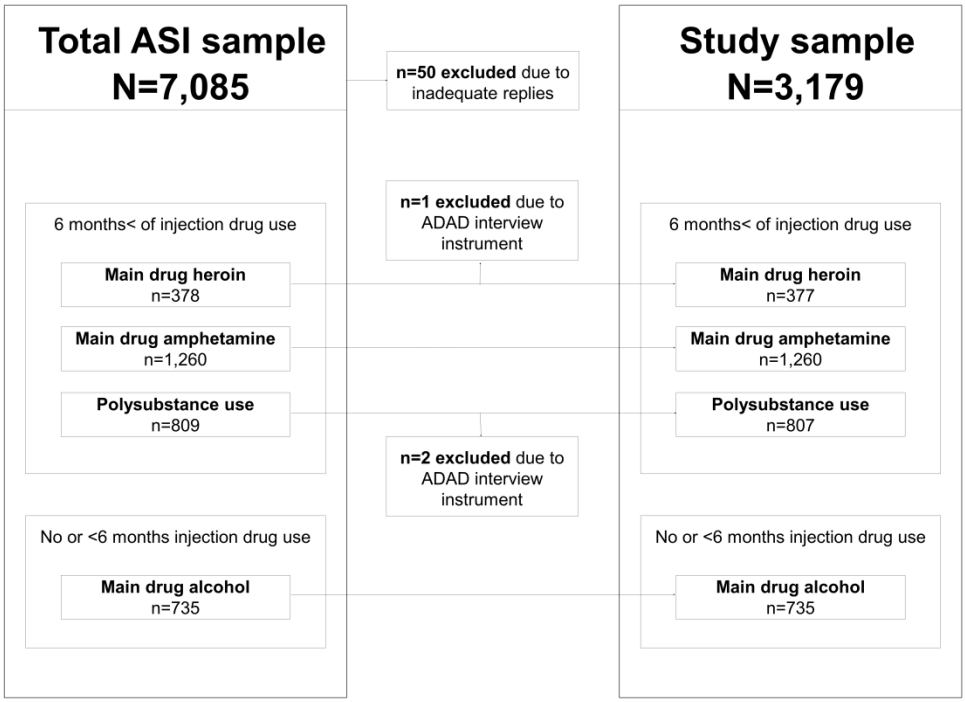

Figure 4. Flow chart showing selection of study subjects to paper III.

ASI, Addiction Severity Index; ADAD, Adolescent Drug Abuse Diagnosis.

In *paper IV*, the study population consisted of patients in the Swedish NPR for inpatient (years 1997, 1999, 2004, 2009, 2013) and outpatient (2004, 2009, 2013) care during the period 1997–2013. The outpatient register was first available in 2004. All patients who were registered in either register with ICD-10 diagnoses opioid dependence (ICD-code F11.2) or amphetamine dependence (ICD-code F15.2) during any of the years were included in the study. All patients with ICD-10 diagnosis alcohol dependence (ICD-code F10.2) during any of the years were also included to serve as a comparison group. In the comparison group, exclusion criteria were any diagnoses related to opioid use (ICD-code F11) or amphetamine use (ICD-

code F15). A total of 73,201 individuals were included in the study. The data was separated for each whole year (hospital admittance/outpatient visit from Jan 1st–Dec 31st) studied, so that each year was considered a measurement point. The number of individuals included at one time point was 55,458, at two time points was 13,055, at three time points 3,515, at four time points 949, and at all five time points 224. The total number of observations was 97,029.

Recruitment of study participants to *paper V* took place at Malmö NEP and at an emergency ward at Malmö Addiction Center in April 2014–June 2015. No compensation was given to the participants in this study, and recruitment was interrupted at N=49 at Malmö NEP (N=60 controls). Staff at Malmö NEP and Malmö Addiction Center conducted random invitation without specific inclusion criteria. Control subjects were excluded if they reported drug injection in the past six months. General exclusion criteria were severe psychiatric illness or influence from drugs, preventing the individual from providing informed consent.

Study procedures

Interview studies: Paper I and II

The questionnaire-based interviews in *paper I* took place at Malmö NEP. The interviews were semi-strictly structured and led by the thesis author (Dahlman). The questions, most of which had yes/no options, were read out literally from a standardized questionnaire, but were explained or clarified to the respondent if needed. The questionnaire was based on a survey used at Research Triangle Institute (RTI) International for assessing abscess prevalence among people who use drugs, "Urban Health Study Abscess Supplemental Questionnaire". The main outcome variable was self-reported experience of SSTI. SSTI symptoms were defined as a combination of redness, swelling and pain and/or pus. The interviewee was asked (translated from Swedish) "Have you [ever/past 12 months/past 30 days] had an abscess or symptoms of skin- and soft tissue infection (redness, swelling, pain, pus)?", and was explicitly asked to distinguish between signs of infection, and irritation caused by extravasal injection.

The structured, questionnaire-based interviews in *paper II* were conducted by professional interviewers. All measures were self-reported and there was no clinical confirmation of drug use or SSTI status. The primary outcome of SSTI status was assessed with a single question: "When did you last have an abscess or symptoms for skin and soft tissue infection (redness, swelling, pain, pus)?" The response options were: "Never had an abscess", "More than a year ago", "In past year, but more than 30 days ago", and "In past 30 days". The candidate covariates were selected based on previous research and divided into two categories: (a) hygiene (needle-licking, skin cleaning, syringe reuse and sharing, etc.) and (b) injection practices (type of drug, injection area, injection method, etc.).

Register studies: Paper III and IV

Follow-up data to *paper III* were retrieved from national Swedish registers from the period 2001–2014, and coupled with baseline data from the ASI register. Outcome variables in paper III were *SSTI during follow-up*; *systemic infection during follow-up*; and *fatal infection*. Data regarding all subjects included at baseline were retrieved from the Swedish NPR for inpatient and outpatient care. Outcome variables were registered ICD-10 diagnoses of infections in skin or soft tissue (ICD-codes L00–L03, L08, A46), cardiac infections (ICD-codes I30.1, I32.0, I33, I38, I39), infections in joints, skeleton or muscles (ICD-codes M00, M46.2, M46.3, M46.5, M60.0, M65.0, M65.1, M86, A48.0), intracranial and intracolumnar infections (ICD-codes G00.3,

G04.2, G06, G07), and septicemia (ICD-codes A40, A41.0–A41.2). Due to small numbers, all systemic infections were collapsed into one variable. Data concerning mortality and causes of death were retrieved on all individuals included at baseline, who were registered in the Swedish CDR 2001–2014. Fatal bacterial infection was defined as any of the ICD-10 diagnoses above that was registered as cause of death. Covariates included in the analyses as potential predictors were incarceration (including prison and custody), main drug, sex and homelessness, retrieved from ASI baseline data. Four potential predictors were identified and included in the model selection analysis: Injection drug use past 30 days, hepatitis C, previous overdose, and being resident in a city with a population of more than 100,000 inhabitants.

The outcome variable in *paper IV* was registered MRSA-diagnosis (based on analyses from local laboratories), and the covariates included were sex, age, and substance dependence diagnosis. Patients with ICD-10 diagnosis opioid dependence (ICD-code F11.2), amphetamine dependence (ICD-code F15.2) or alcohol dependence (ICD-code F10.2) in in- and/or outpatient care once or more during each full year assessed (1997, 1999, 2004, 2009, and 2013) were included in the analyses. The first set of analyses was strictly descriptive, and conducted for each year separately. Patients were divided by substance dependence diagnosis so that opioid and amphetamine dependence were mutually exclusive and patients with both these diagnoses were excluded. Patients were defined as alcohol dependent only if they did not have a registered diagnosis of neither opioid dependence nor amphetamine dependence during the full year assessed. For all included subjects, data was received data on demographic variables and registered ICD-10 diagnoses: age, sex, county where the patient was diagnosed, and MRSA diagnosis (ICD-codes Z22.3C, B95.6, U82.1). Both MRSA infections and known asymptomatic MRSA carriage are noted in the registers. The age registered at the first inpatient episode or outpatient visit for each year was systematically used.

Microbiological study: Paper V

Paper V was based on microbiological methods. Samples were collected using Copan E-swabs (480CE; Copan Italia, Brescia, Italy). Separate swabs were used for the different body sites anterior nares, throat, perineum and from skin lesions. Samples from nares, throat and skin lesions were collected by the patients themselves or by the personnel (nurse/assistant nurse) at Malmö NEP and Malmö Addiction Center. Patients who handled the swab themselves were strictly supervised by personnel. Perineal samples were collected by the patients in both groups after thorough instructions.

One-hundred µl of each sample was added to a BBL CHROMagar Staph aureus plate (CHROMagar, Paris, France) and to a Brilliance MRSA 2 agar plate (PO5196A;

Oxoid, Basingstoke, United Kingdom), respectively. The inoculum was spread on the plates with sterile glass beads and incubated at 35 °C for 48 hours. Colonies with typical color appearance were confirmed by a positive agglutination test (Pastorex Staph Plus [Bio-Rad, Hercules, CA, USA]). Typical color appearance was pink for *S. aureus* growing on BBL CHROMagar Staph aureus plate, and blue for MRSA growing on Brilliance MRSA 2 agar plate.

Positive MRSA colonies were further verified by mecA PCR (268). Disk diffusion test was used for detecting antibiotic resistance. In case of no color change, *S. aureus* was verified by Pastorex Staph Plus (Bio-Rad, Hercules, CA, USA) and MALDI-TOF (269). The number of viable bacteria was measured as colony forming units (CFU). Semi-quantitative evaluation of *S. aureus* growth was made by counting the CFUs. CFU >500 were considered as abundant, 50–499 as intermediate, 1–49 as sparse and 0 as no growth. Paper V also included a short questionnaire and retrieval of patient data from the NEP charts, but the results from the questionnaire were not presented in the final study.

Statistical methods

Cross-sectional studies: Paper I, II and V

In *paper I, II and V*, data analysis was conducted through bivariate analysis (cross tabulations with Chi-2/Fisher's exact test or Mann-Whitney test) to select covariates for the final analyses, and multivariate logistic regression analysis. P-values below 0.05 were considered statistically significant. In paper II, a correlation analysis was performed in order to identify multicollinearity by excluding covariates with correlation 0.7 or more from the multivariate analysis. Statistical analyses were conducted in SPSS 21.0 (270) in paper I and SPSS 22.0 (271) in paper II and V.

Longitudinal studies: Paper III and IV

Statistical analyses of predictors of SSTI, systemic infections and fatal infections in *paper III* were conducted through extended Cox regression analysis, where incarceration was used as a time-varying covariate. The rationale behind this approach was that the baseline assessments were in most cases performed at the start of the prison sentence, so the follow-up data for each individual reflect both the time in and after release from prison, until the first diagnosed episode of SSTI, systemic bacterial infection, or death, respectively. In order to assess the importance of injection drug use as well as main drug, two Cox regression models were conducted with different

reference categories: Non-injection drug use with alcohol as main drug, and injection drug use with heroin as main drug. Prior to the final Cox regression analyses, a model selection was conducted in order to identify the most relevant predictors to include in the final model. All control variables and confounding variables were included in the model selection. Data preparation and statistical analyses were performed in R 3.3.2 (272). The package 'survival' was used for estimating the Cox regression models (273).

In *paper IV*, longitudinal analysis was conducted through generalized estimating equations (GEE) with logit link function and exchangeable correlation structure were used in order to take the repeated measurements of some individuals into account. P-values below 0.05 were considered statistically significant. Data preparation and statistical analyses were performed in SPSS 21.0 (270) and R 3.2.2 (274). The package 'geepack' was used to calculate the GEE models in the R environment (275).

All independent variables were assessed for multicollinearity through bivariate correlation analysis and calculation of variance inflation factor in both paper III and paper IV. In these two studies, all measures of multicollinearity were well within acceptable limits.

Ethical considerations

All studies were approved by either the Regional Ethics Board in Lund Sweden (file number 2013/88 for paper I, file number 2014/478 for paper III, file number 2014/307 for paper IV and V), file number 2014/11 for paper V) or the Institutional Review Board at RTI International (paper II). For paper II, data from RTI International were delivered to the research group at Lund University with consent from the Regional Ethics Board in Lund. There are some general ethical considerations affecting the entire thesis – stigmatizing, economic compensation, and consent – as well as topics more applicable for specific studies.

Stigmatizing of study participants

The studied population in this thesis, people using or injecting drugs, constitute a vulnerable part of society. Injection drug use is a controversial topic, and prejudice and misconceptions about PWID as a group are widespread. Enacted stigma as well as internalized stigma among PWID and negative health consequences thereof has been well described in previous research (276–280). Hypothetically, research that identifies PWID as a high-risk group for certain communicable diseases could be subject to so called dual use (281). Results meant to be used for health improvement in an already exposed group could in worst case be used to further stigmatize PWID and single them out as "guilty" of bacterial transfer to non-PWID (such as in the case of community-acquired MRSA spreading to hospitals) and subsequently be used to motivate repressive interventions focusing PWID. It is unlikely that this would happen within the healthcare system. In a broader political context, however, results could potentially be used rhetorically in political discussions, for example to support stricter legal consequences following injection of illegal drugs.

Economic compensation

Economic compensation to study participants who are part of a vulnerable group of society constitutes an ethical dilemma. In paper I and II, participants were economically compensated (with a gift card in paper I and cash in paper II), while in paper III no compensation was offered.

An argument against economic compensation is that it among PWID might be an "offer one cannot refuse" because of poor financial situation and costly drug use. PWID are subject to allocational vulnerability, meaning that the research provides potential participants with benefits not otherwise accessible (282). On the other hand, an argument in favor of economic compensation would be that if study

participants are known to be poor or socially disadvantaged, they should be compensated for study participation. In an Australian interview-based study assessing motivations for study participation among PWID attending NEPs, reported motivational themes were economic gain in slightly less than half of the study sample (283). Other commonly reported reasons for study participation were expression of citizenship (38%), altruism (19%), personal satisfaction (17%) and drug user activism (16%).

Participation in the clinical studies did not imply any health risks, even though some of the questions might have been perceived as personal. In addition, the economic compensation was small enough to be considered an act of gratitude to the research subjects, while not likely to cause anyone to participate against their will. From a pragmatic standpoint, during the recruitment of study participants it became clear that the recruitment procedure was much more efficient for paper I and II, where the participants received economically compensation, than for paper V where no compensation was offered.

Informed, silent or no consent

Informed consent was obtained from the study participants in paper I, II and V. The two register studies, paper III and IV, did not obtain informed consent.

In paper IV, all data were anonymized, and the researchers did not have access to any identification information. Thus, there was no need to ask permission from the study participants, or to receive informed or silent consent.

For paper III, an opt-out procedure or silent consent was required by the Ethics Board. In this study, personal identification numbers were handled, although not by the researchers. Data retrieval was preceded by an opt-out procedure, through notification of the planned study in the free magazine Metro in the three major Swedish urban areas Stockholm, Gothenburg and Malmö. The baseline data in this study was retrieved from an interview data base where the ASI interview was part of routine procedures in the criminal justice system. The requirement of silent consent can be considered from two perspectives: It is hardly realistic to expect that all persons who participated in ASI interviews 2001–2006 would note the information in a specific paper on a specific day, and the procedure might thus be questioned from an information perspective. On the other hand, de-identified ASI data have been used in several previous studies without silent consent from the participants, and no subjects opted out of the study, which implies that the study procedure was ethically uncontroversial.

Main results

The results are presented thematically rather than according to each separate study. The main results, responding to the study specific aims, were:

Aims I and II) To study self-reported SSTI prevalence and factors associated with SSTI among PWID at Malmö NEP (aim I) and in San Francisco (aim II).

Results I and II) Lifetime SSTI was reported by 58% at Malmö NEP and 70% in San Francisco. Lifetime SSTI was associated with non-powder injection, neck injection, female sex and higher age (paper I). Past 30 days SSTI was associated with receptive syringe/needle sharing (paper II).

Aim III) To investigate incidence rates and predictors of diagnosed SSTI, systemic and fatal bacterial infections among PWID in the Swedish criminal justice system.

Result III) Incidence rates per 1,000 person-years among PWID were 28.3 for SSTI and 9.1 for systemic infection. Fatal infections were rare. SSTI as well as systemic bacterial infection was predicted by injection drug use, with a more pronounced risk increase of SSTI for people mainly using heroin.

Aim IV) To investigate the number of reported MRSA cases among Swedish subjects with opioid and amphetamine dependence.

Result IV) MRSA diagnosis was uncommon but significantly associated with opioid and amphetamine dependence, in comparison with alcohol dependence.

Aim V) To investigate prevalence, quantitative level and body distribution of methicillin-sensitive and -resistant *S. aureus* among PWID at Malmö NEP.

Result V) While MRSA was detected in only one patient, methicillin-sensitive *S. aureus* was detected in 67% of PWID. Perineal *S. aureus* was significantly more common in PWID than in controls.

Demographic and drug use characteristics: Paper I–V

Paper I: Eighty PWID (30% female, median age 45 years [range 23–64]) from Malmö NEP were included in the study. Primary drug was amphetamine in 49% of the cases, and heroin in 39%. Forty percent reported unstable housing in the past 6 months.

Paper II: Self-reported SSTI lifetime prevalence was 70% among 201 community-based PWID (23% female, median age 44) in San Francisco Bay Area.

Paper III: The sample at baseline consisted of 3,179 subjects (14% female, mean age 36 years). Main drug was amphetamine in 40%, polysubstance use in 25%, and heroin in 12%. Twenty-three percent of the sample consisted of non-injectors with alcohol as their main drug.

Paper IV: The sample consisted of 73,201 individuals (22–29% female, median age 47–50 years [range 13–98]). Alcohol dependence was the most common diagnosis for all years, with numbers varying from 76–86% of all included subjects, while opioid dependence constituted 8–20% of the sample, and amphetamine dependence 4–5%.

Paper V: The study sample consisted of 49 PWID from Malmö NEP (31% female, median age 48 years [range 23–68]) and 60 non-injecting control patients (32% female, median age 52 years). In the PWID group, 61% reported amphetamine use and 22% reported heroin use. Sixteen percent of PWID reported unstable housing.

Table 4. Demographic and drug use characteristics of cases and controls in paper I–V.

Data representing number of individuals, median/mean age, and percentage of valid numbers. Study subjects were PWID in paper I–III and V, and patients with opioid or amphetamine dependence in paper IV. Controls were non-injectors with substance use problems. PWID, people who inject drugs.

Characteristic	Paper I	Paper II	Paper III	Paper IV	Paper V
Study participants (n)	80	201	3,179	73,201	109
Study subjects					
Nr of study subjects/PWID	80	201	2,444	1,581–7,332[3]	49
Age in years, median/mean	45 (median)	44 (median)	36 (mean)	36–37[4] (median)	48 (median)
Female sex	30%	23%	14%	33–35%[5]	31%
Unstable housing past 30 days	-	64%	29%	-	16%
Main drug heroin[1]	49%	NA[2]	15%	-	22%
Main drug opioids[1]	-	-	-	60–82%[3]	-
Main drug amphetamine[1]	39%	NA[2]	52%	17–36%[3]	61%
Main drug heroin + amphetamine[1]	7%	-	-	-	4%
Main drug opioids + amphetamine[1]	-	-	-	2–5%[3]	-
Other main drug[1]	5%	-	33%	-	12%
Lifetime injection of non-powder drugs	70%	-	-	-	-
Past 6 months injection of non-powder drugs	-	11%	-	-	-
Control subjects					
Nr of controls	0	0	735	9,676–22,708[3]	60
Age in years, median/mean			36 (mean)	52 (median)	52 (median)
Female sex			12%	27%	32%
Unstable housing past 30 days			10%	-	-

[1] Opioid dependence (F11.2) and amphetamine dependence (F15.2) were mutually exclusive in paper IV, while alcohol dependence was not an exclusion criterion. In paper III all main drugs were mutually exclusive.

[2] 69% reported injection of heroin in the past 6 months. Amphetamine use was not reported. Past 6 months injection of crack or rock cocaine was reported in 69%, powder cocaine in 21%, and methamphetamine in 71%.

[3] Data in paper IV depending on measuring point (1997, 1999, 2004, 2009 or 2013).

[4] Age at first measuring point for each individual. Median 37 years in patients with opioid dependence, 36 years in patients with amphetamine dependence.

[5] 33% in patients with opioid dependence, 35% in patients with amphetamine dependence.

Skin and soft tissue infections: Paper I–III

Prevalence and incidence of SSTI

Among PWID at Malmö NEP (paper I), self-reported SSTI lifetime prevalence was 58%, past 12 months prevalence was 30% and past 30 days prevalence was 11%. Self-reported SSTI lifetime prevalence was 70% among community-based PWID in San Francisco (paper II). In paper III, incidence rates per 1,000 person-years for SSTI was 41.5 among PWID with main drug heroin, 24.0 among PWID with main drug amphetamine, and 29.7 among PWID with polysubstance use, compared to 10.0 among non-injectors with alcohol as their main drug.

Table 5. Skin and soft tissue infections among people who inject drugs: Paper I–III.
Data from Malmö needle exchange (paper I), San Francisco Bay Area (paper II), and the Swedish criminal justice system (paper III). Median follow-up time was 9.8 years (total follow-up time 27,805 person-years) in paper III. SSTI, skin and soft tissue infection; PWID, people who inject drugs.

Characteristic	Paper I	Paper II	Paper III
Study participants (n)	**80**	**201**	**3,179**
Type of data	Self-reported	Self-reported	Register data
Study subjects/PWID (n)	**80**	**201**	**2,444**
SSTI lifetime (%)	58%	70%	-
SSTI past 12 months (%)	30%	29%	-
SSTI past 30 days (%)	11%[1]	11%	-
SSTI incidence rate per 1,000 person-years	-	-	28.3[2]
Control subjects (n)	**0**	**0**	**735**
SSTI incidence rate per 1,000 person-years			10.0

[1] 14% of n=65 recent (past 30 days) injectors.

[2] SSTI incidence was 41.5 per 1,000 person-years among of PWID with main drug heroin, 24.0 of PWID with main drug amphetamine, and 29.7 of PWID with polysubstance use.

Correlates and predictors of SSTI among PWID

Paper I and II were interview studies where the entire study sample consisted of PWID. Paper I showed that in multivariate analysis, independent predictors for SSTI were higher age (adjusted odds ratio [AOR] 1.09, 95% confidence interval [CI] 1.01–1.18), female sex (AOR 6.75, 95% CI 1.40–32.47), having ever injected non-powder drugs (AOR 52.15, 95% CI 5.17–526.67), and having ever injected in the neck (AOR 8.08, 95% CI 1.16–56.08). Having ever injected in the groin was associated with SSTI in bivariate analysis only.

Paper II was focusing on behavioral predictors for SSTI. In bivariate analysis, self-reported SSTI in the past 30 days was significantly associated with injecting non-powder drugs, needle-licking before injection, receptive syringe/needle sharing, being injected by another person, infrequent skin cleaning before injection, and frequent injections. In multivariate logistic regression analysis, the only independent predictor for past 30 days SSTI was receptive syringe/needle sharing (AOR 6.38, 95% CI 1.90–21.46 in the final model).

In paper III, PWID were compared with non-injectors. Among clients in the Swedish criminal justice system, injection drug use was significantly increasing the risk of SSTI during follow-up. The risk increase was hazard ratio (HR) 2.45 (95% CI 1.70–3.52) for PWID who reported that their main drug was heroin at baseline, HR 1.60 (95% CI 1.16–2.20) for those reporting amphetamine as main drug, and HR 1.92 (95% CI 1.39–2.65) for those reporting polysubstance use. Other predictors of SSTI in this study were previous overdose, self-reported hepatitis C, homelessness, and residence in a city with a population over 100,000 inhabitants. Incarceration was associated with lower risk of SSTI. Other main drugs than heroin (amphetamine: HR 0.66, 95% CI 0.52–0.83; polysubstance use: HR 0.79, 95% CI 0.62–1.00) were associated with lower odds of SSTI.

Table 6. Correlates and predictors of SSTI in multivariate analyses: Paper I–III.

Data from Malmö needle exchange (paper I), San Francisco Bay Area (paper II), and the Swedish criminal justice system (paper III). Median follow-up time was 9.8 years (total follow-up time 27,805 person-years) in paper III. SSTI, skin and soft tissue infection; AOR, adjusted odds ratio; HR, hazard ratio; CI, confidence interval; NS, not significant.

Characteristic	Paper I AOR (95% CI)	Paper II AOR (95% CI)	Paper III HR (95% CI)
Study participants (n)	80	200	3,169
Statistical test	Logistic regression	Logistic regression	Cox regression
Outcome variable	Lifetime SSTI	Past 30 days SSTI	SSTI diagnosis during follow-up
Demographics			
Age (years)	1.09 (1.01–1.18)*	-	-
Incarceration	-	-	0.61 (0.47–0.80)***
Female sex	6.75 (1.40–32.47)*	-	NS
Homelessness	-	-	1.23 (1.04–1.46)*
Residence in large city	-	-	1.37 (1.17–1.60)***
Lifetime overdose	-	-	1.39 (1.18–1.64)***
Self-reported hepatitis C	-	-	1.43 (1.15–1.77)**
Main drug			
Heroin vs. alcohol[1]	-	-	2.45 (1.70–3.52)***
Amphetamine vs. alcohol[1]	-	-	1.60 (1.16–2.20)**
Polysubstance use vs. alcohol[1]	-	-	1.92 (1.39–2.65)***
Amphetamine vs. heroin[2]	-	-	0.66 (0.52–0.83)***
Polysubstance use vs. heroin[2]	-	-	0.79 (0.62–1.00[6])*
Injection habits			
Needle-licking past 30 days[3]	-	NS	-
Infrequent skin cleaning[3]	-	NS	-
Neck injection ever	8.08 (1.16–56.08)*	-	-
Non-powder injection ever	52.15 (5.17–525.67)**	-	-
Non-powder inj. past 6 months[4]	-	NS	-
Assisted injection past 30 days[4]	-	NS	-
Receptive syringe/needle sharing past 30 days[5]	-	6.38 (1.90–21.46)**	-
Nr of injections past 30 days[5]	-	1.01 (1.00–1.03)*	-

[1] Paper III, model 1: Alcohol used as reference category for the variable Main drug.

[2] Paper III, model 1: Heroin used as reference category for the variable Main drug.

[3] Paper II, model 1: Adjusted for hygiene variables. Receptive syringe/needle sharing AOR 5.33*.

[4] Paper II, model 2: Adjusted for tissue-damaging practices. Receptive syringe/needle sharing AOR 6.08**.

[5] Paper II, model 3: Adjusted for tissue-damaging practices and injection frequency.

[6] Significant association, upper limit of confidence interval rounded off to two decimals.

* p<0.05. ** p<0.005, *** p<0.001..

Systemic and fatal infections: Paper III

Incidence of systemic and fatal bacterial infections

While fatal bacterial infections were rare, incidence rates per 1,000 person-years for systemic infection were 9.1 among PWID in the Swedish criminal justice system, compared to 2.7 among non-injecting controls. Incidence rates of specific systemic infections are presented in Table 7.

Table 7. Incidence of systemic and fatal bacterial infections: Paper III.

Register data from the Swedish criminal justice system, the Swedish National Patient Register for inpatient and outpatient care, and the Swedish Causes of Death Register. Median follow-up time to systemic bacterial infection was 10.2 years (total follow-up time 30,175 person-years), and to death it was 10.3 years (total follow-up time 31,196 person-years). Incidence rates presented as number of events per 1,000 person-years. N=3,179.

Characteristic	Heroin[1]	Amphet-amine[1]	Polysub-stance use[1]	PWID[2]	Non-injecting controls[3]
Study participants (n)	377	1,260	807	2,444	735
Systemic bacterial infection	**10.4**	**9.5**	**8.0**	**9.1**	**2.7**
Cardiac infection	2.9	2.6	2.3	2.6	0.3
Bone/joint infection	7.3	5.4	4.7	5.4	2.1
Central nervous system infection	0	0.7	0.8	0.6	0.1
Septicemia	4.3	3.8	3.1	3.6	0.7
Fatal bacterial infection	0.6	1.0	0.4	0.7	0.3

[1] Main drug (heroin, amphetamine or polysubstance use) were mutually exclusive.

[2] All subjects with injection drug use and main drug heroin, amphetamine or polysubstance use.

[3] All control subjects had reported problematic alcohol use.

Predictors of systemic bacterial infection

In paper III, systemic bacterial infection was predicted by self-reported hepatitis C (HR 1.58, 95% CI 1.04–2.40), homelessness (HR 1.35, 95% CI 1.03–1.78) and injection drug use with self-reported main drug heroin (HR 2.75, 95% CI 1.41–5.39), amphetamine (HR 2.19, 95% CI 1.20–4.02) and polysubstance use (HR 2.01, 95% CI 1.07–3.76). Incarceration was associated with lower risk of systemic infection, while amphetamine or polydrug use did not significantly affect the risk of systemic infection compared to heroin use. Due to a small number of fatal infections, no multivariate analysis was conducted with infection related death as outcome variable.

Table 8. Predictors of systemic bacterial infection: Paper III.

Multivariate Cox regression analysis. Register data from the Swedish criminal justice system, the Swedish National Patient Register for inpatient and outpatient care. N=3,169. Outcome variable: Systemic bacterial infection during follow-up. Median follow-up time was 10.2 years (total follow-up time 30,175 person-years). HR, hazard ratio; CI, confidence interval; NS, not significant.

Characteristic	HR (95% CI)
Demographics	
Incarceration	0.36 (0.19–0.66)**
Female sex	NS
Homelessness 30 days before baseline	1.35 (1.03–1.78)*
Self-reported hepatitis C	1.58 (1.04–2.40)*
Main drug	
Heroin vs. alcohol[1]	2.75 (1.41–5.39)**
Amphetamine vs. alcohol[1]	2.19 (1.20–4.02)*
Polysubstance use vs. alcohol[1]	2.01 (1.07–3.76)*
Amphetamine vs. heroin[2]	NS
Polysubstance use vs. heroin[2]	NS

[1] Paper III, model 1: Alcohol used as reference category for the variable Main drug.

[2] Paper III, model 1: Heroin used as reference category for the variable Main drug.

* p<0.05. ** p<0.005. *** p<0.001

MRSA and drug dependence: Paper IV and V

MRSA prevalence

Even though the reported MRSA rates in paper IV were low (Table 9), there was a trend towards a more pronounced increase in subjects diagnosed with opioid and amphetamine dependence, compared to overall Swedish MRSA cases in published register data from the Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet; SMI). In paper V, MRSA was detected from bacterial cultures in only one study participant at Malmö NEP.

Table 9. Number of MRSA cases and percent change per measurement: Paper IV.
Data from the Swedish National Patient Register for inpatient and outpatient care. NA, not available; MRSA, methicillin-resistant *Staphylococcus aureus*.

Characteristic	1997	1999	2004	2009	2013
Study subjects, n					
Opioid dependence[1]	944	1,284	1,979	4,672	5,997
Amphetamine dependence[1]	563	512	804	1,322	1,219
Alcohol dependence[2]	9,676	10,149	14,404	20,374	22,708
MRSA cases, n (%)[3]					
Opioid dep.	0	3 (0.2%)	6 (0.3%)	14 (0.3%)	64 (1.1%)
Amphetamine dep.	2 (0.4%)	3 (0.6%)	2 (0.2%)	3 (0.2%)	11 (0.9%)
Alcohol dep.	10 (0.1%)	7 (0.1%)	28 (0.2%)	49 (0.2%)	99 (0.4%)
Nr of notified MRSA cases in Sweden[4]	*NA[5]*	*NA[5]*	*709*	*1,480*	*2,454*
Percent change of MRSA cases[6], %					
Opioid dep.		NA	100%	130%	357%
Amphetamine dep.		50%	-33%	50%	267%
Alcohol dep.		-30%	300%	75%	102%
Nr of notified MRSA cases in Sweden[4]				*109%*	*66%*

[1] Opioid dependence (ICD-code F11.2) and amphetamine dependence (ICD-code F15.2) were mutually exclusive.
[2] All subjects with opioid or amphetamine dependence during the full year were excluded.
[3] Nr of MRSA cases and percent of nr with the actual substance dependence diagnosis, for each year in the study.
[4] According to the Swedish Institute for Communicable Disease Control (SMI). Retrieved from (225,284,285).
[5] MRSA notification was not mandatory (according to the Communicable Disease Act) until year 2000.
[6] Percent change from previous measurement in number of MRSA cases.

Drug dependence correlates of MRSA

In paper IV, MRSA diagnosis was significantly associated with both opioid dependence (AOR 2.67, 95% CI 2.04–3.49) and amphetamine dependence (AOR 2.56, 95% CI 1.61–4.08) compared to alcohol dependence, when adjusting for age, sex and year. Higher age was also significantly associated with MRSA diagnosis.

Table 10. Factors associated with MRSA diagnosis: Paper IV.

Multivariate analysis with generalized estimating equations (GEE). N = 96,596. Number of clusters: 73,025. Maximum cluster size: 5. Estimated within-subject correlation: 0.057. AOR, adjusted odds ratio; CI, confidence interval; ICD, International Classification of Diseases; NS, not significant.

Characteristic	AOR (95% CI)
Amphetamine dependence vs. alcohol dependence	2.56 (1.61–4.08)***
Opioid dependence vs. alcohol dependence	2.67 (2.04–3.49)***
Year	1.11 (1.08–1.15)***
Sex	NS
Age 40–59 years vs. 1-39 years	1.41 (1.05–1.90)*
Age 60–99 years vs. 1-39 years	2.39 (1.70–3.35)***

* p<0.05. *** p<0.001

S. aureus colonization among PWID: Paper V

Prevalence of *S. aureus* among PWID at Malmö NEP

S. aureus in any body site was detected in 67% of PWID and 50% of non-injecting control patients. The anterior nares was the most common site of colonization in both groups. Colonization in the three carriage sites nares, throat and perineum was the most common colonization pattern among PWID. In both groups there were a few individuals with perineal colonization only, and several study participants in both groups were colonized in extra-nasal sites only. *S. aureus* distribution is presented in Table 11.

Association of injection drug use and *S. aureus* colonization

Perineal colonization was significantly associated with injection drug use in bivariate analysis (odds ratio [OR] 2.96, 95% CI 1.13–7.75). This association remained in multivariate analysis, adjusted for sex and age (AOR 4.01, 95% CI 1.34–12.03). In bivariate analysis, injection drug use was associated with overall *S. aureus* colonization on level OR 2.07 (95% CI 0.92–4.68), but did not reach statistical significance (p=0.08). This association was tested in multivariate analysis but was not statistically significant when adjusting for age and sex. There were positive associations between injection drug use and *S. aureus* colonization in nares, throat and skin lesions, as well as multi-site colonization, but none of these associations reached statistical significance.

Table 11. Bacterial colonization pattern with *Staphylococcus aureus* (*S. aureus*).

Cases were people who inject drugs (PWID) participating in Malmö needle exchange program (n=49). Controls were non-injectors from inpatient wards at Malmö Addiction Center (n=60). Fourteen cases were excluded from calculations including perineal colonization due to refusal of perineal sampling. OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; NS, not significant.

***S. aureus* colonization site**	**Cases n (%)**	**Controls n (%)**	**Unadjusted OR (95% CI)**	**AOR (95% CI)[3]**
Any body site	29 (67%)	30 (50%)	2.07 (0.92–4.68)[+]	NS
Nares	20 (41%)	21 (35%)	NS	
Throat	18 (37%)	20 (33%)	NS	
Perineum	13 (37%)[1]	10 (17%)	2.96 (1.13–7.75)*	4.01 (1.34–12.03)*
Skin lesions	7 (15%)[2]	1 (2%)[2]	NS	
One body site	8 (23%)[1]	13 (22%)	NS	
Nares only	1 (3%)[1]	4 (7%)		
Throat only	4 (11%)[1]	7 (12%)		
Perineum only	3 (9%)[1]	2 (3%)		
Two body sites	7 (20%)[1]	13 (22%)	NS	
Nares and throat	2 (6%)[1]	9 (15%)		
Nares and perineum	4 (11%)[1]	4 (7%)		
Throat and perineum	1 (3%)[1]	0		
Three body sites Nares, throat, perineum	5 (14%)[1]	4 (7%)	NS	

[1] Percentage of n=35 with perineal samples.

[2] Percentage of nr with skin lesions were 78% of n=9 for cases; 50% of n=2 for controls.

[3] Adjusted for age and sex.

* $p<0.05$. [+] $p<0.1$.

Discussion

The Discussion section begins with methodological considerations including strengths and limitations of the studies. Thereafter follows an interpretation of the main findings in relation to previous research, as well as novel findings, clinical implications, and finally implications for future research.

Methodological considerations

The methodological discussion is focused on whether the research problems are assessed with an appropriate study design, the right questions and analyses, and in an accurate study sample. The first section, Selection and recruitment of study participants, concerns sample representativeness and potential selection bias including non-response bias. This section also assesses the rationale behind selection of control samples in paper III, IV and V. The Data collection section concerns whether the responses and collected data from paper I–V are valid and reliable, or whether they may be subject to measurement errors and respondent bias.

Selection and recruitment of study participants

Sample selection

The population that was intended to study in all five studies was *people who inject drugs* in general. Participation in Malmö NEP, where injection drug use is a prerequisite for enrollment, was the inclusion criterion in paper I and V, and subjects were excluded only if they were not able to understand the study information and provide informed consent. Injection drug use, confirmed through signs of recent injection, was the inclusion criterion in paper II. The epidemiological register studies, paper III and IV, had large study samples. Use of certain substances was the inclusion criterion in these studies.

In paper IV it was not possible to distinguish between PWID and non-injecting people with opioid and amphetamine dependence, although these drugs are commonly administered through injection (12). Based on ICD-10 diagnoses, heroin

dependence could not be separated from other opioid dependence. All subjects in paper III who were mainly using illicit drugs were PWID at baseline, but their injection habits during follow-up were not possible to assess with the study design of this paper, and their potential cessation of injection drug use during follow-up must be taken into consideration when interpreting the results. They were also criminal justice clients, which affected the generalizability of the results (see below).

Recruitment of study participants

Active recruitment were conducted in paper I, II and V, why these studies may be subject to *selection bias*, specifically *volunteer bias*, *non-response bias*, and (for the control sample in paper V) *hospital patient bias*. Study participants were consecutively included on certain days in paper I and randomly selected in paper II and V. Participants to the clinical studies were recruited from Malmö NEP (paper I and V) and from community field sites in San Francisco Bay Area (paper II). The recruitment was conducted by professional recruiters in paper II, by the thesis author in paper I, and by personnel at Malmö NEP and Malmö Addiction Center in paper V. The samples may be subject to *volunteer bias* since the participants were offered economic compensation in paper I and II. This might have affected the group of participants who gave their consent to study participation, in ways that were not the case in paper V where the participation was not compensated. As mentioned in the Methods section, there is a risk for selection of the most economically vulnerable persons for paper I and II which might affect, for example, the number of homeless participants.

Non-response bias, i.e. missing data and decline of study participation, needs to be kept in mind. The sample sizes in paper I and V were small with 80 and 109 participants (including controls) respectively. The reasons for these small sample sizes were practical – due to time limitations for paper I and because of difficulties recruiting study participants to paper V. In paper V, the recruitment continued for as long as 16 months. The difficulties faced were interpreted to be a result of the lack of economic compensation offered to the participants. No subjects opted out of paper III, and a post-hoc questionnaire to ASI interviewers has shown that a high percentage (94%) of criminal justice clients accepted the ASI interview (263). Reasons for declining participation in the studies were mainly lack of time. None of the studies included a structured analysis of subjects declining study participation, which is a limitation since it was not possible to identify potential non-response bias.

Representativeness of study samples is particularly relevant to discuss concerning paper I and V. In these papers, there was no reason to believe that the samples differed substantially or systematically from the general participants at Malmö NEP were they were recruited, since age, sex and main drug was comparable to the general Malmö NEP participant population (17,30). In paper IV, all patients registered in the NPR with specific diagnoses were selected. A biased selection based on underreported

diagnoses and differences in contacts with the healthcare system between people with alcohol, opioid and amphetamine dependence is difficult to evaluate but cannot be excluded.

Control samples

In three of the studies, patients with non-injection drug use or alcohol dependence were used as controls. In paper V, PWID from Malmö NEP were compared to non-injecting inpatients with substance use disorders. In paper IV, patients with opioid or amphetamine dependence were compared with patients with alcohol dependence. Paper III compared people who had injected drugs for at least six months with individuals with problematic alcohol use but without long-term continuous injection drug use.

A comparison with healthy controls may have resulted in finding more pronounced differences between cases and controls. However, the reason for using individuals with substance problems as controls, rather than healthy subjects, was to compare PWID with a group living under as comparable socioeconomic conditions as possible. Swedish data have shown poor socioeconomic status among both people with problematic alcohol use and people using illicit drugs, who had contact with the Social services (286). In this report, 17% of people using alcohol and 26% of people using illicit drugs had low income. Among people using alcohol and illicit drugs, respectively, 10% and 26% were homeless, and 81% and 94% were unemployed. In paper V, *hospital patient bias* is a possibility since all individuals in the control group were inpatients and might thus have poorer health than non-injecting people with substance problems, not in inpatient care.

Cases and controls were not matched in paper III, IV or V. Mean age in paper III was the same, 36 years, among PWID (range 33–38 depending on main drug) and non-PWID. Female percentage was slightly higher among PWID (14%) than among non-PWID (12%). In paper IV, female percentage ranged between 27–35% in all groups, while median age was higher (52 years) among patients with alcohol dependence than among patients with opioid (37 years) and amphetamine dependence (36 years). In paper V, sex and age distribution was similar in both groups.

Generalizability

The populations in paper I, II and V consisted entirely of PWID, but differed substantially regarding area of residence. Also, all participants in the Swedish studies (paper I and V) were enrolled in Malmö NEP. There is a potential selection bias since PWID participating in a NEP have been shown to have poorer health than other PWID (287). While the results from paper I and V are not necessarily applicable to PWID not participating in a NEP, paper II does not distinguish NEP participants from other PWID and can be generalized to other PWID populations. However, this

study was conducted in a U.S. setting which is not comparable to Sweden with regard to healthcare access or socioeconomic conditions.

The results from paper III were based on self-reported data from convicted PWID in the criminal justice system, and may therefore not be generalizable to other samples of PWID. Prisoners have been shown to have generally poor physical and psychiatric health (29). On the other hand, international (27,288) and Swedish (28) studies have shown that a high percentage of criminal justice clients have substance use disorders, which motivates the use of register data from the Swedish criminal justice system to gain access to detailed interview data from PWID. Age, sex and percentage of people mainly using amphetamine in paper III was comparable with numbers from other studies on PWID in other Swedish settings (17,30), and self-reported hepatitis C in 78% was comparable to the 69% HCV viremia and 88% anti-HCV prevalence shown among Swedish patients in OST (98), and 64% anti-HCV prevalence among PWID participating in Malmö NEP (110).

Data collection

Interview data

The interviews were structured in both paper I and paper II. The interviews were conducted by the thesis author in paper I, and by professional interviewers in paper II. The questions used for assessing drug use, injecting habits and SSTI were not validated – which is a study limitation – but have been used in other studies focusing drug use patterns and abscesses among PWID (139,289).

Paper I and II were based on PWID's self-reports regarding SSTI experience and a variety of behaviors during lifetime, in the past 12 and 6 months, and in the past 30 days. It is thus necessary to take *recall bias* into account. However, previous studies have shown sufficient reliability and validity of PWID's self-reports of drug use history (290), and self-reported data on drug use events among PWID through mixed qualitative and quantitative methods have been shown to be of adequate consistency (289). Except for recall bias, the possibility of *incorrect medical evaluation* should be taken into consideration. Several medical conditions can resemble SSTI (291), and since there was no medical evaluation in paper I and paper II, some cases of self-reported SSTI might have been misinterpretations of other skin lesions. A majority of the interviewees in both paper I and II reported that they were familiar with SSTI symptoms, and in paper I they were specifically asked to separate SSTI symptoms from injection-related irritation. Even though PWIDs self-diagnosing of abscess has been shown to correspond well to clinical evaluation (292), a comparison with SSTI diagnoses from register data in paper I and II would have been valuable from a reliability perspective. *Respondent bias* such as *social desirability bias* is also of importance when assessing drug use and other sensitive issues. Considering the

potential of stigmatizing of study participants or sub-populations mentioned in the Introduction, some participants might have provided "socially desirable" replies. There is a possibility of under-reporting for question regarding for example hygiene, due to embarrassment.

ASI data (paper III), collected by professional interviewers, has been shown to have high reliability and inter-rater accuracy (257). High reliability of the ASI is also shown specifically in a Swedish setting (262). The replies may in some cases, where there was a long time span from intake to the criminal justice facility to the interview, be subject to recall bias. Hepatitis C status was self-reported and may be both overestimated due to spontaneous viral clearance, and underestimated due to ignorance. *Researcher bias* is more often discussed regarding qualitative research, while the interview studies in the thesis were quantitative and used structured interview questionnaires. *Question order bias*, *leading questions and words bias*, and reception and attitude in the interview situation could, however, have affected the results. In paper II, the questions were standardized and asked by trained interviewers, in order to minimize researcher bias.

Register data

The quality of the Swedish NPR for inpatient care is considered high, and 85–95% of registered diagnoses were valid in a study comparing NPR diagnoses with inpatient records (255). However, in both paper III and IV there was no separation between diagnoses registered in the validated inpatient register and the outpatient register, which is not validated. The coverage of the outpatient register is lower than that of the inpatient register, but missing main diagnosis has decreased over time from 25–30% to approximately 1% (258). The rationale behind using diagnoses from both these registers were to include all cases registered with the diagnoses of interest, while the severity of infections (i.e. inpatient care) was not of primary interest in any of the studies. Diagnoses in the CDR are not suspected to be incorrect. More than 96% of all fatalities in Sweden in year 2008 had a certificate of death with registered cause of death (259). Registered causes of death are valid in 77% (256), and cause of death in younger persons with less multi-morbidity and shorter time span of fatal disease or violent cause of death are more often correct (259).

MRSA diagnoses in paper IV included both infection and asymptomatic colonization, and from the results in paper IV it was not possible to distinguish these two, which is an important study limitation. Also, the MRSA diagnoses registered in the NPR are not equivalent to MRSA surveillance data from SMI. It was therefore not possible to differentiate MRSA samples taken on clinical indication from other routes. However, in a validation study of Swedish MRSA surveillance data, Stenhem et al. concluded that MRSA data from routine surveillance may be inadequate for in-depth epidemiological analyses due to low sensitivity regarding reason for MRSA testing, and missing or incorrect information on clinical presentation (infection or

colonization)(293). MRSA rates may also be underestimated before year 2000 when reporting of MRSA became mandatory in Sweden (294). After year 2000, MRSA rates are likely to be accurate, since healthcare institutions in Sweden are economically compensated for each registered episode of MRSA.

Microbiological data

Sampling reliability was an issue in paper V. Bacteriological sampling was conducted by nurses/assistant nurses at Malmö NEP and Malmö Addiction Center – or by the patients themselves in all perineal samples and in some other samples. Sampling conducted by the patients was strictly supervised by the staff. In the case group a quarter of the NEP participants declined perineal sampling, which might have affected the results. Bacterial sampling was conducted only once in each individual and the results might have differed if the sampling was repeated, since *S. aureus* colonization is intermittent and ca 40% of adults have been shown to be intermittent nasal carriers (221).

Data handling and statistical analyses

Three cross-sectional and two longitudinal studies are included in the thesis. For all cross-sectional studies (paper I, II and V), the same type of statistical analyses were conducted; bivariate analysis to find candidate variables at significance level $p<0.1$, followed by logistic regression analysis. In paper IV, the control variables were predefined. In paper III there were both control variables that were predefined, and variables based on a model selection analysis to determine which control variables that improved the statistical model. Paper III thus included the most refined control variable inclusion, and the results from paper I, II and V should be viewed in the light of possible exclusion of important control variables. In paper II, several replies to multiple-choice questions and continuous variables were collapsed into dichotomous variables, which might have affected the results. Missing values were excluded from statistical analyses in all papers.

The number of candidate variables was limited to a maximum of five cases per variable (295) in order to avoid type 1 errors. To identify multicollinearity, correlation analysis was conducted in paper II, III and IV, but not in paper I or V.

Small study samples and weak statistical power was a concern in paper I and V. Non-significant associations and very low prevalence of MRSA should therefore be viewed in the light of low power. The number of participants affected the results from statistical analysis. When comparing confidence intervals for the significant predictor variables in paper I, II and V, it becomes clear that data quality was higher in paper II where a larger number of participants were approached by professional recruiters.

Interpretation of main findings: Towards a better understanding of bacterial infections among PWID

Some of the findings in paper I–V were novel and other findings supported or contrasted previous research. This section includes a broad discussion of these results, relating them to previous research and hypothesizing explanations to bacterial infections among PWID, and leads up to a suggestion of more specific future research areas.

Novel approaches and findings

- While prevalence and correlates of SSTI have been assessed in previous studies, paper I is the first study investigating this subject in a Swedish setting. The approach applied in paper II, strictly focusing behavioral risk factors for SSTI, is also novel.
- Incidence of SSTI and systemic bacterial infections among PWID has not been previously assessed in large-scale register studies. Quantification of risk increase from injection drug use and main drug has not been carried out in large-scale, prospective studies.
- MRSA colonization and infection among PWID has been investigated in clinical surveillance studies, but never in a low-prevalence setting like Sweden. The long-term epidemiological approach, based on national register data, is also novel.
- *S. aureus* colonization in different body sites has been subject to very little research, and paper V is, to the authors' knowledge, the first study assessing semi-quantitative colonization with *S. aureus* in different body sites of PWID specifically.

PWID have high rates and increased risk of SSTI and systemic infections

SSTI were common among PWID at Malmö NEP, in the Swedish criminal justice clients, and in San Francisco Bay Area. Self-reported lifetime SSTI prevalence in Malmö (paper I) as well as San Francisco (paper II) was comparable to previous studies from the U.S. and Mexico (135,138,139) but higher than in Australian studies (136,137). A plausible explanation to this regional difference might be coverage of NEPs, or access to SIFs. The prevalence of SSTI was comparable in Malmö and in San Francisco. One might have expected the SSTI rates to be higher in the U.S. sample, recruited in an area where PWID have been shown to have high rates of unstable housing and food insecurity (19), poor healthcare access (2) and prevalent use of drugs harmful to the tissues such as cocaine and black tar heroin (42). Data collection to paper I and II was conducted within a short time span (less than one year), and SSTI was assessed with almost identical interview questions.

The results from paper III are coherent with the clinical impression that SSTI as well as systemic bacterial infections are associated with injection drug use. Incidence rate of cardiac infection among PWID was more than 30 times higher than the incidence of infective endocarditis previously shown for the general Swedish population (160). An important limitation of paper III is that we did not have access to microbiological data, which would have allowed a more sophisticated analysis of systemic infections.

Fatal bacterial infections were rare among both PWID and non-PWID in paper III, while overall mortality during follow-up was high in both groups. This may be partly explained by the high mortality due to unnatural causes of death (overdose, accidents and suicide) among PWID (51–53,57) in combination with low age. Several studies have shown statistically lower mortality due to bacterial infections among PWID compared to non-PWID, in the case of infective endocarditis (133), necrotizing fasciitis (134), and invasive streptococcal infections (177). Mortality due to left-sided infective endocarditis is higher than due to right-sided endocarditis (182), with PWID usually diagnosed with the latter (146,152,153). Lower age among PWID than non-PWID affected by systemic bacterial infections, in combination with less age-related comorbidity such as diabetes mellitus, have been suggested as reasons for the lower mortality in PWID noted in for example necrotizing fasciitis (134).

Risk factors for SSTI: General aspects

As presented in the Introduction, there are some areas of particular interest concerning PWIDs physical health. PWID often lead demanding lives with poor economy and lack of social security. Bacterial infections can be considered part of a larger problem complex consisting of unmet healthcare needs (65–67,78), chronic conditions including viral infections (8), poor dermatological health – described specifically in people using methamphetamine (79) – and sexual health including transactional sex (26,119,120,296). Previous research has approached bacterial infections among PWID from vastly different perspectives ranging from bacteriological characteristics (218,230,234,235,237) to macro-scale analysis of the drug market including prize and quality of heroin (297).

Through the studies included in the thesis, certain groups or individuals were identified as being of higher risk of SSTI and systemic infection. In paper I and II, four predictors for SSTI were identified: receptive syringe/needle sharing, female sex, non-powder injection and neck injection. In paper III, injection drug use, mainly heroin use compared to other injected drugs, self-reported hepatitis C, homelessness, previous overdose and residence in a large city was predicting SSTI; and injection drug use, homelessness and hepatitis C was predicting systemic infection.

Based on the results from paper I–IV, and previous research, it is possible to abstract three principally different – however overlapping – explanatory models regarding the high rates of bacterial infections among PWID:

1) Bacterial colonization and interpersonal transmission;

2) Injection techniques promoting bacterial growth and transfer; and

3) Demographic and lifestyle factors affecting the susceptibility to infections.

The first two models concern factors directly causing bacterial infections. The third model is more complex and includes structural and behavioral characteristics likely to affect and confound model 1 and 2. A basic attempt to illustrate the complexity of predictors for bacterial infections among PWID, through a simplified overview, is presented in the figure below:

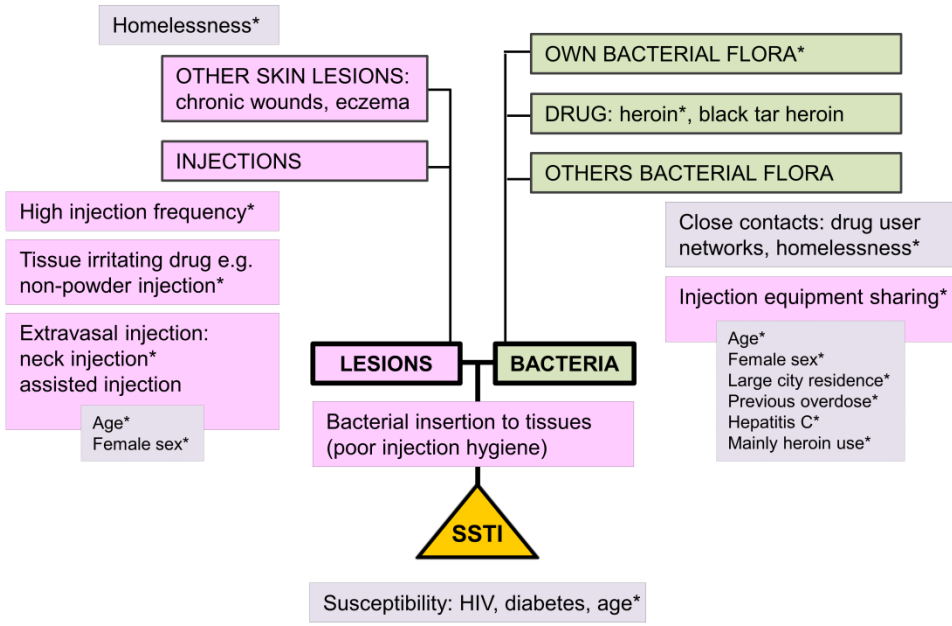

Figure 5. Overview of statistically significant and potential risk factors of skin and soft tissue infections (SSTI) among people who inject drugs, based on results from paper I–V.

The figure represents a flow chart where direct causes of SSTI (lesions in the skin; bacteria) are affected or confounded by the factors in boxes more distally located. Factors marked with * are results from the studies included in the thesis. Green boxes contain microbiological factors; pink boxes contain injection technique factors; and blue boxes contain demographic and lifestyle factors.

Explanatory model 1: PWID have high rates of bacterial colonization

A hypothesis for the high prevalence of bacterial infections is that PWID are susceptible to colonization with potentially pathogenic bacteria such as *S. aureus* including MRSA. This is supported by the results from paper IV, where opioid and amphetamine dependence was associated with MRSA diagnosis compared to alcohol dependence, and paper V where injection drug use was associated with perineal *S. aureus* colonization.

As suggested in previous research, overrepresentation of *S. aureus* and MRSA among PWID can be a result of bacterial transfer between individuals, or long-term colonization potentially due to repeated skin lesions/breaks in the skin barrier (223). The clinical importance of interpersonal bacterial transfer is supported by cluster outbreaks in populations of PWID that have been described for MRSA and methicillin-susceptible *S. aureus* (218,230,234,235,237). Outbreaks of non-injection related bacterial infections among PWID and people who use drugs through non-injection, such as meningitis (130) and tuberculosis (123–125) described in previous research also support this model of explanation.

Previously reported colonization rates of *S. aureus* in 35–39% of PWID (216,220) are lower than the 67% in paper III. Bassetti et al. (220) collected samples in a setting where PWID could receive assistance with injections as well as clean injection equipment, while the harm reduction interventions at Malmö NEP do not include supervised or assisted injections. A potential explanation for the higher colonization rates at Malmö NEP is that injections under unclean conditions are of greater importance for bacterial colonization than injections per se. Perineal colonization rates were higher than in a previous study from 1964 (298), while nasal colonization rates were within the range of the 28–45% previously reported (217–219). MRSA rates among Swedish PWID (paper IV and V) were very low in relation to those described in international research (217–219). To a great part, this can be understood in relation to the low MRSA prevalence in the general Swedish population (225,294), but it also needs to be evaluated with respect to the low statistical power in paper V.

Associations between *S. aureus* colonization and clinically significant infections have been shown in previous research, but not among PWID specifically, and not in this thesis. An increased risk of infection in individuals with nasal *S. aureus* colonization was shown already in the 1930s (221), and has been supported by several more recent studies (221–224). Nasal carriage of *S. aureus* was the most important source of *S. aureus* bloodstream infection in studies by del Rio et al. (299) and von Eiff et al. (224). These associations should be further studied (see Implications for future research).

Explanatory model 2: Injection techniques promote bacterial growth and transfer to the tissues or bloodstream

A second model of explanation is that unsafe or unclean injections that facilitate bacterial transfer to the tissues or bloodstream cause bacterial infections among PWID who engage in risky injection habits. Proper skin cleaning prior to injection is stressed as an important infection preventive intervention in a recent review article by Larney et al. (131). While poor skin or hand cleaning prior to injection has been associated with SSTI previously (135,139,140,195,196,200), no such association was found in paper I or paper II. This might be due to a lack of specific questions regarding skin cleaning with antibacterial substances in the questionnaires. High injection frequency is a known risk factor for SSTI in PWID (135,136,158,196,198,200), shown also in paper II. The reason might be that frequent breakage of the skin barrier facilitates bacterial transfer and long-term bacterial colonization (223). High injection frequency can also be a sign of general high-risk injection behavior and more excessive drug use with effects on physical health and general life situation.

The drug itself has been suggested to cause complications through tissue damage, negative effects on the immune system, and infection through containing microorganisms. Non-powder injection was associated with SSTI in paper I (multivariate analysis) and in paper II (bivariate analysis). This association has been noted previously (210,211). Non-powder injections have also been clinically described as a cause for endocarditis (300), pericarditis (301), skin necrosis (302) and pulmonary disease (303). The reason might be that non-powder injections are more harmful to the tissues than powder drugs. Non-powder drugs tend to clog the syringe, and the use of "washes" has been noted as a potential risk for infections among people who inject prescription drugs (43). Outbreaks of HIV (304) among people injecting prescription opioids have been described in recent reports from the U.S. In addition, non-powder injection of buprenorphine has been associated with polydrug injection (46). The role of non-powder injection as part of a larger drug use pattern might also be of importance when interpreting its association with SSTI.

Injection area (neck injection) was associated with SSTI in paper I. In studies from Mexico and Canada, past six month neck injection was reported by 25–35% (305,306), in comparison to 30% self-reported lifetime neck injecting among PWID at Malmö NEP in paper I. While groin injection could theoretically be a causal risk factor of SSTI due to bacterial colonization in the groin/genital area, this is not likely to explain the association between SSTI and jugular injection. Life history of neck injection is rather interpreted as an indicator of risk injections due to lack of distal vein access. Neck injection has also been shown to be significantly associated with polydrug use and seeking help from a "hit doctor" (305), as well as with with female sex, daily heroin use, daily cocaine use, requiring help injecting, and involvement in

sex trade (306). These findings indicate that neck injection is one of several high-risk injection behaviors that seem to be inter-related.

Receptive syringe/needle sharing was independently associated with SSTI in paper II, which is coherent with previous research (197,199). In some cases, reused syringes or paraphernalia may transfer bacteria (194). In most cases, however, syringe sharing might more likely be viewed as an indicator of general high-risk behavior and is not necessarily a direct cause of SSTI. Among female PWID in San Francisco, syringe sharing was independently associated with young age, homelessness and having a sexual partner who was also injecting drugs (307). A study from the southern U.S. showed that homeless male PWID were 2.6 times more likely to report syringe sharing compared to stably housed men when controlling for age and income (308). Among young PWID, homelessness was a significant risk factor for being part of a large injection network, and cross-over transience (residence in both urban and suburban areas) was a risk factor for syringe sharing (309).

Injection behavior is a complex matter which is not easily analyzed within the framework of medical research. PWID's reasons for unsafe injections have rather been assessed through qualitative research (310), and have not been addressed in the papers in this thesis. High-risk injection, i.e. frequent or unclean injections, equipment sharing and assisted injections are often inter-related. Behaviors and demographic factors such as homelessness, sex, involvement in sex work, and other social factors are likely to interfere and together increase the likelihood of bacterial infections. Johnson et al. showed that risk injection was associated with use of prescription opioids, while prescription opioids, tranquilizers and stimulants were misused in the context of risky sexual behaviors among young PWID (311). Risk injections and risky sexual behaviors are also described among people who misuse prescription drugs in New York City (312). Among PWID in Vancouver, assisting others with injection was associated with syringe sharing, unstable housing, frequent injection of heroin and cocaine, and frequent use of crack cocaine (313). Potential confounders between injection drug use and bacterial colonization among PWID, not assessed in this thesis, are skin lesions and chronic wounds. A more refined analysis of living conditions and clusters of bacteria among PWID would provide further clues regarding routes of infection in this group.

Explanatory model 3: Demographic and lifestyle factors affect susceptibility to bacterial infections

Association between higher age and MRSA (paper IV) has been noted previously in Swedish studies (225,294). Higher age and SSTI is associated in occasional studies (136,196), and this association was identified in paper I even if the risk increase per year was small (AOR 1.09, 95% CI 1.01–1.18). This finding was expected since the

outcome variable in paper I was lifetime SSTI. While incidence of bacterial infections such as endocarditis have been shown to increase with age in the general Swedish population (159), a longitudinal, large-scale Australian study found that each five-year increase in age among PWID was associated with significant reductions in the high-risk injecting habits public injecting and needle-sharing (314). Since risky injecting behaviors have been shown to be more common among younger PWID, age is a complicated variable to interpret.

Female sex, which was associated with SSTI in paper I but not in paper II or III, is a previously noted correlate of SSTI (23,138,158,195–197,201). Two suggested models of explanation are that female PWID are at higher risk of extravasal injection because of smaller veins (202), or that female PWID may be more likely to share injection equipment and seeking help with injection due to gender structures (197,203). Sex work was not assessed in any of the studies included in the thesis, but may be a potential confounder since it is associated with female sex as well as high-risk injection practices (315). Women who are involved in sex work and use drugs are more likely to reuse equipment and have unprotected sex (16,316), and among female PWID, sex work has been associated with skin abscesses (158). In international research, the prevalence of sex work among PWID is widely varying, however more common among female PWID in studies from the U.S. (296), the U.K. (119), and Estonia (120). In a national survey with 2,400 PWID from England, Wales and Northern Ireland, PWID selling sex had injected longer and were significantly more often sharing syringes and injection paraphernalia than non-sex workers. Female sex workers had significantly higher odds than non-sex workers to report an injection site infection in the past year (119). In a Canadian study sex work among male PWID was independently associated with borrowing syringes (317).

Homelessness was associated with SSTI in paper III, and has been noted previously (23,136,197–199). In the U.S., unstable housing is also shown to be associated with unsafe injections such as equipment sharing, which is interpreted in the light of homeless PWIDs' poor economic status, frequent and high-dose drug use, and high rates of psychiatric illness (318). Responses to questions regarding homelessness or unstable housing may be subject to definitional unclarities and difficulties for the respondent to interpret the question. Residential area was associated with bacterial infections in paper III, which is difficult to interpret but can be considered in the light of geographical distribution of drugs in Sweden, where "heavy drug use" is concentrated to the metropolitan areas around Stockholm, Gothenburg and Malmö (24). Interestingly, in an Australian study, residence in a large city was associated with lower odds of injection-related injuries and diseases, which was interpreted in relation to high NEP coverage in urban areas (136).

The association of heroin use and SSTI shown in paper III illustrates the complexity of risk factors among PWID, since it can be interpreted as caused by the drug itself,

but also as an indicator of harmful living conditions and injecting habits. Injection of black tar heroin has been suggested to facilitate infection with skin bacteria resulting in SSTI (212), SSTI-related hospital admissions (297) and necrotizing fasciitis (176). It is also described as a route of *Clostridia* infections including tetanus (319,320) and wound botulism (321,322). In paper II, conducted in San Francisco, a study limitation was that use of black tar heroin was not included in the questionnaire. Use of black tar heroin is more or less non-existent in Sweden. Outbreaks of infections caused by spore-forming bacteria from heroin batches have also been noted before (127–129), but are not described in Sweden and thus not likely to explain the association between heroin use and SSTI in the Swedish criminal justice system. Rather, demographical factors should be taken into consideration. In Sweden, people who use heroin are statistically younger than people using amphetamine, have higher mortality rates, less stable housing, more criminal involvement and more frequent involvement in transactional sex (26,31,323). Housing status and sex work might be of importance for colonization with commensal bacteria such as *S. aureus*. Unstable housing may also increase the possibilities to maintain safe and clean injecting habits. Also, the high rates of psychiatric comorbidity among people with substance use disorders (83,84,86) and depression among PWID using heroin (87) might lead to difficulties maintaining safe injection habits and risk awareness.

The expected and described high prevalence of skin rash and wounds in people injecting or using stimulant drugs (due to effects from the drugs) (79), makes the higher risk of SSTI among people mainly injecting heroin somewhat contra-intuitive. Previously noted associations between injection-related harms including SSTI and specific drugs have been suggested to be caused by tissue ischemia for non-powder drugs (136), and generally high injection frequency for cocaine (due to short half-life) (197). Tissue-damage is, however, not likely to explain the association between heroin use and SSTI in Sweden since powder heroin is not tissue-irritating to the same extent as black tar heroin, stimulant drugs or crushed tablets. A strength in paper III was that self-reported main drug, rather than occasional or intermittent use, was included in the analyses, since this may be a stronger correlate of general living conditions. However, drug use during follow-up could not be assessed, which is an important limitation. While use of amphetamine and opioids/heroin may overlap, previous research has shown clear distinctions between different drug use patterns (31). In paper IV, not more than 1% of the sample was diagnosed with both amphetamine and opioid dependence.

While amphetamine and heroin are the most common injectable drugs in Sweden (10,12), other more rare injection drugs were not included in the analyses. There are several studies clinically describing or showing statistical associations between bacterial infections and use of chemically diverse drugs such as heroin (195), stimulants including cocaine (23,196) and speedball (mix of heroin and cocaine) (140,158), and new psychoactive substances, “bath salts” (mix of cathinone derivates)

(324–326). High injection frequency of heroin has been associated with abscess (135,195), which might be due to the use of heroin or the injection frequency. These diverging findings give at hand that confounders and factors related to injection habits and living standards might be of greater importance than the drug in itself.

In paper III, previous overdose and self-reported hepatitis C were risk factors for superficial and systemic infection. Occasional studies have noted associations between SSTI and recent overdose (200), and between SSTI and hepatitis C (196). Since the interview data were obtained at baseline only, there were no follow-up data regarding housing status, overdose, drug use or injecting habits. The risk factors were, however, interpreted as indicators of chaotic drug use and risk injections rather than having a causal association with bacterial infections. Overdose is strongly associated with opioid use including heroin (53,57), which was a predictor of SSTI compared to amphetamine and polysubstance use in paper III. Mainly amphetamine injection, in contrast to heroin injection, was also significantly associated with lower odds of HCV-seroconversion among PWID at Malmö NEP (110). It is also notable that both overdose (327) and hepatitis C (328) have been associated with high-risk injections such as needle sharing and street injection, likely to affect the risk of bacterial infections.

Potential correlates and confounders affecting the risk of bacterial infections in risk groups, not analyzed in the studies in the theses, include other physical morbidity such as dermatological problems (329–331), HIV (158,332) and diabetes mellitus (333,334). The importance of HIV with regard to bacterial infections among PWID has, however, yielded diverging findings including studies that has not detected any differences between HIV-positive and HIV-negative PWID with regard to infective endocarditis (182). Poor nutritional status and food insecurity among PWID (19,21) may affect susceptibility to infections, but has not been included in any of the studies in the thesis.

It is generally difficult to identify whether the drug or injections themselves are affecting the risk of bacterial infections through contaminated drug batches (127–129) or immuno-modulation (194), or whether the pattern of drug use is rather part of a larger problem complex including cramped housing, other comorbidity and bacterial transfer. Repeated breakage of the skin barrier that follows injection drug use is likely to increase the risk of bacterial colonization. However, the studies in the thesis could not assess potential importance of drug use related factors not necessarily associated with injections. Factors such as dermatological health, immunodeficiency and close personal contact among people who use, but do not inject, drugs should be further analyzed.

Main conclusions

- SSTI is very common among PWID in San Francisco (70% lifetime prevalence; paper II), at Malmö NEP (59% lifetime prevalence; paper I), and in the Swedish criminal justice system (incidence rate 28.3 per 1,000 person-years; paper III).
- Systemic bacterial infections are common among PWID in the Swedish criminal justice system (incidence rate 9.1 per 1,000 person-years; paper III), and predicted by homelessness and self-reported hepatitis C. Bacterial infection is rarely the cause of death among PWID in relation to the high overall mortality in this group.
- In comparison with problematic alcohol use, injection drug use is a strong risk factor for SSTI as well as systemic bacterial infections compared, for clients in the Swedish criminal justice system (paper III).
- Correlates of SSTI among PWID (cross-sectionally assessed) are female sex (paper I), higher age (paper I), lifetime neck injection (paper I), lifetime non-powder injection (paper I), injection frequency (paper II), and equipment sharing (paper II). Risk factors associated with SSTI (assessed through prospective design, paper III) are mainly use of heroin, homelessness, being resident in a large city, previous overdose, and self-reported hepatitis C.
- Opioid and amphetamine dependence, in comparison with alcohol dependence, is associated with MRSA colonization/infection.
- Colonization with *S. aureus* is common among PWID at Malmö NEP, and perineal colonization is statistically more common in PWID than in inpatients with non-injection substance dependence.

Explanations of the high prevalence of bacterial infections among PWID seem to be multifactorial and include both microbiological and behavioral risk factors, which need to be assessed in future studies. The results in the thesis do, however, motivate several clinical implications.

Clinical implications

A decrease of SSTI and invasive bacterial infections among PWID, who are a vulnerable patient group with substantial somatic comorbidity, would result in large humanitarian and economic benefits. Invasive bacterial infections may cause significant morbidity, and having repeated superficial infections is painful and burdensome. The results from paper I–V have three major clinical implications:

1. A need to *inform* high-risk groups about bacterial infections, and make healthcare staff observant on signs of bacterial infections in certain patient groups;

2. A need to *intervene* in order to affect modifiable factors of importance for SSTI and systemic infections; and

3. A need to *investigate* possibly modifiable factors to further clarify causes of bacterial infections and potential interventions.

Information to and about subgroups at risk

Healthcare staff and other personnel encountering PWID need to be observant of the high risk and high prevalence of SSTI and systemic bacterial infections in high risk sub-groups. Low threshold healthcare access for PWID at NEPs, supervised injection facilities and wound clinics have been suggested as a way for PWID to rapidly get suspected SSTI medically evaluated and treated (195,335). The findings from paper I and III identified some risk groups for future preventive work. PWID in general (paper III); female PWID (paper I); PWID mainly using heroin, with hepatitis C, with previous overdose, with unstable housing and PWID resident in a large city (paper III), need extra information and observation focusing SSTI.

Interventions focusing modifiable risk factors

In a recent review article, Larney et al. concluded that the modifiable risk factors for bacterial infections among PWID that needs to be assessed through intervention are cleaning of injection site prior to injection (access to cleaning swabs) and information regarding avoidance of intramuscular and subcutaneous injection (131). Proper injection hygiene was not protective against SSTI in paper I or II, but due to the nature of the questions assessing injection hygiene through skin cleaning, this lacks clinical implications. The findings from paper I and II identified modifiable risk behaviors and risk groups for future preventive work. PWID injecting non-powder

substances (paper I), and sharing injection equipment (paper II) need interventions focusing SSTI. The importance of easy access to clean injection equipment should be stressed, although it is not clear whether syringe sharing is a direct cause of bacterial transfer and subsequent SSTI, or an indicator of destructive drug use. Behavioral interventions to decrease injection equipment sharing, with focus on bloodborne viral infections have been evaluated and seem successful (336,337), indicating that NEPs could be used as a natural platform for healthcare for PWID. Harms from non-powder injections can be reduced through access to filters (0.8/0.2 double membrane filter) to remove debris from the liquid injected (247,248). Ng et al. (249) showed that 0.2 µm filters also reduced bacteria (*S. aureus*, *Streptococcus pyogenes* and *Pseudomonas aeruginosa*) to the limit of detection.

Investigation of potentially modifiable risk factors

The results from paper IV add knowledge about MRSA epidemiology among people with illicit drug dependence and possibly injection drug use. MRSA low-prevalence countries like Sweden provide valuable settings for studying risk factors for MRSA, since the findings can be interpreted without bias from a substantial part of the population being colonized with MRSA. Considering the connection between injection drug use and *S. aureus* colonization and infections, deeper understanding of MRSA in this group is of interest from epidemiological and public health perspectives, as well as of importance for the individuals affected. MRSA should, according to the findings from paper IV, be surveilled in PWID settings such as syringe exchanges – or through register studies. The single MRSA case in paper V does not have clinical implications, with regard to the weak statistical power. Paper V was a small-scale study, but provided clues to an explanation of the microbiological reasons for frequent SSTI among PWID. The findings call for prevention strategies to decrease *S. aureus* colonization among PWID, but the potential effect from decolonization needs to be scientifically evaluated.

Implications for future research

Bacterial colonization and infections among PWID is an under-researched field, and more studies are necessary to minimize these common hazards (131). More specifically, after finalizing the five studies included in this thesis, need for three certain research areas crystalized:

Longitudinal microbiological studies

Paper V was a pilot study with only a small study sample tested cross-sectionally. There is thus a need for large-scale, longitudinal studies following *S. aureus* colonization among PWID and its' association to SSTI and invasive infections. As paper III did not include any microbiological data, more studies are necessary to further evaluate the bacteriology of systemic infections among PWID. There are a few studies indicating that certain strains of *S. aureus* tend to colonize PWID (218,237), possibly from close interpersonal contact or equipment sharing. Genetic testing of detected bacteria in PWID within a geographical area would thus provide better understanding of bacterial spread in this group.

Since neglect of skin wounds has been shown to be a strong risk factor for becoming a *S. aureus* nasal carrier (338), and correlation has been noted between nasal microbiome and SSTI (339), further studies on dermatological health, bacterial colonization and infections would add valuable knowledge to the routes of colonization and infection among PWID.

Intervention studies assessing infection prevention

Even though factors associated with bacterial colonization, SSTI and systemic infections were assessed in this thesis, little is known regarding effective interventions aiming to prevent infections among PWID. Among risk factors, it would be possible to assess injection frequency, syringe sharing, skin lesions and small SSTI that might develop to systemic infection, and bacterial colonization. There is also a potentially protective effect from OST on SSTI among people injecting heroin. OST have been shown to improve quality of life (340) and self-perceived physical health (341), and its potentially protective effect against bacterial infections should be evaluated.

Skin and needle hygiene intervention at NEPs has been evaluated as bacterial infection prevention in small scale, with promising results (238,239). Similar interventions would be valuable to evaluate in Swedish settings. Use of specific filters for non-powder injections should also be scientifically assessed concerning protective

effects against SSTI. An intervention study evaluating SSTI prevention through decolonization would further clarify the pathogenesis and infection prevention among PWID. Marshall and McBryde found that 58% of patients (non-PWID) with bloodstream infection had screening swabs positive for *S. aureus* in the nose, throat, groin axilla or rectum, but less than half of the patients were nasally colonized (342). The authors suggest that this may explain who sole nasal decolonization has not been effective in preventing *S. aureus* infection, and stress the need of studies regarding non-nasal decolonization.

Considering the significant unmet healthcare needs among PWID (2,65–67,78), more easily accessed healthcare, such as wound clinics, focusing skin lesions due to injections but also other wounds and eczema, should be further evaluated. Potential association between SSTI and systemic infections among PWID has not been investigated, and should be subject to future research.

Interdisciplinary mixed methods research

Since physical health among PWID is a complex matter, important factors affecting risk for SSTI and systemic infections might be missed if studies are too methodologically narrow in their design. The studies in this thesis were using different methods, but none of the studies were interdisciplinary.

Mixed methods methodology – including participant-observation ethnography, in-depth qualitative interviewing, epidemiological surveys, photo-documentation, and geographic mapping – has been evaluated for research with structurally vulnerable populations (343). For a deeper understanding of the correlation between bacterial infections, bacterial colonization, hygiene and housing standard, drug use pattern and high-risk injections (possibly expressed through mediators such as overdose, metropolitan residency and hepatitis C), mixed methods research is necessary. Behavioral research in Swedish settings have shown differences in life conditions, contacts with healthcare and social services between female PWID using heroin and amphetamine (26,323), and has provided deeper insight into risk behaviors concerning injections and transmission of bloodborne infections (344). Collaborative research with perspectives from sociology, behavioral science and public health science would thus be of high value for a more sophisticated assessment of behavioral and structural risk factors such as injector networks, gender structures and sex work.

Populärvetenskaplig sammanfattning

Injektion av narkotika för med sig många risker för användaren. Den här avhandlingen handlar om komplikationer till injektion av droger, i form av infektioner som orsakas av bakterier. Utifrån tidigare forskning vet man att både infektioner på hudytan, t.ex. bölder, och infektioner inne i kroppen såsom blodförgiftning och infektion i hjärtat, är vanliga hos personer som injicerar droger. Exakt hur vanligt det är, och vad det beror på, är dock okänt. I Sverige finns det flera studier på blodsmitta, alltså virus som hepatit och HIV, hos personer som injicerar droger, men nästan inga studier på infektioner som orsakas av bakterier. Användning av droger, i synnerhet genom injektion, är ett politiskt laddat ämne. Just därför behövs vetenskapliga studier av hälsoproblem hos människor som injicerar droger.

Syftet med den här avhandlingen var att undersöka hur vanligt det är med bakteriella infektioner hos personer som injicerar droger, och jämföra med risken hos personer som inte injicerar droger. Syftet var också att hitta faktorer som påverkar infektionsrisken och som går att påverka för att färre ska drabbas av infektioner. Detta undersöktes genom fem olika studier:

Den första och andra studien byggde på intervjuer med personer som injicerar droger, på sprutbytet i Malmö och i San Francisco, USA. I intervjuerna ingick frågor om injektionsvanor och erfarenhet av infektioner i hud och mjukdelar. Dessa studier visade att det var mycket vanligt med sådana infektioner, både i Malmö och i San Francisco. Nästan 60% i Malmö och 70% i San Francisco uppgav att de hade haft en hud- och mjukdelsinfektion vid något tillfälle i livet. Det framkom också att kvinnor, de som hade injicerat droger i halsen, de som hade injicerat krossade tabletter (till skillnad från droger i pulverform som bättre löser sig i vätska) och de som hade delat injektionsutrustning med någon annan hade ökad risk för ytliga infektioner.

Den tredje studien undersökte statistiska samband mellan droganvändning och infektioner ytligt på huden och djupt i kroppen. Uppgifterna om droganvändning kom från tidigare intervjumaterial med personer i Kriminalvården, och uppgifterna om infektioner hämtades från patientregistret och dödsorsaksregistret. Studien visade att injektionsbruk av droger ungefär dubblade risken för såväl ytliga som djupa infektioner. Personer som injicerade heroin hade särskilt stor risk för ytliga infektioner, jämfört med dem som främst använde anfetamin eller flera olika droger.

Utifrån studie nummer fyra framkom att patienter som blivit diagnostiserade med beroende av opioider (som heroin och syntetiska morfinläkemedel) eller amfetamin i sjukvården hade större sannolikhet att också bli diagnostiserade med antibiotikaresistenta bakterier, MRSA.

Den femte studien undersökte förekomsten av bakterien *Stafylococcus aureus* (*S. aureus*) hos personer som kom till Malmö sprutbyte för att byta injektionsmaterial. Bakgrunden till studien är att denna bakterie är en vanlig orsak till injektionsrelaterade infektioner. I studien hittades *S. aureus* hos mer än hälften av sprutbytesdeltagarna. Vi jämförde bakterieförekomsten med patienter på Beroendecentrum Malmö, som inte hade injicerat droger det senaste halvåret, men som vårdades på sjukhus för alkoholabstinens och andra beroendetillstånd. Det visade det sig då att personerna som injicerade droger oftare hade bakterier i underlivet (perineum).

Sammanfattningsvis visade studierna i avhandlingen att bakteriella infektioner i hud och mjukdelar är mycket vanliga hos personer som injicerar droger, och att risken för såväl ytliga som djupa bakterieinfektioner i denna grupp är ungefär dubbelt så hög som hos personer som inte injicerar. Resultaten i avhandlingen kan delvis förklara den höga förekomsten av bakterieinfektioner, men fortfarande behövs mer forskning. Förklaringarna är sannolikt både mikrobiologiska och beteenderelaterade:

Resultaten i studie IV och V tydde på att personer som har ett beroende av opioider eller amfetamin, respektive injicerar droger, har mer bakterier på kroppen än andra. Exakt vad detta beror på är okänt, men utifrån andra studier vet man att det påverkar infektionsrisken. Dessutom visade studie I, II och III att kvinnor, de som hade heroin som sin huvuddrog, de som hade injicerat krossade tabletter eller injicerat i halsen, de som hade delat injektionsutrustning, de med hepatit C, de som var hemlösa, de som hade haft en överdos och de som bodde i ett storstadsområde hade ökad sannolikhet för bakteriell infektion. Detta tolkas som att infektionsrisken kan minskas genom att man förbättrar förutsättningarna för säker injektion och ökad uppmärksamhet på grupper med särskilt hög infektionsrisk, som kvinnor och heroinanvändare.

Slutsatserna för avhandlingen är att det behövs mer infektionsförebyggande arbete riktat till personer som injicerar droger, och mer forskning kring effekterna av:

- Tillgång till ren injektionsutrustning,
- Tillgång till filtreringsutrustning för att undvika komplikationer från injektion av krossade tabletter,
- Information om säker injektion till grupper i riskzonen för bakterieinfektion,
- Ökad tillgång till substitutionsbehandling med buprenorfin eller metadon för personer som injicerar heroin,
- Lättillgänglig sjukvård för bedömning av stickskador och mindre hudbesvär som riskerar att utvecklas till allvarliga infektioner,
- Effekt av bakteriedödande medel, som hudrengöring innan injektion men också som ett sätt att minska den totala bakteriemängden på kroppen.

Det behövs också mer forskning om kopplingen mellan infektion och förekomsten av bakterier på kroppen, samt tvärvetenskaplig forskning som genom ett mer beteendevetenskapligt perspektiv kan göra en djupare analys av riskbeteenden och hur de kan förebyggas.

Acknowledgements

First of all I would like to express my deepest gratitude towards all persons with experience of injection drug use who have made this thesis possible; both through their participation in the studies, but also through sharing their life stories and experiences of health issues which has been the clinical rationale and the motivation behind the scientific work.

Several persons have made the process of writing this thesis inspiring, stimulating and joyful:

The single person that I owe the most is Anders Håkansson, my main supervisor, for extraordinary generosity. You have not only shared your skills regarding research design and research work, but also provided invaluable contacts with international research networks and key persons in harm reduction policy and research. Throughout the thesis project I have appreciated your encouraging and inspiring qualities as a supervisor. Thank you, Anders!

Per Björkman has been my co-supervisor since this research project started and your clear academic and scientific gaze has significantly improved the stringency and quality of the research. I was also lucky enough to have Anna Nilsson joining the project as co-supervisor when we introduced a more microbiological perspective in the thesis. I am grateful for your enthusiasm and vast knowledge on bacterial infections and colonization.

Anders, Anna and Per – you are not only excellent teachers of medical research, but you have also created a very inspiring and vivid discussion climate with room for both psychiatry and infectious diseases. I am grateful for having such brilliant supervisors and look forward to having you as my colleges and co-researchers also after finalizing the thesis project.

Thanks to Jonas Berge who conducted the statistical analyses in paper III and IV – your rock solid statistical skills and effectiveness was crucial to these studies. I also want to express my gratitude to collaborators and co-authors Marianne Alanko Blomé for generously welcoming me to Malmö NEP, Farnaz Jalalvand for amazing work with paper V, and Håkan Janson for microbiological knowledge and laboratory competence. Alex Kral at RTI International has been a mentor from the harm reduction field in San Francisco throughout the thesis work. Alex – thank you for all

scientific discussions and advice and for including me in the research community at RTI! The collaboration with you has made the writing of this thesis unusually fun and inspiring. I am also utterly grateful to Scott Novak, Lynn Wenger, and all the staff at Urban Health RTI International for generously sharing your knowledge and enthusiasm, and for introducing me to the world of harm reduction.

Thanks to Susanne Quick, Britt Meijer and Britta Sjöström at Malmö NEP, and Dick Weise at Addiction Center Malmö for invaluable help with recruiting study participants and sampling for paper I and V. Your clinical experience and trustful relationships with your patients was a prerequisite for these studies.

I am grateful to the Swedish Prison and Probation Services for data from the ASI database, and to all the personnel at Clinical Microbiology Laboratory in Malmö for the analyses to paper V.

Caroline Mannerfelt is not only a fabulous friend, but also designed the illustrations in the thesis and the cover picture. Thanks Carro for your creative work!

Thanks to Lars Garpenhag who proofread the entire manuscript with impressive stamina, and to Courtney Meador who helped with the formatting!

Many thanks also to all the staff at LARO Matris and LARO INM for excellent clinical collaboration. Your engagement and compassion about your patients with substance use diseases is contagious! My special thanks to Katja Troberg for being a splendid research partner and clinical collaborator, and to Martin Bråbäck who was my first encounter with OST in Sweden. Without that first visit at LARO Matris in year 2012, I might never have had the opportunity to begin working in the research field of PWID's health.

A special thank you to Elon Öhman for being an excellent discussion partner, and thanks for your curiosity and deep-rooted common sense that has forced me to clarify and verbalize the purpose and clinical importance of my research, to make it reasonable to people outside the medical field. The *Populärvetenskaplig sammanfattning* is written with you in mind.

Life would have been boring if I had not been lucky enough to be part of Surprise Travels with Gudde, Flash & BQ (Good Bad Experience FTW); a sucker for aesthetical creativity and coffee drinker with Ylva (my mom); a car driver and Kraftwerk fan with Bo (my dad); dinner company with Ull; part of my sister Yrsa's weird sense of humor. But above all my strongest and most important identities are as part of the dyads Küngen & Lümpen with my *bästis* Hanna, and Hästen & Mulan with my *käresta* Lars. Thank you all, Darrrlings!

References

1. Hughes A, Williams MR, Lipari RN, Bose J, Copello P, Kroutil LA. Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. NSDUH Data Review. 2016. Substance Abuse and Mental Health Services Administration; 2016. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm. (Access date 25 April 2017)
2. Powelson E, Lorvick J, Lutnick A, Wenger L, Klausner J, Kral AH. Unmet healthcare need among women who use methamphetamine in San Francisco. Subst Use Misuse. 2014;49(3):243–52.
3. Donoghoe MC, Verster A, Pervilhac C, Williams P. Setting targets for universal access to HIV prevention, treatment and care for injecting drug users (IDUs): towards consensus and improved guidance. Int J Drug Policy. 2008;19 Suppl 1:S5–14.
4. van Beek I. Harm reduction--an ethical imperative. Addiction. 2009;104(3):342–3; discussion 345–6.
5. Wodak A. Harm reduction is now the mainstream global drug policy. Addiction. 2009;104(3):343-5; discussion 345-6.
6. Grönbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. Acta Psychiatr Scand. 1990;82(3):223-7.
7. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008;(2):CD002207.
8. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2016. United Nations publication, Sales No. E.16.XI.7.
9. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet. 2008;372(9651):1733-45.
10. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European Drug Report 2016: Trends and Developments. Lisbon: EMCDDA; 2016. Available at: http://www.emcdda.europa.eu/edr2016. (Access date 25 April 2017)
11. Hälsofrämjande och förebyggande arbete med hepatit och hiv för personer som injicerar droger: en vägledning. Solna: Folkhälsomyndigheten; 2015.

12. Byqvist S. Patterns of drug use among drug misusers in Sweden. Gender differences. Subst Use Misuse. 2006;41(13):1817-35.
13. Centralförbundet för alkohol- och narkotikaupplysning (CAN). Drogutvecklingen i Sverige 2014. Rapport nr 144. Stockholm: Centralförbundet för alkohol- och narkotikaupplysning; 2014.
14. Statens folkhälsoinstitut. Narkotikabruket i Sverige. Östersund: Statens folkhälsoinstitut; 2010.
15. Ramstedt M, Sundin E, Landberg J, Raninen J. ANDT-bruket och dess negativa konsekvenser i den svenska befolkningen 2013 – en studie med fokus på missbruk och beroende samt problem för andra än brukaren relaterat till alkohol, narkotika, dopning och tobak. Stockholm: STAD, rapport 55; 2014.
16. Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. Drug Alcohol Depend. 2012;124(1-2):95-107.
17. Alanko Blomé M. Blood Borne Viruses (HIV, HBV and HCV) among Participants of a Swedish Needle Exchange Program. Lund: Lund University; 2016.
18. Heimer R, Barbour R, Palacios WR, Nichols LG, Grau LE. Associations between injection risk and community disadvantage among suburban injection drug users in southwestern Connecticut, USA. AIDS Behav. 2014;18(3):452-63.
19. Schmitz J, Kral AH, Chu D, Wenger LD, Bluthenthal RN. Food insecurity among people who inject drugs in Los Angeles and San Francisco. Public Health Nutr. 2016;19(12):2204-12.
20. Anema A, Wood E, Weiser SD, Qi J, Montaner JS, Kerr T. Hunger and associated harms among injection drug users in an urban Canadian setting. Subst Abuse Treat Prev Policy. 2010;5:20.
21. Strike C, Rudzinski K, Patterson J, Millson M. Frequent food insecurity among injection drug users: correlates and concerns. BMC Public Health. 2012;12:1058.
22. Hendricks K, Gorbach S. Nutrition issues in chronic drug users living with HIV infection. Addict Sci Clin Pract. 2009;5(1):16-23.
23. Lloyd-Smith E, Kerr T, Hogg RS, Li K, Montaner JS, Wood E. Prevalence and correlates of abscesses among a cohort of injection drug users. Harm Reduct J. 2005;2:24.
24. Olsson B, Adamsson Wahren C, Byqvist S. Det tunga narkotikamissbrukets omfattning i Sverige 1998. MAX-projektet, delrapport 3. Stockholm: Centralförbundet för alkohol- och narkotikaupplysning; 2001.
25. Stenström N. Sprutbyte vid intravenöst narkotikamissbruk. En longitudinell studie av deltagarna i sprutbytesprogrammet i Malmö. Östersund: Mid Sweden University, Department of Social Work; 2008.

26. Richert T, Månsson SA, Laanemets L. Kvinnor som injicerar heroin respektive amfetamin – Skillnader i social situation, erfarenhet av behandling och önskemål om hjälp. Soc Tidskr. 2011;18:144-64.
27. Fazel S, Bains P, Doll H. Substance abuse and dependence in prisoners: a systematic review. Addiction. 2006;101(2):181-91.
28. Chang Z, Lichtenstein P, Larsson H, Fazel S. Substance use disorders, psychiatric disorders, and mortality after release from prison: a nationwide longitudinal cohort study. Lancet Psychiatry. 2015;2(5):422-30.
29. Fazel S, Baillargeon J. The health of prisoners. Lancet. 2011;377(9769):956-65.
30. Hakansson A, Medvedeo A, Andersson M, Berglund M. Buprenorphine misuse among heroin and amphetamine users in Malmo, Sweden: purpose of misuse and route of administration. Eur Addict Res. 2007;13(4):207-15.
31. Hakansson A, Schlyter F, Berglund M. Characteristics of primary amphetamine users in Sweden: a criminal justice population examined with the Addiction Severity Index. Eur Addict Res. 2009;15(1):10-8.
32. Watanabe-Galloway S, Ryan S, Hansen K, Hullsiek B, Muli V, Malone AC. Effects of methamphetamine abuse beyond individual users. J Psychoactive Drugs. 2009;41(3):241-8.
33. Shrem MT, Halkitis PN. Methamphetamine abuse in the United States: contextual, psychological and sociological considerations. J Health Psychol. 2008;13(5):669-79.
34. Degenhardt L, Larney S, Chan G, Dobbins T, Weier M, Roxburgh A, et al. Estimating the number of regular and dependent methamphetamine users in Australia, 2002-2014. Med J Aust. 2016;204(4):153.
35. Wada K. The history and current state of drug abuse in Japan. Ann N Y Acad Sci. 2011;1216:62-72.
36. Farrell M, Marsden J, Ali R, Ling W. Methamphetamine: drug use and psychoses becomes a major public health issue in the Asia Pacific region. Addiction. 2002;97(7):771-2.
37. Brecht ML, O'Brien A, von Mayrhauser C, Anglin MD. Methamphetamine use behaviors and gender differences. Addict Behav. 2004;29(1):89-106.
38. Palamar JJ, Ompad DC. Demographic and socioeconomic correlates of powder cocaine and crack use among high school seniors in the United States. Am J Drug Alcohol Abuse. 2014;40(1):37-43.
39. Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015. Available at: http://www.samhsa.gov/data/

40. Haasen C, Prinzleve M, Zurhold H, Rehm J, Güttinger F, Fischer G, et al. Cocaine use in Europe - a multi-centre study. Methodology and prevalence estimates. Eur Addict Res. 2004;10(4):139-46.
41. Ciccarone D. Heroin in brown, black and white: structural factors and medical consequences in the US heroin market. Int J Drug Policy. 2009;20(3):277-82.
42. Ciccarone D, Bourgois P. Explaining the geographical variation of HIV among injection drug users in the United States. Subst Use Misuse. 2003;38(14):2049-63.
43. Roy E, Arruda N, Bourgois P. The growing popularity of prescription opioid injection in downtown Montreal: new challenges for harm reduction. Subst Use Misuse. 2011;46(9):1142-50.
44. Rosenblum A, Parrino M, Schnoll SH, Fong C, Maxwell C, Cleland CM, et al. Prescription opioid abuse among enrollees into methadone maintenance treatment. Drug Alcohol Depend. 2007;90(1):64-71.
45. Lankenau SE, Kecojevic A, Silva K. Associations between prescription opioid injection and Hepatitis C virus among young injection drug users. Drugs (Abingdon Engl). 2015;22(1):35-42.
46. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? Addiction. 2005;100(2):197-205.
47. Winstock AR, Lea T, Sheridan J. Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. Int J Drug Policy. 2008;19(6):450-8.
48. Imbert B, Cohen J, Simon N. Intravenous abuse of methylphenidate. J Clin Psychopharmacol. 2013;33(5):720-1.
49. Tavernise S. C.D.C. painkiller guidelines aim to reduce addiction risk. New York Times. March 15 2016. Available at: http://www.nytimes.com/2016/03/16/health/cdc-opioid-guidelines.html. (Access date 10 March 2016)
50. Office of National Drug Control Policy (ONDCP). Epidemic: Responding to America's prescription drug abuse crisis. 2011. Available at: http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf. (Access date 26 September 2016)
51. Ericsson E, Bradvik L, Hakansson A. Mortality, causes of death and risk factors for death among primary amphetamine users in the Swedish criminal justice system. Subst Use Misuse. 2014;49(3):262-9.
52. Hakansson A, Berglund M. All-cause mortality in criminal justice clients with substance use problems—a prospective follow-up study. Drug Alcohol Depend. 2013;132(3):499-504.
53. Olsson MO, Bradvik L, Öjehagen A, Hakansson A. Risk factors for unnatural death: Fatal accidental intoxication, undetermined intent and suicide: Register follow-up in a criminal justice population with substance use problems. Drug Alcohol Depend. 2016;162:176-81.

54. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry. 1998;173:11-53.
55. Hulse GK, English DR, Milne E, Holman CD. The quantification of mortality resulting from the regular use of illicit opiates. Addiction. 1999;94(2):221-9.
56. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry. 2001;58(5):503-8.
57. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011;106(1):32-51.
58. Fugelstad A, Annell A, Rajs J, Agren G. Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981-1992. Acta Psychiatr Scand. 1997;96(3):169-75.
59. Fuglestad A. Utvecklingen av akuta narkotikarelaterade dödsfall 1994-2011. Rapport 3. Stockholm: Karolinska Institutet, Institutionen för klinisk neurovetenskap; 2012.
60. Folkhälsomyndigheten. Sammanfattning av Toxreg 1994-2014. Solna: Folkhälsomyndigheten; 2015. Available at: https://www.folkhalsomyndigheten.se/documents/livsvillkor-levnadsvanor/andts/narkotika/skadeverkningar/dodlighet/toxreg-1994-2014-sammanfattning.pdf. (Access date 25 April 2017)
61. Socialstyrelsen. Statistikdatabas för dödsorsaker, year 2016. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas/dodsorsaker. (Access date 11 May 2016)
62. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European Drug Report 2015: Trends and Developments. Lisbon: EMCDDA; 2015. Available at: http://www.emcdda.europa.eu/edr2015. (Access date 25 April 2017)
63. Brådvik L, Hulenvik P, Frank A, Medvedeo A, Berglund M. Self-reported and observed heroin overdoses in Malmoe. J Subst Use. 2007;12(2):119-26.
64. Hakansson A, Isendahl P, Wallin C, Berglund M. Respondent-driven sampling in a syringe exchange setting. Scand J Public Health. 2012;40(8):725-9.
65. Chitwood DD, McBride DC, French MT, Comerford M. Health care need and utilization: a preliminary comparison of injection drug users, other illicit drug users, and nonusers. Subst Use Misuse. 1999;34(4-5):727-46.
66. Chitwood DD, Comerford M, McCoy HV. Satisfaction with access to health care among injection drug users, other drug users, and nonusers. J Behav Health Serv Res. 2002;29(2):189-97.
67. Chitwood DD, Sanchez J, Comerford M, McCoy CB. Primary preventive health care among injection drug users, other sustained drug users, and non-users. Subst Use Misuse. 2001;36(6-7):807-24.

68. Federman AD, Arnsten JH. Primary care affiliations of adults in a methadone program with onsite care. J Addict Dis. 2007;26(1):27-34.

69. Kaye S, McKetin R, Duflou J, Darke S. Methamphetamine and cardiovascular pathology: a review of the evidence. Addiction. 2007;102(8):1204-11.

70. Richter KP, Gibson CA, Ahluwalia JS, Schmelzle KH. Tobacco use and quit attempts among methadone maintenance clients. Am J Public Health. 2001;91(2):296-9.

71. Hser YI, Gelberg L, Hoffman V, Grella CE, McCarthy W, Anglin MD. Health conditions among aging narcotics addicts: medical examination results. J Behav Med. 2004;27(6):607-22.

72. Pieper B, Templin T. Lower extremity changes, pain, and function in injection drug users. J Subst Abuse Treat. 2003;25(2):91-7.

73. Pieper B, Kirsner RS, Templin TN, Birk TJ. Injection drug use: an understudied cause of venous disease. Arch Dermatol. 2007;143(10):1305-9.

74. Tsui JI, Herman DS, Kettavong M, Anderson BJ, Stein MD. Chronic pain and hepatitis C virus infection in opioid dependent injection drug users. J Addict Dis. 2011;30(2):91-7.

75. Heimer R, Zhan W, Grau LE. Prevalence and experience of chronic pain in suburban drug injectors. Drug Alcohol Depend. 2015;151:92-100.

76. Del Borgo C, Izzi I, Chiarotti F, Del Forno A, Moscati AM, Cornacchione E, et al. Multidimensional aspects of pain in HIV-infected individuals. AIDS Patient Care STDS. 2001;15(2):95-102.

77. Martin C, Pehrsson P, Österberg A, Sönnerborg A, Hansson P. Pain in ambulatory HIV-infected patients with and without intravenous drug use. Eur J Pain. 1999;3(2):157-64.

78. Robbins JL, Wenger L, Lorvick J, Shiboski C, Kral AH. Health and oral health care needs and health care-seeking behavior among homeless injection drug users in San Francisco. J Urban Health. 2010;87(6):920-30.

79. Gonzales R, Mooney L, Rawson RA. The methamphetamine problem in the United States. Annu Rev Public Health. 2010;31:385-98.

80. Raoult D, Foucault C, Brouqui P. Infections in the homeless. Lancet Infect Dis. 2001;1(2):77-84.

81. Stratigos AJ, Stern R, González E, Johnson RA, O'Connell J, Dover JS. Prevalence of skin disease in a cohort of shelter-based homeless men. J Am Acad Dermatol. 1999;41(2 Pt 1):197-202.

82. Badiaga S, Menard A, Tissot Dupont H, Ravaux I, Chouquet D, Graveriau C, et al. Prevalence of skin infections in sheltered homeless. Eur J Dermatol 2005;15(5):382-6.

83. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and

anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61(8):807-16.

84. Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry. 2008;65(1):28-37.

85. Kokkevi A, Stefanis N, Anastasopoulou E, Kostogianni C. Personality disorders in drug abusers: prevalence and their association with AXIS I disorders as predictors of treatment retention. Addict Behav. 1998;23(6):841-53.

86. Rasmussen K, Levander S. Untreated ADHD in adults: are there sex differences in symptoms, comorbidity, and impairment? J Atten Disord. 2009;12(4):353-60.

87. Darke S, Ross J. Suicide among heroin users: rates, risk factors and methods. Addiction. 2002;97(11):1383-94.

88. McKetin R, Hickey K, Devlin K, Lawrence K. The risk of psychotic symptoms associated with recreational methamphetamine use. Drug Alcohol Rev. 2010;29(4):358-63.

89. Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, et al. Methamphetamine-associated psychosis. J Neuroimmune Pharmacol. 2012;7(1):113-39.

90. Marshall BD, Werb D. Health outcomes associated with methamphetamine use among young people: a systematic review. Addiction. 2010;105(6):991-1002.

91. Rognli EB, Berge J, Håkansson A, Bramness JG. Long-term risk factors for substance-induced and primary psychosis after release from prison. A longitudinal study of substance users. Schizophr Res. 2015;168(1-2):185-90.

92. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry. 1997;170:205-28.

93. Bråbäck M, Nilsson S, Isendahl P, Troberg K, Brådvik L, Håkansson A. Malmö Treatment Referral and Intervention Study (MATRIS)-effective referral from syringe exchange to treatment for heroin dependence: a pilot randomized controlled trial. Addiction. 2016;111(5):866-73.

94. Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry. 2004;184:110-7.

95. Semple DM, McIntosh AM, Lawrie SM. Cannabis as a risk factor for psychosis: systematic review. J Psychopharmacol. 2005;19(2):187-94.

96. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to Pot - A Review of the Association between Cannabis and Psychosis. Front Psychiatry. 2014;5:54.

97. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571-83.

98. Jerkeman A, Westin J, Lagging M, Norkrans G, Lidman C, Frimand J, et al. Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy--factors associated with advanced fibrosis. Scand J Infect Dis. 2014;46(5):340-7.

99. Dahlman D, Förnvik M, Isendahl P, Nilsson S, Bråbäck M, Håkansson A. Attitudes Towards Hepatitis C and Treatment Willingness in Injection Drug Users: A Follow-Up Interview Study. J Alcohol Drug Depend. 2015;3:217.

100. Bradshaw CS, Pierce LI, Tabrizi SN, Fairley CK, Garland SM. Screening injecting drug users for sexually transmitted infections and blood borne viruses using street outreach and self collected sampling. Sex Transm Infect. 2005;81(1):53-8.

101. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl. 2003;9(11):S1-9.

102. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57(3):675-88.

103. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver Int. 2009;29 Suppl 1:89-99.

104. John-Baptiste A, Krahn M, Heathcote J, Laporte A, Tomlinson G. The natural history of hepatitis C infection acquired through injection drug use: meta-analysis and metaregression. J Hepatol. 2010;53(2):245-51.

105. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and metaregression. Hepatology. 2008;48(2):418-31.

106. Planas R, Ballesté B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol. 2004;40(5):823-30.

107. Gibson A, Randall D, Degenhardt L. The increasing mortality burden of liver disease among opioid-dependent people: cohort study. Addiction. 2011;106(12):2186-92.

108. Larney S, Randall D, Gibson A, Degenhardt L. The contributions of viral hepatitis and alcohol to liver-related deaths in opioid-dependent people. Drug Alcohol Depend. 2013;131(3):252-7.

109. Chew KW, Bhattacharya D. Virologic and immunologic aspects of HIV-hepatitis C virus coinfection. AIDS. 2016;30(16):2395-404.

110. Blomé MA, Björkman P, Flamholc L, Jacobsson H, Molnegren V, Widell A. Minimal transmission of HIV despite persistently high transmission of hepatitis C virus in a Swedish needle exchange program. J Viral Hepat. 2011;18(12):831-9.

111. Hillgren K, Sarkar K, Elofsson S, Britton S. [Widespread risk behavior among injecting drug users. Over 80 percent HCV-infected--7 percent have HIV, as demonstrated by the first baseline study]. Lakartidningen. 2012;109(25):1221-5.

112. Semaan S, Leinhos M, Neumann MS. Public health strategies for prevention and control of HSV-2 in persons who use drugs in the United States. Drug Alcohol Depend. 2013;131(3):182-97.

113. Ross MW, Hwang LY, Zack C, Bull L, Williams ML. Sexual risk behaviours and STIs in drug abuse treatment populations whose drug of choice is crack cocaine. Int J STD AIDS. 2002;13(11):769-74.

114. Poulin C, Alary M, Bernier F, Carbonneau D, Boily MC, Joly JR. Prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae among at-risk women, young sex workers, and street youth attending community organizations in Quebec City, Canada. Sex Transm Dis. 2001;28(8):437-43.

115. Kral AH, Lorvick J, Ciccarone D, Wenger L, Gee L, Martinez A, et al. HIV prevalence and risk behaviors among men who have sex with men and inject drugs in San Francisco. J Urban Health. 2005;82(1 Suppl 1):i43-50.

116. Bogart LM, Kral AH, Scott A, Anderson R, Flynn N, Gilbert ML, et al. Condom attitudes and behaviors among injection drug users participating in California syringe exchange programs. AIDS Behav. 2005;9(4):423-32.

117. March JC, Oviedo-Joekes E, Romero M. Inconsistent condom use among socially excluded heroin users. Gac Sanit. 2007;21(4):321-8.

118. Plitt SS, Garfein RS, Gaydos CA, Strathdee SA, Sherman SG, Taha TE. Prevalence and correlates of chlamydia trachomatis, neisseria gonorrhoeae, trichomonas vaginalis infections, and bacterial vaginosis among a cohort of young injection drug users in Baltimore, Maryland. Sex Transm Dis. 2005;32(7):446-53.

119. Croxford S, Platt L, Hope VD, Cullen KJ, Parry JV, Ncube F. Sex work amongst people who inject drugs in England, Wales and Northern Ireland: findings from a National Survey of Health Harms and Behaviours. Int J Drug Policy. 2015;26(4):429-33.

120. Uusküla A, McNutt LA, Dehovitz J, Fischer K, Heimer R. High prevalence of blood-borne virus infections and high-risk behaviour among injecting drug users in Tallinn, Estonia. Int J STD AIDS. 2007;18(1):41-6.

121. Grenfell P, Baptista Leite R, Garfein R, de Lussigny S, Platt L, Rhodes T. Tuberculosis, injecting drug use and integrated HIV-TB care: a review of the literature. Drug Alcohol Depend. 2013;129(3):180-209.

122. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009;48(1):72-82.

123. Oeltmann JE, Oren E, Haddad MB, Lake LK, Harrington TA, Ijaz K, et al. Tuberculosis outbreak in marijuana users, Seattle, Washington, 2004. Emerg Infect Dis. 2006;12(7):1156-9.

124. Pevzner ES, Robison S, Donovan J, Allis D, Spitters C, Friedman R, et al. Tuberculosis transmission and use of methamphetamines in Snohomish County, WA, 1991-2006. Am J Public Health. 2010;100(12):2481-6.

125. Leonhardt KK, Gentile F, Gilbert BP, Aiken M. A cluster of tuberculosis among crack house contacts in San Mateo County, California. Am J Public Health. 1994;84(11):1834-6.

126. Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for tuberculosis, HIV, prison and harm reduction services. Curr Opin HIV AIDS. 2012;7(4):345-53.

127. Werner SB, Passaro D, McGee J, Schechter R, Vugia DJ. Wound botulism in California, 1951-1998: recent epidemic in heroin injectors. Clin Infect Dis. 2000;31(4):1018-24.

128. Abbara A, Brooks T, Taylor GP, Nolan M, Donaldson H, Manikon M, et al. Lessons for control of heroin-associated anthrax in Europe from 2009-2010 outbreak case studies, London, UK. Emerg Infect Dis. 2014;20(7):1115-22.

129. Palmateer NE, Hope VD, Roy K, Marongiu A, White JM, Grant KA, et al. Infections with spore-forming bacteria in persons who inject drugs, 2000-2009. Emerg Infect Dis. 2013;19(1):29-34.

130. Lundbo, LF. Benfield T. Risk factors for community-acquired bacterial meningitis. Infect Dis (Lond). 2017;49(6):433-44.

131. Larney S, Peacock A, Mathers BM, Hickman M, Degenhardt L. A systematic review of injecting-related injury and disease among people who inject drugs. Drug Alcohol Depend. 2017;171:39-49.

132. Harboe ZB, Larsen MV, Ladelund S, Kronborg G, Konradsen HB, Gerstoft J, et al. Incidence and risk factors for invasive pneumococcal disease in HIV-infected and non-HIV-infected individuals before and after the introduction of combination antiretroviral therapy: persistent high risk among HIV-infected injecting drug users. Clin Infect Dis. 2014;59(8):1168-76.

133. Ruotsalainen E, Sammalkorpi K, Laine J, Huotari K, Sarna S, Valtonen V, et al. Clinical manifestations and outcome in Staphylococcus aureus endocarditis among injection drug users and nonaddicts: a prospective study of 74 patients. BMC Infect Dis. 2006;6:137.

134. Chen JL, Fullerton KE, Flynn NM. Necrotizing fasciitis associated with injection drug use. Clin Infect Dis. 20011;33(1):6-15.

135. Phillips KT, Stein MD. Risk practices associated with bacterial infections among injection drug users in Denver, Colorado. Am J Drug Alcohol Abuse. 2010;36(2):92-7.

136. Dwyer R, Topp L, Maher L, Power R, Hellard M, Walsh N, et al. Prevalences and correlates of non-viral injecting-related injuries and diseases in a convenience sample of Australian injecting drug users. Drug Alcohol Depend. 2009;100(1-2):9-16.

137. Topp L, Iversen J, Conroy A, Salmon AM, Maher L. Prevalence and predictors of injecting-related injury and disease among clients of Australia's needle and syringe programs. Aust N Z J Public Health. 2008;32(1):34-7.

138. Pollini RA, Gallardo M, Hasan S, Minuto J, Lozada R, Vera A, et al. High prevalence of abscesses and self-treatment among injection drug users in Tijuana, Mexico. Int J Infect Dis. 2010;14 Suppl 3:e117-22.

139. Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, Edlin BR. High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. Clin Infect Dis. 2000;30(3):579-81.

140. Murphy EL, DeVita D, Liu H, Vittinghoff E, Leung P, Ciccarone DH, et al. Risk factors for skin and soft-tissue abscesses among injection drug users: a case-control study. Clin Infect Dis. 2001;33(1):35-40.

141. Palepu A, Tyndall MW, Leon H, Muller J, O'Shaughnessy MV, Schechter MT, et al. Hospital utilization and costs in a cohort of injection drug users. CMAJ. 2001;165(4):415-20.

142. Bassetti S, Hoffmann M, Bucher HC, Fluckiger U, Battegay M. Infections requiring hospitalization of injection drug users who participated in an injection opiate maintenance program. Clin Infect Dis. 2002;34(5):711-3.

143. Tookes H, Diaz C, Li H, Khalid R, Doblecki-Lewis S. A Cost Analysis of Hospitalizations for Infections Related to Injection Drug Use at a County Safety-Net Hospital in Miami, Florida. PLoS One. 2015;10(6):e0129360.

144. Axelsson A, Søholm H, Dalsgaard M, Helweg-Larsen J, Ihlemann N, Bundgaard H, et al. Echocardiographic findings suggestive of infective endocarditis in asymptomatic Danish injection drug users attending urban injection facilities. Am J Cardiol. 2014;114(1):100-4.

145. Otome O, Guy S, Tramontana A, Lane G, Karunajeewa H. A Retrospective Review: Significance of Vegetation Size in Injection Drug Users with Right-Sided Infective Endocarditis. Heart Lung Circ. 2016;25(5):466-70.

146. Moss R, Munt B. Injection drug use and right sided endocarditis. Heart. 2003;89(5):577-81.

147. Mathew J, Addai T, Anand A, Morrobel A, Maheshwari P, Freels S. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. Arch Intern Med. 1995;155(15):1641-8.

148. Nahass RG, Weinstein MP, Bartels J, Gocke DJ. Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1-negative and -positive patients. J Infect Dis. 1990;162(4):967-70.

149. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. I. Patient characteristics. Arch Intern Med. 1992;152(9):1863-8.

150. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. Ann Intern Med. 1992;117(7):560-6.

151. Hubbell G, Cheitlin MD, Rapaport E. Presentation, management, and follow-up evaluation of infective endocarditis in drug addicts. Am Heart J. 1981;102(1):85-94.

152. Starakis I, Mazokopakis EE. Injecting illicit substances epidemic and infective endocarditis. Infect Disord Drug Targets. 2010;10(1):22-6.

153. Mathura KC, Thapa N, Rauniyar A, Magar A, Gurubacharya DL, Karki DB. Injection drug use and tricuspid valve endocarditis. Kathmandu Univ Med J (KUMJ). 2005;3(1):84-6.

154. Cooper HL, Brady JE, Ciccarone D, Tempalski B, Gostnell K, Friedman SR. Nationwide increase in the number of hospitalizations for illicit injection drug use-related infective endocarditis. Clin Infect Dis. 2007;45(9):1200-3.

155. Watanakunakorn C, Burkert T. Infective endocarditis at a large community teaching hospital, 1980-1990. A review of 210 episodes. Medicine (Baltimore). 1993;72(2):90-102.

156. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA. 2002;288(1):75-81.

157. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463-73.

158. Spijkerman IJ, van Ameijden EJ, Mientjes GH, Coutinho RA, van den Hoek A. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. J Clin Epidemiol. 1996;49(10):1149-54.

159. Berge A, Ekdahl C, Ekspong L, Julander I, Kurland S, Olaison L, et al. Svenska Infektionsläkarföreningen. Vårdprogram Infektiös endokardit. 2016.

160. Ternhag A, Cederström A, Törner A, Westling K. A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. PLoS One. 2013;8(7):e67519.

161. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016;387(10021):882-93.

162. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30(19):2369-413.

163. Sapico FL, Montgomerie JZ. Vertebral osteomyelitis in intravenous drug abusers: report of three cases and review of the literature. Rev Infect Dis. 1980;2(2):196-206.

164. Kak V, Chandrasekar PH. Bone and joint infections in injection drug users. Infect Dis Clin North Am. 2002;16(3):681-95.

165. Jeragh A, Ahmad S, Naseem J, Khan ZU. Candida lusitaniae arthritis in an intravenous drug user. Mycoses. 2007;50(5):430-2.

166. Gifford DB, Patzakis M, Ivler D, Swezey RL. Septic arthritis due to pseudomonas in heroin addicts. J Bone Joint Surg Am. 1975;57(5):631-5.

167. Roca RP, Yoshikawa TT. Primary skeletal infections in heroin users: a clinical characterization, diagnosis and therapy. Clin Orthop Relat Res. 1979;(144):238-48.

168. Brancós MA, Peris P, Miró JM, Monegal A, Gatell JM, Mallolas J, et al. Septic arthritis in heroin addicts. Semin Arthritis Rheum. 1991;21(2):81-7.

169. Muñoz-Fernández S, Maciá MA, Pantoja L, Cardenal A, Peña JM, Martín Mola E, et al. Osteoarticular infection in intravenous drug abusers: influence of HIV infection and differences with non drug abusers. Ann Rheum Dis. 1993;52(8):570-4.

170. Swisher LA, Roberts JR, Glynn MJ. Needle licker's osteomyelitis. Am J Emerg Med. 1994;12(3):343-6.

171. Ferraro K, Cohen MA. Acute septic sacroiliitis in an injection drug user. Am J Emerg Med. 2004;22(1):60-1.

172. Bhavan KP, Marschall J, Olsen MA, Fraser VJ, Wright NM, Warren DK. The epidemiology of hematogenous vertebral osteomyelitis: a cohort study in a tertiary care hospital. BMC Infect Dis. 2010;10:158.

173. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ. Hematogenous pyogenic spinal infections and their surgical management. Spine (Phila Pa 1976). 2000;25(13):1668-79.

174. Kimura AC, Higa JI, Levin RM, Simpson G, Vargas Y, Vugia DJ. Outbreak of necrotizing fasciitis due to Clostridium sordellii among black-tar heroin users. Clin Infect Dis. 2004;38(9):e87-91.

175. Lonergan S, Rodriguez RM, Schaulis M, Navaran P. A case series of patients with black tar heroin-associated necrotizing fasciitis. J Emerg Med. 2004;26(1):47-50.

176. Dunbar NM, Harruff RC. Necrotizing fasciitis: manifestations, microbiology and connection with black tar heroin. J Forensic Sci. 2007;52(4):920-3.

177. Curtis SJ, Tanna A, Russell HH, Efstratiou A, Paul J, Cubbon M, et al. Invasive group A streptococcal infection in injecting drug users and non-drug users in a single UK city. J Infect. 2007;54(5):422-6.

178. Kievlan DR, Gukasyan M, Gesch J, Rodriguez RM. Clinical profile of injection drug users presenting to the ED. Am J Emerg Med. 2015;33(5):674-6.

179. Pedersen M, Benfield TL, Skinhoej P, Jensen AG. Haematogenous Staphylococcus aureus meningitis. A 10-year nationwide study of 96 consecutive cases. BMC Infect Dis. 2006;6:49.

180. Benfield T, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV, et al. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. Clin Microbiol Infect. 2007;13(3):257-63.

181. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME, et al. Clinical management of Staphylococcus aureus bacteraemia. Lancet Infect Dis. 2011;11(3):208-22.

182. Fernández Guerrero ML, González López JJ, Goyenechea A, Fraile J, de Górgolas M. Endocarditis caused by Staphylococcus aureus: A reappraisal of the epidemiologic, clinical, and pathologic manifestations with analysis of factors determining outcome. Medicine (Baltimore). 2009;88(1):1-22.

183. Shrestha NK, Jue J, Hussain ST, Jerry JM, Pettersson GB, Menon V, et al. Injection Drug Use and Outcomes After Surgical Intervention for Infective Endocarditis. Ann Thorac Surg. 2015;100(3):875-82.

184. Faraklas I, Yang D, Eggerstedt M, Zhai Y, Liebel P, Graves G, et al. A Multi-Center Review of Care Patterns and Outcomes in Necrotizing Soft Tissue Infections. Surg Infect (Larchmt). 2016;17(6):773-8.

185. Callahan TE, Schecter WP, Horn JK. Necrotizing soft tissue infection masquerading as cutaneous abcess following illicit drug injection. Arch Surg. 1998;133(8):812-7; discussion 817-9.

186. Gordon RJ, Lowy FD. Bacterial infections in drug users. N Engl J Med. 2005;353(18):1945-54.

187. DiNubile MJ, Lipsky BA. Complicated infections of skin and skin structures: when the infection is more than skin deep. J Antimicrob Chemother. 2004;53 Suppl 2:ii37-50.

188. Salmon AM, Dwyer R, Jauncey M, van Beek I, Topp L, Maher L. Injecting-related injury and disease among clients of a supervised injecting facility. Drug Alcohol Depend. 2009;101(1-2):132-6.

189. Larsen AS, Halvorsen TF. [Bad shots--skin and soft tissue infections following intravenous drug abuse]. Tidsskr Nor Laegeforen. 2000;120(2):199-201.

190. Henriksen BM, Albrektsen SB, Simper LB, Gutschik E. Soft tissue infections from drug abuse. A clinical and microbiological review of 145 cases. Acta Orthop Scand. 1994;65(6):625-8.

191. Wilson J, Guy R, Elgohari S, Sheridan E, Davies J, Lamagni T, et al. Trends in sources of meticillin-resistant Staphylococcus aureus (MRSA) bacteraemia: data from the national mandatory surveillance of MRSA bacteraemia in England, 2006-2009. J Hosp Infect. 2011;79(3):211-7.

192. Dryden MS. Skin and soft tissue infection: microbiology and epidemiology. Int J Antimicrob Agents. 2009;34 Suppl 1:S2-7.

193. Brown PD, Ebright JR. Skin and Soft Tissue Infections in Injection Drug Users. Curr Infect Dis Rep. 2002;4(5):415-9.

194. Kaushik KS, Kapila K, Praharaj AK. Shooting up: the interface of microbial infections and drug abuse. J Med Microbiol. 2011;60(Pt 4):408-22.

195. Fink DS, Lindsay SP, Slymen DJ, Kral AH, Bluthenthal RN. Abscess and self-treatment among injection drug users at four California syringe exchanges and their surrounding communities. Subst Use Misuse. 2013;48(7):523-31.

196. Hope V, Kimber J, Vickerman P, Hickman M, Ncube F. Frequency, factors and costs associated with injection site infections: findings from a national multi-site survey of injecting drug users in England. BMC Infect Dis. 2008; 8:120.

197. Lloyd-Smith E, Wood E, Zhang R, Tyndall MW, Montaner JS, Kerr T. Risk factors for developing a cutaneous injection-related infection among injection drug users: a cohort study. BMC Public Health. 2008;8:405.

198. Hope VD, Marongiu A, Parry JV, Ncube F. The extent of injection site infection in injecting drug users: findings from a national surveillance study. Epidemiol Infect. 2010;138(10):1510-8.

199. Hope VD, Ncube F, Parry JV, Hickman M. Healthcare seeking and hospital admissions by people who inject drugs in response to symptoms of injection site infections or injuries in three urban areas of England. Epidemiol Infect. 2015;143(1):120-31.

200. Hope VD, Hickman M, Parry JV, Ncube F. Factors associated with recent symptoms of an injection site infection or injury among people who inject drugs in three English cities. Int J Drug Policy. 2014;25(2):303-7.

201. Smith ME, Robinowitz N, Chaulk P, Johnson KE. High rates of abscesses and chronic wounds in community-recruited injection drug users and associated risk factors. J Addict Med. 2015;9(2):87-93.

202. Bassetti S, Battegay M. Staphylococcus aureus infections in injection drug users: risk factors and prevention strategies. Infection. 2004;32:163-9.

203. Bourgois P, Prince B, Moss A. The Everyday Violence of Hepatitis C Among Young Women Who Inject Drugs in San Francisco. Hum Organ. 2004;63(3):253-64.

204. Mackenzie AR, Laing RB, Douglas JG, Greaves M, Smith CC. High prevalence of iliofemoral venous thrombosis with severe groin infection among injecting drug users in North East Scotland: successful use of low molecular weight heparin with antibiotics. Postgrad Med J. 2000;76(899):561-5.

205. Aitken CK, Higgs P. Severe vein damage caused by Temezepam injecting. Aust N Z J Public Health. 2002;26(1):79.

206. Barańska-Rybak W, Błażewicz I, Kąkol M, Roter M, Nowicki R. Cutaneous manifestations of injectable drug use: hidden secrets. Cutis. 2014;93(4):185-7.

207. Feeney GF, Gibbs HH. Digit loss following misuse of temazepam. Med J Aust. 2002;176(8):380.

208. Partanen TA, Vikatmaa P, Tukiainen E, Lepäntalo M, Vuola J. Outcome after injections of crushed tablets in intravenous drug abusers in the Helsinki University Central Hospital. Eur J Vasc Endovasc Surg. 2009;37(6):704-11.

209. Yeo AK, Chan CY, Chia KH. Complications relating to intravenous buprenorphine abuse: a single institution case series. Ann Acad Med Singapore. 2006;35(7):487-91.

210. Bouquié R, Wainstein L, Pilet P, Mussini JM, Deslandes G, Clouet J, et al. Crushed and injected buprenorphine tablets: characteristics of princeps and generic solutions. PLoS One. 2014;9(12):e113991.

211. Ho RC, Ho EC, Mak A. Cutaneous complications among i.v. buprenorphine users. J Dermatol..2009;36(1):22-9.

212. Centers for Disease Control and Prevention (CDC). Soft tissue infections among injection drug users--San Francisco, California, 1996-2000. MMWR Morb Mortal Wkly Rep. 2001;50(19):381-4.

213. Ciccarone D, Harris M. Fire in the vein: Heroin acidity and its proximal effect on users' health. Int J Drug Policy. 2015;26(11):1103-10.

214. Robicsek A, Beaumont JL, Peterson LR. Duration of colonization with methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2009;48(7):910-3.

215. Bassetti M, Nicco E, Mikulska M. Why is community-associated MRSA spreading across the world and how will it change clinical practice? Int J Antimicrob Agents. 2009;34 Suppl 1:S15-9.

216. Tuazon CU, Sheagren JN. Increased rate of carriage of Staphylococcus aureus among narcotic addicts. J Infect Dis. 1974;129(6):725-7.

217. Al-Rawahi GN, Schreader AG, Porter SD, Roscoe DL, Gustafson R, Bryce EA. Methicillin-resistant Staphylococcus aureus nasal carriage among injection drug users: six years later. J Clin Microbiol. 2008;46(2):477-9.

218. Gwizdala RA, Miller M, Bhat M, Vavagiakis P, Henry C, Neaigus A, et al. Staphylococcus aureus colonization and infection among drug users: identification of hidden networks. Am J Public Health 2011;101(7):1268-76.

219. Lloyd-Smith E, Hull MW, Hawkins D, Champagne S, Kerr T, Romney MG. Screening for methicillin-resistant Staphylococcus aureus (MRSA) in community-recruited injection drug users: are throat swabs necessary? Epidemiol Infect. 2012;140(9):1721-4.

220. Bassetti S, Wolfisberg L, Jaussi B, Frei R, Kuntze MF, Battegay M, et al. Carriage of Staphylococcus aureus among injection drug users: lower prevalence in an injection heroin maintenance program than in an oral methadone program. Infect Control Hosp Epidemiol. 2004;25(2):133-7.

221. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005;5(12):751-62.

222. Wertheim HF, Vos MC, Ott A, van Belkum A, Voss A, Kluytmans JA, et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. Lancet. 2004;364(9435):703-5.

223. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev. 1997;10(3):505-20.

224. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. Study Group. N Engl J Med. 2001;344(1):11-6.

225. Public Health Agency of Sweden and National Veterinary Institute. Swedres-Svarm 2014. Consumption of antibiotics and occurrence of antibiotic resistance in Sweden. Solna/Uppsala 2015. Available at: https://www.folkhalsomyndigheten.se/pagefiles/20281/Swedres-Svarm-2014-14027.pdf. (Access date 15 March 2016)

226. El-Sharif A, Ashour HM. Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) colonization and infection in intravenous and inhalational opiate drug abusers. Exp Biol Med (Maywood). 2008;233(7):874-80.

227. Atkinson SR, Paul J, Sloan E, Curtis S, Miller R. The emergence of meticillin-resistant Staphylococcus aureus among injecting drug users. J Infect. 2009;58(5):339-45.

228. Saravolatz LD, Markowitz N, Arking L, Pohlod D, Fisher E. Methicillin-resistant Staphylococcus aureus. Epidemiologic observations during a community-acquired outbreak. Ann Intern Med. 1982;96(1):11-6.

229. Charlebois ED, Bangsberg DR, Moss NJ, Moore MR, Moss AR, Chambers HF, et al. Population-based community prevalence of methicillin-resistant Staphylococcus aureus in the urban poor of San Francisco. Clin Infect Dis. 2002;34(4):425-33.

230. Fleisch F, Zbinden R, Vanoli C, Ruef C. Epidemic spread of a single clone of methicillin-resistant Staphylococcus aureus among injection drug users in Zurich, Switzerland. Clin Infect Dis. 2001;32(4):581-6.

231. Kreisel KM, Johnson JK, Stine OC, Shardell MD, Perencevich EN, Lesse AJ, et al. Illicit drug use and risk for USA300 methicillin-resistant Staphylococcus aureus infections with bacteremia. Emerg Infect Dis. 2010;16(9):1419-27.

232. Cohen AL, Shuler C, McAllister S, Fosheim GE, Brown MG, Abercrombie D, et al. Methamphetamine use and methicillin-resistant Staphylococcus aureus skin infections. Emerg Infect Dis. 2007;13(11):1707-13.

233. Gilbert M, MacDonald J, Gregson D, Siushansian J, Zhang K, Elsayed S, et al. Outbreak in Alberta of community-acquired (USA300) methicillin-resistant Staphylococcus aureus in people with a history of drug use, homelessness or incarceration. CMAJ. 2006;175(2):149-54.

234. Fleisch F, Oechslin EC, Gujer AR, Ritzler E, Imhof A, Ruef C, et al. Transregional spread of a single clone of methicillin-resistant Staphylococcus aureus between groups of drug users in Switzerland. Infection. 2005;33(4):273-7.

235. Colombo C, Zink R, Ruef C. Persistence of a methicillin-resistant Staphylococcus aureus clone in a drug-use network. Clin Infect Dis. 2003;37(7):990-1; author reply 991-2.

236. Daly P, Bryce EA, Buxton J. Reply to dr Charlebois et Al. (Clin infect dis 2002; 34:425-33). Clin Infect Dis. 2002;35(9):1135.

237. Quagliarello B, Cespedes C, Miller M, Toro A, Vavagiakis P, Klein RS, et al. Strains of Staphylococcus aureus obtained from drug-use networks are closely linked. Clin Infect Dis. 2002;35(6):671-7.

238. Phillips KT, Stein MD, Anderson BJ, Corsi KF. Skin and needle hygiene intervention for injection drug users: results from a randomized, controlled Stage I pilot trial. J Subst Abuse Treat. 2012;43(3):313-21.

239. Phillips KT, Altman JK, Corsi KF, Stein MD. Development of a risk reduction intervention to reduce bacterial and viral infections for injection drug users. Subst Use Misuse. 2013;48(1-2):54-64.

240. Whitman TJ, Herlihy RK, Schlett CD, Murray PR, Grandits GA, Ganesan A, et al. Chlorhexidine-impregnated cloths to prevent skin and soft-tissue infection in Marine recruits: a cluster-randomized, double-blind, controlled effectiveness trial. Infect Control Hosp Epidemiol. 2010;31(12):1207-15.

241. Ellis MW, Schlett CD, Millar EV, Wilkins KJ, Crawford KB, Morrison-Rodriguez SM, et al. Hygiene strategies to prevent methicillin-resistant Staphylococcus aureus skin and soft tissue infections: a cluster-randomized controlled trial among high-risk military trainees. Clin Infect Dis. 2014;58(11):1540-8.

242. Millar EV, Chen WJ, Schlett CD, Cui T, Crawford KB, Lanier JB, et al. Frequent use of chlorhexidine-based body wash associated with a reduction in methicillin-resistant Staphylococcus aureus nasal colonization among military trainees. Antimicrob Agents Chemother. 2015;59(2):943-9.

243. Davido B, Dinh A, Salomon J, Roux AL, Gosset-Woimant M, Pierre I, et al. Recurrent furunculosis: Efficacy of the CMC regimen--skin disinfection (chlorhexidine), local nasal antibiotic (mupirocin), and systemic antibiotic (clindamycin). Scand J Infect Dis. 2013;45(11):837-41.

244. Roux P, Carrieri MP, Keijzer L, Dasgupta N. Reducing harm from injecting pharmaceutical tablet or capsule material by injecting drug users. Drug Alcohol Rev. 2011;30(3):287-90.

245. Zule, WA, Bobashev G. High dead-space syringes and the risk of HIV and HCV infection among injecting drug users. Drug Alcohol Depend. 2009;100(3):204-13.

246. Zule WA, Cross HE, Stover J, Pretorius C. Are major reductions in new HIV infections possible with people who inject drugs? The case for low dead-space syringes in highly affected countries. Int J Drug Policy. 2013;24(1):1-7.

247. Patel P, Patel RP, Brandon S, McLean S, Bruno R, de Graaff B. Effects of filtration on the presence of particulate and oxycodone content of injections prepared from crushed OxyContin® tablets. Curr Drug Saf. 2012;7(3):218-24.

248. McLean S, Bruno R, Brandon S, de Graaff B. Effect of filtration on morphine and particle content of injections prepared from slow-release oral morphine tablets. Harm Reduct J. 2009;6:37.
249. Ng H, Patel RP, Bruno R, Latham R, Wanandy T, McLean S. Filtration of crushed tablet suspensions has potential to reduce infection incidence in people who inject drugs. Drug Alcohol Rev. 2015;34(1):67-73.
250. MacArthur GJ, van Velzen E, Palmateer N, Kimber J, Pharris A, Hope V, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. Int J Drug Policy. 2014;25(1):34-52.
251. Kimber J, Dolan K, van Beek I, Hedrich D, Zurhold H. Drug consumption facilities: an update since 2000. Drug Alcohol Rev. 2003;22(2):227-33.
252. Wood E, Tyndall MW, Montaner JS, Kerr T. Summary of findings from the evaluation of a pilot medically supervised safer injecting facility. CMAJ. 2006;175(11):1399-404.
253. Salmon AM, van Beek I, Amin J, Kaldor J, Maher L. The impact of a supervised injecting facility on ambulance call-outs in Sydney, Australia. Addiction. 2010;105(4):676-83.
254. Strathdee SA, Pollini RA. A 21st-century Lazarus: the role of safer injection sites in harm reduction and recovery. Addiction. 2007;102(6):848-9.
255. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
256. Johansson LA, Björkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: an investigation of 1,094 deaths in Sweden during 1995. J Clin Epidemiol. 2009;62(11):1202-9.
257. Stöffelmayr BE, Mavis BE, Kasim RM. The longitudinal stability of the Addiction Severity Index. J Subst Abuse Treat. 1994;11(4):373-8.
258. The Swedish National Board of Health and Welfare. The National Patient Register. Available at: http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish. (Access date 2 March 2017).
259. The Swedish National Board of Health and Welfare. Dödsorsaksstatistik – Historik, produktionsmetoder och tillförlitlighet. Artikelnr 2010-4-33. Stockholm 2010.
260. McLellan AT, Cacciola JC, Alterman AI, Rikoon SH, Carise D. The Addiction Severity Index at 25: origins, contributions and transitions. Am J Addict. 2006;15(2):113-24.
261. Tengvald K, Andrén A, Bergman H, Engström C, Nyström S, Sallmén B, et al. Implementing the Addiction Severity Index (ASI) in Swedish human services sectors: Experiences, problems and prospects. J Subst Use. 2004;9(3-4):163-71.
262. Nyström S, Andrén A, Zingmark D, Bergman H. The reliability of the Swedish version of the Addiction Severity Index (ASI). J Subst Use. 2010;15(5):330-9.

263. Hakansson A, Schlyter F, Berglund M. Associations between polysubstance use and psychiatric problems in a criminal justice population in Sweden. Drug Alcohol Depend. 2011;118(1):5-11.

264. Hakansson A, Schlyter F, Berglund M. Factors associated with history of non-fatal overdose among opioid users in the Swedish criminal justice system. Drug Alcohol Depend. 2008;94(1-3):48-55.

265. Kral AH, Malekinejad M, Vaudrey J, Martinez AN, Lorvick J, McFarland W, et al. Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. J Urban Health. 2010;87(5):839-50.

266. Bluthenthal RN, Watters JK. Multimethod research from targeted sampling to HIV risk environments. NIDA Res Monogr. 1995;157:212-30.

267. Friedman AS, Utada A. A method for diagnosing and planning the treatment of adolescent drug abusers (the Adolescent Drug Abuse Diagnosis [ADAD] Instrument). J Drug Educ. 1989;19(4):285-312.

268. Reischl U, Linde HJ, Metz M, Leppmeier B, Lehn N. Rapid identification of methicillin-resistant Staphylococcus aureus and simultaneous species confirmation using real-time fluorescence PCR. J Clin Microbiol. 2000;38(6):2429-33.

269. Seng P, Drancourt M, Gouriet F, La Scola B, Fournier PE, Rolain JM et al. Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Clin Infect Dis. 2009;49(4):543-51.

270. IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

271. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

272. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2016.

273. Thermau T. A Package for Survival Analysis in S. version 2.38. 2015. Available at: http://CRAN.R-project.org/package=survival. (Access data 2 March 2017)

274. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2015.

275. Højsgaard S, Halekoh U, Yan J. The R Package geepack for Generalized Estimating Equations. J Stat Soft. 2006;15(2):1-11.

276. Wilson H, Brener L, Mao L, Treloar C. Perceived discrimination and injecting risk among people who inject drugs attending Needle and Syringe Programmes in Sydney, Australia. Drug Alcohol Depend. 2014;144:274-8.

277. Kulesza M, Matsuda M, Ramirez JJ, Werntz AJ, Teachman BA, Lindgren KP. Towards greater understanding of addiction stigma: Intersectionality with race/ethnicity and gender. Drug Alcohol Depend. 2016;169:85-91.

278. Cama E, Brener L, Wilson H, von Hippel C. Internalized Stigma Among People Who Inject Drugs. Subst Use Misuse. 2016;51(12):1664-8.

279. Rivera AV, DeCuir J, Crawford ND, Amesty S, Lewis CF. Internalized stigma and sterile syringe use among people who inject drugs in New York City, 2010-2012. Drug Alcohol Depend. 2014;144:259-64.

280. Semple SJ, Strathdee SA, Zians J, Patterson TL. Factors associated with experiences of stigma in a sample of HIV-positive, methamphetamine-using men who have sex with men. Drug Alcohol Depend. 2012;125(1-2):154-9.

281. Oltmann S. Dual use research: investigation across multiple science disciplines. Sci Eng Ethics. 2015;21(2):327-41.

282. Kipnis K. Vulnerability in Research Subjects: A Bioethical Taxonomy. In: National Bioethics Advisory Commission [NBAC]. Ethical and Policy Issues in Research Involving Human Participants. Volume II: Commissioned Papers. Rockville, MD: National Bioethics Advisory Commission [NBAC]; 2001: G1-G13.

283. Fry C, Dwyer R. For love or money? An exploratory study of why injecting drug users participate in research. Addiction. 2001;96(9):1319-25.

284. The Swedish Strategic Programme against Antibiotic Resistance, Swedish Institute for Infectious Disease Control. Swedres 2008. A Report on Swedish Antimicrobial Utilisation and Resistance in Human Medicine. Solna 2009. Available at: http://www.folkhalsomyndigheten.se/pagefiles/12892/swedres-2008.pdf. (Access date 15 March 2016)

285. Swedish Institute for Communicable Disease Control and National Veterinary Institute. SWEDRES-SVARM 2012. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala 2013. Available at: http://www.folkhalsomyndigheten.se/pagefiles/12861/swedres-svarm-2012.pdf. (Access date 15 March 2016)

286. Eriksson A, Palm J, Storbjörk J. Kvinnor och män i svensk missbruksbehandling: En beskrivning av klientgruppen inom socialtjänstens missbrukarvård i Stockholms län 2001-2002. Stockholm: Centrum för socialvetenskaplig alkohol- och drogforskning (SoRAD); 2003.

287. Bruneau J, Lamothe F, Franco E, Lachance N, Désy M, Soto J, et al. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study. Am J Epidemiol. 1997;146(12):994-1002.

288. Fazel S, Danesh J. Serious mental disorder in 23000 prisoners: a systematic review of 62 surveys. Lancet. 2002;359(9306):545-50.

289. Dyal SR, Kral AH, Dominguez Gonzalez K, Wenger LD, Bluthenthal RN. Consistency of self-reported drug use events in a mixed methods study of people who inject drugs. Am J Drug Alcohol Abuse. 2015;41(4):332-8.

290. Darke S. Self-report among injecting drug users: a review. Drug Alcohol Depend. 1998;51(3):253-63; discussion 267-8.

291. Wurcel AG, Merchant EA, Clark RP, Stone DR. Emerging and Underrecognized Complications of Illicit Drug Use. Clin Infect Dis. 2015;61(12):1840-9.

292. Morrison A, Elliott L, Gruer L. Injecting-related harm and treatment-seeking behaviour among injecting drug users. Addiction. 1997;92(10):1349-52.

293. Stenhem M, Ortqvist A, Ringberg H, Larsson L, Olsson-Liljequist B, Haeggman S, et al. Validity of routine surveillance data: a case study on Swedish notifications of methicillin-resistant Staphylococcus aureus. Euro Surveill. 2009;14(30):19281.

294. Stenhem M, Ortqvist A, Ringberg H, Larsson L, Olsson-Liljequist B, Haeggman S, et al. Epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) in Sweden 2000-2003, increasing incidence and regional differences. BMC Infect Dis. 2006;6:30.

295. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-8.

296. Kral AH, Bluthenthal RN, Lorvick J, Gee L, Bacchetti P, Edlin BR. Sexual transmission of HIV-1 among injection drug users in San Francisco, USA: risk-factor analysis. Lancet. 2001;357(9266):1397-401.

297. Ciccarone D, Unick GJ, Cohen JK, Mars SG, Rosenblum D. Nationwide increase in hospitalizations for heroin-related soft tissue infections: Associations with structural market conditions. Drug Alcohol Depend. 2016;163:126-33.

298. Boe J, Solberg CO, Vogelsang TM, Wormnes A. Perineal carriers of Staphylococci. Br Med J. 1964;2(5404):280-1.

299. del Rio A, Cervera C, Moreno A, Moreillon P, Miró JM. Patients at risk of complications of Staphylococcus aureus bloodstream infection. Clin Infect Dis. 2009;48 Suppl 4:S246-53.

300. Chong E, Poh KK, Shen L, Yeh IB, Chai P. Infective endocarditis secondary to intravenous Subutex abuse. Singapore Med J. 2009;50(1):34-42.

301. Anderson RJ, Corbett B, Ly BT. A Case of Acute Pericarditis Following Intravenous Injection of Crushed Morphine Tablets. J Psychoactive Drugs. 2016;48(5):355-8.

302. Kluger N, Girard C, Guillot B, Bessis D. Penile and scrotal skin necrosis after injection of crushed buprenorphine tablets. Presse Med. 2010;39(5):610-1.

303. Nguyen VT, Chan ES, Chou SH, Godwin JD, Fligner CL, Schmidt RA, et al. Pulmonary effects of i.v. injection of crushed oral tablets: "excipient lung disease". AJR Am J Roentgenol. 2014;203(5):W506-15.

304. Conrad C, Bradley HM, Broz D, Buddha S, Chapman EL, Galang RR, et al. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. MMWR Morb Mortal Wkly Rep. 2015;64(16):443-4.

305. Rafful C, Wagner KD, Werb D, González-Zúñiga PE, Verdugo S, Rangel G, et al. Prevalence and correlates of neck injection among people who inject drugs in Tijuana, Mexico. Drug Alcohol Rev. 2015;34(6):630-6.

306. Hoda Z, Kerr T, Li K, Montaner JS, Wood E. Prevalence and correlates of jugular injections among injection drug users. Drug Alcohol Rev. 2008;27(4):442-6.

307. Lum PJ, Sears C, Guydish J. Injection risk behavior among women syringe exchangers in San Francisco. Subst Use Misuse. 2005;40(11):1681-96.

308. Salazar LF, Crosby RA, Holtgrave DR, Head S, Hadsock B, Todd J, et al. Homelessness and HIV-associated risk behavior among African American men who inject drugs and reside in the urban south of the United States. AIDS Behav. 2007;11(6 Suppl):70-7.

309. Boodram B, Mackesy-Amiti ME, Latkin C. The role of social networks and geography on risky injection behaviors of young persons who inject drugs. Drug Alcohol Depend. 2015;154:229-35.

310. Adamson K, Jackson L, Gahagan J. Young people and injection drug use: Is there a need to expand harm reduction services and support? Int J Drug Policy. 2017;39:14-20.

311. Johnson KM, Fibbi M, Langer D, Silva K, Lankenau SE. Prescription drug misuse and risk behaviors among young injection drug users. J Psychoactive Drugs. 2013;45(2):112-21.

312. Mateu-Gelabert P, Guarino H, Jessell L, Teper A. Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. J Subst Abuse Treat. 2015;48(1):13-20.

313. Fairbairn N, Wood E, Small W, Stoltz JA, Li K, Kerr T. Risk profile of individuals who provide assistance with illicit drug injections. Drug Alcohol Depend. 2006;82(1):41-6.

314. Horyniak D, Dietze P, Degenhardt L, Higgs P, McIlwraith F, Alati R, et al. The relationship between age and risky injecting behaviours among a sample of Australian people who inject drugs. Drug Alcohol Depend. 2013;132(3):541-6.

315. Ditmore M. When sex work and drug use overlap: Considerations for advocacy and practice. London: Harm Reduction International; 2013.

316. Azim T, Bontell I, Strathdee SA. Women, drugs and HIV. Int J Drug Policy. 2015;26 Suppl 1:S16-21.

317. Kuyper LM, Lampinen TM, Li K, Spittal PM, Hogg RS, Schechter MT, et al. Factors associated with sex trade involvement among male participants in a prospective study of injection drug users. Sex Transm Infect. 2004;80(6):531-5.

318. Des Jarlais DC, Braine N, Friedmann P. Unstable housing as a factor for increased injection risk behavior at US syringe exchange programs. AIDS Behav. 2007;11(6 Suppl):78-84.

319. Bardenheier B, Prevots DR, Khetsuriani N, Wharton M. Tetanus surveillance--United States, 1995-1997. MMWR CDC Surveill Summ. 1998;47(2):1-13.

320. Centers for Disease Control and Prevention (CDC). Tetanus among injecting-drug users--California, 1997. MMWR Morb Mortal Wkly Rep. 19986;47(8):149-51.

321. Passaro DJ, Werner SB, McGee J, Mac Kenzie WR, Vugia DJ. Wound botulism associated with black tar heroin among injecting drug users. JAMA. 1998;279(11):859-63.

322. Centers for Disease Control and Prevention (CDC). Wound botulism--California, 1995. MMWR Morb Mortal Wkly Rep. 1995;44(48):889-92.

323. Richert T. Injektionsmissbrukande kvinnors inkomstkällor och anskaffning av droger. Nordisk alkohol- & narkotikatidskrift. 2009;26(5):365-83.

324. Griffith DJ, Mackintosh CL, Inverarity D. Staphylococcus aureus bacteraemia associated with injected new psychoactive substances. Epidemiol Infect. 2016;144(6):1257-66.

325. Dorairaj JJ, Healy C, McMenamin M, Eadie PA. The untold truth about "bath salt" highs: A case series demonstrating local tissue injury. J Plast Reconstr Aesthet Surg. 2012;65(2):e37-41.

326. Russo R, Marks N, Morris K, King H, Gelvin A, Rooney R. Life-threatening necrotizing fasciitis due to 'bath salts' injection. Orthopedics. 2012;35(1):e124-7.

327. Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, et al. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. Drug Alcohol Depend. 2007;87(1):39-45.

328. Aitken CK, Agius PA, Higgs PG, Stoové MA, Bowden DS, Dietze PM. The effects of needle-sharing and opioid substitution therapy on incidence of hepatitis C virus infection and reinfection in people who inject drugs. Epidemiol Infect. 2017;145(4):796-801.

329. Aly R, Maibach HI, Shinefield HR. Microbial flora of atopic dermatitis. Arch Dermatol. 1977;113(6):780-2.

330. Park HY, Kim CR, Huh IS, Jung MY, Seo EY, Park JH, et al. Staphylococcus aureus Colonization in Acute and Chronic Skin Lesions of Patients with Atopic Dermatitis. Ann Dermatol. 2013;25(4):410-6.

331. Wanke I, Skabytska Y, Kraft B, Peschel A, Biedermann T, Schittek B. Staphylococcus aureus skin colonization is promoted by barrier disruption and leads to local inflammation. Exp Dermatol. 2013;22(2):153-5.

332. Wilson LE, Thomas DL, Astemborski J, Freedman TL, Vlahov D. Prospective study of infective endocarditis among injection drug users. J Infect Dis. 2002;185(12):1761-6.

333. Suaya JA, Eisenberg DF, Fang C, Miller LG. Skin and soft tissue infections and associated complications among commercially insured patients aged 0-64 years with and without diabetes in the U.S. PLoS One. 2013;8(4):e60057.

334. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. Diabetologia. 2007;50(3):549-54.

335. Finnie A, Nicolson P. Injecting drug use: implications for skin and wound management. Br J Nurs. 2002;11(6 Suppl):S17-28.

336. Meader N, Li R, Des Jarlais DC, Pilling S. Psychosocial interventions for reducing injection and sexual risk behaviour for preventing HIV in drug users. Cochrane Database Syst Rev. 2010;(1):CD007192.

337. Strathdee SA, Abramovitz D, Lozada R, Martinez G, Rangel MG, Vera A, et al. Reductions in HIV/STI incidence and sharing of injection equipment among female sex workers who inject drugs: results from a randomized controlled trial. PLoS One. 2013;8(6):e65812.

338. Levine H, Kayouf R, Rozhavski V, Sela T, Rajuan-Galor I, Ferber AT, et al. Neglect of skin wounds and the risk of becoming a Staphylococcus aureus nasal carrier: a cohort study. BMC Public Health. 2015;15:749.

339. Johnson RC, Ellis MW, Lanier JB, Schlett CD, Cui T, Merrell DS. Correlation between nasal microbiome composition and remote purulent skin and soft tissue infections. Infect Immun. 2015;83(2):802-11.

340. Mitchell SG, Gryczynski J, Schwartz RP, Myers CP, O'Grady KE, Olsen YK, et al. Changes in Quality of Life following Buprenorphine Treatment: Relationship with Treatment Retention and Illicit Opioid Use. J Psychoactive Drugs. 2015;47(2):149-57.

341. Padaiga Z, Subata E, Vanagas G. Outpatient methadone maintenance treatment program. Quality of life and health of opioid-dependent persons in Lithuania. Medicina (Kaunas). 2007;43(3):235-41.

342. Marshall C, McBryde E. The role of Staphylococcus aureus carriage in the pathogenesis of bloodstream infection. BMC Res Notes. 2014;7(1):428.

343. Lopez AM, Bourgois P, Wenger LD, Lorvick J, Martinez AN, Kral AH. Interdisciplinary mixed methods research with structurally vulnerable populations: case studies of injection drug users in San Francisco. Int J Drug Policy. 2013;24(2):101-9.

344. Nordén L. Risk behaviour and prevention of blood borne infections among injecting drug users. Stockholm: Karolinska Institutet; 2009.

Printed by Media-Tryck, Lund 2017 NORDIC ECOLABEL, 3041 0903

Skin and soft tissue infections among people who inject drugs

People who inject drugs constitute a vulnerable group in society, who often suffer from poor physical health. Viral bloodborne infections such as HIV and hepatitis C in this group have gained substantial scientific and clinical interest. However, there are other infectious complications to injection drug use that are common but haven't received the same attention. This thesis concerns one such health hazard, namely bacterial skin and soft tissue infections. To what extent are people who inject drugs subject to bacterial infections and colonization? Is it possible to identify behaviors or characteristics that increase the risk for infections of this kind? By answering these questions, the thesis ultimately aims to support the development of evidence based interventions to prevent bacterial infections among people who inject drugs. This has the potential to both raise the quality of life among the affected individuals, and cut costs within the public health care system.

Disa Dahlman (MD, MA) works in primary health care in Malmö, Sweden, and is involved in the development of low-threshold primary health care provided to patients in opioid substitution treatment.

LUND UNIVERSITY
Faculty of Medicine

Dept. of Clinical Sciences
Psychiatry, Lund
Lund University, Faculty of Medicine
Doctoral Dissertation Series 2017:91
ISBN 978-91-7619-471-3
ISSN 1652-8220