Understanding and preventing injecting-related bacterial and fungal infections among people who inject drugs

PhD Epidemiology & Public Health

Thomas Daniel Brothers
Research Department of Epidemiology & Public Health
Institute of Epidemiology & Health Care
University College London (UCL)

Supervisors:

Prof Andrew Hayward

Prof Robert Aldridge

Dr Dan Lewer

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Declaration

I, Thomas Daniel Brothers, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background: Injection drug use-associated bacterial and fungal infections (e.g., skin and soft tissue infections, endocarditis, osteomyelitis, septic arthritis, epidural abscess, etc.) are increasingly common. Risk factors include subcutaneous/intramuscular injecting and lack of skin cleaning, but individual-level educational interventions on safer injecting practices have shown limited effectiveness. There may be value in looking beyond individual injecting behaviours to understand risk and prevention opportunities.

Aims: (1) identify social-structural factors that influence risk for injecting-related infections; (2) estimate the effect of opioid agonist treatment on all-cause mortality or infection-related rehospitalization, after hospital admissions with injecting-related infections; (3) assess how risk for injecting-related infections changes within-individuals over time, in relation to social (i.e., incarceration) and clinical (i.e., opioid agonist treatment) exposures.

Methods: Qualitative systematic review with thematic synthesis; quantitative systematic review with meta-analysis; survival analysis and self-controlled case series using data from a cohort of people with opioid use disorder in New South Wales, Australia.

Results: Injecting-related bacterial and fungal infections are shaped by modifiable social-structural factors, including poor quality unregulated drugs, criminalization and policing enforcement, insufficient housing, limited harm reduction services, and harmful health care practices. People who inject drugs navigate these barriers while attempting to protect themselves and their community. After a hospital admission, opioid agonist treatment is associated with a large reduction in mortality but a modest reduction in risk of infection-related rehospitalization. Risk of injecting-related infections changes substantially within-individuals over time; high-risk moments include release from incarceration and around initiation and discontinuation of opioid agonist treatment.

Conclusions: Risk for injecting-related bacterial and fungal infections, and associated treatment outcomes, are shaped by social-structural factors beyond individuals' control. Offering individual-level education and addiction treatment may be helpful, but is likely insufficient. Prevention and treatment strategies should engage more broadly with the social and material conditions within which people prepare and consume drugs, and access health care.

Impact Statement

This thesis was motivated by a desire to improve prevention and treatment of injection drug use-associated bacterial and fungal infections. My work has potential impact to do this through several ways:

1. **Informing public health and health system approaches:** Public health and health system approaches to health promotion for people who inject drugs (including public funding of needle and syringe programs) are primarily motivated by HIV, hepatitis C virus (HCV), and overdose prevention. My findings on modifiable social determinants, substance use, and health services-related factors provide a "roadmap" to additionally improve prevention and treatment of injecting-related bacterial and fungal infections. Many of the social-structural (e.g., housing, criminalization) and more proximate clinical (e.g., opioid agonist treatment) factors are already known to influence risks of blood-borne viruses and overdose, and so scaling up these environmental and health services interventions may bring additional benefits in preventing bacterial and fungal infections. Some factors more specific to bacterial and fungal infections, including the quality of the unregulated drug supply and transforming hospital policies and practices to create welcoming and supportive environments for people who inject drugs, would be new areas of focus for many health systems. This could reframe concepts of health care quality and patient safety to incorporate the needs of people who inject drugs who are hospitalized with injecting-related infections.

2. **Informing clinical practice, treatment decisions, and care planning:** Hospitals and medical specialists have not traditionally incorporated harm reduction and addiction treatment as secondary-prevention strategies into care planning for injecting-related infections. My thesis work shows that offering opioid agonist treatment may change outcomes for patients with injecting-related infections, so this should be offered in all hospitals and incorporated into treatment plans. However, the potential benefits of opioid agonist treatment alone appear to be modest. This means clinicians should also partner with community agencies to address social determinants of health including housing, transportation, and income support. My published work during this PhD (including empirical research and educational reviews and commentaries) has been cited in several clinical guidance documents on caring for patients who inject drugs, and was cited in a successful business case submission to obtain government funding for a hospital inpatient addiction medicine consultation service.

3. **Contributing to future research on the health of people who use drugs:** In my thesis work, I took existing theories and conceptual models (including the "risk environment" framework, which was first developed to inform HIV prevention among people who inject drugs) and applied them to injecting-related bacterial and fungal infections for the first time. Prior work on injecting-related bacterial infections was focused on individual-level behaviour change (e.g., through safer injecting education or individual addiction treatment). I hope my work will inform research and innovation in this field, recognizing that social-structural forces shape individual behaviours (e.g., injecting practices and health care access) and will need to be considered in prevention and treatment efforts. HIV prevention especially has benefited from broadening

beyond biomedical and/or individualistic approaches and engaging with social science, and I hope my work establishes the importance of this for bacterial and fungal infections.

4. **New projects informed by this work:** During my PhD, and as a result of collaborating with people with lived/living experience, I helped to organize a national Canadian network to improve care for people with injection drug use-associated endocarditis. Citing my work in this thesis, we obtained Canadian federal funding to do a national stakeholder engagement and priority-setting project. Our project is also informed by my thesis' conceptual model, considering factors like social determinants, the unregulated drug supply, and care coordination all as opportunities to improve treatment of injecting-related infections (beyond a reductionist, biomedical- or individual behaviour-only lens).

Abbreviations

aOR: Adjusted Odds Ratio

aHR: Adjusted Hazard Ratio

aIRR: Adjusted Incidence Rate Ratio

CAPUD: Canadian Association of People who Use Drugs

CHeReL: Centre for Health Record Linkage

CI: Confidence Interval

CIHR: Canadian Institutes of Health Research

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HR: Hazard Ratio

ICD: International Classification of Diseases

LGBTQ2SI+: Lesbian, Gay, Bisexual, Transgender, Queer, Two-Spirit, and Intersex

OAT: Opioid agonist treatment

OATS Study: Opioid Agonist Treatment Safety Study

OR: Odds Ratio

SSTI: Skin and soft-tissue infection(s)

SUNAR: Substance User Network of the Atlantic Region

uOR: Univariate Odds Ratio

UK: United Kingdom

USA: United States of America

VANDU: Vancouver Area Network of Drug Users

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All authors contributed to conceptualization of this study protocol, led by TDB and supervised by DL and AH. TDB wrote the first draft. All authors contributed to revisions and approved the final version.

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International Journal of Drug Policy

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All authors contributed to conceptualization and methodology, led by TDB and supervised by DL and AH. TDB performed the analyses, supervised by DL. NJ and LD led data curation. LD led funding acquisition for the OATS Study. TDB wrote the first draft of the manuscript. All authors contributed to revisions and approved the final version.

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Chapter 1 Introduction

1.1 Chapter summary and attribution

In this introductory chapter, I provide an overview of the health of people who use drugs (including by injection), explore how social-structural forces (including social, economic, and policy factors) impact the health of people who use drugs, and engage with theories of social epidemiology. I describe how injection drug use-associated bacterial and fungal infections come about, review the changing epidemiology of these infections (including increasing incidence across multiple settings), and summarize prior prevention research that focused on individual-level safer injecting education interventions. I then introduce the conceptual model and framework for the thesis and propose my objectives and research questions.

I adapted some contents of this chapter from several manuscripts that I published during my PhD fellowship, in which I developed my thinking around the health of people who use drugs, social epidemiology, and harm reduction interventions. While my work and understanding benefitted greatly from the input of colleagues, as with all chapters in this thesis, I led conceptualization, analysis, and write-up of the work.

Manuscripts:

- Brothers TD, Bonn M, Lewer D, Comeau E, Kim I, Webster D, Hayward A, Harris M. Social and structural determinants of injection drug use-associated bacterial and fungal infections: a qualitative systematic review and thematic synthesis. *Addiction*. 2023 May 12. https://doi.org/10.1111/add.16257
- Touesnard N*, Brothers TD*, Bonn M, Edelman EJ. Overdose deaths and HIV infections among people who use drugs: shared determinants and integrated responses. *Expert Rev Anti Infect Ther.* 2022 Aug;20(8):1061-1065. https://doi.org/10.1080/14787210.2022.2081152
  *Co-first authorship with Natasha Touesnard, Executive Director of the Canadian Association of People who Use Drugs (CAPUD)
- Brothers TD, Lewer D, Bonn M, Webster D, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: protocol for a mixed studies systematic review. *BMJ Open*. 2021 Aug 9;11(8):e049924. https://doi.org/10.1136/bmjopen-2021-049924

1.2 The health of people who use criminalized and unregulated drugs

A recent systematic review estimated that there are 14.8 million people who inject drugs living in 190 countries, representing around 0.29% of the world's population aged 15-64 years.[1] Globally, more than 80% of people who inject drugs primarily inject opioids.[1] In general, people who use criminalized and unregulated drugs (including by injection) face worse health and shorter life expectancy than general population estimates. Compared to the general population, standardized mortality rates for people who inject drugs (or people with opioid use disorder more generally) are 10-15 times higher and accidental drug poisoning (overdose) death rates are 58 times higher.[2] An estimated 15% of people who inject drugs live with human immunodeficiency virus (HIV), 39% with hepatitis C virus (HCV), and 8% with hepatitis B virus (HBV).[1]

While some health harms can be attributed to substance use disorders, risk for illness and death are not evenly distributed among people who use drugs. Instead, health harms are concentrated among people who use drugs who face multiple forms of discrimination and social exclusion, and who have least access to harm reduction and addiction treatment services.[3–5] Among people who inject drugs, risk of drug poisoning deaths and blood-borne viruses are associated with poverty and lack of housing,[4,6,7] with criminalization and incarceration,[8–10] and with settler-colonialism and structural racism.[3,5] These negative social determinants of health are unfortunately common in this population. A global systematic review among people who inject drugs estimated that the prevalence of recent exposure to incarceration ranged from 10-42%, homelessness or unstable housing ranged from 9-54%, and engagement in sex work from 6-21%.[1]

Social factors that negatively influence health also tend to be factors that negatively influence access to health care.[11–13] For example, structural racism leads to disproportionate enforcement of drug criminalization and also lower access to evidence-based addiction treatment among racialized people who use drugs, compared to white people who use drugs.[5] A report by the First Nations Health Authority in British Columbia, Canada, found that rates of overdose death among First Nations people were more than five times higher than among non-First Nations people and explored causal pathways for this inequity.[14] The report highlighted Indigenous strengths in the face of experiences of racism and inter-generational trauma that contributed both to riskier substance use and acted as barriers to health care access. Criminalization may have particularly harmful effects on women who use drugs, who are more likely to be the primary caregiver for children; they may stay away from health-care services (and even harm reduction services) for fear of losing child custody.[3] Discrimination against lesbian, gay, bisexual, transgender, queer, two-spirit, and intersex

(LGBTQ2SI+)-identified people contributes to higher rates of substance use disorders than among non-LGBTQ2SI+-identified people, and also to barriers to accessing harm reduction and treatment support that were not often designed for LGBTQSI+-identified people.[3,15]

1.3 Social epidemiology theories, models, and frameworks

Social, political, economic, and material factors (like the ones described above) can shape risks for biological outcomes (e.g., HIV infection, overdose death) in multiple ways. This idea is at the root of "social epidemiology", which emerged in the mid-twentieth century in response to criticisms of mainstream epidemiology's emphasis on individualized biomedical and lifestyle "risk factors", decoupled from the social contexts that influence human behaviour. While there are many different theoretical and practical approaches within social epidemiology, in general social epidemiology argues that distributions of health and disease within populations are patterned by their social context and that as societies change their population distributions of disease will change as well.[16,17] Therefore, a major focus of social epidemiology is identifying and ameliorating inequities in the distribution of health and disease within and between populations.[18,19]

Professor Nancy Krieger has proposed a taxonomy comprising three distinct theoretical trends within social epidemiology:[17,20] *sociopolitical*, *psychosocial*, and *ecosocial* (sometimes also known as "socio-ecological"). Sociopolitical theories (which incorporate "social determinants of health" [19,21–24], "social production of disease"[25,26], "political economy of health"[27,28], "fundamental cause theory"[29–31], "Latin American Social Medicine"[32], and other frameworks) focus on how health is determined by hierarchies of social and economic power. These influence the social and material conditions in which people live, including their exposure to pathogens, violence, injury, pollution, and more, and influence their ability to receive appropriate medical care. Psychosocial theories (including "allostatic load", "minority stress", and "social capital", among others) focus on how health and illness are psychologically mediated, based on individuals' behavioural and biological responses to their perception of their social and material conditions. Krieger has advanced and developed a theory, she termed the "ecosocial theory of disease distribution" that seeks to integrate and build on these other schools of thought. Related socio-ecological frameworks used commonly in social epidemiology include "structural violence", Bronfenbrenner's "ecological systems theory", and Rhodes' "risk environment" framework.[26,33–35] These theories, models, and framework all explicitly examine how individual behaviour is shaped by their social context. This way of thinking purposefully runs counter to reductionistic and individualized approaches in much of mainstream,

traditional epidemiology (that, critics accuse, assumes disease distributions arise from individuals' behaviours and/or biology).[18,19]

1.4 The harm reduction movement as a response to social and policy harms

In the face of harmful social and material conditions, the harm reduction movement grew out of mutual aid practices among people who use drugs.[34,36–41] Harm Reduction International defines harm reduction as:

> *"Harm reduction refers to policies, programmes and practices that aim to minimise the negative health, social and legal impacts associated with drug use, drug policies and drug laws. Harm reduction is grounded in justice and human rights. It focuses on positive change and on working with people without judgement, coercion, discrimination, or requiring that people stop using drugs as a precondition of support."*

Harm reduction is also a social justice movement, built on respecting the rights of people who use drugs. It recognizes that many health harms do not come from drug use *per se*, but rather from the social context around drug use. Established and evidence-based harm reduction practices including needle and syringe programs (also known as "needle exchanges"), supervised consumption sites (also known as "overdose prevention sites", "safe injection sites", and "supervised injection facilities"), and take-home naloxone programs were run by drug user organizations and their allies before they were legalized and taken up by mainstream and government public health agencies.[39,42]

Harm reduction interventions aim to create equitable, just, and safer environments for people who use drugs, promote autonomy, build capacity, and enable options that promote health (and reduce risk) for people who use drugs. For example, increasing coverage and availability of needle and syringe distribution programs enables people to avoid borrowing and reusing others' equipment. Establishing supervised consumption sites provides a hygienic and well-lit environment free from policing enforcement where people who use drugs can take their time, test the substance they intend to consume, connect with community, and have someone respond with oxygen and/or naloxone in the event of an overdose. Opioid agonist treatment (e.g., methadone, buprenorphine) reduces reliance on the unregulated drug supply and enables people with more options about when and how to use drugs, once they are less concerned about withdrawal. This is also true for the emerging practice of prescribing "safe supply" (also known as "safer supply") medications as pharmaceutical alternatives to the unregulated drug supply.[43–47] Needle and syringe programs and supervised consumption sites can also integrate other services, including HIV screening, take-home

naloxone kit distribution, primary care, opioid agonist treatment, safe supply, drug checking, and linkages and referrals to housing, income benefits, and other social services. In this way, harm reduction programs promote access to health care and social services for people who may have otherwise been excluded from access.

The scope of this thesis is informed by a harm reduction approach. While people who stop using drugs entirely are likely to be at reduced risk of injecting-related health harms, my work here focuses on the health of people who inject drugs, without assuming everyone will desire or be able to achieve abstinence from drug use. This approach is also motivated by the well-established evidence showing low rates of abstinence after people first attempt drug treatment, and a desire to promote the health of people who may continue to use drugs.[48–50]

1.5 Injection drug use-associated bacterial and fungal infections

This thesis focuses on a specific drug-related health harm: injection drug use-associated bacterial and fungal infections (e.g., skin and soft-tissue infections [SSTI], endocarditis, osteomyelitis, septic arthritis, epidural abscess, etc.). These are less well-understood and less researched than HIV, HCV, and overdose among people who use drugs, and the impacts of social-structural exposures and potential harm reduction responses are not yet clear. Injecting-related bacterial and fungal infections are associated with significant morbidity and mortality among people who inject drugs and are costly for health care systems.[21,51–55] The prevalence of injecting-related infections in the past month ranges from 6-32% of people who inject drugs, while up to 64% report an SSTI in the past year.[56]

The incidence of hospitalizations for severe injecting-related infections is increasing in many parts of the world, including Australia,[57] Canada,[51,58,59] South Africa,[60] the United Kingdom (UK)[61,62], the United States of America (USA),[63–67] and India.[68] According to social epidemiologic theory, changing population distributions of these infections suggests there are underlying changes in social determinants among these countries. However, these countries have varied unregulated drug supplies, drug policies, harm reduction and addiction treatment funding and delivery approaches, and public health insurance schemes. So there is unlikely to be a single explanation for these observed increases in incidence. While there are few empirical studies to explain increasing incidence, commentators have proposed different explanations in different settings. Increasing incidence of injecting-related infections in North America has been hypothesized as due to increasing prevalence of opioid use disorder in the 2000s and 2010s (in part due to the increased

availability of prescription opioids), followed by drug supply transitions towards heroin and then illicitly-manufactured fentanyl (which has a shorter duration of effect than heroin and prescription opioids, and is associated with more frequent injecting).[51,69,70] However, incidence has increased in regions even with relatively little fentanyl and with more stable unregulated drug supplies.[58,62] In Australia, investigators hypothesized that increasing incidence is due to increased use of amphetamines (which are also associated with more frequent injecting).[57] In the UK, incidence has increased even as the drug supply has remained predominantly heroin and the prevalence of injection drug use has not increased, which points to other social factors like increasing homelessness and underfunding of harm reduction services as part of government austerity policies.[62] Recent work from the UK (to which I contributed as a co-author during my PhD) found the incidence of injecting-related infections paralleled rates of homelessness (as measured with International Classifications of Diseases [ICD] administrative codes), and dropped substantially at the onset of the COVID-19 pandemic response, when everyone living in congregate shelters or sleeping outdoors was offered temporary accommodation as part of the UK government's "Everyone In" initiative.[62] We hypothesized that the decrease in incidence of injecting-related infections reflected improved opportunities for personal hygiene and decreased social mixing.

Preventive efforts for injecting-related bacterial and fungal infections have not received the attention given to other injection drug use-associated health harms (e.g. HIV, HCV, or overdose).[56] Most injecting-related infections derive from commensal skin flora, with bacterial sources much more common than fungi. Injecting-related infections most commonly occur within the skin and soft tissue at injecting sites. If not sufficiently treated, these superficial infections may spread and enter the bloodstream, seeding distant sites like heart valves (leading to endocarditis), vertebral disks (causing vertebral osteomyelitis), or the spine or brain (leading to epidural abscess or brain abscess, respectively).[69,71,72] Contaminated equipment or drug solution may also introduce pathogenic bacteria directly into the bloodstream.

Several practices involved in the drug preparation and injection process may increase risks for injecting-related infections.[56,71] To prepare drugs for injection, people first acquire drugs (most often from a criminalized, unregulated source). These drugs are unlikely to be designed or formulated to dissolve completely for safe consumption by injection, and may therefore damage the skin and vasculature when injected. If people have access to robust harm reduction services where they can obtain necessary equipment, they may be able to combine sterile water with their drug (with or without an acidifier, like vitamin C, to aid dissolution) in a sterile "cooker", draw this solution up into a sterile syringe through a sterile cotton filter, sterilize their skin with an alcohol swab, and use a

dedicated tourniquet to aid in identifying a vein. They would then enter the vein with their needle positioned “bevel up” to minimize vein damage, wait until they identify a flash of blood in the syringe chamber, and inject the drug solution directly into the vein.[42]

There are many opportunities throughout this process where contamination may occur, especially if people do not have access to appropriate or sufficient harm reduction supplies, nor a hygienic, warm, and well-lit space to prepare their drugs. While harm reduction advice for HIV and HCV prevention emphasizes not sharing needles and syringes (sometimes known colloquially as “rigs” or “gear”), reusing one’s own equipment likely increases risks of bacterial infections.[42] Needles are blunted or “barbed” after only one use, and needles and syringes may be contaminated with one’s own commensal skin flora. Filters containing residual drug solution are sometimes kept and reused or sold for later use, during which time bacteria can proliferate.[73] Reusing contaminated injecting equipment is more common in settings without sufficient access to harm reduction services (e.g. needle and syringe programs, supervised consumption sites).

In a 2017 systematic review, Larney and colleagues identified several risk factors for injecting-related bacterial infections.[56] Most of the literature focused on SSTI, but all injecting-related bacterial and fungal infections likely share many risk factors due to their common etiology and pathophysiology. More frequent injecting, intramuscular injecting (as opposed to intravenous injecting), and a lack of skin cleaning were associated with SSTI at injecting sites.[56] They did not perform meta-analyses. The authors noted that there was limited (and largely poor quality) research on injecting-related infections, and more research would be needed to understand risks and opportunities for prevention. They recommended that harm reduction services distribute alcohol swabs with every needle, to help ensure that people would be able to clean their skin. They also highlighted that variation in risk for injecting-related infections likely reflects differential access to harm reduction services, hygienic injecting environments, and injecting techniques, but further research is needed to understand this. In a different, 2018 systematic review, Moradi-Joo and colleagues found that only higher injecting frequency was associated with risk for injecting-related SSTI.[74] These authors called for educational and awareness campaigns to reduce risks of injecting-related infections.

Social epidemiologic theories would suggest that contextual and environmental factors (like access to harm reduction services and hygienic injecting environments) influence both individuals’ risk practices and the likelihood of injecting-related infections among people with a given risk practice. For example, several studies identified higher rates of injecting-related infections among people experiencing homelessness and this may be because people cannot access hygienic environments to

prepare and consume drugs.[75,76] Conversely, while intramuscular injection is a risk practice associated with skin infections,[77] SSTI are very rare among people who intramuscularly inject their "heroin-assisted treatment" dose (when pharmaceutical-grade, liquid formulation of diamorphine is injected intramuscularly under sterile conditions).[78] While prior evidence syntheses and conceptual models have focused on how social-structural exposures shape risks of HIV transmission among people who inject drugs,[26,33,48,79–84] this has not been a focus of research for injecting-related bacterial and fungal infections.[21]

1.6 Individual-level health and behaviour change interventions as a response to injection drug use-associated bacterial and fungal infections

Prevention research to date on injecting-related bacterial and fungal infections (while limited) has focused on individual-level behaviour change interventions to promote sterile drug preparation, skin cleaning, and overall safer drug injecting techniques.[85–87] Unfortunately, these have shown mixed results[85–87] and have had limited impact on a population level.[21] I review these here.

Phillips, Stein, and colleagues conducted a randomized controlled trial of an educational, behavioural intervention (named "SKIN") aiming to reduce risk of SSTI among 252 people who inject drugs recruited from hospital inpatient units in the USA.[85,86] The intervention consisted of two individually delivered in-person sessions (an initial 60-minute session and then a 30-minute session one month later) incorporating motivational interviewing and a personalized risk assessment. The authors did not report the absolute frequencies of outcomes, but found that the intervention reduced the rate of self-reported "uncleaned skin injections" – but not the rate of self-reported infections – at 12 months follow-up.[85] The intervention also did not reduce the total number of all-cause hospitalizations or ED visits, nor injection drug use-related hospitalizations.[86] They found that it did reduce the number of injection drug use-related ED visits over 12 months follow-up.[86] The authors did not discuss whether their study participants had access to sufficient sterile injecting equipment to apply the instructions from the educational intervention. Further, 62% of study participants self-identified as homeless and so may not have had access to a hygienic environment for drug preparation and injection. The study was conducted in Boston, USA, where supervised injection sites are criminalized.

In a non-randomized, before-and-after study, Roux and colleagues recruited 307 people who inject drugs from harm reduction programs in Bulgaria, Greece, Portugal, and Romania to evaluate a different educational intervention, the "Individually Tailored Support and Education for Safer

Injection (ITSESI)".[87] This intervention consisted of an individual risk assessment interview about injecting practices, direct observation of a participant's drug preparation and injecting technique in a dedicated, hygienic room, and an educational interview with suggestions to improve injecting practices. The study was not randomized, and participants self-selected into the intervention group; eligible people who declined to engage with the intervention were included in the control group. Recognizing limitations in the non-randomized study design (including selection bias), the investigators observed a reduction in recent syringe sharing (past month; from 25% to 16%) and a reduction in self-reported skin abscesses (prior six months; from 27% to 14%) in the intervention group. They also observed reductions in the control group, from 29% to 24% for syringe sharing and from 23% to 18% for skin abscesses. The authors noted several policy factors that interfered with the uptake of the intervention, including three of the four study countries experiencing severe shortages of sterile drug-injecting equipment. The fidelity of the educational intervention was low in Greece, because it is illegal for service providers to observe injection drug use by their clients in that country.[87]

While these interventions are promising, they are resource intensive and their population-level impact outside of research settings may be limited. Both educational interventions described above were developed based on psychological frameworks (i.e., the Information-Motivation-Behavioural Skills model for "SKIN" in Boston, USA, and Self-Determination Theory for "ITSESI" in Europe) aiming to enhance perceptions of autonomy. The rationale for such behaviour-change interventions relies on assumptions that people who inject drugs will be able to apply the learnings if only they are educated and motivated enough. The mixed signals of effectiveness of individual-level behaviour change interventions may be in part because of social and structural factors (e.g. criminalization, discrimination, lack of access to housing, harm reduction services, and supervised injection sites) that constrain the ability of people to inject more safely[21,71] and that push people away from health care.[88] There is some empirical research to support this theory; a secondary analysis of the SKIN trial data found that people who injected subcutaneously had higher rates of SSTI compared to those who only injected intravenously, but both groups demonstrated similar knowledge of safer injecting practices and risks (and knowledge scores were not associated with SSTI risk).[89] As the incidence of hospitalizations for severe injecting-related infections continues to rise, innovative approaches to primary and secondary prevention are urgently needed.[21,64,88]

1.7 Could harm reduction and addiction treatment interventions prevent injecting-related bacterial and fungal infections?

Effective interventions aimed at reducing the burden of other injecting-related health harms (e.g. HIV, HCV, and overdose) among people who inject drugs have looked beyond individual behaviours to understand how environmental factors (e.g., social determinants, policy factors, availability of harm reduction and addiction treatment) shape risks for individuals.[26,33,48,79–84] There may be great value in looking beyond individual injecting behaviours to understand risk for injecting-related bacterial and fungal infections and identify novel opportunities for intervention.

Several studies have evaluated associations between access to harm reduction services (including use of needle and syringe programs and opioid agonist treatment) and risk for injecting-related infections. These services may reduce the risks of injecting-related infections by empowering people to change individual-level risk practices. Effective access to needle and syringe programs increases the likelihood of skin cleaning and may reduce the frequency of reusing contaminated equipment.[90–92] For people who inject drugs who have opioid use disorders, opioid agonist treatment is associated with many benefits including reduced risks of death and of blood-borne viral infections.[93,94] Opioid agonist treatment limits opioid withdrawal symptoms, reduces reliance on illicit drug markets, and empowers people to inject less frequently and/or in a safer way.[95,96] Engagement in opioid agonist treatment is also associated with regular health care contacts where superficial injecting-related infections may be treated before they progress and become more severe or spread through the bloodstream.[88,97,98]

Larney and colleagues' 2017 systematic review identified limited and mixed evidence for the impact of harm reduction services on risk for injecting-related SSTI. In two studies,[99,100] there was no significant association (but with imprecise effect estimates, with wide confidence intervals) between use of needle and syringe programs and injecting-related infections. In a third study of people who inject drugs recruited through harm reduction and addiction treatment programs, people reporting use of a needle exchange in the past year had higher odds of injecting-related infections in unadjusted analyses – though this may indicate some survey participants who were continuing to inject compared to participants who had stopped injecting entirely.[101] They also identified one study that found people who reported regularly using a supervised consumption site reported fewer injecting-related infections compared to people who less-regularly used a supervised consumption site, in Vancouver, Canada.[102] In an additional study published in 2017 (and not included in Larney's review), Dunleavy and coauthors found that injecting-related skin and soft-tissue infections were

less likely among people in Scotland who reported obtaining at least twice as much injecting equipment as needed from harm reduction programs (compared to people who obtained less injecting equipment than this).[92]

Larney and colleagues' 2017 review also identified several observational studies investigating associations between use of opioid agonist treatment and risk for injecting-related skin infections, and concluded research here was also very limited. One study reported no significant association (without including any numbers).[103] A second study found that people who inject drugs who had ever used opioid agonist treatment were at higher risk for injecting-related infections than people who had never used it.[101] A third study found that risks for injecting-related infections were lower among people currently using opioid agonist treatment and who had never used it, compared to people who had previously been on opioid agonist treatment but discontinued it.[104] This same relationship was observed in the 2017 Dunleavy study.[92]

Overall, there is a lack of research on prevention strategies for injecting-related bacterial and fungal infections. While individual-level interventions may be effective for people who (due to social, economic, and material circumstances) can adopt these practices,[86,87] they have not translated into reductions in the population-level incidence of severe bacterial and fungal infections, which continue to rise. The lack of convincing evidence for individual-level interventions to prevent injecting-related infections may be because of social and structural factors (e.g. criminalization, discrimination, lack of access to housing, harm reduction services) that constrain the ability of people to inject more safely,[21,71] that push people away from health care,[88] and that contribute to a dangerous, caustic, or non-soluble unregulated drug supply.

1.8 Conceptual model for the thesis

Like other drug-related harms, risk for injecting-related bacterial and fungal infections likely reflects contributions of multiple, interacting factors external to individuals that influence risk behaviours and therefore shape health outcomes. For example, homelessness may constrain an individual's ability to wash their hands or use sterile water for injecting,[105] and policy constraints on needle and syringe programs (from criminalisation to reduced operating hours) create a situation in which an individual is more likely to reuse a blunted or contaminated needle. Stigma and criminalization of people who use drugs may keep people away from primary health care, causing superficial bacterial infections to remain untreated and progress to enter the bloodstream. In response to research showing increases in incidence, calls to enhance understanding of the social determinants of

injecting-related bacterial and fungal infections have emerged from both people who use drugs[106] and academic[71,87,88,107] communities. Better understanding of the social determinants of health can help to shift beliefs about responsibility and risk from individual behaviours to the places and social circumstances in which individuals exist, and inform the development of innovative interventions addressing both social and individual-level factors.[26,108] Learning from the successes of HIV prevention efforts in particular, applying a socio-ecological model for injecting-related bacterial and fungal infections could inform new prevention efforts that target social and structural causes.[80,109]

The "risk environment" conceptual framework, as developed by Rhodes and others,[26,34,35,79] describes how interactions between social and structural factors external to the individual influence individual behaviours, and therefore structure or create health harms.[3] The risk environment framework has informed clinical and public health efforts at reducing other drug-related harms, including HIV transmission,[26,79,110] HCV treatment,[111] and overdoses.[112,113] The risk environment framework is the most prominent socio-ecological model in substance use research; it comprises risk factors external to individuals, considering types and levels of environmental influence.[3,33–35] As first developed in the context of HIV prevention, the risk environment framework describes four different types of environmental influences: social, physical, economic, and policy. These can occur at two different levels, microenvironmental or macroenvironmental.[110] Microenvironmental factors operate at the level of interpersonal relationships, community and group norms, and institutional or organizational responses.[26] This could include local norms about the culture of substance use and acceptability of sharing or reuse of potentially contaminated injecting equipment (a social factor), or increasing housing prices (an economic factor) contributing to homelessness and lack of access to soap and water (physical factors). Macroenvironmental factors operate at the level of states, societies, and laws, and interact with microenvironmental factors.[26] This could include state policing crackdowns on heroin importation leading instead to increased importation of fentanyl (a policy factor), which has a shorter half-life and associated risks of increased injecting frequency.[70] Macro-, micro-, and individual-level factors interplay to influence health practices and outcomes.[3] The risk environment model encourages thinking about how people interact with and modify constraining environments (e.g., drug users' unions organizing to repeal laws banning supervised consumption sites).[33] Collins and colleagues recently extended the risk environment model to incorporate intersectionality, considering how social-structural factors affect people who use drugs differently depending on social identities and locations within power hierarchies, including race and gender.[3]

1.9 Developing a framework for the thesis

As described above, injecting-related bacterial and fungal infections occur through introducing bacteria or fungi (often commensal organisms on the skin) into sterile sites and are precipitated by particulate matter that damages blood vessels, lymphatics, and heart valves.[71,114] To conceptualise how environments create and perpetuate risk for injecting-related infections at different moments (and to identify opportunities for potential future interventions), I developed a framework[21] (see Figure 1) illustrating a pathway from (a) drug acquisition (e.g. solubility); (b) preparation (e.g., using sterile water); (c) injection (e.g., venous access); (d) development of and care for superficial infections (e.g., self-treatment); (e) development of and care for severe infections (e.g., hospitalization); and (f) outcomes after infections (e.g. access to follow-up care). Not every person would progress through all stages. Some do not develop infections; many never access treatment.

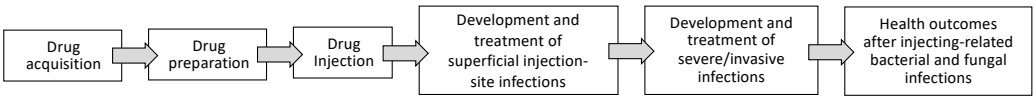

Figure 1. Illustrative schematic of pathway model to conceptualize how the risk environment shapes risk for injecting-related bacterial and fungal infections at different moments. Macro-environmental, micro-environmental, and individual-level factors interplay to influence risk at each moment. Republished from Brothers TD et al. Addiction 2023. (CC-BY license; does not require permission)

Figure 2 and Figure 3, below, show illustrative schematics that I developed describing how selected macro- and micro-environmental factors might influence individual-level factors and may increase risks of injecting-related bacterial infections at two different stages in the pathway from drug acquisition to outcomes after severe/invasive infections.

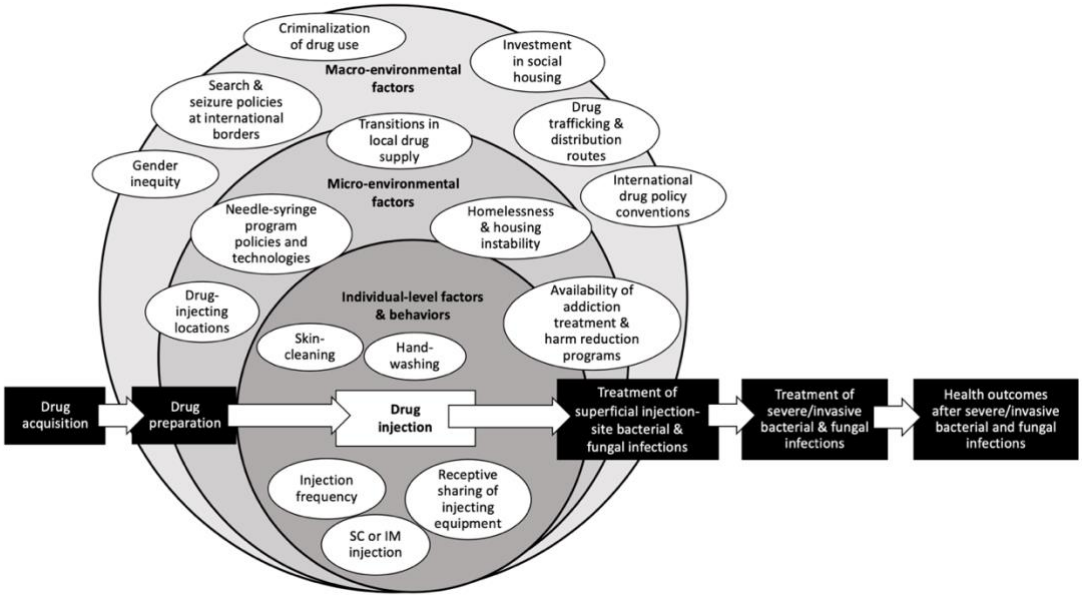

Figure 2. Illustrative schematic of a potential risk environment for injecting-related bacterial and fungal infections, as it may structure or create infection risk during the process of drug injection/consumption. Environmental factors, which are external to individuals, interact to influence individual-level factors and health behaviours across stages of a potential pathway: drug acquisition; drug preparation; drug injection; treatment of superficial injection-site bacterial and fungal infections (e.g. in primary care or emergency departments); treatment of severe/invasive bacterial and fungal infections (e.g. in hospital for intravenous antibiotics and/or surgery); and health outcomes after severe/invasive bacterial and fungal infections (e.g. disability, death). Republished from [21]Brothers TD et al. BMJ Open 2021. (CC-BY license; does not require permission)

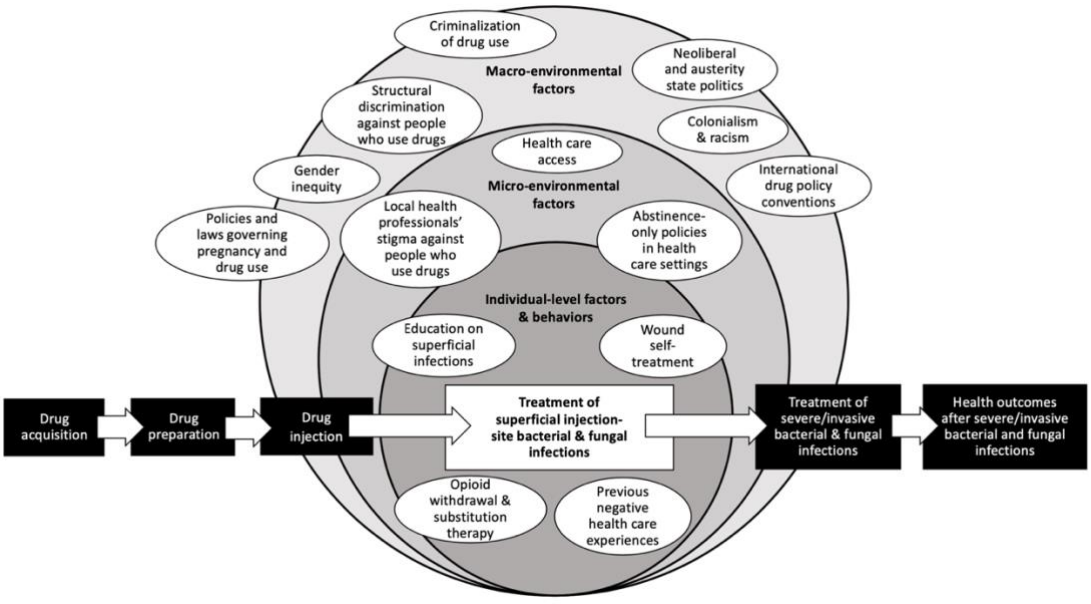

Figure 3. Illustrative schematic of a potential risk environment for injecting-related bacterial and fungal infections, as it may structure or create infection risk during the process of recognition and adequate treatment of superficial injection-site infections. Environmental factors, which are external to individuals, interact to influence individual-level factors and health behaviours across stages of a potential pathway: drug acquisition; drug preparation; drug injection; treatment of superficial injection-site bacterial and fungal infections (e.g. in primary care or emergency departments); treatment of severe/invasive bacterial and fungal infections (e.g. in hospital for intravenous antibiotics and/or surgery); and health outcomes after severe/invasive bacterial and fungal infections (e.g. disability, death). Republished from [21]Brothers TD et al. BMJ Open 2021. (CC-BY license; does not require permission)

While individual drug preparation and injecting practices (e.g., skin-cleaning, safer injecting techniques) may be essential to preventing injecting-related infections, I hypothesized that these are influenced by other individual-level factors (e.g. engagement in opioid agonist treatment, use of stimulants) and micro- and macro-environmental factors that shape, constrain, and facilitate risk and protective behaviours. These social-structural factors would also influence individual behaviours across different stages in this proposed framework, including treatment access and outcomes after an infection.

1.10 Personal experience and reflexivity

I first became interested in injecting-related bacterial and fungal infections among people who inject drugs in medical school at Dalhousie University in Halifax, Nova Scotia, Canada, where I am currently a subspecialty resident physician training in general internal medicine and addiction medicine. Early in medical school I did elective rotations with local harm reduction outreach organizations, including Mainline needle exchange and Mobile Outreach Street Health (MOSH; our local street nursing service). I got to know many of their clients and patients, and I learned from the harm reduction workers and nurses about compassionate, patient-centred care and supporting people to meet their immediate needs and most important goals (including addiction treatment, if that is what people wanted).

When these patients were admitted to hospital – most often with serious injecting-related infections – it was a completely different situation. The health professionals working in the hospital had no understanding about substance use, addiction, harm reduction practices, management of opioid withdrawal, or how to prescribe opioid agonist treatment. Patients were supposed to be in hospital for weeks of intravenous antibiotics, and would end up with untreated withdrawal and undertreated pain. To relieve their own suffering (because we did not), they would consume drugs while hidden in

hospital bathrooms or leave the hospital against medical advice, while still septic. They would often be readmitted through the emergency department, even sicker.

I began to ask the community organizations and affiliated low-threshold, harm reduction-oriented opioid agonist treatment clinic how I might improve hospital care for people who use drugs. With their support and supervision, I sought out training in addiction medicine and helped to organize a team of medical residents to begin to provide this care informally on evenings and weekends. Since 2017, I have published needs assessments and evaluations of our early work on in-hospital addiction care.[97,115–121] I continue to be involved in this work improving harm reduction care in hospitals locally in Halifax and in the UK with the UCL Collaborative Centre for Inclusion Health and their "improving Hospital Opiate Substitution Therapy" (iHOST) study. After five years of sustained advocacy, the Nova Scotia provincial government has recently committed to funding a hospital inpatient addiction medicine consultation service at our tertiary care, teaching hospital. I hope to work for this service after I complete my clinical training.

Many of my patients with injecting-related infections (especially endocarditis) have died. They inspired this work and it is dedicated to them. The director of our local needle exchange in Halifax (Mainline) provided me with a copy of this informational pamphlet that a client made after she and her husband were both admitted to hospital with endocarditis (Figure 4, below). She was trying to raise awareness about risk and prevention of injecting-related bacterial infections, but she and her husband both ended up being reinfected. It was clear to me that (1) education alone was not enough, and (2) people who inject drugs care about their health.

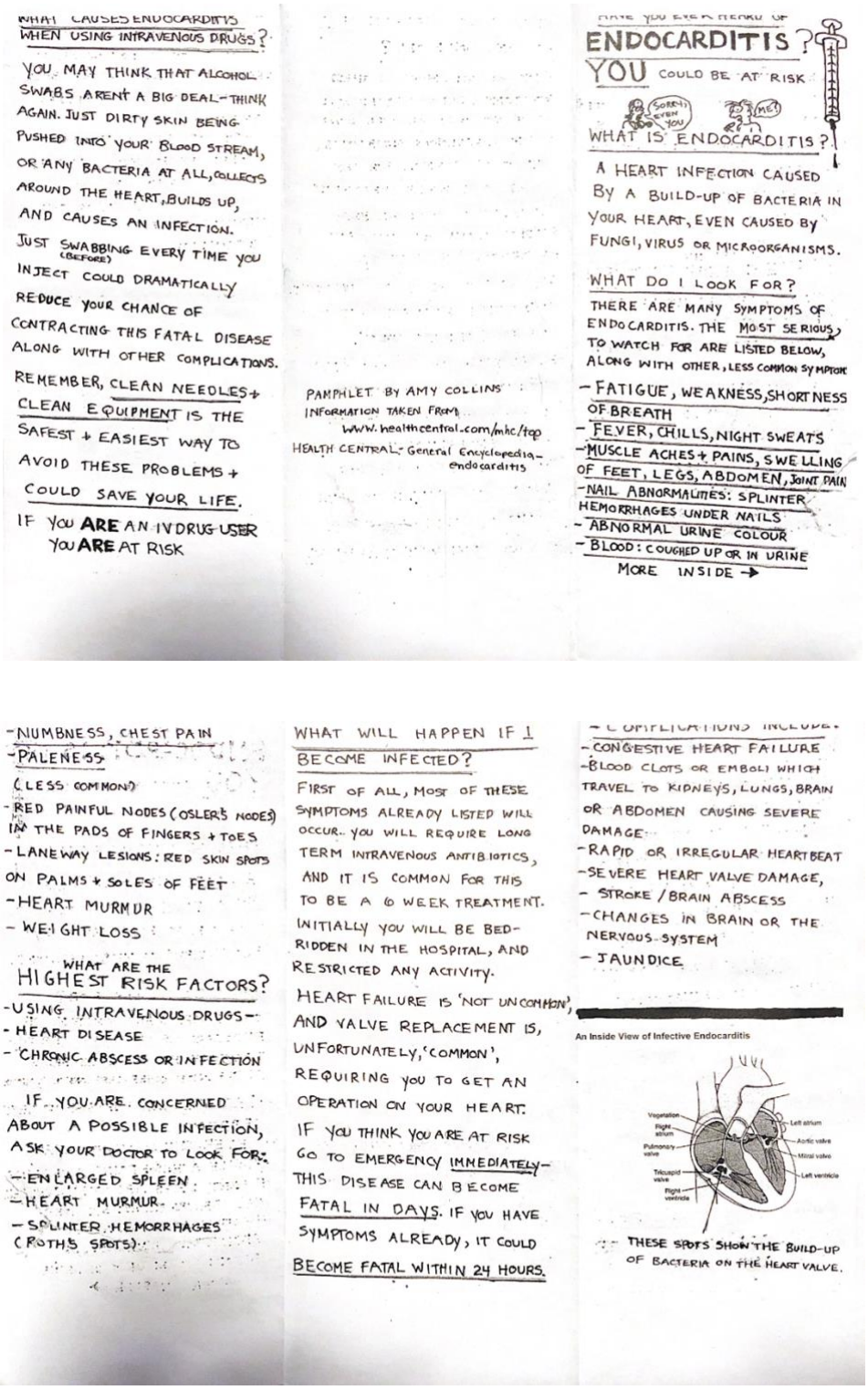

Figure 4. Amy's pamphlet on endocarditis she asked to be available to all clients at Mainline needle exchange. To learn more about Amy, see this link: https://www.thecoast.ca/news-opinion/chasing-amy-960789

As I became more focused on primary and secondary prevention of these infections, I also helped to organize and found our city's first safe injection site, HaliFIX Overdose Prevention Site (Figure 5). Our

organization included people with lived experience (including a local drug user organization, Halifax Area Network of Drug Using People [HANDUP]), harm reduction workers, academics, clinicians, lawyers, and parents of people with lived experience. We did this without support or approval from our provincial government. Because the site operation went so well, the government is now supporting and funding it.

Figure 5. Inside HaliFIX Overdose Prevention Site.

Since beginning the PhD, I have continued to work with Canadian drug user organizations (including the Canadian Association of People who Use Drugs [CAPUD] and the Substance User Network of the Atlantic Region [SUNAR]) and local harm reduction programs. Initially, much of this work involved contributing to the clinical and public health responses to the COVID-19 pandemic with people who use drugs, including supporting people in COVID-19 isolation hotel shelters. Then it included writing and evaluation, as I developed further research skills. In my future career, I hope to be a clinician-scientist and continue to contribute to both.

I have also been involved in several related knowledge translation activities, helping to facilitate putting knowledge into practice and policy change. Along with leaders from CAPUD and SUNAR, I helped to organize a national network in Canada aimed at improving care for people with injection drug use-associated endocarditis (the Canadian Injection Drug Use-associated Endocarditis Working Group; https://www.youtube.com/@canadianiduendocarditiswor1305). I also contributed to clinical guidelines for take-home naloxone program (as a member of the Guideline Development Group and

a co-author) and the ongoing 2023 update of Canada's national opioid use disorder treatment guideline (as Clinical Lead for the Atlantic Region and a co-author). See Appendix 1 for a list of journal publications since beginning my PhD,

Appendix 2 for a list of grant applications during my PhD, and

Appendix 3 for other knowledge translation activities during my PhD.

1.11 Patient and public involvement

The research team for several of my thesis projects includes people with lived (past) and living (present) experience and expertise of injection drug use, and clinicians who care for people with injecting-related bacterial and fungal injections. I do not identify as a person who uses drugs, but I am a clinician, and a primary focus of my practice is caring for people with medical complications of substance use disorders. The conceptual model, research questions, and analysis approach have been designed with input from these team members (as listed in the Acknowledgments section, above). This topic and approach was inspired by the deaths of my patients to injecting-related bacterial infections, and experiences with medical colleagues considering injecting-related infections as inevitable or as the result of individual moral failings.[97,115,116]

1.12 Aims and objectives

This thesis comprises four related research projects aiming to answer three research questions:

1. "Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"
2. "Among people with opioid use disorder who have been hospitalised with injection drug use-associated bacterial or fungal infections, does the use of opioid agonist treatment after hospital discharge decrease risks of mortality or infection-related rehospitalization?"
3. "What is the effect of incarceration and opioid agonist treatment transitions on the risk of injection drug use-associated bacterial infections?"

See Table 1 for a summary of research questions and associated methods, organized by chapter. Chapter 2 and Chapter 3 describe results from complementary qualitative and quantitative systematic reviews seeking to answer research question #1 ("Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"). Chapter 3 reports the qualitative systematic review and a

thematic synthesis; 0 reports the quantitative systematic review and a series of meta-analyses for specific exposure-outcome pairs. Chapter 4 includes a survival analysis within a large cohort of people with opioid use disorder in New South Wales, Australia, aiming to answer question #2 ("Among people with opioid use disorder who have been hospitalised with injection drug use-associated bacterial or fungal infections, does the use of opioid agonist treatment after hospital discharge decrease risks of mortality or infection-related rehospitalization?"). Chapter 5 describes a self-controlled case series within the same Australian cohort, seeking to answer question #3 ("What is the effect of incarceration and opioid agonist treatment transitions on the risk of injection drug use-associated bacterial infections?").

Table 1. Thesis chapters, research questions, and methods used.

Chapter	**Research question**	**Methods**
2	Question 1. "Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"	Systematic review of qualitative studies Thematic synthesis
3	Question 1. "Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"	Systematic review of quantitative studies Inverse variance meta-analyses, to estimate summary unadjusted and adjusted odds ratios
4	Question 2. "Among people with opioid use disorder who have been hospitalised with injection drug use-associated bacterial or fungal infections, does the use of opioid agonist treatment after discharge decrease risks of mortality or infection-related rehospitalization?"	Survival analysis Cox proportional hazards models to estimate adjusted hazard ratios for effect of time-varying opioid agonist treatment exposure on all-cause mortality and infection-related rehospitalization
5	Question 3. "What is the effect of incarceration and opioid agonist treatment transitions on the risk of injection drug use-associated bacterial infections?"	Self-controlled case series Conditional logistic regression to estimate adjusted incident rate ratios for effect of focal time windows (related to incarceration and opioid agonist treatment receipt) on incident injecting-related infections

Chapter 2 Qualitative systematic review and thematic synthesis: Social and structural determinants of injecting-related bacterial infections among people who inject drugs

2.1 Attribution and outputs

I adapted the contents of this chapter from a published manuscript describing the protocol and rationale, and a published manuscript summarizing the qualitative systematic review and thematic synthesis. I led all aspects of the development, data collection, analysis, and write-up.

This work has also been presented as oral presentations at the International Network on Health and Hepatitis in Substance Users (INSHU) conference in Glasgow, Scotland (where my abstract submission won the award for top social science abstract by a PhD student) and at the Dalhousie University Department of Medicine Research Day (where I won the award for best presentation by a subspecialty medical resident).

Manuscripts:

- **Brothers TD**, Lewer D, Bonn M, Webster D, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: protocol for a mixed studies systematic review. *BMJ Open*. 2021;11:e049924. http://doi.org/10.1136/bmjopen-2021-049924
- **Brothers TD**, Bonn M, Lewer D, Comeau E, Kim I, Webster D, Hayward A, Harris M. Social and structural determinants of injection drug use-associated bacterial and fungal infections: a qualitative systematic review and thematic synthesis. *Addiction.* 12 May 2023. https://doi.org/10.1111/add.16257

Conference presentations:

- **Brothers TD**, Bonn M, Lewer D, Kim I, Comeau E, Webster D, Hayward A, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: qualitative systematic review and thematic synthesis. [Oral presentation.] International Network on Health & Hepatitis in Substance Users (INHSU). October 21, 2022 at Glasgow, Scotland.
- **Brothers TD**, Bonn M, Lewer D, Kim I, Comeau E, Webster D, Hayward A, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: qualitative systematic review and thematic synthesis. [Oral presentation.]

Dalhousie University Department of Medicine Research Day. April 20, 2023 at Halifax, NS, Canada

2.2 Abstract

Background: Injection drug use-associated bacterial and fungal infections are increasingly common, and social contexts shape individuals' injecting practices and treatment experiences. I sought to synthesize qualitative studies of social-structural factors influencing incidence and treatment of injecting-related infections.

Methods: I searched PubMed, EMBASE, Scopus, CINAHL, and PsycINFO from January 1, 2000, to February 18, 2021. Informed by Rhodes' "risk environment" framework, and in collaboration with the investigator team, I performed thematic synthesis in three stages: (1) line-by-line coding; (2) organizing codes into descriptive themes, reflecting interpretations of study authors; (3) consolidating descriptive themes into conceptual categories to identify higher-order analytic themes.

Results: I screened 4,841 abstracts and included 26 qualitative studies on experiences of injecting-related bacterial and fungal infections. I identified six descriptive themes organized into two analytic themes. The first analytic theme, *social production of risk*, considered macro-environmental influences. Four descriptive themes highlighted pathways through which this occurs: (1) *unregulated drug supply*, leading to poor drug quality and solubility; (2) *unsafe spaces*, influenced by policing practices and insecure housing; (3) *health care policies and practices*, leading to negative experiences that discourage access to care; and (4) *harm reduction programs*, including structural barriers to effective service provision. The second analytic theme, *practices of care among people who use drugs*, addresses protective strategies that people who inject drugs employ within infection risk environments. Associated descriptive themes were: (5) *mutual care*, including assisted-injecting and sharing sterile equipment; and (6) *self-care*, including vein health and self-treatment. Within constraining risk environments, some protective strategies for bacterial infections precipitated other health risks (e.g., HIV transmission).

Conclusions: Injecting-related bacterial and fungal infections are shaped by modifiable social-structural factors, including poor quality unregulated drugs, criminalization and policing enforcement, insufficient housing, limited harm reduction services, and harmful health care practices. People who inject drugs navigate these barriers while attempting to protect themselves and their community.

2.3 Introduction

As described in Chapter 1, injection drug use-associated bacterial and fungal infections (e.g., skin and soft-tissue infections [SSTI], endocarditis, osteomyelitis, epidural abscess, etc.) cause significant morbidity and mortality among people who inject drugs.[21,51–55] The incidence of hospitalizations for severe injecting-related infections is increasing in Australia,[57] Canada,[51,58] the United Kingdom,[61] and the United States of America (USA).[63–67]

Efforts to prevent injecting-related bacterial and fungal infections have focused on individual-level behavioural interventions,[56,72] including education on hand-washing before drug preparation,[124] skin-cleaning before injecting,[125] and avoiding subcutaneous/intramuscular injecting.[126] While individual-level interventions may be helpful for people who can adopt these practices, evaluations of these interventions have shown mixed results[85–87] and the incidence of injecting-related infections continues to rise.

Risk for injecting-related bacterial and fungal infections reflects contributions of multiple factors external to individuals that enable and/or constrain injecting practices and influence health outcomes.[20,27,29,127] Identifying, measuring, and ameliorating social-structural factors has informed clinical and public health responses to other drug-related harms, including HIV,[26,79,110] HCV,[111] and overdose.[112,113] Understanding the influence of social context on health can broaden awareness of the causes of illness[128] and inform more appropriate prevention and treatment interventions.[26,108,114]

2.3.1 Objectives

To understand social-structural determinants of injecting-related bacterial and fungal infections and to identify opportunities for potential intervention, I aimed to: (1) systematically review qualitative studies on experiences of injecting-related bacterial and fungal infections, and (2) synthesize qualitative research into factors influencing risk for injecting-related infections, their treatment, and subsequent health outcomes.

2.4 Methods

Before conducting the search, I published a protocol[21] and registered with PROSPERO (CRD42021231411). This Chapter follows Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines[129] and is informed by the ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) statement[130] on qualitative systematic

reviews. I modified the protocol after our search and full-text review. The protocol specified a "mixed studies review" of quantitative, qualitative, and mixed-methods studies.[131,132] As I identified more and richer qualitative sources than anticipated, I decided to consider qualitative and quantitative data separately. In this Chapter, I report the qualitative systematic review and thematic synthesis. The quantitative systematic review and meta-analysis is reported below, in Chapter 3.

2.4.1 Eligibility criteria

Informed by the Population, Exposures, Outcomes approach,[133] I included peer-reviewed papers describing eligible qualitative studies according to the following criteria. Quantitative study eligibility criteria are described below, in Chapter 3.

2.4.1.1 Study designs

I included qualitative studies reporting on people who inject drugs' experiences and perspectives on injection drug use-associated bacterial and fungal infections and their treatment. I excluded nonempirical studies (including reviews, commentaries, and editorials).

2.4.1.2 Participants

I included studies examining people who inject drugs of any age or nationality. By 'people who inject drugs', I am referring to people who inject opioids (e.g., heroin, fentanyl, hydromorphone, morphine), stimulants (e.g., cocaine, methamphetamines), or other psychoactive substances via intravenous, intramuscular, or subcutaneous routes. Studies that focus only on people who inject performance-enhancing drugs (e.g., anabolic steroids) or gender-affirming hormones were excluded.

2.4.1.3 Exposures

Exposures were social or environmental factors that may affect risk of infections or their treatment, such as housing, service availability, or policing. Where studies assessed individual-level practices known to increase risks for infection (e.g., reusing nonsterile equipment) or affecting treatment (e.g., leaving hospital before medically advised), I was interested in social-structural factors that influenced these practices.

2.4.1.4 Outcomes

Outcomes included incidence, treatment, or sequelae after injecting-related bacterial and fungal infections. Bacterial and fungal infections include skin and soft-tissue infections (cellulitis, abscess, necrotizing fasciitis), bloodstream infections (bacteraemia), vascular infections (endocarditis, septic

or suppurative phlebitis), bone and joint infections (osteomyelitis, septic arthritis, discitis), and central nervous system infections (epidural abscess, brain abscess, meningitis, encephalitis). I excluded studies identifying only non-injecting related bacterial and fungal infections as outcomes, such as tuberculosis, pneumonia, chlamydia, or gonorrhoea, and bacterial infections that are primarily sexually transmitted, e.g., syphilis.

2.4.1.5 Time frame, setting, language

I included studies published between January 1, 2000, and the search date, February 18, 2021, to capture contemporary research that would be more likely to inform policy and clinical practice. There were no restrictions by study setting. I included articles in English and French because these were the languages spoken by the review team.

2.4.2 Information sources

I searched PubMed, EMBASE, Scopus, CINAHL, and PsycINFO databases. Electronic database searches were supplemented by manually reviewing reference lists of included studies, and forward "snowball" searching by identifying articles that cite included studies.[134] I also circulated a final bibliography of the included articles to the systematic review team, which includes people with lived (past) and living (current) expertise of injection drug use and clinicians who care for people with injection-associated infections. I included articles identified from the personal files of the systematic review team that were not identified in the bibliography.

2.4.3 Search strategy

I developed the final search strategy in consultation with our review team and with a health information specialist-librarian with systematic review expertise. The final search strategy is included in Appendix 4. I first conducted a pilot search in PubMed and validated it by checking for inclusion of key, recent studies (already known to me) that assessed either risk factors for severe bacterial or fungal infections among people who inject drugs[135,136], social/structural determinants of these infections[105,137–140], or complex interventions to reduce risk of injecting-related bacterial infections.[87] This validation process led to several iterative changes, including specific search terms related to "acidifiers" and "groin injecting".

2.4.4 Data management and reference selection

Search results were uploaded into Covidence, a cloud-based software program, where they were automatically checked for de-duplication. Two reviewers screened titles and abstracts against the inclusion criteria. I acted as one screener for all titles and abstracts, and several co-authors acted as the second screener. This included Inhwa Kim and Emilie Comeau (two research assistant medical students at Dalhousie University, in Halifax, Canada), Dan Lewer (public health registrar at UCL), and Matt Bonn (a drug user activist and a person with living experience of injection drug use and injecting-related infections). Discrepancies were resolved through discussion and consensus.

I then obtained full text reports for all titles that appeared to meet the inclusion criteria, or for where there was uncertainty. I had initially planned to have two reviewers independently evaluate the full text reports for inclusion, but due to competing priorities among other members of the review team I ended up being a sole reviewer for each full text report. I recorded reasons for exclusion.

2.4.5 Data collection process

I developed and pilot-tested a data extraction form. For eligible qualitative studies, I extracting data on:

- Study date
- Study country
- Qualitative study design
- Sample size and demographic characteristics (age, gender, housing status) as reported
- Focus of interviews/analysis
- Conceptual or explanatory model(s)
- Summary of study analysis and findings

2.4.6 Critical appraisal

I applied a formal, validated critical appraisal tool for mixed studies reviews, the Mixed Methods Appraisal Tool (MMAT), 2018 edition, which is designed for use with quantitative, qualitative, and mixed methods studies.[141,141,142] It includes five core quality criteria for each of five categories of study designs: (a) qualitative, (b) randomized controlled/interventional, (c) nonrandomized controlled, (d) quantitative descriptive, and (e) mixed methods. For qualitative studies, five criteria

questions focus on appropriateness of study methods and whether findings are supported by the data. I followed a "user guide" provided by MMAT developers.[143]

A medical student research assistant (Emilie Comeau) and I independently reviewed each included study against the MMAT criteria, with discrepancies resolved through discussion. For this review, I included studies which met both MMAT screening questions for studies of all study designs. These are, "1. Are there clear research questions?" and "2. S2. Do the collected data allow to address the research questions?" I report MMAT results for each study, but this did not inform our qualitative synthesis beyond the screening questions.

2.4.7 Qualitative thematic synthesis

Following Thomas and Harden,[144–147] thematic synthesis comprises three stages: (1) line-by-line open coding; (2) organizing codes into descriptive themes reflecting content of studies and study authors' interpretations; (3) translating descriptive themes and associated codes across studies to generate analytic themes. Coding and generation of descriptive themes focuses on study authors' analysis and interpretation because reviewers do not have full knowledge of the original study data.[144,145]

First, I familiarized myself with all the included studies by reading them each at least twice. Next, Matt Bonn (researcher and drug policy activist with lived/living experience of injecting-related infections) and I independently performed line-by-line coding on the same three purposefully selected, data rich sources.[95,148,149] We compared and contrasted codes and revised them in an iterative, deductive-inductive process, informed by the 'risk environment' conceptual model (as described in Chapter 1) and the risk pathway framework developed for this thesis (summarized visually in Figure 6).

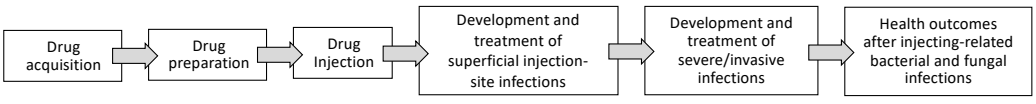

Figure 6. Illustrative schematic of pathway model to conceptualize how the risk environment shapes risk for injecting-related bacterial and fungal infections at different moments. Macro-environmental, micro-environmental, and individual-level factors interplay to influence risk at each moment. Republished from Brothers TD et al. Addiction 2023. (CC-BY license; does not require permission)

The whole review team met to provide feedback on these candidate codes. In addition to myself and Matt Bonn, this also included Dan Lewer (public health specialist), Emilie Comeau and Inhwa Kim (medical students), Duncan Webster (infectious diseases and addiction medicine physician), Prof.

Andrew Hayward (infectious disease epidemiologist), and Prof. Magdalena Harris (health sociologist with lived experience of injection drug use). I coded the remaining papers over several rounds, including adding and revising new candidate codes after discussing with the team and through collaborative online writing.

I developed descriptive themes by comparing and contrasting codes across studies, seeking to organize codes into related social-structural categories and proposed them to the team for feedback. I then consolidated descriptive themes into conceptual categories to generate analytic themes that were finalized over several iterations and team meetings.

2.5 Results

Following de-duplication, myself and a second reviewer screened 4,841 titles/abstracts, and I evaluated 631 full-text reports. After considering 16 additional reports identified outside the search, I identified 131 eligible studies (quantitative, qualitative, and mixed-methods) for the "mixed studies" review. In this Chapter, I report on the 26 studies with qualitative data and analysis (19 qualitative-only, seven mixed-methods). Results for the quantitative systematic review and meta-analysis are presented below, in Chapter 3. See Figure 7 for PRISMA flow diagram. All 26 qualitative studies met quality criteria for inclusion (see Appendix 5 and Appendix 6 for full MMAT results of included qualitative and mixed-methods studies, respectively).

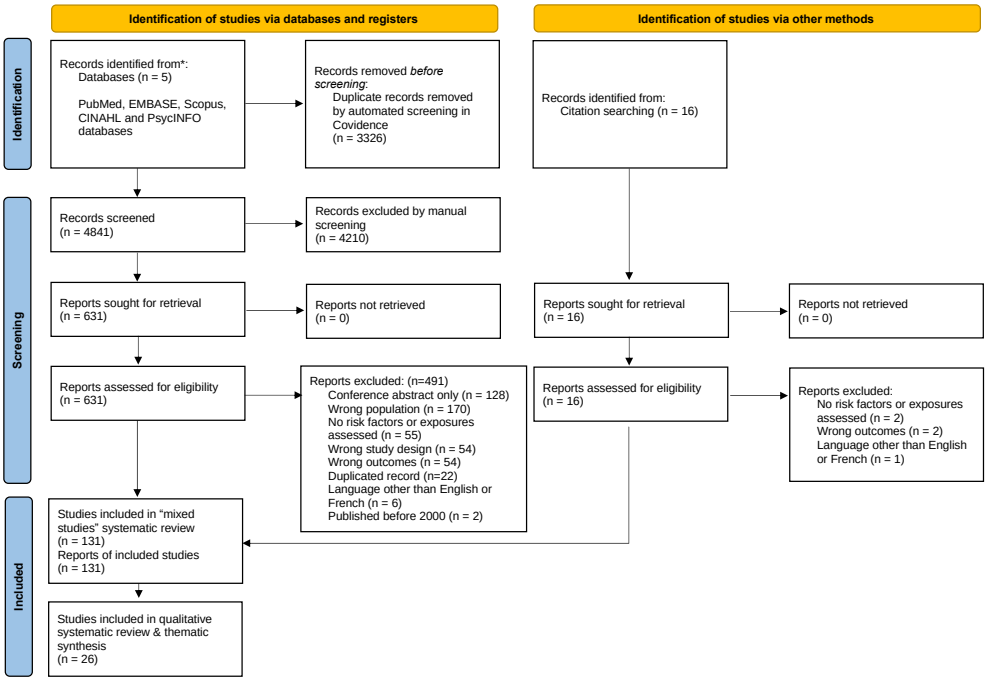

Figure 7. PRISMA flow diagram for qualitative systematic review on social-structural determinants of injection drug use-associated bacterial and fungal infections. Initial search includes qualitative, quanitatitive, and mixed-methods studies.

2.5.1 Study characteristics

See Table 2 for summaries of individual studies. The majority (n=20 studies) were conducted in North America. Qualitative data came from individual interviews (n=23), observation/ethnography (n=4), and focus groups (n=2). Studies included experiences of injecting-related skin and soft-tissue infections (n=22), endocarditis (n=7), bacteraemia (n=3), and osteomyelitis (n=2). All 26 studies included bacterial infections; only one study[138] included fungal infections (candida ophthalmitis).

Table 2. Characteristics of included studies in qualitative systematic review and thematic synthesis of social and structural determinants of injection drug use-associated bacterial and fungal infections.

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Bearnot 2019[150]	USA	Individual interviews Grounded theory	11 people with opioid injection-associated endocarditis 55% women; median age 38 years; 55% with "unstable housing"	Experiences of endocarditis care	None specified	Poor health outcomes among people with opioid injection-associated endocarditis are caused by stigma, delays or discontinuity of care, social and medical comorbidities, perceptions of addiction as a chronic and relapsing disease, and prolonged hospitalizations.
Bearnot 2020[151]	USA	Secondary analysis of interview data from Bearnot 2019[150] Journey mapping analysis Grounded theory	Same as Bearnot 2019	Patterns of care for endocarditis	None specified	People with opioid injection-associated endocarditis left care before medically advised because of poor care experiences, including undertreatment of withdrawal and pain and discrimination from clinicians. Following hospitalization, participants commonly engaged in outpatient addiction treatment and follow-up endocarditis care. Leaving outpatient addiction treatment often preceded rehospitalizations with recurrent infections.
Bodkin 2015[152]	Canada	Individual interviews Qualitative descriptive analysis	14 people who inject drugs recruited from an outreach program for sex workers in London, Ontario 100% women; age range 23-49 years; housing status not reported	Access to health care among people who inject drugs who do sex work	None specified	Sex workers who inject drugs avoided primary care and emergency department treatment of injecting-related infections because of experiences of stigmatization and criminalization. Participants experienced involuntary discharge from hospital and received suboptimal oral antibiotics because of abstinence-requiring policies in hospital.
Bourgois 2006[153]	USA	Mixed methods Participant-observation ethnography (field notes, interviews, photographs)	Sample not specifically described, but includes African American and white men who inject heroin in San Francisco, California	How social-structural determinants interface with drug consumption practices and survival strategies among African American and	"…a social science theoretical understanding of the link between large-scale power relations and individual risky	Higher rates of abscesses among white compared to African American people who inject drugs reflect socially produced differences in norms between racial/ethnic groups, including social acceptability of subcutaneous injecting among white people. Conversely, police are more likely to repeatedly search and confiscate sterile injecting equipment from African American people who inject drugs.

				white people who inject drugs	practices that shape the spread of blood-borne disease among injectors."	
Case 2008[154]	Mexico	Individual interviews Thematic content analysis	43 people who inject drugs recruited through street-based outreach, shooting galleries, and drug treatment programs in Tijuana (n=20) and Ciudad Juárez (n=23) 42% women; median age 30; 30% lived or slept "on streets" in past six months	Injection methamphetamine use in two Mexican border cities	Structural vulnerability	Greater availability of methamphetamine in Tijuana is associated with widespread use, compared to Ciudad Juárez. Injecting methamphetamine is perceived to be associated with increased risk of injecting-site abscesses, described more commonly in Tijuana.
Colwill 2021[155]	USA	Individual interviews Grounded theory	11 people undergoing surgical evaluation for injecting-related endocarditis 45% women; mean age 31; 9% "Homeless"	Experiences of endocarditis	"PWID [people who inject drugs] with Endocarditis Cyclical Experiences (PEaCE) model"	People with injecting-related endocarditis avoid health care because of stigmatizing and discriminatory experiences. The experience of endocarditis motivated some participants to enter addiction treatment and pursue abstinence.
Dunleavy 2019[148]	Scotland	Individual interviews Framework analysis	22 people who had experienced an injecting-related skin and soft-tissue infection within past year, recruited from needle and syringe program (Glasgow; n=14) or drug treatment service (Edinburgh; n=8) 32% women; median 36 years; 59% experienced homelessness during the past six months	Experiences of injecting-related skin and soft-tissue infections	Rhodes' risk environment	Stigma associated with skin and soft-tissue infections motivated some participants to try to reduce risks, including use of sterile equipment and safer injecting techniques. No participants had learned about infections and associated risks from harm reduction programs. Social and environmental factors contributing to infection risk included insufficient access to sterile injecting equipment, caustic adulterants in the local drug supply, and a lack of hygienic spaces to prepare and consume drugs.

Epele 2002[156]	USA	Individual interviews, observations, and participation in everyday life settings Analysis approach not specified	35 people who inject drugs recruited through syringe service program and snowball sampling 71% women; mean age of women was 34; all "do not consider themselves as homeless"	Risk conditions and care practices related to HIV among Latino women	Political economy of health Biopower	Some women who inject drugs rely on injecting assistance from others to avoid intramuscular injection and associated abscesses and scars, because these lead to loss of social status and negatively affect relationships and potential income generation through sex work. Participants recognized that assisted-injecting increases risks for HIV infection. Injection assistance is provided by friends, romantic or sexual partners, and paid "hit doctors".
Gilbert 2019[157]	USA	Secondary analysis of interview data from Summers 2018[158] Thematic analysis	Same sample as qualitative sample in Summers 2018[158] 12 clients of a syringe services program in Boston (n=6) and Sacramento (n=6) 25% women; median 46 years; housing status not reported	Experience of skin and soft-tissue infections	Health belief model (HBM) of health-seeking behaviors Conceptual Model of Medical Care Avoidance	Participants had good knowledge about skin infections and avoided formal health care due to traumatic experiences, discrimination, and unnecessarily painful procedures. Participants described multiple strategies for prevention and treatment of injecting-related infections including hydration, topical applications, non-prescribed antibiotics, and incision and drainage by non-medical providers.
Harris RE 2018a[95]	USA	Individual interviews Analysis approach not specified	19 clients of a syringe services program in Philadelphia 53% women; median age 39 [27-59 years]; housing status not reported	Experiences of skin and soft-tissue infections	None specified	Participants described good knowledge about risks of injecting-related skin infections, but were prevented from using hygienic techniques as they lacked of safe places to use drugs. Participants therefore injected abandoned buildings or outdoors, with inadequate lighting, or fear of assault or arrest, leading to drug contamination and intramuscular injection. Participants tended to avoid medical care for injecting-related infections due to prior negative healthcare experiences, including stigma and inadequate treatment of withdrawal and pain. Some participants described self-treatment of infections, including increased drug use for pain control and performing incision and drainage on themselves.
Harris RE 2018b[159]	USA	Individual interviews Thematic analysis	Same sample as Harris RE 2018a[95].	Perceptions of safe injecting facilities	Rhodes' risk environment	Participants described commonly being forced to inject in public spaces, which led them to rush and inject intramuscularly or subcutaneously for fear of assault or arrest. Participants supported the idea of a supervised injection site to reduce these risks and inject more

			19 clients of a syringe services program in Philadelphia. 53% women; median 39 years; housing status not reported			safely. Participants with stable housing preferred to inject at home and described that this reduced risks of injecting-related infections due to less fear of assault or arrest, adequate light and heat, running water, and space to store sterile injecting equipment.
Harris M 2019[138]	England	Mixed methods Individual interviews Constructivist grounded theory	31 people who inject drugs recruited through drug treatment services, homeless hostels, and day centres across London, UK 29% women; mean age 43 years; housing status not reported	Use of acidifiers	Rhodes' risk environment	Excessive acidifier use in drug preparation for injection is common and contributes to venous damage and risk for bacterial infections. Some participants determined the amount of acidifier to use through expert practice (e.g., visual cue of solution clarity) and others through external factors (e.g., using one whole packet of acid, even if that is excessive and causes pain and injury). Some participants decreased acidifier use over time, in response to new information or pain/injury. The authors infer a need to revisit design and distribution of acidifiers within harm reduction programs.
Harris M 2020a[88]	England	Individual interviews Constructivist grounded theory	36 people who inject drugs, recruited through specialist drug services, homeless hostels, and day centres across London, UK. 12% women; mean 46 years; 64% unstably housed in past 12 months.	Experiences of injecting-related injuries and infections	Everyday violence Structural violence Cultural safety	Engagement with the medical system (including for injecting-related infections) is a "last resort"; often participants delayed as long as possible to the point that they were critically ill. Participants avoided or delayed accessing medical care for their own protection, including because of experiences of discrimination and undertreated withdrawal and pain; one participant specifically worried of stigma against mothers who use drugs and associated risks of child apprehension. Participants described leaving hospital prematurely and self-treating wounds instead.
Harris M 2020b[105]	England	Mixed methods Individual interviews Constructivist grounded theory	32 people who inject drugs, recruited through specialist drug services, homeless hostels, and day centres across London, UK. 31% women; mean age 43 years; 94% had experienced homelessness	Water for preparing injecting solutions	Rhodes' risk environment	Environmental constraints to sourcing sterile water for injection preparation (and staying hydrated to promote vein health) include lack of housing, public washrooms, or sterile water from harm reduction programs. When injecting in public places, fear of arrest would lead people to rush their preparation and inject as fast as possible. As a result, participants described using more readily available but unsafe alternative water sources including puddle water, toilet cistern water, whisky, cola soda, and saliva to prepare injections, which were associated with bacterial infections. Participants

						described several strategies to promote health and safety despite these environmental constraints, including filtering water through alcohol swabs or asking passers-by for bottled water.
Jafari 2015[160]	Canada	Mixed methods Individual interviews; direct observation and field notes Narrative analysis	8 people with injecting-related infections who were clients at a harm reduction-oriented medical respite program Gender, age, and current housing status not reported	Experiences of care for injecting-related infections	None specified	Participants described past experiences of leaving hospital before completion of their medical treatment because of judgmental and stigmatizing care. Clients with severe injecting-related infections who were being cared for at a harm reduction-oriented medical respite describe receiving less judgmental and stigmatizing care compared to their experience in acute care hospitals.
Krüsi 2009[161]	Canada	Individual interviews Thematic analysis	22 people who inject drugs, recruited as clients at an HIV-focused residential and outpatient care facility in Vancouver 32% women; mean 44 years; housing status not reported	Use of a supervised injection site integrated within a community-based HIV care facility	Rhodes' risk environment	Participants accessing the supervised injection site found it a uniquely valuable setting to receive education on (and to implement) safer drug preparation and injecting techniques, which they attributed to reduced frequency of abscesses. When they did not have access to the supervised injecting facility, participants described rushing their drug preparation and injection out of fear, including not using water to dissolve their heroin sufficiently.
Mars 2016[162]	USA	Ethnography and individual interviews Grounded theory	41 people who inject drugs recruited during ethnographic insertion in drug using community and with snowball sampling in Philadelphia (n=22) and San Francisco (n=19) 49% women; age unknown; homelessness "common".	Comparing perspectives of people who inject drugs in two different heroin markets.	Rhodes' risk environment	In San Francisco, where heroin was mostly in "tar" form, participants attributed abscesses to the characteristics of tar heroin including poor solubility. In Philadelphia, where more-soluble powder heroin as well as cocaine was widely available, participants attributed abscesses to missing veins (i.e., injecting subcutaneously or intramuscularly) and when injecting cocaine. The authors attribute regional differences in abscess risk to geopolitical forces that have segmented the U.S. heroin market.
McNeil 2014[163]	Canada	Individual interviews Thematic analysis	30 people who inject drugs who had experienced hospital discharge against medical advice within	Hospital care experiences	Rhodes' risk environment Social violence	Participants left hospital prematurely (before the completion of their recommended treatment) because of inadequate pain and withdrawal management, and because of discriminatory, stigmatizing, and racist care

			the prior two years, recruited from within a prospective cohort study in Vancouver 43% women; mean 45 years; 27% staying in emergency shelters or unhoused			experiences. These were influenced by hospital policies, written and unwritten.
Meyer 2020[164]	Kyrgyzstan	Individual interviews Content analysis	11 people who were incarcerated and injected diphenhydramine 10% women; average age not reported; all currently incarcerated	Diphenhydramine injecting in Kyrgyz prisons	Rhodes' risk environment	Participants attributed severe skin infections to injecting diphenhydramine while incarcerated, particularly in comparison to injecting heroin. Infectious risks associated with diphenhydramine were influenced by the denial of access to the prison's needle and syringe program to people taking methadone (which was common among people injecting diphenhydramine) and stigmatization and punishment of diphenhydramine users in the prison (which led people to delay seeking care for skin infections).
Paquette 2018[165]	USA	Individual interviews "Mixed inductive and deductive approach"	46 people who attended syringe service programs or health services in Fresno, California (n=22) or community services agencies or street-based recruitment in Kern, California (n=24) 37% women; mean 39 years; housing status not reported	Stigmatizing health care experiences	Rhodes' risk environment	Participants described delaying or avoiding medical care ("until it was absolutely necessary") for injecting-related infections because of previous stigmatizing experiences. Instead, some people treat their own infections. Participants in rural areas also described feeling as if they could not attend their local harm reduction program for sterile injecting equipment as this would "out" them as a drug user to the small community.
Phillips 2013[149]	USA	Mixed methods Focus group interviews Qualitative analysis approach not specified	32 people who inject drugs recruited through street outreach in Denver, Colorado 50% women; mean age 50 years; housing status not reported	Perspectives on injecting-related bacterial infections, to inform development of a behaviour change intervention	Information-Motivation-Behavioral Skills model	Most participants had experienced injecting-related bacterial infections. Participants attributed increased risk of infections to poor quality (or adulterated or contaminated) unregulated drugs, including tar heroin (compared to powder heroin or pharmaceutical opioid tablets); to injecting intramuscularly or subcutaneously; to reusing needles; and to not cleaning skin. Barriers to practicing safer drug preparation and injecting included lack of access to sterile equipment (influenced by a

						"paraphernalia law" that prohibited carrying a hypodermic needle without "proof of medical need"). Participants described delaying or avoiding medical care for infections due to negative health care experiences.
Pollini 2010[166]	Mexico	Mixed methods Focus groups Grounded theory	47 people who inject drugs invited from among participants in a cohort study that used respondent-driven sampling 14% women; age not reported; housing status not reported	Barriers to sterile syringe access, including purchase from pharmacies	Rhodes' risk environment	Participants described many challenges in accessing sterile needles and syringes via purchasing at local pharmacies, including discrimination from pharmacists and pharmacists disclosing fear of "trouble with police" (despite syringe sales being legal). This led to syringe reuse being common practice. Participants did not spontaneously attribute risks for abscesses to needle and syringe reuse, until asked by a focus group facilitator.
Pollini 2021[167]	USA	Individual interviews Thematic analysis	20 people who inject drugs recruited through provider referral, street-based recruitment and snowball sampling 45% women; median age 26; housing status not reported	Scarcity of sterile needles and syringes in a rural environment	Rhodes' risk environment	Scarcity of sterile needle and syringes led participants to share and re-use syringes. Factors limiting sterile syringe access included pharmacies refusing to sell them or requiring an ID, and a state "drug paraphernalia" law that criminalizes possession of syringes. Participants would travel out-of-state to pharmacies that would sell syringes, but police were aware of this and would stop and search cars with out-of-state license plates after visiting a pharmacy. One participant obtained sterile syringes from a family member with diabetes and distributed them to people in her community who inject drugs.
Sheard 2008[168]	England	Individual interviews Grounded theory	45 women who inject drugs recruited among clients of needle and syringe programs and addiction treatment programs in semirural North Nottinghamshire and urban Leeds, and through snowball sampling of participant contacts.	Assistance with injecting among women.	None specified	All participants (100% women) were injected by others, sometimes by a male partner who exerted power and control. Some participants shared needles and injecting equipment with partners as an intimate practice. Participants attributed injecting-related bacterial infections to unintentional subcutaneous injecting when self-injecting, caused by inexperience and a lack of knowledge about how to inject safely. Self-injecting was a positive experience for some women as it promoted independence; for others, it caused harm visible scars which worsened social marginalization. Most participants accessed a local needle exchange and had ample supply of sterile drug preparation and injecting

			100% women; age rage 16 – 46 years.			equipment. Cleanliness and hygiene were commonly raised as important reasons to avoid reusing or sharing of equipment.
Small 2008[169]	Canada	Individual interviews Thematic analysis	50 people who use supervised injection sites in Vancouver. 42% women; median age 38; housing status not reported	Impact of the supervised consumption site on access to care for injecting-related bacterial infections.	None specified, but motivated by exploration of "social and structural barriers to care"	Participants described delaying or avoiding medical care because of previous negative experiences. By providing nonjudgmental care within a setting where drug use is accommodated, contact with nurses at a supervised injection site facilitated access to care for injecting-related infections.
Summers 2018[158]	USA	Mixed methods Individual interviews Thomas' general inductive approach	12 people who inject drugs recruited from needle and syringe programs in Boston, Massachusetts and Sacramento, California	Prevention and treatment of skin infections	Rhodes' risk environment Health Belief Model (HBM) of health-seeking behaviours Conceptual Model of Medical Care Avoidance	Participants described delaying, avoiding, or prematurely leaving medical care for injecting-related skin and soft-tissue infections because of experiences of unaddressed pain and withdrawal symptoms, stigma.

2.5.2 Thematic synthesis

2.5.2.1 Summary

I identified six descriptive themes, organized into two analytic themes (see Figure 8). The first analytic theme, *social production of risk*, considers how macro-environmental factors, including criminalization, poverty, structural stigma, mandated abstinence, and racism, shape risks for injecting-related infections. Four associated descriptive themes highlighted pathways through which this occurs: (1) *unregulated drug supply*, leading to poor drug quality and solubility; (2) *unsafe spaces,* influenced by insecure housing and policing practices, and ameliorated by supervised consumption sites; (3) *health care policies and practices*, leading to experiences of discrimination and undertreated pain and withdrawal, which worsened infectious complications by discouraging access to care; and (4) *harm reduction programs*, including structural barriers to effective service delivery.

The second analytic theme, *practices of care among people who use drugs*, addresses attempts to prevent and self-care for bacterial infections within constraining risk environments. Two associated descriptive themes categorized these as (5) *mutual care*, including sharing sterile injecting equipment, assisting others with injecting into veins (rather than intramuscularly), and treating abscesses outside of medical settings; and (6) *self-care*, including promoting vein health and sourcing safer alternatives when sterile injecting equipment was unavailable. Within constraining risk environments, some mutual- and self-care protective strategies for bacterial infections precipitated other health risks, including HIV or arterial injury.

Themes are detailed below. My analysis is supplemented by quotations from study authors and participants (indicated in italics).

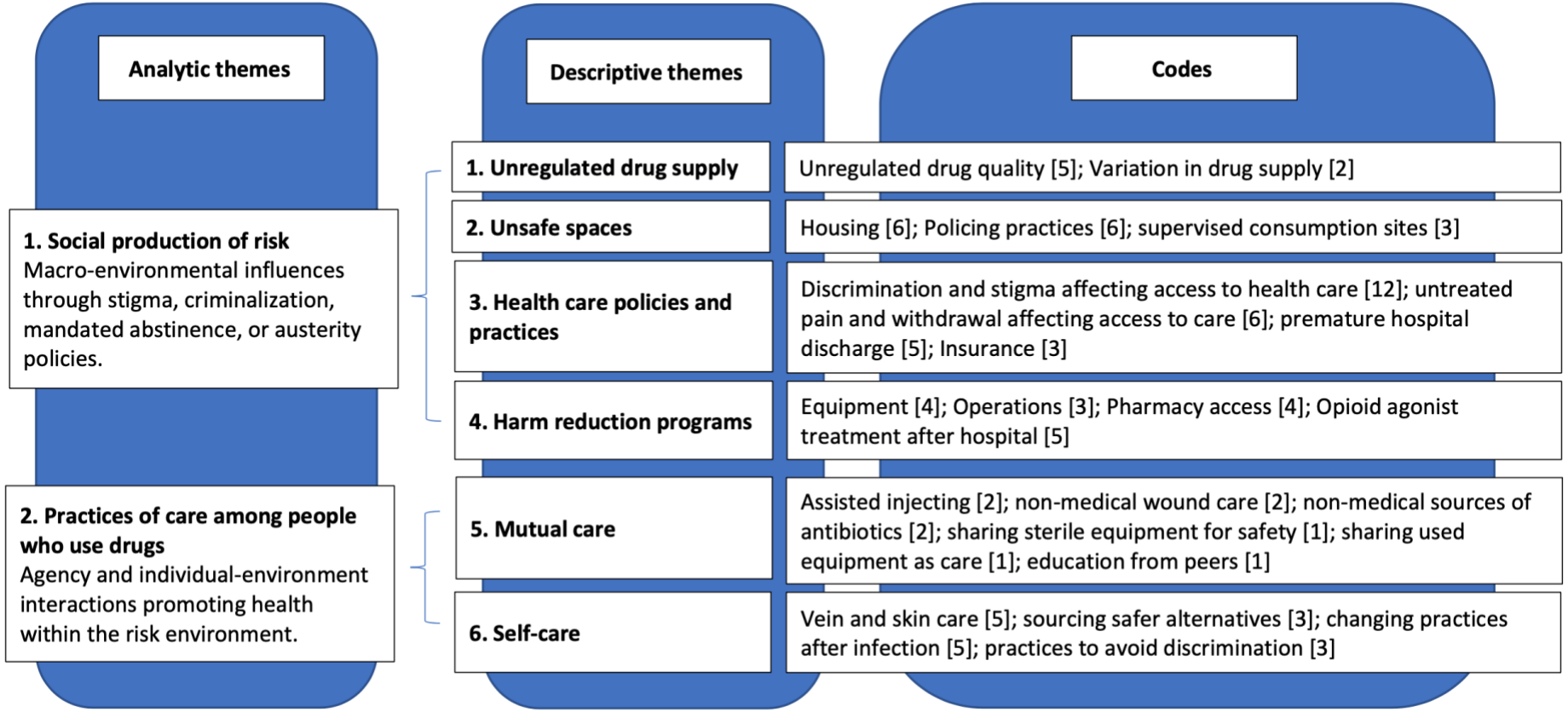

Figure 8. Schematic summary of analytic and descriptive themes with associated codes.

2.5.2.2 Social production of risk

2.5.2.2.1 Unregulated drug supply

In five studies,[105,138,148,149,162] authors presented perspectives from people with injecting-related infections who attributed infections to the quality of unregulated drugs, including adulterants,[138,148,149,162] poor solubility,[105,138,148,149,162] and bacterial contamination,[149] especially through precipitating skin abscesses and vein sclerosis. Phillips and colleagues[149] reported that participants in Denver, USA, commonly linked their bacterial infections to poor drug quality:

> *"I think it's the dope because… I'll use a clean needle every time, and it still, it just depends on what they cut it with. You know, sometimes when you're cooking it, it's an okay color, and then the next time you're doing it you've got all this shit floating up, and it's all burnt around the sides." (USA)[149]*

In two studies,[138,162] authors analysed drivers of variation in the unregulated drug supply and associated infection risks. Mars and co-authors[162] identified that participants in Philadelphia, USA, could purchase only tar heroin (less soluble than powder heroin, and associated with greater bacterial infection risk) due to regional demarcation of supply networks. In London, England, Harris and colleagues[138] highlighted participants' accounts of changing drug quality over time which has impacted widespread overuse of citric acid, used to dissolve poorly soluble cutting agents or adulterants such as paracetamol and quinine.

2.5.2.2.2 Unsafe spaces

In eight studies,[88,95,105,149,153,156,159,167] investigators attributed bacterial infections to suboptimal drug preparation and injecting techniques created by unsafe spaces, including when participants lacked housing and tried to avoid being seen by police when using outdoors.

In six of these studies,[88,95,105,151,156,159] authors explored influences of being without housing. Lack of housing made it harder to prepare and inject drugs safely, including no hygienic surfaces to prepare drugs,[88,95,105] inadequate lighting to find veins (leading to "missed hits" and inadvertent subcutaneous injection),[95] and no clean, running water to wash hands/skin or to dissolve drugs (leading people to use unhygienic water alternatives):[88,105,156,159]

> *"…there was no water actually and I had to use a bit of saliva. …It worked, I still got my hit, but I also got the worst infection of my life, I nearly died …Yeah, I was in hospital for nearly 3 months. Septicaemia." (England)[105]*

In research with people with injecting-related endocarditis, Bearnot and colleagues[150,151] noted that being unhoused interfered with participants' follow-up care, including ineligibility for outpatient parenteral antimicrobial therapy and having no fixed address for clinic contacts.

In six studies[95,105,149,153,159,167] authors analysed how criminalizing possession of drugs or injecting equipment (and associated police enforcement) increased risk. When lacking safer indoor places to prepare and consume drugs, participants engaged in riskier practices to avoid being seen by police. This included preparing and injecting drugs in unhygienic abandoned buildings,[159] and compromising injecting preparation practice when hurrying and not using filters or sterile water, and/or inadvertently injecting subcutaneously:[95,105,159]

> *"I don't even use cotton [filters]... boom and I usually get it done. Like that. So, if the cops raid and... several times the cops have pulled over, come right up to me and I've already injected it in my arm before they hit me." (USA)*[95]

In ethnographic research, Bourgois and colleagues[153] observed "greater and more antagonistic police surveillance" of African American than of white participants in San Francisco, USA, leading to racist, differential seizure of sterile syringes (obtained from legal needle and syringe programs). Police evicted homeless encampments and confiscated possessions, causing participants to miss medical appointments.

Three studies[159,161,169] explored how supervised consumption sites create safer spaces to reduce infection risks caused by lack of housing and criminalization, by facilitating individualized education on safer injecting techniques[161] and access to wound/abscess care.[161,169]

2.5.2.2.3 Health care policies and practices

In 13 studies,[88,95,149,150,152,155–158,160,163–165] authors analysed why participants delayed or avoided medical care for injecting-related infections, often until infections had progressed. Contributing factors were prior experiences of stigmatizing or discriminatory care (in 12 studies[88,95,149,150,152,155–158,163–165]) and of untreated pain and withdrawal (in six studies[88,95,150,151,157,158]). In several studies, participants described both:

> *"I'm not trying to get drugs. I'm trying to get you to take your sharp scalpel, cut this fucking thing open, squeeze this shit out of me, and get me the fuck out of here. That's the pain relief that I want you to give me...I can do heroin; your little 5mg Percocet ain't*

doing nothing for me. But they automatically think when you come in, 'I got an abscess. I'm hurting', 'Oh, you're trying to get drugs', this and that… it does prevent a lot of people from going." (USA)[95]

Some negative experiences were driven by hospital policies. Harris[88] explains how a London, England, hospital policy mandates that urine drug screens be obtained before methadone can be dispensed, even if doses are confirmed by pharmacies or treatment programs. This caused delays or missed dosages of methadone, and resulting experiences of opioid withdrawal led people to stay away:

"Mainly because how I have been treated at the hospitals, which is just like fucking dirt you'd find on your shoe… also being scared that I was going to be rough [sick] ...because if they didn't [give] me methadone, like someone's said he [doctor] won't do it unless he would have to, and if you don't know your rights, but yeah, it was that that really scared me more than anything, was being sick [in withdrawal] in a hospital." (England)[88]

Four studies[88,155,156,163] included analyses of how care delays due to negative health care experiences had disproportionate impacts by race or gender. Assessing hospital experiences in Vancouver, Canada, McNeil and colleagues[163] described, "Many participants of Aboriginal (Indigenous) ancestry further expressed that institutionalized racism reinforced the view among hospital staff that they were 'drug-seeking'". Three studies included descriptions of how mothers were discouraged from accessing care for injecting-related infections, including feelings of shame at disclosing substance use as a mother,[156] and fear of child apprehension if their substance use was reported by health professionals.[88,155]

In four studies,[151,152,160,163] participants described leaving hospital prematurely, before completing treatment for injecting-related infections. Explanations included leaving hospital in response to discrimination[160,163] and because restrictions on their movements in hospital triggered post-traumatic stress.[151] Two studies[152,163] highlighted participants being involuntarily discharged from hospital because of drug use, despite ongoing medical need. Jafari and colleagues[160] evaluated experiences with a care model in Vancouver, Canada, intending to overcome these issues: clients at a residential, harm-reduction oriented program for people with severe injecting-related infections described receiving less judgmental and stigmatizing care compared to experiences in mainstream hospitals.

Only one study specifically explored insufficient health insurance as a barrier to care.[155] In other studies, authors explained that insurance is a barrier to health care for others but their study participants had access to public health insurance (universally in Canada[163], and Medicaid in USA[150,151]).

2.5.2.2.4 Harm reduction programs

In four studies,[105,138,148,157] authors analysed consequences of participants having insufficient or nonpreferred drug preparation and injecting equipment distributed from harm reduction programs. In their study of experiences of skin and soft-tissue infections in Glasgow, Scotland, Dunleavy and colleagues[148] report: "reasons for re-using [needles and syringes included having been] accidentally supplied with the wrong sized needles and preferring to re-use than use the wrong needle". Three studies describe participants lacking needed equipment and repurposing alcohol swabs distributed by harm reduction programs: to clean up blood after injecting,[148,157] to filter visible particulate matter from puddle water,[105] and burning swabs to obtain an adequate flame to heat drug solutions.[148] In two studies, Harris and colleagues explored how legal/regulatory and funding restrictions on harm reduction programs limited distribution of sterile water[105] or single-use ascorbic acid packets.[138]

In three studies participants described structural barriers to needle and syringe programs that limited effectiveness, including limited operating hours (e.g. closures on weekends[148]) and restricting eligibility.[163,164] McNeil and colleagues[163] assessed consequences of participants being unable to access sterile equipment in hospital, leading to reuse of contaminated equipment:

> "*[Nurses] don't give rigs [syringes] to us. …I think that they should. If not, we're reusing our rigs or we're having to risk getting kicked out for stealing them or people'll be sharing them. …I know one girl was using her same rig for days to the point where it was tearing and she was suffering every time she'd do her fix. She just didn't have it in her to go and try and steal clean rigs."* (Canada)[163]

Four further studies focused on places without needle and syringe programs (in USA and Mexico), where pharmacists refused to sell syringes to participants:[154,165–167]

> *"I think that many [pharmacists] think that by prohibiting the sale of syringes that they are going to stop the usage of drugs...but what they are doing is wrong, because of that we have a harder time finding syringes. We need to use drugs in order to feel well, since when we are*

in need of a fix we feel desperate enough that we don't care and borrow one from a friend, since it's a desperate feeling..." (Mexico)[166]

Paquette and colleagues[165] explored how people would prefer having multiple access points for sterile injecting equipment, including pharmacies and needle and syringe programs: "…one participant indicated that using the [needle and syringe program] could out him as a [person who injects drugs] and expose him to stigma... If [people] could consistently access syringes at a pharmacy without fear of discrimination, some might prefer this option because it offers a higher level of anonymity than [needle and syringe programs]."[165]

Two studies highlighted how suboptimal delivery of opioid agonist treatment (e.g. methadone, buprenorphine) after hospital discharge could increase risks for recurrent infections, including involuntary discharge from opioid agonist treatment because of ongoing use,[151] waiting lists,[150,151] and a lack of coordination:[150]

"*I had methadone maintenance while I was in the hospital and I did not really have anything lined up when I left* [hospital]*, which, ultimately, could be one of the many reasons why I ended up re-infecting my valve and back in the hospital.*" (USA)[150]

2.5.2.3 Practices of care among people who use drugs

2.5.2.3.1 Mutual care

Five studies[95,148,156,157,167] included descriptions of people who use drugs caring for each other to promote health and reduce risks of infections. Within constraining risk environments, some of these protective strategies for bacterial infections precipitated other health risks.

Mutual care practices included providing or receiving education from other people who use drugs,[148] sharing sterile needles or injecting equipment in settings of scarcity,[167] and offering or receiving assistance with injecting to reduce bacterial infection risks[95,156]:

"I have my boyfriend. I only hit with him, always with him. I do not like to do it with strangers or people to whom I do not know so well. …My boyfriend helps me, because when I do it, it swells up." (USA)[156]

Once infections developed, participants described providing or receiving wound care, abscess treatment, or antibiotics from peers in order to avoid negative experiences with the health care system.[95,157]

While navigating risk environments, protective strategies for bacterial infections could precipitate other health risks. For example, three studies[138,156,168] assessed particular risks that women face when relying on injecting assistance, in the context of gendered power dynamics. In their study, Epele[156] explored these trade-offs: "Abscesses and scars that are more frequent with muscle injection lead to further subordination within the hierarchies of their social networks, and deteriorate the women's precarious strategies of income production. Although being injected by another increases the probability of HIV infection, it simultaneously prevents the visible physical damage that subjects these women to greater vulnerability." Similarly, nonmedical abscess treatment or use of potentially inappropriate antibiotics from nonmedical sources can lead to worsening infections, but participants described employing these strategies to avoid negative experiences in health care settings.[95,157]

2.5.2.3.2 Self-care

Twelve studies[95,105,148,150,151,156,157,159,161,162,165,166] included analyses of participants' practices to prevent and self-treat bacterial infections. These included practices to promote vein and skin care, including staying hydrated,[157] rotating injecting sites,[156] taking time to access veins,[95,157,162] asking for help to access veins,[156,168] and self-treating superficial abscesses (e.g., incision and drainage; nonmedical sources of antibiotics) before they progressed:[95,157,165]

> *"Little things like drink a lot of liquids, …make sure you get enough sleep, …eat regularly." (USA)[157]*

In three of these studies,[105,138,166] authors highlighted actions to mitigate the risks of poor-quality drugs or injecting equipment, including sharpening the tips of used needle tips to avoid vein damage (when unable to access new needles),[166] sourcing safer water by asking passers-by for bottled water,[105] and using ascorbic acid (which is safer than citric acid or lemon juice) when preparing heroin.[138]

In five studies,[138,148,150,151,161] participants described changing their drug use practices after experiencing an infection, to avoid another. This included applying new learnings on safer injecting techniques,[148,150,161] switching from injecting to smoking,[148] getting wounds assessed by a nurse,[148]

using minimum required acidifier to dissolve drugs,[138] and seeking addiction treatment to reduce or abstain from injection use.[151]

Three studies[95,156,159] included descriptions of self-care practices to avoid discrimination and structural stigma. This included injecting in central veins at hidden sites to avoid scars at more visible sites,[148,156] and using in unhygienic abandoned buildings to avoid being seen in public.[159]

Similar to mutual care practices, some protective self-care strategies employed within constraining risk environments led to other health risks. For example, injecting in central veins in the groin to avoid discrimination from visible scars, increases risks of thrombosis and arterial injury, and may increase risks for bacterial infections (as the groin has a higher burden of bacterial colonisation). Considering unintended harms of inappropriate self-treatment of bacterial infections, Gilbert and colleagues[157] write: "There are certainly risks conferred by the self-care practices that [people who inject drugs] are forced to resort to. However, these risks are not taken lightly…; they are weighed against the risk of inaction and worsening infections, which is well known in these communities."

2.6 Discussion

In this Chapter, I reviewed qualitative studies on experiences of injection drug use-associated bacterial and fungal infections, and used thematic synthesis to identify social-structural factors influencing risk for these infections and their treatment. In collaboration with the review team (which included people with lived/living experience of injection drug use and clinicians), I identified two analytic themes (*social production of risk* and *practices of care among people who use drugs*) comprising six descriptive themes: *unregulated drug supply; unsafe spaces; health care policies and practices; harm reduction programs; mutual care;* and *self-care*. I found that injecting-related bacterial and fungal infections are shaped by modifiable social-structural factors, including poor quality unregulated drugs, criminalization and policing enforcement, insufficient housing, limited harm reduction services, and harmful health care practices. Facing constraining risk environments, some protective strategies that people employ for bacterial infections (e.g., receiving injecting assistance) precipitated other health risks (e.g., HIV infection). Social-structural factors influenced all stages of a pathway from drug acquisition to preparation and injecting, development of superficial and deep infections, and health outcomes after infections. Most studies focused on infection development, and fewer focused on sequelae post-infection. While the importance of education on safer injecting technique came up in several studies,[95,138,148,166,169] my findings suggest that individual-level behavioural interventions alone are likely insufficient to reduce risk without changes to the

social and material conditions within which people prepare and inject drugs, and receive treatment for infections. Safer environment interventions that address these social-structural factors could further empower people who inject drugs to protect themselves and their community.[108,170,171]

Several social-structural determinants of bacterial and fungal infections (as well as practices of mutual- and self-care[37,114,172,173]) that I identified are consistent with prior research examining risk for HIV and HCV among people who inject drugs.[3,5,25,26,48,79,174,175] Insecure housing, hurrying injections to avoid police, insufficient harm reduction services, and laws restricting sterile injecting equipment are known to contribute to HIV[9,79,82,84,174] and HCV[6,25] transmission. Stigmatizing and discriminatory health care experiences similarly discourage HIV and HCV treatment access and exacerbate health inequities.[111,176] Conversely, some factors confer different risks for bacterial and viral infections. Within studies included in this qualitative systematic review, participants attributed abscesses to tar heroin entering the unregulated drug supply, as it was less soluble and damaged veins. However prior research suggests tar heroin may be associated with lower risk of HIV transmission at a population-level, because it requires thorough heating to sufficiently dissolve and this process kills viruses.[177] Compared to the literature on HIV and HCV among people who inject drugs,[5,48,178] I identified relatively little published research considering intersectionality and risk for injecting-related bacterial or fungal infections.[3]

Two qualitative studies were published after my search. Interviewing people admitted to hospital with injecting-related infections in New York, USA, Hrycko and colleagues[69] identified social-structural factors contributing to risk for severe bacterial infections, including availability and use of drugs (e.g. fentanyl, stimulants) associated with a shorter duration of effect and more frequent injecting, and lack of access to sterile water. High injecting frequency has previously been identified as a risk factor for HIV, especially where there is limited access to sterile injecting equipment.[4,179] In their ethnography in Dhaka, Bangladesh, Khan and colleagues[180] describe how poverty and insufficient housing prevented people from cleaning their skin or being able to prepare drugs in a hygienic way, and lack of sterile injecting equipment led people to reuse contaminated equipment. Fear of arrest or harassment by police kept people away from public areas where health and social outreach services would have been available. Chronic and insufficiently treated infections led to pain and disability, and they interfered with employment.

A key motivation for this review was to identify potential opportunities to reduce risks for injecting-related bacterial and fungal infections. Interventions that reshape social and environmental contexts of drug use and mediate access to resources and health care services can be conceptualized as

"safer environment interventions",[108] operating at micro-environmental (e.g. supervised consumption sites) and macro-environmental (e.g. decriminalization) levels. Many social-structural factors I identified are modifiable, and some have already been ameliorated in certain settings; though specific impacts on bacterial infection risk have rarely been assessed. These include people who use drugs organizing to access better quality, regulated drugs including via injectable opioid agonist treatment (iOAT; with liquid formulations of diacetylmorphine [also known as "heroin-assisted treatment"], hydromorphone, and fentanyl), and through "safe supply" prescribing programs or compassion clubs.[43,44,181] Injectable opioid agonist treatment is associated with low risk for bacterial infections even when injected intramuscularly, since sterile, liquid formulations of drugs are provided in a hygienic and safe environment.[78] Prescribed safer supply programs involve health professionals providing pharmaceutical-grade alternatives to unregulated drugs, which patients/clients can take home and consume how they prefer (including crushing and injecting tablets); this is often offered alongside primary care and other health and social services.[47,182–184] One study found participants in a prescribed safer supply program in London, Canada, were less likely to be hospitalized with injecting-related bacterial infections compared to before they entered the program.[185] Social and supportive housing (including Housing First) can help people who use drugs access and maintain housing; some models combine housing with iOAT, safe supply, and/or supervised consumption sites.[45,186,187] In some jurisdictions, people who use drugs and their allies have successfully advocated for decriminalization of drug and/or syringe possession and for laws enabling supervised consumption sites.[188] Several initiatives have improved health care experiences for people with injecting-related infections,[97,189] including incorporating harm reduction and cultural safety principles,[88,190] specialized addiction medicine consultation services,[191–193] needle and syringe programs,[117,194] and supervised consumption sites[195–197] into hospital care. Policy changes are needed at many hospitals to facilitate these initiatives.[198,199]

2.6.1 Limitations

This study has three key limitations. First, my review only included studies describing experiences of injecting-related infections and I did not include all studies investigating determinants of risky injecting practices (e.g., subcutaneous injecting; reuse of contaminated equipment) unless explicitly connected to infections. Second, I did not include grey literature that might have discussed further social-structural factors beyond those I identified in peer-reviewed papers. Third, some commentators[144,200] have argued that qualitative evidence syntheses decontextualize the nuanced findings of qualitative studies (conducted in different settings, with different methods) and consolidate knowledge that is not generalizable. I undertook this approach to understand how social

and structural factors shape risks for injecting-related infections in ways that may be impossible to assess with quantitative research.[131,201]

2.6.2 Conclusions

The qualitative thematic synthesis presented in this Chapter suggests that injecting-related bacterial and fungal infections are shaped by modifiable social-structural factors, including unregulated drug quality, criminalization, insufficient housing, limited harm reduction services, and harmful health care practices. Safer environment interventions that address these factors could further empower people who inject drugs to protect themselves and their community.

These findings also suggest potential mechanisms and causal pathways by which social-structural exposures (e.g. being houseless) and clinical exposures (e.g. the organization and delivery of opioid agonist treatment) may influence individual drug preparation and injecting practices, and therefore contribute to risks of infections. They also highlight how stigma and policies in heath care settings influence treatment of injecting-related infections. These potential mechanisms and causal pathways can help to explain quantitative associations identified in observational studies, as explored in the next Chapter.

Chapter 3 Quantitative systematic review and meta-analysis: Social determinants, substance use, and health services correlates of injection drug use-associated bacterial infections and treatment outcomes

3.1 Attribution and outputs

The work in this chapter has not yet been presented at an academic conference, nor submitted to a journal. I led all aspects of the development, data collection, analysis, and write-up. Contributions from others include being a secondary reviewer on title and abstract screening, and on data extraction, and these are listed in the text below. Contributors to conceptualization and analysis are mentioned in the Acknowledgments at the start of the thesis.

3.2 Abstract

Background: Specific high-risk injecting practices (e.g., intramuscular injection, lack of skin cleaning) are known risk factors for injection drug use-associated bacterial and fungal infections. However, less is known about how social contexts shape individual injecting practices and influence risk for injecting-related infections and their treatment. I sought to synthesize quantitative studies assessing potential social contextual influences on injecting-related infections, treatment, and outcomes.
Methods: I searched PubMed, EMBASE, Scopus, CINAHL, and PsycINFO for studies published between January 1, 2000, and February 18, 2021. I included quantitative studies of association (etiology) assessing potential social determinants, substance use, and health services exposures that might influence risk for injecting-related infections and treatment outcomes. I extracted and synthesized univariate and covariate-adjusted effect estimates in separate models via inverse variance meta-analyses, when possible, using random effects models.
Results: I screened 4,841 abstracts and assessed 631 full-text reports, and included 107 quantitative studies. This included 60 studies where the outcome was incident or prevalent injecting-related infections, 26 studies assessing outcomes during treatment (e.g., premature hospital discharge against medical advice), 29 studies assessing outcomes after treatment (e.g., infection-related rehospitalizations; all-cause mortality after hospital discharge), and 5 studies assessing colonisation with pathogenic bacteria. I found evidence that the following factors were associated with risk of incident or prevalent injecting-related bacterial infections in meta-analyses of adjusted effect estimates: woman/female gender/sex (adjusted odds ratio [aOR] 1.57, 95% confidence interval [CI] 1.36-1.83; n=20 studies), homelessness or unstable housing (aOR 1.29, 95%CI 1.16-1.45; n=13

studies), cocaine (aOR 1.31, 95%CI 1.02–1.69; n=10 studies), amphetamines (aOR 1.74, 95%CI 1.39-2.23; n=2 studies), injecting in public (aOR 1.40, 95%CI 1.05–1.88; n=2 studies), requiring injecting assistance (aOR 1.78, 95%CI 1.40–2.27; n=8 studies), and use of opioid agonist treatment (aOR 0.92, 95%CI 0.89–0.95; n=9 studies). Studies assessing outcomes during or after treatment typically had smaller sample sizes and imprecise effect estimates, and findings were commonly inconsistent between studies. Significant associations identified in meta-analyses of adjusted effect estimates include (a) lacking health insurance associated with increased risk of premature hospital discharge against medical advice (aOR 2.07, 95%CI 1.09-3.91; n=4 studies); and (b) woman/female gender/sex was associated with increased risk of all-cause rehospitalization after initial hospital admission with injecting-related infections (aOR 1.22, 95%CI 1.08-1.38; n=3 studies).

Conclusions: Injecting-related infections, their treatment, and subsequent outcomes are shaped by multiple social determinants, substance use, and health services-related factors. Public health and clinical approaches to prevention and treatment should look more broadly than individual injecting practices, towards addressing the social and material conditions within which people live, acquire and consume drugs, and access health care.

3.3 Introduction

As described in Chapter 1, injection drug use-associated bacterial infections are associated with significant morbidity and mortality among people who use drugs, and the incidence of these infections has been increasing in North America, Europe, and Australia.[21,51,56,202–204] Individual injecting practices have been identified as risk factors, including not sterilizing skin before injecting, reusing blunted or contaminated needles and syringes, and subcutaneous or intramuscular injecting.[56] However, individual injecting practices are shaped by their social context; for example, people without secure housing are more likely to inject in public or in unhygienic spaces (e.g., abandoned buildings). People may need to reuse contaminated equipment if they have insufficient access to harm reduction programs. Treatment of injection drug use-associated bacterial infections is also suboptimal.[205] People who inject drugs describe negative experiences of untreated pain and withdrawal in health care settings, and clinicians caring for them describe a lack of knowledge on how best to help.[205,206] Most hospitals do not integrate substance use and addiction care,[117,193,207,208] and many hospitals have abstinence-based policies that lead patients to surreptitiously use drugs (e.g., in locked bathrooms) or leave the hospital prematurely against medical advice.[198,199]

Prevention and treatment strategies for injecting-related infections may be greatly improved if public health and health care systems look more broadly to the social and structural factors that

shape individual injecting practices and treatment experiences. Chapter 2, above, described my qualitative systematic review and thematic synthesis of studies on peoples' experiences of injecting-related infections.[202] I found that risk for injecting-related bacterial and fungal infections is shaped by multiple modifiable social-structural factors beyond individual injecting practices, including unregulated drug quality (e.g., poorly soluble drugs or adulterants contributing to skin and vein damage), insufficient housing (e.g. people not having access to running water to prepare drugs, or adequate lighting to find a vein), criminalization and enforcement (e.g., people compromising their drug preparation practices and rushing to inject their drugs intramuscularly in anticipation of police search and seizure), and operational limitations on harm reduction services (e.g. insufficient funding, or geographic restrictions). I also identified that harmful health care policies and practices lead to negative experiences of undertreated pain and withdrawal that discourage people from accessing care until infections had worsened and spread, or otherwise contribute to people leaving hospital prematurely against medical advice (before their treatment is complete). I identified examples of factors affecting outcomes after hospital treatment, for example opioid agonist treatment started in hospital with no outpatient follow-up arranged by the clinical team. This qualitative synthesis provided valuable insights into mechanisms by which social and structural factors influence risks of injecting-related infections and their treatment.

3.3.1 Objectives

To better understand and quantify the influence of social-structural factors on injecting-related infections and their treatment, I sought to systematically review and meta-analyze the quantitative literature on the topic. This systematic review seeks to answer the question, "Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"

3.4 Methods

I published a protocol[21] and registered with PROSPERO (CRD42021231411) before conducting the search. As explained in Chapter 2, I modified the protocol after conducting the search and full-text review. The protocol specified a "mixed studies review" of quantitative, qualitative, and mixed-methods studies.[131,132] As I identified more sources than anticipated, I decided to review and synthesize quantitative and qualitative studies separately, in sequence. Here, I report the quantitative systematic review and meta-analysis. Qualitative results were reported separately, in Chapter 2 (above).[202] My approach to quantitative systematic review and meta-analysis in this

chapter is informed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[209] and Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E)[210] guidance. This chapter follows Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement reporting guidance.[129]

3.4.1 Eligibility criteria

Informed by the Population, Exposures, Outcomes approach,[133] I included peer-reviewed papers (published in academic journals) reporting quantitative studies of association (etiology). I excluded case-reports, case series, and descriptive-only studies that do not include analyses of association, and I excluded reviews, commentaries, and editorials, as they do not include original data. "Participants" were people who inject any psychoactive substances (excluding people who only inject performance enhancing or gender affirming hormones). "Exposures" were social or environmental factors that could affect risk of infections or influence their treatment. This includes social determinants of health such as housing and income, and other exposures that are socially patterned such as access to (or use of) different substances, harm reduction services, addiction treatment, and health care. As the conceptual model (described in Chapter 1) engages with the "intersectional risk environment"[3], I also looked for socially constructed identities and locations within social power hierarchies, including by gender/sex and race/ethnicity.[3] While some sociodemographic characteristics (like gender, sex, or age) may confer effects on health through biological as well as social-structural pathways, social and biological effects are often interlinked and I expected that the quantitative studies I identified would not attempt to isolate purported biological-only effects.[5,211] For example, potential differences by gender/sex may reflect structural sexism, and potential differences by race/ethnicity may reflect structural racism.[5,48] "Outcomes" were injecting-related bacterial or fungal infections (or related outcomes during and after treatment of these infections), including skin and soft tissue infections (i.e., abscess, cellulitis, necrotizing fasciitis), sepsis or bacteraemia, vascular infections (endocarditis, septic phlebitis), bone and joint infections (osteomyelitis, septic arthritis, discitis), and central nervous system infections (epidural abscess, brain abscess, meningitis, encephalitis). I excluded studies that assessed infections not typically transmitted through injection drug use (e.g., tuberculosis, chlamydia, gonorrhea, syphilis). I included pneumonia as an outcome only if study authors explicitly conceptualized it as related to injection drug use. I included studies published between January 1, 2000 and February 18, 2021 (the search date) and those published in English or French (the languages understood by the review team).

3.4.2 Information sources, search strategy, and data management

I searched PubMed, EMBASE, Scopus, CINAHL, and PsycINFO databases. I supplemented database searches by manually reviewing reference lists of included studies, and forward "snowball" searching by identifying articles that cite included studies.[134] I also included articles identified from the personal files of the systematic review team that were not identified in the bibliography; the team includes people with lived (past) and living (current) expertise of injection drug use and clinicians who care for people with injection-associated infections. I developed the final search strategy in consultation with a health sciences librarian. The final "mixed studies" search strategy for all databases is included in Appendix 4.

Search results were uploaded into Covidence and automatically de-duplicated. Two reviewers (myself and either Dan Lewer [public health consultant], Matthew Bonn [researcher with lived/living experience and drug policy activist], Inwha Kim [medical student], or Emilie Comeau [medical student]) screened titles and abstracts against the inclusion criteria, resolving discrepancies through consensus. I alone then assessed full-text reports for inclusion, and recorded reasons for exclusion.

3.4.3 Data collection

I developed and pilot-tested a data extraction form for studies with quantitative data. Data was extracted by one investigator (myself) and checked independently by a second investigator (Mary Figgatt [PhD student in epidemiology] or William Eger [interdisciplinary PhD student focused on substance use and health]). For each study, I extracted data on:

- First author and publication year
- Social and structural exposures included in the review
- Main exposure or estimand of the study (and whether all exposures assessed in our review reflect the study estimand)
- Infection types (e.g., SSTI, endocarditis, osteomyelitis, etc.)
- Infection-related outcomes
- Country (city) where study took place
- Sample size
- Sampling method (and parent study name, if applicable)
- Data collection period
- Inclusion criteria

- % of sample that are women/female
- Age of sample
- Drugs used by ≥50% of the sample

As suggested in COSMOS-E guidance,[210] I manually extracted both univariate and fully adjusted effect estimates (with 95% confidence intervals) from studies, wherever possible. Following Kaufman, I conceptualized univariate analyses as associative (e.g., "are people experiencing homelessness more likely to have injecting-related infections?") and covariate-adjusted effect estimates as attempting to identify causal relationships (etiology; e.g., "does homelessness contribute to injecting-related infections?").[212]

In some studies identified in this review, investigators aimed to estimate the effect of one exposure as accurately as possible (e.g., the implementation of a change in drug policy)[139], informed by pre-specified hypotheses and adjusted for known confounders. This has been termed an "estimand", meaning the real-world quantity that is to be estimated in a study and to distinguish from the method used (known as an "estimator") and the specific value obtained in the study (known as the "estimate").[213,214] In causal inference approaches within contemporary epidemiology, this is done through prespecifying the relationships between exposures and outcomes (including potential confounders and colliders) via the use of Directed Acyclic Graphs (DAGs).[215–217] However, many studies I identified did not specify any estimand (and were therefore not attempting to estimate an effect size or causal relationship as accurately as possible) but instead sought to identify various "factors associated with" an outcome. Often this was done through testing all potentially "statistically significant" exposures using an automated or rules-based stepwise regression approach.[218] The end result is multiple "adjusted" effect estimates that are supposedly adjusted for other significant exposures. This approach may introduce new biases and other issues with statistical inference, including problems with multiple hypothesis testing, collider stratification bias (the so-called "Table 2" Fallacy),[219] over-adjustment bias ("adjusting" for factors on a causal pathway between a main exposure and the outcome),[220] and effect estimates that are not as specific as possible. For included studies in this review, I extracted information on whether a study specified an estimand (most often indicated by testing an explicit hypothesis) and whether the effect estimates I included in the review reflect the study estimand. As I wanted to understand the breadth of existing evidence (despite its potential flaws), I included effect estimates derived from all eligible studies, including the atheoretical "factors associated with" studies.

Effect estimates were extracted by one investigator (myself) and checked independently by Mary Figgatt or William Eger. Where summary effect estimates (e.g., odds ratios) were not reported, I extracted frequencies of outcomes and sample sizes within exposed and unexposed groups to calculate univariate odds ratios and standard errors. Many studies only reported pre-calculated effect size estimates and did not provide specific frequencies or raw data, so I could not extract these for all studies. When a study reported only stratified analyses (e.g., only separate effect estimates among women and among men) I kept both effect estimates for meta-analyses. When a study reported highly related effect estimates (e.g., separate odds ratios for measures of "lifetime homelessness" and for "homeless in past six months"[92]) from the same sample, I included only one in the meta-analysis to avoid double counting and documented reasons for inclusion or exclusion.[221] As most studies reported effect estimates in odds ratios, I treated all relative effect estimates (including hazard ratios and rate ratios) as if they were odds ratios for meta-analysis. When outcomes under study are not rare (e.g., >5%) the odds ratio will be greater than the relative risk.[210,222] However, I noted where metrics were something other than odds ratios and include this in a supplementary appendix. Many studies did not report statistics for null or nonsignificant findings, but instead reported something like, "no associations found" or "did not differ". These null findings could not be included in meta-analysis because no statistics were provided. I extracted data on where this was reported, but for many multivariable analyses it was not explicitly reported (instead just reporting, e.g., that an exposure that had no statistically significant association in univariate testing did not progress to multivariable testing in stepwise regression).

3.4.4 Critical appraisal

I applied a formal, validated critical appraisal tool, the Mixed Methods Appraisal Tool (MMAT), 2018 edition, which is designed for use with quantitative, qualitative, and mixed methods studies.[141,141,142] Following the same approach as my qualitative systematic review described above in Chapter 2, I followed a "user guide" from the MMAT developers.[143] I included all studies which met both MMAT screening questions for studies of all study designs. These are, "Are there clear research questions?" and "Do the collected data allow to address the research questions?". For quantitative studies of association/etiology, the five MMAT criteria questions focus on whether the sample is representative of the target population, measurement error, whether confounders are accounted for in design and analysis, and whether the exposure occurred as intended. While the MMAT considers several forms of potential bias in observational studies (including selection bias, misclassification bias, and confounding), it scores these only once per study; many of the studies included here contained many potential exposure-outcome analyses that might have differing risks

of bias. I scored the relevant MMAT question as "No" if any exposure-outcome analysis in the study did not meet the criteria (e.g., if the timeline of exposure and outcome ascertainment did not align for one of the many potential exposures). Also, the MMAT only ask whether confounders were considered, not how they were selected or if they are appropriate. I therefore scored "Yes" for studies that included covariate-adjusted analyses, even if these were not informed by specific hypotheses. I assigned each study a score out of 5, by summing how many of the MMAT appraisal questions were answered, "Yes". I report MMAT scores for each study but did not otherwise use critical appraisal evaluations.

3.4.5 Meta-analysis

I conducted separate inverse variance meta-analyses for each category of exposure-outcome pairs in *R* (version 4.2.2), using the *meta* package. I performed random-effects meta-analyses because I assumed there would be between-study heterogeneity (including different exposure and outcome definitions, study settings, and sampling frames).[210,222] I applied the DerSimonian-Laird estimator for τ^2 because it is commonly used and because it is appropriate for both binary and continuous outcome data (though in the end, all outcome data was binary).[222,223] I applied the Knapp-Harding adjustment, which assumes a t-distribution of the standard error of the pooled effect size and reduces the chance of false positives (this can result in wider confidence intervals for the pooled effect).[224] I measured the percentage of total statistical variability attributable to between-study heterogeneity using I^2 statistics. I considered I^2 values of 25%, 50%, and 75% as low, moderate, and high, respectively.[225] I identified an individual effect estimate as an outlier if its confidence interval did not overlap with the confidence interval of the pooled effects (i.e., the effect size of the outlier is so extreme that it differs significantly from the meta-analysis summary effect).[226] I planned to identify outliers in this way because I expected substantial between-study heterogeneity (as described above), which could lead to one extreme effect estimate influencing the summary meta-analysis. Since these were statistical outliers identified *post hoc,* I compared meta-analysis results with outliers included and omitted to understand the impact of omitting them.

3.5 Results

3.5.1 Summary of included studies

As described above in Chapter 2, the mixed-studies search identified 8,167 references; after automated de-duplication, I screened 4,841 titles and abstracts and 631 full-text reports. I reviewed 16 additional full-text reports identified outside the search. For this quantitative systematic review, I

excluded four quantitative studies because they failed the MMAT screening questions (i.e., there were not clear research questions, or the data did not address the research question). See Appendix 7 for details on studies identified outside search and studies excluded through MMAT screening.

Overall, this quantitative systematic review included 107 studies (see Figure 9 for PRISMA flow diagram). This includes 60 studies looking at risk of developing an infection (incidence or prevalence), 26 studies assessing outcomes during treatment (e.g., in-hospital mortality, against medical advice discharge, etc.), 29 studies assessing outcomes after treatment (e.g., infection-related rehospitalization, all-cause mortality), and five studies assessing risks for colonization with pathogenic bacteria among people who inject drugs.

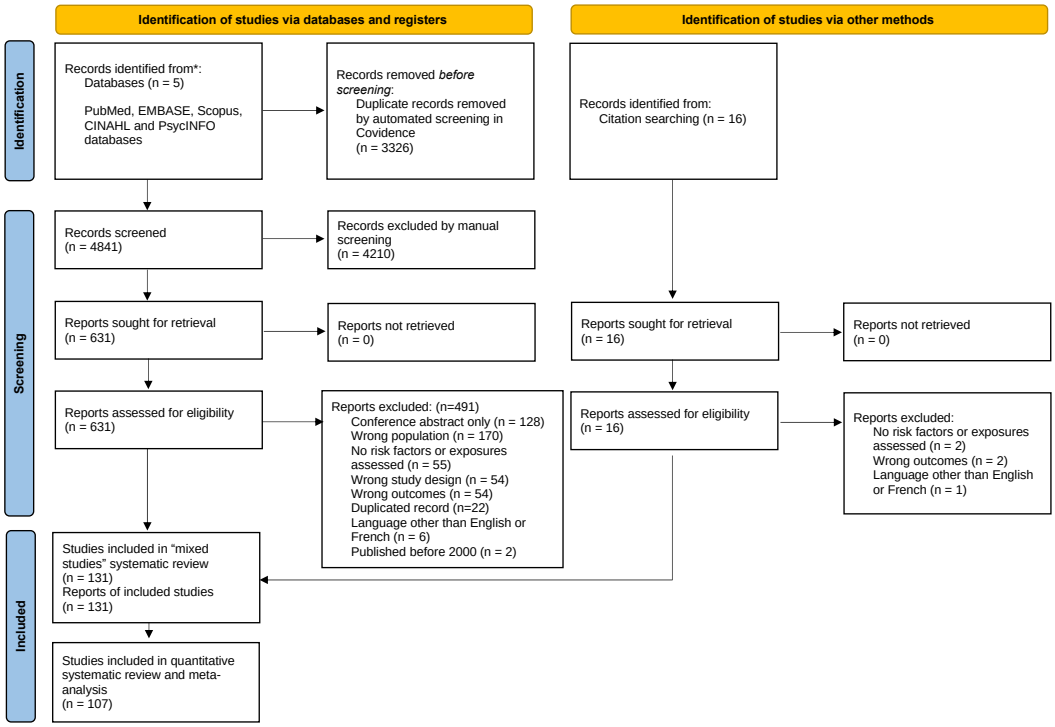

Figure 9. PRISMA 2020 flow diagram of included studies in quantitative systematic review of injecting-related infections.

See Table 3 for summary of characteristics of included studies. While I aimed to include studies on injecting-related bacterial and fungal infections, only two studies[227,228] (both on endogenous endophthalmitis) incorporated fungal infections. The remaining 105 studies focused on injecting-related bacterial infections only. Among the 60 studies where the outcome was incident or prevalent injecting-related infections, 83% (n=50) included SSTI and the median average measure of gender/sex was 28.6% women/female. For studies focused on outcomes during or after treatment,

most studies focused on endocarditis (73% and 86%, respectively); woman/female participants were more common in these studies (48.2% and 43.2%, respectively) where participants had already developed injecting-related infections.

Table 3. Summary of included studies in quantitative systematic review on injecting-related bacterial and fungal infections.

Characteristic	Level	Studies on incident or prevalent infections	Studies on outcomes during treatment for infection	Studies on outcomes after infection	Studies on colonization
Studies (n)		60 studies	26 studies	29 studies	5 studies
Sample sizes (no. of participants)	Median (range)	623 (45 – 60,529)	244 (20 – 605,859)	125 (19 – 27,432)	282 (78 – 497)
Age (mean or median), years	Median (range)	37 (27.5 – 47.1)	38 (25.8 – 47.2)	35.9 (28.5 – 46)	40.5 (38.7 – 47.6)
Gender/sex (% women/female)	Median (range)	28.6% (0.0% - 77%)	43.2% (2.9% - 69.0%)	48.2% (12.5% - 70%)	21.1% (16.0% - 41.0%)
Infection type/syndrome[a]	No. (%) of studies				
	Skin and soft-tissue infections	50 (83%)	13 (50%)	4 (14%)	-
	Endocarditis	14 (23%)	19 (73%)	25 (86%)	-
	Sepsis/bacteremia	5 (8%)	6 (23%)	3 (10%)	-
	Osteomyelitis	4 (7%)	9 (35%)	7 (24%)	-
	Septic arthritis	3 (5%)	6 (23%)	4 (14%)	-
	Spinal epidural abscess	2 (3%)	2 (8%)	3 (10%)	-
	Other	Pneumonia: 1 (2%)	Fungemia: 2 (8%) Pneumonia: 1 (4%) Botulism: 1 (4%) Endophthalmitis: 1 (4%)	Endophthalmitis: 1 (3%)	S. aureus colonization: 2 (40%) Methicillin-resistant S. aureus (MRSA): 5 (100%)
	Not specified	3 (5%)	0	0	0
	Multiple	9 (15%)	9 (35%)	7 (24%)	2 (40%)
Country	No. (%) of studies				
	United States	25 (42%)	18 (69%)	18 (62%)	3 (60%)
	Canada	11 (18%)	3 (12%)	3 (10%)	0
	United Kingdom	12 (20%)	2 (8%)	1 (3%)	1 (20%)
	Australia	1 (2%)	0	2 (7%)	0
	France	1 (2%)	0	0	0
	Germany	1 (2%)	0	0	0
	India	1 (2%)	0	0	0
	Sweden	1 (2%)	0	1 (3%)	0
	Switzerland	1 (2%)	1 (4%)	0	1 (20%)
	Thailand	1 (2%)	0	0	0
	South Africa	0	1 (4%)	0	0
	Spain	0	1 (4%)	0	0

Publication year	2018-2021	18 (30%)	15 (58%)	26 (90%)	2 (40%)
	2014-2017	16 (27%)	1 (4%)	2 (7%)	1 (20%)
	2010-2013	11 (18%)	4 (15%)	1 (3%)	1 (20%)
	2006-2009	8 (13%)	3 (12%)	0	1 (20%)
	2000-2005	7 (12%)	2 (8%)	0	0
No estimand[b]	No. (%) of studies	30 (50%)	16 (62%)	11 (38%)	5 (100%)

[a]Total adds up to greater than 100% as several studies included more than one infection syndrome

[b]These are studies that did not aim to model a specific exposure or treatment effect as accurately as possible, but rather aimed to identify "factors associated with" an outcome. They either tested several univariate analyses (e.g., in case-control study) or tested multiple exposures at once in multivariable regression (e.g., stepwise regression, without a hypothesis or main exposure).

See supplementary appendices for full characteristics of included studies where outcome is incident or prevalent infections (Appendix 8), outcomes occur during treatment for infections (Appendix 9), outcome is after treatment of infections (**Appendix** 10), or outcome is colonization with pathogenic bacteria (Appendix 11). Full MMAT scoring results are included in Appendix 12, Appendix 13, Appendix 14, and Appendix 15. See Appendix 16 for a description of handling and selecting effect estimates for inclusion in meta-analyses for all studies.

3.5.2 Incident or prevalent injecting-related infections

Sixty studies assessed factors associated with incident or prevalent injecting-related infections. Demographic characteristics included gender/sex; age; race/ethnicity; education; income/employment; relationship status; and migration status. Social and housing support characteristics included incarceration history; sex work; food insecurity; unstable housing/homelessness. Substance use factors included overdose history; heroin formulation; heroin use; prescription-type opioids; cocaine use; amphetamines; prescription-type stimulants; other/combined stimulant use; speedball use; other/polysubstance use; alcohol use; and smoking. Drug policy and injecting context factors included drug policy changes; drug purchasing network; injecting in public; shooting gallery; police contacts and arrests; assisted injecting/requiring help to inject; and injecting with others. Health and social services factors included access to needle and syringe programs; opioid agonist treatment; supervised consumption sites.

See Figure 10 below, for a summary of exposures and associated meta-analytic effect estimates. See Appendix 17 for a list of all extracted effect estimates in this section. Briefly, we identified evidence to support associations between several factors with incident or prevalent injecting-related infections, in meta-analyses of covariate-adjusted effect estimates: woman/female gender/sex (adjusted odds ratio [aOR] 1.57, 95% confidence interval [CI] 1.36-1.83; I^2 47%; n=20 studies), unstable housing and homelessness (aOR 1.29, 95%CI 1.16-1.45; I^2 9%; n=13 studies; Figure 3), cocaine use (aOR 1.31, 95%CI 1.02–1.69; I^2 75%; n=10 studies), amphetamine use (aOR 1.74, 95%CI 1.39-2.23; I^2 0%; n=2 studies), public injecting (aOR 1.40, 95%CI 1.05–1.88; I^2 0%; n=2 studies), requiring/receiving injecting assistance (aOR 1.78, 95%CI 1.40–2.27; I^2 48%; n=8 studies), and use of opioid agonist treatment (aOR 0.92, 95%CI 0.89–0.95; I^2 50%; n=9 studies). For several other exposures, we identified evidence to support an association only in meta-analyses of unadjusted (but not covariate-adjusted) effect estimates: lower income/unemployment (unadjusted odds ratio [uOR] 1.44, 95%CI 1.22-1.71; I^2 79%; n=16 studies), incarceration history (uOR 1.27, 95%CI 1.06-1.53; I^2 81%; n=6 studies; Figure 3), sex work (uOR 1.49, 95%CI 1.06-2.09; I^2 89%; n=8 studies), heroin use

(uOR 1.35, 95%CI 1.13-1.61; I^2 75%; n=20 studies), speedball (heroin and cocaine together) or goofball (heroin and methamphetamines together) use (uOR 1.34, 95%CI 1.15-1.55; I^2 40%; n=12 studies). For all other exposures (including needle and syringe program use; Figure 3), we did not identify evidence to support an association in meta-analyses of unadjusted or covariate-adjusted effect estimates.

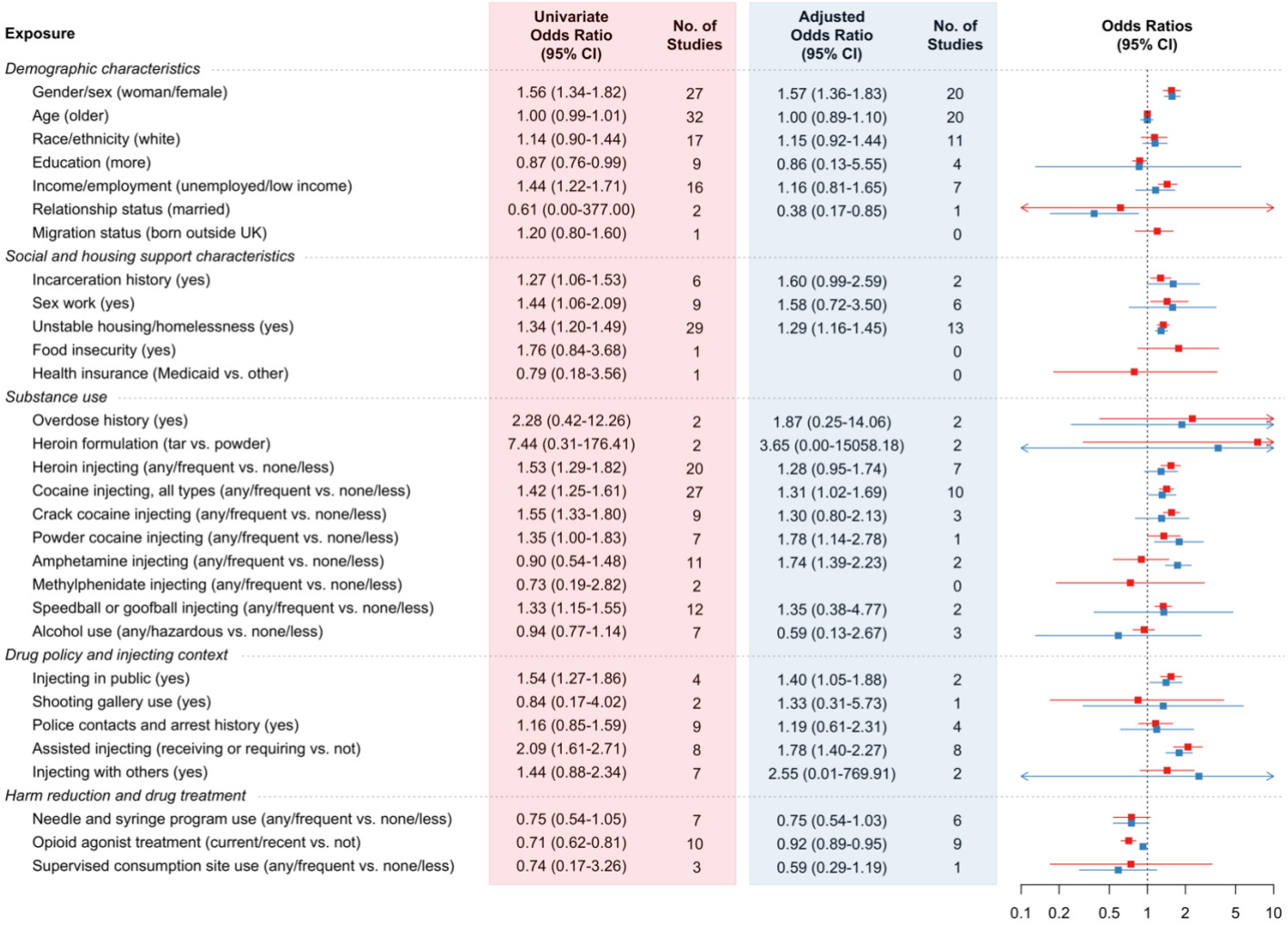

Figure 10. Summary of exposures and meta-analytic effect estimates among studies where outcome is incident or prevalent injecting-related bacterial infection.

3.5.2.1 Demographic characteristics

3.5.2.1.1 Gender/sex

35 studies investigated associations between gender/sex and incident or prevalent injecting-related infections.[59,63,75,92,99–101,104,125,229–254] I combined gender and sex into one category because studies tended to use these terms interchangeably and did not typically define how they were ascertained. Doran 2020[232] reported effect estimates from two different study samples (the "Care & Prevent Study" [C&P] and the Unlinked Anonymous Monitoring survey [UAM]) and I included both of these.

Thirty-one univariate effect estimates were included in meta-analysis, resulting in a summary univariate odds ratio (uOR) for woman/female (vs. man/male) of 1.56 (95% confidence interval [CI] 1.34-1.82; Figure 11). There were four outliers [Hope 2010; Morin 2020; Dunleavy 2017; Lloyd-Smith 2005].[59,92,101,235] Removing these changed the summary to uOR 1.65 (95CI% 1.47-1.86; I^2 56.8%, p=0.0002).

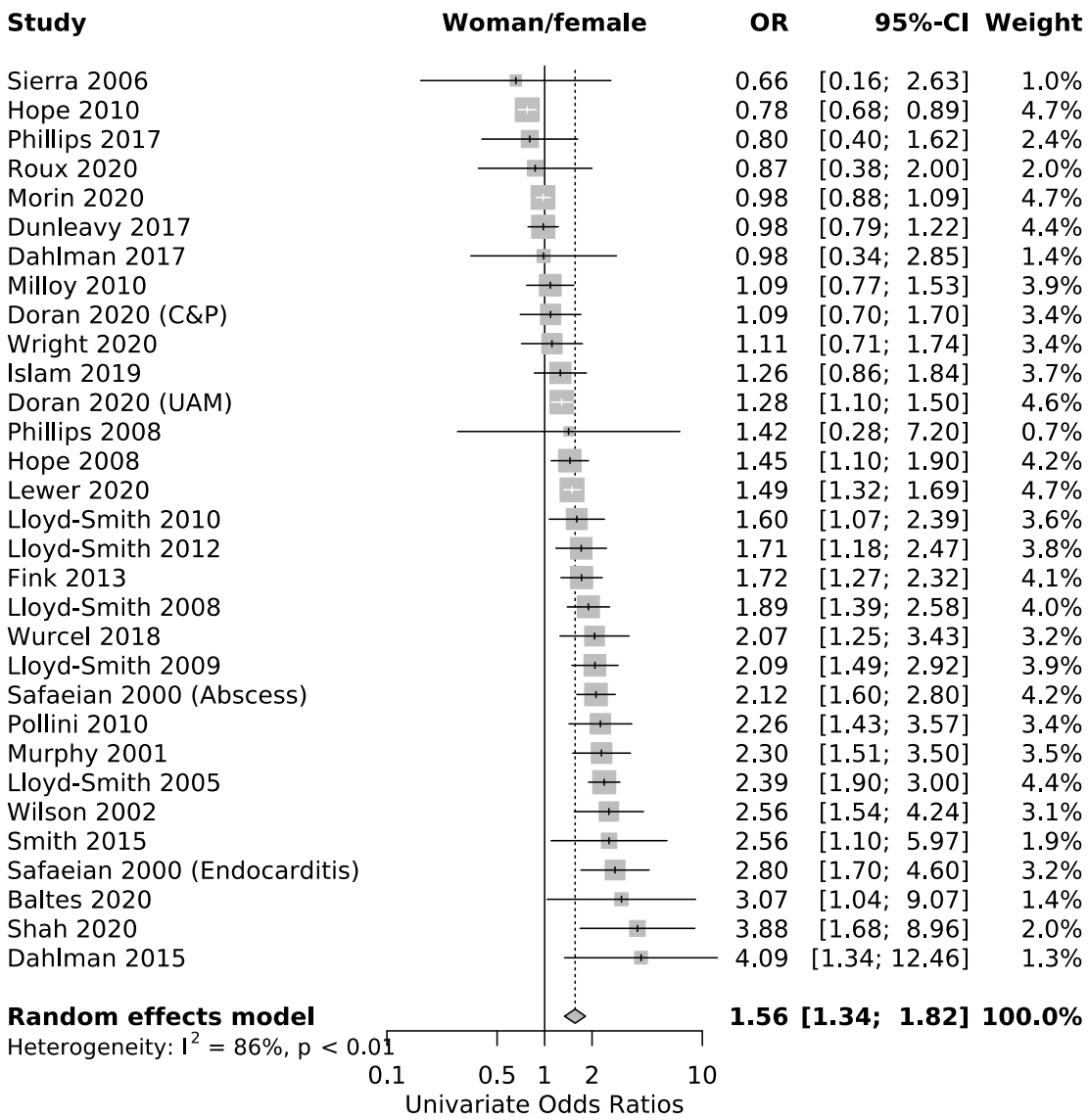

Figure 11. Meta-analysis of univariate effect estimates of relationship between woman/female gender/sex and incident or prevalent injection drug use-associated bacterial infections.

Twenty-two fully-adjusted effect estimates were included in meta-analysis, resulting in an adjusted odds ratio (aOR) of 1.59 (95%CI 1.33-1.89) for woman/female gender (Figure 12). There were two outliers [Morin 2020; Safaeian 2000 (Endocarditis)],[59,246] and removing these changed aOR to 1.57 (95%CI 1.36-1.83; I^2 46.8%, p=0.01).

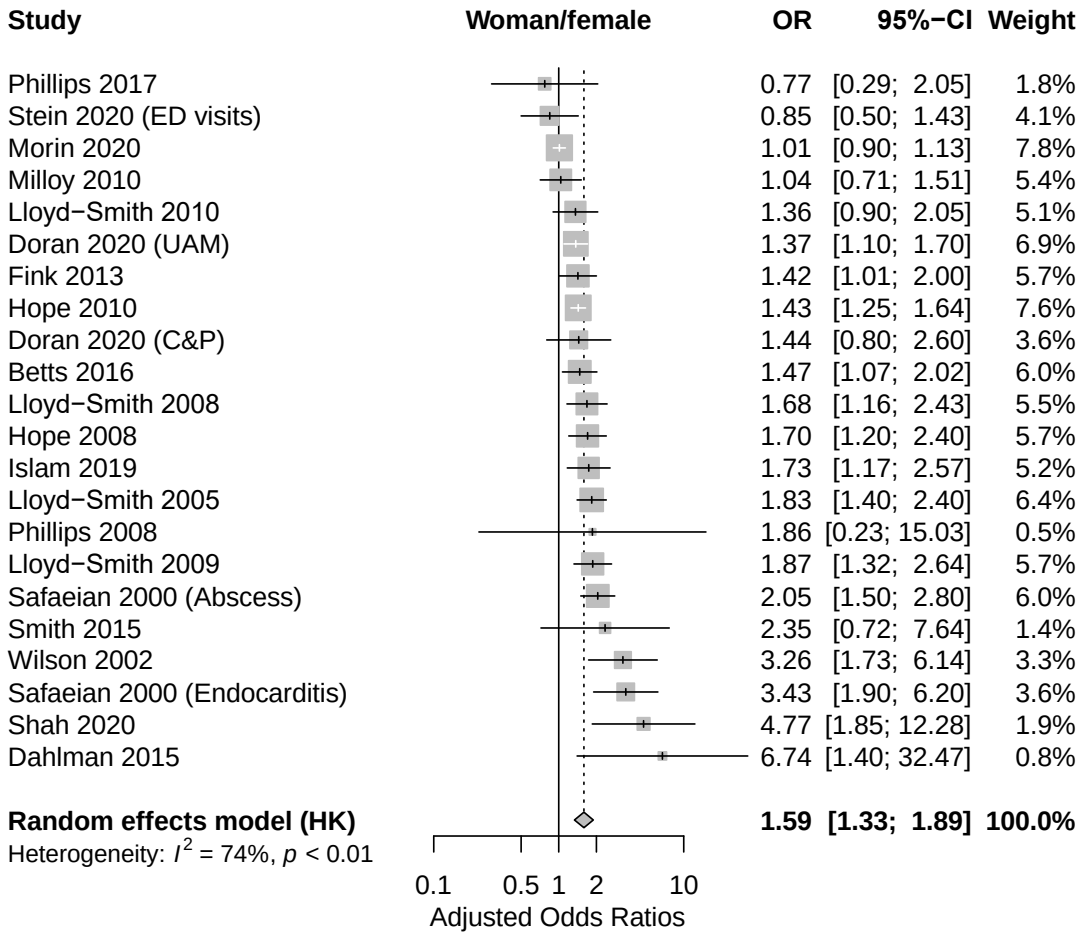

Figure 12. Meta-analysis of fully-adjusted effect estimates of relationship between woman/female gender/sex and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.1.2 Age

Thirty-nine studies reported analyses of age and incident or prevalent infections.[59,63,75,92,99–101,104,125,229–233,236–248,250–261] In most studies, participants were grouped by categories of older vs. younger ages, but definitions varied (e.g., age 30 years or older vs. younger; age 35 years or older vs. younger than 35; increasing age in years, treated continuously). Two studies [Lloyd-Smith 2012; Wurcel 2018] provided only sex-stratified effect estimates, and I included all of these.[236,253]

Summary results for 32 univariate effect estimates for older age (vs. younger) was uOR 1.00 (95%CI 0.96-1.03; Figure 13). Removing 10 outlier effect estimates changed the univariate meta-analysis summary estimate to uOR 1.00 (95%CI 0.99-1.01; I^2 25.3%, p=0.14).

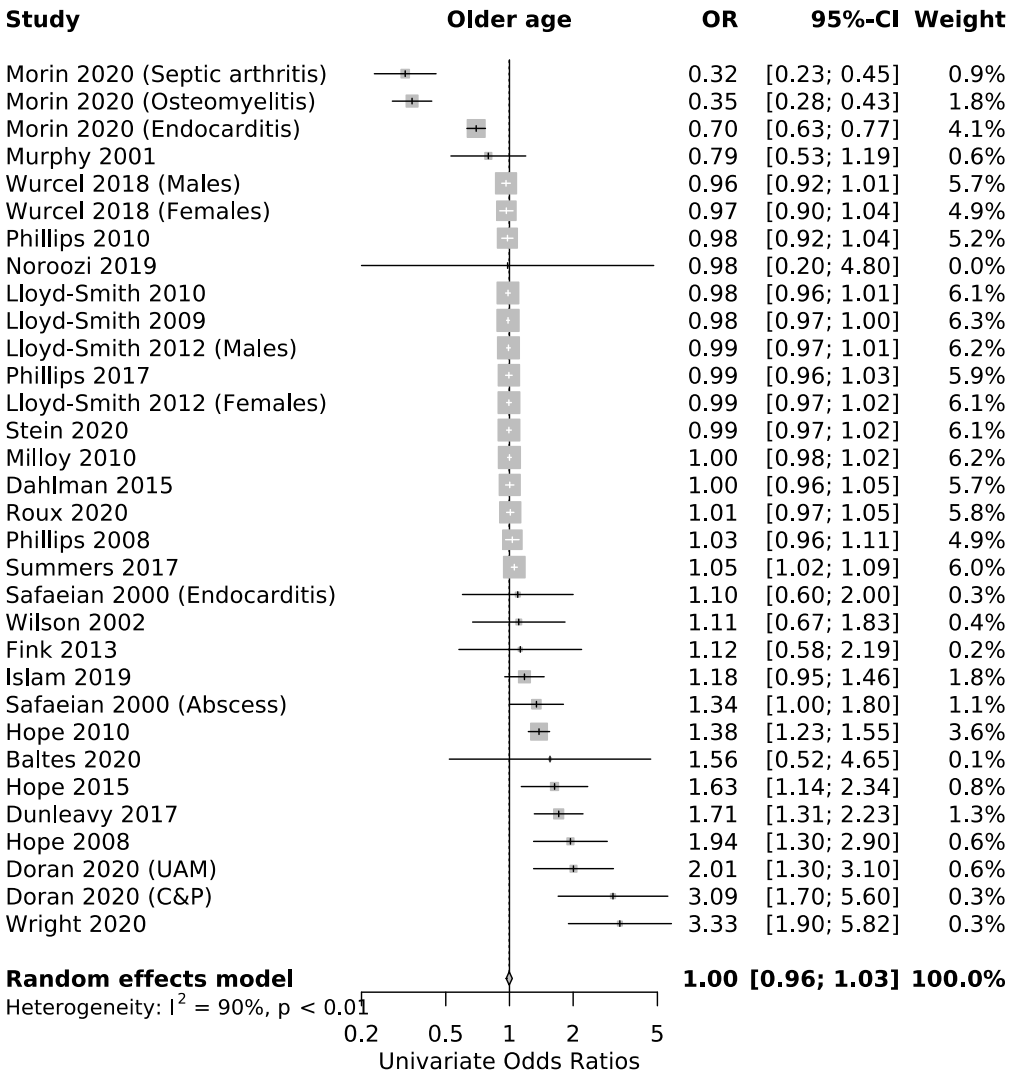

Figure 13. Meta-analysis of univariate effect estimates of relationship between older age and incident or prevalent injection drug use-associated bacterial infections.

Meta-analytic summary for 20 adjusted effect estimates was aOR 0.97 (95%CI 0.76-1.24; Figure 14). Removing seven outlier adjusted effect estimates changed the summary estimate to aOR 1.00 (95%CI 0.89-1.10; I^2 84.1%, p<0.0001).

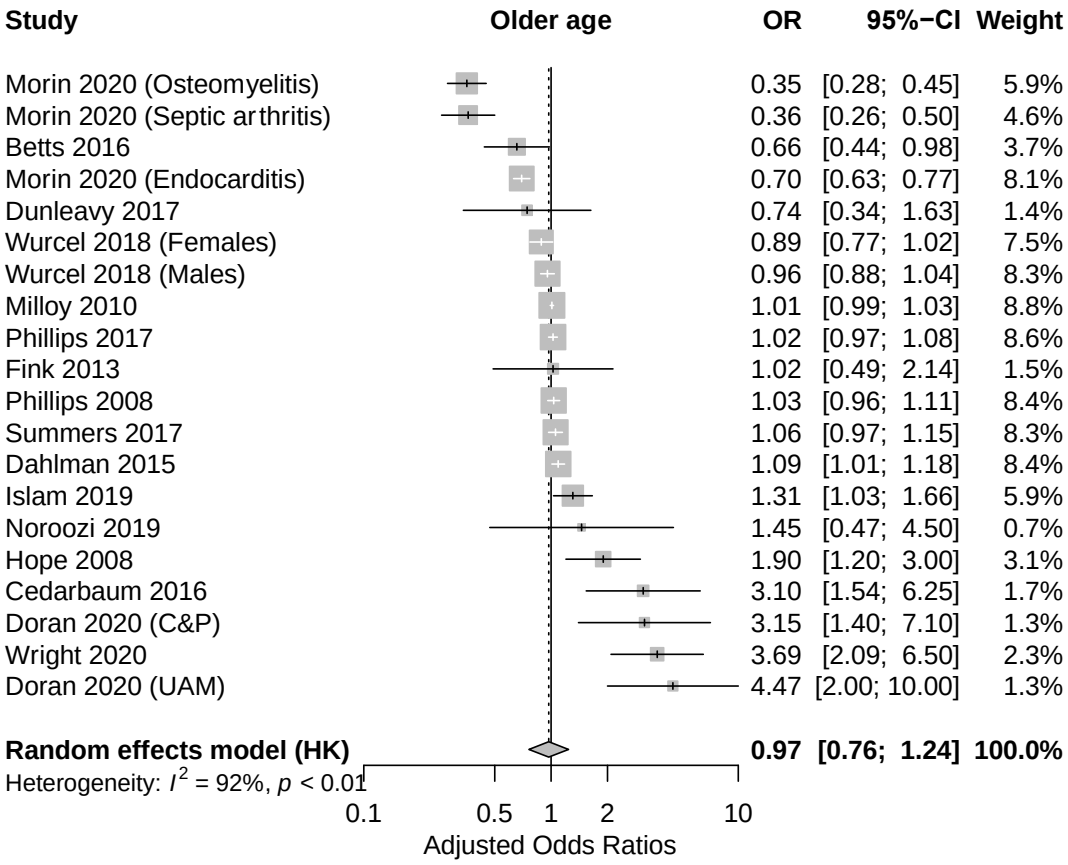

Figure 14. Meta-analysis of fully-adjusted effect estimates of relationship between older age and incident or prevalent injection drug use-associated bacterial infections.

Several of the studies reported age distributions among participants with and without infections, and so were not included in the above meta-analyses of binary effect estimates. In three studies [Pollini 2010[245], Saeland 2014[259]; Sierra 2006[248]] the age distributions did not significantly differ between groups. In one study [Shah 2020][247] participants with endocarditis (mean age 35.5, SD 8.4 years) were younger than participants without (mean age 40.0, SD 11.0 years, p=0.03).

3.5.2.1.3 Race/ethnicity

Seventeen studies included analyses of race/ethnicity and risk of incident or prevalent injecting-related bacterial infections.[63,100,231,232,240,241,243,244,246,247,249,250,253,256,258,260] Most samples were majority white participants (sometimes defined as "non-Hispanic white"), and as a result most investigators compared risk among white participants to non-white participants (which among various studies included Black, Indigenous, and Latino participants). Few studies described explicitly how participants' race was identified (i.e., if it was self-reported or presumed by the researcher).

Among 18 univariate effect estimates, meta-analysis summary for white race vs. non -white was uOR 0.99 (95%CI 0.97-1.01). Since Cooper 2005 was an ecological study (i.e., the exposure was proportion of neighbourhood residents that were non-Hispanic white, rather than an individual-characteristic), I repeated the meta-analysis without Cooper 2005. Cooper 2005 had also contributed >98% of the weighting in meta-analysis. The updated summary uOR was 1.14 (95%CI 0.90-1.44; Figure 15). Among 12 fully-adjusted effect estimates the summary aOR was 0.99 (95%CI 0.98-1.00). Without Cooper 2005, this changed to aOR 1.15 (95%CI 0.92-1.44; Figure 16).

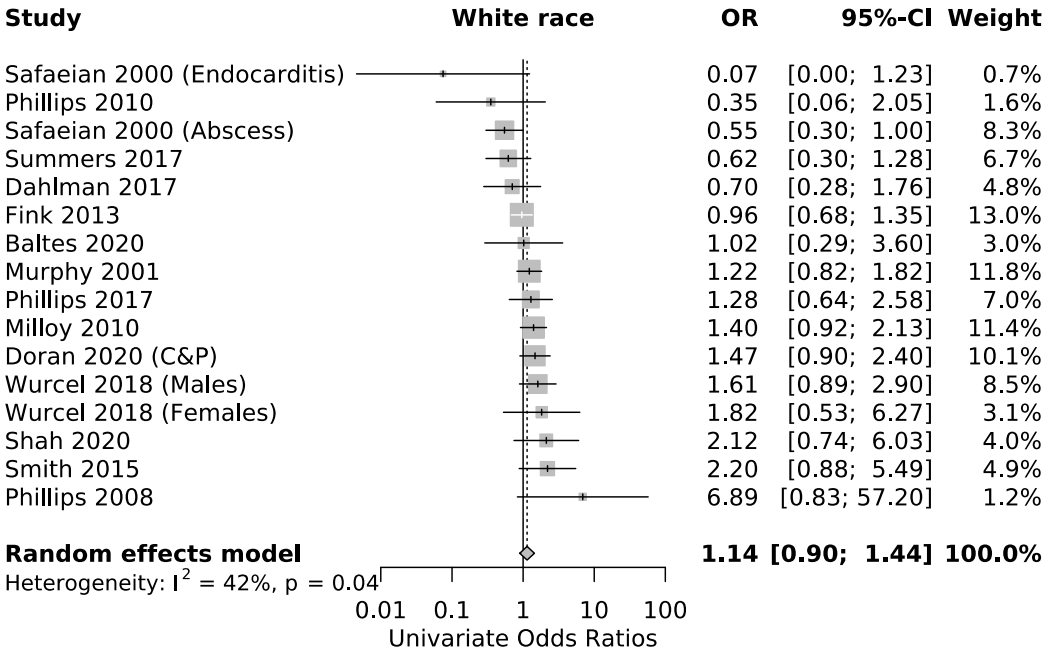

Figure 15. Meta-analysis of univariate effect estimates of relationship between white race (vs. other races) and incident or prevalent injection drug use-associated bacterial infections. (Without Cooper 2005.)

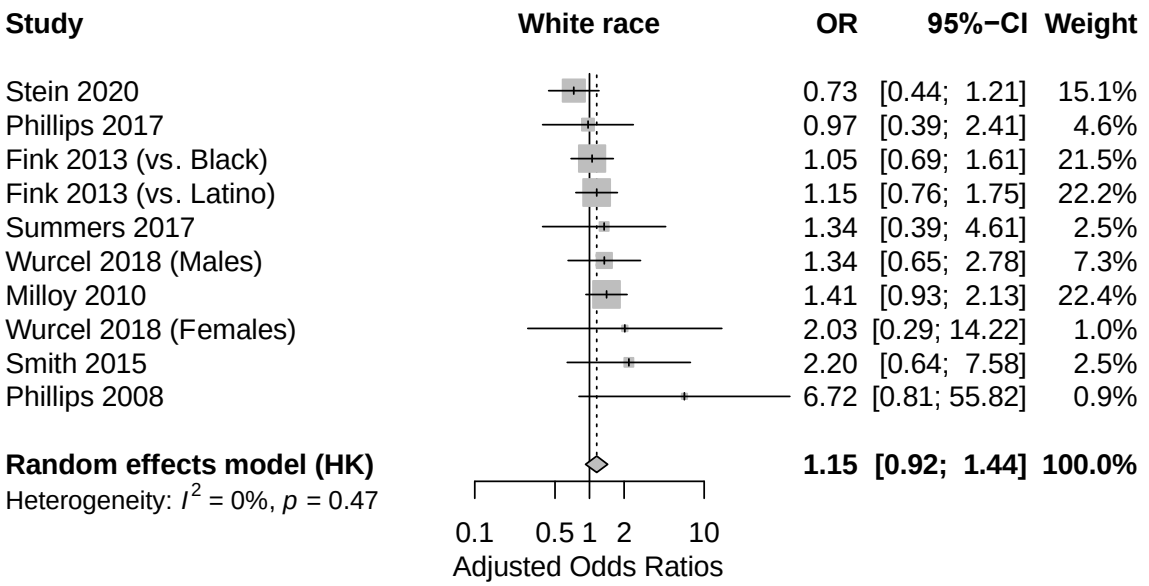

Figure 16. Meta-analysis of fully-adjusted effect estimates of relationship between white race (vs. other races) and incident or prevalent injection drug use-associated bacterial infections. (Without Cooper 2005.)

3.5.2.1.4 Education

In eleven studies, investigators assessed relationships between level of education and incident or prevalent injecting-related bacterial infections.[100,229,241–243,246,247,251,253,257,259] Most studies compared a binary measure of more vs. less years of education (typically, completing secondary school vs. did not complete secondary school). Eleven univariate effect estimates were available for inclusion in meta-analyses, and the summary was uOR 0.98, 95%CI 0.80-1.21; Figure 17). Two studies [Shah 2020[247]; Phillips 2017[243]] were outliers. After removing these, summary odds ratio was uOR 0.87 (95%CI 0.76-0.99; I^2 0.0%, p=0.6). There were four fully-adjusted effect estimates, and the meta-analytic summary was aOR 0.86 (95%CI 0.13-5.55; Figure 18).

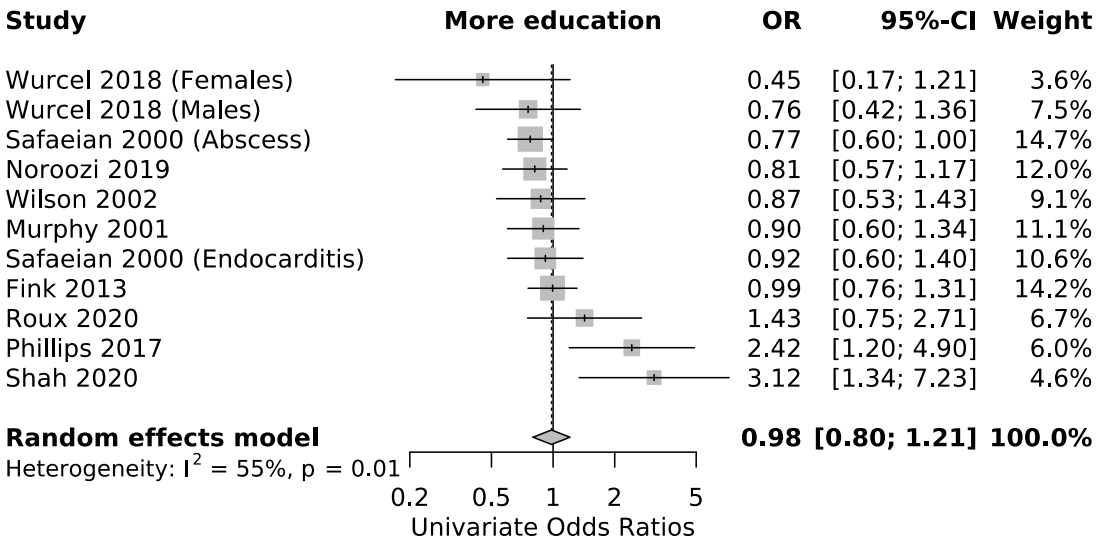

Figure 17. Meta-analysis of univariate effect estimates of relationship between greater educational attainment and incident or prevalent injection drug use-associated bacterial infections.

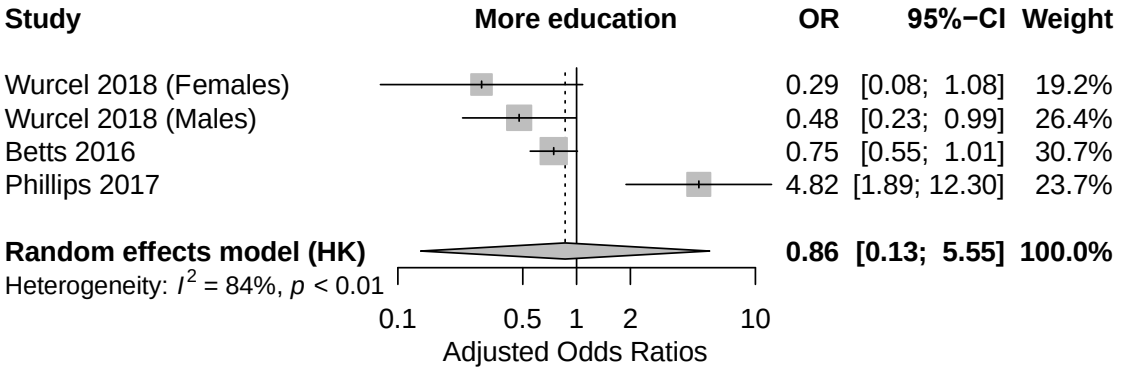

Figure 18. Meta-analysis of fully-adjusted effect estimates of relationship between greater educational attainment and incident or prevalent injection drug use-associated bacterial infections.

One study [Saeland 2014][259] reported distributions of years in school among people with abscess (median 11; IQR 9-13 years) and people without (median 11 ; IQR 9-12 years; p=0.6).

3.5.2.1.5 Income/employment

Thirteen studies reported assessments between income or employment and injecting-related bacterial infections.[59,75,125,137,232,241,242,245–247,256,257,260] In most studies, investigators treated lower income, poverty, unemployment, or illicit/illegal income generation as exposed and higher income/legal employment as the referent group. Meta-analysis of 16 univariate effect estimate resulted in summary uOR 1.44 (95% 1.22-1.71; Figure 19) for lower income and unemployment or

illicit/illegal work vs. higher income and employment or legal work. Meta-analysis of 7 fully-adjusted effect estimates resulted in summary aOR 1.16 (95%CI 0.81-1.65; Figure 20).

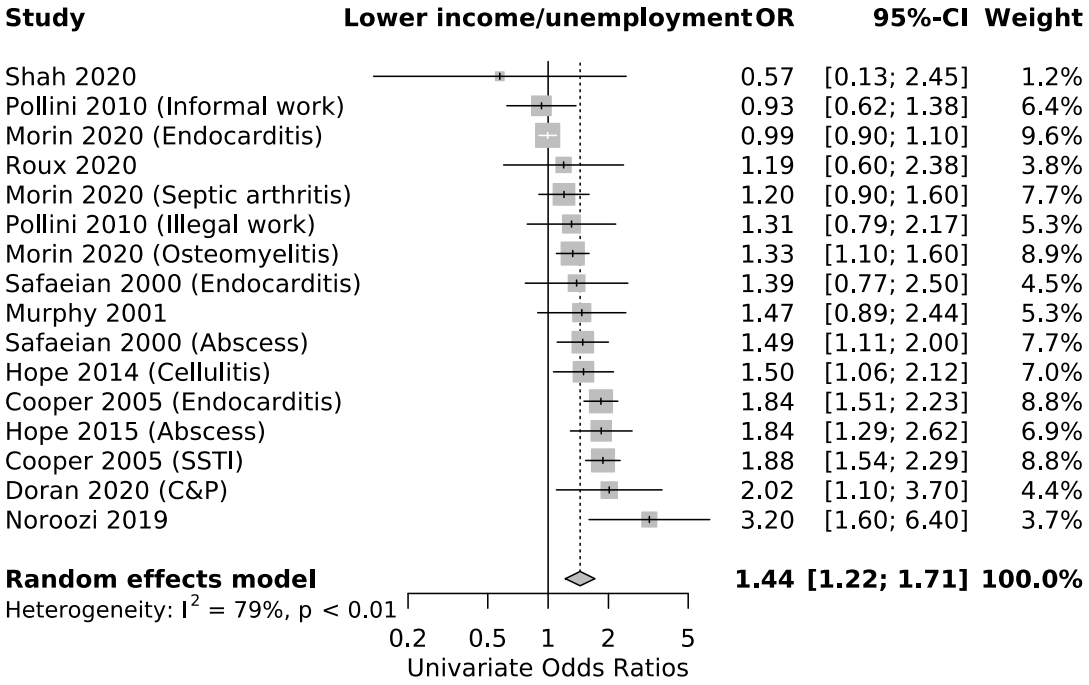

Figure 19. Meta-analysis of univariate effect estimates of relationship between lower income/unemployment and incident or prevalent injection drug use-associated bacterial infections.

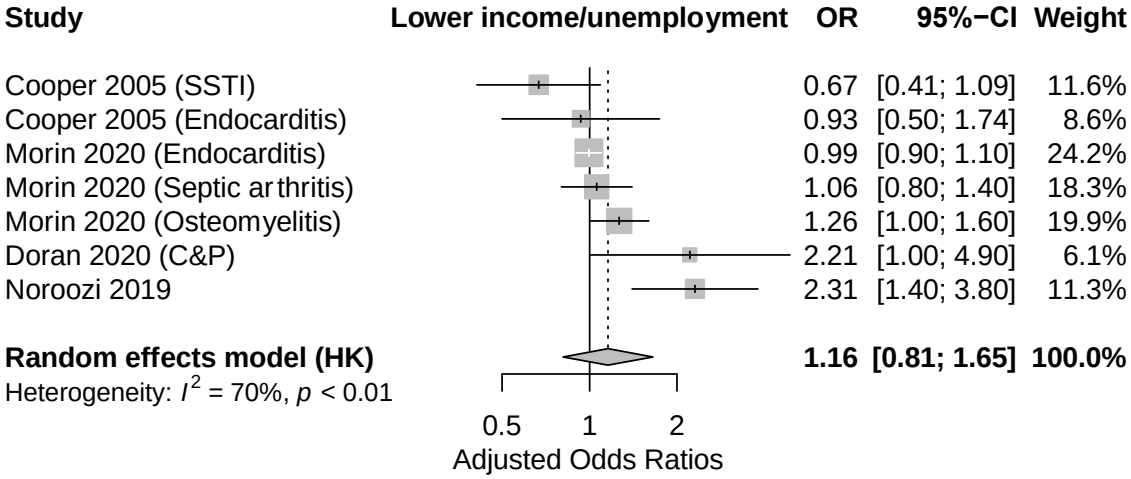

Figure 20. Meta-analysis of fully-adjusted effect estimates of relationship between lower income/unemployment and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.1.6 Relationship status

Two studies assessed associations between relationship status and incident or prevalent injecting-related infections.[242,257] Summary meta-analysis for two univariate effect estimates (for married or

living with spouse, vs. not) was uOR 0.61 (95%CI 0.001-377.0; I^2 83.9%, p=0.01) and one adjusted odds ratio was aOR 0.38 (95%CI 0.17-0.85).

3.5.2.1.7 Migration

Two studies analysed injecting-related infection risk and migration. Doran 2020[232] did not find that people with SSTI in the past year were more likely to be born in the UK vs. outside the UK (uOR 1.2, 95%CI 0.8–1.6). In Hope 2015[75], the number of years lived in the current area was associated with having had abscess in the past year in univariate analyses (e.g., 10.9% among people who had lived in the current area up to 1 year, and 18.7% among people who had lived in the current area more than 20 years, p=0.02). This relationship was reported as "not associated" in fully adjusted analyses (following stepwise regression) in the manuscript. While I am unable to tell from the data presented, it is possible that people who lived the current area for more than 20 years tended to be older than people who lived in the area up to 1 year, and older age was associated with increased risk of abscess in this study. Migration was also "not associated" with cellulitis (no data reported), in a separate analysis in the same study.

3.5.2.2 Social and housing support characteristics

3.5.2.2.1 Incarceration history

I identified 11 studies assessing associations between incarceration history with incident or prevalent injecting-related bacterial infections.[75,92,101,104,125,232,235,240,245,259] Meta-analytic summary for six univariate effect estimates was uOR 1.27 (95%CI 1.06-1.53; Figure 21) and for two fully-adjusted effect estimates was aOR 1.60 (95%CI 0.99-2.59; Figure 22).

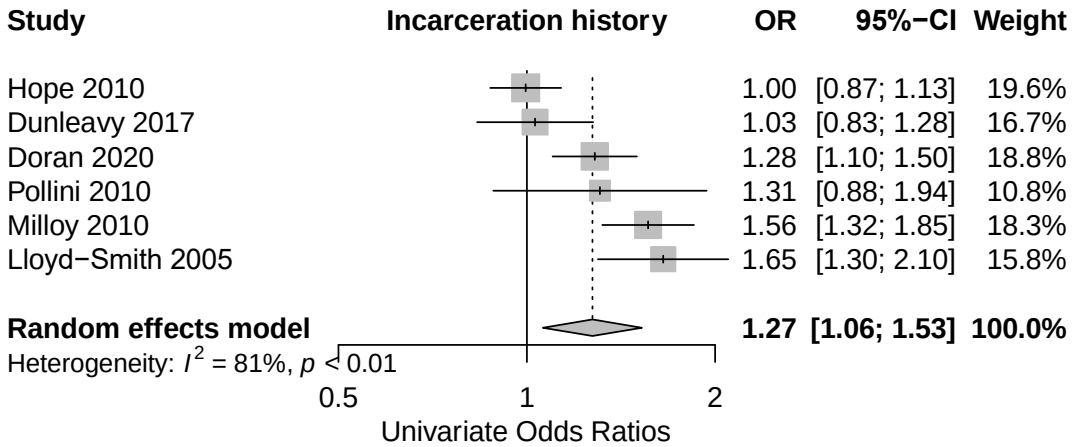

Figure 21. Meta-analysis of univariate effect estimates of relationship between incarceration history and incident or prevalent injection drug use-associated bacterial infections.

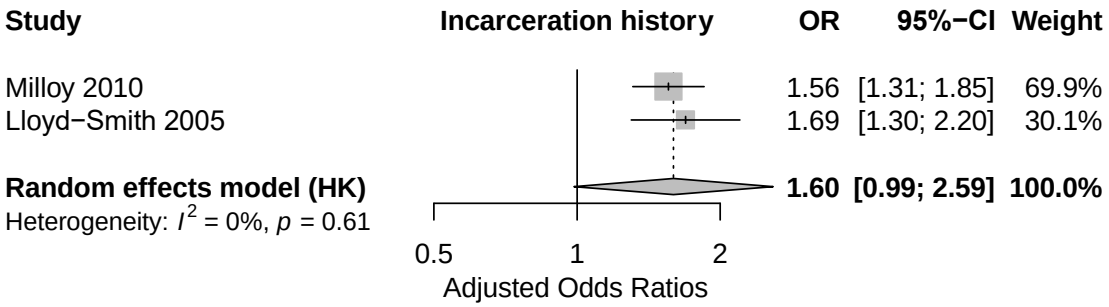

Figure 22. Meta-analysis of fully-adjusted effect estimates of relationship between incarceration history and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.2.2 Sex work

Seven studies assessed relationships between sex work and incident or prevalent injecting-related bacterial infections.[75,232,235,237,240,245,253] The summary odds ratio for nine univariate effect estimates was uOR 1.66 (95%CI 1.09–2.53; Figure 23) and for six fully adjusted effect estimates was aOR 1.58 (95%CI 0.72–3.50; Figure 24). Removing the one outlier [Pollini 2010] changed the summary uOR to 1.49 (95%CI 1.06-2.09, I^2 88.6%, p<0.001)

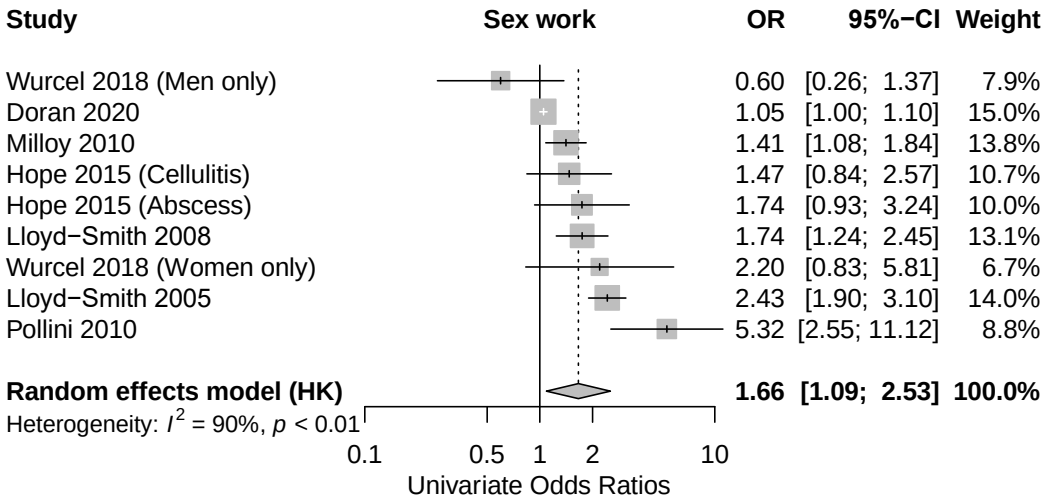

Figure 23. Meta-analysis of univariate effect estimates of relationship between sex work and incident or prevalent injection drug use-associated bacterial infections.

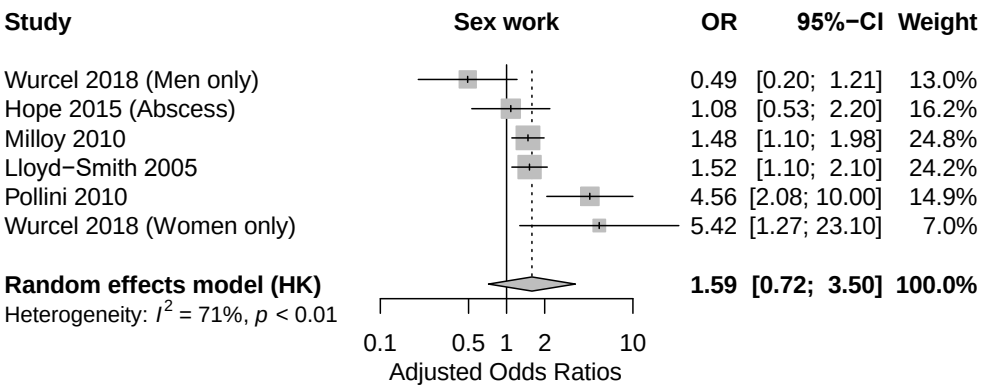

Figure 24. Meta-analysis of fully-adjusted effect estimates of relationship between sex work and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.2.3 Unstable housing and homelessness

There were 31 studies assessing relationships between unstable housing/homelessness and incident or prevalent injecting-related bacterial infections.[75,92,99–101,104,125,229,231,232,235–240,242–245,247–249,251–254,257,258,260,261] The summary odds ratio for 32 univariate effect estimates was uOR 1.34 (95%CI 1.16–1.55; Figure 25). There were three outliers [Fink 2013; Dunleavy 2017; Noroozi 2019][92,100,257]. Removing these changed the summary to uOR 1.34 (95%CI 1.20-1.49; I^2 43.3%, p=0.008).

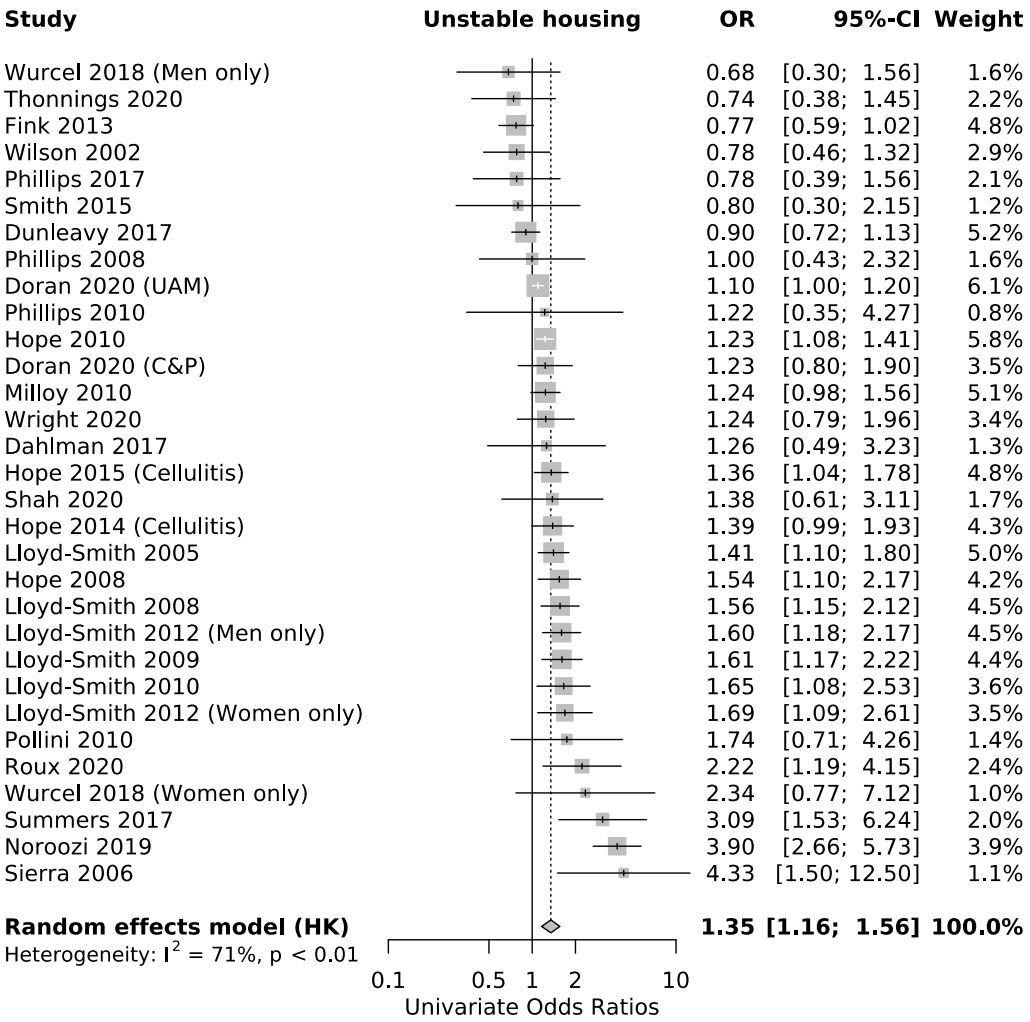

Figure 25. Meta-analysis of univariate effect estimates of relationship between unstable housing and incident or prevalent injection drug use-associated bacterial infections.

Meta-analytic summary for 14 fully adjusted effect estimates was aOR 1.29 (95%CI 1.10–1.50; Figure 26). Removing the single outlier [Wurcel 2018 (Men only)][253], changed the summary to aOR 1.29 (95%CI 1.16-1.45; I^2 8.7%, p=0.4).

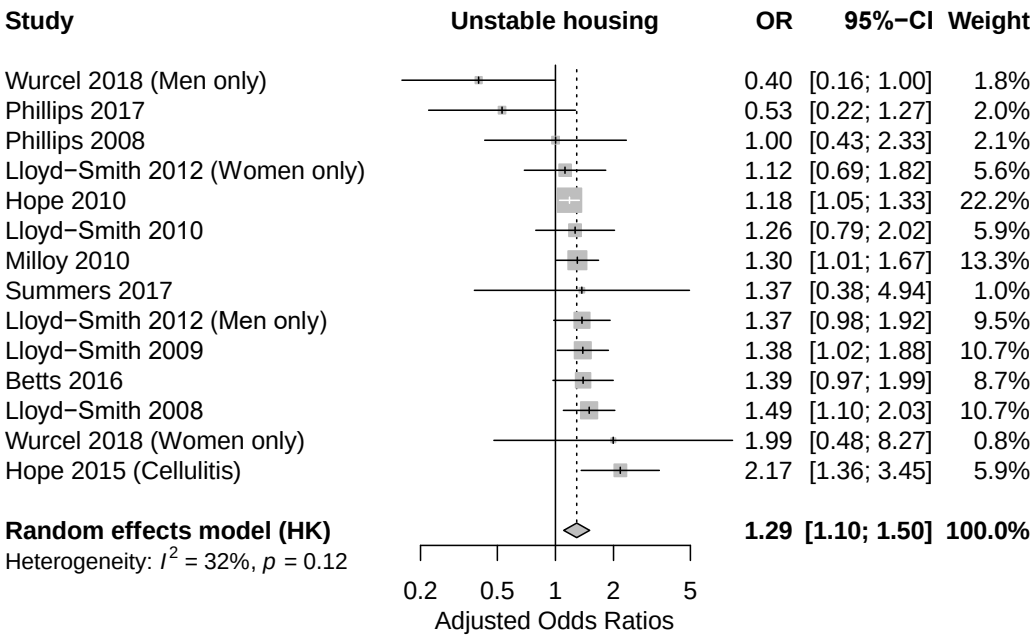

Figure 26. Meta-analysis of fully-adjusted effect estimates of relationship between unstable housing and incident or prevalent injection drug use-associated bacterial infections.

For this analysis, five studies[236–240] used data from the Scientific Evaluation of Supervised Injecting (SEOSI) cohort study in Vancouver, British Columbia, Canada. They reported separate but related outcomes (e.g., self-reported abscess, emergency department visit for injecting-related infection, hospital admission, etc.) for very similar or identical samples of participants. I performed two sensitivity analyses to test the impact of having multiple related estimates from the same sample. Keeping only the earliest study [Lloyd-Smith 2008][237] and removing the rest changed the summary effect estimates to uOR 1.29 (95%CI 1.13-1.47; I^2 72.6%, p<0.0001) and aOR 1.34 (95%1.02-1.75; I^2 42.9%, p=0.09). Keeping only Milloy 2010[240] (which was the only one of these studies where incarceration history was specified in the research question or treated as the main exposure of interest) changed the summary effect estimates to uOR 1.26 (95%CI 1.12-1.43; I2 71.7%, p<0.0001) and aOR 1.29 (95%CI 1.02-1.64; I2 36.3%, p=0.1). In this case, the meta-analyses appeared robust (i.e., remained significant) after removing these additional effect estimates from the SEOSI cohort.

3.5.2.2.4 Food insecurity

One study [Saeland 2014][259] reported two analyses of associations between food insecurity and risk for injecting-related infections. Participants who had a current injecting-related abscess reported fewer meals in the past 24 hours (median 2, IQR 1-3) compared to participants who did not have a current abscess (median 3, IQR 2-4). “Limited access to food” (not otherwise defined) was associated

with an imprecise effect estimate (uOR 1.76; 95%CI 0.84 – 3.68) that could include meaningful differences in risk.

3.5.2.2.5 Health insurance

One study [Baltes 2002][254] assessed health insurance status among people with and without injecting-related SSTI, and estimated an imprecise effect size with a wide confidence interval that could include meaningful differences (uOR 0.79, 95%CI 0.18-3.56).

3.5.2.3 Substance use-related factors

3.5.2.3.1 Overdose history

Three studies[75,125,259] report analyses of associations between overdose history and risk of injecting-related infections. Meta-analysis summary effect estimates for two univariate odds ratios was uOR 2.28 (95%CI 0.42-12.26; Figure 27). For two fully adjusted effect estimates, the summary was aOR 1.87 (95%CI 0.25-14.06; Figure 28).

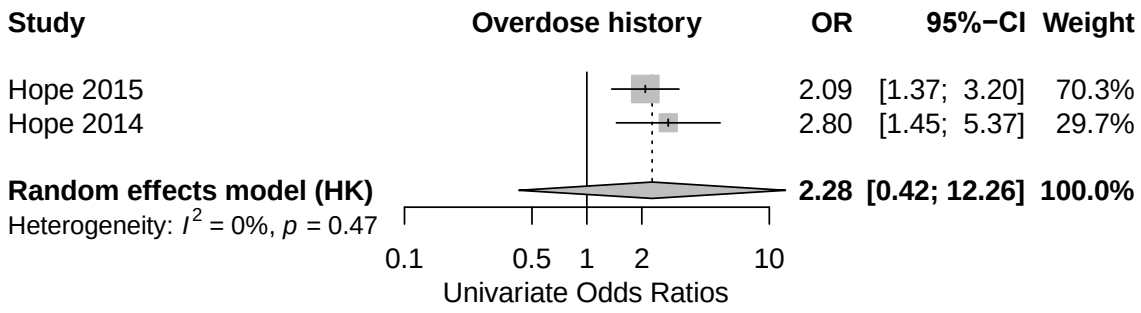

Figure 27. Meta-analysis of univariate effect estimates of relationship between history of overdose and incident or prevalent injection drug use-associated bacterial infections.

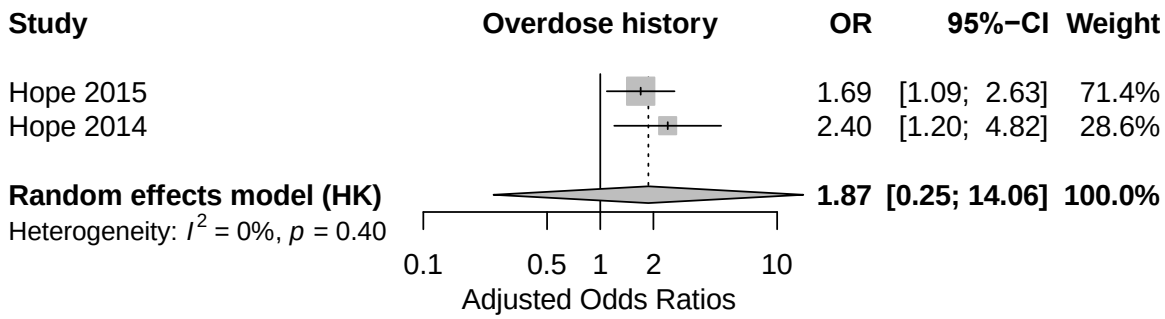

Figure 28. Meta-analysis of fully-adjusted effect estimates of relationship between history of overdose and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.3.2 Heroin type/formulation

Three studies assessed associations between heroin formulation and risk of infection.[137,245,260] One ecological study [Ciccarone 2016][137] across U.S. cities found that the proportion of opiate-related hospital admissions comprising skin and soft-tissue infections was 10.7% in Mexican "tar" heroin-dominant cities vs. 5.2% in Colombian "powder" heroin-dominant cities (p<0.001). Two studies [Pollini 2010; Summers 2017][245,260] assessed individual use of tar vs. powder heroin. Meta-analysis of two unadjusted effect estimates was uOR 7.44 (95%CI 0.31-176.41; Figure 29) and two fully adjusted effect estimates was aOR 3.65 (95%CI 0.0009-15058; Figure 30).

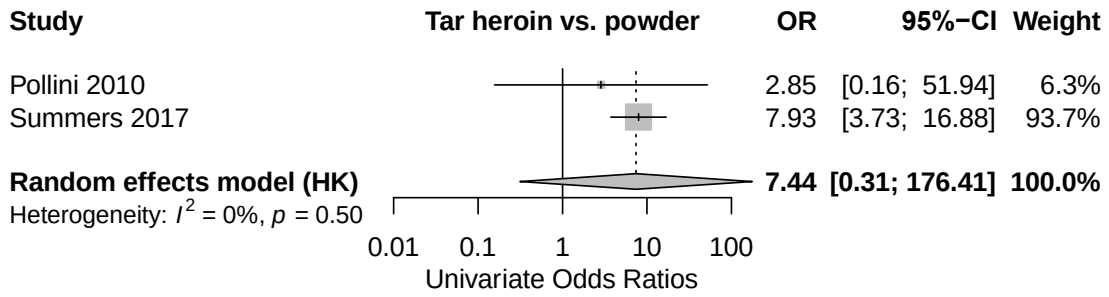

Figure 29. Meta-analysis of univariate effect estimates of relationship between heroin type (tar vs. powder) and incident or prevalent injection drug use-associated bacterial infections.

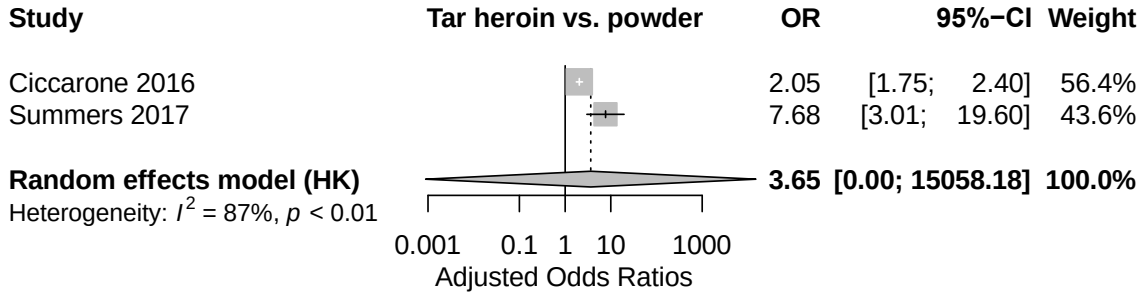

Figure 30. Meta-analysis of fully-adjusted effect estimates of relationship between heroin type (tar vs. powder) and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.3.3 Heroin

Twenty-two studies assessed relationships between heroin use and risk of infections.[75,100,101,125,230,231,235–238,240–242,244,245,247–249,253,254,258,259] Twenty-three univariate effect estimates were eligible for inclusion in meta-analysis, with summary effect estimate of uOR 1.34 (95%CI 1.13-1.61; Figure 31). There were three outliers [Sierra 2006; Milloy 2010; Phillips 2008].[240,244,248] Removing these changed the summary to uOR 1.53 (1.29-1.82; I^2 66.2%, p<0.0001). Heroin use exposures were categorized differently across studies as "heroin is main drug", "any heroin use" (vs. no heroin use), and "frequent heroin use" (e.g., at least daily; vs. less frequent use).

Among these exposure subgroupings, only “any heroin use” (vs. no heroin use) had a statistically significant association with incident or prevalent injecting-related infections. “Heroin is main drug” and “heroin only” had imprecise effect estimates that could include meaningful differences.

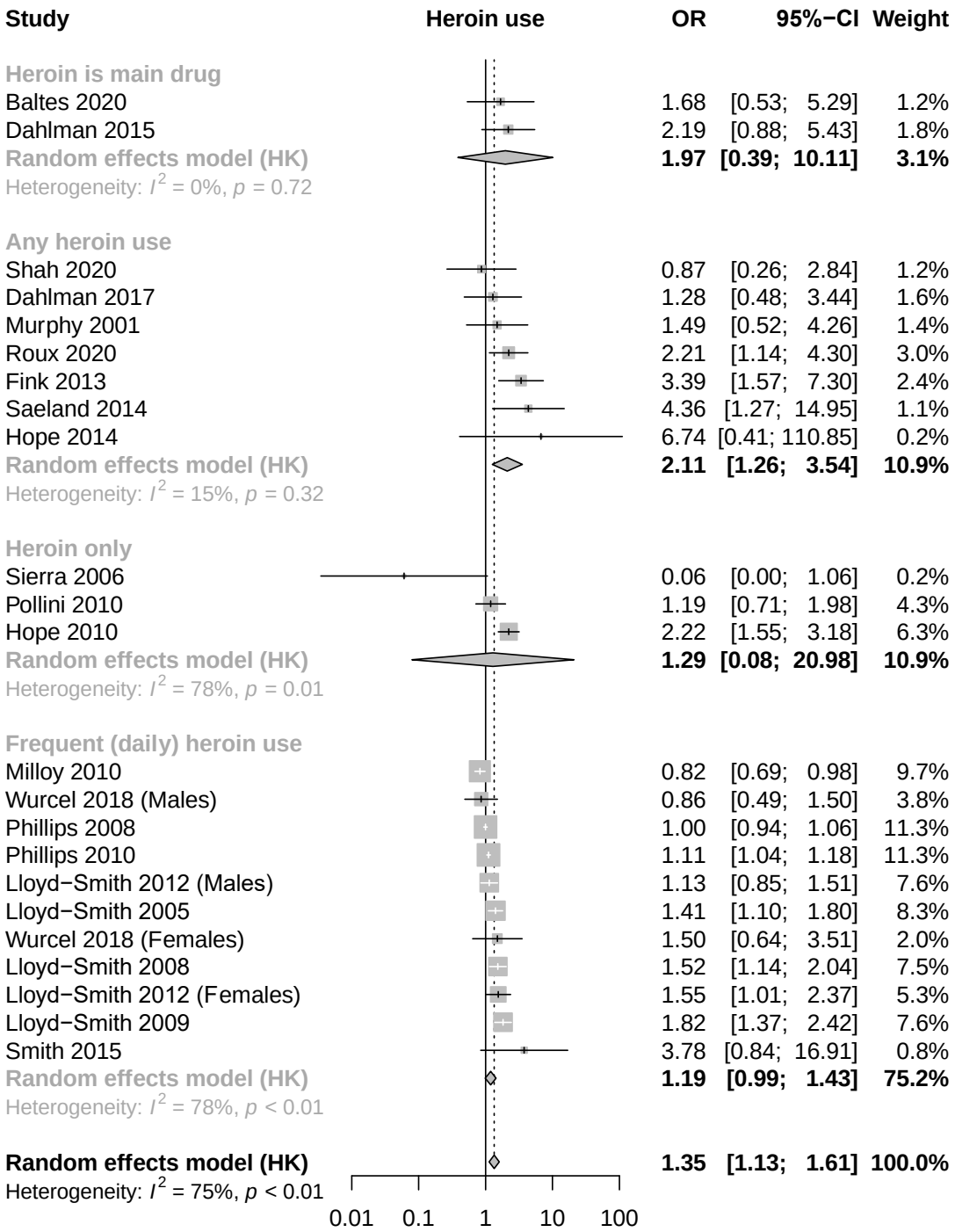

Figure 31. Meta-analysis of univariate effect estimates of relationship between heroin use and incident or prevalent injection drug use-associated bacterial infections.

Among seven adjusted effect estimates, summary was aOR 1.28 (0.95-1.74; Figure 32).

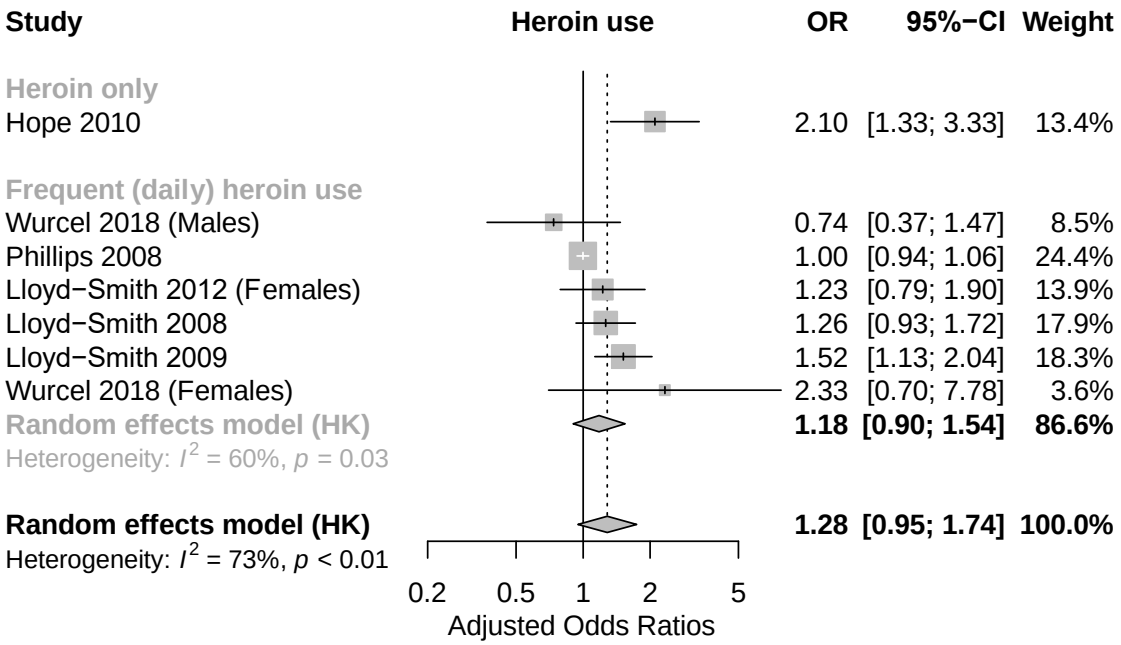

Figure 32. Meta-analysis of fully-adjusted effect estimates of relationship between heroin use and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.3.4 Prescription opioids

Six studies[230,247,254,262,263] assessed relationships between injecting prescription-type opioids (prescription fentanyl, oxycodone, hydromorphone, methadone, or buprenorphine) and development of injecting-related infections.

One study [Shah 2020][247] assessed injecting prescription fentanyl formulations and risk of endocarditis, in a case-control study. Fentanyl patch injection use (uOR 10.1, 95%CI 1.01–100.70) and fentanyl tablet injection use (uOR 0.76; 95%CI 0.08-7.10) were both associated with imprecise effect estimates, but fentanyl patch injection demonstrated statistically significantly elevated risk. I did not identify any studies assessing exposure to unregulated or illicit sources of fentanyl use and risk of infections.

The same study [Shah 2020][247] found no evidence of an association (with imprecise effect estimates) between prevalent injecting-related infections and injection use of oxycodone (uOR 0.83, 95%CI 0.36-1.90), controlled-release hydromorphone capsules (uOR 2.29, 95%CI 0.63-8.29), or immediate-release hydromorphone tablets (uOR 0.59, 95%CI 0.26-1.38). A second study [Silverman 2020][262] (among people with health care administrative codes consistent with injection drug use) found that

compared with people who had recently filled prescriptions for opioids other than hydromorphone, people who filled a prescription for controlled-release hydromorphone had higher rates of injecting-related endocarditis (aOR 3.3, 95%CI 2.1-5.6) while people who filled a prescription for immediate-release hydromorphone did not (aOR 1.7, 95%CI 0.9-3.6).

There were no significant associations between injecting-related infections and injecting methadone identified in three studies [Baltes 2020; Dahlman 2015; Roux 2020][230,242,254], and injecting buprenorphine in one study [Dahlman 2015[230]].

3.5.2.3.5 Cocaine

Twenty-one studies assessed relationships between cocaine injecting and infections.[75,100,104,125,231,235–244,247–249,253,254,264] Thirty univariate effect estimates were eligible for inclusion in meta-analysis, and the summary unadjusted effect estimate was uOR 1.29 (95%CI 1.10-1.51; Figure 33). When categorized by whether the study assessed "crack" cocaine (base) use or powder cocaine (hydrochloride) use, crack use was associated with excess risk (uOR 1.37, 95%CI 1.04-1.82) but powder cocaine was not (uOR 1.19; 95%CI 0.78-1.81). Note that these studies did not compare risks of crack vs. powder use, but instead asked participants whether they used crack or powder vs. did not use crack or powder cocaine. When sub-grouped by frequent (e.g. daily) use vs. less frequent use, summary was uOR 1.29 (95%CI 1.07-1.55); and when grouped by any use vs. no use, summary was uOR 1.26 (95%CI 0.92-1.71).

There were three outliers [Hope 2014 (Crack); Hope 2014 (Powder); Phillips 2008][125,244], and removing these changed the summary uOR to 1.42 (95%CI 1.25-1.61; I^2 49.3%, p=0.003). The updated summary for the crack cocaine subgroup was uOR 1.55 (95%CI 1.33-1.80; I^2 0%, p=0.56) and powder cocaine subgroup was uOR 1.35 (95%CI 1.00-1.83; I^2 46%, p=0.09).

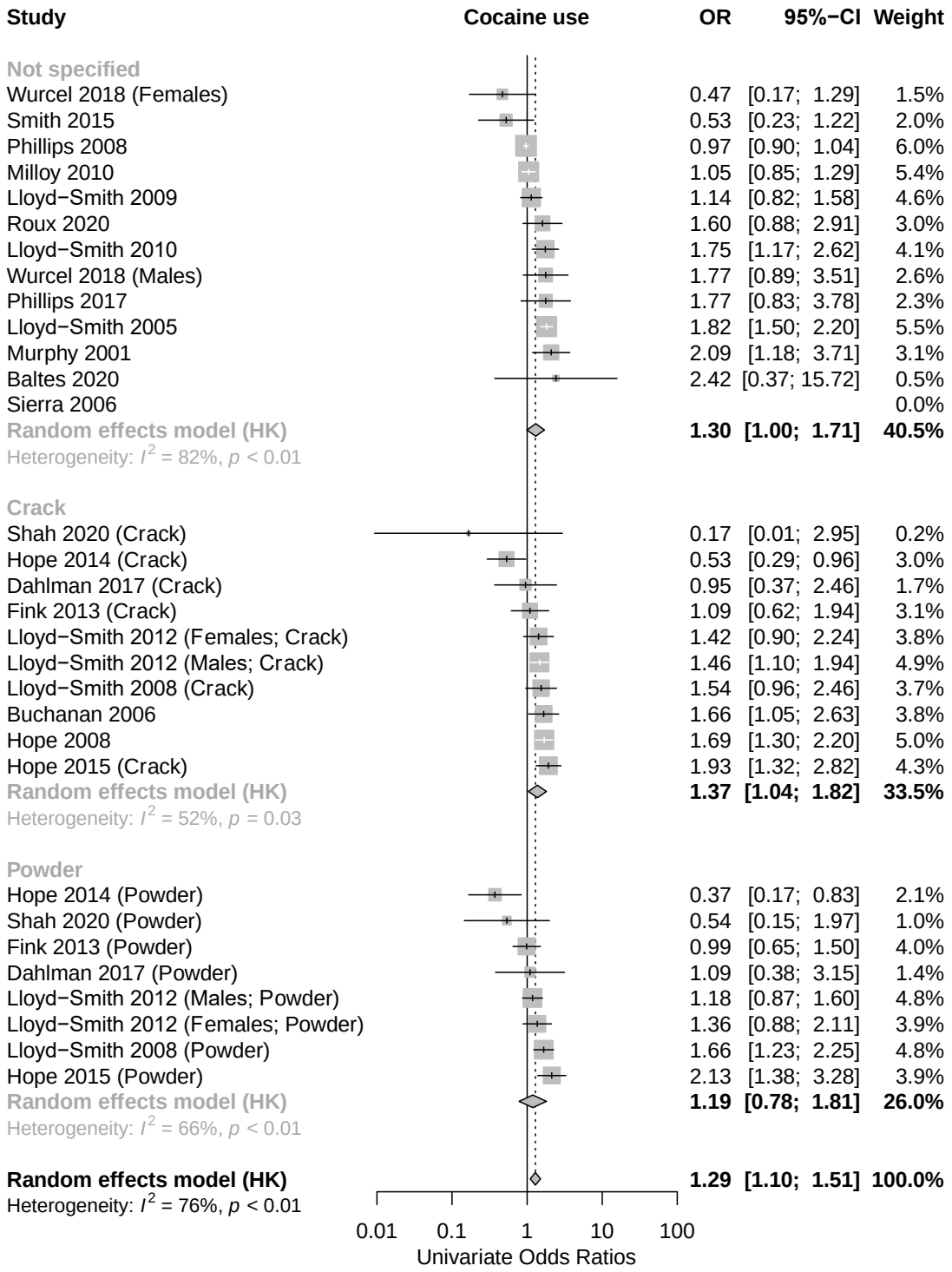

Figure 33. Meta-analysis of univariate effect estimates of relationship between cocaine and incident or prevalent injection drug use-associated bacterial infections. Subgroups by whether study assessed "crack" or "powder" forumluations of cocaine, or did not specify.

Meta-analytic summary for 10 adjusted effect estimates was aOR 1.31 (95%CI 1.02–1.69; Figure 34). When separated by frequency of use, frequent (daily) use vs. less-often was aOR 1.27 (95%CI 0.82-1.99; I2 80%, p<0.01) and any use vs. no use was aOR 1.41 (95%CI 0.92-2.15; I2 17.1%, p=0.3).

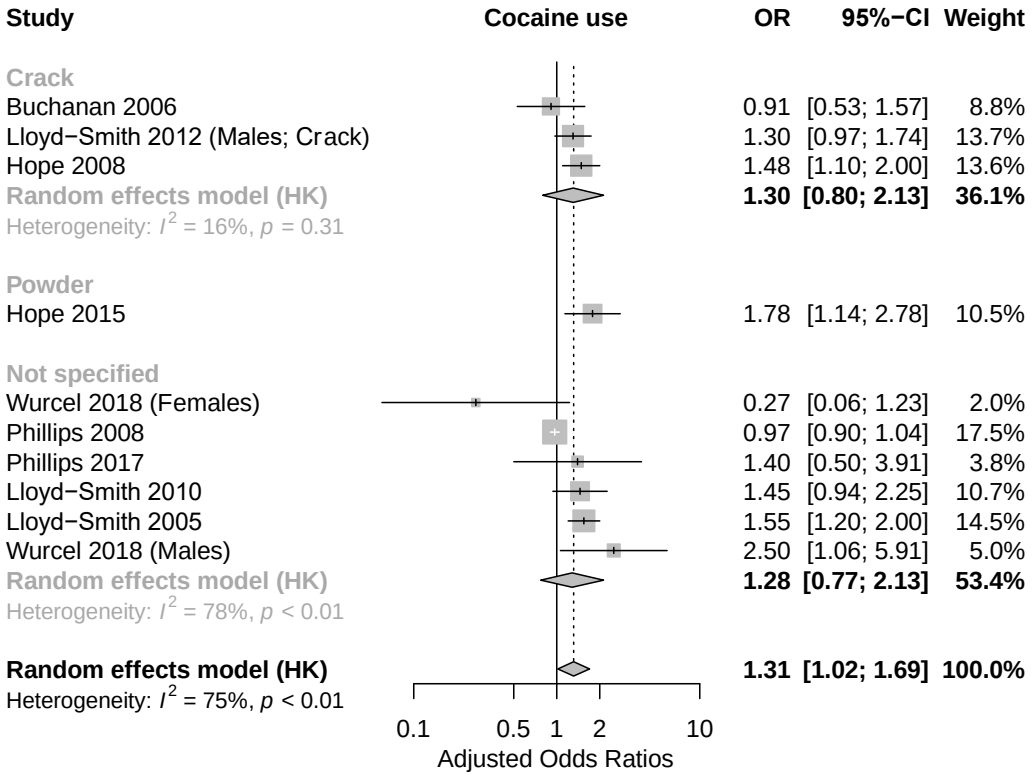

Figure 34. Meta-analysis of fully-adjusted effect estimates of relationship between cocaine and incident or prevalent injection drug use-associated bacterial infections. Subgroups by whether study assessed "crack" or "powder" formulations of cocaine, or did not specify.

3.5.2.3.6 Amphetamines (including methamphetamine)

Fourteen studies assessed unregulated/illicit amphetamines (including methamphetamine) and incident or prevalent injecting-related infections.[75,100,104,125,231,232,237,241,245,247,254,257,259,265] Twelve univariate effect estimates were eligible for inclusion in meta-analysis, with summary uOR 0.81 (95%CI 0.49-1.33; Figure 35). One study [Murphy 2001][241] was an outlier; removing this changed summary to uOR 0.90 (95%CI 0.54-1.48; I^2 82.4%, p<0.0001).

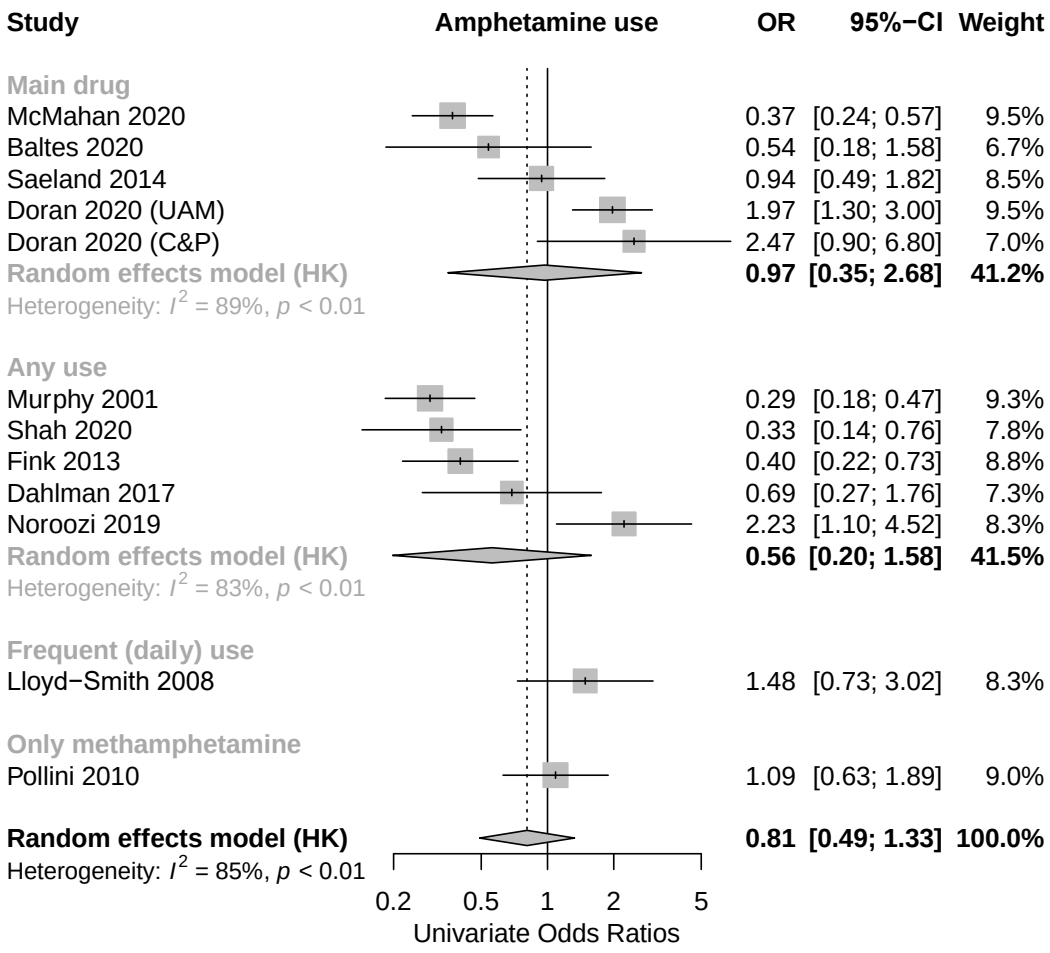

Figure 35. Meta-analysis of univariate effect estimates of relationship between amphetamines (including methamphetamine) and incident or prevalent injection drug use-associated bacterial infections.

Two fully-adjusted effect estimates were eligible for inclusion in meta-analysis, with aOR 1.74 (1.39-2.23; Figure 36).

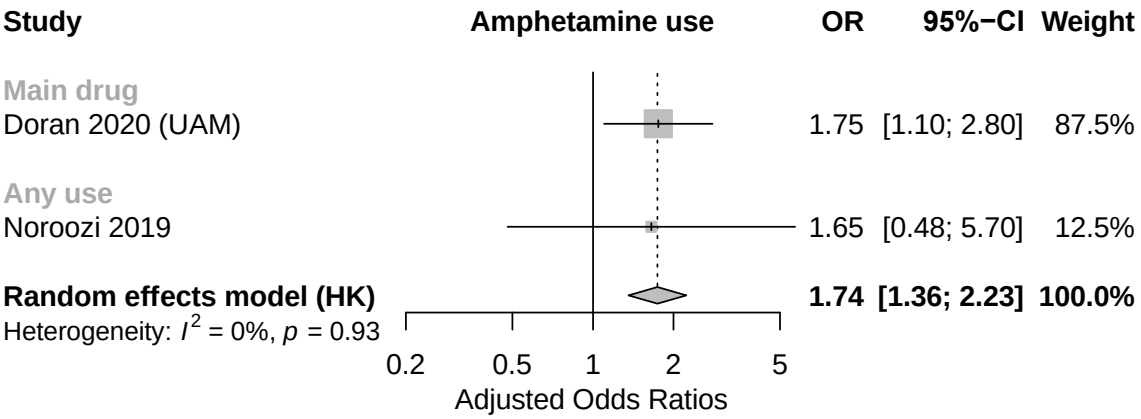

Figure 36. Meta-analysis of fully-adjusted effect estimates of relationship between amphetamines (including methamphetamine) and incident or prevalent injection drug use-associated bacterial infections.

One study [Pollini 2010][245] assessed colour of methamphetamine and past 6-months abscess. For people who used "clear" methamphetamine vs. "other", the effect estimate was uOR 1.37 (95%CI 0.86-2.19).

3.5.2.3.7 Prescription stimulants

Two studies [Dahlman 2015; Shah 2020][230,247] included assessments of relationship between injecting prescription stimulants and injecting-related infections, and did not find evidence of an association with injecting methylphenidate (summary uOR 0.73, 95%CI 0.19-2.82, Figure 37) or bupropion (n=1 study; uOR was infinity, as only one participant reported bupropion injecting and they developed an infection).

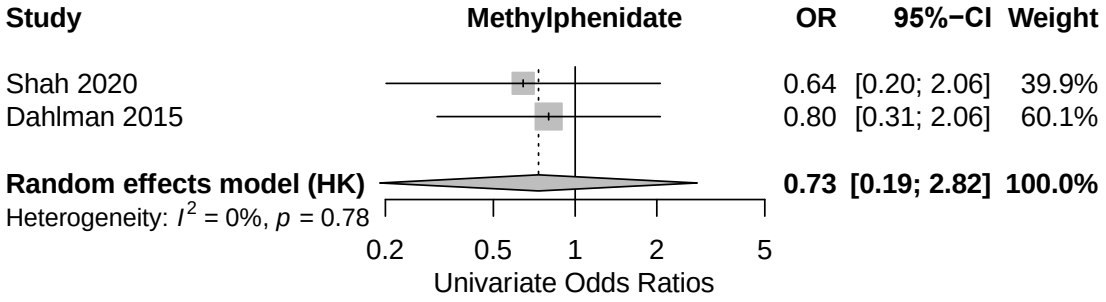

Figure 37. Meta-analysis of univariate effect estimates of relationship between methylphenidate injecting and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.3.8 Novel psychoactive stimulants

Yeung 2017[139] found that people self-reporting use of ethylphenidate (a novel psychoactive stimulant associated with high frequency of injecting) had higher weekly rates of S. pyogenes or S. aureus infections compared to people who did not report use of ethylphenidate (aRR 1.81, 95%CI 1.12-2.93).

3.5.2.3.9 Speedball (cocaine and heroin together) and goofball (methamphetamine and heroin together)

Nine studies assessed use of speedball or goofballs and injecting-related infections.[100,231,236,238–241,249,258] Twelve eligible univariate effect estimates had summary uOR 1.33 (95%CI 1.15-1.55; Figure 38). When separated, goofball (n=2; uOR 1.22, 95%CI 0.98-1.52) and speedball (n=10; uOR 1.38, 95%CI 1.15-1.65) summary estimates had similar point estimates. Two fully adjusted effect estimates for speedball use had summary aOR 1.35 (95%CI 0.38-4.77; I^2 0.0%, p=0.6).

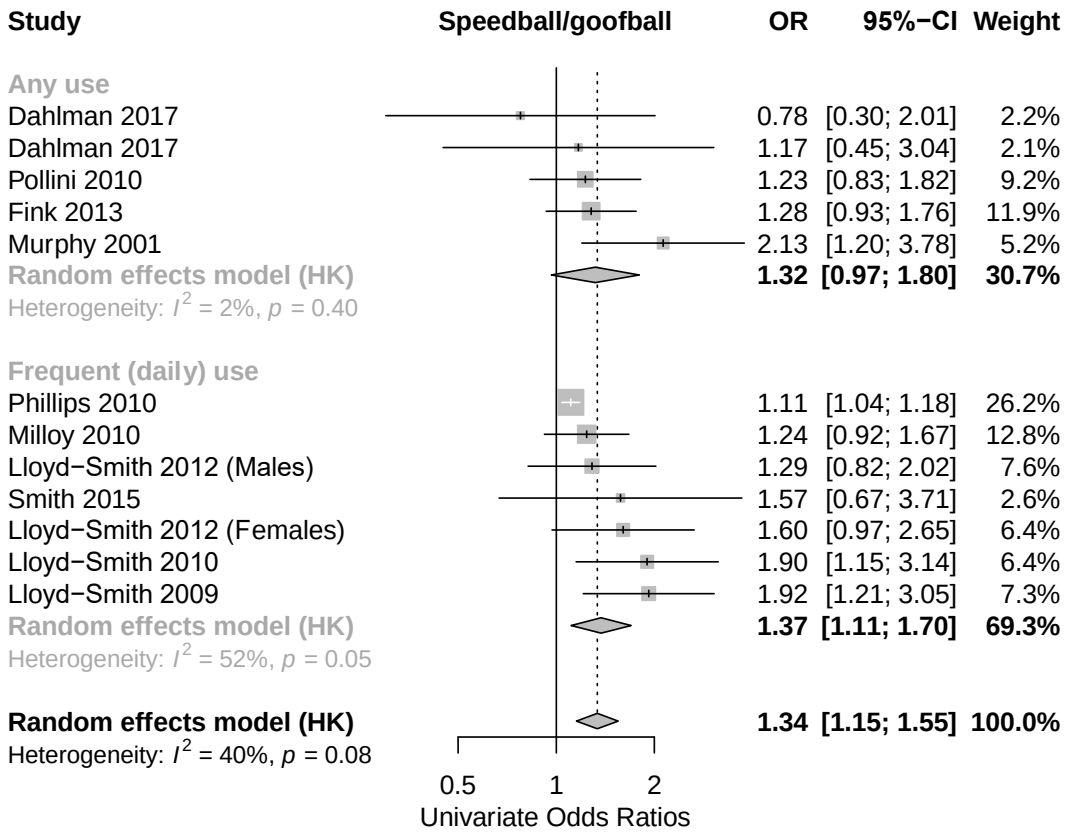

Figure 38. Meta-analysis of univariate effect estimates of relationship between speedball/goofball injection and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.3.10 Alcohol use

Seven studies assessed relationships between alcohol use and incident or prevalent infections.[92,241–244,246,251] When seven eligible univariate effect estimates were combined in meta-analysis, summary uOR was 0.94 (95%CI 0.77-1.14; Figure 39). Alcohol use exposures included "any" use or measures of hazardous alcohol use (e.g., Alcohol Use Disorders Identification Test [AUDIT]). Three eligible fully-adjusted effect estimates were combined in meta-analysis, with summary aOR 0.59 (95%CI 0.13-2.67; Figure 40). All of these studies assessed measures of hazardous alcohol use.

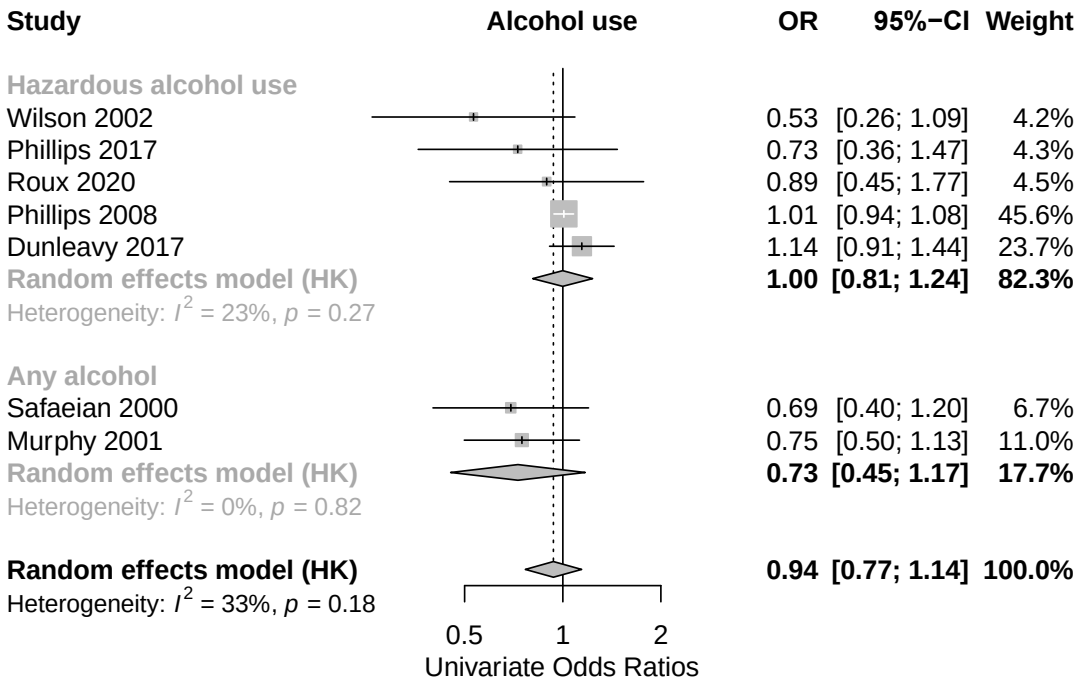

Figure 39. Meta-analysis of univariate effect estimates of relationship between alcohol use and incident or prevalent injection drug use-associated bacterial infections.

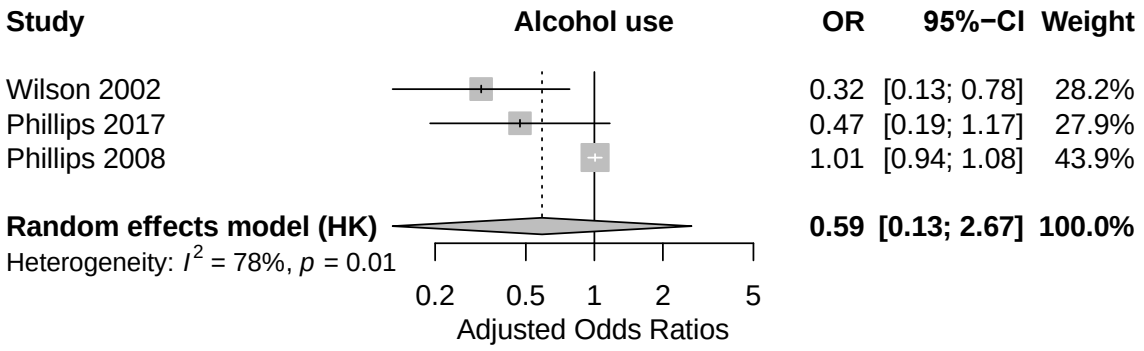

Figure 40. Meta-analysis of fully-adjusted effect estimates of relationship between alcohol use and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.3.11 Smoking

Four studies assessed relationships between smoking substances and incident or prevalent injecting-related infections. Three studies included univariate effect estimates for cigarette smoking and injecting-related infections. Murphy 2001 (uOR 1.73; 95%CI 0.79-3.79) and Safaeian 2000 (uOR 0.6; 95%CI 0.3-1.2) did not find evidence of an association between smoking with abscess and endocarditis, respectively. In the same sample, Safaeian 2000 found an association between cigarette smoking and abscess (aOR 1.8; 95%CI 1.1-3.2).

Pollini 2010 found people who smoked methamphetamine were more likely to report having had an abscess (aOR 1.65; 95%CI 1.05-2.62), and Saeland 2014 did not find evidence of a relationship between smoking cannabis and current abscess (uOR 1.16; 95%CI 0.60-2.25).

3.5.2.4 Drug policy and injecting context

3.5.2.4.1 Drug policy change

Four studies assessed the impact of drug policy changes on risk of injecting-related infections.[139,263,266,267] DiGiorgio 2019[266] and Nagar 2015[267] assessed the impact of state-wide opioid prescribing restrictions on rates of hospital admissions for injection drug use-associated spinal epidural abscess in Louisiana and Kentucky, respectively. In both states, increases were seen after state-wide restrictions on opioid prescribing – both thought to be due to people switching from prescription oral pills to injecting heroin when they could no longer access prescription tablets. Weir 2019[263] found no relationship between delisting of extended-release oxycodone in Ontario and the proportion of hospital admissions for endocarditis attributable to injection drug use. Yeung 2017[139] found no immediate step-change but a gradual trend reduction in the weekly rate of *S. pyogenes* and *S. aureus* infections associated with injection drug use in Lothian, Scotland, after a temporary class order on ethylphenidate (a novel psychoactive stimulant associated with high frequency of injecting).

3.5.2.4.2 Drug purchasing network

One case-control study [Sierra 2006][248] assessed drug purchasing networks as part of an outbreak investigation into invasive *S. pyogenes* infections in Barcelona. Exposures including purchasing from one drug seller who was likely colonized (uOR 73, 95%CI 8-3090) and purchasing drugs from one physical location where this drug seller worked (uOR 34, 95%CI 7-175).

3.5.2.4.3 Injecting in public

I identified four studies reporting analyses of associations between public injecting and risk of injecting-related bacterial infections.[140,231,240,242] The summary odds ratio for four univariate effect estimates was uOR 1.54 (95%CI 1.27-1.86; Figure 41) and for two fully adjusted effect estimates was aOR 1.40 (95% CI 1.05–1.88; Figure 42).

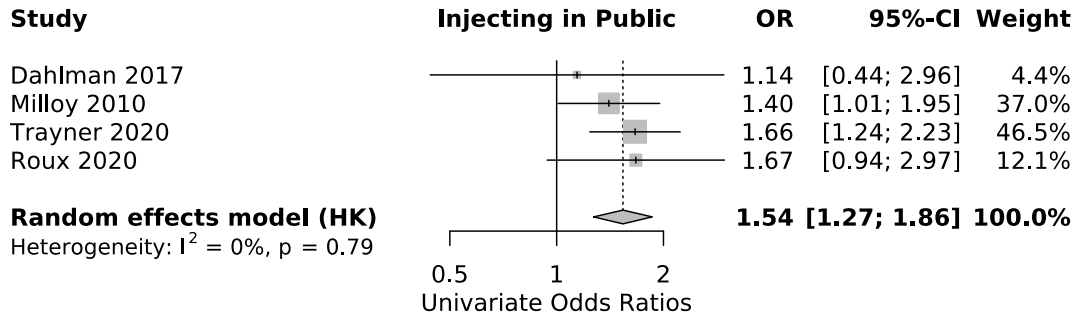

Figure 41. Meta-analysis of univariate effect estimates of relationship between public injecting and incident or prevalent injection drug use-associated bacterial infections.

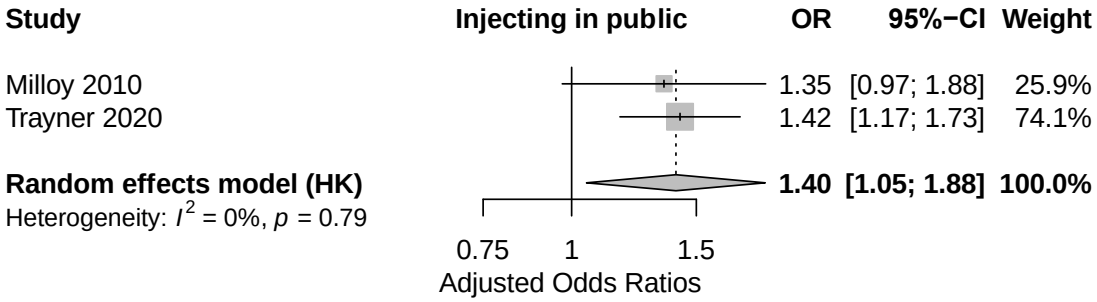

Figure 42. Meta-analysis of fully-adjusted effect estimates of relationship between public injecting and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.4.4 Shooting galleries

Two studies assessed associations between use of "shooting galleries" (central locations where people can rent or borrow needles and syringes, and inject) and risk for injecting-related infections.[244,245] Meta-analysis summary for two univariate effect estimates was uOR 0.84 (95%CI 0.17–4.02; Figure 43). One fully adjusted effect estimate from Phillips 2008[244] was aOR 1.33 (95%CI 0.31–5.73).

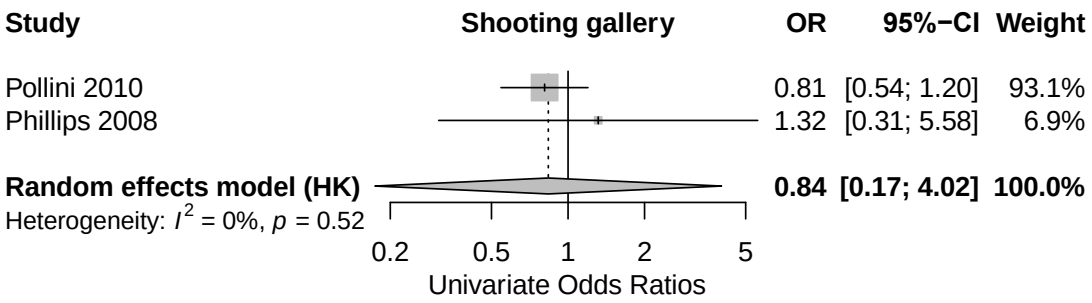

Figure 43. Meta-analysis of univariate effect estimates of relationship between "shooting gallery" use and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.4.5 Police contacts and arrests

I identified four studies reporting analyses of associations between policing contacts (including arrests) and incident injecting-related bacterial infections.[75,125,245,256] The meta-analytic summary for nine univariate effect estimates was uOR 1.16 (95%CI 0.85-1.59; Figure 44) and for four fully adjusted effect estimates was aOR 1.19 (95%CI 0.61-2.31; Figure 45).

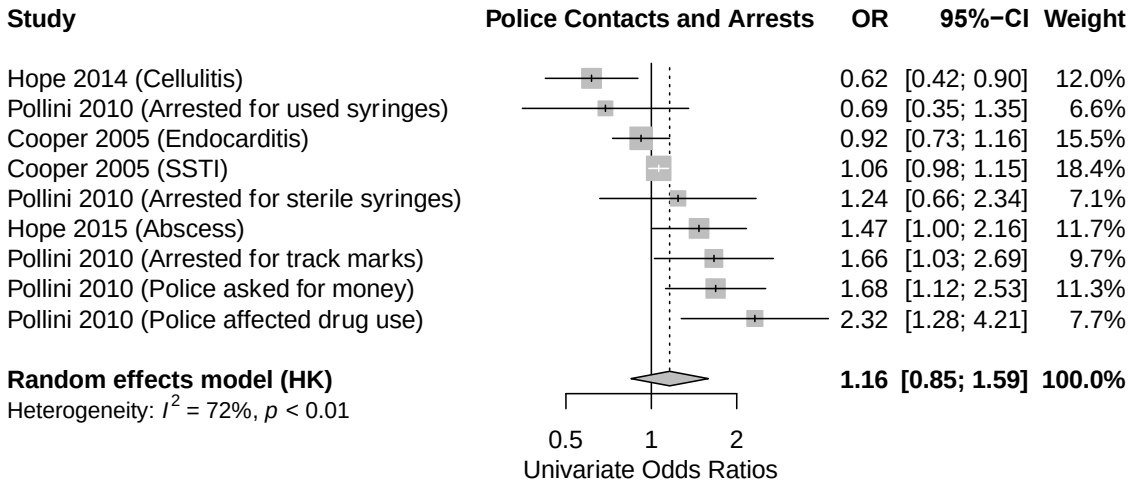

Figure 44. Meta-analysis of univariate effect estimates of relationship between police contacts and incident or prevalent injection drug use-associated bacterial infections.

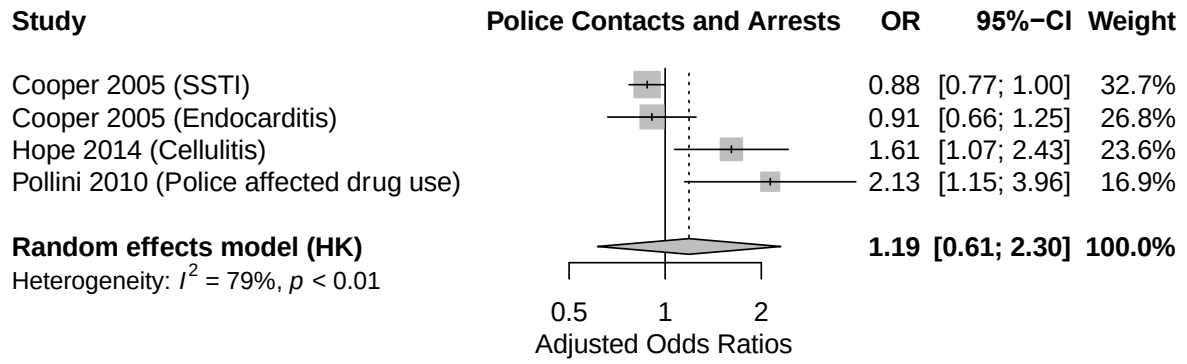

Figure 45. Meta-analysis of fully-adjusted effect estimates of relationship between police contacts and incident or prevalent injection drug use-associated bacterial infections.

Since Cooper 2005[256] is an ecological study design and does not include exposure information for individual participants, I conducted a sensitivity analysis excluding Cooper 2005. It made no meaningful difference to the summary effect estimate for univariate (uOR 1.26, 95%CI 0.80–1.98; I2 75.8%, p=0.0004) or adjusted analyses (aOR 1.76, 95%CI 0.34-9.06; I2 0%, p=0.5).

3.5.2.4.6 Assisted injecting, or requiring help to inject

I identified eight studies[231,236–238,242,245,268,269] reporting analyses of associations between requiring (or receiving) injecting assistance and risk for injecting-related infections. There were eight unadjusted effect estimates and eight fully adjusted effect estimates for meta-analysis. Meta-analysis of eight univariate analyses results in uOR 2.09 (95%CI 1.61–2.71; Figure 46) and of eight covariate-adjusted analyses results in aOR 1.78 (95%CI 1.40–2.27; Figure 47).

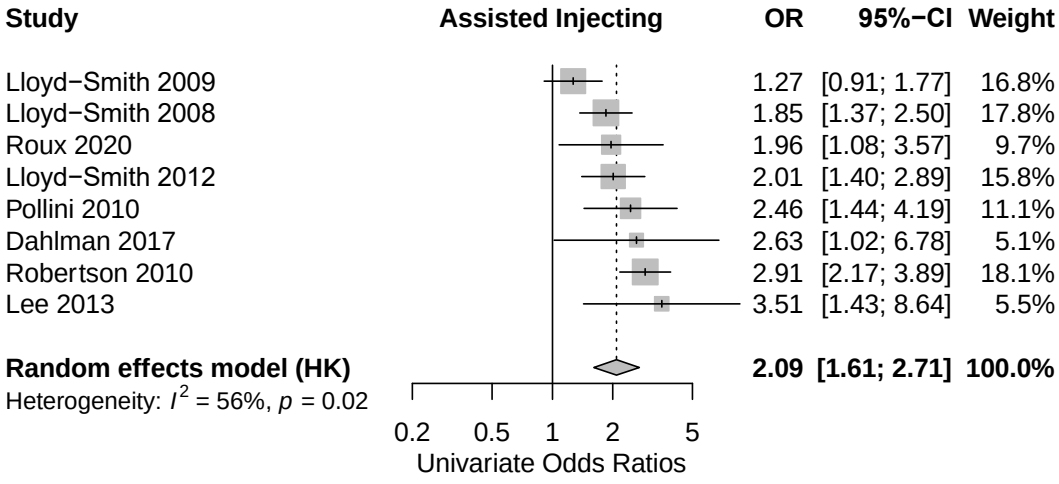

Figure 46. Meta-analysis of univariate effect estimates of relationship between requiring/receiving injecting assistance and incident or prevalent injection drug use-associated bacterial infections.

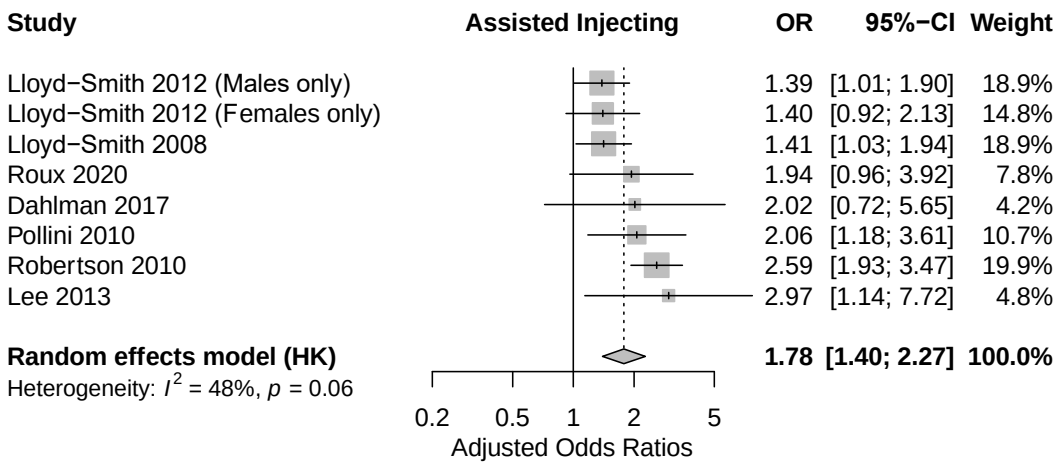

Figure 47. Meta-analysis of fully-adjusted effect estimates of relationship between requiring/receiving injecting assistance and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.4.7 Injecting with others

Three studies assessed the impact of injecting with others or in groups, on infection risk.[242,245,249] Seven eligible univariate effect estimates resulted in summary uOR 1.44 (95%CI 0.88-2.34; Figure 48). Two fully adjusted effect estimates, both from Smith 2015[249], assessed whether a participant injects with friends (aOR 1.65, 95%CI 0.42-6.47) or with family/spouse (aOR 4.05, 95%CI 0.99-16.58). Summary aOR was 2.55 (95%CI 0.008-769.91; I^2 0.0%, p=1.00).

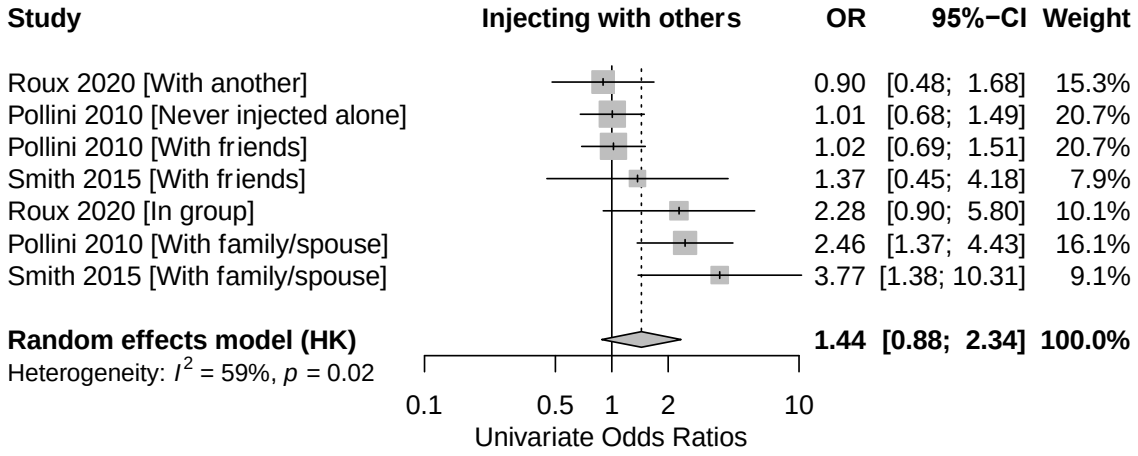

Figure 48. Meta-analysis of univariate effect estimates of relationship between injecting in groups and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.5 Harm reduction and drug treatment

3.5.2.5.1 Needle and syringe distribution programs

I identified eight studies reporting analyses of associations between use of needle and syringe programs and risk of injecting-related bacterial infections.[92,99–101,253,257,270,271] There were eight eligible univariate effect estimates, with a summary uOR 0.85 (95%CI 0.58-1.25; Figure 49). There

were seven fully adjusted effect estimates, with summary aOR 0.84 (95%CI 0.53-1.34; Figure 50). Hope 2010 was an outlier for both analyses. Removing Hope 2010 changed the summary estimates to uOR 0.75 (95% 0.54-1.05; I^2 63.9%, p=0.01)) and aOR 0.75 (95% CI 0.54-1.03; I^2 47.1%, p=0.09).

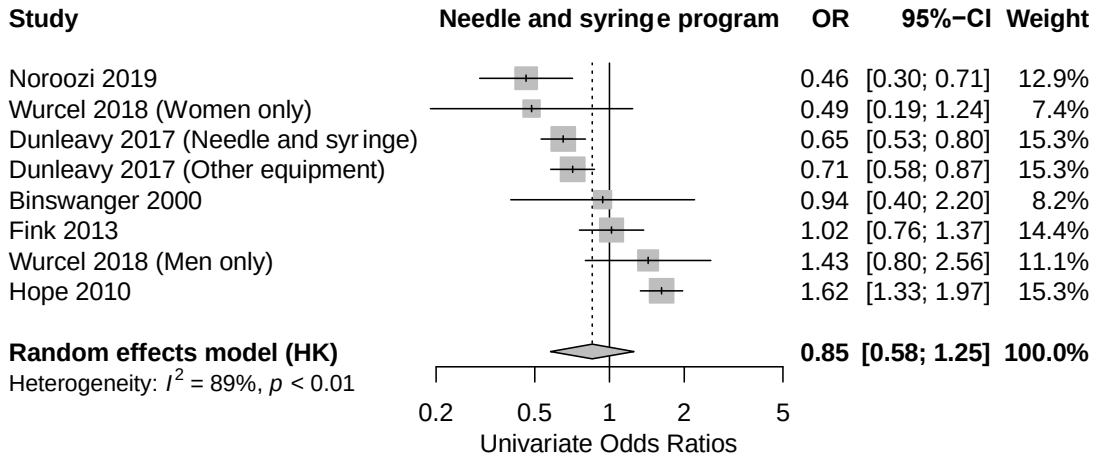

Figure 49. Meta-analysis of univariate effect estimates of relationship between needle/syringe program use and incident or prevalent injection drug use-associated bacterial infections.

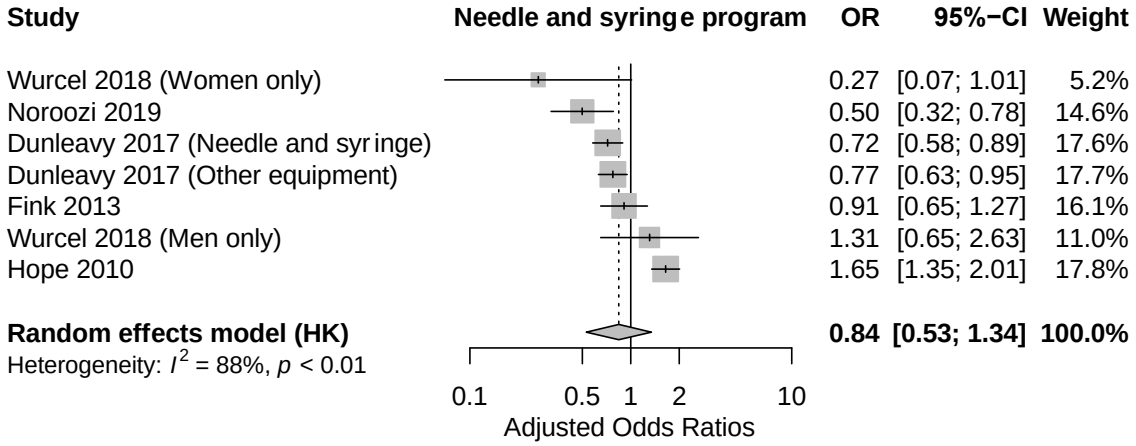

Figure 50. Meta-analysis of fully-adjusted effect estimates of relationship between needle/syringe program use and incident or prevalent injection drug use-associated bacterial infections.

One study [Bhattacharya 2006][270] was an ecological study assessing the proportion of local people who inject drugs with injection-site abscesses before and after the implementation of a needle and syringe program. Abscess prevalence was 23% in the month before implementation and declined to very low levels (at times 0%; e.g. one year after implementation). There was no statistical analysis or reported frequencies, so I could not include this in meta-analysis.

Another study [Tomolillo 2007][271] included an ecological analysis, correlating the weekly number of abscesses treated at a community clinic with the activity of the associated and co-located needle exchange program. A time series analysis identified "significant negative relationships" between the number of abscesses treated and both the number of needles exchanged (b = -0.001, p=0.002) and the number of needle exchange program visits (b = -0.12m p<0.001) per week. The authors report unstandardized coefficients from their regression model but do not provide any other detail on the model methods. I could not include these in meta-analysis. It also reports a second individual-level study correlating self-reported abscesses with number of needles exchanged (R2 = 0.10, p=0.01) and "more use of sterile equipment" (R2 = 0.10, p=0.10), with no timelines or frequencies reported. I also could not include this in meta-analysis. Finally, Tomolillo and co-authors describe the average weekly rate of abscesses treated at the community clinic before and after the implementation of a policy restricting the number of needles and syringes to be distributed to each client and requiring pre-arranged appointments for access. The average weekly number of needles distributed decreased from mean (SD) 3268 (965) needles to 471 (321) needles, and the average weekly number of abscesses treated at the community clinic increased from 8.5 (3.2) to 14.3 (6.0). No statistics or frequencies are reported for us to calculate.

One additional study [Pollini 2010b][166] assessed relationships between being refused/overcharged syringes when trying to purchase at a pharmacy in Tijuana, Mexico. There were imprecise effect estimates for having an abscess in the past 6 months (uOR 0.97, 95%CI 0.57–1.65), nor with ever having had an abscess (uOR 1.10, 95%CI 0.71–1.69). There was a small positive associated with average number of life abscesses (aOR 1.02, 95%CI 1.00–1.03).

3.5.2.5.2 Opioid agonist treatment

I identified 13 studies reporting analyses of associations between opioid agonist treatment use and risk for injecting-related infections.[92,101,104,229,240,242,248,250,261,272–274] Eleven univariate effect estimates and ten multivariable effect estimates for meta-analysis. Only four studies provided both, and otherwise univariate and adjusted effect estimates were from separate studies. Only two of the studies [Bassetti 2002; Milloy 2010] assessed exposure to opioid agonist treatment and development of injecting related infections over the same time period; otherwise, the timelines did not align, which may represent misclassification bias and undermines our ability to infer any causal relationship. For example, Betts 2016 assessed currently taking opioid agonist treatment in relation to risk of SSTI in the past month; Dunleavy 2017 assessed current opioid agonist treatment use in relation to risk of SSTI in the past year.

Summary effect estimates for 11 univariable effect estimates was uOR 0.75 (95%CI 0.63-0.89; Figure 51). One study [Hope 2010][101] was an outlier. Removing this changed the summary effect estimate to uOR 0.71 (95%CI 0.62-0.81; I^2 18.1%, p=0.28).

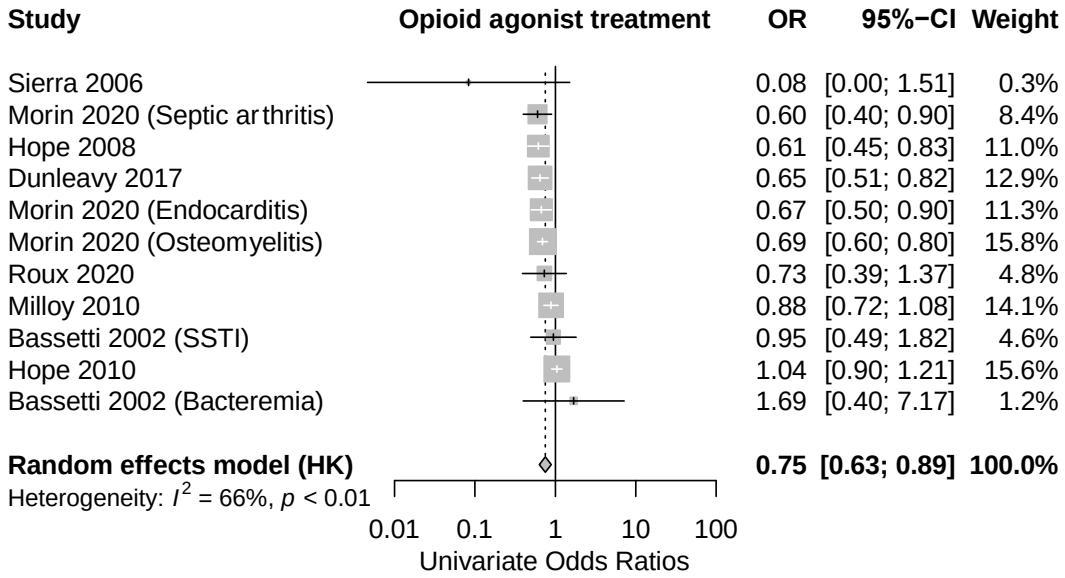

Figure 51. Meta-analysis of univariate effect estimates of relationship between opioid agonist treatment (OAT) use and incident or prevalent injection drug use-associated bacterial infections.

Summary effect estimate for 10 multivariable adjusted analyses was aOR 0.92 (95%CI 0.86–0.97; Figure 52). One study [Hope 2008][104] was an outlier; removing this changed summary aOR to 0.92 (95%CI 0.89-0.95; I^2 50.2%, p=0.04)

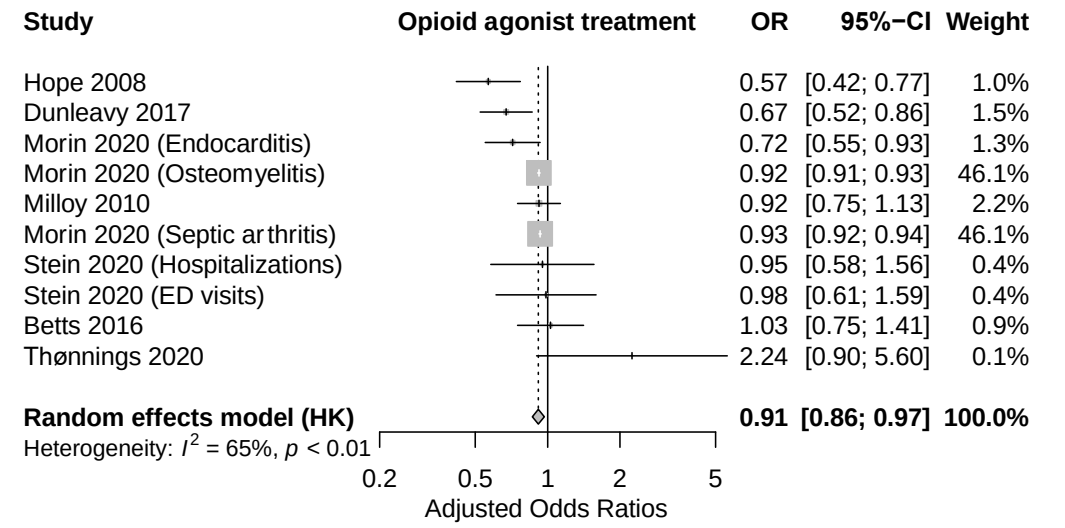

Figure 52. Meta-analysis of fully-adjusted effect estimates of relationship between opioid agonist treatment (OAT) use and incident or prevalent injection drug use-associated bacterial infections.

Two studies [Bertin 2020; Oviedo-Joekes 2017] compared multiple types of opioid agonist treatment, rather than any vs. no opioid agonist treatment. Bertin 2020 compared incidence of hospitalization with injecting-related bacterial infections amongst patients prescribed first-line treatment with buprenorphine or methadone, and second-line/alternative treatment with morphine sulfate. The crude incidence per 100,000 person-years in the buprenorphine group was 2.2 (95%CI 1.8-2.5), in the methadone group was 1.6 (95%CI 1.2-2.0), and in the morphine group was 7.0 (4.7-10.6). For patients receiving morphine, aHR was 2.8 (1.8-4.4) compared to buprenorphine and aHR 3.6 (2.2-5.9) compared to methadone. One study [Oviedo-Joekes 2017][274] reported rates of cellulitis or abscess as potential adverse effects within a randomized trial of injectable hydromorphone (7 episodes among 100 patients) vs. injectable diacetylmorphine (17 episodes among 102 patients; no statistical test reported).

3.5.2.5.3 Combined harm reduction interventions

I identified one study [Dunleavy 2017][92] assessing exposure of combined needle and syringe program and opioid agonist treatment use. “High” use (defined as currently prescribed opioid agonist treatment and >200% uptake of needles and syringes) was associated with reduced risk of past year SSTI (uOR 0.55, 95%CI 0.41–0.73; aOR 0.62, 95%CI 0.46–0.83).

3.5.2.5.4 Supervised consumption sites

I identified three studies reporting analyses of relationships between supervised consumption site use and risk for injecting-related infections.[237,240,275] Meta-analysis of three univariate effect estimates resulted in summary uOR 0.74 (95%CI 0.17-3.26; Figure 53). Only one study [Lloyd-Smith 2008][237] reported an adjusted effect estimate (aOR 0.59, 95% 0.29-1.19). Overall, these summary effect estimates were imprecise and confidence intervals were wide enough to include potentially meaningful differences in risk.

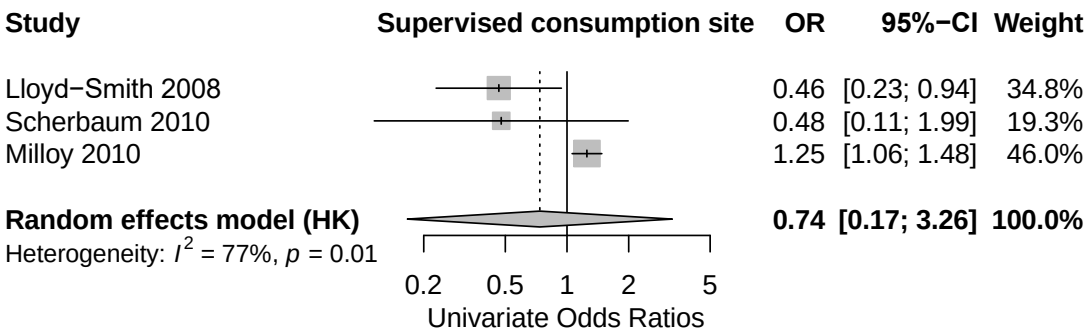

Figure 53. Meta-analysis of univariate effect estimates of relationship between supervised consumption site use and incident or prevalent injection drug use-associated bacterial infections.

3.5.2.6 Intersectionality

Few studies assessed the intersections of multiple identities or social positions in relation to risk of injecting-related bacterial infections. For example, no studies examined differential health risks across multiple intersections of race and gender categories. Several studies presented analyses stratified by gender-sex. In Wurcel 2018[253], sex work was associated with ever having had an abscess among females but not males. In Smith 2015[249], women with abscesses more often reported unstable housing (n=6, 40.0% versus n=6, 14.6%; P=0.119). In Wurcel 2016[63], the investigators found that among U.S.-wide hospital admissions for endocarditis the proportion attributed to injection drug use increased especially quickly among younger white people (from 57.0% in 2000 to 80.3% in 2013, p<0.001). In Lloyd-Smith 2012, requiring injecting assistance was associated with increased risks of injecting-related infections among men and women in univariate analyses, but in fully-adjusted analyses this was only significant among men.

3.5.3 Studies with outcomes occurring during treatment for injecting-related infections

I identified 26 studies assessing several different outcomes that occur during treatment/care of injecting-related bacterial infections. See Table 4 for the eight groups of outcomes, and list of exposures assessed in relation to each.

Table 4. Summary of outcomes and associated exposures assessed among studies where outcome occurs during treatment for injecting-related infections.

Outcomes	Exposures assessed	Number of studies
1. Health care-seeking for injecting-related infections	gender/sex; age; income/employment; sex work; unstable housing; incarceration; overdose history; migration status; heroin use; cocaine use; amphetamine use; opioid agonist treatment; supervised consumption site use	4[75,104,236,239]
2. Self-treatment of abscess	gender/sex; age; race/ethnicity; unstable housing; heroin use; cocaine use; needle and syringe programs; several measures of access to health care (e.g., having a primary care provider or having health insurance)	2[75,277]
3. Hospital admissions among people with an injecting-related SSTI	gender/sex; age; race/ethnicity; education; income/employment; sex work; migration status; unstable housing/homelessness; incarceration history; overdose history; heroin; cocaine; amphetamines; alcohol use; needle and syringe program use; access to health care (e.g., insurance, having a primary care provider); self-treatment of infections; hospital admission history	2[75,277]
4. Premature hospital discharges against medical advice, among people hospitalized with	gender/sex; age; race/ethnicity; income/employment; unstable housing; overdose history; opioid use; cocaine; alcohol; other substance use; health care access; opioid agonist treatment; in-hospital addiction	10[278–288]

injecting-related infections	treatment; hospital characteristics; hospital policy; surgery during hospitalization	
5. New/secondary bloodstream infections among people receiving antibiotic treatment	gender/sex; age; unstable housing and homelessness; substance use (heroin, stimulants, polysubstance use, other); substance use treatment; insertion of peripherally-inserted intravenous central catheters (PICC lines) for parenteral antimicrobial treatment	1[289]
6. In-hospital death	gender/sex; age; race/ethnicity; overdose history; substance use (opioids, stimulants); health care access (insurance); hospital policies; surgery during hospital admission	5[60,281,283,290,291])
7. Development of endogenous endophthalmitis	gender/sex; race/ethnicity; alcohol use; infection of central venous catheter	1[227]
8. Respiratory failure among people with botulism	gender/sex; age	1[293]

Studies assessing outcomes during treatment for injecting-related infections typically had smaller sample sizes and imprecise effect estimates (compared to studies assessing incident or prevalent injecting-related infections) and findings were inconsistent between studies. Many exposures were only assessed in one study, limiting meta-analyses. See Appendix 18 for a detailed narrative synthesis and several meta-analyses for studies in the section. See Appendix 19 for a list of all extracted effect estimates in this section.

Among these 26 studies, only one exposure-outcome association was found to have supporting evidence in meta-analyses of multiple studies. Lacking health insurance associated with increased risk of premature hospital discharge against medical advice (aOR 2.07, 95%CI 1.09-3.91; n=4 studies[279,280,282,283]; Figure 54).

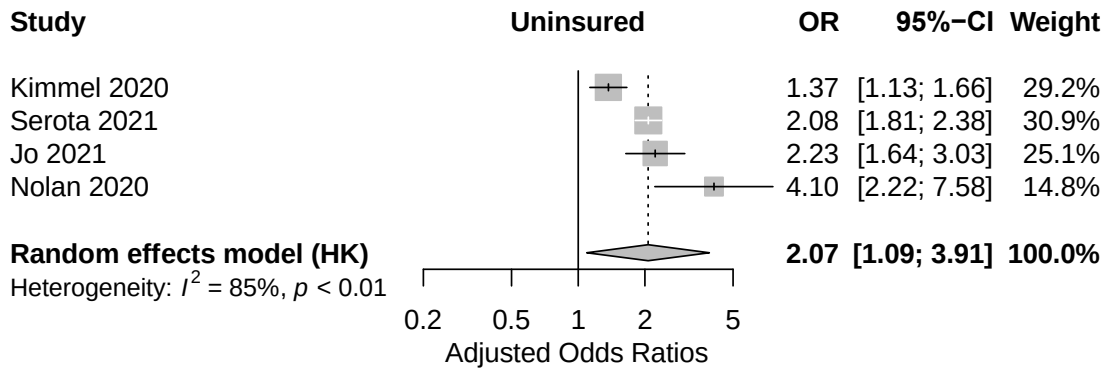

Figure 54. Meta-analysis of fully-adjusted effect estimates of relationship between lack of health insurance and premature hospital discharge against medical advice, among people hospitalized with injection drug use-associated bacterial infections

3.5.4 Studies with outcomes occurring after initial treatment of injecting-related infection

I identied 29 studies that assessed several different outcomes occuring after initial treatment for injecting-related infections. See Table 5 for the six groups of outcomes, which exposures were assessed in relation to each.

Table 5. Summary of outcomes and associated exposures assessed among studies where outcome occurs after initial treatment for injecting-related infections.

Outcomes	Exposures assessed	Number of studies
1. Infection-related rehospitalization (after discharge from an initial hospital admission with injecting-related infections)	gender/sex; age; race/ethnicity; rural residency; substance use (injecting prescription opioids); opioid agonist treatment; other substance use treatment; hospital policy; premature hospital discharge against medical advice; cardiac surgery during admission	8[261,294–300]
2. All-cause rehospitalization	gender/sex; age; race/ethnicity; unstable housing; access to healthcare (health insurance); substance use (heroin, cocaine, methamphetamine, other); opioid agonist treatment; other addiction treatment; hospital policies; antibiotic treatment models; surgery during hospital admission	9[279,284,287,288,294,299,301–303]
3. Overdose-related rehospitalization	gender/sex; age; substance use; opioid agonist treatment; hospital policy	2[301,287]
4. All-cause mortality	gender/sex; age; unstable housing; substance use (opioid, stimulant, polysubstance use); premature hospital discharge against medical advice; opioid agonist treatment; other addiction medicine treatment; hospital policy; surgery during hospital admission	14[284,287,289,296,300,303–311]
5. Failure of outpatient parental antimicrobial therapy [OPAT]	age; discharge setting	3[312–314]
6. Change in visual acuity following treatment for endogenous endophthalmitis	gender/sex; age	1[228]

Similar to the preceding section, studies assessing outcomes after treatment typically had imprecise effect estimates and inconsistent findings between studies, and opportunities for meta-analyses were limited. See Appendix 20 for a detailed narrative synthesis and several meta-analyses amongst studies in this section and see Appendix 21 for a list of all extracted effect estimates in this section.

Only two exposure-outcome associations were found to be significant in meta-analyses incorporating more than one effect estimate. First, woman/female gender/sex was associated with increased risk of all-cause rehospitalization. Summary meta-analysis of three fully-adjusted effect estimates was aOR 1.22 (95%CI 1.08-1.38; Figure 55). One univariate effect estimate was nonsignificant at uOR 1.23 (95%CI 0.77-1.96).

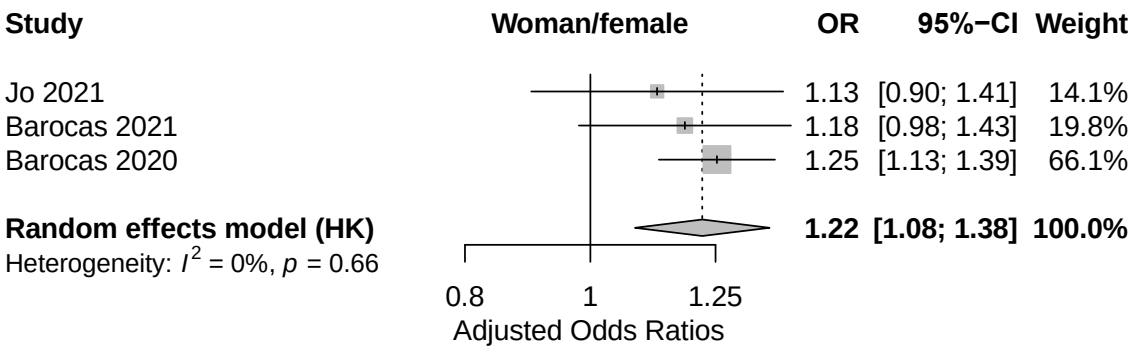

Figure 55. Meta-analysis of fully-adjusted effect estimates of relationship between woman/female gender/sex and all-cause rehospitalization, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

Second, receiving an inpatient addiction medicine consultation was associated with reduced risk of all-cause rehospitalization; summary of two univariate effect estimates was uOR 0.46 (95%CI 0.33-0.63) and one fully-adjusted effect estimate was aOR 0.57 (95%CI 0.38–0.86; Marks 2019[285]).

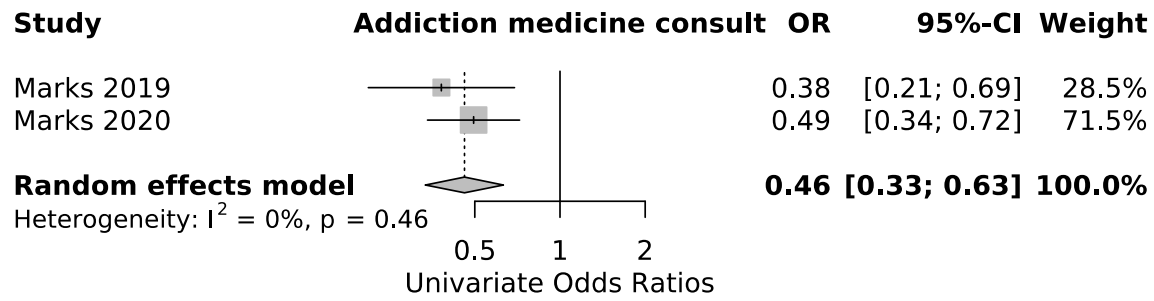

Figure 56. Meta-analysis of univariate effect estimates of relationship between receiving an addiction medicine consultation (during hospitalization) and all-cause rehospitalization, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

I was also particularly interested in the impact of opioid agonist treatment after hospitalization with injecting-related infections, as this would inform my analyses in Chapter 4, below. Four studies assessed relationships between opioid agonist treatment and infection-related

rehospitalization.[261,294,297,300] In univariate analyses, people prescribed opioid agonist treatment had lower rates of rehospitalization (10.3 [95%CI 9.87-10.64] per 100 person-years vs. 18.7 [95%CI 18.53-18.78] per 100 person-years) in one study [Barocas 2020[294]], but rates did not differ between groups in three other studies [Hilbig 2020[297]; Suzuki 2020[300]; Thønnings 2020[261]]. Two fully-adjusted effect estimates for opioid agonist treatment from within one study [Barocas 2020[294]], were aHR 0.49 (95%CI 0.18-1.23) for infection-related rehospitalization by 30 days and aHR 0.41 (95%CI 0.42–0.91) for infection-related rehospitalization by 1 year. A new hospital policy to identify opioid use disorder and facilitate opioid agonist treatment did not change 90-day rates of infection-related rehospitalization in one study [Ray 2020[299]].

Four studies assessed relationships between opioid agonist treatment and all-cause mortality after hospital discharge.[300,305,306,310] Three studies provided univariate effect estimates of the relationship between opioid agonist treatment prescriptions provided at hospital discharge and risk of all-cause mortality. Meta-analysis summary was uOR 0.58 (95%CI 0.24-1.45;Figure 57). In the only fully-adjusted effect estimate [Kimmel 2020[305]], opioid agonist treatment was associated with reduced risks of all-cause death in the month within which it was received (when treated as a time-varying exposure; aHR 0.30; 95% CI 0.10-0.89).

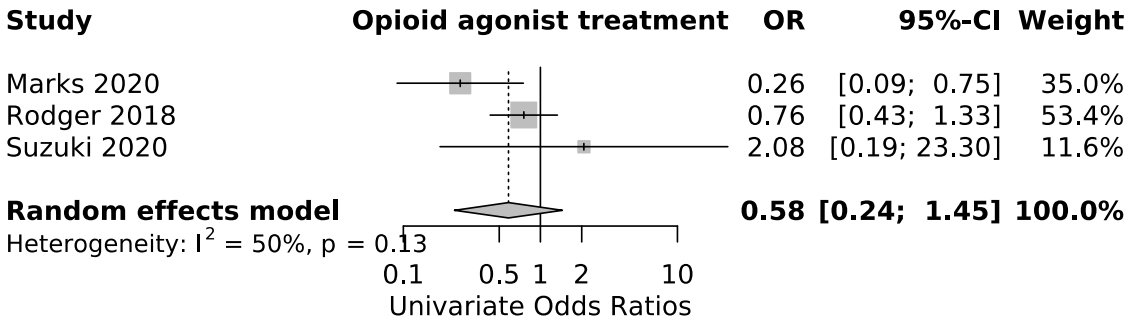

Figure 57. Meta-analysis of univariate effect estimates of relationship between receiving opioid agonist treatment at hospital discharge and all-cause mortality, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

3.5.5 Studies on colonisation

Five studies assessed factors associated with colonization with specific pathogenic bacteria among people who inject drugs, including *Staphylococcus aureus* and methicillin-resistant *S. aureus*.[315–319] Several exposures had significant associations in single studies but none were significant in meta-analyses of multiple studies. See Appendix 22 for narrative synthesis of studies on colonization and see Appendix 23 for all effect estimates extracted for this section. Meta-analysis for four univariate

effect estimates on the relationship between homelessness and colonization with pathogenic bacteria was uOR 1.84 (95%CI 0.81-4.18; Figure 58). I identified no fully-adjusted effect estimates.

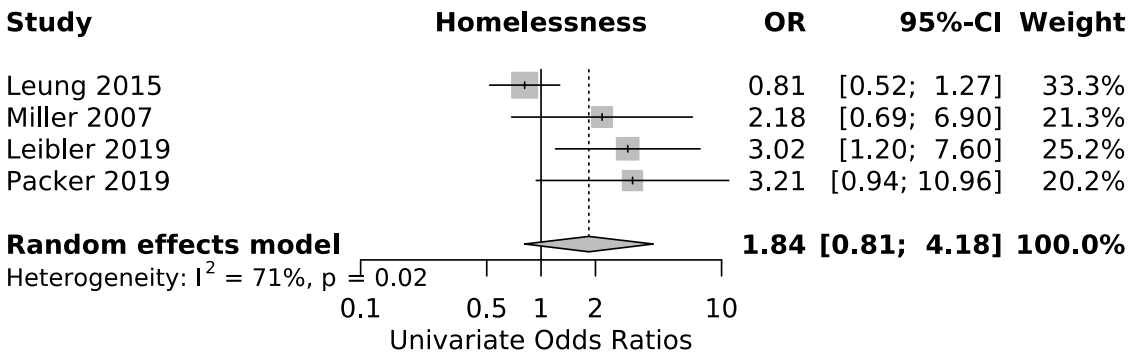

Figure 58. Meta-analysis of univariate effect estimates of relationship between homelessness and colonization with pathogenic bacteria among people who inject drugs.

3.6 Discussion

In this quantitative systematic review and meta-analysis, I identified 107 studies that assessed social determinants, substance use, and health services factors associated with injecting-related bacterial infections and their treatment. Individual injecting risk practices (like intramuscular injecting or reuse of contaminated equipment) were already known to be risk factors, and I was interested in the social contextual factors that can influence injecting practices and treatment experiences. In meta-analyses of unadjusted or covariate-adjusted effect estimates, I found some evidence that risk for injecting-related infections was increased with several of these exposures, including woman/female gender/sex, less education, a history of incarceration, sex work, unstable housing and homelessness, heroin use, cocaine use, amphetamine use, speedball/goofball use, public injecting, and requiring or receiving injecting assistance. Among harm reduction and addiction treatment factors, opioid agonist treatment was associated with a modest reduction in risk (i.e., ~8% lower odds). Overall, there were many more studies where the outcome was incident or prevalent injecting-related infections than there were studies assessing health outcomes occurring during or after infection treatment (e.g., premature hospital discharge against medical advice; all-cause mortality). Most studies that did focus on outcomes occurring during or after infection treatment had small sample sizes and imprecise effect estimates, and most exposures assessed in this setting were only addressed in one study (so could not be meta-analysed). Social and health services exposures associated with these outcomes in meta-analyses of multiple studies included lack of health

insurance (associated with premature hospital discharge against medical advice), woman/female gender/sex (associated with all-cause rehospitalization after discharge from an initial hospital admission), and inpatient addiction medicine consultation (associated with decreased risk of all-cause rehospitalization). While this review incorporated a broad scope, there was insufficient evidence for many exposures and interpreting meta-analyses was commonly limited by high clinical and statistical heterogeneity. Nevertheless, the importance of social-structural factors on risk of injecting-related infections and their treatment suggests that future approaches to improving prevention and treatment should look more broadly than individual-level injecting practices and engage with the social and material conditions within which people live, acquire drugs, consume them, and access health care.

The findings of this quantitative systematic review and meta-analysis complement the qualitative systematic review and thematic synthesis, reported above in Chapter 2. In the qualitative thematic synthesis, I identified several potential mechanisms through which social-structural factors could influence risk for injecting-related infections and their treatment. In the quantitative meta-analyses here, I identified consistent evidence of population-level effects for some exposures, but not for others. For example, in the qualitative review, people who were unhoused described not having hygienic or well-lit spaces to prepare and inject drugs with safe technique; many people without secure housing would need to inject outside where they would rush and compromise their drug preparation and injecting process (e.g., not using a filter, or injecting intramuscularly). In this quantitative systematic review, increased risk of incident or prevalent injecting-related infection was indeed associated with having unstable housing or homelessness (aOR 1.29, 95%CI 1.10–1.50; n=15 studies) and injecting in public (aOR 1.40, 95%CI 1.05–1.88). In the qualitative synthesis, participants described fear of policing contacts and arrest as a major factor leading them to rush and compromise their injecting technique when using outside (so they would not be found in possession of drugs). In the quantitative meta-analysis, a history of police contacts and arrests may have been associated with risk for infections (aOR 1.19, 95%CI 0.61-2.31; n=2 studies), with imprecise confidence intervals that could include meaningful differences. But of course, this is measuring a different phenomenon than a concurrent police encounter contributing to a specific abscess for an individual.

In the qualitative systematic review, participants highlighted the important role of harm reduction programs, like sufficient needle and syringe program coverage and access to supervised consumption sites, in enabling their ability to reduce risk for infections. This was not borne out in the quantitative meta-analysis. While use of opioid agonist treatment was associated with a modest

reduction in risk for injecting-related infections (aOR 0.92, 95%CI 0.89-0.95; n=9 studies), there were nonsignificant associations with use of needle and syringe programs (aOR 0.75, 95%CI 0.54-1.03; n=6 studies) and supervised consumption sites (aOR 0.59, 95%CI 0.29-1.19; n=1 study and uOR 0.74, 95%CI 0.17-3.26; n=3 studies). While effect estimates are imprecise and may include clinically meaningful reductions in risk, these statistics from (mostly) cross-sectional observational studies may also show that needle and syringe programs and supervised consumption sites are successfully engaging people at highest risk of infections. This same phenomenon was observed in early research on HIV infection among people accessing needle and syringe programs.[91,320,321] In addition, there were two ecological studies (that I could not include in meta-analyses) showing a reduction in injecting-related infections after people started accessing needle and syringe programs. Further, in many studies, the timing of exposures (e.g. time period when accessing opioid agonist treatment) and of outcomes (e.g. time period when experienced an infection) did not line-up. Overall, despite these relevant studies, the observational evidence-base for harm reduction programs and risk of injecting-related infections seems insufficient (with relatively few studies, heterogenous in design and measurement, and with imprecise confidence intervals).

I also identified several sociodemographic characteristics associated with risks of injecting-related bacterial infections, including woman/female gender/sex, low educational attainment, low income/unemployment, incarceration history, and sex work. In the context of the "risk environment" conceptual model (and the closely related concepts of structural vulnerability and structural violence), I was interested in how these social identities and locations within societal power hierarchies may enable or constrain the ability of people who inject drugs to prevent injecting-related infections and/or access treatment.[3,33–35] Women may face excess risks of bacterial infections in the context of gendered power dynamics, for example that would lead them to "go second" and reuse contaminated equipment when injecting with male partners.[3,168,253] Women may be less likely to know how to inject themself, and more likely to rely on assisted-injecting (which could reduce risks of intramuscular injection and abscesses in some people, but was associated with increased risks of bacterial infections in this review).[175,322] Women may also be less likely to engage with harm reduction programs (which are more likely to have been designed for men); very few harm reduction programs (e.g., supervised consumptions sites) are gender-attentive or gender-specific.[3,323–325] Some investigators have also hypothesized that excess risk of infections among women is attributable to deeper peripheral veins, due to different distributions of adipose tissue (and so women may have more difficulty accessing veins and may be more likely to inject in subcutaneous tissue).[71] These differing risks are reflected in the greater proportion of woman/females in studies during and after treatment of injecting-related infections compared to

studies assessing risk of incident or prevalent infections. Fewer studies focused on outcomes during and after treatment, which led to inconsistent findings. For example, woman/female gender/sex appeared associated with higher risks of all-cause rehospitalization but not infection-related rehospitalization, and it is unclear to me why this would be the case.

While my quantitative meta-analysis here identified no evidence of differences in risks by race/ethnicity, my qualitative systematic review (in Chapter 2) identified one ethnographic and mixed methods study (by Bourgois and colleagues)[153] that found higher rates of abscesses among white compared to African American participants. They attributed this to a greater willingness among white participants to inject subcutaneously, while African American participants committed much more time and effort to accessing a vein and avoiding subcutaneous or intramuscular injection. Conversely, African American participants were more likely to be stopped and searched by police and have their sterile injecting equipment confiscated, compared to white participants. Other qualitative studies among people who use drugs have described how structural racism and racialized violence prevents racialized people who use drugs from accessing harm reduction programs (e.g., supervised consumption sites).[325] In one study identified in my qualitative systematic review (by McNeil and colleagues)[163], an Indigenous participant who was hospitalized with an injecting-related infection described how racist attitudes from hospital staff negatively affected their care and made them feel unsafe in hospital.

I also found that several substances were associated with higher risks of injecting-related bacterial infections. In meta-analyses incorporating multiple fully-adjusted effect estimates, this includes frequent or any use (vs. less or no use) of injection heroin, cocaine, and amphetamines. Studies that compared "frequent" (typically "daily or more") use to less use did not consistently find that more frequent use of these substances was associated with greater risks of infections. It is unclear to me how to interpret these findings in the context of potential risk-reduction interventions, given that reporting use of opioids and stimulants both seem to be associated with increased risk – and nearly all participants in the included studies use either opioids, cocaine, or amphetamines. Several studies also assessed specific formulations of unregulated drugs. Use of tar heroin (compared to powder heroin) was associated with nearly eight-fold increased risk of injecting-related bacterial infections in a covariate-adjusted analysis in one study, and twice-fold increased risk in a second (ecological) study. This may be because tar heroin is less soluble (leading to more undissolved particulate matter that can damage veins) and also that tar heroin requires the addition of acidifiers to dissolve and prepare for injection (and overuse of acidifiers contributes to vein sclerosis).[71,326] "Crack" cocaine (base) formulations also require the addition of acidifiers to prepare the drug solution for injecting

(while powder cocaine hydrochloride does not), but use of both crack and powder cocaine were associated with increased risks in meta-analyses of univariate analyses.

Other specific substances were associated with increased risk of injecting-related infections in individual studies, including of ethylphenidate (a novel psychoactive substance / stimulant, associated with high frequency of injecting). In research external to this review, investigators have hypothesized that the North American drug supply transition to fentanyl has driven increasing incidence of injecting-related infections, as fentanyl has a shorter half-life than fentanyl and is also associated with more frequent injecting.[51,70] I identified no studies directly assessing illicit fentanyl use and risks of infections. Investigators of several studies included in this review (and others, external to this review) have raised concerns that injection of controlled-release prescription opioids may confer particular risks of injecting-related bacterial infections due to (a) the controlled-release beads being insoluble in water, leading to injection of particulate matter damaging veins, and (b) some people keeping and reusing cotton filters that contain left-over prescription opioids (and bacteria growing out on the cotton filter between the initial drug preparation and the time it is reused).[73,262] This has been a criticism[247,327,328] against prescribed "safer supply" programs, where people who use drugs are provided with pharmaceutical-grade alternatives to the unregulated drug supply;[43,184] as a result, most prescribed "safer supply" programs use only immediate-release formulations of prescription opioids.[183] I identified one study[262] in which people who filled a prescription for controlled-release hydromorphone (vs. non-hydromorphone opioids) had higher rates of injecting-related endocarditis while people who filled a prescription for immediate-release hydromorphone did not; but this may simply reflect that people who are actively injecting opioids seek out the higher doses typical of controlled-release formulations (and most people with injecting-related endocarditis did not have recent prescriptions). A second study[247] in identified in this systematic review identified no significant associations between prescription opioid injecting and infection risk. A recent systematic review on infectious risks associated with injecting controlled-release hydromorphone concluded, "Very low-quality and scant evidence suggests uncertainty around the risks of blood-borne infections… to [people who inject drugs] using these medications".

3.6.1 Limitations

This systematic review has several important limitations. First, the inclusion of so many exposures and outcomes (and, potentially, meta-analyses of univariate and covariate-adjusted effect estimates for each) could lead to false positive findings through simply random chance (the so-called "multiple comparisons problem"). However, I wanted to take as broad a scope as possible and applied a socio-

ecological conceptual model to try to characterize factors contributing to the "risk environment". Second, the summary effect estimates from meta-analyses were likely not entirely accurate for several reasons: (a) I could not incorporate "negative" or "null" effect estimates from several studies that reported no statistics (saying only that the exposure and outcome were "not associated") or reported univariate associations but dropped the variable in stepwise approaches to multivariable regression; (b) I combined effect estimates from studies with high clinical heterogeneity (with different exposure and outcome definitions, sampling strategies, inclusion criteria, and study settings) which was often reflected in high measures of between-study statistical heterogeneity (e.g., I^2 vales); (c) most studies did not specify a hypothesis or estimand (and most did not take a causal approach to covariate selection), which meant that most effect estimates that I extracted and/or combined in meta-analysis did not come from studies trying to model as accurate as an effect as possible. (It is notable that these potential sources of bias are not captured in the MMAT critical appraisal tool, with which most studies typically scored 3 to 5 out of the 5 criteria). Third, the observational cohort, cross-sectional, and case-control studies included in this review rarely contributed to understanding of mechanisms by which specific exposures affect the risk of infections or other treatment outcomes. This is where the qualitative thematic synthesis (from Chapter 2) can complement the quantitative findings. Future research focused on specific exposures and potential interventions could incorporate mixed-methods and critical realist methods to improve understanding of how these risks come about.[321,329,330]

3.6.2 Conclusions

Injecting-related infections, their treatment, and subsequent outcomes are shaped by multiple social determinants, substance use, and health services-related factors. Public health and clinical approaches to prevention and treatment should look more broadly than individual injecting practices, towards addressing the social and material conditions within which people live, acquire and consume drugs, and access health care.

Chapter 4 Opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections: a retrospective cohort study

4.1 Attribution and outputs

I adapted the contents of this chapter from a manuscript published in *PLOS Medicine*. Manuscript coauthors are listed in Acknowledgments and in the citations below. I led all aspects of the conceptualization, design, analysis, and write-up.

This work has also been presented as oral presentations at the European Conference on Addictive Behaviours and Dependencies in Lisbon, Portugal; the U.S. College on Problems of Drug Dependence in Minneapolis, USA; and at the Dalhousie University Department of Medicine Research Day. It was also presented as a poster presentation at the International Network on Health & Hepatitis in Substance Users (INHSU) conference in Glasgow, Scotland.

Manuscripts:

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections: a cohort study in New South Wales, Australia. *PLOS Medicine.* 2022;19(7):e1004049. https://doi.org/10.1371/journal.pmed.1004049

Conference presentations:

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Oral presentation.] Lisbon Addictions -- European Conference on Addictive Behaviours and Dependencies. November 23, 2022 at Lisbon, Portugal.
- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Oral presentation.] College on Problems of Drug Dependence (CPDD) Annual Conference. June 15, 2022 at Minneapolis, Minnesota, USA.
- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections:

linkage cohort study. [Oral presentation.] Dalhousie University Department of Medicine Research Day. April 21, 2022 at Halifax, NS, Canada.

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Poster presentation.] International Network on Health & Hepatitis in Substance Users (INHSU). October 21, 2022 at Glasgow, Scotland.

4.2 Abstract

Background: Injecting-related bacterial and fungal infections are associated with significant morbidity and mortality among people who inject drugs, and they are increasing in incidence. Following hospitalization with an injecting-related infection, use of opioid agonist treatment (OAT; methadone or buprenorphine) may be associated with reduced risk of death or infection-related rehospitalization.

Methods: Data came from the Opioid Agonist Treatment Safety study, an administrative linkage cohort including all people in New South Wales, Australia, who accessed OAT between 1 July 2001 and 28 June 2018. Included participants survived a hospitalization with injecting-related infections (i.e., skin and soft-tissue infection, sepsis/bacteraemia, endocarditis, osteomyelitis, septic arthritis, or epidural/brain abscess). Outcomes were all-cause death and rehospitalization for injecting-related infections. OAT exposure was classified as time-varying by days on or off treatment, following hospital discharge. I used separate Cox proportional hazards models to assess associations between each outcome and OAT exposure.

Results: The study included 8,943 participants (mean age 39, standard deviation 11 years; 34% women). The most common infections during participants' index hospitalizations were skin and soft tissue (7,021; 79%), sepsis/bacteraemia (1,207; 14%), and endocarditis (431; 5%). During median 6.56 years follow-up, 1,481 (17%) participants died; use of OAT was associated with lower hazard of death (adjusted Hazard Ratio [aHR] 0.63, 95% confidence interval [CI] 0.57-0.70). During median 3.41 years follow-up, 3,653 (41%) were rehospitalized for injecting-related infections; use of OAT was associated with lower hazard of these rehospitalizations (aHR 0.89, 95% CI 0.84-0.96). Study limitations include the use of routinely collected administrative data, which lacks information on other risk factors for injecting-related infections including injecting practices, injection stimulant use, housing status, and access to harm reduction services (e.g., needle exchange, supervised injecting sites). I also lacked information on OAT medication dosages.

Conclusions: Following hospitalizations with injection drug use-associated bacterial and fungal infections, OAT is associated with reduced risks of death and recurrent injecting-related infections among people with opioid use disorder.

4.3 Introduction

As described in Chapter 1, Injection drug use-associated bacterial and fungal infections (eg. skin and soft-tissue infections, endocarditis, osteomyelitis, septic arthritis, epidural abscess) are associated with significant morbidity and mortality among people who inject drugs and are costly for health care systems.[21,51–55] The incidence of hospitalization for injecting-related infections is increasing in many parts of the world, including Australia,[57] Canada,[51,58,59] South Africa,[60] the United Kingdom,[61] the USA,[63–67] and India.[68]

Prevention efforts to date have focused on individual-level behaviour change interventions to promote more sterile drug preparation and safer drug injecting techniques. Unfortunately, as explored in Chapter 1, these have shown mixed results[85–87] and have had limited impact on a population level.[21] This may be in part because of social and structural factors (e.g. criminalization, discrimination, lack of access to housing, harm reduction services, and supervised injection sites) that constrain the ability of people to inject more safely[21,71] and that push people who inject drugs away from health care.[88] Improved primary and secondary prevention approaches are urgently needed.[21,64,88]

One promising potential intervention to prevent injecting-related bacterial and fungal infections is opioid agonist treatment (OAT; e.g. methadone or buprenorphine). For people with opioid use disorder, OAT is associated with many benefits including reduced risks of death and of viral infections including HIV and HCV.[93,94] OAT limits opioid withdrawal symptoms, reduces reliance on illicit drug markets, and empowers people to inject less frequently or in a safer way.[95,96] Engagement in OAT is also associated with regular health care contacts where superficial infections may be treated before they progress and become more severe or spread through the bloodstream.[88,97,98]

Despite these possible benefits, in many acute care hospitals OAT is not prioritized as part of treatment planning during and after hospitalization with injecting-related bacterial and fungal infections.[88,115,117,331] This is represented in low rates of OAT prescribing for these patients in multiple studies from North America[117,331,332] and in qualitative studies from the United Kingdom.[88] Suboptimal access to OAT may reflect system-level issues which separate addiction care from

specialized, acute medical care for infections.[21,88,115,117] In some hospitals, clinicians have tried to overcome this by establishing specialized addiction medicine consultation services[192,193,208,285] or by infectious diseases specialists prescribing OAT directly.[117,333] While OAT is known to be beneficial for other injecting-related health outcomes, there has been relatively little research on OAT and risk for injecting-related infections. A better understanding of how OAT affects outcomes after injecting-related infections could help inform treatment planning during and following hospitalization.

As systematically reviewed in Chapter 3, analyses of potential benefits of OAT after hospitalization with injecting-related infections have been limited by small sample sizes with wide confidence intervals.[272,334] Three administrative linkage cohort studies (all from U.S. insurance claims data) have assessed associations between use of OAT and outcomes after hospitalization with injecting-related bacterial or fungal infections.[294,334,335] One study identified a reduced risk of death after hospitalizations with injecting-related endocarditis, but did not assess rehospitalizations.[335] A second study identified no significant effect (with wide confidence intervals) on risk of rehospitalization after endocarditis and did not assess mortality.[334] A third identified a reduced risk of rehospitalization for skin and soft-tissue infections at one year.[294] Reflecting suboptimal access, use of OAT (or of naltrexone, an opioid antagonist medication used for opioid use disorder treatment in the United States) was reported as 24% within 3 months following hospital discharge in the first study[335] and as 6% within 30 days following discharge in the second and third studies.[294,334] The latter two studies also only included information on buprenorphine use, as they did not have access to insurance claims or prescribing records for methadone.

The Opioid Agonist Treatment Safety Study is an administrative data linkage cohort study in New South Wales, Australia, that includes OAT permit records (with methadone or buprenorphine) for every person accessing OAT for opioid use disorder treatment in New South Wales from 2001 to 2018.[336,337]

4.3.1 Objectives

Using data from the Opioid Agonist Treatment Safety Study, I aimed to evaluate whether use of OAT, after discharge from hospital with injecting-related bacterial and fungal infections, is associated with decreased risk of subsequent mortality or infection-related rehospitalization.

4.4 Methods

I conducted a retrospective cohort study using linked data from the Opioid Agonist Treatment Safety Study, which has been described in detail elsewhere.[336,337] This manuscript follows the REporting of studies Conducted using Observational Routinely collected health Data statement for PharmacoEpidemiology (RECORD-PE) guidelines.[338] Ethics approval was obtained from the NSW Population & Health Services Research Ethics Committee (2018/HRE0205), the NSW Corrective Services Ethics Committee, and the Aboriginal Health and Medical Research Council Ethics Committee (1400/18).

4.4.1 Setting and data sources

The Opioid Agonist Treatment Safety study cohort includes all patients prescribed methadone or buprenorphine for OAT in New South Wales (NSW), which is Australia's most populous state and includes over one-third of all people receiving OAT in the country. Clinicians in NSW must apply to the state government and receive an authority to prescribe OAT for each patient. OAT may be prescribed and dispensed in specialized clinics or prescribed in primary care settings with medications dispensed in community pharmacies. In NSW there is no charge for OAT in public clinics or prisons, however private specialized clinics and community pharmacies charge clients daily dispensing fees (usually $A5–$A8 per day).[339] Most people initiate OAT in specialized clinics, and then many transition their prescribing to primary care settings.

In NSW, clinicians follow state-wide OAT prescribing guidelines.[340] In keeping with international OAT guidelines, OAT is recommended for all patients with moderate or severe opioid use disorder (termed "opioid dependence" in NSW guidelines), and methadone and buprenorphine are both recommended as first-line treatment options. Patients start OAT episodes with entirely daily-observed dosing, typically during the first three months of a treatment episode for methadone, and the first month for buprenorphine (which has less risk of respiratory depression and is relatively safer if used in ways other than prescribed, e.g., medication sharing or diversion). Patients who have missed more than five consecutive daily doses of OAT have their prescription discontinued and must see their clinician to initiate a new treatment episode. Planned discontinuations of OAT typically occur after slow, long-term tapers of the dose.

To generate the Opioid Agonist Treatment Safety study cohort, all individuals with an OAT permit were linked to state-wide hospitalization records, incarceration records, and vital statistics/death

records between August 2001 and August 2018 using probabilistic linkage based on names, gender, date of birth and Indigenous status, as described in the parent Opioid Agonist Treatment Safety study protocol.[337] Linkage is managed by the Centre for Health Record Linkage (CHeReL) within the NSW state government. The database includes dates of OAT initiation and discontinuation, but does not include information on OAT medication dosages or reliable information on reasons for OAT discontinuation.

4.4.2 Participants

I included Opioid Agonist Treatment Safety study participants who survived at least one unplanned hospitalization with skin and soft-tissue infection, sepsis or bacteraemia, endocarditis, osteomyelitis, septic arthritis, or central nervous system infections (brain or spine abscess), identified using ICD-10 codes (see Figure 59 for study inclusion flow diagram; see Appendix 24 for ICD codes). I began with codes used in prior studies[58,117,294,334,335] and adapted the final list based on literature review and input from the full investigator team.

To be eligible, these hospitalizations had to end with the participant discharged alive to the community (rather than transfer to another hospital) so that participants could be eligible for OAT outside the hospital (see Figure 59). This was so that the timing of potential exposure and potential outcome were aligned, to avoid problems with "immortal time bias" when participants would be unable to experience either the exposure (OAT outside of acute care hospitals) or the outcomes (rehospitalization or death).[341] Eligible hospitalizations also had to be emergency (unplanned) admissions. I excluded routine or planned admissions (e.g. for physical therapy or diagnostic procedures) because they are unlikely to represents episodes of acute illness attributable to injecting-related infections.

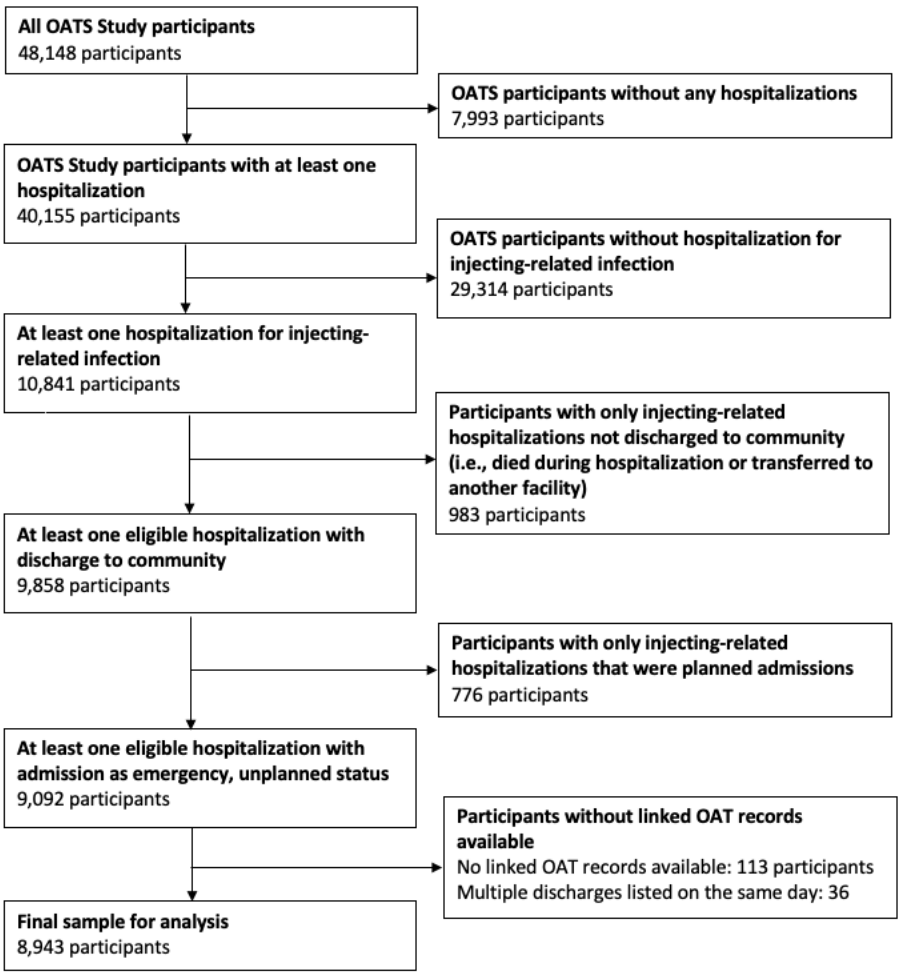

Figure 59. Study flow diagram for study on opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections. OATS Study: Opioid Agonist Treatment Safety Study. OAT: Opioid Agonist Treatment.

4.4.3 Outcomes

Primary outcomes were all-cause mortality and rehospitalization with an injecting-related bacterial or fungal infection. Observed time at risk (time = 0) begins the day of discharge from participants' earliest eligible hospitalization for injecting-related infections (see Figure 60 for graphical summary of study design). Rehospitalizations for injecting-related infections were identified using the same criteria as index hospitalizations, and therefore also had to be coded as emergency (unplanned) admissions. These could occur at any time point in follow-up, so may have included both hospitalizations for new infections and for failed treatments of initial infections. Participants were censored if they were still event-free on 29 June 2018.

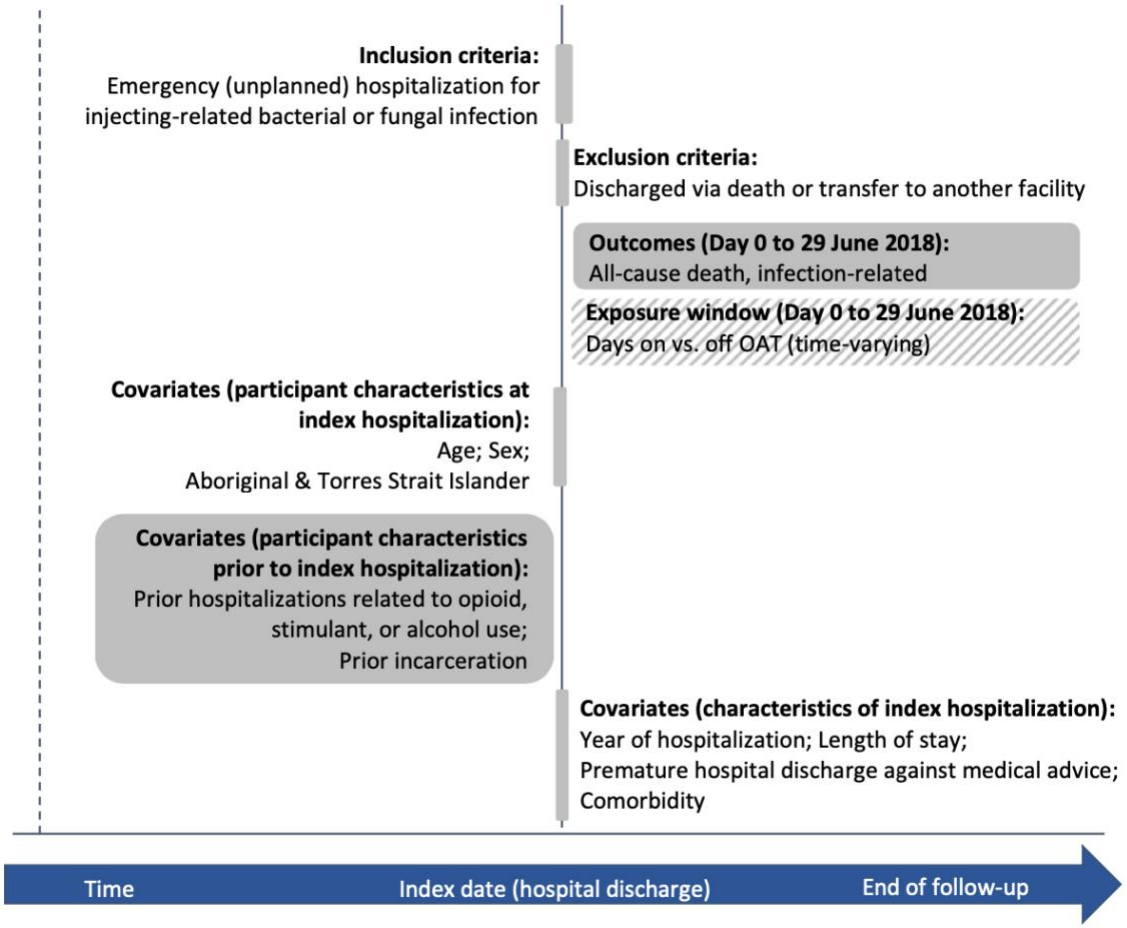

Figure 60. Study design for study on opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections.

4.4.4 Primary exposure

The primary exposure was use of OAT, defined by dates with an active OAT prescription. OAT exposure was treated as time-varying, by day of receipt. This means that each participant's follow-up time was divided into exposed (on OAT) and unexposed (off OAT) episodes (i.e., medication status was not necessarily constant through follow-up).[342] I did not stratify by type of OAT (i.e., methadone or buprenorphine) as I had no hypothesis that the protective effect would differ.

Consistent with previous studies, a new OAT episode was defined as one commencing seven or more days after the end date of a prior treatment episode.[339,343–345] The same definition was used for defining the end of OAT episodes, treating the six days following the final day of the prescription as part of the episode. The decision to incorporate the six days following an OAT episode into the exposure definition was originally based on consultation with clinicians and pharmacologists;[345] it has been used in previous studies by members of our group,[345,346] and similar cut-offs (e.g. three to six days) have been used by other investigators.[347,348] This approach may introduce bias by allocating

outcomes to the treatment period when they actually occurred after leaving treatment; this may over-estimate rates of outcomes in-treatment (on OAT) and under-estimate rates of outcomes out-of-treatment (off OAT), resulting in conservate estimates of potential benefit.

4.4.5 Covariates

See Figure 80 (in Appendix 25) for a directed acyclic graph (DAG) describing the hypothesized relationships between OAT status, the outcomes of interest, and potential confounders. All covariates were extracted from linked hospital administrative records, unless otherwise specified.

Participant characteristics measured at the time of index hospitalization included age in years (centered to mean and standardized to units of one standard deviation), sex (female or not female), Indigenous status (identification as Aboriginal/Torres Strait Islander or not Indigenous), and comorbidity (defined by the count of unique ICD-10 chapters recorded in any diagnostic position for the index admission). Participant characteristics measured prior to the index hospitalization (all treated as binary) include any prior acute care hospitalizations related to poisoning or toxicity from opioids (as indicators of addiction severity; T40.0 – T40.6), alcohol (F10.0, X45, X65, Y15, T51.0), or stimulants (T40.5 T43.6), and a history of incarceration. Dates of incarceration were derived from linked incarceration administrative records.

Characteristics of the index hospitalization include the year of admission (grouped as 2001− 2006, 2007− 2011, or 2012− 2018), length of stay in days (as an indicator of initial illness severity; centered to mean and standardized to units of one standard deviation), and premature patient-initiated discharge against medical advice (AMA; treated as binary). For descriptive purposes, I also classified hospitalizations by the presence of each type of injecting-related infection.

4.4.6 Analysis

All analyses were conducted using R version 3.6.3. I calculated the incidence rate (with Poisson confidence intervals) of each outcome per person-time while exposed to OAT and per person-time while unexposed to OAT during follow-up. I then described the cumulative hazard of each outcome, by OAT exposure, using Kaplan-Meier curves and the Simon-Makuch extension for time-varying exposures.[349] In this approach, the conditional survival estimations are similar to the traditional Kaplan-Meier method for time-fixed exposures (as a function of the number of events vs. the number of participants at risk, updated at each day of follow-up). However, in the Simon-Makuch extension method, participants' exposure status is also updated at each day of follow-up; in this

way, it calculates conditional survival estimates during time on treatment vs. time off treatment. The resulting survival curves can be interpreted as the estimated survival of participants who did not change their OAT exposure status during follow-up (i.e., one curve includes only days exposed to OAT and the second curve includes only days unexposed to OAT). I then used Cox proportional hazards models to estimate the association between OAT receipt (also as time-varying, by day) and the study outcomes to generate hazard ratios, adjusting for covariates.

4.4.6.1 Supplementary analysis

The relationship between OAT use and the outcomes (mortality or rehospitalization with injecting-related infection) may vary over time, and OAT may have a larger effect closer to the time of initial hospital discharge (when one may be at higher risk of readmission or other adverse outcomes). As such, I performed a *post hoc* (not prespecified) supplementary analysis to generate period-specific hazard ratios within the first year after hospital discharge, within years 2 to 3, and within years 4 to 6. I did this as an extension of our final multivariable models in the main survival analyses, adjusting for all prespecified covariates.

4.4.6.2 Sensitivity analyses

I conducted several *post hoc* sensitivity analyses to test the robustness of our main analysis. First, I tested the impact of alternative OAT exposure period definitions. In our main analysis (described above), I prespecified that the six days following the end of an OAT episode is counted as part of the exposure. I tested whether I found similar results when reducing this exposure period to the two days following the OAT episode, and when extending it to 10 days following the OAT episode.

I then conducted a sensitivity analysis to address a potential source of "immortal time bias" in the mortality outcome survival analysis. Immortal time occurs when, within an observation period, there is a period of time where an outcome event cannot possibly have occurred.[341,350] Because linkage between OAT record data and hospitalization data was retrospective, some participants may have had their initial hospitalization before their initial OAT record and would have been unable to experience death during this time (in other words, the fact that they have a future OAT record means they could not have died before then). I therefore constructed a new analytic sample only among participants who experienced hospitalization for injecting-related infection after their first record of OAT. I did not feel this potential issue with immortal time bias would affect the rehospitalization outcome survival analysis because participants could have experienced a rehospitalization event at any time (in this case, the fact that they have a future OAT record does not necessarily mean they could not have been hospitalized before then).

4.5 Results

4.5.1.1 Participants

I identified 8,943 participants with at least one hospitalization for injecting-related bacterial or fungal infections. Characteristics of the sample are summarized in Table 1. Participants were mostly men (66.0%) and median age at study entry was 38 years. Skin and soft tissue infections were present during most hospitalizations, and 14% of participants experienced a premature discharge "against medical advice" (see Table 6). Length of stay had a right-skewed distribution, with median four days, 75th percentile eight days, and 99th percentile 65 days.

Table 6. Descriptive characteristics of the sample in study on opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections.

Variable	Levels	Total (100%)
Sample	N (%)	8,943 (100%)
Participant characteristics		
Age	Mean (SD)	39 (11)
	Median [IQR]	38 [31 – 46]
Sex	Female	3,080 (34%)
	Male	5,863 (66%)
Aboriginal or Torres Strait Islander	Yes	1,321 (15%)
	No	7,554 (85%)
	Unknown	66 (<1%)
Comorbidities[1]	Median [IQR]	3 [2 – 5]
	1	1183 (13%)
	2	1620 (18%)
	3	1825 (20%)
	4	1418 (16%)
	5	1040 (12%)
	6+	1857 (21%)
Prior opioid-related hospitalization	Yes	749 (8%)
	No	8194 (92%)
Prior stimulant use-related hospitalization	Yes	205 (2%)
	No	8,738 (98%)
Prior alcohol use-related hospitalization	Yes	929 (10%)
	No	8,014 (90%)
Prior experience of incarceration	Yes	3845 (43%)
	No	5098 (57%)
Index hospitalization characteristics		
Year of hospitalization	2001-2006	2772 (30%)
	2007-2011	2412 (27%)
	2012-2018	3809 (43%)
Distribution of infections[2]	Total	8943 (100%)
	Skin & soft tissue	7021 (79%)
	Sepsis/Bacteraemia	1207 (14%)
	Endocarditis	431 (5%)

	Osteomyelitis	375 (4%)
	Septic arthritis	323 (4%)
	Central nervous system	69 (1%)
OAT prescription active at time of discharge	Yes	4,292 (48%)
	No	4,651 (52%)
Length of stay (days)	Mean (SD)	8.9 (42)
	Median [IQR]	4 [2 – 8]
Discharge against medical advice	Yes	1,246 (14%)
	No	7,697 (86%)

[1]Comorbidities defined by the number of ICD-10 chapters listed during the index hospital admission
[2]Percentages sum to greater than 100% because each hospitalization may have codes for multiple infection categories

Just under half of participants (4,292; 48%) were receiving OAT at the time of their index hospitalization for injecting-related infections. Of 4,651 (52%) participants without an active OAT prescription at the time of their index hospitalization, most did not access OAT soon after discharge. For example, 199 (4%) participants initiated OAT within one week of hospital discharge, 410 (9%) participants initiated OAT within four weeks, and 706 (15%) within 12 weeks.

4.5.1.2 Main results

4.5.1.2.1 All-cause mortality

Out of 8,943 participants, 1,481 (17%) died during follow-up. In total, participants were followed for 65,240 person-years (median 6.56 years of follow-up per person), including 34,146 (52%) person-years exposed to OAT and 31,094 (48%) person-years unexposed. Of all participants, 2,174 (24%) remained exposed to OAT throughout the entire follow-up period and 1,341 (15%) remained unexposed throughout (with the remainder of participants having intermittent use of OAT).

Of the deaths, 643 (43%) occurred during an OAT exposure period, and 838 (57%) occurred while unexposed to OAT. Mortality rates were 1.88 deaths (95% CI 1.17 – 2.03) per 100 person-years exposed to OAT, and 2.69 (2.51 – 2.88) per 100 person-years unexposed to OAT.

Extended Kaplan-Meier survival curves for time-to-death are presented in Figure 61. Cumulative hazard for death in OAT treatment vs. non-treatment periods was 0.3% vs. 1.2% at 30 days, 0.8% vs. 2.1% at 90 days, and 2.4% vs. 4.3% at 365 days.

Results of survival models are presented in Table 7. In the adjusted model, OAT was associated with reduced hazard of all-cause death (adjusted Hazard Ratio [aHR] 0.63, 95% CI 0.57 - 0.70).

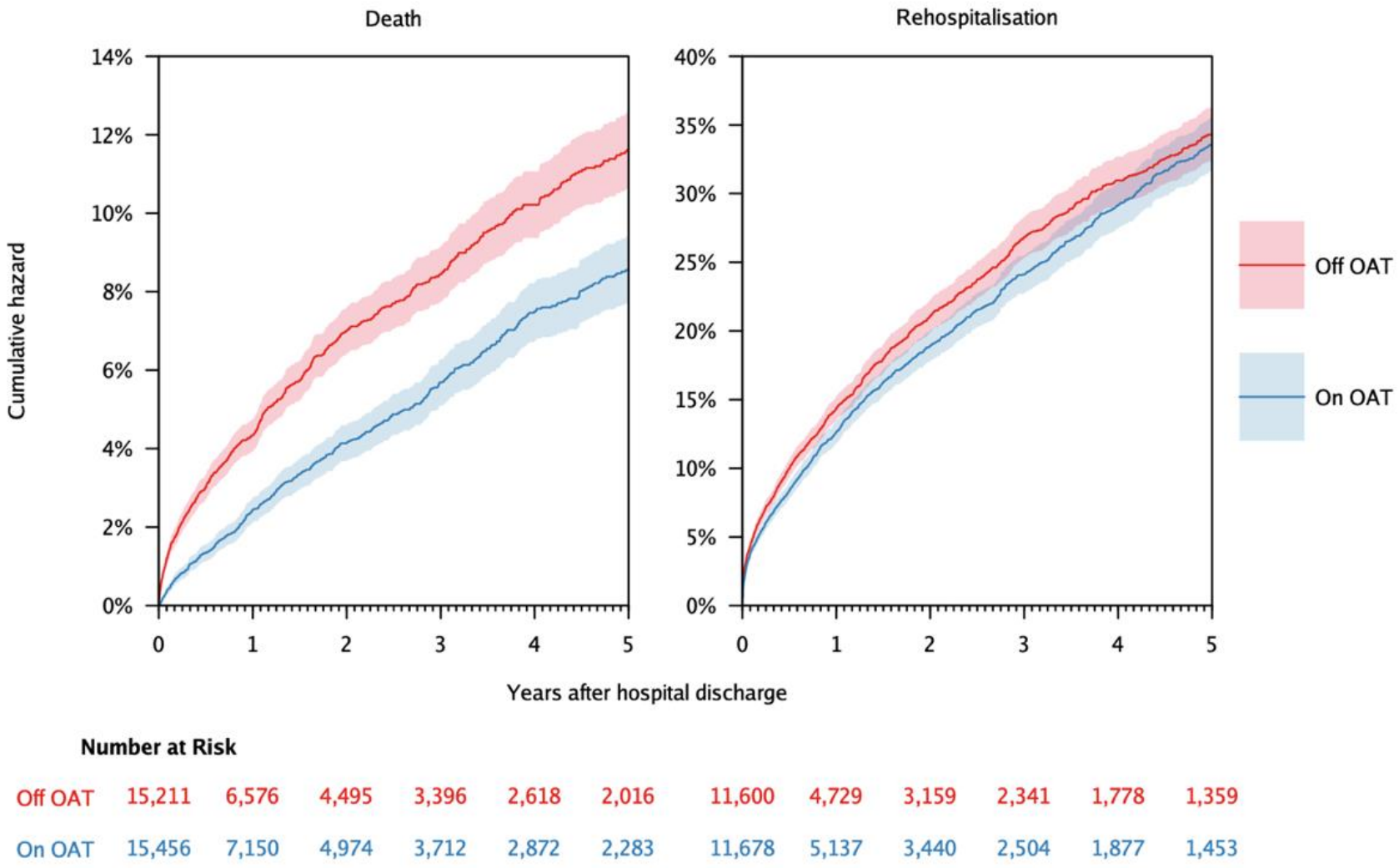

Figure 61. Extended Kaplan-Meier curves for time-to-death and time-to-rehospitalization among participants in the OATS Study who survived an initial hospitalization with injecting-related bacterial or fungal infections. Both analyses involve 8,943 participants. The death analysis was based on 30,667 treatment or non-treatment periods, and the rehospitalization analysis was based on 23,278 treatment or non-treatment periods.

Table 7. Results of Cox regression for survival following discharge from index hospitalization with an injecting-related bacterial or fungal infection.

Variable	Levels	Mortality outcome		Rehospitalization outcome[1]	
		Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[2]	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[2]
Primary exposure					
Opioid agonist treatment	Exposed day	0.72 (0.64 – 0.79)	0.63 (0.57 - 0.70)	0.95 (0.89 – 1.01)	0.89 (0.84 - 0.96)
Participant characteristics					
Age	Years (scaled)	2.15 (2.04 – 2.26)	2.04 (1.93 - 2.17)	1.33 (1.29 – 1.37)	1.26 (1.22 - 1.31)
Sex	Female	0.83 (0.74 – 0.92)	0.92 (0.82 - 1.02)	1.05 (0.99 – 1.13)	1.09 (1.02 – 1.17)
Aboriginal or Torres Strait Islander	Yes	0.72 (0.61 – 0.85)	1.02 (0.86 - 1.20)	0.95 (0.86 – 1.04)	1.00 (0.91 - 1.10)
	Unknown	0.92 (0.52 – 1.62)	0.95 (0.54 - 1.69)	0.57 (0.37 – 0.88)	0.62 (0.41 - 0.96)
Comorbidities	1	Reference	Reference	Reference	Reference
	2	1.46 (1.14 - 1.89)	1.39 (1.09 - 1.78)	1.14 (1.01 – 1.28)	1.09 (0.97 - 1.23)
	3	1.88 (1.49 - 2.38)	1.74 (1.38 - 2.20)	1.15 (1.02 – 1.29)	1.10 (0.98 - 1.24)
	4	2.19 (1.73 - 2.79)	1.98 (1.55 - 2.51)	1.29 (1.14 – 1.46)	1.20 (1.06 - 1.36)
	5	3.18 (2.50 – 4.05)	2.58 (2.03 - 3.30)	1.54 (1.35 – 1.75)	1.34 (1.18 - 1.54)
	6+	5.09 (4.09 - 6.34)	3.49 (2.79 - 4.36)	1.83 (1.63 – 2.06)	1.49 (1.32 - 1.68)

Prior opioid-related hospitalization	Yes	1.15 (1.02 – 1.30)	1.12 (0.98 - 1.28)	1.33 (1.18 – 1.49)	1.11 (0.98 - 1.25)
Prior stimulant use-related hospitalization	Yes	0.83 (0.66 – 1.06)	1.05 (0.82 - 1.34)	1.20 (0.96 - 1.49)	1.07 (0.85 – 1.34)
Prior alcohol use-related hospitalization	Yes	1.09 (0.96 – 1.24)	1.06 (0.93 - 1.21)	1.31 (1.18 – 1.46)	1.16 (1.04 - 1.30)
Prior experience of incarceration	Yes	0.76 (0.68 – 0.84)	1.00 (0.89 - 1.12)	0.99 (0.93 – 1.06)	1.02 (0.96 - 1.10)
Index hospitalization characteristics					
Era of hospitalization	2001-2006	Reference	Reference	Reference	Reference
	2007-2011	1.25 (1.11 – 1.41)	0.94 (0.83 - 1.07)	1.13 (1.04 – 1.23)	1.02 (0.94 - 1.11)
	2012-2018	1.64 (1.44 – 1.87)	0.83 (0.72 - 0.96)	1.73 (1.60 – 1.87)	1.33 (1.22 - 1.46)
Length of stay	Days (scaled)	1.04 (1.02 – 1.06)	1.02 (0.99 - 1.06)	1.03 (1.01 – 1.04)	1.01 (0.99 - 1.04)
Discharge against medical advice	Yes	0.94 (0.81– 1.10)	1.10 (0.94 - 1.28)	1.41 (1.30 – 1.54)	1.47 (1.34 – 1.60)

[1]Rehospitalization with injecting-related infection

[2]Fully adjusted model includes all variables listed in the table

4.5.1.2.2 Rehospitalization with injecting-related infections

Out of 8,943 participants, 3,653 (41%) were rehospitalized with an injecting-related bacterial or fungal infection. The distribution of infection type for these rehospitalizations was similar to the distribution during the index hospitalization. This included 2,718 (78%) hospitalizations with skin and soft-tissue infections, 556 (15%) with sepsis, 255 (7%) with endocarditis, 254 (7%) with osteomyelitis, 144 (4%) with septic arthritis, and 53 (1%) with central nervous system infections.

Participants were followed for 44,690 person-years (median 3.41 years per participant), which included 22,987 (51%) person-years exposed to OAT and 21,703 (49%) person-years unexposed. Of all 8,943 participants, 2,693 (30%) remained exposed to OAT throughout the entire follow-up period and 2,157 (24%) remained unexposed throughout.

Of the rehospitalizations, 1,820 (50%) occurred during an OAT exposure period, and 1,833 (50%) occurred while unexposed to OAT. Incidence rates for rehospitalization with injecting-related infection were 7.92 (95% CI 7.66 – 8.29) per 100 person-years exposed to OAT, and 8.45 (8.06 – 8.84) per 100 person-years unexposed to OAT.

Extended Kaplan-Meier survival curves for time-to-rehospitalization are presented in Figure 3. Cumulative hazard for rehospitalization in OAT treatment vs. non-treatment periods was 3.7% vs. 4.3% at 30 days, 6.0% vs. 7.1% at 90 days, and 12.7% vs. 14.4% at 365 days.

In the adjusted model, OAT was also associated with reduced hazard of rehospitalization (aHR 0.89, 95% CI 0.84 - 0.96; Table 7).

4.5.1.3 Other results

4.5.1.3.1 Supplementary analyses

In a *post hoc* supplementary analysis, I explored associations between OAT and mortality or rehospitalization for injecting-related infections at different points in follow-up using period-specific hazard ratios (Table 8).

Table 8. Period-specific adjusted hazard ratios for associations between opioid agonist treatment and all-cause mortality or rehospitalization for injecting-related infections.

Time since hospital discharge	Mortality outcome	Rehospitalization outcome
	Adjusted Hazard Ratio (95% CI)[1]	Adjusted Hazard Ratio (95% CI)[1]
Within first year	0.47 (0.40 – 0.55)	0.83 (0.77 – 0.91)
Year 2-3	0.66 (0.54 – 0.81)	0.87 (0.76 – 0.99)
Year 4-6	0.76 (0.58 – 0.98)	1.10 (0.91 – 1.33)

[1]Hazard ratios (with 95% confidence intervals) are for opioid agonist treatment exposure in fully adjusted models for all covariates.

4.5.1.3.2 Sensitivity analyses

I conducted *post hoc* sensitivity analyses exploring the impact of alternative OAT exposure timing definitions. Changing the exposure definition to incorporate the two days following the end of the OAT episode (reduced from six days in the main analysis) demonstrated similar results for the association between OAT with all-cause mortality (aHR 0.51, 95% CI 0.46 – 0.57) and with rehospitalization (aHR 0.88, 95% CI 0.83 - 0.95). Extending the exposure period to incorporate 10 days following the end of the OAT episode also demonstrated similar results for mortality (aHR 0.72, 95% CI 0.65 – 0.80) and for rehospitalization (0.89, 95% CI 0.84 – 0.95).

I then conducted a *post hoc* sensitivity analysis for the mortality outcome, reconstructing the analytic sample only among participants who experienced hospitalization for injecting-related infection at a date following their first record of OAT. This sample was slightly smaller (n=7,641). Compared to the main analysis, more participants (59%) had an active OAT permit at the time of discharge from their index hospitalization and more follow-up time was exposed to OAT (59%). In the fully adjusted model in this smaller sample, OAT was also associated with reduced hazard of all-cause death (aHR 0.56, 95% CI 0.51 – 0.62).

4.6 Discussion

Amongst a large cohort of people with opioid use disorder who have been hospitalized with injecting-related bacterial or fungal infections, I found that OAT receipt after hospital discharge was associated with decreased risk of mortality and of rehospitalization with these infections. The magnitude of the association between OAT and reduced rehospitalization risk was more modest, but I am not aware of other interventions shown to reduce risk of reinfection in this setting. Rates of death and rehospitalization remained high for this young cohort of patients, even among those

exposed to OAT. Half of the sample were not prescribed OAT at the time of discharge from their initial infection-related hospitalization, and only 15% of these participants initiated OAT in the three months following. This suggests that OAT should be offered as part of a multi-component treatment strategy for injecting-related infections, aiming to reduce death and reinfection. In a *post hoc* supplementary analysis modelling time periods after hospital discharge, effect sizes were larger soon after discharge. The findings were robust to several sensitivity analyses. Our findings of an association between OAT and reduced risk of death among people with opioid use disorder following a hospital admission with injection drug use-associated bacterial and fungal infections are also consistent with prior evidence.

Our findings on the benefits of OAT engagement for patients after injecting-related infection in Australia build on mixed evidence from USA insurance claims databases with lower rates of OAT exposure and smaller sample sizes, as summarized in the quantitative systematic review in Chapter 3. One previous study, among patients with injecting-related infective endocarditis in Massachusetts, USA, showed time-varying exposure to OAT or extended-release naltrexone (an opioid antagonist) after hospitalization was associated with reduced risk of death.[335] A study of patients with injecting-related infective endocarditis in a US nationwide commercial insurance claims database examined associations between buprenorphine or naltrexone within 30 days after hospital discharge and risk of rehospitalization; effect estimates were associated with wide confidence intervals that could include both beneficial or harmful effects.[334] The sample was smaller than than in my study reported here (768 participants), and less than 6% of patients were exposed to these medications during follow-up.[334] In another study analyzing patients with injecting-related skin and soft tissue infections in the same US insurance claims database, 5.5% were exposed to buprenorphine or naltrexone in 30 days following hospital discharge and this was associated with lower risk of rehospitalization with skin and soft tissue infections at one year of follow-up.[294] In a retrospective chart review study of patients admitted to a Missouri, USA, hospital with injecting-related bacterial or fungal infections, those who received OAT during their hospitalization and continued it at discharge were less likely to be readmitted for injecting-related infections.[351] Our findings offer more robust supportive evidence of the beneficial effects of OAT exposure following hospitalization with multiple types of injecting-related infections, a larger sample size, and higher rates of OAT exposure with more specific effect estimates.

In the present study, I identified larger effect estimates for associations between OAT use and mortality than for associations between OAT use and rehospitalization with injecting-related infections. My findings of a large protective effect of OAT on mortality risk reduction are in keeping

with prior research, including multiple observational studies showing protective effects on all-cause mortality, opioid overdose deaths, and multiple other specific causes of death (including suicide, cancer, alcohol-related, and cardiovascular-related).[93,352] Future research should investigate associations between OAT and specific causes of death after hospitalization with injecting-related infections. I hypothesized several pathways through which OAT might reduce risks of recurrence of injecting-related infections, including reducing frequency of opioid injecting, improving health care contacts, and reducing the impacts of criminalization and violence, but I was unable to explore specific mechanisms in this study of administrative data.[21,96] People accessing OAT may still be at risks of injecting-related infections through several pathways, including ongoing injection opioid use while on OAT, suboptimal access to safe housing and harm reduction services (e.g. needle exchange, supervised consumptions sites) and by injecting stimulants. OAT is known to reduce risks of death even among people who continue to use nonmedical or criminalized opioids,[353] who may still be at risk of injecting-related infections. More research is needed to understand how to further reduce risks of injecting-related infections for people both on and off OAT.

Despite the known benefits of OAT for mortality risk reduction, less than half of participants in my study reported here had an active prescription for OAT at the time of discharge from their index hospitalization with injecting-related bacterial or fungal infections. Published rates of OAT engagement as part of discharge planning following hospitalization with injecting-related infections vary widely, with published rates including 8% in Boston, Massachusetts, USA[331] and 81% in Saint John, New Brunswick, Canada.[117] Improving access to OAT requires clinical and regulatory changes, including improved education for health professionals, increasing the number of points of access and availability on-demand, facilitating multiple medication options, and decreasing out-of-pocket patient costs.[354] Infectious disease specialists should consider integrating OAT into their care of patients with injecting-related infections.[117,355] Addiction medicine physicians can be incorporated into multidisciplinary teams to help care planning for these patients.[115] The time period immediately following discharge from acute care hospitalization is a particularly dangerous time for people with opioid use disorder,[356] and so hospital-based health care providers should offer OAT initiation and facilitate a seamless transition to ongoing, outpatient care.[97,117,285,351] This is supported by our findings that the protective effects of OAT may be greatest soon after hospital discharge. Unfortunately, risks of death and rehospitalization remain high among people with opioid use disorder even when engaged in OAT. Addiction treatment should be considered as part of a multi-component secondary prevention strategy that could include consideration of environmental determinants like housing and access to other harm reduction services.[21,357]

While planning and conducting the analyses presented in this Chapter, I also contributed to a study led by Colledge-Frisby assessing OAT use and risk of injecting-related infections and diseases in the whole Opioid Agonist Treatment Safety study sample (rather than specifically in the time after hospital discharge).[358] In that study, the incidence rate ratio for hospital admissions was also relatively modest (adjusted rate ratio [aRR] 0.92; 95%CI 0.87–0.97) and generally consistent with my findings here in the post-discharge period (aHR 0.89; 95%CI 0.84 - 0.96). In Colledge-Frisby's study, the first four weeks of an OAT episode was associated with an increased rate (aRR 1.53, 95%CI 1.38–1.70), which we hypothesized may be explained by referrals from community OAT services to hospital.[358] This informed our subsequent analyses (in Chapter 5, below) where I was able to assess changes over time in the relationship between OAT use and injecting-related infections.

4.6.1 Limitations

Our study has some important limitations. First, the Opioid Agonist Treatment Safety study cohort does not include all people who inject opioids in NSW (only those who have accessed OAT at least once during the study period are eligible for linkage and inclusion), so my findings may only be generalizable to people who have accessed OAT at some point. However, this has previously been estimated to include >75% of people with opioid use disorder in NSW[98] and, to my knowledge, this study includes the largest sample to date of people with opioid use disorder following hospitalization with injecting-related infections. Second, as this is a study of administrative health care data, I have no information on additional factors that may influence risk for these infections, including individual injecting practices, housing status, and access to needle exchange or supervised consumption sites (known in Australia as "medically supervised injecting centres").[21] I had only limited information on other social determinants, aside from prior incarceration (reflecting experiences of criminalization and possible unsafe injecting technique while incarcerated) and Indigenous identity (reflecting cultural strengths as well as experiences of colonialism and structural racism).[21] Third, I did not have reliable information on the dose received each day, so did not include dosing information. Fourth, oral methadone and sublingual buprenorphine were the only OAT medications used in NSW during the study period, so I were unable to estimate the effects of other treatment and harm reduction modalities including slow-release oral morphine, injectable OAT (with diamorphine or hydromorphone), or the emerging practice prescribing a "safe supply" of pharmaceutical opioids to substitute for illicitly manufactured heroin or fentanyl.[43]

4.6.2 Conclusion

Among people with opioid use disorder following hospitalization for injecting-related bacterial or fungal infections, use of OAT is associated with reduced risk of death or infection-related hospitalization. Our findings suggest that patients with opioid use disorder and injecting-related bacterial or fungal infections might reduce their risk of death or reinfection by engaging in OAT. Clinicians, hospitals, and health systems should facilitate access to OAT and support adherence.

In the next chapter, I perform self-controlled (within-person) analyses in the Opioid Agonist Treatment Safety study data to understand how risk for injecting-related infections changes over time in relation to OAT receipt (as a clinical exposure) and incarceration (as a social and environmental exposure).

Chapter 5 Effect of incarceration and opioid agonist treatment transitions on the risk of severe injection drug use-associated bacterial infections: a self-controlled case series in New South Wales, Australia

5.1 Attribution and outputs

I adapted the contents of this chapter from a study protocol that I posted publicly as a PDF on UCL Discovery before conducting the analyses. I have prepare these results as a manuscript and submitted for peer-review, but the findings are not yet published. I led all aspects of the conceptualization, design, analysis, and write-up.

Manuscripts:

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Bonn M, Wheeler A, Grebely J, Farrell M, Hickman M, Hayward A, Degenhardt L. Effect of incarceration and opioid agonist treatment transitions on the risk of hospitalisation with injection drug use-associated bacterial infections: a self-controlled case series in New South Wales, Australia. *Submitted*. (currently under review at *International Journal of Drug Policy*).

Pre-registered protocol:

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Bonn M, Wheeler A, Grebely J, Farrel M, Hayward A, Hickman M, Degenhardt L. Time periods of altered risk for severe injection drug use-associated skin and soft-tissue infections: protocol for a self-controlled case series in New South Wales, Australia, 2001-2018. *UCL Discovery Repository.* https://doi.org/10.14324/000.rp.10157481

5.2 Abstract

Background: Transitional times in opioid use, such as incarceration and discharge from opioid agonist treatment (OAT), are associated with fatal overdose. These transitions may also increase risks of injecting-related bacterial infections due to changing drug use practices and reduced access to health and social services, including harm reduction programs.

Methods: I performed a self-controlled case series within a cohort of people with opioid use disorder in New South Wales, Australia, 2001-2018. The outcome was hospitalisation with injecting-related bacterial infections. I divided participants' observed days into time windows related to (a)

incarceration and (b) OAT receipt. I compared hospitalization rates during focal (exposure) windows and referent (control) windows (i.e., 5-52 weeks continuously not incarcerated and continuously receiving OAT). I calculated incidence rate ratios (aIRR) using conditional logistic regression, adjusted for time-varying confounders.

Results: There were 7,590 participants (35% female; median age 38 years; 78% skin and soft-tissue infections). Risk for injecting-related bacterial infections was elevated for two weeks following release from prison (aIRR 1.45; 95%CI 1.22–1.72). Risk was increased during two weeks before (aIRR 1.89; 95%CI 1.59–2.25) and after (aIRR 1.91; 95%CI 1.54–2.36) discontinuation of OAT, and during two weeks before (aIRR 3.63; 95%CI 3.13–4.22) and after (aIRR 2.52; 95%CI 2.09–3.04) OAT initiation.

Conclusions: Rates of injecting-related bacterial infections vary greatly within individuals over time. Risk is raised immediately after prison release, and around initiation and discontinuation of OAT. Social contextual factors likely contribute to the substantially raised risks around transitions in incarceration and OAT exposure.

5.3 Introduction

Injecting-related bacterial infections (e.g., skin and soft-tissue infections, endocarditis, osteomyelitis, etc.) are common among people who inject drugs, causing pain, disablement, and death.[56,71,204] As described in Chapter 1, the incidence of severe injecting-related bacterial infections is rising in the United Kingdom,[62] Australia,[358] Canada,[51] and USA.[204] Also as explored in Chapters 1, 2, and 3, individual injecting practices (e.g. skin sterilization, intramuscular/subcutaneous injecting, reusing contaminated equipment, etc.) are known risk factors for injecting-related infections.[56,71] Individual-level educational interventions have been developed to promote safer injecting techniques,[85–87] but these show inconsistent efficacy and have not reduced population incidence. Better understanding of social and clinical factors influencing risk is urgently needed to inform new prevention approaches, as I previously explored in qualitative (Chapter 2) and quantitative (Chapter 3) systematic reviews and evidence syntheses.[21,62,202]

Incarceration and opioid agonist treatment (OAT; e.g., methadone, buprenorphine) are social and clinical exposures, respectively, that may modify risks for injecting-related bacterial infections. People in prison could face increased risks because they often need to hide drug use and reuse contaminated or blunted/dull needles, due to prohibitive drug use policies and inadequate access to

harm reduction supplies (e.g., sterile needles).[359–361] Risk could alternatively be reduced in some prisons, because of decreased access to drugs.[360] Time periods immediately following release from prison are known to be associated with increased risks of overdose, which may be due to return to injection use and disconnection from health and social services (including harm reduction programs).[361,362] These factors could also increase risks of bacterial infections after release. However, these hypotheses have not been previously tested.

OAT may reduce risks of injecting-related bacterial infections. OAT enables some people to decrease or stop injection opioid use, and facilitates access to primary care where superficial infections may be treated before they progress.[21,96,202,358,363] However, many people on OAT continue injecting and infections continue to occur.[358,363] Prior studies found reduced risk of bacterial infections among people receiving OAT[92,104,358,363] but several others identified no effect.[87,240,364] This may be due to the relatively poor quality of many of these observational studies, which limits inference. For example, in my quantitative systematic review (Chapter 3), I identified 13 studies reporting analyses of associations between opioid agonist treatment receipt and risk for injecting-related infections.[92,101,104,229,240,242,248,250,261,272–274] Only two of the studies assessed exposure to OAT and development of injecting related infections over the same time period; otherwise, the timelines did not align (e.g. Betts 2016[229] assessed currently taking OAT in relation to risk of SSTI in the past month; Dunleavy 2017[92] assessed current OAT use in relation to risk of SSTI in the past year).

Relationships between OAT receipt and infection risk may also change over time; for example, Colledge-Frisby and colleagues[358] found that the first four weeks of an OAT episode were associated with an increased rate of hospitalization with injecting-related bacterial infections. They hypothesized this was due to pre-existing infections being identified in OAT clinics and subsequent referrals to hospital. In a post-hoc analysis, they found the rate of infections was even higher in the two weeks preceding OAT initiation, which may reflect increased motivation to start OAT after developing infections. The time period immediately following discontinuation of OAT has been associated with excess risks of overdose, and this might also be true for injecting-related infections.[347,348]

A major limitation of these studies is that people who are incarcerated or receive OAT differ from people who never experience these exposures in important ways that are difficult to measure.[356,365–369] Self-controlled study designs make within-person comparisons in the probability of an event occurring at during different time periods in a person's life, and therefore control unmeasured confounding factors that do not vary over time (because people serve as their own control). Self-

controlled studies can also identify time periods of excess risk, to inform time-specific health and social care responses (i.e., "critical time interventions")[356,361,370] This has been investigated in the relationship between prison release and overdose risk,[362,370] but to my knowledge has not been explored for injecting-related infections.

5.3.1 Objectives

Using a self-controlled study design, I aimed to assess the relative incidence of injecting-related bacterial infections before, during, and after incarceration and receipt of OAT, among a large sample of people with opioid use disorder.

5.4 Methods

This was a self-controlled case series. This method includes only cases (i.e., people who experienced an outcome) and focuses on the timing of outcomes in relation to exposure status.[366–368,371] With coauthors, I published a protocol before beginning the analyses (which is included here as Appendix 26).[372] This chapter follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[373]

5.4.1 Setting and data sources

Data came from the Opioid Agonist Treatment Safety study, which I also used for Chapter 4.[336,358,363] This is an administrative data cohort including everyone in New South Wales, Australia, who accessed OAT (methadone or buprenorphine) for opioid use disorder from 2001 to 2018, linked to health services and criminal-legal administrative databases.

5.4.2 Participants

As self-controlled case series are case-only designs, the sample included those who experienced at least one outcome (i.e., hospitalization with injecting-related infection) after their first recorded use of OAT (making them eligible for inclusion in the parent study) and after 1 August 2001 (to align the timing of the linked databases). Study entry was the latter of these. Observation period end was the latter of censoring through death or 29 June 2018. Participants' observed time was not censored when they were hospitalized. See Figure 62 for a participant flow diagram.

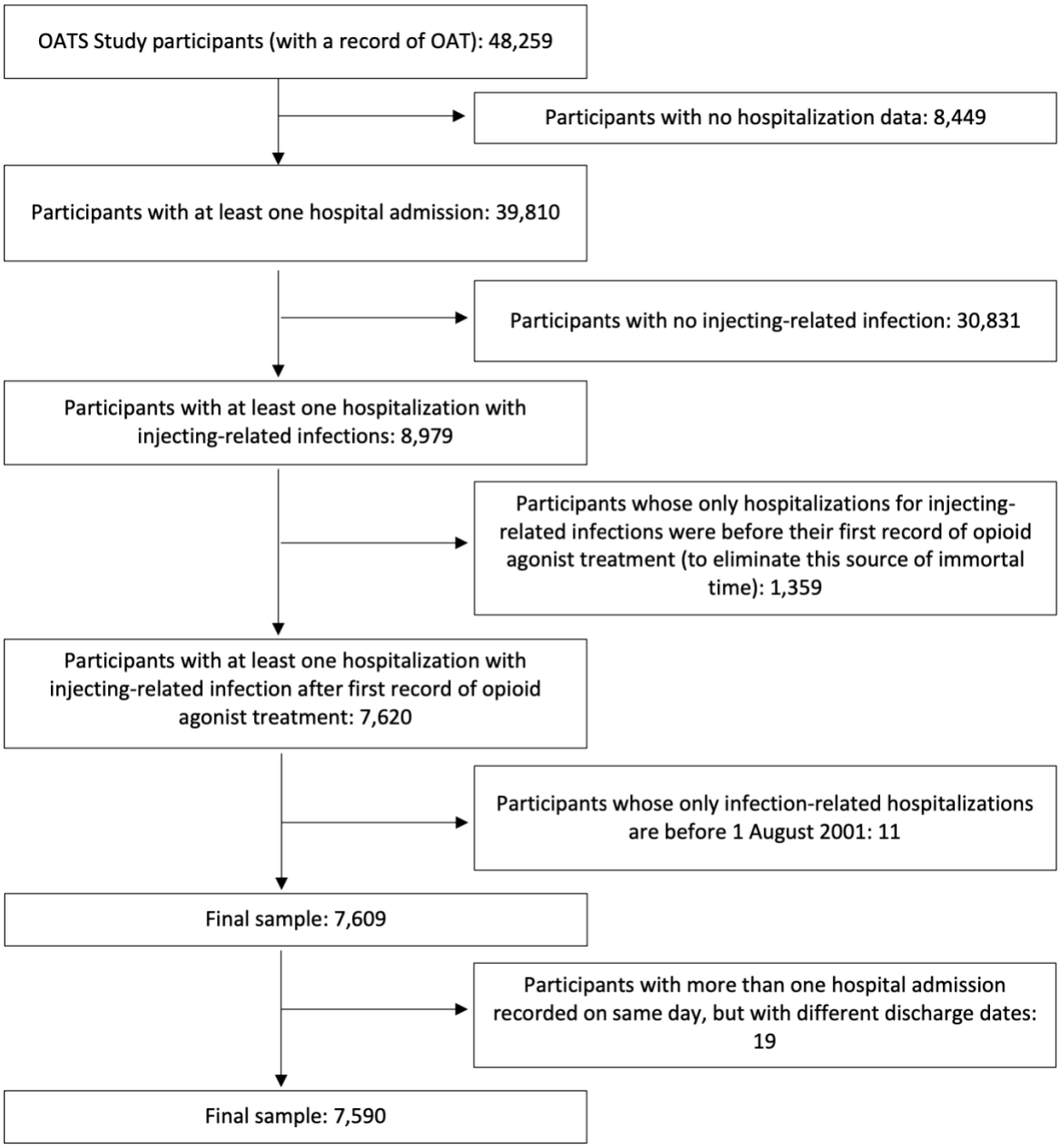

Figure 62. Flow diagram for participant inclusion in self-controlled case series on timing of severe injection drug use-associated bacterial infections in relation to incarceration and opioid agonist treatment.

5.4.3 Outcomes

The primary outcome was emergency (i.e., unplanned) hospital admissions with primary or secondary diagnoses of injecting-related bacterial infections (i.e., skin and soft-tissue infection, sepsis or bacteraemia, endocarditis, osteomyelitis, septic arthritis, or central nervous system infections [brain or spine abscess]), defined using ICD-10 code groupings consistent with prior studies.[358,363] See Appendix 24 for ICD codes.

In my preregistered protocol, the proposed primary outcome included only hospitalizations with skin and soft-tissue infections (rather than multiple types of injecting-related bacterial infections); I have

included results using this approach in Appendix 27. I chose to include all injecting-related infections in the main analysis given the shared pathophysiology and risk factors among multiple types of injecting-related infections, and because of the larger sample size.

Self-controlled case-series require recurrent outcome events to be independent, meaning that experiencing one event does not directly increase the likelihood of subsequent events. Developing one injecting-related infection may increase risk of subsequent infections (due to damage to skin, vascular, and lymphatics, and/or repeat hospitalisations for treatment of the same infection), so recurrent infections may be dependent. Therefore, I limited the primary analysis to participants' first hospitalization with injecting-related infections during the study period.[366,368] I conducted a sensitivity analysis including all of participants' hospitalizations for injecting-related bacterial infections (rather than just their first hospitalization).

5.4.4 Exposures

5.4.4.1 Timing of focal and referent windows

In separate models, I examined pre-specified time periods, known as "focal windows."[371] Focal windows for the two main time-varying exposures (incarceration and OAT episodes) were defined as: (a) first two weeks of an exposed/unexposed episode; (b) weeks three and four of an exposed/unexposed episode; (c) weeks five to 52 of an exposed/unexposed episode; and (d) remaining time during an exposed/unexposed episode, beyond 52 weeks. See Figure 63 for an illustrative schematic.

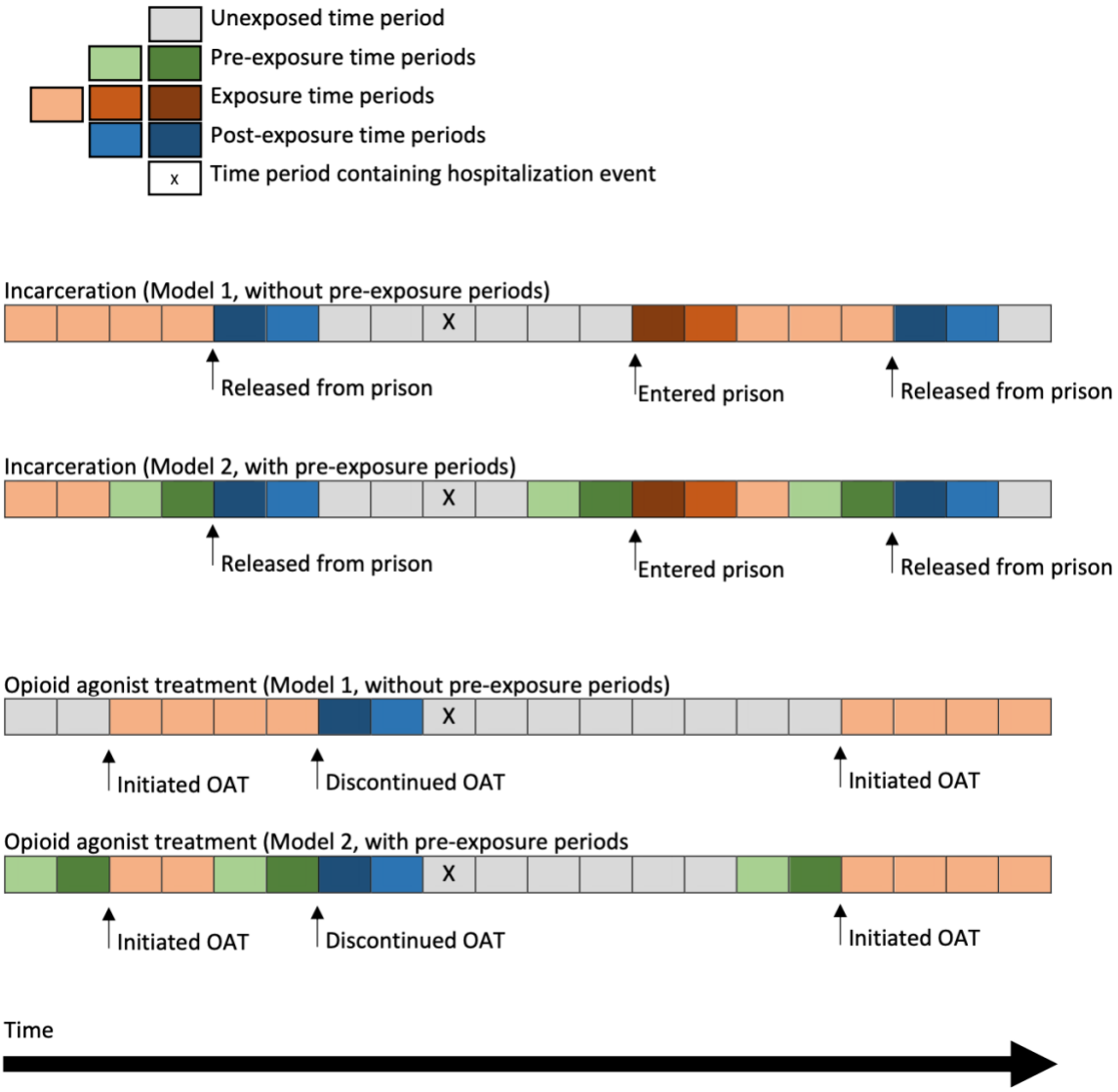

Figure 63. Time periods of potentially altered risk for injecting-related infections in the self-controlled case series. Each horizontal bar represents the same single study participant, with each shaded block representing a different time window. The top two horizontal bars represent exposure changes over time related to incarceration, in models without pre-exposure time periods (first row) and with pre-exposure periods (second row). The bottom two horizontal bars represent exposure changes over time related to opioid agonist treatment receipt, in models without pre-exposure time periods (third row) and with pre-exposure periods (fourth row).

I also assessed windows comprising days 28 to 15 and days 14 to one before a transition in exposure status (i.e. incarceration admission/release and OAT initiation/discontinuation). If I were to observe increasing risk of injecting-related infections in time windows preceding a transition (e.g. discontinuation of OAT), it may point to a third factor (e.g. life stressors) contributing to both the outcome and change in exposure. If risk of injecting-related infections is elevated immediately following the beginning of incarceration or OAT episodes, this could reflect a process of recognizing pre-existing infections in these settings and facilitating. A potential bias is introduced when including pre-exposure windows, as these rely on "immortal time" (i.e., I can only identify pre-exposure time retrospectively). Also, as I recoded these days to be negative, this changes how shorter exposure

time windows (e.g., periods of less than 28 days) are handled in regression models. I therefore present regression models both with and without pre-exposure time periods.

For the incarceration exposure, the referent window included time periods from week five through week 52 of a continuous episode of community living (i.e., not incarcerated). For the OAT exposure, the referent window was the time period from week five through 52 of a continuous OAT episode.

Consistent with prior studies (and with my previous analysis in Chapter 4),[345,358,363] I defined a new OAT episode as one starting more than six days after the end of a previous episode. The same definition was used for defining the end of OAT episodes, interpreting the six days following the final day as exposed to OAT. This was originally based on consultation with clinicians and pharmacologists[345] and similar approaches (e.g., 3 to 6 days) have been used by other investigators.[347,348] In a sensitivity analysis, I limited the OAT exposure window to two days after the final date of the OAT treatment episode, as done in my prior study (in Chapter 4).[363]

5.4.4.2 Covariates

Time-invariant confounders (e.g., sex; Aboriginal or Torres Strait Islander identity) are eliminated by the self-controlled study design. I incorporated time-varying potential confounders into multivariable regression models: calendar year; age; time since first OAT episode; and OAT or incarceration (i.e., time on OAT treated as covariate in the regression models for incarceration, and vice-versa).

5.4.5 Analysis

I reported the characteristics of cases, including age, sex, and Aboriginal or Torres Strait Islander identity. I calculated adjusted incidence rate ratios (aIRRs) using conditional logistic regression, adjusted for time-varying covariates. These compared the incidence of hospitalizations with injecting-related bacterial infections during focal time windows and referent windows. In the sensitivity analysis incorporating as all of participants' hospitalizations for injecting-related bacterial infections, I used conditional Poisson regression to calculate adjusted aIRRs. All statistical analyses were conducted with R version 4.0.4.

5.5 Results

The study included 7,590 participants who experienced at least one hospitalization with injection drug use-associated bacterial infections. The median age was 38 years and just over 1/3 were female

(Table 9). Most hospital admissions included diagnoses of skin and soft tissue infections (5,895; 77.5%). The next most common diagnoses were sepsis/bacteremia (1,048; 13.8%), endocarditis (406; 5.3%), and osteomyelitis (347; 4.6%).

Table 9. Descriptive characteristics of sample in self-controlled case series on timing of severe injection drug use-associated bacterial infections in relation to incarceration and opioid agonist treatment.

Variable	Level	Value
Sample size	N (%)	7,590 (100%)
Age at study entry	Median (IQR)	38.1 (31.6 – 45.7)
Age at first hospital admission for injecting-related infection	Median (IQR)	39.6 (32.7 – 47.1)
Sex	Female, N (%)	2,655 (34.9%)
Aboriginal or Torres Strait Islander	Yes, N (%)	970 (12.8%)
Ever incarcerated during observation period	Yes, N(%)	3,748 (49.4%)
Ever on OAT during observation period	Yes, N(%)	7,590 (100%)
Infection type in first hospital admission for injecting-related infection	N (%)[a]	
	Skin and soft-tissue infections	5,895 (77.5%)
	Sepsis/bacteraemia	1,048 (13.8%)
	Endocarditis	406 (5.3%)
	Osteomyelitis	347 (4.6%)
	Septic arthritis	290 (3.8%)
	Central nervous system	63 (0.8%)

IQR: Interquartile range. OAT: Opioid agonist treatment.
[a]Values sum to greater than 100% because each hospital admission can have more than one infection diagnosis.

Around half the sample experienced incarceration during follow-up, and the entire sample received OAT at least once (as OAT records were used as the sampling frame). Among the 3,748 participants who were in prison at some point, the median number of incarceration episodes was four (IQR 2-9). Incarceration episodes were median 16 days in duration (IQR 1-135 days). Participants had median two OAT episodes during the observation period (IQR 1-4), and OAT episodes were median 223 days duration (IQR 33-937 days). See Tables 10 and 11 for the distribution of outcome events and of observed time, categorized within each time window.

5.5.1.1 Main results

5.5.1.1.1 Incarceration exposure

Compared to the referent window (i.e., days between five and 52 weeks continuously living in the community/not incarcerated), the risk of hospitalization with injecting-related bacterial infections was elevated during two weeks immediately following release from prison (aIRR 1.45; 95%

confidence interval [CI] 1.22-1.72). When participants were incarcerated, risk of injecting-related infections was similar during the first two weeks (aIRR 1.10; 95%CI 0.85–1.40) then reduced significantly starting at week three (e.g., aIRR 0.23, 95%CI 0.13–0.40 during weeks three and four of incarceration) and remained low during the remaining time in prison. See

Table 10 for all effect estimates, and Figure 64 for a visual summary.

In the model incorporating pre-exposure time windows, risk for injecting-related infections was increased during three to four weeks prior to an incarceration episode (aIRR 1.28; 95%CI 1.06–1.54) and was not significantly different in the two weeks immediately preceding incarceration (aIRR 1.18; 95%CI 0.98–1.43).

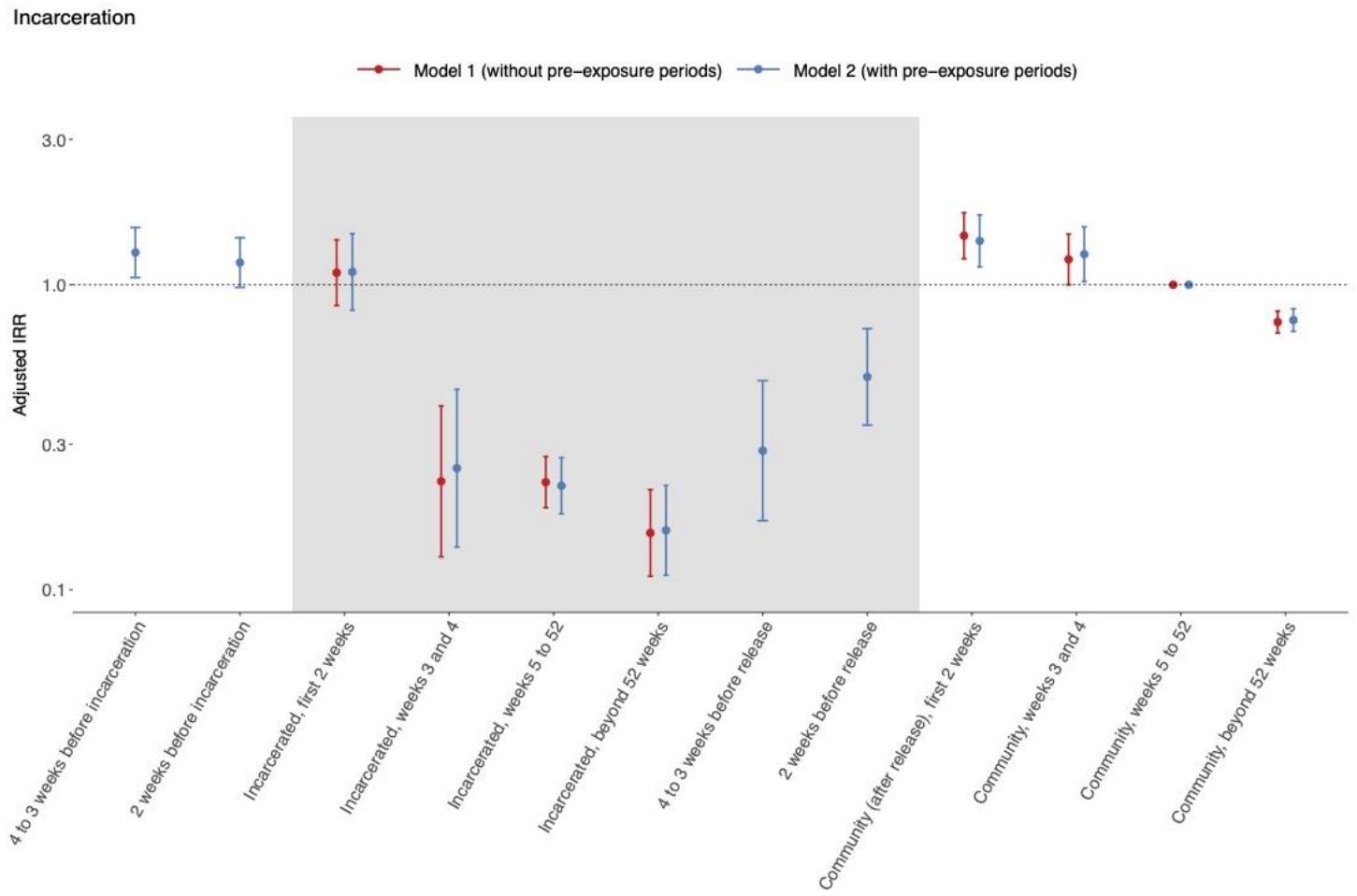

Figure 64. Visual summary of relative incidence of injecting-related infections in relation to timing of incarceration; the referent time window is time living in the community from 5 to 52 weeks after release from prison, and the grey box highlights time while in prison.

Table 10. Risk of first hospitalization for injecting-related bacterial infections according to time period in relation to incarceration (results of self-controlled case series).

		Model 1 (Not including pre-exposure periods)				Model 2 (Including pre-exposure periods)			
Exposure	Levels	Person-years in this time window (% of total person-years observed)[a]	Events	Incidence rate (per person-year)	aIRR (95% CI)[b]	Person-years in this time window (% of total person-years observed)[a]	Events	Incidence rate (per person-year)	aIRR (95% CI)[b]
Incarceration	4 to 3 weeks before incarceration	-	-	-	-	932 (1.79%)	122	0.13	1.28 (1.06 - 1.54)
	2 weeks before incarceration	-	-	-	-	1026 (1.97%)	125	0.12	1.18 (0.98 - 1.43)
	Incarcerated, first 2 weeks	571 (1.10%)	67	0.12	1.10 (0.85 - 1.40)	414 (0.79%)	49	0.12	1.10 (0.83 - 1.47)
	Incarcerated, weeks 3 and 4	487 (0.93%)	12	0.02	0.23 (0.13 - 0.40)	411 (0.79%)	11	0.03	0.25 (0.14 - 0.45)
	Incarcerated, weeks 5 to 52	4745 (9.11%)	121	0.03	0.23 (0.19 - 0.27)	4067 (7.80%)	99	0.02	0.22 (0.18 - 0.27)
	Incarcerated, beyond 52 weeks	2030 (3.90%)	43	0.02	0.15 (0.11 - 0.21)	1896 (3.63%)	40	0.02	0.16 (0.11 - 0.22)
	4 to 3 weeks before release from incarceration	-	-	-	-	464 (0.89%)	14	0.03	0.29 (0.17 - 0.49)
	2 weeks before release from incarceration	-	-	-	-	581 (1.12%)	30	0.05	0.50 (0.35 - 0.72)

	Community (after release), first 2 weeks	957 (1.84%)	145	0.15	1.45 (1.22 - 1.72)	796 (1.53%)	112	0.14	1.39 (1.14 - 1.69)
	Community, weeks 3 and 4	924 (1.77%)	117	0.13	1.21 (1.00 - 1.47)	786 (1.51%)	100	0.13	1.26 (1.02 - 1.55)
	Community, weeks 5 to 52	11357 (21.8%)	1158	0.1	Reference (1.00)	10427 (20.02%)	1030	0.1	Reference (1.00)
	Community, beyond 52 weeks	31023 (59.6%)	2085	0.07	0.75 (0.69 - 0.82)	30296 (58.2%)	2016	0.07	0.77 (0.70 - 0.83)
Opioid agonist treatment	1 day intervals	-	-	-	0.79 (0.72 - 0.86)	-	-	-	0.79 (0.73 - 0.86)
Age	10 year intervals	-	-	-	0.95 (0.85 - 1.07)	-	-	-	0.95 (0.85 - 1.07)
Calendar year	1 year intervals	-	-	-	1.01 (0.99 - 1.03)	-	-	-	1.01 (0.99 - 1.02)
Time since first opioid agonist treatment	1 year intervals	-	-	-	1 (0.98 - 1.02)	-	-	-	1.00 (0.98 - 1.02)

[a]In this analysis, 3,842 participants, associated with 48,950 years of observation time, are excluded because these participants were never incarcerated (so their time under observation could not be categorized in relation to incarceration).
[b]Adjusted incident rate ratio. Estimated from conditional logistic regression model incorporating all covariates listed in the table.

5.5.1.1.2 OAT exposure

Risk of hospitalization with injecting-related bacterial infections was almost twice as high (aIRR 1.85; 95%CI 1.52–2.24) during the first two weeks after stopping OAT, compared to the referent time window (i.e., time during week five to 52 of a continuous OAT episode). Risk was persistently elevated during the remainder of time off OAT, until greater than 1 year continually off treatment. See

Table 11 for all effect estimates, and Figure 65 for a visual summary.

In the model incorporating pre-exposure time windows, risk for injecting-related infections increased prior to both stopping and starting OAT. The highest relative incidence was in the two weeks preceding OAT initiation (aIRR 3.63; 95%CI 3.13–4.22). Risk of injecting-related infections was similar during the two weeks prior to stopping OAT (aIRR 1.89; 95%CI 1.59–2.25) compared to two weeks after stopping OAT.

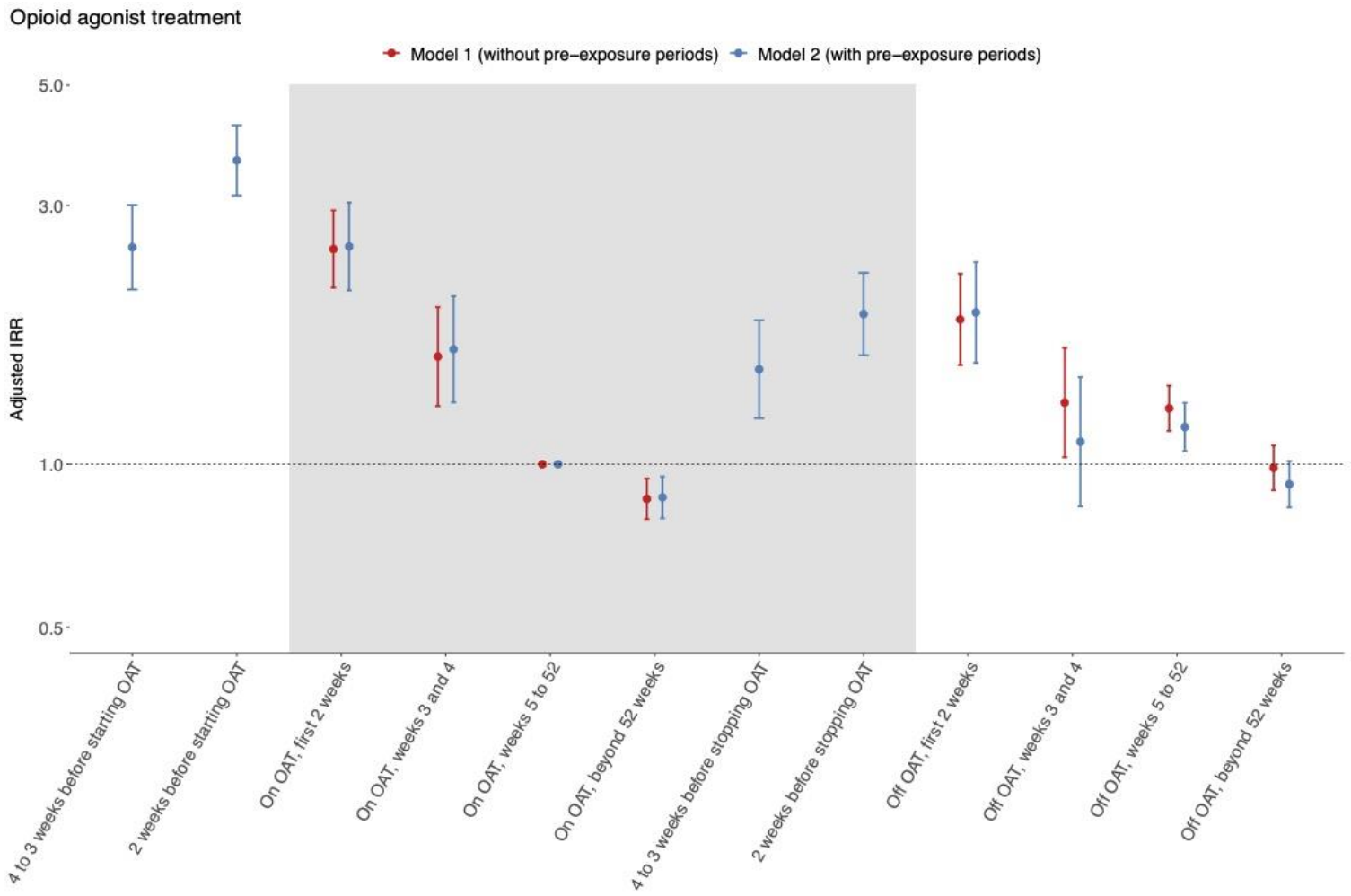

Figure 65. Visual summary of relative incidence of injecting-related infections in relation to timing of opioid agonist treatment; the referent time window is time from 5 to 52 weeks continually on opioid agonist treatment, and the grey box highlights time while receiving OAT.

Table 11. Risk of first hospitalization for an injecting-related bacterial infection according to time period in relation to opioid agonist treatment (results of self-controlled case series).

		Model 1 (Not including pre-exposure periods)				Model 2 (Including pre-exposure periods)			
Exposure	Levels	Person-years in this time window (% of total person-years)	Events	Incidence rate (per person-year)	aIRR (95% CI)[a]	Person-years in this time window (% of total person-years)	Events	Incidence rate (per person-year)	aIRR (95% CI)[a]
Opioid agonist treatment	4 to 3 weeks before starting OAT	-	-	-	–	738 (0.73%)	145	0.20	2.51 (2.10 - 3.01)
	2 weeks before starting OAT	-	-	-	–	825 (0.82%)	232	0.28	3.63 (3.13 - 4.22)
	On OAT, first 2 weeks	830 (0.82%)	174	0.21	2.49 (2.12 - 2.94)	628 (0.62%)	129	0.21	2.52 (2.09 - 3.04)
	On OAT, weeks 3 and 4	732 (0.72%)	97	0.13	1.58 (1.28 - 1.95)	634 (0.63%)	84	0.13	1.63 (1.30 - 2.04)
	On OAT, weeks 5 to 52	10785 (10.7%)	881	0.08	Reference (1.00)	10186 (10.1%)	802	0.08	Reference (1.00)
	On OAT, beyond 52 weeks	48999 (48.5%)	3234	0.07	0.86 (0.79 - 0.94)	48161 (47.7%)	3119	0.06	0.87 (0.80 - 0.95)
	4 to 3 weeks before stopping OAT	-	-	-	–	795 (0.79%)	101	0.13	1.50 (1.22 - 1.84)
	2 weeks before stopping OAT	-	-	-	–	942 (0.93%)	151	0.16	1.89 (1.59 - 2.25)
	Off OAT, first 2 weeks	773 (0.76%)	119	0.15	1.85 (1.52 - 2.24)	630 (0.62%)	96	0.15	1.91 (1.54 - 2.36)

	Off OAT, weeks 3 and 4	735 (0.73%)	79	0.11	1.30 (1.03 - 1.64)	629 (0.62%)	55	0.09	1.10 (0.84 - 1.45)
	Off OAT, weeks 5 to 52	9804 (9.70%)	992	0.10	1.27 (1.15 - 1.40)	9124 (9.03%)	828	0.09	1.17 (1.06 - 1.30)
	Off OAT, beyond 52 weeks	28386 (28.1%)	2014	0.07	0.98 (0.90 - 1.08)	27752 (27.5%)	1848	0.07	0.92 (0.83 - 1.01)
Incarcerated	1 day intervals	-	-	-	0.28 (0.24 - 0.32)	-	-	-	0.30 (0.26 - 0.35)
Age	10 year intervals	-	-	-	0.98 (0.90 - 1.06)	-	-	-	0.98 (0.90 - 1.06)
Calendar year	1 year intervals	-	-	-	1.02 (1.01 - 1.03)	-	-	-	1.02 (1.01 - 1.03)
Time since first OAT	1 year intervals	-	-	-	0.97 (0.96 - 0.99)	-	-	-	0.98 (0.97 - 0.99)

[a]Adjusted incident rate ratio. Estimated from conditional logistic regression model incorporating all covariates listed in the table.

5.5.1.2 Sensitivity analyses

When I included all of participants' hospitalizations with injecting-related infections (rather than just their first hospitalization), there were 13,958 hospitalizations, and participants had mean 1.48 hospital admissions each. Results were consistent with the main analysis, except the excess risk observed in the two weeks preceding incarceration was now statistically significant (aIRR 1.18, 95%CI 1.03-1.35). When I limited the OAT exposure definition to include two days after the final date of OAT (rather than six days), results were similar to the main analysis. See Appendix 28 for full results of sensitivity analyses.

5.6 Discussion

Within a large cohort of people with opioid use disorder in New South Wales, Australia, I performed a self-controlled case series to test the effect of incarceration and OAT transitions on the risk of hospitalization with injection drug use-associated bacterial infections. Compared to time between five and 52 weeks continuously living in the community, incidence of injecting-related infections increased before incarceration, was similar during the first two weeks of incarceration, and then substantially decreased among people in prison for more than three weeks. Risk was again elevated in the weeks immediately following release from prison. Compared to time between five and 52 weeks continuously receiving OAT, incidence of injecting-related infections was highest during the weeks both before and after OAT initiation and OAT discontinuation. Overall, I found that rates of injecting-related bacterial infections vary greatly within-individuals over time. Social contextual factors likely contribute to the substantially raised risks around transitions in incarceration and OAT exposure. People entering and leaving prison, and people starting and stopping OAT, may benefit from improved access to harm reduction programs and health and social services to prevent injecting-related bacterial infections.

I confirmed hypotheses that risk for injecting-related infections changes over time, and is increased immediately following release from prison. This may reflect return to injection drug use and disconnection from social supports, health services, and harm reduction programs that is typical upon release from prison.[361] These factors contribute to the known excess risk of overdose upon release,[362] and underscore that people leaving prison would benefit from better linkages to health and social supports, and harm reduction services. The excess risk for injecting-related infections (around 1.85 times relative incidence in our study) was more modest than that seen for overdose (e.g., 2.44 times higher fatal overdose rate in a cohort study from New South Wales, Australia;[344] 2.76 times higher nonfatal overdose risk in a self-controlled cases series from British Columbia,

Canada[369]). Incarceration often leads to loss of opioid tolerance (especially among people not receiving OAT in prison)[344,362], which likely increases overdose risk more so than infection risk. Excess risk of infection-related hospitalization during this time may also reflect people seeking treatment for infections that initially developed while in prison.

Several prior studies have assessed whether people who were recently incarcerated (i.e., past year) were more likely to experience injecting-related infections than people who had not been incarcerated. Some found increased risk[235,240,358,364] and some found similar risks.[75,125,245] These mixed findings may be, in part, because people who ever (or recently) experienced incarceration likely differ from people who never experienced incarceration in important ways that are difficult to measure and adjust-for in cohort studies. My self-controlled (within-person) analysis, reported here, found changing risk of injecting-related infections over time among a subsample of people who all experienced incarceration at some point. Decreased incidence of severe injecting-related infections while in prison likely reflects decreased access to drugs and reduced frequency of injection use. A longitudinal study in New South Wales found the prevalence of self-reported injection drug use dropped by around two-thirds once people were incarcerated.[360]

I also confirmed hypotheses that risk for injecting-related bacterial infections is increased immediately following discontinuation of OAT. While some excess risk may be attributable to loss of the protective effect of OAT medications, I observed that risk began to increase in the weeks preceding OAT discontinuation. This suggests that underlying stressors or other contextual factors in peoples' lives may increase risks for both injecting-related bacterial infections and OAT discontinuation. Similarly, I observed increased risk for injecting-related infections during the first two weeks of OAT compared to time more stable on OAT (after one month continually on treatment), but the highest relative risks were in the two weeks preceding OAT initiation. This suggests that changes in risk of injecting-related infections seen around times of OAT transitions may reflect other contextual factors, rather than the benefits of OAT alone.

These within-person findings support the results of a cohort study by Colledge-Frisby and colleagues (which used the same parent study dataset, and to which I contributed as a co-author) that risk for injecting-related infections was highest before starting OAT.[358] This suggests that developing an injecting-related infection may motivate people to initiate OAT. This could also represent referrals to OAT from health care settings when people seek treatment for injecting-related infections.

My findings that risk of injecting-related infections was modestly higher while off OAT (e.g., around 1.3 times) compared to time receiving OAT is consistent with several recent studies.[92,104,358,363] This suggests that OAT should be offered as part of a strategy to prevent injecting-related infections, but OAT alone is unlikely to prevent a large proportion of infections. Preventing injecting-related infections likely requires more broadly addressing the social determinants of health, including the social and material conditions within which people obtain drugs, prepare and inject them, and access health and social care.[21,202]

5.6.1 Limitations

This study has five key limitations. First, self-controlled designs do not produce estimates of absolute risk, only relative risk.[368] However, estimates of relative risk in self-controlled studies are applicable to the wider population from which the cases were drawn.[365,368] Second, some time-varying confounders are not measured in the administrative data, including individual injecting behaviours, the evolving unregulated drug supply, housing, income supports, life stressors, and access to harm reduction services; these may be important contributors to infections that I could not account for. Third, onset duration of injecting-related infections might vary from days to weeks between an initial abscess and hospitalization, so timing might differ from (or overlap) the focal windows as defined here. To account for this, I pre-specified time windows to comprise at least two weeks duration. Fourth, this study excludes people who were never on OAT, so the findings may only be generalizable to people who received OAT at some point. However, prior work suggests most people with opioid use disorder in New South Wales have accessed OAT.[336,358,363] Fifth, I do not have reliable data on people's reasons for discontinuing OAT; future work accounting for motivations to discontinue OAT could help with understanding risks observed around this time.

5.6.2 Conclusion

Risk for severe injection drug use-associated bacterial infections varies greatly within individuals over time. Time periods leading up to, and immediately following release from, incarceration are associated with excess risk, as are time periods around initiation and discontinuation of OAT. People entering and leaving prison, and people starting and stopping OAT, may benefit from improved access to harm reduction programs and health and social services to prevent injecting-related bacterial infections. Social contextual factors likely contribute to the substantially raised risks around transitions in incarceration and OAT exposure

Chapter 6 Thesis Discussion

6.1 Chapter summary

In this final chapter, I consider my research questions and explain how my work in this thesis has answered them. I return to the conceptual framework informing my analysis across chapters; summarize my new understanding of how risk for injecting-related infections and treatment outcomes are shaped across different moments; consider how my work contributes to existing knowledge; and propose implications for clinical practice, health and social policy, and future research directions.

6.2 Research questions and main findings

The aim of this thesis was to improve understanding of how injection drug use-associated bacterial and fungal infections, and their treatment, are shaped by social and environmental contextual factors – especially those beyond individual injecting behaviours alone. My overarching goal was to identify novel opportunities for injecting-related infection prevention and treatment strategies, especially where these social and structural determinants are modifiable. This is consistent with the philosophy of "harm reduction" and could contribute to the health of people who inject drugs without requiring abstinence as a prerequisite. Previous work on risk factors for injecting-related infections has focused on individual behaviours like drug preparation and injecting practices, or abstinence from drug use. I applied a socio-ecological conceptual model to explore how social, political, and health system factors shape and constrain individual behaviours and influence health outcomes. I also developed and applied a multi-stage framework, where risk could be influenced at multiple steps in a pathway including drug acquisition, preparation, consumption, development and treatment of superficial infections, and development and treatment of severe or invasive infections, and outcomes after treatment (Figure 66).

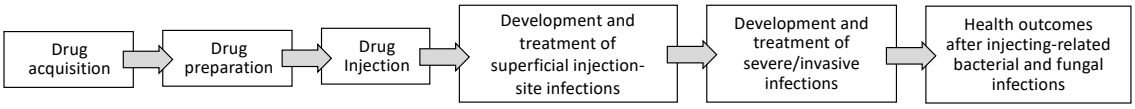

Figure 66. Illustrative schematic of pathway model to conceptualize how the risk environment shapes risk for injecting-related bacterial and fungal infections at different moments. Macro-environmental, micro-environmental, and individual-level factors interplay to influence risk at each moment. Reproduced from Brothers TD, et al. Addiction. 2023 (CC-BY copyright, does not require permission).

The thesis comprised four substantive chapters, comprising three related research questions. The research questions, what was already known, and what my thesis work adds are summarized in Table 13. Below, I discuss this in more detail.

Table 12. Summary of what my thesis work contributes to each research area.

Research area	Associated thesis chapters and methods	What was already known	What my thesis work adds
Question 1. "Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"	Chapter 2: Systematic review of qualitative studies and thematic synthesis Chapter 3: Systematic review of quantitative studies and meta-analyses	• Injection drug use-associated bacterial and fungal infections are increasing in incidence in several regions of the world. • Risk factors include female sex, more frequent injecting, intramuscular or subcutaneous injecting, lack of skin cleaning. • Needle and syringe programs provide sterile injecting equipment and education on safer injecting practices, in part to reduce risks of bacterial infections (in addition to reducing risks of HIV and HCV transmission). • Individual-level educational and behavioural interventions have been developed, and show inconsistent effectiveness. • Treatment of injecting-related infections is suboptimal; people who inject drugs describe negative experiences in health care settings.	• Injecting-related bacterial and fungal infections are shaped by modifiable social-structural factors, including poor quality unregulated drugs, criminalization and policing enforcement, insufficient housing, limited harm reduction services, and harmful health care practices. • People who inject drugs navigate these barriers while attempting to protect themselves and their community. • To account for these social contextual factors that shape individual injecting practice, health care seeking, and infection treatment outcomes, public health and clinical approaches should look towards addressing the social and material conditions within which people live, acquire and consume drugs, and access health care.
Question 2. "Among people with opioid use disorder who have been hospitalised with injection drug use-associated bacterial or	Chapter 4: Survival analysis with Cox proportional hazards models	• OAT is associated with reduced risks of death in multiple observational studies. • Following hospitalization with an injecting-related infection, OAT is associated with reduced risks of death.	• Following hospitalizations with injection drug use-associated bacterial and fungal infections, OAT is associated with reduced risks of death and recurrent injecting-related

fungal infections, does the use of opioid agonist treatment after discharge decrease risks of mortality or infection-related rehospitalization?"		• People receiving OAT are at modestly reduced risk of incident or prevalent injecting-related infection, compared to people not receiving OAT.	infections among people with opioid use disorder. • As modelled under an optimistic scenario of perfect adherence (i.e., comparing hazards of recurrent hospitalization during time on vs. time off OAT), the protective effect is modest. • OAT should be offered as part of infection treatment planning to prevent recurrent infections, but OAT alone is unlikely to substantially reduce risks of recurrence.
Question 3. "What is the effect of incarceration and opioid agonist treatment transitions on the risk of injection drug use-associated bacterial infections?"	Chapter 5: Self-controlled case series with conditional logistic regression	• Risks of other drug-related harms (e.g., overdose) vary greatly over time within-individuals, but this has not been assessed for injecting-related infections. • Specific transitional time periods, including immediately following release from prison and discontinuation of OAT, are associated with excess risks of harm.	• Rates of injecting-related bacterial infections vary greatly within individuals over time. • Risk for injecting-related infections is raised before incarceration, immediately after prison release, and around initiation and discontinuation of OAT. • People entering and leaving prison and people initiating and discontinuing OAT may benefit from targeted harm reduction supports and linkages to health and social services, to reduce risks of injecting-related infections.

6.2.1 Question 1. "Among people who inject drugs, what social and structural factors influence the development of, treatment of, and outcomes of injecting-related bacterial and fungal infections?"

I answered this question with complementary qualitative (Chapter 2) and quantitative (Chapter 3) systematic reviews and syntheses. Novel findings from my work on opioid agonist treatment after hospitalization with injecting-related infections (Chapter 4) and on the effect of transitions in exposure to incarceration and opioid agonist treatment (Chapter 5) also contributed to my understanding of how social and structural forces (beyond individual behaviour alone) shape risk for infections and treatment outcomes. Here, I provide a summary of the findings integrated across studies, at each stage of the pathway model (Figure 66).

I identified that risk for injecting-related infections and treatment outcomes are shaped by several, potentially modifiable social-structural exposures, including poor quality unregulated drugs, criminalization and policing enforcement, insufficient housing, limited harm reduction services, and harmful health care practices. My qualitative systematic review and synthesis on experiences of people who inject drugs (Chapter 2) not only identified some social-structural exposures influencing risk (e.g., homelessness), but also suggested specific potential mechanisms by which this may occur (e.g., homelessness causes people to inject outside or in abandoned buildings with inadequate lighting, preventing people from identifying veins, and leading them to inject into muscles, causing an abscess). My quantitative systematic review and meta-analysis (Chapter 3) provided estimates of associations between exposures (e.g. current/recent/lifetime history of homelessness) and outcomes (e.g. prevalent injecting-related abscess), without consideration of causal mechanisms. The quality of much of this quantitative research was relatively poor for drawing causal inferences, without incorporating causal theories/hypotheses and with timeline mismatches between exposures (e.g., homeless at any time in the past year) and outcomes (e.g., current SSTI). The "risk environment" conceptual model that I brought into the work enabled me to hypothesize about the interplay between factors at micro-environmental (e.g., individual homelessness caused by insufficient access to social housing) and macro-environmental (e.g., state housing policies and investments in social housing) levels, and how these may explain the empirical findings from the systematic reviews. In Table 13 (below), I propose a summary of micro-environmental and macro-environmental social-structural exposures identified in my thesis work, classified at each stage of the pathway model.

Table 13. Social and structural exposures identified within my thesis work that may influence risk for injecting-related bacterial and fungal infections or their treatment.

Stage in pathway model	Micro-environment	Macro-environment
Drug acquisition (including drug supply)	• Quality and solubility of local drug supply • Lack of income and employment opportunities • Availability of injectable opioid agonist treatment (e.g., heroin-assisted therapy), prescribed safer supply, and other regulated sources of drugs • Incarceration	• Interdiction and prohibitionist drug policy (lack of regulation) • Regional demarcation of unregulated drug distribution routes • Laws and regulations related to harm reduction programs • Stigma against people who use drugs • Public discourses around drug use • Universal health coverage and public insurance policies
Drug preparation	• Homelessness and access to social housing • Policing practices and crackdowns • Access to supervised consumption sites • Adequate coverage of needle and syringe programs • Incarceration	• Social housing policies and investments • Interdiction and prohibitionist drug policy • Laws and regulations related to harm reduction programs • Public discourses around drug use
Drug injection	• Gendered power relations • Racist power relations • Low income/unemployment • Less education • Homelessness and access to social housing • Policing practices and crackdowns • Access to supervised consumption sites • Adequate coverage of needle and syringe programs • Incarceration • Local availability of drugs with short half-lives, especially stimulants	• Sexism • Structural racism and settler-colonialism • Social housing policies and investments • Interdiction and prohibitionist drug policy • Laws and regulations related to harm reduction programs • Stigma against people who use drugs • Public discourses around drug use
Development and treatment of superficial infections	• Food insecurity • Stigmatizing and discriminatory attitudes by local health care providers • Local health care policies and practices related to treatment of withdrawal and pain • Access to supervised consumption sites • Access to primary health care	• Interdiction and prohibitionist drug policy • Stigma against people who use drugs • Universal health coverage and public insurance policies • Social welfare policies
Development and treatment of severe/invasive infections	• Food insecurity • Stigmatizing and discriminatory attitudes by local health care providers • Hospital policies and practices related to treatment of withdrawal and pain • Interpersonal and institutional racism in health care settings • Substance use and addiction care resources available in hospital • Availability of public or socialized health insurance	• Interdiction and prohibitionist drug policy • Stigma against people who use drugs • Structural racism and settler-colonialism • Universal health coverage and public insurance policies
Outcomes after infection treatment	• Access to social housing • Policing practices and crackdowns • Delivery of opioid agonist treatment • Substance use and addiction care resources available in hospital	• Social housing policies and investments • Interdiction and prohibitionist drug policy • Universal health coverage and public insurance policies • Laws and regulations related to harm reduction programs • Stigma against people who use drugs

6.2.1.1 Drug acquisition (including quality of unregulated drug supply)

The contribution of poor-quality unregulated drugs to infection risk was a major finding from my qualitative thematic synthesis (Chapter 2; Section 2.5.2.2.1 Unregulated drug supply). Findings from my quantitative systematic review were mixed (Chapter 3; Section 3.5.2.3 Substance use-related

factors). Qualitative study participants attributed their bacterial infections to worsening quality of the local drug supply through poorly soluble adulterants damaging veins, and/or requiring the use of additional, potentially harmful acidifiers to dissolve their drug solution.[138,326] This was supported by some findings in the quantitative systematic review, where I identified two covariate-adjusted effect estimate linking tar heroin (which is poorly soluble and requires acidifiers to dissolve) to increased risks vs. powder heroin;[260] however, meta-analytic effect estimates were imprecise with wide confidence intervals (in part due to large between-study heterogeneity). An additional ecological study found rates of SSTI to be higher in tar heroin predominant regions of the USA.[137] Other findings from the quantitative systematic review on the contributions of specific substances were less clear. Risks were increased with frequent/any (vs. less/no) crack cocaine injecting, which requires acidifiers to dissolve, but risk was also increased with powder cocaine injecting, which is typically cold water-soluble without requiring acidifiers. Increased risks of infections were seen with frequent/any use (vs. less/no use) of heroin, cocaine, and amphetamines. My theoretical framework and thesis results suggest that risk for injecting-related infections is shaped by multiple, interacting exposures across multiple levels of influence; it is possible that the signal of effects from individual substances is real but is harder to demonstrate in quantitative data isolated from broader social contextual factors that influence the availability and use of individual substances.

Several investigators have surmised that transitions in regional drug supplies towards more fentanyl and methamphetamine have contributed to the increasing incidence of injecting-related infections in North America, because these drugs are associated with short half-lives and more frequent injecting.[51,69,70] I identified no quantitative studies on the use of illicitly-manufactured fentanyl, and the incidence of injecting-related infections is rising even in places where there is very little fentanyl and the drug supply has remained predominantly heroin.[62] Few quantitative studies assessed the effects of changes in the drug supply on infection risks. One study described how a public health investigation attributed increases in injecting-related infections in Lothian, Scotland, to the emergence of ethylphenidate (a novel psychoactive stimulant associated with high-frequency injecting).[139] An interrupted time series analysis showed decreasing rates of injecting-related infections after ethylphenidate had been placed under temporary class order. The authors reported that social contextual factors made people more vulnerable to infections from the increased frequency of injecting ethylphenidate, including homelessness and public injecting, and insufficient coverage of needle and syringe programs. Two before-and-after studies[266,267] found increases in rates of injecting-related spinal epidural abscess after the implementation of U.S. state-wide opioid prescribing restrictions, presumably reducing access to prescription opioids and leading people to transition to injecting heroin. In my self-controlled case series study (Chapter 5), I identified

substantially decreased incidence of injecting-related infections after several weeks in prison; this likely reflects decreased availability of drugs in this highly controlled setting, leading to decreased injecting frequency.

People who inject drugs typically have little control over the quality of drugs available to them from criminalized sources, which are often determined by regional demarcation of illicit supply routes. People with more material resources may be able to pay for higher quality drugs (e.g., that might dissolve more effectively or come from regulated sources), and I identified some evidence of relationships between infection risk and educational attainment, income/employment status, housing status, and food security (Chapter 3; Section 3.5.2 Incident or prevalent injecting-related infections). People who inject drugs have led advocacy to facilitate access to regulated sources of drugs, including via injectable OAT (also known as "heroin-assisted treatment") and through "safe supply" prescribing programs or compassion clubs.[43,44,181] Availability of these regulated sources of drugs for injecting differs widely legal jurisdictions, and is influenced by public perceptions and discourse around substance use and harm reduction.[374–377] Existing models of injectable OAT and safe supply prescribing programs in Canada rely on public sources of funding and insurance, which differ by region.

There have been relatively few studies on access to safer drugs and changes in the subsequent risks of injecting-related infections. As described in Chapter 2 (Section 2.6 Discussion), one Canadian before-and-after study (published after I conducted the systematic review) found participants in a prescribed safer supply program were less likely to be hospitalized with injecting-related bacterial infections compared to before they entered the program.[185] However, this program (and many other prescribed safer supply programs in Canada) facilitates access to primary health care, where superficial infections could be identified and treated to prevent hospital admissions; the before-and-after study is unable to isolate the potential beneficial effects of access to a regulated drug supply alone. A Swiss before-and-after study of participants in an injectable OAT program (with liquid diacetylmorphine) found no difference in rates of hospitalization with injecting-related infections.[272]

Critics of prescribed safer supply programs in Canada have raised concerns over potential risks of injecting-related infections when people in these programs are dispensed tablets for oral consumption.[327,378,379] Some of these critics have cited a French observational study (included in my quantitative systematic review) that showed people prescribed morphine sulphate as "second-line" OAT had higher rates of hospitalization with injecting-related infections than people prescribed traditional, "first-line" OAT with buprenorphine or methadone.[380] It is likely that people requiring

"second-line" OAT face higher risks than people who receive first-line OAT (because "first-line" treatment was unhelpful or insufficient), so it is unclear if the prescription morphine actually increases risks. A recent systematic review on the potential harms of injecting controlled-release hydromorphone found some preclinical and ecological research but concluded that overall there was insufficient evidence to inform clinical practice.[379] The beneficial findings of the Canadian before-and-after safer supply program evaluation (cited above) support the relative safety of prescribed safer supply programs on infection risks.[185]

6.2.1.2 Drug preparation

I identified several social-structural exposures that could influence risks of injecting-related infections by affecting drug preparation practices. Unstable housing and homelessness were significantly associated with increased risk in my quantitative meta-analysis (Chapter 3). My qualitative thematic synthesis (Chapter 2; Section 2.5.2.2.2 Unsafe spaces) provided potential mechanisms through which homelessness could impede drug preparation practices. These included lack of access to hygienic surfaces or adequate lighting, lack of access to sterile water, or injecting in public (where people are more likely to rush their process and described skipping steps like filtration). Injecting in public was also associated with increased risk in quantitative meta-analysis. Qualitative study participants who lacked housing and injected outside discussed how police contacts and crackdowns caused them to rush their drug preparation process, though a history of police contacts and arrests was not associated with infection risk in quantitative meta-analysis. Qualitative study participants described how access to supervised consumption sites ameliorated these concerns by providing hygienic and well-lit space with unlimited equipment, where they could take their time without fear of harassment or arrest. In this way, supervised consumption sites have been conceptualized as a "safer environment intervention",[108] at the micro-environmental level. Quantitative effect estimates of supervised consumption site use and infection risk were not statistically significant, but were imprecise with wide confidence intervals that could include meaningful differences (e.g., aOR 0.59, 95%CI 0.29-1.19). Experiences of homelessness, policing contacts, and access to supervised consumption sites may all shape infection risk; these are influenced by broader, "macro-environmental" factors including public investments in social housing, drug policy, laws around harm reduction services, and public attitudes and discourses around drug use and harm reduction.

Inadequate coverage of needle and syringe programs was another potentially modifiable factor contributing to infection risk by affecting drug preparation practices. Qualitative study participants described reusing contaminated equipment when they did not have sufficient access, due to

closures on weekends or restricted eligibility. In two qualitative studies, Harris and colleagues explored how regulatory and funding restrictions on harm reduction programs limited distribution of sterile water[105] or single-use ascorbic acid packets.[138] Use of needle and syringe programs was not statistically significantly associated with reduced incidence or prevalence of injecting-related infections in my quantitative meta-analysis, but again had imprecise confidence intervals (e.g., aOR 0.75, 95%CI 0.54-1.03). This could reflect inadequate statistical power to identify a more precise effect, or rather it could show that needle and syringe programs are effectively engaging clients at relatively high risk of injecting-related infections. Further, two quantitative ecological studies (that I could not include in meta-analyses) showed reductions in injecting-related infections after people started accessing needle and syringe programs.[270,271]

My survival analysis on OAT and risk of recurrent infections (Chapter 4) and self-controlled case series (Chapter 5) did not specifically address drug preparation practices, but some findings from those studies may apply. OAT enables some people to have more control over their drug preparation practices, as they experience less severe withdrawal symptoms; this may be one mechanism by which OAT use is associated with reduced risks of injecting-related infections after hospital discharge (Chapter 4). While my self-controlled case series found the incidence of injecting-related infections decreased after several weeks in prison, injecting-related infections continued to occur. This may be because drugs are still available in prison settings and people are forced to use in unsafe ways. Prisons in New South Wales, Australia (the study setting) offer some harm reduction services, including OAT and access to an ammonium disinfectant to cleanse injecting equipment, but do not offer sterile drug preparation and injecting equipment.[48–50] In the time period immediately following release from prison people are often disconnected from local harm reduction programs, which may make them more likely to reuse nonsterile drug preparation equipment. This may be one explanation for the excess risk of infections during this time.

6.2.1.3 Drug injection

Risks of injecting-related infection can be affected in several ways at the drug injecting stage. Many exposures affecting drug preparation also contribute directly to riskier injection (e.g., insufficient coverage of needle and syringe programs leading to reuse of blunted/dull needles). My qualitative systematic review (Chapter 2) highlighted several ways in which people who use drugs care for each other and promote safer injecting, including educating peers, sharing sterile needles and syringes, and offering or receiving assistance with injecting to reduce bacterial infection risks. Assisted injecting (to help people find and access a vein in which to inject) has a complex relationship with risk for injecting-related infection. Qualitative study participants described how assisted injecting

enables people to avoid intramuscular or subcutaneous injecting, which are known risk factors for abscesses. However, people who reported requiring or receiving assisted injecting had increased risks of injecting-related infections in the quantitative meta-analysis (aOR 1.78, 95%CI 1.40-2.27); it is unclear if this effect is happening during episodes where people receive injecting assistance or during episodes when they require it but do not receive it. Providing or receiving injecting assistance is prohibited at some supervised consumption sites, which may further increase risks to people who are unable to inject themselves. People who use drugs have organized to overcome these policy barriers, for example the Vancouver Area Network of Drug Users (VANDU) established an "injection support team" to help provide safer assisted injecting.[381]

Intersectionality and the "risk environment" model encourage thinking about how social identities and locations within societal power hierarchies may constrain the ability of people to inject as safely as possible.[3,33–35] In my quantitative meta-analysis (Chapter 3), greater education and income/employment were associated with decreased risks of injecting-related infection. Though qualitative studies did not specifically address education or income, people with greater socioeconomic status may be better able to navigate harm reduction resources (including access to material resources, social supports, and education on how to inject most safely). Woman/female gender/sex was also associated with increased risk of injecting-related infections in quantitative meta-analysis. As reviewed in Chapter 3 (Section 3.6 Discussion), this may occur in the context of gendered power dynamics that would lead women to need to use contaminated equipment that has already been used by a male partner.[3,168,253] Women may be less likely to know how to inject themself, and more likely to require assisted-injecting (which was associated with increased risks of bacterial infections in the quantitative meta-analysis).[175,322] Very few harm reduction programs are gender-attentive or gender-specific, which discourages some women from accessing education and sterile equipment[3,323–325] Some investigators have also highlighted that women may be more likely to inject subcutaneously and have more difficulty accessing peripheral veins, due to different distributions of adipose tissue.[71]

Also as reviewed in Chapter 3 (section 3.6 Discussion), I did not identify varying risks of injecting-related infections by race/ethnicity in the quantitative meta-analyses (Chapter 3), but race/ethnicity was raised as an important factor the qualitative thematic synthesis (Chapter 2). One ethnographic and mixed methods study identified in my qualitative systematic review, by Bourgois and colleagues, [153] observed higher rates of injecting-related abscesses among white compared to African American participants, and they attributed this to a greater willingness among white participants to inject subcutaneously. Conversely, African American participants were more likely to be searched by police

and have their sterile injecting equipment confiscated. Other qualitative studies among people who use drugs (not identified in my qualitative systematic review, as not specifically related to bacterial or fungal infections) have described how structural racism and racialized violence prevents racialized people who use drugs from accessing harm reduction programs (e.g., supervised consumption sites).[325]

My self-controlled case series (Chapter 5) showed that risks for injecting-related infections can change substantially within-individuals over time, as social/environmental contexts affecting drug preparation and injection change. While I observed a decreased rate of injecting-related infections while people were in prison, incarceration can lead to riskier injecting practices. This is due to heavily restricted access to harm reduction services, including no access to needle and syringe distribution programmes and lack of education on safer injecting technique. For example, a study on HCV risks in Australian prisons found that of 1,926 study participants with any history of injection drug use, 1,134 (59%) reported injecting in prison.[48] Of the 797 who reported injecting in the previous month, 598 (75% of these) reported injecting at least once per week and 722 (91%) reported re-using injecting equipment after someone else had used it.

6.2.1.4 Development and treatment of superficial injection-site infections

In one study[259] identified in my quantitative systematic review (Chapter 3), participants who had a current injecting-related abscess reported fewer meals in the past day compared to participants who did not have a current abscess. While this could reflect an increased risk of infection from malnutrition-associated immune suppression, the same study found no evidence that reporting "limited access to food" was associated with increased risk of infections. Malnutrition or food insecurity was not addressed by participants in the qualitative studies I identified in my qualitative systematic review (Chapter 2).

My qualitative thematic synthesis highlighted that, after people developed injecting-site abscesses and other skin infections, harmful healthcare policies and practices discouraged them from accessing traditional or mainstream healthcare (Chapter 2). Qualitative study participants described negative experiences of discrimination and untreated pain and withdrawal in mainstream healthcare settings leading them to seek alternatives, including self-treatment or treatment from a nonmedical person in their community. Stigma against people who use drugs intersected with other social identities. For example, mothers described additional motivations to stay away from healthcare because they feared child apprehension if they disclosed that they were using drugs. Quantitative evidence at this stage was more mixed, and few quantitative studies assessed what influences treatment of

superficial infections (Chapter 3). In one study,[75] recent incarceration was associated with decreased rates of healthcare seeking for one injecting-related infection (cellulitis) but not a second (abscess). Recent incarceration was not associated with decreased healthcare seeking in another study.[104] Self-treating abscesses was less likely among people who reported having a "usual place" to access health care[100], but was not significantly associated with other measures of health care access (e.g., having a primary care provider or having health insurance). These analyses also had wide confidence intervals that could potentially include meaningful differences.

My qualitative thematic synthesis (Chapter 2) identified supervised consumption sites as an important way to access primary care and appropriately treat abscesses and other superficial infections before they spread. For severe infections, nurses in the supervised injection site could assess, monitor, and facilitate a hospital visit. This phenomenon was addressed in two quantitative studies [236,239], where people who received a referral from a nurse at a supervised consumption site were more likely to have ED visit or hospital admission (respectively) for an injecting-related infection compared to supervised consumption site clients who did not receive a referral. However, these analyses were certainly confounded, as people with infections would be referred to treatment more often than people without infections.

As my work in Chapter 4 and 5 used administrative data from hospital admissions for severe infections, it did not directly address the treatment (or lack of treatment) of superficial injecting-related infections.

6.2.1.5 Development and treatment of severe/invasive infections

Once severe/invasive injecting-related infections develop and people require hospital admission, several factors influence infection treatment. Similar to the treatment of superficial infections, study participants in my qualitative systematic review (Chapter 2) described negative experiences in health care settings as either keeping them away from hospital or leading them to have a premature hospital discharge against medical advice. In one qualitative study[163], an Indigenous participant who was hospitalized with an injecting-related infection described how racist attitudes from hospital staff negatively affected their care and made them feel unsafe in hospital. In several qualitative studies, people were involuntarily discharged from hospital for drug use, despite ongoing medical need. Study participants described needing to leave hospital prematurely (before medically advised) because the hospital environment and policies, including restrictions on mobility, triggered symptoms of post-traumatic stress.

Quantitative studies on factors contributing to premature hospital discharges against medical advice were less clear. Several studies identified that women/females face higher risks of premature discharge than men/males, but this was not statistically significant in meta-analysis (e.g., aOR 1.22, 95%CI 0.99-1.50). Three studies assessed relationships between race/ethnicity and risk of premature hospital discharge, with mixed results.[279,280,283] One study found Hispanic patients had higher risk than non-Hispanic white patients, but two other studies found no differences by race/ethnicity. People with unstable housing/homelessness were more likely to have premature hospital discharge in one study but not in a second. In-hospital consultation with an addiction medicine specialist was associated with reduced risks of premature discharge in the one study that assessed it, but receipt of OAT was not statistically significantly associated with premature discharge in meta-analysis (e.g., uOR 0.65, 95%CI 0.42-1.01).

In one study quantitative study[284], following implementation of a new hospital-wide policy (to search patient's belongings, supervise and limit all visitation, restrict cell phone access, provide analgesics and sedatives only in liquid formulation, make patients who inject drugs wear self-identifying gowns, and flag their medical chart), premature hospital discharges increased from 6% to 35% ($p<0.001$). While lacking health insurance did not come up as a major focus in my qualitative systematic review (Chapter 2), lacking health insurance was associated with increased risk of premature hospital discharge against medical advice in quantitative meta-analysis (Chapter 3; aOR 2.07, 95%CI 1.09-3.91).

For my analyses in Chapters 4 and 5, the outcome was hospital admissions with injecting-related infections – which captures only severe infections. The risk of hospital admissions was modestly reduced while people were receiving OAT in both survival analysis (Chapter 4) and self-controlled case series (Chapter 5). Risk was greatly reduced while people were incarcerated, in the self-controlled case series (Chapter 5), which (as discussed above) most likely reflects decreased access to drugs and decreased frequency of injecting. Also in the self-controlled case series (Chapter 5), risk for hospital admission with injecting-related infections increased before and after incarceration and OAT receipt.

6.2.1.6 Health outcomes after injecting-related bacterial and fungal infections

The final stage of my pathway model focused on how social-structural factors might influence outcomes after initial treatment of injecting-related infections. There were relatively few qualitative studies that focused on this stage, though some qualitative work highlighted the role of housing in

restricting outpatient treatment options and disrupting follow-up care. In one study, police eviction of encampments and destruction of belongings led people to miss medical appointments.

Qualitative study participants spoke about how interruptions to OAT on hospital discharge (particularly affected by U.S. federal restrictions on the prescribing and dispensing of methadone) contributed to a return to injection drug use and recurrent endocarditis. In the quantitative meta-analysis, there were several studies assessing the potential impact of OAT during or after hospital discharge and this was the focus of my work in Chapter 4. For a detailed consideration of the potential role of OAT after hospital discharge, see below (section 6.2.2 Question 2. "Among people with opioid use disorder who have been hospitalised with injection drug use-associated bacterial or fungal infections, does the use of opioid agonist treatment after discharge decrease risks of mortality or infection-related rehospitalization?"). An inpatient addiction medicine consultation (before hospital discharge) was associated with decreased risks of all-cause rehospitalization (uOR 0.46, 95%CI 0.33-63; n=2 studies), though both studies were from overlapping samples and were unadjusted estimates in retrospective cohort studies.

In the qualitative systematic review (Chapter 2), study participants also spoke about changes they made to their drug use after experiencing an infection. This included applying new education on safer injecting techniques, switching from injecting to smoking, getting wounds assessed by a nurse, using minimum required acidifier to dissolve drugs, and seeking addiction treatment to reduce or abstain from injection use. While not explicitly addressed by study participants or authors, all these changes after experiencing an infection would also depend on social contextual factors, including the availability of harm reduction education, safer smoking equipment, low-barrier nursing care, appropriate acidifiers distributed by harm reduction programs, and accessible and evidence-based addiction treatment. None of these phenomena were assessed in the quantitative studies in Chapter 3. My self-controlled case series analysis (Chapter 5) shows increased rates of hospitalization with injecting-related infections before OAT initiation, which supports the qualitative participants' reports of increased motivation to start treatment after experiencing an injecting-related infection.

6.2.2 Question 2. "Among people with opioid use disorder who have been hospitalised with injection drug use-associated bacterial or fungal infections, does the use of opioid agonist treatment after discharge decrease risks of mortality or infection-related rehospitalization?"

This question was motivated in part by my clinical practice in hospital, caring for people with untreated opioid use disorder who were admitted to hospital with severe injecting-related infections. I was aware of the evidence that OAT is associated with reduced risks of death and of HIV and HCV transmission, and so I assumed that it would reduce risks of further bacterial infections as well. During my clinical medical training, our teaching hospital had no infrastructure or resources to initiate OAT, which caused many serious problems (including undertreating opioid withdrawal in hospital leading patients to leave prematurely against medical advice; and feelings of futility among health care professionals) and was a symptom of a lack of awareness and training in caring for people who use drugs across the hospital. I sought out training and mentorship, and I organized a team of medical trainees to begin offering OAT – largely with the intention of reducing the risks of recurrent infections for these hospitalized patients. While OAT can help some patients completely abstain from injection drug use, as discussed in Chapter 4 it can provide other benefits in the context of the "risk environment". Patients may have more control over their use when less worried about opioid withdrawal and OAT can facilitate access to primary health care and other health and social supports.[95,96] I was also interested in evaluating OAT within my thesis because it is a clinical intervention that can be easily delivered, but it was underused in our setting and in many hospitals. This seemed like an easy opportunity to reduce risk. I thought better understanding of the potential benefits of OAT might help hospital-based specialists (e.g., infectious diseases physicians, cardiologists, cardiac surgeons) incorporate OAT into treatment plans for injecting-related infections and facilitate OAT access in hospital.

My quantitative systematic review, reported in Chapter 3, showed that the evidence for OAT reducing risks of recurrent injecting-related infections (especially after discharge from an initial hospitalization with injecting-related infections) was not as convincing as I had assumed it would be. For primary prevention (reducing risks of incident or prevalent infections), there was some evidence of a modest risk reduction. I identified a reduction in risk from combining univariate analyses (uOR 0.71, 95%CI 0.62-0.81; n=10 studies) and a more modest reduction in covariate-adjusted analyses (aOR 0.92, 95%CI 0.89-0.95; n=9 studies). In my self-controlled analysis in Chapter 5 I calculated an effect estimate of aIRR 0.78 (95%CI 0.71-0.87) comparing time stable on OAT (between five and 52 weeks continuously on OAT) to time out of OAT (between five and 52 weeks continuously out of

OAT). During my PhD fellowship I also contributed to an observational study led by Dr. Samantha Colledge-Frisby (also using Opioid Agonist Treatment Safety study cohort data, from New South Wales, Australia) that compared the incidence of hospitalizations with injecting-related infections during time on and off of OAT.[358] This study demonstrated an adjusted rate ratio of 0.92 (95%CI 0.87–0.97) with an effect size similar to that of my meta-analysis. Adding these two new studies into the meta-analysis (using the same methods as in Chapter 3) results in an updated aOR of 0.91 (95%CI 0.87-0.95; n=11 studies; I^2 61.3%, p=0.004).

There was less evidence to support the protective effect of OAT for secondary prevention (to prevent recurrence) identified in my quantitative systematic review. Four studies assessed relationships between opioid agonist treatment and infection-related rehospitalization.[261,294,297,300] In a univariate analysis in one study,[294] people prescribed OAT soon after discharge had lower rates of rehospitalization than people not prescribed OAT, but rates did not differ between groups in three other studies [Hilbig 2020[297]; Suzuki 2020[300]; Thønnings 2020[261]]. The only two fully-adjusted effect estimates came from the same study [Barocas 2020[294]]: aHR 0.49 (95%CI 0.18-1.23) for infection-related rehospitalization by 30 days and aHR 0.41 (95%CI 0.42–0.91) for infection-related rehospitalization by 1 year. A new hospital policy to identify opioid use disorder and facilitate opioid agonist treatment did not change rates of infection-related rehospitalization in another study [Ray 2020[299]]. Limitations of this work include small sample sizes and suboptimal exposure definitions: all the studies defined their OAT exposure as whether OAT was received in hospital or at any point soon after discharge. Presumably, OAT benefits people primarily when they are receiving it and these studies did not account for time-varying OAT use.

Despite longstanding evidence of OAT reducing all-cause mortality in observational studies, there were also few studies assessing OAT and all-cause mortality in the post-hospital setting among people with injecting-related infections. Of four univariate effect estimates, the result was non-significant but relatively imprecise (uOR 0.58; 95%CI 0.24-1.45). In the only fully-adjusted effect estimate [Kimmel 2020[305]], opioid agonist treatment was associated with reduced risks of all-cause death in the month within which it was received (when treated as a time-varying exposure; aHR 0.30; 95% CI 0.10-0.89).

In Chapter 4, I analysed the relationship between OAT receipt and risk of infection-related rehospitalization or all-cause mortality. Within a large administrative data linkage cohort in New South Wales, Australia (including everyone who had accessed OAT with methadone or buprenorphine from 2001-2018), I identified 8,943 participants who had been hospitalized with injecting-related infections. I treated OAT receipt as time-varying, comparing the hazard of the

outcomes on OAT vs. off OAT. This modelled the potential effect of OAT with perfect adherence (i.e., all time during follow-up was exposed to OAT) vs. not using OAT at all. Despite this optimistic assumption, the potential risk reduction with OAT was modest (aHR 0.89, 95% CI 0.84-0.96). When I modelled period-specific hazard ratios for different times since hospital discharge, there was a greater apparent benefit in the first year (aHR 0.83, 95%CI 0.77–0.91) compared to later. Combining my overall summary hazard ratio with the 1-year follow-up analysis from Barocas 2020[294] in meta-analysis (using the same method as in my quantitative meta-analysis in Chapter 3) resulted in an imprecise summary effect estimate with high heterogeneity (aHR 0.78; 95%CI 0.08-7.77; I^2 71.3%, p=0.40). Combining the first-year hazard ratio from my study with Barocas 2020 had similar results (aHR 0.76, 95%CI 0.13-4.45; I2 55.7%, p=0.13). The mortality benefit I calculated in my study (in Chapter 4) had a larger effect size (aHR 0.63, 95%CI 0.57-0.70). Combining this with the estimate from Kimmel 2020[305] resulted in another imprecise and nonsignificant effect estimate (aHR 0.53, 95%CI 0.01-28.74; I^2 44.2%, p=0.18).

There are several potential ways to interpret these findings on the relationship between OAT receipt after hospital discharge and risk of injecting-related infection recurrence or death. Under assumptions of perfect adherence (when treated as a time-varying variable), there may be a specific benefit of OAT on reducing recurrence of injecting-related infections. This benefit may be attenuated further under more realistic conditions, where most people start and stop OAT often. For example, a recent systematic review found the median retention rate of OAT at six months was 57%.[382] This means that, based on the limited evidence now in existence, OAT has a modest benefit or no specific benefit on reducing risk of recurrence of injecting-related infections.

Does this mean that we need more and better research in this area to guide policy and practice? Perhaps not. First, given the known benefits of OAT in general (including enabling people to change their opioid use and reducing their risks of overdose and death) it should already be offered in all health care settings. Second, given these known benefits, it would be unethical to perform a randomized controlled trial offering OAT to some patients and restricting it from others. Third, also given these known benefits, further observational research with more realistic assumptions (e.g., an emulated target trial[383–385] of OAT initiation after hospital discharge with injecting-related infections) may not contribute meaningfully to practice decisions; if the study were negative, OAT should still be offered for other reasons. I discuss the implications of this in section 6.3 (Implications for policy, clinical practice, and future research), below.

6.2.3 Question 3. "What is the effect of incarceration and opioid agonist treatment transitions on the risk of injection drug use-associated bacterial infections?"

This question was also motivated in part by my clinical experience in hospital, caring for patients admitted with injecting-related infections. Many patients were admitted in times of crisis, during major life transitions. This often included recently becoming homeless, recently being released from prison, stopping OAT, or losing steady sources of income or social support. From my clinical perspective, it seemed as if these times of social transition and crisis were making people more vulnerable to injecting-related infections through precipitating returns to injection drug use or reducing peoples' control over their use, their skin hygiene, and their drug preparation practices. I would often see people admitted and readmitted several times in quick succession and then they would stay out of hospital for a long while, presumably in periods of relative life stability. However, life experiences of homelessness, incarceration, starting and stopping addiction treatment, and loss of income opportunities are unfortunately common among people who use criminalized drugs and many of these transitions or experiences of crisis occur without triggering an injecting-related infection. Changes in peoples' risk of hospitalization with injecting-related infections may not actually reflect changes in these life circumstances. The cluster of admissions followed by long periods out of hospital may simply reflect random variation and regression to the mean, rather than a causal relationship.

I learned about self-controlled study designs and the ability to examine the potential "triggering" effects of specific time periods (e.g., immediately following release from prison). Within the OATS cohort, there was information on dates of entering and leaving prison and dates of starting and stopping OAT. In this administrative data, unfortunately there was no available information on other important life transitions like losing housing, income, or other stressors. Therefore, I thought I could look at the potential effects of transitions in incarceration and OAT in this large cohort.

In Chapter 5, I approached this question using a self-controlled study design, calculating the relative incidence of injecting-related bacterial infections before, during, and after incarceration and receipt of OAT. It confirmed that risks of hospital admission with injecting-related infections changes substantially within-individuals over time, in relation to changes in these social and clinical exposures. Risk for hospitalisation with injecting-related bacterial infections increased in the weeks leading up to incarceration, was similar to during the first two weeks in prison, then decreased substantially following week three continuously incarcerated. Relative incidence increased again immediately following release from prison and was higher than the average baseline rate while living

in the community (out of prison). Similarly, compared to time "stable" on OAT (between five and 52 weeks continuously receiving OAT), incidence of injecting-related infections was elevated in the weeks leading up to OAT initiation and during the first month on OAT, and in the weeks before and after OAT discontinuation.

The systematic reviews in Chapter 2 and Chapter 3 contributed relatively little to answering this research question, in part because existing observational studies had cross-sectional and cohort designs that did not assess the effects of transitions or specific time periods. For example, several quantitative studies assessed whether people who were recently incarcerated (i.e., in the past year) were more likely to experience injecting-related infections than people who had not been incarcerated. Some found increased risk[235,240,358,364] and some found similar risks.[75,125,245] The meta-analytic results from Chapter 3 for associations between history of incarceration and incident or prevalent injecting-related infections were uOR 1.27 (95%CI 1.06-1.53; n=6 studies) and aOR 1.60 (0.99-2.59; n=2 studies). Similarly for OAT, as reviewed above in section 6.2.2, there is some evidence from observational studies that current or recent OAT use is associated with a modest reduction in risk for injecting-related infections. Despite these cohort studies adjusting analyses on measured covariates, this prior evidence primarily compared people who experienced incarceration or OAT to those who did not – and these study participants would differ in many other ways that are not measured (or adjusted-for) in cohort studies. The self-controlled study design helps to solve this problem because participants serve as their own control.

While I confirmed my hypotheses concerning elevated risks of injecting-related infections immediately following release from prison and discontinuation of OAT (based on known risks of overdose seen during this time), one of the more interesting findings in trying to answer this research question was the elevated risk seen preceding incarceration and preceding OAT initiation and discontinuation. This is another unique strength of self-controlled study designs, as I could identify and assess these "pre-exposure" time windows. Increasing risk of injecting-related infections prior to incarceration may reflect underlying stressors in peoples' lives leading up to periods of incarceration, but investigating this phenomenon would require further research. My self-controlled case series study is unable to explain mechanisms behind this observation, and my qualitative systematic review in Chapter 2 included no studies focused on this time period.

For OAT, my findings support the results of the cohort study by Colledge-Frisby and colleagues (which used the same parent study dataset, and to which I contributed as a co-author) that risk for injecting-related infections was highest before starting OAT and remained elevated during the first

weeks of an OAT episode.[358] This suggests that developing an injecting-related infection may motivate people to initiate OAT, and also that starting OAT could lead people to seek treatment for also represent referrals to OAT from health care settings when people seek treatment for injecting-related infections.

6.2.4 Strengths and weaknesses

My thesis has several strengths. By taking a socio-ecological approach to injection drug use-associated bacterial and fungal infections, I was able to interrogate potential risk and protective factors at multiple levels and encourage thinking about prevention and treatment beyond individual-level behaviours. I proposed and explored a multi-stage pathway, where opportunities for risk reduction could be identified before, during, and after the development of injecting-related infections. My systematic reviews in Chapter 2 and Chapter 3 were purposefully broad in scope and complementary in their epistemological and methodological approaches. The qualitative findings, based on the experiences of people who inject drugs, provided several potential mechanisms by which social-structural factors may work to shape individual behaviours and influence risk; the quantitative findings, based largely on cross-sectional and cohort studies, provided some sense of where quantitative associations have been demonstrated related to social determinants, substance use, and health services factors. My work with data from the Opioid Agonist Treatment Safety study cohort, in Chapter 4 and 5, provided the largest sample sizes yet on studies of OAT, incarceration, and injection drug use-associated bacterial infections. My survival analysis in Chapter 4 applied a time-varying approach to overcome limitations of existing research on OAT after hospital discharge, avoiding “immortal time” bias. My self-controlled case series analysis in Chapter 5 took advantage of this innovative and emerging study design to assess changes in within-individual risk of injecting-related infections.

However, the work I present in this thesis has several important limitations. First, the qualitative and quantitative systematic reviews only included studies where the outcome was injecting-related infections (or related to their treatment) so I did not include studies that assessed determinants of risky injecting practices (e.g., intramuscular injecting, reuse of needles/syringes) unless these were related to infections. I made this decision to be pragmatic and ensure the project would be feasible to complete. Future research could more broadly assess determinants of risky injecting practices themselves.

Second, most observational studies in the quantitative systematic review were of poor quality in terms of causal inference (e.g., most studies did not specify a hypothesis or estimand, and most did not take a causal approach to covariate selection). Instead, most covariate-adjusted effect estimates that I identified came from studies attempting to identify "factors associated with" an outcome, typically via stepwise regression. This approach can introduce new biases, including problems with multiple hypothesis testing; collider stratification bias (the so-called "Table 2" Fallacy),[219] over-adjustment bias ("adjusting" for mediating factors on a causal pathway between a main exposure and the outcome),[220] and effect estimates that are not as specific as possible. These weaknesses were not captured in the MMAT critical appraisal tool, which I had selected in order to use one tool for the planned "mixed studies" review. Other critical appraisal tools, such as "Risk Of Bias In Non-randomised Studies of Interventions" (ROBINS-I) tool,[386] have been developed to assess how closely an observational study emulates an ideal "target trial" to assess the relationship between a specific exposure and a specific outcome. My quantitative systematic review in Chapter 3 included dozens of exposure-outcome pairs, and I did not have capacity to undertake the ROBINS-I tool for each relationship.

Third, I did not include a prespecified plan or formal approach to mixed-methods analysis, integrating the findings of the qualitative and quantitative systematic reviews. This was because I did not expect to identify so many sources, and my original analysis plan for the "mixed studies" review (incorporating qualitative, quantitative, and mixed-methods studies) comprised a relatively superficial directed content analysis.[21] Because I identified so many rich sources, I was able to separately conduct a qualitative thematic synthesis and a series of quantitative meta-analyses. The comparing and contrasting of qualitative and quantitative findings that I undertook in Chapter 3 (section 3.6 Discussion) and Chapter 6 (section 6.2 Research questions and main findings) is similar to a parallel, convergent mixed methods analysis, wherein the qualitative and quantitative arms of the study are undertaken separately and then integrated afterwards.[131,387] Future work could take a formal, prespecified approach to contrasting and comparing quantitative and qualitative findings, for example through the use of a convergence coding matrix.

Fourth, my work with the Opioid Agonist Treatment Safety study data in Chapter 4 and 5 used administrative health care data on OAT receipt, hospital admissions, incarceration, and death. I did not have access to important information on individual-level or social-structural exposures, including individual injecting practices, housing status, use of other substances (e.g., injecting stimulants) and use of harm reduction programs.

Fifth, my thesis work was not a detailed, descriptive study of how risk comes about in a specific place or setting. The systematic reviews were broad and global in scope, and tried to integrate potential social-structural exposures from multiple settings. My work in Opioid Agonist Treatment Safety cohort data was set in New South Wales, Australia, a place with universal health insurance and relatively good access to OAT and harm reduction programs (especially in urban areas). My findings from Chapter 4 and Chapter 5 might not apply in places with different drug policies, drug supplies (e.g., places with more fentanyl), public health insurance schemes, and approaches to OAT funding and delivery.

6.3 Implications for policy, clinical practice, and future research

As injecting-related bacterial and fungal infections are an increasingly common cause of pain, disability, and death among people who inject drugs, novel approaches to prevention and treatment are urgently needed. A key motivation of my thesis was to understand what factors influence risk for injecting-related infections and treatment outcomes, to inform potential policy and clinical responses. While I identified several relevant social-structural factors, in many cases the quality of existing quantitative research was poor and effect estimates were imprecise, and it is challenging to draw causal inferences. Further, I did not identify many high-quality studies assessing specific structural or environmental interventions to reduce risks of injecting-related infections or improve their treatment. This does limit specific policy and clinical recommendations that can be derived from my thesis. Nevertheless, many of the social determinants, substance use, and health services factors I identified (in systematic reviews and in my own work) affect people who use drugs in multiple ways, beyond shaping risks for injecting-related bacterial or fungal infections alone.[48] Many potential policy strategies to prevent injecting-related bacterial and fungal infections have stronger existing evidence for preventing other drug-related harms, including HIV and HCV transmission, and overdose. Novel strategies that would address social-structural drivers of infection risk could be conceptualized as "safer environment interventions",[108] which change social and environmental contexts of drug use and mediate access to resources and health care services – and could benefit people who use drugs in multiple ways.

To reduce infection risks from reliance on adulterated and poorly soluble unregulated drugs, people who use drugs should be offered multiple, accessible options for harm reduction and addiction treatment. This could include traditional oral opioid agonist treatment (OAT), to potentially reduce frequency of injecting (or abstain), and injectable opioid agonist treatment (iOAT; e.g., "heroin-assisted treatment") to provide liquid formulations of drugs to inject under hygienic conditions. While evidence is still emerging, clients of novel "prescribed safer supply" programs appear to be a lower risk of injecting-related infections while enrolled in these programs, and these could be offered as well. People who continue to inject should be offered sufficient sterile injecting equipment, including equipment of their preferred size and type, and supervised consumption sites. These harm reduction programs have multiple benefits beyond potentially reducing risks of injecting-related infections, including reducing overdose, HIV and HCV transmission, and helping people who use drugs to engage with health and social services. Similarly, secure housing has many physical and mental health benefits beyond reducing bacterial infection risks. People who use drugs and are experiencing homelessness should be offered permanent and supportive housing.

Decriminalization of drug possession would also have many health and social benefits for people who use drugs, and could be part of a policy strategy to reduce risks of injecting-related bacterial and fungal infections.

Once infections do develop, people who inject drugs would benefit from flexible, accessible, and compassionate primary care (including wound and abscess care) that could help treat superficial infections before they progress and spread. One example of this is Mobile Outreach Street Health (MOSH), who provide primary care alongside needle and syringe program outreach in Halifax, Nova Scotia, Canada. Primary care (including wound and abscess care) could also be integrated into needle and syringe programs, supervised consumption sites, and OAT clinics.

Many hospital environments cause distress and harm to people who use drugs, as hospital policies are unrealistically prohibitive of drug use. Several initiatives can improve health care experiences for people with injecting-related infections,[97,189] including incorporating harm reduction and cultural safety principles,[88,190] specialized addiction medicine consultation services,[191–193] needle and syringe programs,[117,194] and supervised consumption sites[195–197] into hospital care. Clinical practice changes include aggressively treating pain and opioid withdrawal with short-acting opioids.[97,189,192,388] Policy changes are needed at many hospitals to facilitate these initiatives.[198,199]

People who use drugs support one another to reduce risks, and future research on injecting-related infections should prioritize meaningful partnerships between academics and people who use drugs to support these efforts. There appears to be promise in scaling up existing harm reduction strategies to reduce risks of injecting-related infections, so future research could focus on how to optimize their delivery. Research could incorporate implementation science strategies to understand and overcome barriers to scale-up of harm reduction programs. There is specific controversy in Canada regarding potential infectious risks from crushing and injecting oral tablets distributed from prescribed safer supply programs, so further research in this area could help improve safer supply programs and support their scale-up. Given the relatively high rate of recurrence of hospital admissions with injecting-related infections (i.e., 41% at median 3.4 years in my study in Chapter 4) more research is needed to inform optimal treatment planning for injecting-related infections including decisions like discharge location, antibiotic mode of delivery (oral, intravenous, or long-acting injecting), risks and benefits of heart valve surgery for endocarditis, care navigation and engagement with social determinants of health (including housing). Research priorities could include optimal care planning for patients with opioid use disorder who decline OAT (e.g., because they do

not find it helpful) and/or patients with injecting-related infections who do not have opioid use disorder (e.g., because they inject only stimulants).

I have several related research opportunities after my PhD. In collaboration with the Canadian Injection Drug use-associated Endocarditis (CIDUE) working group, the Canadian Association of People who Use Drugs (CAPUD), and the Substance User Network of the Atlantic Region (SUNAR), we have successfully obtained grant funding from the Canadian Institutes of Health Research to conduct a national research priority-setting exercise to improve care for people with injection drug use-associated infective endocarditis. I am principal investigator for the grant, in partnership with principal knowledge user Natasha Touesnard (executive director of CAPUD and a person with lived-experience of injection drug use-associated endocarditis). We also have obtained government support for a formal hospital inpatient addiction medicine consultation service at the tertiary care hospital where I am doing my clinical training, and we have designed harm reduction-oriented hospital policies with people with lived experience. Implementing these and evaluating them will provide great learning opportunities, and a platform for future research studies.

Chapter 7 References

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Chapter 8 Appendices

8.1 Appendix 1. Journal publications and pre-prints during PhD outside of this thesis

8.1.1 First author journal publications during PhD fellowship:

1. **Brothers TD**, Bonn M, Lewer D, Comeau E, Kim I, Webster D, Hayward A, Harris M. Social and structural determinants of injection drug use-associated bacterial and fungal infections: a qualitative systematic review and thematic synthesis. *Addiction.* 12 May 2023. https://doi.org/10.1111/add.16257
    - Highlighted by journal with editorial commentary and podcast interview.
2. **Brothers TD**, Lewer D, Bonn M. Sublingual buprenorphine-naloxone and dental disease. *JAMA: Journal of the American Medical Association*. 2023;329(14):1224. https://doi.org/10.1001/jama.2023.1498
3. **Brothers TD**, Walley AY, Rivers-Bowerman H, McLeod M, Genge L. Between a rock and a hard place? A 37-year-old man with acute liver injury while enrolled in a managed alcohol program for severe alcohol use disorder. *Addiction Science & Clinical Practice*. 2023;18:14. https://doi.org/10.1186/s13722-023-00370-5
4. **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections: a cohort study in New South Wales, Australia. *PLOS Medicine.* 2022;19(7):e1004049. https://doi.org/10.1371/journal.pmed.1004049
5. **Brothers TD**, Leaman M, Bonn M, Lewer D, Atkinson J. Fraser J, Gillis A, Gniewek M, Hawker L, Hayman H, Jorna P, Martell D, O'Donnell T, Rivers-Bowerman H, Genge L. Evaluation of an emergency safe supply drugs and managed alcohol program in COVID-19 isolation hotel shelters for people experiencing homelessness. *Drug and Alcohol Dependence*. 2022 Jun 1;235:109440. https://doi.org/10.1016/j.drugalcdep.2022.109440
6. Touesnard N*, **Brothers TD***, Bonn M, Edelman EJ. Overdose deaths and HIV infections among people who use drugs: shared determinants and integrated responses. *Expert Review of Anti-infective Therapy.* 2022 Jun 7;1-5. https://doi.org/10.1080/14787210.2022.2081152
    - *Co-first authors; collaboration with Canadian Association of People who Use Drugs (CAPUD)
7. **Brothers TD,** Mosseler K, Kirkland S, Melanson P, Barrett L, Webster D. Unequal access to opioid agonist treatment and sterile injecting equipment among hospitalized patients with injection drug use-associated infective endocarditis. *PLOS One*. 2022;17(1):e0263156. https://doi.org/10.1371/journal.pone.0263156
8. **Brothers TD**, Bahji A. Patients with infective endocarditis deserve evidence-based addiction treatment. *Annals of Thoracic Surgery*. 2022;113(3):1048-9. https://doi.org/10.1016/j.athoracsur.2021.01.085
9. **Brothers TD**, Lewer D, Bonn M, Webster D, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: protocol for a mixed studies systematic review. *BMJ Open*. 2021;11:e049924. http://doi.org/10.1136/bmjopen-2021-049924
10. **Brothers TD**, Lewer D, Thakrar A. Linking opioid use disorder treatment from hospital to community. *Addiction*. 2021;116(8):2244-2245. https://doi.org/10.1111/add.15460
11. **Brothers TD**, Fraser J, MacAdam E, Morgan B, Webster D. Uptake of slow-release oral morphine as opioid agonist treatment among hospitalized patients with opioid use disorder. *Drug and Alcohol Review.* 2022 Feb;41(2):430-434. https://doi.org/10.1111/dar.13365

12. **Brothers TD**, Kaulbauch J, Tran A. Decisions: Unhealthy alcohol use in a 65-year-old man with awaiting surgery. *CMAJ: Canadian Medical Association Journal.* 2021;193(32):E1250-E1252. https://doi.org/10.1503/cmaj.202128
    - Translated and published in French edition of the journal: Brothers TD, Kaulbauch J, Tran A. Consommation malsaine d'alcool chez un homme de 65 ans en attente d'une chirurgie. CMAJ: Canadian Medical Association Journal. 2021;193(40):E1575-E1577. https://doi.org/10.1503/cmaj.202128-f
13. **Brothers TD**, Fraser J, Webster D. Caring for people who inject drugs when they are admitted to hospital. *CMAJ: Canadian Medical Association Journal.* 2021;193(12):E423-E424. https://doi.org/10.1503/cmaj.202124
    - Translated and published in French edition of the journal: Brothers TD, Fraser J, Webster D. Les soins hospitaliers aux personnes qui consomment des drogues injectables. *CMAJ: Canadian Medical Association Journal*. 2021;193(22):E829-30. https://doi.org/10.1503/cmaj.202124-f
14. **Brothers TD**, Fraser J, MacAdam E, Morgan B, Francheville J, Nidumolu A, Cheung C, Hickcox S, Saunders D, O'Donnell T, Genge L, Webster D. Implementation and evaluation of a novel, unofficial, trainee-organized hospital addiction medicine consultation service. *Substance Abuse.* 2020 Dec 17; 1-8. https://doi.org/10.1080/08897077.2020.1856291

8.1.2 Co-author journal publications during PhD fellowship:

15. Bonn M, Palayew A, Touesnard N, **Brothers TD**, Bodkin C. Safe supply in the midst of a crisis of unregulated toxic drug deaths - a commentary on Roberts and Humphreys (2023). *Journal of Studies on Alcohol and Drugs*. Accepted; in press.
    - Collaboration with lead authors from Canadian Association of People who Use Drugs (CAPUD).
16. Kiepek N, Ausman C, Murphy A, **Brothers T**. Socially situated experiences of substance use: A photo elicitation pilot study. *SAGE Open*. Accepted; in press.
17. Ferguson M, Rittenbach K, Leece P, Adams A, Ali F, Elton-Marshall T, Burmeister C, **Brothers TD**, Medley A, Choisil P, Strike C, Ng J, Lorenzetti D, Buxton JA, and the Guidance Development Group. Guidance on take-home naloxone distribution and use by community overdose responders in Canada. *CMAJ: Canadian Medical Association Journal*. 2023 Aug 28;195(33):E1112-E112. https://doi.org/10.1503/cmaj.230128
18. Lewer D, **Brothers TD**, Harris M, Rock KL, Copeland CS. Opioid-related deaths during or shortly after hospital admissions in the United Kingdom: a qualitative framework analysis of coroner reports. *PLOS One.* 18(4): e0283549. https://doi.org/10.1371/journal.pone.0283549
19. Lewer D, **Brothers TD**, Croxford S, Desai M, Emanuel E, Harris M, Hope VD. Opioid injection-associated bacterial infections in England, 2002-2021: a time series analysis of seasonal variation and the impact of COVID-19. *Clinical Infectious Diseases*. 14 March 2023. https://doi.org/10.1093/cid/ciad144
    - Highlighted as "Editor's Choice"
20. Lewer D, **Brothers TD**, Gasparrini A, Strang J. Seasonal, weekly, and other cyclical patterns in deaths due to drug poisoning in England and Wales. *Addiction*. 26 February 2023. https://doi.org/10.1111/add.16175
21. Bahji A, **Brothers TD**, Mauer-Vakil D, Priest KC, Danilewitz M, Chopra N, Lamba W, George TP. The effectiveness of inpatient addiction consult services: a systematic review and narrative synthesis. *Canadian Journal of Addiction.* 2023;14(2):9-19. https://doi.org/10.1097/cxa.0000000000000173

22. Kleinman R, **Brothers TD**, Morris N. Retiring the "Against Medical Advice" Discharge. *Annals of Internal Medicine*. 2022 Dec;175(12):1761-2. https://doi.org/10.7326/M22-2964
23. Zolopa C, **Brothers TD,** Leclerc P, Mary J-F, Morisette C, Bruneau K, Hyshka E, Martin N, Larney S. Changes in supervised consumption site use and emergency interventions in Montréal, Canada in the first twelve months of the COVID-19 pandemic: An interrupted time series study. *International Journal of Drug Policy*. 2022. 103894. https://doi.org/10.1016/j.drugpo.2022.103894
24. Ferguson M, Medley A, Rittenback K, **Brothers TD**, Strike C, Ng J, Leece P, Elton-Marshall T, Ali F, Lorenzetti DL, Buxton JA. Priority setting for Canadian take-home naloxone best practice guideline development: an adapted online Delphi method. *Harm Reduction Journal.* 2022;19:71. https://doi.org/10.1186/s12954-022-00650-4
25. Glegg S, McCrae K, Kolla G, Touesnard N, Turnbull J, **Brothers TD**, Brar R, Sutherland C, Le Foll B, Sereda A, Goyer ME, Rai N, Bernstein S, Fairbairn N. "COVID just kind of opened a can of whoop-ass": The rapid growth of safer supply prescribing during the pandemic documented through an environmental scan of addiction and harm reduction services in Canada. *International Journal of Drug Policy.* 2022 Jun 6;106:103742. https://doi.org/10.1016/j.drugpo.2022.103742
26. Colledge-Frisby S, Jones N, Larney S, Peacock A, Lewer D, **Brothers TD**, Hickman M, Farrell M, Degenhardt L. The impact of opioid agonist treatment on hospitalisations for injecting-related diseases among an opioid dependent population: A retrospective data linkage study. *Drug and Alcohol Dependence*. 2022 Jul 1;236:109494. https://doi.org/10.1016/j.drugalcdep.2022.109494
27. Lewer D, **Brothers TD**, Van Hest N, Hickman M, Holland A, Padmanathan P, Zaninotto P. Causes of death among people who used illicit opioids in England between 2001 and 2018: a matched cohort study. *The Lancet Public Health*. 2022 Feb;7(2):e126-e135. https://doi.org/10.1016/S2468-2667(21)00254-1
    - Highlighted by journal with editorial commentary and podcast interview
28. Kleinman RA, **Brothers TD**, Danilewitz M, Bahji A. Office-based methadone prescribing for opioid use disorder: the Canadian model. *Journal of Addiction Medicine*. 2022 Sep-Oct;16(5):499-504. https://doi.org/10.1097/ADM.0000000000000950
29. Bahji A, **Brothers TD**, Danilewitz M. Considering cannabis use in differential diagnosis: a teachable moment. *JAMA Internal Medicine*. 2022 Jan 1;182(1):66-67. https://doi.org/10.1001/jamainternmed.2021.6901
30. Lewer D, Eastwood B, White M, **Brothers TD**, McCusker M, Copeland C, Farrell M, Petersen I. Fatal opioid overdoses during and shortly after hospital admissions in England: case-crossover study. *PLOS Medicine*. 2021 Oct 5; 18(10):e1003759. https://doi.org/10.1371/journal.pmed.1003759
31. Harney BL, Korchinski M, Young P, Scow M, Jack K, Linsley P, Bodkin C, **Brothers TD**, Curtis M, Higgs P, Sawicki Mead T, Hart A, Kilroy D, Bonn M, Bartlett SR. It is time for us all to embrace person-centred language for people in prison and people who were formerly in prison. *International Journal of Drug Policy.* 2021;99:103455. https://doi.org/10.1016/j.drugpo.2021.103455
32. Bonn M, Palayew A, Bartlett S, **Brothers TD**, Touesnard N, Tyndall M. "The times they are a-changin'": Addressing common misconceptions about the role of safe supply in North America's overdose crisis. *Journal of Studies of Alcohol and Drugs.* 2021;82(1):158-160. https://doi.org/10.15288/jsad.2021.82.158
    - #5 most downloaded article from journal website in 2020

8.1.3 Pre-registered protocols during PhD fellowship (not otherwise published in a journal)

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Bonn M, Wheeler A, Grebely J, Farrel M, Hayward A, Hickman M, Degenhardt L. Time periods of altered risk for severe injection drug use-associated skin and soft-tissue infections: protocol for a self-controlled case series in New South Wales, Australia, 2001-2018. *UCL Discovery Repository.* https://doi.org/10.14324/000.rp.10157481
- Lewer D, **Brothers TD**. Association between drug poisoning deaths and season, week, weekday, and public holidays: protocol for a time series analysis of daily counts in England and Wales, 1993-2018. *UCL Discovery Repository.* https://doi.org/10.14324/000.rp.10154051

8.1.4 Manuscripts submitted and under review

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Bonn M, Wheeler A, Grebely J, Farrell M, Hickman M, Hayward A, Degenhardt L. Effect of incarceration and opioid agonist treatment transitions on the risk of hospitalisation with injection drug use-associated bacterial infections: a self-controlled case series in New South Wales, Australia. *Under review.*
- Van Hest N, **Brothers TD,** Williamson A, Lewer D. Healthcare resource use among people who use illicit opioids in England, 2010 to 2020: a matched cohort study. *Revisions submitted.*

8.2 Appendix 2. Grant applications during PhD outside of this thesis

8.2.1 Successfully funded

1. Principal investigator. “Research priority-setting to improve care for people who inject drugs with infective endocarditis in Canada: the Canadian Injection Drug Use-associated Endocarditis Working Group”. Canadian Institutes of Health Research (CIHR) Planning and Dissemination Grant - Institute Community Support. $13,256. 2023.
2. Co-applicant. “Representing (de)polarised understandings of substance use across lived experience, medical, and legal perspectives”. (Principal investigator: Niki Kiepek). Social Sciences and Humanities Research Council (SSHRC) Insight Grant. $88,755. 2022.
3. Co-investigator. “MARCO:POLO - Marginalization & COVID-19: Promoting Opportunities for Learning & Outreach". (Principal investigator: Ahmed Bayoumi). Canadian Institutes of Health Research (CIHR) Operating Grant: Emerging COVID-19 Research Gaps & Priorities. $313,804. 2021.
4. Co-investigator. “Evaluation of supervised consumption services in Montreal in the context of COVID-19.” (Principal investigator: Sarah Larney). Canadian Institutes of Health Research (CIHR) Operating Grant: Evaluation of Harm Reduction Approaches to Address the Opioid Crisis in the Context of COVID-19. $249,900. 2021.

8.2.2 Submitted but unsuccessful

5. Co-investigator. “Prevention of overdoses: from network action to the production of innovations.” (Nominated principal investigator: André-Anne Parent). Social Sciences and Humanities Research Council (SSHRC).

6. Co-investigator. “An implementation science approach to the development of an Academic Detailing Service for alcohol use disorder in primary care settings.” (Nominated principal investigator: Matthew Grandy). Dalhousie University Medical Education Living Lab Research Fund.

8.3 Appendix 3. Selected knowledge translation and exchange activities during PhD

8.3.1 Committees / service

- Member & coordinator, Canadian Injection Drug Use-associated Infective Endocarditis Working Group
- Member, Nova Scotia Provincial Drug Checking Committee

8.3.2 Continuing professional development & academic detailing

- Consultant, "Drug Treatment and Harm Reduction Course", International Network on Health and Hepatitis in Substance Users (INHSU)
- Consultant, "Hepatitis C Treatment in Drug & Alcohol Settings Course", International Network on Health and Hepatitis in Substance Users (INHSU)

8.3.3 Clinical service development

- Consultant, Inpatient Addiction Medicine Consultation Service, Nova Scotia Health
- Member, COVID-19 harm reduction physician group, Nova Scotia Health

8.3.4 Invited government/policy consultation & engagement

- External reviewer, "Somerville Supervised Consumption Site Needs Assessment and Feasibility Report". City of Somerville, Department of Health and Human Services, and Brown University School of Public Health. Somerville, MA, USA. 2021.

8.3.5 Teaching experience and responsibilities

8.3.5.1 Course development

- Course co-lead & faculty, "Homeless and Inclusion Health" MSc module, University College London, London, UK. 2021.

8.3.5.2 Graduate students

- Guest lecture: "Community-engaged research", co-presented with Matthew Bonn (Canadian Association of People who use Drugs; CAPUD). Clinical Epidemiology Methods Course, Department of Community Health & Epidemiology, Dalhousie University. 4 May 2023.
- Lecture: "COVID-19 and the health of people who use criminalized drugs in North America." Homeless and Inclusion Health MSc module, University College London, London, UK. 20 May 2021.

8.3.5.3 Medical residents and fellows

- Residents academic half-day: “Research”. Core Internal Medicine Residency Program, Department of Medicine, Dalhousie University, Halifax, NS, Canada. 9 Feb 2023.
- Residents academic half-day: “Substance use disorders in older adults.” Division of Geriatric Medicine, Dalhousie University, Halifax, NS, Canada. 9 Feb 2023.
- Residents academic half-day: “Substance use disorders in older adults.” Division of Geriatric Medicine, Dalhousie University, Halifax, NS, Canada. 14 Feb 2022.

8.3.5.4 Nursing and allied health professionals

- Nursing Education Day: “Harm reduction & caring for patients who inject drugs when admitted to hospital.” QEII Health Sciences Centre. Halifax, NS, Canada. 16 September 2022.
- Nursing Education Day: “Harm reduction & caring for patients who inject drugs when admitted to hospital.” QEII Health Sciences Centre. Halifax, NS, Canada. 3 June 2021.
- Nursing Education Day: “Harm reduction & caring for patients who inject drugs when admitted to hospital.” QEII Health Sciences Centre. Halifax, NS, Canada. 23 February 2021.
- Nursing Education Day: “Harm reduction & caring for patients who inject drugs when admitted to hospital.” QEII Health Sciences Centre. Halifax, NS, Canada. 11 February 2021.
- Nursing Education Day: “Caring for patients who inject drugs when admitted to hospital.” Dartmouth General Hospital. Dartmouth, NS, Canada. 11 December 2020.

8.3.6 Clinical and public health guidelines

8.3.6.1 Guidelines author

- Clinical Lead (Atlantic Region), “Canadian National Guideline for the Clinical Management of Opioid Use Disorder”, *Canadian Research Initiative on Substance Misuse*
- Member, Guideline Steering Committee & Guideline Development Panel, “Canadian National Community-Base Naloxone Guidelines”, *Canadian Research Initiative on Substance Misuse*
- Member, Expert Working Group, *“*National Supervised Consumption Services Operational Guidelines”, *Canadian Research Initiative on Substance Misuse*

8.3.6.2 Guidelines reviewer

- Canadian Research Initiative on Substance Misuse, “Supporting people who use substances in emergency shelter settings during COVID-19”

8.3.7 Invited & public presentations

8.3.7.1 International meetings

- Plenary & panel: “Funding strategies for community-driven research”. Co-presented with Matthew Bonn (Canadian Association of People who Use Drugs). National Survivors Union & Drug Policy Alliance. Hosted online, USA. 2023-Apr-27.
- Conference rapporteur for Clinical Science. International Network on Hepatitis and Health in Substance Users (INHSU) annual conference. Glasgow, Scotland. 2022-Oct-21.
- Plenary & panel: “Approaches to community-involved research as an early-mid-career researcher (EMCR)”. Co-presented with Matthew Bonn (Canadian Association of People who Use Drugs). International Network on Hepatitis and Health in Substance Users (INHSU) Early-Mid-Career Researchers Special Interest Group. Virtual meeting. 2022-Sep-28.
- Plenary: “Between a rock and a hard place? Managed alcohol programs and liver disease” Boston Medical Center CARE Unit Case Conference. Boston, Massachusetts, USA. 2021-Dec-2.
- Panel: “Trainee engagement in advocacy and practice in addiction medicine.” International Society of Addiction Medicine-Canadian Society of Addiction Medicine joint virtual conference. 2020-Nov-14.

8.3.7.2 National & regional meetings

- Plenary, “Managing opioid and alcohol use and withdrawal in hospital when patients are acutely ill”. Canadian Society of Hospital Pharmacy. Halifax, Nova Scotia. 2023-May-27.
- Moderator, “Expanding flexible models of care for opioid use disorder - Atlantic Roundtable Discussion”, Canadian Research Initiative in Substance Misuse (CRISM). Virtual/online. 2023-Jan-31.
- Plenary: “Harm reduction approaches to reduce barriers to health care”. Medicine Matters Continuing Professional Development Annual Conference, Dalhousie University Department of Medicine. Halifax, NS, Canada. 2022-Nov-4.
- Plenary: “Management of alcohol use disorder in the context of alcohol-related hepatitis and liver transplant”. Atlantic Transplant Conference. Halifax, NS, Canada. 2022-Nov-4.
- Plenary: “Opioid agonist treatment and harm reduction for people with opioid use disorder”. Atlantic Pain Conference. Halifax, NS, Canada. 2022-Oct-21.
- Plenary & panel: “Evidence on safer supply”. Atlantic Safer Supply Regional Meeting. Halifax, NS, Canada. Hosted by Substance User Network of the Atlantic Region (SUNAR) and the National Safer Supply Community of Practice. 2022-Jun-27.
- Plenary: “Can we make hospitals safe for people who use drugs?” Saint John Harm Reduction Symposium. Virtual, hosted in Saint John, NB, Canada. 2022-Apr-27.
- Plenary: “Harm reduction across the health care continuum.” Harm Reduction Speaker Series. Virtual, hosted by the Saint John Harm Reduction Symposium. 2021-July-14.
- Panel: “International research training experiences.” Virtual, hosted by Clinician-Investigator Trainee Association of Canada (CITAC). 2021-Jun-29.
- Plenary & panel: “COVID-19 & the health of people who use criminalized drugs.” Thomas Fear and Alice Morgans Fear Memorial Conference on Medical Education. Virtual, hosted by Dalhousie University, Halifax, NS, Canada. 2021-Jun-15.
- Plenary & panel: “The impact of COVID-19 on treatment delivery within addiction medicine.” Addiction Medicine Symposium. Virtual, hosted by McMaster University. 2021-May-29.

- Plenary & panel: “Towards understanding the opioid crisis: naloxone training and advocacy.” Hosted by Ontario Medical Students Association. Virtual. 2021-Apr-1

8.3.7.3 Institutional & departmental meetings

- Grand Rounds: “Caring for people who use drugs/substances when they come to the hospital.” Department of Medicine, Dalhousie University, Halifax, NS, Canada. 2022-Dec-6.
- Grand Rounds: “Addiction care for patients with injection drug use-associated infective endocarditis.” Division of Cardiology, Dalhousie University, Halifax, NS, Canada. 2022-Jan-17.
- Grand Rounds: “Addiction care for patients with injection drug use-associated infective endocarditis.” Division of Cardiac Surgery, Dalhousie University, Halifax, NS, Canada. 2022-Jan-5.
- Grand Rounds: “Adverse childhood experiences and chronic illness in adults.” Co-presented with Stephen Workman. Dalhousie University Department of Medicine. Halifax, NS, Canada. 2021-Mar-30.

8.3.8 Peer-reviewed abstracts & conference presentations

(Underline indicates student/trainee under direct supervision)

8.3.8.1 International meetings

- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Oral presentation.] Lisbon Addictions -- European Conference on Addictive Behaviours and Dependencies. November 23, 2022 at Lisbon, Portugal.
- **Brothers TD**, Bonn M, Lewer D, Kim I, Comeau E, Webster D, Hayward A, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: qualitative systematic review and thematic synthesis. [Oral presentation.] International Network on Health & Hepatitis in Substance Users (INHSU). October 21, 2022 at Glasgow, Scotland.
- **Brothers TD,** Leaman M, Bonn M, Lewer D, Atkinson J. Fraser J, Gillis A, Gniewek M, Hawker L, Hayman H, Jorna P, Martell D, O’Donnell T, Rivers-Bowerman H, Genge L. Evaluation of an emergency safe supply drugs and managed alcohol program in COVID-19 isolation hotel shelters for people experiencing homelessness. [Oral presentation.] International Network on Health & Hepatitis in Substance Users (INHSU). October 21, 2022 at Glasgow, Scotland.
- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Poster presentation.] International Network on Health & Hepatitis in Substance Users (INHSU). October 21, 2022 at Glasgow, Scotland.
- **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Oral presentation.] College on Problems of Drug Dependence (CPDD) Annual Conference. June 15, 2022 at Minneapolis, Minnesota, USA.
- Colledge S, Jones N, Larney S, Peacock A, Lewer D, **Brothers TD**, Hickman M, Farrell M, Degenhardt L. The impact of opioid agonist treatment on hospitalisations for injecting-related diseases among an opioid dependent population: A retrospective data linkage study. [Poster

presentation.] College on Problems of Drug Dependence (CPDD) Annual Conference. June 15, 2022 at Minneapolis, Minnesota.

- Bonn M, Touesnard N, Cheng B, Pugliese M, Comeau E, Bodkin C, **Brothers TD**, Genge L, Lepage C, Scheim A, Werb D, Wildeman S, Herder M. Securing "Safe Supply" during COVID-19 and beyond: scoping review and knowledge mobilization. [Poster presentation.] International Network on Health and Hepatitis in Substance Users (INHSU) Annual Conference. October 13-15, 2021 at Sydney, Australia + Virtual.

8.3.8.2 National meetings

1. Lepage C, Genge L, **Brothers TD**. Implementation and early outcomes of a Managed Alcohol Program in Halifax, Nova Scotia: a qualitative study of staff and community stakeholders. [Poster presentation.] Canadian Centre on Substance Use and Addiction "Issues of Substance" conference. November 20-22, 2023 at Vancouver, BC, Canada
2. **Brothers TD**, Leaman M, Bonn M, Lewer D, Atkinson J. Fraser J, Gillis A, Gniewek M, Hawker L, Hayman H, Jorna P, Martell D, O'Donnell T, Rivers-Bowerman H, Genge L. Evaluation of an emergency safe supply drugs and managed alcohol program in COVID-19 isolation hotel shelters for people experiencing homelessness in Halifax, Nova Scotia. [Oral presentation]. Canadian Society of Addiction Medicine Annual Scientific Conference. November 4, 2022 at Saskatoon, SK, Canada.
3. Speed K, Kerr T, Abele B, **Brothers T,** Gagnon M, Kennedy MC, McDougall P, McNeil R, O'Gorman C, Pauly B, Ranger C, Schoen E, Strike C, Hyshka E. Developing a national operational guidance document for the implementation of supervised consumption services in Canada. Canadian Public Health Association Annual Conference. June 2022. Virtual, hosted from Ottawa, ON, Canada.

8.3.8.3 Local/Institutional meetings

4. Lepage C, Genge L, **Brothers TD**. Implementation and early outcomes of a Managed Alcohol Program in Halifax, Nova Scotia: a qualitative study of staff and community stakeholders. [Poster presentation.] Dalhousie University Department of Medicine Research Day. April 20, 2023 at Halifax, NS, Canada
5. **Brothers TD**, Bonn M, Lewer D, Kim I, Comeau E, Webster D, Hayward A, Harris M. Social and structural determinants of injecting-related bacterial and fungal infections among people who inject drugs: qualitative systematic review and thematic synthesis. [Oral presentation.] Dalhousie University Department of Medicine Research Day. April 20, 2023 at Halifax, NS, Canada
6. **Brothers TD**, Lewer D, Jones N, Colledge-Frisby S, Farrell M, Hickman M, Webster D, Hayward A, Degenhardt L. Association of opioid agonist treatment with mortality and rehospitalization following injection drug use-associated bacterial and fungal infections: linkage cohort study. [Oral presentation.] Dalhousie University Department of Medicine Research Day. April 21, 2022 at Halifax, NS, Canada.
7. **Brothers TD**, Leaman M, Bonn M, Lewer D, Atkinson J. Fraser J, Gillis A, Gniewek M, Hawker L, Hayman H, Jorna P, Martell D, O'Donnell T, Rivers-Bowerman H, Genge L. Evaluation of an emergency safe supply drugs and managed alcohol program in COVID-19 isolation hotel shelters for people experiencing homelessness. [Poster presentation.] Dalhousie University Department of Medicine Research Day. April 21, 2022 at Halifax, NS, Canada.
8. **Brothers TD**, Fraser J, MacAdam E, Morgan B, Webster D. Uptake of slow-release oral morphine as opioid agonist treatment among hospitalized patients with opioid use disorder. [Poster

presentation.] Dalhousie Department of Medicine Research Day. April 26, 2021 at Halifax, NS, Canada.

9. **Brothers TD,** Fraser J, Cameron E, Morgan B, Francheville J, Nidumolu A, Cheung C, Hickcox S, Saunders D, O'Donnell T, Genge L, Webster D. Impact of a novel hospital inpatient addiction medicine consultation service on the cascade of care for opioid use disorder. [Oral presentation.] Dalhousie Department of Medicine Research Day. November 3, 2020, at Halifax, NS, Canada.

8.3.9 Selected media coverage/interviews in lay press

- MacLean A. "New study highlights effectiveness of Halifax safe supply drug program." Global News. April 16, 2022. Available at: https://globalnews.ca/news/8764466/halifax-safe-supply-program-effectiveness/
- Bonn M. "How Halifax's Safe Supply Hotels Brought Hope in the Early Pandemic." Filter Magazine. February 9, 2022. Available at: https://filtermag.org/halifax-safe-supply-hotels/
- MacLean A. "Halifax doctor strives to improve hospital care, supports for patients with addiction." Global News. February 4, 2022. Available at: https://globalnews.ca/news/8595716/halifax-doctor-study-patients-with-addiction/
- "Safe substance supply in COVID isolation shelters for people experiencing homelessness." CBC Radio Information Morning. Available at https://www.cbc.ca/listen/live-radio/1-27-information-morning-ns/clip/15890466-safe-substance-supply-covid-isolation-shelters-people-experiencing
- Lambie C. "Booze and drugs helped Halifax homeless exposed to COVID obey isolation rules." The Halifax Chronicle-Herald. Jan 19, 2022. Available at https://www.saltwire.com/nova-scotia/news/booze-and-drugs-helped-halifax-homeless-exposed-to-covid-obey-isolation-rules-100682525/
- "What physicians should do when people who inject drugs are admitted to hospital." CBC Information morning. March 26, 2021. Available at https://www.cbc.ca/player/play/1878193731915

8.3.10 Podcast interviews

- Addiction Audio, the podcast from the journal *Addiction*. "Bacterial infections and social determinants of health with Thomas Brothers". July 12, 2023. https://shows.acast.com/addiction-audio/episodes/bacterial-infections-and-social-determinants-of-health-with-
- Canadian Society of Cardiac Surgeons podcast. "Injection drug use-related infective endocarditis". March 2023. https://www.youtube.com/watch?v=gsRU1kI38EI

8.4 Appendix 4. Search strategy used in mixed studies systematic review of injecting-related infections

Concepts	PubMed MEDLINE	EMBASE	Scopus	CINAHL	PsycINFO
People who inject drugs, or drug preparation and injection	("Substance-Related Disorders"[MeSH] OR	('substance abuse'/exp OR	(	(	
	"Substance Abuse, Intravenous"[MeSH] OR	'intravenous drug abuse'/exp OR			
	"Drug Users"[MeSH] OR	'drug use'/exp OR			
	"Needle Sharing"[MeSH] OR	'needle sharing'/exp OR			
	"people who inject drugs"[tiab] OR "persons who inject drugs"[tiab] OR PWID[tiab] OR	"people who inject drugs":ab,ti OR "persons who inject drugs":ab,ti OR PWID:ab,ti OR	TITLE-ABS("people who inject drugs") OR TITLE-ABS("persons who inject drugs") OR TITLE-ABS("PWID") OR	TI("people who inject drugs" OR "persons who inject drugs" OR "PWID") OR AB("people who inject drugs" OR "persons who inject drugs" OR "PWID") OR	TI("people who inject drugs" OR "persons who inject drugs" OR "PWID") OR AB("people who inject drugs" OR "persons who inject drugs" OR "PWID") OR
	"people who use drugs"[tiab] OR "persons who use drugs"[tiab] OR PWUD[tiab] OR	"people who use drugs":ab,ti OR "persons who use drugs":ab,ti OR PWUD:ab,ti OR	TITLE-ABS("people who use drugs") OR TITLE-ABS("persons who use drugs") OR TITLE-ABS("PWUD") OR	TI("people who use drugs" OR "persons who use drugs" OR "PWUD") OR AB("people who use drugs" OR "persons who use drugs" OR "PWUD") OR	TI("people who use drugs" OR "persons who use drugs" OR "PWUD") OR AB("people who use drugs" OR "persons who use drugs" OR "PWUD") OR
	"injection drug"[tiab] OR IDU[tiab] OR	"injection drug":ab,ti OR IDU:ab,ti OR	TITLE-ABS("injection drug") OR TITLE-ABS("IDU") OR	TI("injection drug" OR "IDU") OR AB("injection drug" OR "IDU") OR	TI("injection drug" OR "IDU") OR AB("injection drug" OR "IDU") OR
	"intravenous drug"[tiab] OR IVDU[tiab] OR	"intravenous drug":ab,ti OR IVDU:ab,ti OR	TITLE-ABS("intravenous drug") OR TITLE-ABS("IVDU") OR	TI("intravenous drug" OR "IVDU") OR AB("intravenous drug" OR "IVDU") OR	TI("intravenous drug" OR "IVDU") OR AB("intravenous drug" OR "IVDU") OR
	"drug abuse"[tiab] OR	"drug abuse":ab,ti OR	TITLE-ABS("drug abuse") OR	TI("drug abuse") OR AB("drug abuse") OR	TI("drug abuse") OR AB("drug abuse") OR
	"illicit drugs"[MeSH] OR "illicit drug"[tiab] OR	'illicit drug'/exp OR "illicit drugs":ab,ti OR	TITLE-ABS("illicit drug") OR	TI("illicit drug") OR AB("illicit drug") OR	TI("illicit drug") OR AB("illicit drug") OR
	"Heroin"[MeSH] OR Heroin[tiab] OR	"heroin":ab,ti OR	TITLE-ABS("Heroin") OR	TI("Heroin") OR AB("Heroin") OR	TI("Heroin") OR AB("Heroin") OR
	"Heroin Dependence"[MeSH] OR	'heroin dependence'/exp OR			
	"Opiate use disorder"[tiab] OR "opioid use disorder"[tiab] OR "opiate dependence"[tiab] OR "opioid dependence"[tiab] OR "opiate abuse"[tiab] OR "opioid abuse"[tiab] OR	'narcotic dependence'/exp OR "opioid use disorder":ab,ti OR "opiate use disorder":ab,ti OR	TITLE-ABS("Opiate use disorder") OR TITLE-ABS("opioid use disorder") OR TITLE-ABS("opiate dependence") OR TITLE-ABS("opioid dependence") OR TITLE-ABS("opiate abuse") OR TITLE-ABS("opioid abuse") OR	TI("Opiate use disorder" OR "opioid use disorder" OR "opiate dependence" OR "opioid dependence" OR "opiate abuse" OR "opioid abuse") OR AB("Opiate use disorder" OR "opioid use disorder" OR "opiate dependence" OR "opioid dependence" OR "opiate abuse" OR "opioid abuse") OR	TI("Opiate use disorder" OR "opioid use disorder" OR "opiate dependence" OR "opioid dependence" OR "opiate abuse" OR "opioid abuse") OR AB("Opiate use disorder" OR "opioid use disorder" OR "opiate dependence" OR "opioid dependence" OR "opiate abuse" OR "opioid abuse") OR
	"Cocaine"[MeSH] OR cocaine[tiab] OR	'cocaine'/exp OR 'cocaine dependence'/exp OR cocaine:ab,ti OR	TITLE-ABS("cocaine") OR	TI("cocaine") OR AB("cocaine") OR	TI("cocaine") OR AB("cocaine") OR
	"Crack Cocaine"[MeSH] OR	"crack cocaine":ab,ti OR	TITLE-ABS("crack cocaine") OR	TI("crack cocaine") OR AB("crack cocaine") OR	TI("crack cocaine") OR AB("crack cocaine") OR
	"groin injecting"[tiab] OR "femoral injecting"[tiab] OR	"groin injecting":ab,ti OR "femoral injecting":ab,ti OR	TITLE-ABS("groin injecting") OR TITLE-ABS("femoral injecting") OR	TI("groin injecting" OR "femoral injecting") OR AB("groin injecting" OR "femoral injecting") OR	TI("groin injecting" OR "femoral injecting") OR AB("groin injecting" OR "femoral injecting") OR

	"Harm Reduction"[MeSH] OR "harm reduction"[tiab] OR	'harm reduction'/exp OR "harm reduction":ab,ti OR	TITLE-ABS("harm reduction") OR	TI("harm reduction") OR AB("harm reduction") OR	TI("harm reduction") OR AB("harm reduction") OR
	"Needle-Exchange Programs"[MeSH] OR				
	"needle exchange"[tiab] OR "syringe exchange"[tiab] OR "syringe services"[tiab] OR	"needle exchange":ab,ti OR "syringe exchange":ab,ti OR "syringe services":ab,ti OR	TITLE-ABS("needle exchange") OR TITLE-ABS("syringe exchange") OR TITLE-ABS("syringe services") OR	TI("needle exchange" OR "syringe exchange") OR "syringe services") OR AB("needle exchange" OR "syringe exchange") OR "syringe services") OR	TI("needle exchange" OR "syringe exchange") OR "syringe services") OR AB("needle exchange" OR "syringe exchange") OR "syringe services") OR
	acidifier*[tiab] OR	acidifier*:ab,ti OR	TITLE-ABS("acidifier*") OR	TI("acidifier*") OR AB("acidifier*") OR	TI("acidifier*") OR AB("acidifier*") OR
	"Opiate Substitution Treatment"[MeSH] OR (("opiate substitution" OR "opiate agonist" OR "opioid substitution" OR "opioid agonist") AND (treatment or therapy)) OR	'opiate substitution treatment'/exp OR "opioid agonist":ab,ti OR "opiate substitution":ab,ti OR	TITLE-ABS("opiate substitution") OR TITLE-ABS("opiate agonist") OR TITLE-ABS("opioid substitution") OR TITLE-ABS("opioid agonist") OR	TI("opiate substitution") OR AB("opiate substitution") OR	TI("opiate substitution") OR AB("opiate substitution") OR
	"Medications for opioid use disorder"[tiab] OR MOUD[tiab] OR	"medications for opioid use disorder":ab,ti OR MOUD:ab,ti OR	TITLE-ABS("Medications for opioid use disorder") OR TITLE-ABS("MOUD") OR	TI("Medications for opioid use disorder" OR "MOUD) OR AB("Medications for opioid use disorder" OR "MOUD") OR	TI("Medications for opioid use disorder" OR "MOUD) OR AB("Medications for opioid use disorder" OR "MOUD") OR
	Methadone[tiab] OR	'methadone treatment'/exp OR methadone:ab,ti OR	TITLE-ABS("Methadone") OR	TI("Methadone") OR AB("Methadone") OR	TI("Methadone") OR AB("Methadone") OR
	Buprenorphine[tiab])	Buprenorphine:ab,ti)	TITLE-ABS("Buprenorphine"))	TI("Buprenorphine") OR AB("Buprenorphine"))	TI("Buprenorphine") OR AB("Buprenorphine"))
Injecting-related infections	AND	AND	AND	AND	AND
	("injection-related infections"[tiab] OR "injection-related infection"[tiab] OR	('injection site abscess'/exp OR "injection-related infections":ab,ti OR "injection-related infection":ab,ti OR	((TITLE-ABS("injection-related infections") OR TITLE-ABS("injection-related infection") OR	(TI("injection-related infections" OR "injection-related infection") OR AB("injection-related infections" OR "injection-related infection") OR	(TI("injection-related infections" OR "injection-related infection") OR AB("injection-related infections" OR "injection-related infection") OR
	"bacterial infection"[tiab] OR "bacterial infections"[tiab] OR	"bacterial infection":ab,ti OR	TITLE-ABS("bacterial infection") OR TITLE-ABS("bacterial infections") OR	TI("bacterial infection" OR "bacterial infections") OR AB("bacterial infection" OR "bacterial infections") OR	TI("bacterial infection" OR "bacterial infections") OR AB("bacterial infection" OR "bacterial infections") OR
	Bacteremia[MeSH] OR bacteremia[tiab] OR	'bacteremia'/exp OR bacteremia:ab,ti OR	TITLE-ABS("bacteremia") OR	TI("bacteremia") OR AB("bacteremia") OR	TI("bacteremia") OR AB("bacteremia") OR
	Fungemia[MeSH] OR	'fungemia'/exp OR			
	Cellulitis[MeSH] OR cellulitis[tiab] OR	'cellulitis'/exp OR cellulitis:ab,ti OR	TITLE-ABS("cellulitis") OR	TI("cellulitis") OR AB("cellulitis") OR	TI("cellulitis") OR AB("cellulitis") OR
	Abscess[MeSH] OR abscess*[tiab] OR	'abscess'/exp OR abscess*:ab,ti OR	TITLE-ABS("abscess*") OR	TI("abscess*") OR AB("abscess*") OR	TI("abscess*") OR AB("abscess*") OR
	"skin infection"[tiab] OR "skin infections"[tiab] OR	"skin infection":ab,ti OR "skin infections":ab,ti OR	TITLE-ABS("skin infection") OR TITLE-ABS("skin infections") OR	TI("skin infection" OR "skin infections") OR AB("skin infection" OR "skin infections") OR	TI("skin infection" OR "skin infections") OR AB("skin infection" OR "skin infections") OR
	"skin and soft tissue"[tiab] OR SSTI*[tiab] OR	"skin and soft tisuuse":ab,ti OR SSTI*:ab,ti OR	TITLE-ABS("skin and soft tissue") OR TITLE-ABS("SSTI*") OR	TI("skin and soft tissue" OR "SSTI*") OR AB("skin and soft tissue" OR "SSTI*") OR	TI("skin and soft tissue" OR "SSTI*") OR AB("skin and soft tissue" OR "SSTI*") OR
	Endocarditis[MeSH] OR endocarditis[tiab] OR	'endocarditis'/exp OR endocarditis:ab,ti OR	TITLE-ABS("endocarditis") OR	TI(endocarditis) OR AB(endocarditis) OR	TI(endocarditis) OR AB(endocarditis) OR
	Bone Diseases, Infectious[MeSH] OR				
	Osteomyelitis[MeSH] OR Osteomyelitis[tiab] OR	'osteomyelitis'/exp OR osteomyelitis:ab,ti OR	TITLE-ABS("osteomyelitis") OR	TI("osteomyelitis") OR AB("osteomyelitis") OR	TI("osteomyelitis") OR AB("osteomyelitis") OR

	“septic arthritis”[tiab] OR	“septic arthritis”:ab,ti OR	TITLE-ABS("septic arthritis"))	TI("septic arthritis") OR AB("septic arthritis"))	TI("septic arthritis") OR AB("septic arthritis"))
	Central Nervous System Infections[MeSH] OR				
	Gram-Positive Bacterial Infections[MeSH] OR				
	Candidiasis[MeSH])	'candidiasis'/exp)			
Social and structural determinants, or risk environment	AND	AND	AND	AND	AND
	("risk factor"[tiab] OR “risk factors”[tiab] OR	('risk factor'/exp OR “risk factor”:ab,ti OR	(TITLE-ABS("risk factor") OR TITLE-ABS("risk factors") OR	(TI("risk factor” OR "risk factors") OR AB("risk factor” OR "risk factors") OR	(TI("risk factor” OR "risk factors") OR AB("risk factor” OR "risk factors") OR
	correlate*[tiab] OR	correlate*:ab,ti OR	TITLE-ABS(correlate*) OR	TI("correlate*") OR AB("correlate*") OR	TI("correlate*") OR AB("correlate*") OR
	determinant*[tiab] OR	determinant*:ab,ti OR	TITLE-ABS("determinant*") OR	TI("determinant*") OR AB("determinant*") OR	TI("determinant*") OR AB("determinant*") OR
	environment*[tiab] OR	environment*:ab,ti OR	TITLE-ABS("environment*") OR	TI("environment*") OR AB("environment*") OR	TI("environment*") OR AB("environment*") OR
	“social factors”[tiab] or “structural factors”[tiab] OR	'social determinants of health'/exp OR “social factors”:ab,ti OR “structural factors”:ab,ti OR	TITLE-ABS("social factors") OR TITLE-ABS("structural factors") OR	TI("social factors" OR "structural factors") OR AB("social factors" OR "structural factors") OR	TI("social factors" OR "structural factors") OR AB("social factors" OR "structural factors") OR
	Cohort*[tiab] OR	'cohort analysis'/exp OR cohort*:ab,ti OR	TITLE-ABS(cohort*) OR	TI("Cohort*") OR AB("Cohort*") OR	TI("Cohort*") OR AB("Cohort*") OR
	Longitudinal[tiab] OR	Longitudinal:ab,ti OR	TITLE-ABS("Longitudinal") OR	TI("Longitudinal") OR AB("Longitudinal") OR	TI("Longitudinal") OR AB("Longitudinal") OR
	Prospective[tiab] OR retrospective[tiab] OR	Prospective:ab,ti OR retrospective:ab,ti OR	TITLE-ABS("Prospective") OR TITLE-ABS("retrospective") OR	TI("Prospective" OR "retrospective") OR AB("Prospective" OR "retrospective") OR	TI("Prospective" OR "retrospective") OR AB("Prospective" OR "retrospective") OR
	Randomized[tiab] OR randomised[tiab] OR	Randomized:ab,ti OR randomised:ab,ti OR	TITLE-ABS("Randomized") OR TITLE-ABS("randomised") OR	TI("Randomized" OR "randomised") OR AB("Randomized" OR "randomised") OR	TI("Randomized" OR "randomised") OR AB("Randomized" OR "randomised") OR
	Comparative[tiab] OR	Comparative:ab,ti OR	TITLE-ABS("Comparative") OR	TI("Comparative") OR AB("Comparative") OR	TI("Comparative") OR AB("Comparative") OR
	Case-control[tiab] OR	Case-control:ab,ti OR	TITLE-ABS("Case-control") OR	TI("Case-control") OR AB("Case-control") OR	TI("Case-control") OR AB("Case-control") OR
	Time-series[tiab] OR	'time series analysis'/exp OR “time-series”:ab,ti OR	TITLE-ABS("Time-series") OR	TI("Time-series") OR AB("Time-series") OR	TI("Time-series") OR AB("Time-series") OR
	Survey*[tiab] OR	Survey*:ab,ti OR	TITLE-ABS("Survey*") OR	TI("Survey*") OR AB("Survey*") OR	TI("Survey*") OR AB("Survey*") OR
	Epidemiolog*[tiab] OR	Epidemiolog*:ab,ti OR	TITLE-ABS("Epidemiolog*") OR	TI("Epidemiolog*") OR AB("Epidemiolog*") OR	TI("Epidemiolog*") OR AB("Epidemiolog*") OR
	Qualitative[tiab] OR	Qualitative:ab,ti OR	TITLE-ABS("Qualitative") OR	TI("Qualitative") OR AB("Qualitative") OR	TI("Qualitative") OR AB("Qualitative") OR
	Interview[tiab] OR	'interview'/exp OR interview:ab,ti OR	TITLE-ABS("Interview") OR	TI("Interview") OR AB("Interview") OR	TI("Interview") OR AB("Interview") OR
	Ethnograph*[tiab] OR	'ethnography'/exp OR ethnograph*:ab,ti OR	TITLE-ABS("Ethnograph*") OR	TI("Ethnograph*") OR AB("Ethnograph*") OR	TI("Ethnograph*") OR AB("Ethnograph*") OR
	Mixed-methods[tiab] OR “mixed methods”[tiab]	Mixed-methods:ab,ti OR “mixed methods”:ab,ti OR	TITLE-ABS("Mixed-methods") OR TITLE-ABS("mixed methods") OR	TI("Mixed-methods" OR "mixed methods") OR AB("Mixed-methods" OR "mixed methods") OR	TI("Mixed-methods" OR "mixed methods") OR AB("Mixed-methods" OR "mixed methods") OR

	gender[tiab] OR	Gender:ab,ti OR	TITLE-ABS(gender) OR	TI(gender) OR AB(gender) OR	TI(gender) OR AB(gender) OR
	homeless*[tiab] OR	homeless*:ab,ti OR	TITLE-ABS(homeless*) OR	TI(homeless*) OR AB(homeless*) OR	TI(homeless*) OR AB(homeless*) OR
	race[tiab] OR racism[tiab] OR	race:ab,ti OR racism;ab,ti OR	TITLE-ABS(race OR racism) OR	TI(race or racism) OR AB(race or racism) OR	TI(race or racism) OR AB(race or racism) OR
	incarcerat*[tiab] OR prison*[tiab] OR criminal*[tiab] OR	incarcerat*:ab,ti OR prison*:ab,ti OR criminal*ab,ti OR	TITLE-ABS(incarcerat* OR prison* OR criminal*) OR	TI(incarcerat* OR prison* OR criminal*) OR AB(incarcerat* OR prison* OR criminal*) OR	TI(incarcerat* OR prison* OR criminal*) OR AB(incarcerat* OR prison* OR criminal*) OR
	stigma*[tiab] OR discrimination[tiab] OR exclusion[tiab])	stigma*ab,ti OR discrimination:ab,ti OR exclusion:ab,ti)	TITLE-ABS(stigma* OR discrimination OR exclusion*))	TI(stigma* OR discrimination OR exclusion) OR AB(stigma* OR discrimination OR exclusion))	TI(stigma* OR discrimination OR exclusion) OR AB(stigma* OR discrimination OR exclusion))
	NOT ("case report"[Title]) *NOT ("case series"[Title])*	NOT "case report":ti NOT "case series":ti NOT "rare case":ti			
	Filter: 2000-Present	Filter:2000-2021	Filter:2000-2021	Limit to 2000-2021	Limit to 2000-2021
		Filter: AND ('**article**'/it OR '**article in press**'/it OR '**conference abstract**'/it OR '**conference paper**'/it OR '**letter**'/it OR '**short survey**'/it) [**To remove review articles]			

8.5 Appendix 5. Critical appraisal of qualitative studies using the Mixed Methods Appraisal Tool (MMAT) for mixed studies systematic reviews, included in qualitative systematic review

		Screening questions		Qualitative studies				
	Study	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**1. Is the qualitative approach appropriate to answer the research question?**	**2. Are the qualitative data collection methods adequate to address the research question?**	**3. Are the findings adequately derived from the data?**	**4. Is the interpretation of results sufficiently substantiated by data?**	**5. Is there coherence between qualitative data sources, collection, analysis and interpretation?**
1	Bearnot 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Bearnot 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Bodkin 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Case 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Colwill 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Dunleavy 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Epele 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Gilbert 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Harris RE 2018a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Harris RE 2018b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Harris M 2020a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Krüsi 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Mars 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	McNeil 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15	Meyer 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16	Paquette 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes

17	Pollini 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Sheard 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Small 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes

8.6 Appendix 6. Critical appraisal of mixed methods studies using the Mixed Methods Appraisal Tool (MMAT) for mixed studies systematic reviews, included in qualitative systematic review

		Screening questions		Mixed methods studies				
	Study	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**1. Is there an adequate rationale for using a mixed methods design to address the research question?**	**2. Are the different components of the study effectively integrated to answer the research question?**	**3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?**	**4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?**	**5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?**
1	Bourgois 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Harris M 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Harris M 2020b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Jafari 2015	Yes	Yes	Yes	Yes	No	No	No
5	Phillips 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Pollini 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Summers 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes

8.7 Appendix 7. Information on studies identified outside of search, and on studies excluded after critical appraisal.

Eight quantitative studies added and included from outside the search:

1. Scherbaum N, Specka M, Schifano F, Bombeck J, Marrziniak B. Longitudinal observation of a sample of German drug consumption facility clients. Substance Use & Misuse. 2010;45(1-2):176-189
2. Marks LR, Munigala S, Warren DK, Liang SY, Schwarz ES, Durkin MJ. Addiction Medicine Consultations Reduce Readmission Rates for Patients With Serious Infections From Opioid Use Disorder. Clin Infect Dis. 2019 May 17;68(11):1935-1937. doi: 10.1093/cid/ciy924.
3. Tomolillo CM, Crothers LJ, Aberson CL. The damage done: a study of injection drug use, injection related abscesses and needle exchange regulation. Substance use & misuse. 2007 Sep 21;42(10):1603-11.
4. Takahashi TA, Baernstein A, Binswanger I, Bradley K, Merrill JO. Predictors of hospitalization for injection drug users seeking care for soft tissue infections. Journal of general internal medicine. 2007 Mar;22(3):382-8.
5. Serota DP, Bartholomew TS, Tookes HE. Evaluating differences in opioid and stimulant use-associated infectious disease hospitalizations in Florida, 2016–2017. Clinical infectious diseases. 2021 Oct 1;73(7):e1649-57.
6. Morin KA, Prevost CR, Eibl JK, Franklyn MT, Moise AR, Marsh DC. A retrospective cohort study evaluating correlates of deep tissue infections among patients enrolled in opioid agonist treatment using administrative data in Ontario, Canada. PloS one. 2020 Apr 24;15(4):e0232191.
7. Meel R. Striking increase in the incidence of infective endocarditis associated with recreational drug abuse in urban South Africa. South African Medical Journal. 2018 Aug 5;108(7).
8. 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. Epidemiology & Infection. 2015 Jan;143(1):120-31.

Four potentially eligible studies that did not meet the MMAT screening questions and were therefore excluded. These were, “1. Are there clear research questions?” and “2. S2. Do the collected data allow to address the research questions?”

1. Annie FH, Bates MC, Uejio CK, Bhagat A, Kochar T, Embrey S, Uejio CK. The impact of the drug epidemic on the incidence of sepsis in West Virginia. Cureus. 2018 Oct 30;10(10).
    - No to S2: unclear unit of analysis, unclear outcomes.
2. Bates MC, Annie F, Jha A, Kerns F. Increasing incidence of IV-drug use associated endocarditis in southern West Virginia and potential economic impact. Clinical Cardiology. 2019 Apr;42(4):432-7.
    - No to S1 and S2: unclear unit of analysis, unclear outcomes
3. Jafari S, Joe R, Elliot D, Nagji A, Hayden S, Marsh DC. A community care model of intravenous antibiotic therapy for injection drug users with deep tissue infection for "reduce leaving against medical advice". International Journal of Mental Health and Addiction. 2015 Feb;13:49-58.
    - No to S2: Exposure is listed as community care vs. hospital, but entire sample was in the hospital.
4. Thakarar K, Rokas KE, Lucas FL, Powers S, Andrews E, DeMatteo C, Mooney D, Sorg MH, Valenti A, Cohen M. Mortality, morbidity, and cardiac surgery in Injection Drug Use (IDU)-associated versus non-IDU infective endocarditis: The need to expand substance use disorder treatment and harm reduction services. PLoS One. 2019 Nov 26;14(11):e0225460.
    - No to S2: Most of the study describes sample of patients with injection drug use-associated endocarditis and compares to people with endocarditis with no drug use. There is a subgroup analysis comparing outcomes among people with injection drug use-associated endocarditis who were prescribed opioid agonist treatment at hospital discharge vs. were not, but the proportions seem inadvertently reported as proportions of the whole sample so I cannot extract denominators.

8.8 Appendix 8. Characteristics of included studies with outcome as incident or prevalent injecting-related infection in quantitative systematic review of social and structural determinants of injection drug use-associated bacterial and fungal infections.

Study	Included exposures in this review	Main exposure / estimand in study	Do exposures included in this review reflect study estimand	Infections	Outcomes	Country (City)	Sample size	Sampling method (parent study name)	MMAT quality rating (out of 5)	Data collection period	Inclusion criteria	Women/female	Age	Drugs used by ≥50%
Baltes 2020[254]	• Gender/sex • Age • Race/ethnicity • Education • Housing • Health insurance • Heroin • Cocaine • Amphetamines • Prescription opioids • Other prescription drugs	Not specified. Aimed to identify factors associated with having had an SSTI in the past year.	No estimand	• SSTI	Self-reported skin and soft-tissue infections in past year, not otherwise defined	USA (Brown, Douglas, Eau Claire, La Crosse, Outagamie, and Marathon counties, Wisconsin)	80	Respondent-driven sampling, starting with rural clients of needle and syringe program	3	May to July 2019	15 years or older, injected drugs within 30 days prior to survey response, and resided in a rural community	40%	42.5% between ages 30 and 39 years	Methamphetamine
Bassetti 2002[272]	• Opioid agonist treatment	Effect of enrolling in injectable opioid agonist treatment program on risk for injecting-related bacterial infections	Yes	• Multiple • SSTI • Bacteremia	Incidence per 100 patient-years of infections requiring hospitalization, identified via electronic medical records Skin (abscesses, phlegmonous infections, erysipelas, ulcerations, and necrosis) and bloodstream	Switzerland (Basel)	175	Consecutive patients enrolling in an injection opioid agonist treatment program (heroin, methadone, or morphine)	4	1 November 1991 to 31 October 1998	All participants who underwent their first evaluation from 1 November 1994 through 31 January 1997 Eligibility criteria for the opiate program were residence in the canton of Basel City, age ≥20 years, a ≥2-year history of addiction to injected heroin, failure of previous addiction treatment, and social distress	30%	Mean 31.4 years (range, 21-53)	Heroin

											and/or health problems that resulted from injection drug use.			
Bertin 2020[273]	• Opioid agonist treatment	Effect of different opioid agonist treatment options on risk for multiple outcomes (including bacterial infections)	Yes	• Multiple • Not specified	Hospital admissions for bacterial infections, identified using ICD-10 codes. Specific infections not defined.	France (nationwide)	31,687	Nationwide administrative data of linked hospital and pharmacy records (French Nationwide Healthcare Data System, which covers 98.8% of the French population)	4	1 April 2012 to 31 December 2015	All patients aged 15 years or older who received opioid agonist treatment with methadone, buprenorphine, or morphine sulfate from a community pharmacy at least once between 1 April 2012 and 31 December 2014, with no dispensing during the 3 months prior to inclusion, with the aim to recruit only incident patients. Excluded patients with cancer, receiving palliative care, or in treatment for chronic pain.	Morphine: 23.4% Buprenorphine: 21% Methadone: 28.2%	Mean (SD): Morphine: 34.7 (8.7) Buprenorphine: 34.5 (9.1) Methadone 33.5 (8.2)	Not reported
Betts 2016[229]	• Gender/sex • Age • Education • Housing • Opioid agonist treatment	Effect of opioid agonist treatment on substance use and health outcomes	Partly (1 of 5 exposures)	• SSTI	Past-month abscess, self-report (not otherwise specified)	Australia (nationwide)	2,677	Purposive convenience sampling, recruited through needle and syringe programs and snowball sampling in each state's capital city. (Illicit Drug Reporting System; IRDS)	4	2011 to 2013	Eligible participants are aged 16 years or older, report injecting an illicit drug at least monthly in the 6 months prior to interview and report living in their recruitment city for 12 months prior to interview	34.2%	17-35: 35.8% (957) 36-45: 38.4% (1025) 46-71: 25.7% (686)	None (e.g., 29.8% of participants reported weekly heroin use; 17.1% reported weekly crystal methamphetamine use)
Bhattacharya 2006[270]	• Needle and syringe program	Effect of implementing a needle and syringe program on	Yes	• SSTI	Monthly prevalence of skin abscess, as observed by outreach	India (Tiljala slum area, Kolkata, West Bengal)	4,736 participants observ	Sampling method not described ("Observations	2	January 2000 to March 2002	Not described	Not described	Not described	Not described

		the rate of SSTI among PWID			workers (not otherwise specified)		ved over 27 months (unknown number of participants with multiple observations)	were made in a cohort of street IDUs… observed daily through peer outreach workers supervised by field supervisors")						
Binswanger 2000[99]	• Gender/sex • Age • Other substance use • Housing • Needle and syringe program	Not specified (case-control study)	No estimand	• SSTI	Current "pain, swelling, redness, hardness under their skin, heat, pus, or oozing" at injection site, self-reported and confirmed via physical examination	USA (San Francisco, California)	169	Targeted and snowball sampling through outreach, health and social services, and word-of-mouth (Urban Health Study)	4	May 1997	Age >18 years and physical evidence of drug injection (e.g., track marks) or previous participation in the Urban Health Study.	25%	54% were aged 40-49 years	Heroin
Buchanan 2006[264]	• Cocaine	Effect of "crack" cocaine injection (vs. injecting other drugs) on multiple outcomes	Yes, but timeline mismatch	• SSTI	Ever hard "abscess" (not otherwise specified), self-reported	USA (New Haven and Hartford, Connecticut; Springfield, Massachusetts)	989	Targeted sampling via street outreach (Syringe Access, Use and Discard research project)	4	January 2000 to May 2002	18 years of age or older, not currently in drug treatment, resident in targeted neighborhood and injection drug use within the past 30 days; current use was confirmed by physical examination of site of injections	Recent crack cocaine injection: 19.0% Lifetime/ever: 25.8% Never: 29.8%	Mean age Recent crack cocaine injection: 37.8 Lifetime/ever: 38.4 Never: 38.8	Cocaine, heroin
Cedarbaum 2016[255]	• Age	Effect of being under 30 years old (vs. being older) on	Yes	• SSTI	Past year "abscess" (not otherwise	USA (Seattle, Washington)	389	Convenience sample of needle and syringe	5	July 2013	Needle and syringe program clients; recent heroin use and who had	29.3% ("Transgen	Under 30 years: 32.9%	Heroin, methamphetamines,

		multiple outcomes			specified), self-report			programs clients			adequate data recorded for the injection and age-related questions	der" coded as separate category from "Male" or "Female"	30 years and older: 67.1%	benzodiazepines
Ciccarone 2016[137]	• Class • Heroin type	Effect of geographic area and heroin type on risk of SSTI	Partly (1 of 2 exposures)	• SSTI	Hospitalization for opioid injection-related skin and soft tissue infections	USA (nationwide)	Not reported	20% stratified national random sample of United States Community Hospitals (Nationwide Inpatient Sample)	5	1993 to 2010	Hospital admission with ICD-9 codes 681.1–682.9, were between the ages of 15 and 65 and did not have a diagnosis of diabetes type 1 or type 2.	Not reported	Not reported	Not reported
Cooper 2005[256]	• Age • Race/ethnicity • Class • Police contacts/arrests	Effect of police crackdowns on risk of hospitalization with injecting-related infections	Partly (1 of 4 exposures)	• Multiple • SSTI • Endocarditis	Monthly rate of hospitalisation for abscess/cellulitis or endocarditis	USA (New York, New York)	27 police precincts (2,727,000 population; unknown number of people who inject drugs)	Hospital records from New York State Statewide Planning and Research Cooperative System (SPARCS) database, which covers all individuals admitted to community-based hospital facilities within NYC	5	1995 to 1999	Hospital discharge diagnosis codes for endocarditis, abscess, or cellulitis, and also between 18 and 64 years old without diabetes; had an accompanying illicit-drug-related co-diagnosis or procedure mentioned in their medical record; infection was not iatrogenic	Not reported	Precinct age structure (mean, standard deviation) 0-17 years: 23.1% (7.8) 18-64 years: 64.7% (6.7) >65 years 12.2% (4.0)	Not reported
Dahlman 2015[230]	• Gender/sex • Age • Heroin • Prescription opioids • Prescription stimulants	Not specified. Aimed to identify factors associated with having ever had an SSTI.	No estimand	• SSTI	Ever had "an abscess or symptoms of skin and soft tissue infection (redness, swelling, pain, pus)", self-report	Sweden (Malmö)	80	Consecutive clients attending needle and syringe program	4	2012	Reporting current or previous injection drug use, age ≥ 20 years, consent to HIV testing. Exclusion criteria were inability to understand the	30%	Median (range) 44.5 (23–64)	None

	• Other prescription drug				Participants were asked to distinguish between signs of infection, and irritation caused by extravasal injection						informed consent or perform the interview due to Swedish language difficulties, psychiatric disability, or intoxication.			
Dahlman 2017[231]	• Gender/sex • Age • Race/ethnicity • Heroin • Cocaine • Amphetamine • Speedball • Other prescription drug • Housing • Inject in public • Received injecting assistance	Not specified. Aimed to identify factors associated with recently having had an SSTI.	No estimand	• SSTI	Past-30 days "abscess or symptoms for skin and soft tissue infection (redness, swelling, pain, pus)" at injection site, self-report	USA (San Francisco, California)	201	Recruited from community settings using targeted sampling methods	4	November 2011 through April 2014	injection drug use in the past 30 days, being 18 years of age or older, and the ability to provide informed consent	22.9%	18–29: 15.4% 30–44: 36.3% 45–54: 27.9% 55 and older: 20.4%	Cocaine, methamphetamine, heroin
DiGiorgio 2019[266]	• Drug policy change	Effect of opioid prescribing prescription policy on risk of injecting-related epidural abscess	Yes	• Epidural abscess	Monthly rate of hospitalisation with injection drug use-associated spinal epidural abscess	USA (New Orleans, Louisiana)	45	Hospital patients admitted to tertiary care center with billing codes or imaging tests indicating epidural abscess	2	July 2013 through July 2018	Recent "intravenous drug use" recorded in medical charts. Not otherwise specified.	24%	Mean (range) 47.1 (25–71)	Not reported
Doran 2020[232] (UAM)	• Gender/sex • Age • Migration • Sex work • Incarceration • Amphetamine	Not specified. Aimed to identify factors associated with risk of SSTI.	No estimand	• SSTI	Past year "swelling containing pus (abscess), sore or open wound" at injection site, self-report	England, Wales, and Northern Ireland (87% outside of London)	2,874	Recruited from clients attending needle and syringe programs and addiction treatment programs	4	2017 and 2018 annual surveys	Age 18 and older, injected drugs in the past year.	29%	68% aged 35 years and older	Not reported. "Majority … report injecting heroin or a heroin/crack

	• Housing							(Unlinked Anonymous Monitoring Survey)						cocaine combination."
Doran 2020[232] (Care & Prevent)	• Gender/sex • Age • Race/ethnicity • Class • Amphetamine • Housing	Not specified. Aimed to identify factors associated with risk of SSTI.	No estimand	• SSTI	Ever had SSTI, self-report. "Participants were provided with photographs of mild, moderate and severe abscesses, cellulitis and leg ulcers to aid their recall, ensure correct SSTI identification and provide a comparative measure to assess SSTI severity."	England (London)	455	Recruited from clients of drug treatment programs, homeless hostels, and outreach services (Care and Prevent Study)	4	October 2017 through March 2019	Aged 18 and older, ever injected drugs	25%	57% aged 35 years and older	Not reported. "Majority … report injecting heroin or a heroin/crack cocaine combination."
Dunleavy 2017[92]	• Gender/sex • Age • Incarceration • Other polysubstance • Housing • Needle and syringe program • Opioid agonist treatment • Alcohol	Effect of needle and syringe program uptake, and of opioid agonist treatment uptake, on risk of SSTI	Partly (2 of 8 exposures)	• SSTI	"In the last year, have you had a swelling containing pus (abscess), a sore or open wound at an injection site?", self-report	Scotland	1,876	Recruited from clients at pharmacies and needle and syringe programs (National Exchange Surveillance Initiative Scotland study)	4	February 2013 through February 2014	Injected drugs in the past 6 months	29%	Age (years) 25 or younger: 8% 26-30: 15% 31-35: 25% 36 or older: 52%	Heroin
Fink 2013[100]	• Gender/sex • Age • Race/ethnicity • Education • Heroin	Not specified. Aimed to identify factors associated with risk of SSTI.	No estimand	• SSTI	"During the last six months, did you have an abscess related to injection drug use? (Including any enduring lumps, even if	USA (Los Angeles, Oakland, and Berkeley, California)	858	Recruited through community outreach and clients of needle and syringe programs	4	2003 through 2005	Aged 18 years or older, and injected drugs in the past 30 days	29%	Age (years) 29 or younger: 5% 30-39: 16%	Heroin

	• Cocaine • Amphetamine • Speedball • Housing • Needle and syringe program				they did not "come to a head," drain, or require treatment of any kind", self-report								40-49: 37% 50+: 41%	
Hope 2014[125]	• Gender/sex • Age • Class • Incarceration • Overdose history • Heroin • Cocaine • Amphetamine • Housing • Police contacts/arrests	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Past 28-days, "redness, swelling and tenderness; an abscess (a swelling containing pus); or a sore/open wound" at an injection site, self-report	England (Bristol, Leeds, and Birmingham)	855	Respondent-driven sampling, with seed participants identified via street outreach and key informant referrals	5	2006 (Bristol), 2008 (Leeds), and 2009 (Birmingham)	Aged 15 and older, injected drugs in the past four weeks, living within survey area	25%	Mean 32, median 31 years	Heroin, crack cocaine
Hope 2015[75]	• Gender/sex • Age • Class • Migration • Sex work • Overdose • Heroin • Cocaine • Amphetamine • Housing • Police contacts/arrests	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Past year, "redness, swelling and tenderness; an abscess; or a sore/open wound" at an injection site, self-report	England (Bristol, Leeds, and Birmingham)	855	Respondent-driven sampling, with seed participants identified via street outreach and key informant referrals Same sample as Hope 2014	5	2006 (Bristol), 2008 (Leeds), and 2009 (Birmingham)	Aged 15 and older, injected drugs in the past four weeks, living within survey area	25%	Mean 32, median 31 years	Heroin, crack cocaine
Hope 2010[101]	• Gender/sex • Age • Incarceration	Not specified. Aimed to identify factors	No estimand	• SSTI	Past year "swelling containing pus (abscess), sore, or	England, Wales, and Northern Ireland	5,209	Recruited from clients attending needle and syringe	4	2006 through 2008	Injected drugs in the past year.	25%	Mean 32.5, median 32 years	Heroin, stimulants (not otherwis

	• Other stimulant • Other polysubstance • Housing • Needle and syringe program • Opioid agonist treatment	associated with SSTI.			open wound at an injection site", self-report			programs and addiction treatment programs (Unlinked Anonymous Monitoring Survey)						e specified)
Hope 2008[104]	• Gender/sex • Age • Incarceration • Cocaine • Amphetamine • Housing • Opioid agonist treatment	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Past year "abscess (pus filled swelling)" or "open wound/sore" at injection site, self-reported	England, Wales, and Northern Ireland	1,058	Recruited from clients attending needle and syringe programs and addiction treatment programs (Unlinked Anonymous Monitoring Survey)	4	Autumn 2003 through summer 2005	Injected drugs in past 28 days	23%	Median 30 years, range 16 to 72 years	Opiates
Islam 2019[233]	• Gender/sex • Age	Effect of reducing or stopping injection use on injecting-elated infections	No	• Multiple • Endocarditis • Sepsis/bacteremia • Pneumonia	Invasive bacterial infection (pneumonia, sepsis, endocarditis) at 9 months and 12 months following baseline study visit, self-report & confirmed with medical chart review Conceptualized as injecting-related, despite including pneumonia	USA (Baltimore, Maryland)	2,247	Recruitment through community-based outreach and through clients of health and social services (AIDS Linked to the Intravenous Experience; ALIVE) Similar sample as Safaeian 2000 and Wilson 2002	4	December 1988 through June 2012	Age 18 years and older, history of injection drug use and high-frequency injection drug use (defined as >1 time daily)	27.8%	Not reported	Heroin, cocaine
Lee 2013[268]	• Received injecting assistance	Not specified. Aimed to identify factors associated	No estimand.	• SSTI	Past 6 month soft-tissue infections (not otherwise	Thailand (Bangkok)	430	Recruited through community outreach (Mitsampan	5	July 2011 to October 2011	Adults, residing in Bangkok or adjacent provinces, injected drugs in past six months	19.3%	Median 38 years (interquartile range	Heroin, midazolam

		with receiving injecting assistance.			specified), self-reported			Community Research Project)					34 - 48 years)	
Lewer 2020[234]	• Gender/sex	Effect of gender/sex on injecting-related infections	Yes	• Multiple • SSTI • Sepsis/bacteremia • Endocarditis • Septic arthritis • Osteomyelitis	Rate of hospital admissions for heroin-injection associated bacterial infections	England (London)	2,335	Electronic health records of people entering community-based substance use treatment, with reported use of heroin and drug injection (Clinical Records Interactive Search resource at the South London and Maudsley NHS Foundation Trust Biomedical Research Centre)	5	1 January 2006 and 31 March 2017	Age 18-64 who were entering community-based substance use treatment, reported heroin use and drug injection	26%	Mean 36.3 (SD 8.4) years	Heroin, crack cocaine, alcohol
Lloyd-Smith 2005[235]	• Gender/sex • Sex work • Incarceration • Heroin • Cocaine • Housing	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Past 6-months abscess ("lasting for more than 3 days"), self-report	Canada (Vancouver, British Columbia)	1,585	Recruitment through community-based outreach (Vancouver Injection Drug Users Study; VIDUS)	5	1 May 1996 to May 31 2004	Lived in Vancouver area, injected drugs in past month	36%	Not reported	Not reported
Lloyd-Smith 2012[236]	• Gender/sex • Age • Heroin • Cocaine • Speedball • Housing • Received injecting assistance	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	ED visit for cutaneous injecting-related infection, via administrative data	Canada (Vancouver, British Columbia)	1,083	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised Injection; SEOSI) Similar sample to Lloyd-Smith	4	1 January 2004 to 31 January 2008	Not reported	29%	Median (interquartile range) was 35.1 (28.7 to 41.5) years among females and 39.7 (33.7 to 45.3) years among males	Not reported

								2008 and Milloy 2010, and same sample as Lloyd-Smith 2009 and Lloyd-Smith 2010						
Lloyd-Smith 2008[237]	• Gender/sex • Age • Sex work • Heroin • Amphetamine • Housing • Received injecting assistance • Supervised consumption site	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Current "any sores or abscesses from where you have been injecting", self-report and confirmed by study nurse	Canada (Vancouver, British Columbia)	1,065	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised Injection; SEOSI) Similar sample to Lloyd-Smith 2012, Lloyd-Smith 2009, Lloyd-Smith 2010, and Milloy 2010	4	1 January 2004 to 31 December 2005	Age 19 years and older, performed at least two injections at the supervised injection facility	29%	Median (interquartile range) was 36 (31-43) among participants with current SSTI at baseline interview and 39 (33-45) among participants without	Not reported
Lloyd-Smith 2009[238]	• Gender/sex • Age • Heroin • Housing • Received injecting assistance • Cocaine • Speedball	Not specified. Aimed to identify factors associated with incidence of SSTIsupervised injecting facility.	No estimand	• SSTI	Current SSTI cared for at supervised injecting facility, from nursing notes	Canada (Vancouver, British Columbia)	1,080	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised Injection; SEOSI) Similar sample to Lloyd-Smith 2008 and Milloy 2010, and same sample as Lloyd-Smith 2012 and Lloyd-Smith 2010	4	1 December 2003 and 31 January 2008	Second visit to supervised injecting facility	29%	Median (interquartile range) 38.4 (32.7 - 44.3) years	Not reported

Lloyd-Smith 2010[239]	• Gender/sex • Age • Speedball • Housing	Not specified. Aimed to identify factors associated with SSTI hospitalization.	No estimand	• Multiple • SSTI • Osteomyelitis • Endocarditis • Septic arthritis	Hospitalization for injecting-related infection (cellulitis, abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis), identified via administrative data	Canada (Vancouver, British Columbia)	1,083	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised Injection; SEOSI) Similar sample to Lloyd-Smith 2008 and Milloy 2010, same sample as Lloyd-Smith 2009 and Lloyd-Smith 2012	4	1 January 2004 to 31 January 2008	Not reported	29%	Median (interquartile range), 38.4 (32.7 - 44.3)	Not reported
McMahan 2020[389]	• Amphetamine	Not specified. Aimed to identify factors associated with interest in reducing/stopping substance use	No estimand	• Multiple • SSTI • Sepsis/bacteremia • Endocarditis	Past-year injecting-related infection ("an abscess, skin infection such as cellulitis, blood clot or blood infection like sepsis, or endocarditis"), self-report	USA (Washington state)	583	Attempted census of all needle and syringe program clients (Washington State Syringe Exchange Survey)	4	June 2019-August 2019	Needle and syringe program clients who reported that methamphetamine or opioids were their main drug, and they were not currently receiving addiction treatment. Excluded participants whose main drug was "goofball" (i.e., heroin and methamphetamine mixed together)	45%	Median 35 (IQR 30-45) years	Heroin
Milloy 2010[240]	• Gender/sex • Age • Race/ethnicity • Sex work • Incarceration • Heroin • Cocaine • Speedball • Housing	Effect of recent incarceration on risk of SSTI	Partly (1 of 12 exposures)	• SSTI	ED visit for abscess or cellulitis, identified via administrative codes	Canada (Vancouver, British Columbia)	901	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised Injection; SEOSI) Similar sample to Lloyd-Smith	4	June 2004 to December 2006	Not reported	29.5%	Median (IQR) was 37.5 (32.8-42.3) years among people reporting recent ED visit for SSTI at baseline interview, and 39.9 (33.7-46.1)	Not reported

	• Inject in public • Supervised consumption site • Opioid agonist treatment							2008 and Lloyd-Smith 2010, and same sample as Lloyd-Smith 2009 and Lloyd-Smith 2012					among people not reporting this	
Morin 2020[59]	• Gender/sex • Age • Class • Opioid agonist treatment	Not specified. Aimed to identify factors associated with injecting-related infections.	No estimand	• Multiple • Endocarditis • Osteomyelitis • Septic arthritis	Diagnostic codes in medical records (outpatient/ambulatory, emergency department, or hospitalization). Timing unclear.	Canada (Ontario)	55,924	Patients with claims in public health insurance databases for (a) any billing code associated with opioid agonist treatment, or (b) opioid agonist treatment medications via drug identification numbers (not specified)	3	1 January 2011 to 31 December 2016	Age 15 years and older, resident in Ontario	35%	15 to 24 years: 18% 25 to 34 years: 34% 35 to 44 years: 22% 45 to 54 years: 18% 54 to 65 years: 7% 66 years and older: 2%	Not reported
Murphy 2001[241]	• Gender/sex • Age • Race/ethnicity • Education • Class • Heroin • Cocaine • Amphetamine • Speedball • Alcohol • Smoking	Effect of HTLV-II infection on risk of SSTI. Also aimed to identify factors associated with SSTI.	No	• SSTI	ED visit or hospitalization for injecting-related abscess (case-control study)	USA (San Francisco, California)	424	Cases were hospital or ED patients with abscess who had injected drugs within the past 6 months. Sampling approach not specified. Controls were hospital or ED patients who were also enrolled in a local community-based cohort study of people who inject drugs,	3	Not reported	Age 18 years and older, spoke English	32%	29 years and younger: 12% 30 to 39 years: 27% 40 to 49 years: 45% 50 years and older: 17%	Heroin, cocaine, speedball, amphetamine

								matched 2:1 on age, sex, and race. Parent study not specified.						
Nagar 2015[267]	• Drug policy change	Effect of opioid prescribing prescription policy on risk of injecting-related epidural abscess	Yes	• Epidural abscess	Annual frequency of hospitalisation with spinal epidural abscess and substance use	USA (Lexington, Kentucky)	172	Hospital patients admitted with billing codes indicating epidural abscess	3	1 July 2010 to 30 June 2014	Patients with ICD-9 codes indicating substance dependence, abuse, or withdrawal	Not reported	Not reported	Not reported
Noroozi 2019[257]	• Age • Education • Class • Relationships • Amphetamine • Other polysubstance • Housing • Needle and syringe program	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Participants were asked "Have you ever had skin infections (such abscess *[sic]* or cellulitis) at your injection sites?"	Iran (Tehran)	500	Convenience and snowball sampling from drop-in centres	4	March 2016 to August 2016	Age 18 years and older, injection drug use at least once during the last month.	0%	Mean 31.2 (SD 7.2) years	Heroin, methamphetamine
Oviedo-Joekes 2017[274]	• Opioid agonist treatment	Effect of hydromorphone vs. diacetylmorphine injectable opioid agonist treatment on risk of SSTI.	Yes	• SSTI	Cellulitis or abscess identified during clinical trial via MedDRA codes	Canada (Vancouver, British Columbia)	202	Not reported (Study to Assess Longer-term Opioid Medication Effectiveness; SALOME)	5	December 2011 to December 2013	Age 19 years and older; at least 5 years of "illicit opioid dependence", regular injection of illicit opioids in the prior year; at least one prior episode of opioid agonist treatment; no severe medical conditions contraindicated for treatment with diacetylmorphine or hydromorphone	30.7%	Mean 44.3 (SD 9.63) years	Not reported
Phillips 2017[243]	• Gender/sex • Age • Race/ethnicity	Not specified. Aimed to identify factors	No estimand	• SSTI	Past year "skin abscesses (defined as red, hard infected lumps that	USA (Boston, Massachusetts)	143	Consecutive inpatients in medical units at an academic hospital	4	January 2014 to October 2015	Age 18 years and older; injected drugs at least 3 days during the week before hospital	40.6%	Mean 38.7 (SD 10.7) years	Heroin, cocaine

	• Education • Cocaine • Housing • Alcohol	associated with SSTI.			contain pockets of pus), ulcers (defined as open, infected sores), or cellulitis (defined as a more widespread skin infection)", self-reported						admission; without psychosis or homicidal/suicidal ideation			
Phillips 2008[244]	• Gender/sex • Age • Race/ethnicity • Heroin • Cocaine • Housing • Shooting gallery • Alcohol	Not specified. Aimed to identify factors associated with injecting-related infections.	No estimand	• SSTI • Osteomyelitis • Endocarditis	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis in 6 months before study visit; self-report	USA (Providence, Rhode Island)	109	Recruited through placing fliers at community health and social services	4	April 2001 to December 2004	Injection drug use; hepatitis C virus negative; heroin or cocaine use in past month; not experiencing psychotic symptoms	25.7%	Mean 38.7 (SD 8.8) years	Not reported
Phillips 2010[258]	• Age • Race/ethnicity • Heroin • Speedball • Housing	Not specified. Aimed to identify factors associated with SSTI	No estimand	• SSTI	Past year "abscess or other skin infection (such as an ulcer or cellulitis) at a place where you injected drugs—that is, any pain, swelling, redness, hardness under your skin, heat, pus, or oozing anywhere you inject?", self-reported	USA (Denver, Colorado)	51	Recruited through drop-in center, drug treatment center, and newspaper advertisement	4	November 2007 to August 2008	Age 18 years and older; not experiencing psychotic symptoms; injection drug use in past month	33.3%	Mean 39.2 (SD 9.7) years	Heroin
Pollini 2010[245]	• Gender/sex • Age • Race/ethnicity • Class • Sex work • Incarceration	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Past 6-months abscess ("Have you ever had an abscess?'', ''When was the last time you had an abscess?''), self-report	Mexico (Tijuana, Baja California)	623	Respondent-driven sampling (El Cuete Phase III) Similar sample to Pollini 2010b and Robertson	5	April 2006 to April 2007	Age 18 years or older; injected drugs in past month; no plans to move out of the city in the next 18 months	18%	Median 37 (IQR 32-43)	Heroin; Methamphetamine

	• Heroin • Heroin type • Amphetamine • Speedball • Housing • Inject with others • Inject in public • Received injecting assistance • Police contacts/arrests • Shooting gallery • Smoking							2010. Unclear overlap.						
Pollini 2010b[166]	• Barriers to needle/syringe access	Effect of being refused/overcharged when trying to purchase syringes at pharmacy on SSTI.	Yes	• SSTI	Past 6-months abscess and lifetime history of abscess, self-report	Mexico (Tijuana, Baja California)	649	Respondent-driven sampling (El Cuete Phase III) Similar sample to Pollini 2010a and Robertson 2010. Unclear overlap.	5	April 2006 to April 2007	18 years or older; injected drugs in the past month	18%	Median 38 (IQR 33-44) years	Heroin; methamphetamine
Robertson 2010[269]	• Received injecting assistance	Not specified. Aimed to identify factors associated with "seeking injection assistance".	No estimand	• SSTI	Past 6-months abscess, self-report	Mexico (Tijuana, Baja California)	1056	Respondent-driven sampling (El Cuete Phase III) Similar sample to Pollini 2010a and Pollini 2010b. Unclear overlap.	5	April 2006 to April 2007	Age 18 years or older; injected drugs in past month; no plans to move out of the city in the next 18 months	15%	Median 37 (IQR 31-42) years	Heroin; otherwise not reported
Roux 2020[242]	• Gender/sex • Age • Class	Effect of an educational intervention on risk of SSTI	No	• SSTI	At least one cutaneous abscess in the previous six	Bulgaria; Greece; Portugal; Romania	307	Recruited from clients of harm reduction programs	4	1 December 2017 to 30	Age 18 years or older; injected drugs during the previous week	17%	Median 38 (IQR 34-43) years	Heroin

	• Relationships • Heroin • Other polysubstance • Prescription opioids • Housing • Inject with others • Inject in public • Received injecting assistance • Opioid agonist treatment • Alcohol				months, self-reported					November 2019				
Saeland 2014[259]	• Age • Education • Sex work • Incarceration • Food insecurity • Overdose history • Heroin • Other prescription drug • Smoking	Effect of malnutrition on risk of SSTI	Partly (1 of 9 exposures)	• SSTI	Current abscess. Self-report and confirmed by physical examination.	Norway (Oslo)	188	Recruited via street outreach and through health and social services	3	November 2001 to April 2003	Not reported	Not reported	With abscess: Mean 36.9 (SD 7.7) Without abscess: Mean 35.1 (SD 7.6)	Heroin; flunitrazepam
Safaeian 2000[246]	• Gender/sex • Age • Race/ethnicity • Education • Class • Alcohol • Smoking	Effect of HTLV-II virus infection on risk of SSTI and endocarditis. Also aimed to identify factors associated with SSI and endocarditis.	No	• SSTI • Endocarditis	Infective endocarditis, self-report confirmed through medical chart review Abscess, self-report	USA (Baltimore, Maryland)	86 cases with endocarditis and 567 controls 356 cases	Recruited through street outreach and snowball sampling (AIDS Link to Intravenous Experience; ALIVE) Similar sample as Islam 2019	4	1988 to 1982	Age 18 years and older	Endocarditis analysis: 50% Abscess analysis: 77%	Percentage older than 34 years Endocarditis analysis: cases 48%, controls 45%	Not reported

							with abscess and 1436 controls Unclear overlap	and Wilson 2002					Abscess analysis: Cases 50%, controls 46%	
Scherbaum 2010[275]	• Supervised consumption site	Effect of supervised consumption site attendance on risk of SSTI	Yes	• SSTI	"During the last month, did you visit a physician because of an abscess?", self-reported	Germany (Essen, Ruhr zone)	129	Invited consecutive clients at supervised consumption site	4	November 2002 to December 21 2003	New attendance (first time or at least 6 weeks since last visit) at supervised consumption site	25%	Mean 31 (SD 6) years	Opiates; cocaine; cannabis; alcohol
Shah 2020[247]	• Gender/sex • Age • Race/ethnicity • Education • Class • Heroin • Fentanyl • Cocaine • Amphetamine • Prescription opioids • Prescription stimulant • Housing	Effect of injecting hydromorphone controlled release formulation on risk of endocarditis. Also aimed to identify factors associated with endocarditis.	Partly (1 of 12 exposures)	• Endocarditis	Current hospital admission with diagnosis of "definite infective endocarditis" according to the Modified Duke Criteria	Canada (London, Ontario)	135 (33 cases with endocarditis, 102 controls)	Cases were recruited from among inpatients or recently discharged outpatients with endocarditis among three hospitals Controls were recruited from community-based health and social services, addiction treatment programs, and outpatient infectious diseases clinic Matching approach not reported	4	11 August 2016 to 27 July 2018	Age 18 years or older; injected drugs within past 4 months	27%	Cases: Mean 30.0 (SD 11.0) years Controls: 35.5 (SD 8.4) years	Hydromorphone controlled-release capsules; methamphetamine; hydromorphone tablets
Sierra 2006[248]	• Gender/sex • Age • Cocaine • Speedball	Not specified. Aimed to identify factors associated	No estimand	• SSTI	Hospital admission with invasive soft-tissue Group A Strep (S.	Spain (Barcelona)	73 (15 cases, 58 locall	Cases recruited from among hospitalized patients with	3	Fall 2002	Age 18 year and older, injected drugs (timeline not defined), did not live	26%	Cases: Mean 30.1 years	Heroin; cocaine

	• Supply network • Housing • Opioid agonist treatment	with SSTI (specifically, invasive S. pyogenes)			pyogenes) infections		y recruited controls)	S. pyogenes identified in bacterial cultures (sites not specified) Controls recruited among clients of a local needle and syringe program who had attended the same hospital			in an institution (not defined)		Controls: 27.5 years	
Silverman 2020[390]	• Prescription opioids	Effect of recently being prescribed controlled-release hydromorphone on risk of endocarditis	Yes	• Endocarditis	Hospital admission for endocarditis and injection drug use, identified via administrative codes	Canada (Ontario province)	46,505 (for ecological analysis) 13,823 (for individual-level analysis)	Province-wide hospital and prescription administrative data	5	1 April 2006 to 30 September 2015	Age between 18 and 55 years old; at least one hospital admission with evidence of injection drug use; at least one opioid prescription through public insurance	Matched cohort for any hydromorphone exposure analysis: 43.9% Matched cohort for controlled-release hydromorphone exposure analysis: 43.5%	Matched cohort for any hydromorphone exposure analysis: mean 44.4 (SD 8.4) years Matched cohort for controlled-release hydromorphone exposure analysis: 44.6 (SD 8.4) years	Not reported.
Smith 2015[249]	• Gender/sex • Race/ethnicity • Cocaine	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Current abscess, "defined as swollen, red, painful lumps under the skin that may or may	USA (Baltimore, Maryland)	152	Recruited from clients at Baltimore City Needle Exchange Program	4	May 2012 to November 2013	Age 18 years or older	36.8%	Median 45 (IQR 35-52) years	Heroin

	• Speedball • Housing • Inject with others •				not be open and that have lasted <8 weeks". Self-reported and visually confirmed by researcher.									
Stein 2020[250]	• Gender/sex • Age • Race/ethnicity • Opioid agonist treatment	Effect of an educational intervention on risk of injecting-related infections	No	• Multiple • SSTI • Endocarditis • Sepsis • Not specified	Number of ED visits for injecting-related infections in 12 months following educational intervention Number of hospitalizations visits for injecting-related infections in 12 months following educational intervention	USA (Boston, Massachusetts)	252	Recruited from among hospital inpatients with "an indication" of current or past injection drug use or a current skin abscess or cellulitis in electronic medical record	4	January 2014 to August 2019	Injected drugs at least 3 days out of the week prior to hospital admission; ability to return to hospital for follow-up; at least two additional contacts with active telephone numbers; no planned move from the region	41.7%	Mean 37.9 (SD 10.7) years	Not reported
Summers 2017[260]	• Age • Race/ethnicity • Class • Heroin type • Housing	Effect of tar heroin on risk of SSTI. Also aimed to identify factors associated with SSTI.	Partly (1 of 5 exposures)	• SSTI	Past year abscess, defined as, "a painful, hot, swollen skin infection with pus inside", self-report	USA (Sacramento, California; Boston, Massachusetts)	145	Recruited from clients attending harm reduction programs	4	December 2014 to February 2015	Age 18 years or older; self-reported heroin injection in preceding month	29%	Mean 40 (95% CI 38.09, 41.90)	Heroin; otherwise not reported
Thønnings 2020[261]	• Age • Housing • Opioid agonist treatment	Not specified. Aimed to identify factors associated with bacteremia	No estimand	• Sepsis/bacteremia	Bacteraemia, among hospitalised PWID	Denmark (Hvivdovre, Region Hovedstaden)	257	Retrospectively identified via hospital administrative codes	3	2000 to 2006	Not reported	Not reported	Median 39 (IQR 34-45) years	Not reported
Tomolillo 2007[271] (Ecological time series study)	• Needle and syringe program	Effect of needle and syringe program use on risk of SSTI. Effect of policy restricting needle and syringe program	Yes	• SSTI	Number of abscesses treated at clinic associated with needle and syringe program, per week	USA (Eureka, California)	2942 visits (participant count unknown)	Administrative data (number of needles exchanged) and health records (number of abscesses treated)	4	January 1, 2002 to February 28, 2004	All client visits	35.5%	Not reported	Not reported

		effectiveness on risk of SSTI												
Tomolillo 2007[271] (Cross-sectional study)	• Needle and syringe program	Effect of needle and syringe program use on risk of SSTI	Yes	• SSTI	Self-report occurrences of abscesses (timeline not specified)	USA (Eureka, California)	62	Recruited "former intravenous drug users from local 12-step meetings"	3	January 1, 2002 to February 28, 2004	"former intravenous drug users"	41.9%	Not reported	Not reported
Trayner 2020[391]	• Inject in public	Effect of public injecting on risk of SSTI	Yes	• SSTI	Past year SSTI, self-report	Scotland	1469	Recruited through clients at harm reduction programs (Needle Exchange Surveillance Initiative)	4	2017 to 2018	Injected drugs within past 6 months	25%	Mean 39.6 years	Heroin
Weir 2019[263]	• Prescription opioids • Drug policy change	Effect of removal of controlled-release oxycodone from market on risk of endocarditis. Also, effect of population rate of hydromorphone prescribing on risk of endocarditis.	Yes	• Endocarditis	Quarterly trend in proportion of hospital admissions with evidence of injection drug use that include endocarditis diagnosis	Canada (Ontario)	60,529 hospital admissions	Hospital admissions with evidence of injection drug use, identified via administrative data	3	2006 to 2015	Age 18 to 55 years; hospital admissions with diagnostic codes indicating opioid or stimulant use, or hepatitis C	Endocarditis admisions: 53% Other admisions: 44%	Endocarditis admissions: Mean 36.3 (SD 9.5) years Other admissions: Mean 40.2 (SD 10.8) years	Not reported
Wilson 2002[251]	• Gender/sex • Age • Education • Housing • Alcohol	Not specified. Aimed to identify factors associated with endocarditis.	No estimand	• Endocarditis	Infective endocarditis, self-report and/or medical chart review	USA (Baltimore, Maryland)	470 in nested case-control study (79 cases with endocarditis, 391 controls matched	Not reported (AIDS Link to Intravenous Experiences; ALIVE) Similar sample as Islam 2019 and Safaeian 2000	4	February 1988 to December 1998	For nested case-control study: person with HIV, age 18 years or older, injected drugs at least once after 1977, no AIDS diagnosis at study entry, returned for at least one follow-up study visit	26%	Age 39 or older Endocarditis cases: 48.1% Controls: 45.8%	Not reported

							on date and duration follow-up)							
Wright 2020[252]	• Gender/sex • Age • Housing	Not specified. Aimed to identify factors associated with SSTI.	No estimand	• SSTI	Lifetime SSTI, self-report Question supported by pictures of abscesses and/or cellulitis at different stages	England (London)	455	Recruitment through street outreach and drug treatment services (Care & Prevent study)	4	October 2017 to March 2019	Age 18 years or older; any prior injection drug use	25%	Median 46 (IQR 39 to 52) years	Not reported
Wurcel 2016[63]	• Gender/sex • Age • Race/ethnicity	Effect of age, race/ethnicity, and gender on trends in incidence of endocarditis	Yes	• Endocarditis	Percentage of hospital admissions for endocarditis that also have diagnostic codes suggestive of injection drug use	USA (national)	Not reported	Nationwide hospital administrative database (Nationwide Inpatient Sample)	4	2000 to 2013	Age 15 to 64 years; Hospitalization with ICD-9 codes consistent with endocarditis and also substance use or hepatitis C	40.9%	Not reported	Not reported
Wurcel 2018[253]	• Gender/sex • Age • Race/ethnicity • Education • Sex work • Heroin • Cocaine • Housing • Needle and syringe program	Effect of sex work on risk of SSTI, depending on gender	Partly (1 of 9 exposures)	• SSTI	Lifetime abscess, "Has a medical professional ever told you that you had an abscess?", self-reported Past 30 days abscess, self-reported	USA (Boston and Worcester, Massachusetts)	298	Recruited via street outreach and clients at needle and syringe programs and local health services (Responding to the Epidemic of Addiction and Hepatitis C Virus Together; REACTS; and HCV and HIV-HCV Hotspots Study)	4	2015 to 2016	Age 18-45 years; injected drugs in past 30 days	30%	Median 33 (IQR 30 to 39) years	Heroin
Yeung 2017[139]	• Other stimulant • Drug policy change	Effect of drug policy change (temporary class drug order on ethylphenidate) on STTI	Partly (1 of 2 exposures)	• Not specified	Weekly rate of *S. pyogenes* or *S. aureus* infections	Scotland (Lothian)	Estimated 3000 people who inject	Microbiology samples that grew *S. pyogenes* or *S. aureus* were investigated for injection	5	February 2014 to December 2015	Injection drug use	Among cases: 27.5%	Among cases: 20 and under: 0.5% 21-25: 4.3%	Novel psychoactive substances (not otherwis

							drugs in Lothian (211 cases)	drug use and use of ethylphenidate					26-30: 13.7% 31-35: 28.0% 36-40: 23.2% 41-45: 17.1% 46-50: 10.9% 51+: 2.4%	e specified)

8.9 Appendix 9. Characteristics of included studies with outcome during infection treatment in quantitative systematic review of social and structural determinants of injection drug use-associated bacterial and fungal infections.

Study	Included exposures in this review	Main exposure / estimand in study	Do exposure and outcome pairs included in this review reflect study estimand	Infections	Outcomes	Country (City)	Sample size	Sampling method (parent study name)	MMAT quality rating (out of 5)	Data collection period	Inclusion criteria	% women/female	Age	Drugs used by ≥50%
Cooksey 2020[284]	• Housing • Hospital policy	Effect of hospital policy on all-cause readmission, after hospital discharge	No	• Endocarditis	• Hospital discharge against medical advice • In-hospital mortality	USA (Knoxville, Tennessee)	168	Retrospectively identified admitted to tertiary care hospital with endocarditis and injection drug use, via electronic medical records	5	January 2013 to January 2019	Age 19 years and older, diagnosis of definite infective endocarditis by modified Duke criteria, and active injection drug use (defined as self-reported in past 30 days, "positive urine drug screen for illicit substances", or reported in infectious diseases consultant's note) Excluded patients who underwent invasive cardiac procedure in prior 30 days, had history of congenital or rheumatic	Pre-Intervention group: 54% Post-Intervention group: 69%	Pre-Intervention group: Median 32 (IQR 26-41) years Post-Intervention group: Median 36 (IQR 28-43) years	Opioids

											heart disease, or "were missing finalized diagnostic test and/or culture results from an outside facility were excluded"			
Eaton 2020[278]	• Gender/sex • Opioid agonist treatment	Not specified. Aimed to identify factors associated with in-hospital illicit drug use and with premature hospital discharge against medical advice	No estimand	• Multiple • SSTI • Endocarditis • Osteomyelitis • Septic arthritis • Sepsis/bacteremia	• Hospital discharge against medical advice	USA (Birmingham, Alabama)	83	Retrospectively identified patients admitted to tertiary care hospital and referred to a specialized "Intravenous Antibiotic and Addiction Team"	2	2016 to 2017	First hospitalization during the study period	43%	Median 36 years	Opioids
Fink 2013[100]	• Gender/sex • Age • Race/ethnicity • Housing • Needle and syringe program • Access to healthcare	Not specified. Aimed to identify factors associated with abscess self-treatment	No estimand	• SSTI	• Self-treatment. "Thinking about the last abscess you had, how did you deal with it?"	USA (Los Angeles, Oakland, and Berkeley, California)	858	Recruited through street outreach and from clients at four large, government-sanctioned needle and syringe programs, and also	**4**	2003 to 2005	Age 18 and older, self-reported injection drug use in past 30 days	29%	Less than 30 years: 5% 30-39 years: 16% 40-49 years: 37% 50+ years: 40%	Heroin
Hope 2008[104]	• Gender/sex • Age • Housing • Incarceration • Overdose history • Cocaine • Amphetamines	Not specified. Aimed to identify factors associated with seeking health care for abscess.	No estimand	• SSTI	• Healthcare seeking, self-reported	England (nationwide)	1,058	Recruited through street outreach and from clients of health and social services (Unlinked Anonymous Monitoring Survey)	4	Fall 2003 to Summer 2005	Injected drugs in past 28 days	23%	Median 30 (range 16 to 72) years	Opiates

	• Opioid agonist treatment													
Hope 2015[75]	• Gender/sex • Age • Income/employment • Sex work • Housing • Incarceration • Overdose history • Migration status • Heroin • Cocaine • Amphetamines	Not specified. Aimed to identify factors associated with seeking health care for abscess and with hospital admission	No estimand	• SSTI	• Healthcare seeking, "sought medical advice (i.e. from a doctor or nurse) about that symptom." • Hospital admission, "if they had then been admitted to hospital as a result of that symptom"	England (Bristol, Leeds, and Birmingham)	855	Respondent-driven sampling	5	2006 (Bristol), 2008 (Leeds), 2009 (Birmingham)	Age 16 years or older, injected drugs in preceding 4 weeks, and live within the survey area	25%	Median 31 years, mean 32 years	Heroin; crack cocaine
Jo 2021[279]	• Gender/sex • Age • Race/ethnicity • Access to healthcare • Opioid agonist treatment • Stimulants	Effect of opioid agonist treatment on multiple outcomes	Partly (1 of 6 exposures)	• Multiple • Endocarditis • Osteomyelitis	• Hospital discharge against medical advice	USA (143 hospitals across 21 states)	1407	Patients admitted to one large nationwide hospital system with concurrent diagnostic codes for opioid use disorder and endocarditis or osteomyelitis	5	1 January 2014 to 31 December 2018	Age 18 to 65	44%	Mean 42.7 years	Opioids
Kimmel 2020[280]	• Gender/sex • Age • Income/employment • Access to healthcare • Unhealthy alcohol use • Other substance use	Not specified. Aimed to identify factors associated with hospital discharge against medical advice	No estimand	• Endocarditis	• Hospital discharge against medical advice	USA (nationwide)	7,259	Patients admitted to hospital with diagnostic codes for native valve endocarditis and opioids, stimulants, and/or hepatitis C virus (Nationwide	5	January 2010 to September 2015	Age 18-64 years	43.3%	18-24 years: 10.8% 25-34 years: 31.8% 35-44 years: 21.1% 45-55 years: 22.6% 56-65	Not reported

	• Surgery in-hospital • Hospital characteristics							Inpatient Sample)					years: 13.8%	
Kimmel 2020[292]	• Hospital policy	Effect of initiating public outcomes reporting for aortic valve surgery on multiple outcomes	Yes	• Endocarditis	• In-hospital mortality	USA (nationwide)	7,322	Patients admitted to hospital with diagnostic codes for native valve endocarditis and opioids, stimulants, and/or hepatitis C virus (Nationwide Inpatient Sample)	5	1 January 2010 to 31 August 2015	Age 18-65 years	Pre-intervention: 39.2% Post-intervention: 45.5%	Pre-intervention: 41.2 years Post-intervention: 38.5 years	Not reported
Lloyd-Smith 2012[236]	• Supervised consumption site	Not specified. Aimed to identify factors associated with emergency department visit for SSTI	No estimand	• SSTI	• Healthcare seeking, defined by emergency department visit identified via administrative data	Canada (Vancouver, British Columbia)	1,083	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised Injection; SEOSI) Similar sample to Lloyd-Smith 2008 and Milloy 2010, and same sample as Lloyd-Smith 2009 and Lloyd-Smith 2010	4	1 January 2004 to 31 January 2008	Not reported	29%	Median (interquartile range) was 35.1 (28.7 to 41.5) years among females and 39.7 (33.7 to 45.3) years among males	Not reported
Lloyd-Smith 2010[239]	• Supervised consumption site	Not specified. Aimed to identify factors associated with hospital	No estimand	• Multiple • SSTI • Osteomyelitis • Endocarditis	• Healthcare seeking, defined as hospital admission identified via administrative data	Canada (Vancouver, British Columbia)	1,083	Randomly recruited clients at supervised injecting facility (Scientific Evaluation of Supervised	4	1 January 2004 to 31 January 2008	Not reported	29%	Median (interquartile range), 38.4 (32.7 - 44.3)	Not reported

		admission for SSTI		• Septic arthritis				Injection; SEOSI) Similar sample to Lloyd-Smith 2008 and Milloy 2010, same sample as Lloyd-Smith 2009 and Lloyd-Smith 2012						
Marks 2020a[285]	• Addiction treatment	Effect of hospital inpatient addiction medicine consultation on multiple outcomes	Yes	• Multiple • Endocarditis • Fungemia • Bacteremia • SSTI • Septic arthritis • Epidural abscess • Osteomyelitis	• Hospital discharge against medical advice	USA (St. Louis, Missouri)	125	All hospital admissions with diagnoses of injecting-related infection and opioid use disorder at at one tertiary care hospital who received infectious diseases consultation , identified via electronic medical records	4	January 2016 to January 2018	Infection attributable to injection drug use by the infectious diseases consultant; greater than 2 weeks of intravenous antibiotics treatment was recommended; patient was not eligible to receive outpatient treatment	Consultation group: 55% No consultation group: 52%	Consultation group: Median 36 (range 19-63) years No consultation group: Median 35 (range 19-67) years	Heroin
Marks 2020b[310]	• Opioid agonist treatment	Effect of opioid agonist treatment on multiple outcomes	Yes	• Endocarditis	• Hospital discharge against medical advice	USA (St. Louis, Missouri)	123	Consecutive patients referred for infectious diseases consultation with opioid injection-associated infections, identified prospectively	4	1 July 2017 to 1 May 2020	Confirmed as injection opioid use-associated endocarditis by study physician on retrospective review of medical records	47%	Median 34 (IQR 25-48) years	Opioids
Martín-Dávila 2005[290]	• Gender/sex	Not specified. Aimed to identify factors associated with in-	No estimand	• Endocarditis	• In-hospital mortality	Spain (Madrid)	220	All patients with diagnosis of endocarditis, identified retrospectively via electronic	5	1 January 1985 to 31 December 1999	"Injection drug users". Operational definition not reported.	14%	Median 27.8 (range 18-44) years	Not reported

		hospital mortality						health records						
Meel 2018[60]	• Age	Not specified. Aimed to identify factors associated with in-hospital mortality	No estimand	• Endocarditis	• In-hospital mortality	South Africa (Johannesburg)	68	All patients seen at cardiology clinic with endocarditis "secondary to IV nyaope use", identified retrospectively.	4	December 2014 to February 2017	Age 18 years and older; definite or possible infective endocarditis by modified Duke criteria; "history of IV nyaope use" (not otherwise specified)	2.9%	Mean 25.8 (SD 4.5) years	Nyaope
Mertz 2008[281]	• Gender/sex • Age • Unhealthy alcohol use	Not specified. Aimed to identify factors associated with multiple outcomes.	No estimand	• Multiple • SSTI • Endocarditis • Osteomyelitis • Septic arthritis • Sepsis/bacteraemia • Pneumonia	• Hospital discharge against medical advice • In-hospital mortality	Switzerland (Basel)	216	Among all patients admitted to tertiary care hospital, identified "intravenous drug users" (not defined) and those referred for infectious diseases consultation	4	January 2001 to December 2006	Not reported	33%	Median 38 (range 18-58) years	Opioids
Monteiro 2020[392]	• Gender/sex • Age • Race/ethnicity • Access to healthcare • Heroin • Cocaine	Not specified. Aimed to identify factors associated with self-treatment of SSTI	No estimand	• SSTI	• Self-treatment, self-reported	USA (Boston, Massachusetts)	162	Recruited from among hospital inpatients with "an indication" of current or past injection drug use or a current skin abscess or cellulitis in electronic medical record Similar sample as Stein 2020	4	January 2014 to June 2018	Age 18 years or older; self-reported injection drug use at least three times during week prior to hospitalization	40.7%	Mean 38 (SD 10.5) years	Not reported

Nolan 2020[282]	• Gender/sex • Housing • Heroin/fentanyl • Polysubstance use • Access to healthcare • Opioid agonist treatment	Effect of OAT on hospital discharges against medical advice. Also aimed to identify factors associated with hospital discharges against medical advice.	Partly (1 of 6 exposures)	• Multiple • Endocarditis • Osteomyelitis Septic arthritis • Epidural abscess • Sepsis/bacteraemia	• Hospital discharge against medical advice	USA (St. Louis, Missouri)	262	All hospital admissions with diagnoses of injecting-related infection and opioid use disorder at at one tertiary care hospital who received infectious diseases consultation , identified via electronic medical records Similar sample as Marks 2020a (10.1093/cid/ciy924.)	4	January 2016 to July 2019	Not reported	Inpatient OAT group: 60.1% No OAT group: 41.1%	Inpatient OAT group: mean 38 (SD 9) years No OAT group: mean 41 (SD 12) years	Opioids (fentanyl or heroin)
Rudasill 2019[288]	• Surgery in-hospital	Effect of valve surgery for endocarditis on multiple outcomes	Yes	• Endocarditis	• Hospital discharge against medical advice • In-hospital mortality	USA (nationwide)	27,432	All hospitalized patients with endocarditis in nationwide hospital admissions database (National Readmissions Database)	4	January 2010 to September 2015	Age 16 to 64; diagnostic codes for illicit drug use; no congenital or rheumatic heart disease; no cardiac procedures	45.3%	Mean 38.3 (SD 0.1) years	Not reported
Sandrock 2001[293]	• Gender • Age	Not specified. Aimed to identify factors associated with respiratory failure.	No estimand	• Botulism	• Respiratory failure	USA (Sacramento, California)	20	Consecutive patients with a discharge diagnosis of botulism	4	1990 to 1999	Injection drug use “within the months preceding hospitalization”, or “a positive result on toxicology screen”	25%	Median 47 years	Heroin
Saydain 2010[291]	• Gender/sex • Age • Race/ethnicity	Not specified. Aimed to identify factors associated	No estimand	• Endocarditis	• In-hospital mortality	USA (Detroit, Michigan)	33	Patients admitted to teaching hospital intensive care unit with	4	January 2001 to December 2006	Not reported	45%	Mean 47.2 (SD 10.5) years	Heroin

		with in-hospital mortality.						diagnosis of endocarditis by modified Duke criteria and "were injection drug users"						
Serota 2021[283]	• Gender/sex • Age • Race/ethnicity • Overdose history • Opioids • Stimulants • Polysubstance • Access to healthcare	Effect of stimulant use and stimulant/opioid co-use vs. opioid use-only on multiple outcomes	Partly (3 of 8 exposures)	• Multiple SSTI • Sepsis/bacteraemia • Endocarditis • Osteomyelitis	• Hospital discharge against medical advice • In-hospital mortality	USA (Florida, statewide)	31,964	Census of all patients admitted to all hospitals in Florida (Agency for Health Care Administration Hospital Inpatient Limited Data Set)	5	1 January 2016 to 31 December 2017	Hospital admissions with ICD-10 code for injecting-related infections and opioid- or stimulant-related diagnostic codes	46%	Median 44 (IQR 33-56) years	Opioids
Suzuki 2020[286]	• Opioid agonist treatment	Effect of opioid agonist treatment on hospital discharge against medical advice	Yes	• Endocarditis	• Hospital discharge against medical advice	USA (Boston, Massachusetts)	84	All patients admitted to tertiary care hospital with discharge diagnosis including endocarditis and opioid/heroin or injection drug use, identified retrospectively via electronic medical records	5	1 January 2016 to 31 December 2018	Diagnosis of opioid use disorder and hospital admission with endocarditis attributed to injection drug use; recent injection drug use (not otherwise specified)	46.4%	Mean 36.2 (SD 10.3) years	Opioids; cocaine; tobacco
Takahashi 2007[277]	• Age • Gender/sex • Race/ethnicity • Education • Income/employment • Housing • Heroin	Not specified. Aimed to identify factors associated with hospital admission	No estimand	• SSTI	• Hospital admission	USA (Seattle, Washington)	136	Prospectively recruited emergency department patients who inject drugs with SSTI	4	May 2001 to March 2002	English-speaking; provided informed consent	38%	Mean 43 (SD 8) years	Not reported

	• Needle and syringe program • Unhealthy alcohol use • Access to healthcare													
Tan 2020[289]	• Gender/sex • Age • Housing • Opiates • Stimulants • Polysubstance • Other prescription medications • Addiction treatment • PICC line	Not specified. Aimed to identify factors associated with new bloodstream infections	No estimand	• Endocarditis	• New bloodstream infection during treatment	Canada (London, Ontario)	309	Patients admitted to three urban hospitals with discharge diagnosis codes for endocarditis, identified via administrative data	4	1 April 2007 to 31 March 2018	Diagnosis of definite endocarditis by modified Duke criteria; injected drugs in prior 3 months	49.3%	Mean 35.7 (SD 9.7) years	Opiates; stimulants
Uppuluri 2021[227]	• Gender/sex • Age • Race/ethnicity • Cocaine • Amphetamines • Unhealthy alcohol use • Other substance use • PICC line	Not specified. Aimed to identify factors associated with endogenous endophthalmitis	No estimand	• Multiple SSTI • Sepsis/bacteraemia • Endocarditis • Osteomyelitis • Candidemia • Endophthalmitis	• Development of endogenous endophthalmitis	USA (nationwide)	605,859	Hospital admissions (at a hospital contributing to nationwide database) with diagnosis codes for opioid use disorder or overdose, and injecting-related infections (National Inpatient Sample)	5	2002 to 2014	Age 21-65 years;	42.7%	"Average" 42.7 years	Not reported
Wang 2020[287]	• Opioid agonist treatment • Hospital policy	Effect of hospital policy and of opioid agonist treatment on	Yes	• Multiple SSTI • Sepsis/bacteraemia • Endocarditis	• Hospital discharge against medical advice	USA (Concord, New Hampshire)	147	Patients admitted to a suburban hospital with diagnoses of "intravenous drug use" or "opioid use	4	1 January 2018 to 1 October 2019	Infection related to "intravenous opioid use" (excluding people only injecting stimulants);	48.3%	Average 35.9 years	Not reported

				• Osteomyelitis • Septic arthritis				disorder" and injecting-related infections, identified retrospectively via electronic medical records search			not currently in law enforcement custody; not critically ill			

8.10 Appendix 10. Characteristics of included studies with outcome after initial treatment in quantitative systematic review of social and structural determinants of injection drug use-associated bacterial and fungal infections.

Study	Included exposures in this review	Main exposure / estimand in study	Do exposures included in this review reflect study estimand	Infections	Outcomes	Country (City)	Sample size	Sampling method (parent study name)	MMAT quality rating (out of 5)	Data collection period	Inclusion criteria	Women /female	Age	Drugs used by ≥50%
Barocas 2020[294]	●Age ●Gender/sex ●Opioid agonist treatment ●Other substance use	Effect of opioid agonist treatment on multiple outcomes	Partly (1 of 4)	• SSTI	• Infection-related rehospitalization • All-cause rehospitalization • Overdose-related rehospitalization	USA (Nationwide)	6,538	Private/commercial health insurance claims database, with hospital admissions for injecting-related infections identified via discharge diagnosis codes.	4	2010 to 2017	Age 18-64 years, hospital admission for SSTI, minimum 30-day follow-up after hospital discharge, diagnostic codes for opioid use disorder within 6 months before or after the index SSTI hospitalization. Excluded people who had a pharmacy claim for opioid agonist treatment in three months preceding hospitalization.	48%	Mean 40 (SD 14.5) years	Opioids
Barocas 2021[301]	●Age ●Gender/sex ●Opioid agonist treatment ●Other substance use	Effect of opioid agonist treatment on multiple outcomes	Partly (1 of 4)	• Endocarditis	• All-cause rehospitalization	USA (Nationwide)	768	Private/commercial health insurance claims database, , with hospital admissions for injecting-related infections identified via discharge	4	1 July 2020 to 30 June 2016	Age 18 years and older, hospital admission for endocarditis, minimum of 30-day follow-up after hospital discharge,	48.7%	Mean 39 (SD 15.5) years	Opioids

								diagnosis codes.						
Buehrle 2017[312]	●Age ●Discharge location	Not specified. Aimed to identify factors associated with OPAT failure.	No estimand	• Multiple infections • Endocarditis • Epidural abscess • Sepsis/ bacteremia • SSTI • Osteomyelitis	• OPAT complications	USA (Pittsburgh, Pennsylvania)	118	Retrospective chart review of hospital records. Sampling approach not specified.	4	December 2013 to January 2015	Self-reported injection drug use in 4 weeks preceding hospitalization, or "a positive urine drug screen plus suspicion of" injection drug use	Not reported	Median 34.5 years	Not reported
Clarelin 2021[304]	●Age ●Gender/sex	Not specified. Aimed to identify factors associated with all-cause mortality	No estimand	• Endocarditis	• All-cause mortality	Sweden (nationwide)	586	Registry of patients admitted to hospital with endocarditis, with voluntary reporting by physicians (Swedish Registry on Infective Endocarditis)	5	2008 to 2019	Assessed by physician to be person who injects drugs	Left-sided endocarditis: 23% Right-sided endocarditis: 40%	Left-sided endocarditis: Mean 46 (SD 12) years Right-sided endocarditis: Mean 35 (SD 9) years	Not reported
Connell 2010[228]	●Age ●Gender/sex	Effect of age and gender on change in visual acuity after treatment of endogenous	Yes	• Endophthalmitis	• Visual acuity after treatment	Australia (Melbourne, Victoria)	19	Consecutive patients with endogenous fungal endophthalmitis admitted to a specialized, quaternary care hospital for	4	2001 to 2007	A history of injection drug use (not otherwise specified)	58%	Mean 32.7 (SD 8) years	Not reported

		endophthalmitis						eye and ear disorder						
Cooksey 2020[284]	●Health care access ●Hospital policy	Effect of hospital policy on all-cause readmission, after hospital discharge	Partly (1 of 2)	• Endocarditis	• All-cause rehospitalization • All-cause mortality	USA (Knoxville, Tennessee)	168	Retrospectively identified admitted to tertiary care hospital with endocarditis and injection drug use, via electronic medical records	5	January 2013 to January 2019	Age 19 years and older, diagnosis of definite infective endocarditis by modified Duke criteria, and active injection drug use (defined as self-reported in past 30 days, "positive urine drug screen for illicit substances", or reported in infectious diseases consultant's note) Excluded patients who underwent invasive cardiac procedure in prior 30 days, had history of congenital or rheumatic heart disease, or "were missing finalized diagnostic test and/or culture results from an outside facility were excluded"	Pre-Intervention group: 54% Post-Intervention group: 69%	Pre-Intervention group: Median 32 (IQR 26-41) years Post-Intervention group: Median 36 (IQR 28-43) years	Opioids
D'Couto 2018[313]	●Discharge location	Effect of discharge location (home vs. skilled nursing facility) on OPAT failure	Yes	• Multiple infections • Endocarditis • Osteomyelitis • Septic arthritis	• OPAT complications	USA (Boston, Massachusetts)	52	All patients enrolled in OPAT program at tertiary care hospital	3	1 January 2010 to 31 December 2015	Recent or active injection drug use (as documented in the medical record)	Discharged home: 29% Discharged to skilled nursing facility: 32%	Not reported	Not reported
Fanucchi 2020[314]	●Discharge location	Effect of discharge location (outpatient with integrated care vs. remaining	Yes	• Multiple • Endocarditis • Osteomyelitis	• OPAT complications	USA (Lexington, Kentucky)	20	Recruited patients hospitalized at a tertiary care hospital with injecting-	3	1 March 2017 to 2 October 2018	Age 18 to 65 years; moderate to severe opioid use disorder; injecting-related infection requiring 2 or more weeks of intravenous antibiotics; accepting buprenorphine opioid agonist treatment; living within 45 minutes of	Outpatient: 70% Inpatient: 70%	Outpatient: Mean 32.9 (range 26-38) years	Opioids, stimulants

		in hospital).						related infections			the hospital; home discharge expected Excluded people with central nervous system complications of infection (e.g. embolic stroke), end-stage renal disease, Class III or IV congestive heart failure, decompensated cirrhosis, prosthetic valve or fungal endocarditis, concurrent dependence on sedative-hypnotics, homelessness, current pregnancy, or incarceration		Inpatient: Mean 31.3 (range 21-48) years	
Hilbig 2020[297]	●Opioid agonist treatment	Not specified. Aimed to identify factors associated with multiple outcomes.	No estimand	● Endocarditis	● Infection-related rehospitalization	Australia (Melbourne, Victoria)	46	Patients hospitalized with endocarditis at a tertiary care hospital, identified retrospectively using discharge diagnosis codes	3	2008 to 2015	Diagnosis of definite or possible infective endocarditis, by Duke criteria; documentation of reporting injection drug use within prior 3 months; age younger than 70 years	41%	Median 39 (IQR 34-47.5) years	None
Huang 2018[295]	●Age ●Gender/sex ●Race/ethnicity ●Rural/urban ●Prescription opioids	Not specified. Aimed to identify factors associated with recurrence of endocarditis	No estimand	● Endocarditis	● Infection-related rehospitalization	USA (Winston-Salem, North Carolina)	87	Patients hospitalized with endocarditis at a tertiary care hospital, identified retrospectively using discharge	5	January 2004 to January 2017	Age 18 years or older; no intracardiac device; diagnosis of definite or possible infective endocarditis by modified Duke criteria; documentation of reporting injection drug use within prior 3 months	50%	Median 28.5 years	Prescription opioids

								diagnosis codes						
Jo 2021[279]	●Age ●Race/ethnicity ●Health care access ●Cocaine/amphetamines ●Opioid agonist treatment	Effect of initiating opioid agonist treatment in-hospital on multiple outcomes	Partly (1 of 5)	• Multiple infections • Endocarditis • Osteomyelitis	• All-cause rehospitalization	USA (nationwide)	1407	Patients hospitalized with (a) endocarditis or osteomyelitis and (b) opioid use disorder at a large health system, identified retrospectively using discharge diagnosis codes	4	1 January 2014 to 31 December 2018	Age 18 to 65 years	44%	Mean 42.7	Opioids
Kimmel 2020[305]	●Age ●Gender/sex ●Unstable housing ●Opioid agonist treatment	Effect of opioid agonist treatment after hospital discharge on all-cause mortality	Partly (1 of 4)	• Endocarditis	• All-cause mortality	USA (Massachusetts)	679	People in a state-wide hospital medical claims database with (a) endocarditis-related hospital admission and (b) opioid, cocaine, or amphetamine use, or hepatitis C virus infection, identified retrospectively using discharge diagnosis codes	5	1 January 2011 to 31 December 2015	Age 18 to 65 years	39.2%	Mean 39.2 (SD 12.1) years	Opioids

Marks 2020a[302]	●Age ●Gender/sex ●Race/ethnicity ●Unstable housing ●Heroin/fentanyl ●Cocaine ●Amphetamines ●Other substance use ●Inpatient addiction medicine consultation service ●Antibiotic treatment mode ●Surgery during hospitalization	Effect of antibiotic treatment mode on rehospitalization	Partly (1 of 11 exposures)	• Multiple infections • Endocarditis • Septic arthritis • Sepsis/bacteremia • Osteomyelitis • Epidural abscess	• All-cause rehospitalization	USA (St. Louis, Missouri)	293	Patients hospitalized with bacterial infections potentially consistent with injection drug use, identified retrospectively using discharge diagnosis codes	5	1 January 2016 to 30 July 2019	Infectious diseases consultation occurred; infection related to injection drug use, as determined by Infectious Diseases consultant physician May be overlapping sample with Marks 2020b[285] and Marks 2020c[310]	Complete IV: 45.5% Partial IV, no oral: 59.7% Partial IV, partial oral: 48.2%	Complete IV: Mean 40 (range 20-71) years Partial IV, no oral: Mean 38 (range 20-71) years Partial IV, partial oral: Mean 39 (range 26-61) years	Heroin or fentanyl
Marks 2020b[285]	●Inpatient addiction medicine consultation	Effect of inpatient addiction medicine consultation on multiple outcomes	Yes	• Multiple infections • Osteomyelitis • Epidural abscess • Septic arthritis SSTI	• All-cause rehospitalization	USA (St. Louis, Missouri)	125	Patients hospitalized with bacterial infections potentially consistent with injection drug use, identified retrospectively using discharge diagnosis codes	4	January 2016 to January 2018	Infectious diseases consultation occurred; infection related to injection drug use, as determined by Infectious Diseases consultant physician; recommended >2 weeks antibiotic course; patient ineligible for OPAT May be overlapping sample with Marks 2020a[302] and Marks 2020c[310]	Addiction medicine consultation: 55% No addiction medicine consultation: 52%	Addiction medicine consultation: Median 36 (range 19-63 years) No addiction medicine consultation: Median 35 (range 19-67 years)	Heroin

Marks 2020c[310]	●Opioid agonist treatment	Effect of opioid agonist treatment on multiple outcomes	Yes	● Endocarditis	● All-cause mortality	USA (St. Louis, Missouri)	123	Consecutive patients hospitalized with injecting related infections and opioid use disorder, who were referred for infectious diseases consultation. Enrolled in a prospective registry.	4	1 July 2017 to 1 May 2020	Infective endocarditis caused by injection drug use, as determined by infectious diseases consultant May be overlapping sample with Marks 2020a[302] and Marks 2020b[285]	47%	Median 37 (IQR 25-48) years	Opioids
Nguemeni Tiako 2020[311]	●Inpatient addiction medicine consultation	Effect of hospital inpatient addiction on all-cause mortality	Yes	● Endocarditis	● Drug rehabilitation program attendance	USA (New Haven, Connecticut)	56 (subgroup of 42 with "active drug use" used for mortality analysis)	Consecutive patients undergoing cardiac surgery for injecting-related endocarditis. Sampling approach not described.	3	2011 to 2016	Infective endocarditis diagnosis by USA Center for Disease Control and Prevention (CDC) criteria; history of injection drug use	12.5%	Mean 44 (SD 13) years	Heroin
Pericàs 2021[296]	●Gender/sex ●Surgery during hospitalization	Not specified. Aimed to identify factors associated with multiple outcomes	No estimand	● Endocarditis	● Infection-related rehospitalization ● All-cause mortality	International (30 countries)	591	Patients with endocarditis enrolled in one of two prospective cohort studies. Sampling approach not described.	3	1 January 2000 to 31 December 2006 and 1 September 2008 to 31 December 2012	"People who inject drugs", not otherwise defined	27.5%	Median 37.0 (IQR 29.5-44.2) years	Not reported

								(International Collaboration on Endocarditis [ICE] Prospective Cohort Study and ICE-Plus study)						
Ray 2020[299]	●Hospital policy	Effect of change in hospital policy on multiple outcomes	Yes	• Endocarditis	• Infection-related rehospitalization • All-cause rehospitalization	USA (Milwaukee, Wisconsin)	70	Patients admitted to tertiary care hospital with endocarditis and opioid use, identified retrospectively via discharge diagnosis codes	4	1 January 2015 to 31 December 2016 and 1 April 2017 to 31 March 2018	Self-reported "intravenous drug use", as documented in the medical record	Pre-intervention: 56.8% Post-intervention: 57.6%	Pre-intervention: Median 31 (range 18-54) years Post-intervention: Median 31 (range 25 to 52) years	Tobacco; otherwise, not reported
Rodger 2018[306]	●Age ●Gender/sex ●Opioids ●Stimulants ●Polysubstance use ●Opioid agonist treatment ●Hospital discharge against medical advice ●Other substance use/addict	Not specified. Aimed to identify factors associated with all-cause mortality.	No estimand	• Endocarditis	• All-cause mortality	Canada (London, Ontario)	202	All patients admitted to three hospitals with discharge diagnosis of infective endocarditis, identified retrospectively Sample largely	3	1 April 2007 to November 2017	Definite infective endocarditis by modified Duke criteria; self-reported injection drug use, as per medical record	48%	Median 34 (IQR 28-42) years	"Polysubstance"

	ion treatment ●Surgery during hospitalization							overlaps with Rodger 2019 and Tan 2020						
Rodger 2019[298]	●Other substance use/addiction treatment ●Surgery during hospitalization ●Hospital discharge against medical advice	Not specified. Aimed to identify factors associated with recurrent endocarditis	No estimand	● Endocarditis	● Infection-related rehospitalization	Canada (London, Ontario)	212	All patients admitted to three hospitals with discharge diagnosis of infective endocarditis, identified retrospectively Sample largely overlaps with Rodger 2018 and Tan 2020	5	February 2007 to March 2016	Age 18 years and older; Definite infective endocarditis by modified Duke criteria; self-reported injection drug use in preceding three months, as per medical record	48.6%	Median 34 (IQR 28-42 years)	"Polysubstance"
Rohn 2020[307]	●Age ●Gender/sex	Not specified. Aimed to identify factors associated with all-cause mortality	No estimand	● Endocarditis	● All-cause mortality	Czech Republic (Prague, Motol)	72	All patients undergoing cardiac surgery for endocarditis. Sampling approach not described.	3	March 2006 to December 2015	"Active intravenous drug use was confirmed by both the patient and the attending physician"	38.9%	Mean 29.4 (SD 5.8) years	Not reported
Rudasill 2019[288]	●Age ●Surgery during hospitalization	Not specified. Aimed to identify factors associated with all-cause	No estimand	● Endocarditis	● All-cause rehospitalization	USA (nationwide)	27,432 (survey-weighted)	All patients admitted to hospitals reporting to nationwide administrative database, identified	5	January 2010 to September 2015	Age 16 to 64 years and older;	45.3%	Mean 38.3 (SD 0.1) years	Not reported

		rehospitalization						retrospectively via discharge diagnosis codes for (a) endocarditis and (b) use of cocaine, heroin, or methamphetamine (National Readmissions Database)			Excluded patients with diagnosis codes for congenital or rheumatic heart disease			
Slaughter 2019[303]	●Age ●Surgery during hospitalization	Effect of type of surgery on multiple surgery	Partly (1 of 2 exposures)	• Endocarditis	• All-cause rehospitalization • All-cause mortality	USA (nationwide)	1,613	Patients enrolled in a national cardiac surgery registry. Sampling approach not described. (Society of Thoracic Surgeon Adult Cardiac Surgical Database)	2	July 2011 to December 2016	Undergoing cardiac surgery for tricuspid valve endocarditis Excluded patients with severe aortic or mitral valve insufficiency	60%	Median 30 (IQR 26-36) years	Not reported

Straw 2020[308]	●Age ●Gender/sex ●Surgery during hospitalization	Effect of cardiac surgery on all-cause mortality	Partly (1 of 3 exposures)	• Endocarditis	• All-cause mortality	England (Leeds, Yorkshire)	92	Prospectively collected data on consecutive patients admitted to hospital with endocarditis	5	1 January 2006 to 31 December 2016	Definite or possible endocarditis by modified Duke criteria; "IVDU within 90 days" (not otherwise defined)	29%	Mean 36.7 (SD 8.4) years	Not reported
Suzuki 2020[300]	●Opioid agonist treatment	Effect of opioid agonist treatment on multiple outcomes	Yes	• Endocarditis	• Infection-related rehospitalization • All-cause mortality	USA (Boston, Massachusetts)	26	Consecutive patients admitted to a tertiary care hospital with infective endocarditis, and referred for in-hospital addiction consultation	2	2013 to 2015	None specified	50%	Mean 33.8 (SD 12.0) years	Heroin; cocaine
Tan 2020[289]	●Other substance use/addiction treatment	Not specified. Aimed to identify factors associated with multiple outcomes.	No	• Endocarditis	• All-cause mortality	Canada (London, Ontario)	309	All patients admitted to three hospitals with discharge diagnosis of infective endocarditis, identified retrospectively Sample largely overlaps with Rodger 2018 and	4	1 April 2007 to 31 March 2018	Definite infective endocarditis by modified Duke criteria; self-reported injection drug use in preceding three months, as per medical record	49.3%	Mean 35.7 (SD 9.7) years	Opiate; stimulant; "polysubstance"

								Rodger 2019						
Thønnings 2020[261]	●Age ●Opioid agonist treatment ●Other substance use/addiction treatment	Not specified. Aimed to identify factors associated with recurrent bacteremia.	No estimand	• Sepsis/ bacteraemia	• Infection-related rehospitalization	Denmark (Hvidovre)	58	Patients admitted to one tertiary care hospital with electronic medical record entries consistent with injection drug use	2	1 January 2000 to 31 December 2006	Age 19 years or older; "drug abuse including injection of drugs"; bacteraemia during hospital admission	Not reported	Median 40 (SD 35-45) years	Not reported
Wang 2020[287]	●Opioid agonist treatment ●Hospital policy	Effect of opioid agonist treatment and of hospital policy change on multiple outcomes	Yes	• Multiple infections • Osteomyelitis • Endocarditis • SSTI • Septic arthritis	• All-cause rehospitalization • Overdose-related rehospitalization • All-cause mortality	USA (Concord, New Hampshire)	147 (146 with bacterial infections, 1 with acute hepatitis C)	Patients admitted to one suburban community hospital with medical records describing (a) intravenous drug use or opioid use disorder and (b) injecting-related infections. Identified retrospectively via electronic medical record search.	4	1 January 2018 to 1 October 2019	Primary indication for hospital admission is injecting-related infection from injection opioid use. Excluded patients injecting only stimulants; in law enforcement custody; critical illness	48.3%	Average 35.9 (summary statistic not defined)	Opioids

Weymann 2014[309]	●Age ●Gender/sex	Not specified. Aimed to identify factors associated with all-cause mortality.	No estimand	• Endocarditis	• All-cause mortality	Germany (Heidelberg)	20	Consecutive patients undergoing cardiac surgery for endocarditis at one tertiary care hospital	5	January 1993 to July 2013	Definite infective endocarditis by modified Duke criteria; medical record documentation of "acknowledgment by the patient of active intravenous drug abuse (heroin) until the day of admission"	35%	Mean 35 (SD 7.7) years	Heroin

8.11 Appendix 11. Characteristics of included studies where outcome is colonization with pathogenic bacteria in quantitative systematic review of social and structural determinants of injection drug use-associated bacterial and fungal infections.

Study	Included exposures in this review	Main exposure / estimand in study	Do exposures included in this review reflect study estimand	Infections	Outcomes	Country (City)	Sample size	Sampling method (parent study name)	MMAT quality rating (out of 5)	Data collection period	Inclusion criteria	% women/female	Age	Drugs used by ≥50%
Colombo 2012[315]	• Gender/sex • Age	Not specified. Aimed to identify factors associated with MRSA colonisation	No estimand	• Colonisation	• MRSA colonisation (nasal/throat or wound swab)	Switzerland (Zurich)	497	Clients of harm reduction programs and other health and social services. All clients during given day invited to participate.	4	November 2008 to September 2009	History of intravenous drug use	21.1%	Median 41 (range 18-60) years	Not reported
Leibler 2019[318]	• Unstable housing	Not specified. Aimed to identify factors associated with MRSA colonisation	No estimand	• Colonisation	• MRSA colonisation (nasal swab)	USA (Boston, Massachusetts)	78	Patients recruited from hospital inpatient units at an urban, "safety net" tertiary care hospital	4	October 2016 to April 2018	Self-reported injection drug use in at least 3 days out of the week prior to hospital admission; spoken English language proficiency; ability to return for follow-up; at least two	36%	Mean 38.7 (SD 11) years	"nearly 90%"

											additional contacts with valid phone numbers; no known upcoming prison sentences or planned move away			
Leung 2015[316]	• Gender/sex • Age • Race/ethnicity • Education • Income/employment • Relationship status • Unstable housing • Incarceration • Heroin • Cocaine • Amphetamines • Speedball • Prescription opioids • Other substance use • Recent hospitalization • Other substance use/addiction treatment	Not specified. Aimed to identify factors associated with S. aureus colonisation	No estimand	• Colonisation	• MRSA and MSSA colonisation (nasal swab)	USA (Houston, Texas)	440	Respondent driven sampling	5	September 2012 to December 2012	Having a valid recruitment coupon (for RDS); not already enrolled in the study; age 18 years or older; lived in the local area; injected drugs in the past 12 months; completed the interview in English/Spanish; visible evidence of recent injection (e.g., "track marks"); knowledge of drug preparation, injection,	19%	Colonized: Mean 43.7 (SD) 12.6) years Not colonized: Mean 47.6 (SD 11.1) years	Heroin

											and needles/syringes Additional inclusion criteria for "seed" participants (at beginning of RDS): recruited by study staff; not transgender (not otherwise explained)			
Miller 2007[317]	• Gender/sex • Age • Race/ethnicity • Income/employment • Unstable housing • Incarceration • Recent hospitalization • Opioid agonist treatment	Not specified. Aimed to identify factors associated with S. aureus colonisation	No estimand	• Colonisation	• MRSA and MSSA colonisation (nasal swab)	USA (Bronx, New York)	282	Not reported (though cites prior publication of potential parent study that describes recruiting methadone clinic patients)	4	February 1999 to September 2000	Not reported	41%	30 years and younger: 7% 31-45 years: 67% 46 years and older: 26%	None
Packer 2019[319]	• Unstable housing • Public injecting • Recent hospitalization	Not specified. Aimed to identify factors associated with MRSA	No estimand	• Colonisation	• MRSA colonisation (nasal and groin swabs)	England (Bristol)	149	Recruited needle and syringe program clients, using non-probability	4	2012 to 2017	Reported injecting drugs in the past year	16%	Men: Median 39 (IQR 34.5-46) years Women:	None

		colonisation						quota sampling					Median 40 (IQR 31-45) years	

8.12 Appendix 12. Critical appraisal of studies using the Mixed Methods Appraisal Tool (MMAT) for studies where outcome is incident or prevalent injecting-related bacterial infections, included in quantitative systematic review

	SCREENING QUESTIONS		3. NON-RANDOMIZED STUDIES (observational or interventional)				
Study	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	3.1. Are the participants representative of the target population?	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	3.3. Are there complete outcome data?	3.4. Are the confounders accounted for in the design and analysis?	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?
Baltes 2020	Yes	Yes	Yes	Yes	Yes	No	No
Bassetti 2002	Yes	Yes	Yes	Yes	Yes	No	Yes
Bertin 2020	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes
Betts 2016	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Bhattacharya 2006	Yes	Yes	Can't tell	Can't tell	Yes	No	Yes
Binswanger 2000	Yes	Yes	Yes	Yes	Yes	No	Yes
Buchanan 2006	Yes	Yes	Yes	Yes	Yes	Yes	No
Cedarbaum 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ciccarone 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cooper 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dahlman 2015	Yes	Yes	Yes	Yes	Yes	Yes	No
Dahlman 2017	Yes	Yes	Yes	Yes	Yes	Yes	No
DiGiorgio 2019	Yes	Yes	Can't tell	Yes	Can't tell	No	Yes
Doran 2020 (UAM)	Yes	Yes	Yes	Yes	Yes	Yes	No
Doran 2020 (C&P)	Yes	Yes	Yes	Yes	Yes	Yes	No
Dunleavy 2017	Yes	Yes	Yes	Yes	Yes	Yes	No
Fink 2013	Yes	Yes	Yes	Yes	Yes	Yes	No
Hope 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hope 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hope 2010	Yes	Yes	Yes	Yes	Yes	Yes	No

Hope 2008	Yes	Yes	Yes	Yes	Yes	Yes	No
Islam 2019	Yes	Yes	Yes	Yes	Yes	Yes	No
Lee 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lewer 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lloyd-Smith 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lloyd-Smith 2012	Yes	Yes	Yes	Yes	Yes	Yes	No
Lloyd-Smith 2008	Yes	Yes	Yes	Yes	Yes	Yes	No
Lloyd-Smith 2009	Yes	Yes	Yes	Yes	Yes	Yes	No
Lloyd-Smith 2010	Yes	Yes	Yes	Yes	Yes	Yes	No
McMahan 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Milloy 2010	Yes	Yes	Yes	Yes	Yes	Yes	No
Morin 2020	Yes	Yes	Yes	No	Yes	Yes	No
Murphy 2001	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Nagar 2015	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Noroozi 2019	Yes	Yes	Yes	Yes	Yes	Yes	No
Phillips 2017	Yes	Yes	Yes	Yes	Yes	Yes	No
Phillips 2008	Yes	Yes	Yes	Yes	Yes	Yes	No
Phillips 2010	Yes	Yes	Yes	Yes	Yes	Yes	No
Pollini 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pollini 2010b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Robertson 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roux 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Saeland 2014	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Safaeian 2000	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Scherbaum 2010	Yes	Yes	Yes	Yes	Yes	No	Yes
Shah 2020	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Sierra 2006	Yes	Yes	Can't tell	Yes	Yes	No	Yes

Silverman 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Smith 2015	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell
Stein 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Summers 2017	Yes	Yes	Yes	Yes	Yes	Yes	No
Thønnings 2020	Yes	Yes	Can't tell	Yes	Yes	Yes	Can't tell
Tomolillo 2007 (Ecological time series study)	Yes	Yes	Yes	Yes	Yes	No	Yes
Tomolillo 2007 (Cross-sectional study)	Yes	Yes	No	Yes	Yes	No	Yes
Trayner 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Weir 2019	Yes	Yes	Yes	No	Yes	No	Yes
Wilson 2002	Yes	Yes	Yes	Yes	Yes	Yes	No
Wright 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Wurcel 2016	Yes	Yes	Yes	Yes	Yes	No	Yes
Wurcel 2018	Yes	Yes	Yes	Yes	Yes	Yes	No
Yeung 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	SCREENING QUESTIONS		**2. RANDOMIZED CONTROLLED TRIALS**				
Study	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**2.1. Is randomization appropriately performed?**	**2.2. Are the groups comparable at baseline?**	**2.3. Are there complete outcome data?**	**2.4. Are outcome assessors blinded to the intervention provided?**	**2.5 Did the participants adhere to the assigned intervention?**
Oviedo-Joekes 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes

8.13 Appendix 13. Critical appraisal of studies using the Mixed Methods Appraisal Tool (MMAT) for studies where outcome occurs during treatment for injecting-related bacterial infection, included in quantitative systematic review

	SCREENING QUESTIONS		3. NON-RANDOMIZED STUDIES (observational or interventional)				
First author, year	S1. Are there clear research questions?	S2. Do the collected data allow to address the research questions?	3.1. Are the participants representative of the target population?	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	3.3. Are there complete outcome data?	3.4. Are the confounders accounted for in the design and analysis?	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?
Cooksey 2020	Yes	No	Yes	Yes	Yes	Yes	Yes
Eaton 2020	Yes	Yes	Can't tell	Can't tell	Can't tell	Yes	Yes
Fink 2013	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell
Hope 2008	Yes	Yes	Yes	Yes	Yes	Yes	No
Hope 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jo 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kimmel 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kimmel 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lloyd-Smith 2012	Yes	Yes	Yes	Yes	Yes	Yes	No
Lloyd-Smith 2010	Yes	Yes	Yes	Yes	Yes	Yes	No
Marks 2020	Yes	Yes	Yes	Yes	Yes	No	Yes
Marks 2020	Yes	Yes	Yes	Yes	Yes	No	Yes
Martín-Dávila 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Meel 2018	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Mertz 2008	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Monteiro 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Nolan 2020	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell

Rudasill 2019	Yes	Yes	Yes	Yes	Yes	No	Yes
Sandrock 2001	Yes	Yes	Yes	Yes	Yes	No	Yes
Saydain 2010	Yes	Yes	No	Yes	Yes	Yes	Yes
Serota 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Suzuki 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Takahashi 2007	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Tan 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Uppuluri 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang 2020	Yes	Yes	Yes	Yes	Yes	No	Yes

8.14 Appendix 14. Critical appraisal of studies using the Mixed Methods Appraisal Tool (MMAT) for studies where outcome occurs after initial treatment for injecting-related bacterial infection, included in quantitative systematic review

	SCREENING QUESTIONS		3. NON-RANDOMIZED STUDIES (observational or interventional)				
Study	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**3.1. Are the participants representative of the target population?**	**3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**3.3. Are there complete outcome data?**	**3.4. Are the confounders accounted for in the design and analysis?**	**3.5. During the study period, is the intervention administered (or exposure occurred) as intended?**
Barocas 2020	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Barocas 2021	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Buehrle 2017	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Clarelin 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Connell 2010	Yes	Yes	Yes	Yes	Yes	No	Yes
Cooksey 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D'Couto 2018	Yes	Yes	Yes	Yes	No	No	Yes
Hilbig 2020	Yes	Yes	Yes	Yes	Yes	No	Can't tell
Huang 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jo 2021	Yes	Yes	Yes	Yes	Yes	Yes	No
Kimmel 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Marks 2020a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Marks 2020b	Yes	Yes	Yes	Yes	Yes	No	Yes

Marks 2020c	Yes	Yes	Yes	Yes	Yes	No	Yes
Nguemeni Tiako 2020	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Pericàs 2021	Yes	Yes	Can't tell	Yes	Can't tell	Yes	Yes
Ray 2020	Yes	Yes	Yes	Yes	Yes	No	Yes
Rodger 2018	Yes	Yes	Yes	Yes	No	Yes	No
Rodger 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rohn 2020	Yes	Yes	Can't tell	Yes	Yes	No	Yes
Rudasill 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Slaughter 2019	Yes	Yes	Can't tell	Yes	Can't tell	No	Yes
Straw 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Suzuki 2020	Yes	Yes	Yes	Yes	Can't tell	No	Yes
Tan 2020	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes
Thønnings 2020	Yes	Yes	Can't tell	No	Yes	No	Yes
Wang 2020	Yes	Yes	Yes	Yes	Yes	No	Yes
Weymann 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	SCREENING QUESTIONS		**2. RANDOMIZED CONTROLLED TRIALS**				
Study	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**2.2. Are the groups comparable at baseline?**	**2.3. Are there complete outcome data?**	**2.4. Are outcome assessors blinded to the intervention provided?**	**2.5 Did the participants adhere to the assigned intervention?**	**2.2. Are the groups comparable at baseline?**
Fanucchi 2020	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes

8.15 Appendix 15. Critical appraisal of studies using the Mixed Methods Appraisal Tool (MMAT) for studies where outcome is colonization with pathogenic bacteria among people who inject drugs, included in quantitative systematic review

	SCREENING QUESTIONS		3. NON-RANDOMIZED STUDIES (observational or interventional)				
Study	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**3.1. Are the participants representative of the target population?**	**3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**3.3. Are there complete outcome data?**	**3.4. Are the confounders accounted for in the design and analysis?**	**3.5. During the study period, is the intervention administered (or exposure occurred) as intended?**
Colombo 2012	Yes	Yes	Yes	Yes	Yes	No	Yes
Leibler 2019	Yes	Yes	Yes	Yes	Yes	No	Yes
Leung 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miller 2007	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Packer 2019	Yes	Yes	Yes	Yes	Yes	No	Yes

8.16 Appendix 16. Details on handling of variables for meta-analysis of social determinants of injection drug use-associated bacterial and fungal infections

8.16.1 Studies where outcome is incident or prevalent injecting-related infection.

8.16.1.1 Demographic factors

8.16.1.1.1 Gender

Multiple related outcomes:

- Islam 2019[233] had two related sets of unadjusted and adjusted effect estimates, one at 3 months follow-up and one at 6 months follow-up. I included only the 6 month follow-up to avoid double-counting.
- Morin 2020[59] had three separate infectious outcomes (based on different discharge diagnosis codes), and provided only 1 decimal point in ORs and confidence intervals. I could not include these in meta-analysis when 95% confidence interval differs by 0.1 or less (because this implies the standard error is 0). The authors provided more detailed ORs by email follow-up, but only for one compound outcome variable. I used this one outcome variable here.
- Stein 2020[250] had OR for hospitalizations and for ED visits (same participants). Kept ED visits and dropped hospitalizations. Also, reference group for ORs was female, so took inverse of OR and 95% CI.
- Wurcel 2018[253]: Kept OR for abscess "ever" (because this was aligned with more of the exposures). Dropped OR for "abscess past 30 days".

Subsamples:

- Islam 2019[233] had separate effect estimates for whole sample and for subset of "high frequency injectors" (>1 injection per day). Kept estimate for whole sample only.
- Hope 2010[101] had one OR for whole sample (for abscess in past year) and one OR for subsample reporting injecting in past 4 weeks. Since exposure is time-fixed, took whole sample OR.

Studies with "not significant" findings (but no statistics presented):

- Binswanger 2000[99]: "Did not significantly differ"

- Hope 2014[125]: “No associations found” for abscess outcome or cellulitis outcome
- Wurcel 2016[63]: “No significant changes”
- Hope 2015[75]: “Not associated” for abscess outcome or cellulitis outcome

8.16.1.1.2 Age

Multiple related outcomes:

- Stein 2020[250], has highly related outcomes for ED visits for injecting-related infections and hospitalizations for injecting-related infections in same sample. Kept only ED visits.

Collapsed more than two levels of exposure:

- Baltes 2020[254] (combined <40 and 40 or older)
- Betts 2016[229] (kept only age 36-45 vs. 35 or less, and excluded OR for age 46-71
- Doran 2020[232] (UAM and for C&P): (kept 35+ years vs. less than 25, excluded 25-34 years)
- Dunleavy 2017[92] (combined >30 vs. 30 years or less for uOR, because this was assessed in aOR
- Fink 2013[100] kept 50+ years vs. under 30 years
- Hope 2010[101] combined 35 years or older vs. under 35 for uOR; aOR not reported (because not included in stepwise regression)
- Hope 2008[104] kept uOR and aOR for 35 years and older vs. under 25 years
- Hope 2015[75] combined frequencies for uOR 30 and olver vs. under 30
- Murphy 2001[241] Combined 40 years and older vs. and less than 40 for uOR frequencies, for two comparable sized groups
- Noroozi 2019[257] for uOR and aOR kept 40 years and older vs. under 30
- Wright 2020[252] kept only 45+ years vs. less than 35
- Morin 2020[59] reference was 65+ and broken into six levels. Kept 25-34 vs. 65+ (because CI did not have same values as point estimate, so could include in meta-analysis) and inverted it.

Inverted effect estimates (study treated “older” as reference group, so took inverse for meta-analysis):

- Cedarbaum 2016[255] was aOR 0.32 (0.16-0.65), now aOR 3.13 (1.54 - 6.25)
- Morin 2020[59] reference was 65+ and broken into six levels. Kept 25-34 vs. 65+ (because CI did not have same values as point estimate, so could include in meta-analysis) and inverted it.

Studies with “not significant” findings (but no statistics presented):

- Binswanger 2000[99]; Dahlman 2017[231]; Hope 2014[125]; Hope 2015[75] (cellulitis)

Other:

- Cooper 2005[256], in an ecological study, assessed effect of percent of neighborhood residents aged 18-64 years, vs. less than 18 OR older than 64 years (so not younger or older).
- Thønnings 2020[261]: reported as p=0.21 but confidence interval does not cross one. This is impossible. So excluded both uOR and aOR
- Wurcel 2016[63] "…the percentage of IDU-IE hospitalizations among young adults (15–34 years) steadily increased from 2000 to 2013, with a steep increase from 2008 to 2013 (27.7%–42.0%; P < .001 using χ2 test for trend in proportions). In contrast, IDU-IE rates among middle-aged adults (ages 35–54) steadily decreased between 2000 and 2013 (67.2%–39.9%; P < .001)."

8.16.1.1.3 Race/ethnicity

Inverted effect estimates

- Fink 2013[100]: had White as referent for adjusted odds ratios, and separate categories for Black, Latino, Other. Inverted Black category from aOR 0.95 (0.62-1.45) to 1.05 (0.69-1.61). Inverted Latino category from aOR 0.87 (0.57-1.31) to aOR 1.15 (0.76-1.75)
- Milloy 2010[240]: had White as referent and Aboriginal (ndigenous) for incident rate ratios. Inverted uRR from 0.72 (0.47-1.09) to 1.39 (0.92-2.13) and aRR from 0.71 (0.47–1.07) to 1.41 (0.93-2.13)
- Safaeian 2000[246] Black as exposure and other (?white) as referent. Inverted from uOR 1.8 (1.0-3.3) to 0.56 (0.30-1.00)

Multiple related outcomes

- Stein 2020[250] included as separate outcomes for ED visit and hospitalization with injecting-related infections. We included only ED visits.

Other:

- Smith 2015[249] includes African American as referent group, so could include OR vs. "Caucasian" but could not include OR vs. Native American. With Native American as the exposure (uOR 7.50; 95%CI 0.92-60.90 and aOR 7.35; 95%CI 0.48-113.36). The study also included a race category for "Other" including Hispanic, Asian, or "multiple" that had two few participants for regression.

- Wurcel 2016[63] was a USA nationwide ecological study of hospital records, and reported that the percentage of hospital admissions for endocarditis that were attributable to injection drug use increased among white people from 40.2% in 2000 to 68.9% in 2013 (P < .001). The proportion of hospital admissions for endocarditis that were attributable to injection drug use for "non-white" people appeared stable, but a missing data category decreased substantially over time.

8.16.1.1.4 Education

Inverted effect estimates:

- Betts 2016[229] had tertiary education as reference group. Was aOR 0.74 (0.55-1.01), now 1.35 (0.99 – 1.82)

Outliers:

- Shah 2020[247] was outlier (uOR 3.12, 95%CI 1.34-7.23) for summary uOR including it (0.98, 95% 0.80-1.21). Removing Shah 2020 changed summary uOR to 0.92 (95%CI 0.77-1.09).
- After removing Shah 2020, then Phillips 2017[243] (uOR 2.4249 [1.2000; 4.9000]) became an outlier. Removing Phillips 2017 changed summary uOR to 0.8711 [0.7642; 0.9929]

8.16.1.1.5 Income/employment

Could not include in meta-analysis:

- Ciccarone 2016[137] included "percent unemployment" and "percent poverty" in multivariable regression but did not define these and we were unable to extract the confidence intervals from the figure where they were presented. It seems like "Percent unemployment" had point estimate of OR 1.00 and was not statistically significant, and "Percent poverty" had point estimate of OR 0.98 with p<0.05.
- Summers 2017[260]: "Reported income" was exposure but categories undefined. uOR and aOR were both 1.00 (1.00-1.00) so could not include in inverse-weight meta-analysis. So excluded.

Multiple related outcomes:

- Hope 2014[125] reported highly related outcomes of abscess and cellulitis (redness, swelling, tenderness). Included only cellulitis as this was more common.

- Noroozi 2019[257] it seems like employment status and monthly income were combined into "socioeconomic status", so only used the latter

Collapsed more than two levels:

- Murphy 2001[241] collapsed three levels into annual family income less than 10,000 or 10,000+
- Morin 2020[59] for all outcomes, took OR of lowest neighbourhood income vs. highest (quintiles).

Inverted effect estimates

- Roux 2020[242] had "employed" as exposed and unemployed as referent. Inverted from uOR 0.84 (0.42-1.66) to 1.19 (0.60 – 2.38)
- Safaeian 2000[246] for both Endocarditis and Abscess outcomes has lower income as reference and higher income has exposures. Inverted from uOR 0.7 (0.4-1.3) to 1.42 (0.77-2.5) and from uOR 0.7 (0.5-0.9) to 1.43 (1.11-2.00)

8.16.1.2 Social and housing support characteristics

8.16.1.2.1 Incarceration history

Multiple related outcomes:

- Two studies [Hope 2014; Hope 2015][75,125] provided separate effect estimates for two related outcomes measures (abscess and cellulitis, both of which we categorized as SSTI), but reported only "no associations found" so we could not include them in meta-analyses.

Reporting no difference without statistics:

- Two further studies [Hope 2008; Saeland 2014][104,259] reported no significant association but did not provide data.

Other:

- One study [Pollini 2010][245] found no evidence of an association between self-reported injecting during incarceration in past 6 months and self-reported abscess in past 6 months.

8.16.1.2.2 Sex work

Multiple related outcomes:

- One study [Hope 2015][75] included two separate analyses for related (but different) outcomes in the sample, self-reported abscess and self-reported "redness, swelling, or tenderness" (we have labelled as cellulitis); there is a univariate analyses for both and an adjusted analysis only for abscess. We included both analyses in the main meta-analysis and then performed a sensitivity analysis including only the abscess outcome analysis. In sensitivity analysis omitting Hope 2015 cellulitis outcome from univariate analysis (including only abscess outcome), the summary effect estimate was generally the same: OR 1.68 (1.04 – 2.75).

Multiple related exposures:

- One study [Pollini 2010][245] provided effect estimates for two related exposure measures of sex work ("Principal source of income was through sex work" and "Traded sex or money for drugs"); we included only the "Principal source of income" measure.

Reporting no difference without statistics:

- In one study [Saeland 2014][259], the association between sex work and injecting-related infection was found to be not statistically significant but the data was not reported, so this could not be included in meta-analysis.

8.16.1.2.3 Unstable housing and homelessness

Multiple related exposures:

- One study [Dunleavy 2017][92] provided effect estimates for two related exposure measures of homelessness (lifetime history [OR 0.90, 95% CI 0.72-1.13] vs. past 6 months [OR 0.90, 95% CI 0.72-1.13]) in relation to SSTI in the past year, so only the past 6 months analyses was included in meta-analysis.

Collapsing more than two levels:

- Two studies [Hope 2014; Hope 2015][75,125] categorized their homelessness exposure into three levels as "Never"; "Yes but not in last year"; and "Yes in last year". For univariate odds ratios we treated this as "Yes in last year" vs. other, but in adjusted odds ratios (provided only in Hope 2015) the pre-calculated odds ratio provided was for "Yes in last year" vs. "Never" as the reference group.

Reporting no difference without statistics:

- Across three studies [Biswanger 2000; Hope 2014; Hope 2015],[75,99,125] three tests of association were found to be not statistically significant but the data was not reported, so we could not include them in the meta-analyses.

8.16.1.3 Substance use-related factors

8.16.1.3.1 Overdose history

Reported no difference, without providing statistics:

- Saeland 2014[259] reports only that groups with and without history of overdose, "did not differ", so was not included in meta-analysis.

Multiple related exposures and outcomes

- Hope 2014[125] and Hope 2015[75] had separate exposure categories for (a) history of overdose in preceding year and (b) history of overdose, but not in preceding year, and compared these to reference category of "never" overdosed. We kept only history of overdose in preceding year, noting that the effect estimate is only in reference to people who never overdosed and excludes people that overdosed prior to the past year. Also both papers had separate effect estimates for abscess and for cellulitis ("redness, swelling, and tenderness". All were statistically significantly increased. For meta-analysis, we only include estimates of abscess.

8.16.1.3.2 Heroin use

Multiple related outcomes:

- Hope 2014[125] and Hope 2015[75] had separate analyses for abscess outcome and cellulitis ("redness, swelling, or tenderness") outcome. In Hope 2014, only statistics for abscess outcome were reported, and for cellulitis was only "no associations found". For Hope 2015, only reported as "not associated" and so not included in meta-analysis.

Collapsed more than two levels of exposures:

- Hope 2010[101] separated out "Opiate, no stimulant"; "Stimulant, no opiate", and "Stimulant and opiate". We compared only "Opiate, no stimulant" and "Stimulant, no opiate" (interpreted as opiate/heroin only vs. no opiate use). Since "Opiate, no stimulant" was reference group for multivariable/adjusted odds ratio, took inverse; transformed aOR 0.47 (0.30-0.75) (for stimulant

use) to 2.12 (1.33 - 3.33). Also had separate estimates for whole sample and sample injecting in past 4 weeks (but outcome was any SSTI in past year), so kept estimate for whole sample.

Other:

- Lloyd-Smith 2009[238] and Milloy 2010[240] reported odds ratios for statistics assessed during baseline study visits, and hazard ratios or rate ratios for incidence studies during follow-up. We included the hazard ratios and rate ratios rather than the baseline odds ratios.

Reported no difference, without providing statistics:

- Other studies reporting "no associations found" (and therefore providing no statistics to include in meta-analysis) include Lloyd-Smith 2005[235] (for multivariable analysis), Lloyd-Smith 2012[236] (for multivariable analysis among men, but did include stats among women [because was "significant" in univariate analysis within stepwise regression], Milloy 2010[240] (for multivariable analysis, dropped in stepwise regression), Pollini 2010[245] (for multivariable analysis, dropped in stepwise regression).

Heroin type/formulation

- One ecological study [Ciccarone 2016][137] found that rates of SSTI was higher in cities with predominantly Mexican-sourced (tar) heroin compared to cities with predominantly Colombian-sourced (powder) heroin; this was true after covariate adjustment (aOR 2.05, p<0.001) but the units and increments of the exposure were not reported for this analysis, so we did not include it in the meta-analysis or narrative results.

8.16.1.3.3 Cocaine

Multiple related outcomes:

- Hope 2014[125] and Hope 2015[75] had separate estimates for abscess and cellulitis ("redness, swelling, and tenderness"), so we kept only abscess
- Lloyd-Smith 2010[239] and Milloy 2010[240] have baseline/cross-sectional OR and longitudinal/incidence HR (or RR). So we kept only HR (or RR) and not OR.

Other:

- Roux 2020[242] did not specify cocaine the text (only saying "stimulant"), but next variable described is "speedball" (which is a combination of cocaine and heroin), so we interpret "stimulant" here to mean specifically cocaine.
- Hope 2010[101] found that people who reported injecting only "stimulants" (not otherwise specified) had a lower risk of prevalent injecting-site infection than people who inject only opiates, for abscess (aOR 0.49, 95%CI 0.34-0.71) and cellulitis (aOR 0.47, 0.30-0.75). However, a small minority of participants used only stimulants (206 out of 4,484; 4.6%). As not specified (and would be outlier for cocaine anyway), left out of synthesis.

8.16.1.3.4 Methamphetamine and amphetamines

Reported no difference, without statistics:

- Hope 2014[125] and Hope 2015[75] had separate estimates for abscess and cellulitis, but all were reported as "not associated" with no statistics, so were excluded.
- Hope 2008[104] reported only "not associated" so was excluded

8.16.1.3.5 Speedball (cocaine and heroin together) and goofball (methamphetamine and heroin/fentanyl together)

Multiple related outcomes

- Lloyd-Smith 2012, Lloyd-Smith-2009, and Milloy 2010[236,238,240] all had cross-sectional/baseline odds ratios and longitudinal/incidental HRs or RRs, so only kept longitudinal measurements

8.16.1.3.6 Alcohol use

Multiple related exposures:

- Phillips 2008[244] had two related exposure measurements of hazardous alcohol use, AUDIT >= 8 and alcohol intoxication days in past month. We kept alcohol intoxication days in past month.

Collapsing multiple levels of exposure

- Wilson 2002[251] had three levels: no alcohol; 1-21 drinks per week, and >21 drinks. We kept only >21 drinks per week and categorized as "Hazardous"

8.16.1.4 Drug policy factors

8.16.1.4.1 *Police contacts and arrests*

Multiple related outcomes:

- One study [Cooper 2005][256] was an ecological study assessing the impact of policing crackdowns on local rates of hospitalization for injection drug use-associated SSTI and endocarditis. While multiple effect estimates are presented, we included the IRR for the "first crackdown quarter" based on the authors' stated hypothesis.
- Two studies [Hope 2014; Hope 2015][75,125] provided two related effect estimates for associations between arrest in the past year with abscess and with cellulitis (in the past month for Hope 2014, and in the past year for Hope 2015). Hope 2014 reported only "no associations found" between arrest and the abscess outcomes, so we included only the cellulitis outcome. Hope 2015 reported only "not associated" for the cellulitis outcome, so we included only the abscess outcome.

Multiple related exposures:

- One study [Pollini 2010][245] assessed several different exposures related to police contacts amongst the same sample of PWID in Tijuana, Mexico. This included univariate effect estimates for being arrested for sterile syringes, arrested for used syringes, arrested for track marks, and police asking you for money, and univariate and adjusted estimates for "Police affected where you used drugs". We included all these separate estimates.

8.16.1.4.2 Assisted injecting, or requiring help to inject

Other:

- One study [Lloyd-Smith 2012][236] provided one unadjusted OR for the whole sample, but for adjusted OR only provided sex-stratified estimates.

8.16.1.4.3 Injecting with others

Multiple related exposures:

- Pollini 2010[245] assessed three different exposures in the same sample (alone/never injected alone, with friends, with family/spouse). Included all.
- Roux 2020[242] had sample broken up into three levels, (a) injected alone or did not inject (as reference), (b) with someone else, (c) in group. Included all.
- Smith 2015[249] had exposure in three levels: (a) injected alone (as reference), (b) with friends, (c) with family/spouse. Included all.

8.16.1.5 Harm reduction and drug treatment

8.16.1.5.1 Needle and syringe distribution programs

Multiple related exposures:

- Dunleavy 2017[92] reported two separate effect estimates for uptake of sterile needles and syringes and for uptake of sterile "paraphernalia" (i.e., filters and cookers/spoons), both of which we included. They reported a third effect estimate which was a composite of these two variables; we excluded this to avoid double-counting.

Multiple estimates from subsamples:

- Hope 2010[101] reported one effect estimate for the whole sample and a second effect estimate for the subsample of participants who reported injecting in the past four weeks; since the exposure and outcome definitions related to the past year (rather than only the past four weeks) we included the effect estimate for the full sample and excluded the one for the subsample to avoid double-counting.

8.16.1.5.2 Opioid agonist treatment

Continuity correction:

- In Sierra 2006[248] there were zero injecting-related infections in the methadone group, resulting in an infinity confidence interval that could not be included in meta-analysis. When we perform a continuity correction by adding 0.5 to all cells in the 2 by 2 table, the study OR changes from 0.03 (0.00 – 0.19) to 0.08 (0.00 – 1.50) and the summary uOR changes from uOR 0.76 (95%CI 0.65-0.89) to 0.75 (0.63 – 0.89).

Inverted effect esimates:

- Two studies [Betts 2016; Hope 2008][104,229] provided an effect estimate for NOT being on OAT, so we took inverse.

Handling more than two exposure levels

- Several studies [Dunleavy 2017; Hope 2010; Hope 2008][92,101,104] assessed currently being on OAT vs. previously being on OAT, treating never on OAT as a distinct category. We included this current OAT vs. previous OAT effect estimate. In these studies, being "previously" on OAT was associated with higher risk of infections compared to never being on OAT. This may include people without opioid use disorder or people without substance dependence.

Other:

- Several studies compared multiple types of OAT, rather than OAT vs. no OAT, and were excluded from the meta-analysis of OAT vs. no OAT.
- One study [Bertin 2020][273] compared incidence of injecting-related bacterial infections amongst patients starting buprenorphine, methadone, and second-line/alternative OAT with morphine sulfate:
    - Crude incidence per 100,000 PY, by cohort -- MS: 7.0 (4.7 – 10.6); Bupe: 2.2 (1.8 – 2.5); Methadone: 1.6 (1.2 – 2.0)
    - aHR 2.8 (1.8-4.4) for MS vs. patients starting buprenorphine
    - aHR 3.6 (2.2-5.9) for MS vs. patients starting methadone
    - aHR Adjusted for age, sex, socioeconomic status, chronic alcohol consumption, concurrent BZD use, major chronic somatic or psychiatric comorbid disease
- One study [Oviedo-Joekes 2017][274] reported rates of cellulitis or abscess as potential adverse effects within a randomized trial of injectable hydromorphone (7 episodes among 100 patients) vs. injectable diacetylmorphine (17 episodes among 100 patients).

8.16.1.5.3 Supervised consumption sites

Multiple related outcomes:

- One study [Scherbaum 2010][275] reported rates of past-month skin abscesses among PWID at their first time attending a supervised consumption site and compared this to past-month rates at one, two, and three months follow-up. Since these three effect estimates are among the same

sample, we included only the data at the first month follow-up because most the sample was lost to follow-up after that.

8.16.2 Outcomes during treatment for injecting-related infections

8.16.2.1 Healthcare-seeking for injecting-related infections

Multiple related outcomes:

- Hope 2015[75] had highly related outcomes of abscess and cellulitis ("redness, swelling, tenderness"). Kept abscess because it may be more persistent and recognized as a medical issue.

8.16.2.2 Against medical advice discharge

8.16.2.2.1 Gender/sex

Inverted effect estimates:

- Jo 2021[279] had male as exposure. Inverted from aOR 0.83 (0.62 – 1.11) to aOR 1.20 (0.90 – 1.61)
- Mertz 2008[281] had male gender as exposure. Inverted from aOR 1.2 (0.6 – 2.2) to aOR 0.83 (0.45 – 1.67)
- Serota 2021[283] had male gender as exposure. Inverted from aOR 0.86 (.80, .92) to aOR 1.16 (1.09-1.25)

8.16.2.2.2 Age

Inverted effect estimates:

- Jo 2021[279] inverted to aOR 1.04 (95%CI 1.03-1.06)
- Mertz 2008[281] inverted to aOR 1.25 (95%CI 0.83-2)

8.16.2.2.3 Health insurance

Multiple levels of exposures:

- Jo 2021[279]: uninsured is reference (vs. levels government-funded insurance or private insurance). Inverted government funded insurance from aOR 0.45 (0.33, 0.61) to aOR 2.22 (1.64 – 3.03)
- Kimmel 2020[280]: Medicaid is reference. Kept "self" as source of payment; aOR 1.37 (1.13 – 1.66)

8.16.2.3 All-cause rehospitalization

8.16.2.3.1 Gender/sex

Inverted effect estimates

- Jo 2021[279] had females as reference. Inverted to aOR 1.12 (95%CI 0.9-1.41)

8.16.2.3.2 Opioid agonist treatment

Multiple outcomes:

- Barocas 2020[294] had separate effect estimates for hazard of all-cause rehospitalization within 30 days and within 1 year. Since exposure was OAT within 30 days, that outcome likely affected by immortal time. Kept 1 year outcome.
- Wang 2020[287] had separate effect estimates for binary yes/no rehospitalization within 30 days and within 90 days. Since exposure was OAT provided on hospital discharge, kept 30 days outcome

8.16.3 Colonization outcomes

Multiple related exposures:

- Leibler 2019[318] had multiple related exposures, kept "sleeping in homeless shelter" and excluded sleeping on the street ("no associations were observed"). Moved :"sleeping >1 place during the last week" and "use of public shower facilities" and "sharing bedding" to it's own "other" category.
- Miller 2007[3] had two related exposures: "Homeless during past six months" and "spent time in a homeless shelter during the past six months". Kept only "Homeless" in meta-analysis, as assumed this was inclusive of both.

8.17 Appendix 17. List of exposure-outcome pair effect estimates for studies where outcome is incident or prevalent injecting-related bacterial infections drug use-associated bacterial and fungal infections, included in quantitative systematic review.

Study		Exposures	Outcomes	Unadjusted effect estimate	Adjusted effect estimate	
Sociodemogaphic factors						
Gender/Sex						
Baltes 2020[254]		Female sex	Past-year SSTI, self report	Female: 11/32 Male: 7/48		
Betts 2016[229]		Female gender	Past-month abscess, self-report		aOR 1.47 (1.07 – 2.02)	
Binswanger 2000[99]		Sex (not defined)	Current abscess or cellulitis on physical examination	"did not differ significantly"		
Dahlman 2015[230]		Female sex (vs. male)	Ever had an SSTI	OR 4.08 (1.34 – 12.46)	aOR 6.75 (1.40-32.47)	
Dahlman 2017[231]		Female sex (vs. male)	Past-30 day skin and soft-tissue infections	Female: 17/46 (36.9%) Male: 5/155 (3.2%) Reported in paper: OR 0.99 (0.34 – 2.85) Calculated by me: 17.59 (6.01 – 51.45)		
Doran 2020[232] (UAM)		Female gender	Past year SSTI	OR 1.3 (1.1 – 1.5)	aOR 1.4 (1.1 – 1.7)	
Doran 2020[232]		Female gender	Ever SSTI	OR 1.1 (0.7 – 1.7)	aOR 1.4 (0.8 – 2.6)	
Dunleavy 2017[92]		Male vs. female	SSTI in past year	Male: 374/1306 (29%) Female: 156/553 (28%), p=0.852		
Fink 2013[100]		Gender	Abscess in past 6 months, self-report	Male: 206/612 (33.6%) Female: 114/245 (46.5%) p=0.0004	aOR 1.42 (1.01 – 2.00)	
Hope 2014[125]		Gender	Self-reported abscess "(a swelling containing pus)", past 28 days	"No associations found"		
Hope 2014[125]		Gender	Self-reported "redness, swelling, and tenderness", past 28 days	"No associations found"		

Hope 2010[101]		Gender	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	Male: 1338/3896 (34%) Female: 525/1313 (40%) p<0.001	aOR Male: 1.00 Female: 1.43 (1.25-1.64)	
Hope 2010[101]		Gender	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months (among subgroup of patients reporting injecting in past 4 weeks)	Male: 989/2820 (35%) Female: 386/913 (42%) p<0.001	aOR Male: 1.00 Female: 1.41 (1.19-1.66)	
Hope 2008[104]		Gender	Self-reported symptoms of injection site infections (abscess or open wound) in last year	ORs Male: 1.0 Female: 1.4 (1.1 – 1.9)	aORs Male: 1.0 Female: 1.7 (1.2 – 2.4)	
Islam 2019[4233]		Gender (female)	Invasive bacterial infection (pneumonia, sepsis, endocarditis) at 9 months (self-report & confirmed with medical chart review) (among high-frequency injectors [>1 injection per day])	ORs 1.26 (0.86–1.84)	aORs 1.74 (1.17–2.57)	
Islam 2019[233]		Gender (female)	Invasive bacterial infection (pneumonia, sepsis, endocarditis) at 12 months (self-report & confirmed with medical chart review) (among high-frequency injectors [>1 injection per day])	ORs 1.50 (1.14–1.97)	aORs 1.76 (1.34–2.32)	
Lewer 2020[234]		Sex	Rate of hospital admissions for heroin-injection associated bacterial infections	IRR 1.50 (1.32 – 1.69)		

Lloyd-Smith 2005[235]		Gender	Self-report abscess ("lasting for more than 3 days"), past 6 months	OR 2.4 (1.9 – 3.0)	aOR 1.7 (1.4 – 2.4)	
Lloyd-Smith 2012[236]		Female	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	OR 1.71 (1.18 – 2.47)		
Lloyd-Smith 2008[237]		Sex	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Male: Ref Female: 1.90 (1.39 - 2.58)	aOR 1.68 (1.16 – 2.43)	
Lloyd-Smith 2009[238]		Sex (female)	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR 1.89 (1.35 – 2.63) HR 2.08 (1.49 – 2.92)	aHR 1.87 (1.32 – 2.64)	
Lloyd-Smith 2010[239]		Sex (female)	Hospitalization for injecting-related infection (cellulitis, abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis)	HR 1.59 (1.07 – 2.39)	aHR 1.36 (0.90 – 2.05)	
Milloy 2010[240]		Gender	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: Male: 49/380 Female: 23/165 P=0.741 RR for number of ED visits for CIRI during follow-up: 1.08 (0.77–1.53) (female vs. male)	aRR for number of ED visits for CIRI during follow-up: 1.04 (0.71–1.51)	
Murphy 2001[241]		Sex	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Male: 85/289 Female: 66/135 P<0.001	Not tested	
Roux 2020[242]		Gender	At least one cutaneous abscess in the previous six months	OR Male: Ref Female or transgender: 0.87 [0.38,2.00]		
Phillips 2017[243]		Female	Past year SSTI, self-report	OR 0.80 (0.40, 1.62)	aOR 0.77 (0.29, 2.05)	

Phillips 2008[244]		Gender (male)	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 1.42 (0.28–7.20)	aOR 1.86; 0.23–15.03	
Pollini 2010[245]		Gender	Past 6-months abscess	Male: 91/513 Females: 36/110 p<0.001		
Safaeian 2000[246]		Gender	Infective endocarditis, self-report confirmed through medical chart review	OR Male: Ref Female: 2.8 (1.7 – 4.6)	aOR 3.4 (1.9-6.2)	
Safaeian 2000[246]		Gender	Abscess, self-report	OR Male: Ref Female: 2.2 (1.6-2.8)	aOR 2.0 (1.5-2.8)	
Shah 2020[247]		Female	Endocarditis	Female: 16/37 Male: 17/98 p=0.002 OR 3.85 (1.68-8.96)	aOR 4.65 (1.85-12.28)	
Sierra 2006[248]		Sex	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	Female: Reference Male: 2.82 (0.4-23.4) Female: 3/19 Male: 12/54 P=0.27		
Smith 2015[249]		Gender	Current abscess	OR Male: Reference Female: 2.56 (1.10 – 5.97)	aOR 2.35 (0.72 – 7.64)	
Stein 2020[250]		Sex (male)	Number of ED visits for injecting-related infections in 12 months following educational intervention		IRR 1.18 (0.70, 1.99)	
Stein 2020[250]		Sex (male)	Number of hospitalizations visits for injecting-related infections in 12 months following educational intervention		IRR 0.91 (0.55, 1.51)	
Wilson 2002[251]		Female sex	Infective endocarditis, self-report + medical chart review	OR 2.56 (1.54–4.24)	aOR 3.26 (1.73–6.14)	
Wright 2020[252]		Sex	Lifetime SSTI, self-report	Male: 216/341		

				Female: 75/114 p=0.64		
Wurcel 2016[63]8/29/2023 5:27:00 PM		Gender	Percentage of hospital admissions for IE that are IDU	"There were no significant changes in IDU-IE hospitalizations by gender over time (data not shown)."		
Wurcel 2018[253]		Gender	Abscess ever	Female: 48/88 Male: 77/210 p=0.004		
Wurcel 2018[253]		Gender	Abscess past 30 days	Female: 3/88 Male: 2/210 P=0.044		
Morin 2020[59]		Sex	Infective Endocarditis (diagnostic code in administrative data, but date/timing unclear)	OR Female: 1.2 (1.1–1.3) Male: Ref	aOR Female: 1.2 (1.2–1.3) Male: Ref	
Morin 2020[59]		Sex	Osteomyelitis (diagnostic code in administrative data, but date/timing unclear)	OR Female: 1.0 (0.9–1.2) Male: Ref	aOR Female: 1.1 (1.0–1.2) Male: Ref	
Morin 2020[59]		Sex	Septic Arthritis (administrative data, but date/timing unclear)	OR Female: 1.0 (0.9–1.2) Male: Ref	aOR Female: 0.8 (0.7–1.0) Male: Ref	
Hope 2015[75]		Gender	Abscess, past 12 months, self-reported	"not associated"		
Hope 2015[75]		Gender	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"not associated"		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Age						
Baltes 2020[254]		Age	Past-year SSTI, self report	18-29: 4/21 30-39: 7/34 40-49: 6/15 50-59: 1/9 60+: 0/1		
Betts 2016[229]		Age 36-45 (Ref 17-35)	Past-month abscess, self-report		aOR Age 17-35: Reference Age 36-45: 0.66 (0.44, 0.98) Age 46-71: 0.84 (0.58, 1.22)	
Binswanger 2000[99]		Age (not defined)	Current abscess or cellulitis on physical examination	"did not differ significantly"		

Cedarbaum 2016[255]		Age <30 years old (vs. 30 or older)	Abscess in past year, self-report	22% vs. 48% (p<0.001)	aOR 0.32 (0.16 – 0.65)	
Cooper 2005[256]		Percent neighborhood residents aged 18-64 (vs. <18 or >64)	Monthly rate of hospitalisation for abscess/cellulitis	IRR 0.94 (0.91–0.97)	aIRR 0.96 (0.95–0.98)	
Cooper 2005[256]		Percent neighborhood residents aged 18-64 (vs. <18 or >64)	Monthly rate of hospitalisation for endocarditis	IRR 0.94 (0.92–0.97)	aIRR 0.98 (0.95–1.01)	
Dahlman 2015[230]		Age (years), continuous	Ever had an SSTI	OR 1.00 (0.96 – 1.05)	aOR 1.09 (1.01 – 1.18)	
Dahlman 2017[231]		Age, grouped into 4 groupings (18-29, 30-44, 45-54, 55+)	Past 30-day SSTI	OR not calculated, p = 0.58		
Doran 2020[232] (UAM)		Age (25-34 and 35+ vs. <25 as ref)	Past year SSTI	25-34 years: OR 1.9 (1.2 – 2.9) 35+ years: OR 2.0 (1.3 – 3.1)	25-34 years: aOR 3.9 (1.7 – 8.9) 35+ years: aOR 4.4 (2.0 – 10.0)	
Doran 2020[232] (C&P)		Age (25-34 and 35+ vs. <25 as ref)	Ever SSTI	25-34 years: OR 2.1 (1.1-3.8) 35+ years: OR 3.1 (1.7-5.6)	25-34 years: aOR 2.2 (1.0 – 5.2) 35+ years: aOR 3.2 (1.4 – 7.1)	
Dunleavy 2017[92]		Age (years)	Past year SSTI	<25: 40/149 (27%) 26-30: 75/277 (27%) 31-35: 116/462 (25%) >35: 302/980 (31%) P=0.129		
Fink 2013[100]		Age (years)	Past 6 months abscess, self-reported	<30 years: 15/42 (36%) 30-39 years: 42/139 (30%) 40-49 years: 124/318 (39%) 50+ years: 135/351(38%) P=0.31	aOR <30 years: 1 30-39 years: 0.74 (0.34-1.63) 40-49 years: 1.05 (0.51-2.17) 50+ years: 1.02 (0.49-2.14)	
Hope 2014[125]		Age	Self-reported abscess "(a swelling containing pus)", past 28 days	"No associations found"		
Hope 2014[125]		Age	Self-reported "redness, swelling, and tenderness", past 28 days	"No associations found"		
Hope 2010[101]		Age	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	<25: 249/821 (30%) 25-29: 397/1214 (33%) 30-34: 410/1174 (35%) 35-39: 419/1045 (40%) >=40: 388/955 (41% p<0.001	"Not in final multivariable model"	

Hope 2008[104]		Age in years	Self-reported symptoms of injection site infections (abscess or open wound), past year	ORs <25: 1.0 25-29: 1.8 (1.2 – 2.7) 30-34: 2.1 (1.4 – 3.2) 35+: 1.9 (1.3 – 2.9)	aORs <25: 1.0 25-29: 1.6 (1.0 – 2.6) 30-34: 2.0 (1.3 – 3.2) 35+: 1.9 (1.2 – 3.0)	
Islam 2019[233]		Age (per 10 years)	Invasive bacterial infection (pneumonia, sepsis, endocarditis) at 9 months (self-report & confirmed with medical chart review) (among high-frequency injectors [>1 injection per day])	ORs 1.18 (0.95–1.46)	aORs 1.30 (1.03–1.66)	
Islam 2019[233]		Age (per 10 years)	Invasive bacterial infection (pneumonia, sepsis, endocarditis) at 12 months (self-report & confirmed with medical chart review) (among high-frequency injectors [>1 injection per day])	ORs 1.21 (1.04–1.42)	aORs 1.34 (1.13–1.59)	
Lloyd-Smith 2012[236]		Age, per year older	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	HR, only separate models by sex/gender Among females: HR 1.00 (0.97 – 1.02) Among males: HR 0.99 (0.97 – 1.01)		
Lloyd-Smith 2008[237]		Age, per year older	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR 0.98 (0.96 – 1.00)	aOR 1.00 (0.98 – 1.02)	
Lloyd-Smith 2009[238]		Age, per year older	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR 0.99 (0.97 – 1.01) HR 0.99 (0.97 – 1.00)		
Lloyd-Smith 2010[239]		Age, per year older	Hospitalization for injecting-related infection (cellulitis,	HR 0.98 (0.96 – 1.01)		

			abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis)			
Milloy 2010[240]		Age, per year older	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: Median (IQR): CIRI: 37.5 (32.8-42.3) No CIRI: 39.9 (33.7–46.1) p=0.194 RR for number of ED visits for CIRI during follow-up: 1.00 (0.98–1.02)	aRR for number of ED visits for CIRI during follow-up: 1.01 (0.99–1.03)	
Murphy 2001[241]		Age	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	<30: 16/51 30-39: 47/111 40-49: 67/189 50+: 21/73 p=0.73		
Noroozi 2019[257]		Age	Lifetime injection site infection	ORs <30: 1 30-39: 1.3 (0.1-5.3) 40+: 1.4 (0.2-4.8)	aORs <30: 1 30-39: 1.2 (0.56-2.5) 40+: 1.6 (0.47-4.5)	
Roux 2020[242]		Age, years	At least one cutaneous abscess in the previous six months	OR 1.01 [0.97,1.05]		
Phillips 2017[243]		Age, years	Past year SSTI, self-report	OR 0.99 (0.96, 1.03)	aOR 1.03 (0.97, 1.08)	
Phillips 2008[244]		Age, years	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 1.03 (0.96–1.11)	aOR 1.03 (0.96–1.11)	
Phillips 2010[258]		Age, years	Past year SSTI, self-report	OR 0.98; 0.92–1.04		
Pollini 2010[245]		Age, years	Past 6-months abscess	Median age (IQR) Abscess: 39 (33-43) No abscess: 37 (32-43) p=0.14		
Saeland 2014[259]		Age, years	Current abscess. Self-report and confirmed by physical examination.	Mean age (SD) Abscess: 36.9 (7.7)		

				No abscess: 35.1 (7.6) p=0.181		
Safaeian 2000[246]		Age	Infective endocarditis, self-report confirmed through medical chart review	OR <34 years: Ref >34 years: 1.1 (0.6-2.0) [unclear what happens to people who are exactly 34]		
Safaeian 2000[246]		Age	Abscess, self-report	OR <34 years: Ref >34 years: 1.4 (1.0-1.8) [unclear what happens to people who are exactly 34]		
Shah 2020[247]		Age, years	Endocarditis	Mean (SD) Endocarditis: 35.5 (8.4) No endocarditis: 40.0 (11.0) p=0.034		
Sierra 2006[248]		Age, years	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	Mean (range) Cases: 30.1 (22-41) Controls: 27.5 (20-43) P=0.9		
Stein 2020[250]		Age	Number of ED visits for injecting-related infections in 12 months following educational intervention		IRR 1.10 (0.97, 1.02)	
Stein 2020[250]		Age	Number of hospitalizations visits for injecting-related infections in 12 months following educational intervention		IRR 1.01 (0.99, 1.03)	
Summers 2017[260]		Age (categories undefined)	Past year abscess, self-report	OR 1.05 [1.02, 1.09]	aOR 1.06 [0.97, 1.15]	
Thønnings 2020[261]		Age (years)	Bacteraemia, among hospitalised PWID	OR 1.02 (0.99-1.05)	aOR 3.46 (1.30 – 9.23)	
Wilson 2002[251]		Age, >38 years	Infective endocarditis, self-report + medical chart review	OR 1.11 (0.67–1.83)		
Wright 2020[252]		Age	Lifetime SSTI, self-report	OR <35 years: Ref 35-44 years: 1.92 (1.05 – 3.51)	aOR <35 years: Ref 35-44 years: 2.03 (1.11–3.71)	

				45+ years: 3.32 (1.90 – 5.82)	45+ years: 3.68 (2.09–6.50)	
Wurcel 2016[63]		Age groups, over time	Percentage of hospital admissions for IE that are IDU	"…the percentage of IDU-IE hospitalizations among young adults (15–34 years) steadily increased from 2000 to 2013, with a steep increase from 2008 to 2013 (27.7%–42.0%; P < .001 using χ2 test for trend in proportions). In contrast, IDU-IE rates among middle-aged adults (ages 35–54) steadily decreased between 2000 and 2013 (67.2%–39.9%; P < .001)."		
Wurcel 2018[253]		Age, years	Abscess ever	OR Among females: 0.97 (0.90, 1.04) Among males: 0.96 (0.92, 1.01)	aOR Among females: 0.89 (0.77, 1.02) Among males: 0.96 (0.88, 1.04)	
Morin 2020[59]		Age, years	Infective Endocarditis (diagnostic code in administrative data, but date/timing unclear)	OR 15-24: 0.9 (0.8–0.9) 25-34: 1.4 (1.3–1.6) 35-44: 2.4 (2.2–2.7) 45-54: 4.2 (3.8–4.7) 55-65: 10.0 (8.7–11.6) 65+: Reference	aOR 15-24: 0.9 (0.8–0.9) 25-34: 1.4 (1.3–1.6) 35-44: 2.3 (2.1–2.6) 45-54: 3.9 (3.5–4.3) 55-65: 8.6 (7.4-10.0) 65+: Reference	
Morin 2020[59]		Age, years	Osteomyelitis (diagnostic code in administrative data, but date/timing unclear)	OR 15-24: 1.4 (1.1–1.7) 25-34: 2.9 (2.3–3.6) 35-44: 4.4 (3.5–5.5) 45-54: 7.0 (5.4–9.0) 55-65: 8.3 (5.8–11.8) 65+: Reference	aOR 15-24: 1.4 (1.1–1.7) 25-34: 2.8 (2.2–3.5) 35-44: 3.9 (3.1–5.0) 45-54: 6.0 (4.7–7.8) 55-65: 6.6 (4.6-9.4) 65+: Reference	
Morin 2020[59]		Age, years	Septic Arthritis (administrative data, but date/timing unclear)	OR 15-24: 1.3 (0.9–1.8) 25-34: 3.1 (2.2–4.3) 35-44: 3.9 (2.8–5.4) 45-54: 5.1 (3.5-7.4) 55-65: 10.2 (6.4-16.1) 65+: Ref	aOR 15-24: 1.3 (0.9–1.8) 25-34: 2.7 (2.0–3.8) 35-44: 3.2 (2.3–4.4) 45-54: 4.1 (2.8–6.1) 55-65: 8.3 (5.2–13.3) 65+: Ref	
Hope 2015[75]		Age, years	Abscess, past 12 months, self-reported	<25: 8/113 25-29: 46/263 30-34: 35/186 >=35: 68/293		

Hope 2015[75]		Age, years	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"not associated"		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Race/Ethnicity						
Baltes 2020[254]		Race	Past-year SSTI, self report	Caucasian: 14/62 African American: 2/4 American Indian: 1/11 Mixed race: 1/3		
Cooper 2005[256]		Percent residents non-Hispanic white (continuous variable)	Monthly rate of hospitalisation for abscess/cellulitis	IRR 0.99 (0.98–1.00)	aIRR 0.99 (0.98–1.00)	
Cooper 2005[256]		Percent residents non-Hispanic white (continuous variable)	Monthly rate of hospitalisation for endocarditis	IRR 0.98 (0.98–0.99)	aIRR 0.99 (0.98–1.00)	
Dahlman 2017[231]		Race, in multiple groups (White, Black, Hispanic, Other, Refused to answer)	Past 30 day SSTI	No effect size calculated, p=0.44 for distribution? When I calculate Non-Hispanic White vs. else, I get: OR 0.70 (0.28 – 1.76)		
Doran 2020[232] (C&P)		Race (White/White British vs. other as ref)	Ever SSTI	OR 1.5 (0.9 – 2.4)		
Fink 2013[100]		Race	Past 6 months SSTI, self-report	Black: 116/311 (37%) White: 66/182 (36%) Latino: 110/302 (36%) Other: 20/48 (42%) P=0.91 When I calculate Non-Hispanic White vs. else, I get: OR 0.96 (0.68-1.35)	Black: 0.95 (0.62-1.45) White: 1 Latino: 0.87 (0.57-1.31) Other: 1.32 (0.66-2.64)	
Milloy 2010[240]		Ethnicity (Aboriginal vs. other)	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: Non-aboriginal: 60/440 Aboriginal: 12/105 p=0.548 RR for number of ED visits for CIRI during follow-up:	aRR for number of ED visits for CIRI during follow-up: 0.71 (0.47–1.07)	

				0.72 (0.47–1.09) (aboriginal vs. other)		
Murphy 2001[241]		Race	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	White: 86/228 Black: 42/140 Hispanic: 14/31 Asian/other: 9/25 p=0.86	Not tested	
Phillips 2017[243]		Non-Latino Caucasian (vs. other)	Past year SSTI, self-report	OR 1.29 (0.64, 2.58)	aOR 0.97 (0.39, 2.41)	
Phillips 2008[244]		Race (Caucasian vs. other)	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 6.91; 0.83–57.20	aOR 6.71; 0.81–55.82	
Phillips 2010[258]		Race (Caucasian vs. other)	Past year SSTI, self-report	OR 0.36; 0.06–2.05		
Safaeian 2000[246]		Race	Infective endocarditis, self-report confirmed through medical chart review	Other: 0/34 Black: 86/533 [Study did not calculate/report OR because 100% of cases were Black people]		
Safaeian 2000[246]		Race	Abscess, self-report	Other: Ref Black: 1.8 (1.0-3.3)		
Shah 2020[247]		Caucasian	Endocarditis	Caucasian: 28/102 Other: 5/33 p=0.17		
Smith 2015[249]		Race	Current abscess	OR African American: Reference Caucasian: 2.20 (0.88 – 5.49) Native American: 7.50 (0.92 – 60.90)	OR African American: Reference Caucasian: 2.21 (0.64–7.58) Native American: 7.35 (0.48–113.36)	
Stein 2020[250]		Non-Latinx white	Number of ED visits for injecting-related infections in 12 months following educational intervention		IRR 0.73 (0.44, 1.21)	
Stein 2020[250]		Non-Latinx white	Number of hospitalizations visits for injecting-related infections in 12 months following educational intervention		IRR 0.91 (0.56, 1.49)	
Summers 2017[260]		White race	Past year abscess, self-report	OR 0.62 [0.30, 1.28]	aOR 1.34 [0.39, 4.61]	

Wurcel 2016[63]		Race	Percentage of hospital admissions for IE that are IDU	"Injection drug use-related IE increased in whites from 40.2% in 2000 to 68.9% in 2013 (P < .001) (Figure 1C)." "Non-white" category appeared stable, but missing data category hugely dropped off so that may explain part of increase in white people?		
Wurcel 2018[253]		White	Abscess ever	OR Among females: 1.82 (0.53, 6.27) Among males: 1.61 (0.89, 2.90)	aOR Among females: 2.04 (0.29, 14.22) Among males: 1.35 (0.65, 2.78)	
Education						
Baltes 2020[254]		Education	Past-year SSTI, self report	Less than high school: 3/15 High school equivalent: 8/31 Some college: 7/29 Associate's degree: 0/4 Bachelor's degree or higher: 0/1		
Betts 2016[229]		No tertiary education (vs. tertiary education)	Past-month abscess, self-report		aOR 0.74 (0.55, 1.01)	
Fink 2013[100]		High school education or greater (vs. less than high school)	Past 6-month abscess, self-report	Yes: 186/512 No: 140/384, p=0.46		
Murphy 2001[241]		Education	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Less than high school: 66/178 High school graduate: 85/246 p=0.62		
Noroozi 2019[257]		Education	Lifetime injection site infection	High school diploma or less: 90/210 More than high school: 110/290 P=0.02		
Roux 2020[242]		Education	At least one cutaneous abscess in the previous six months	Less than high school diploma: Ref High school diploma or more: 1.43 [0.75,2.71] OR		
Phillips 2017[243]		Education	Past year SSTI, self-report	OR High school diploma or more: 2.43 (1.20, 4.90)	aOR 4.81 (1.89, 12.3)	

Saeland 2014[259]		Years in school	Current abscess. Self-report and confirmed by physical examination.	Median (IQR) Abscess: 11.0 (9.0, 13.0) No abscess: 11.0 (9.0, 12.0) P=0.617		
Safaeian 2000[246]		Education	Infective endocarditis, self-report confirmed through medical chart review	OR No HS diploma: Ref HS diploma: 0.9 (0.6-1.4)		
Safaeian 2000[246]		Education	Abscess, self-report	OR No HS diploma: Ref HS diploma: 0.8 (0.6-1.0)		
Shah 2020[247]		Completion of secondary	Endocarditis	Completion: 19/50 No completion: 12/73 p=0.010		
Wilson 2002[251]		Education >= 12 years	Infective endocarditis, self-report + medical chart review	OR 0.87 (0.53–1.43)		
Wurcel 2018[253]		High school education or greater	Abscess ever	OR Among females: 0.46 (0.17, 1.21) Among males: 0.75 (0.42, 1.36)	aOR Among females: 0.28 (0.08, 1.08) Among males: 0.48 (0.23, 0.99)	
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Poverty/income/employment						
Ciccarone 2016[137]		Percent unemployment & percent povery (Not otherwise defined)	Proportion of opiate-related hospital admissions comprised of skin and soft-tissue infections	Presented only in figure and does not list numbers. It seems like “Percent unemployment” had point estimate of OR 1.00 and was not statistically significant, and “Percent poverty” had point estimate of OR 0.98 with p<0.05	Unclear / uninterpretable	
Cooper 2005[256]		>/=20% of neighbourhood residents living below poverty level	Monthly rate of hospitalisation for abscess/cellulitis	IRR 1.88 (1.54–2.29)	aIRR 0.67 (0.41–1.09)	
Cooper 2005[256]		>/=20% of neighbourhood residents living below poverty level	Monthly rate of hospitalisation for endocarditis	IRR 1.83 (1.51–2.23)	aIRR 0.93 (0.50–1.74)	
Doran 2020[232] (C&P)		Main Income source (Social Welfare/Illicit	Ever SSTI	OR 2.0 (1.1-3.7)	aOR 2.2 (1.0-4.9)	

		Activities/Other vs. Regular/Temporary Job/Family Support as ref)				
Hope 2014[125]		Main source of income (licit vs. illicit)	Self-reported abscess "(a swelling containing pus)", past 28 days	Licit: 28/588 (4.8%) Illicit: 24/267 (9.0%)		
Hope 2014[125]		Main source of income (licit vs. illicit)	Self-reported "redness, swelling, and tenderness", past 28 days	Licit: 109/588 (19%) Illicit: 68/267 (25%) p=0.023		
Hope 2015[75]		Main source of income (licit vs. illicit)	Abscess, past 12 months, self-reported	Licit: 92/588 Illicit: 68/267		
Hope 2015[75]		Main source of income (licit vs. illicit)	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"Not associated"		
Murphy 2001[241]		Annual family income	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	<$10,000: 125/334 $10,000 to $19,999: 20/70 >=$20,000: 6/20 p=0.24		
Noroozi 2019[257]		Socioeconomic status	Lifetime injection site infection	ORs Low: 3.3 (1.6- 6.4) Moderate: 1.8 (1.2- 4.7) High: 1	aORs Low: 2.4 (1.4- 3.8) Moderate: 1.3 (1.14- 2.16) High: 1	
Noroozi 2019[257]		Employment status	Lifetime injection site infection	Employed: 94/250 Uneployed: 106/250 P=0.02		
Noroozi 2019[257]		Monthly income	Lifetime injection site infection	Less than USD$150: 114/228 USD$150+: 86/272 p=0.01		
Pollini 2010[245]		Income through informal work/odd jobs (vs. not?)	Past 6-months abscess	Yes: 75/377 No: 52/246 P=0.74		
Pollini 2010[245]		Income through legal job with pau (vs. not?)	Past 6-months abscess	Yes: 24/99 No: 103/524 P=0.33		
Roux 2020[242]		Employment	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 0.84 [0.42,1.66]		

Safaeian 2000[246]		"Socioeconomic status" (NOS)	Infective endocarditis, self-report confirmed through medical chart review	OR <$5,000 U.S.: Ref >=$5,000 U.S.: 0.7 (0.4 – 1.3)		
Safaeian 2000[246]		"Socioeconomic status" (NOS)	Abscess, self-report	OR <$5,000 U.S.: Ref >=$5,000 U.S.: 0.7 (0.5 – 0.9)		
Shah 2020[247]		Employed or seasonally employed	Endocarditis	Employed: 3/9 Not employed: 27/121 p=0.43		
Summers 2017[260]		Reported income (categories undefined)… could literally be continuous dollars?	Past year abscess, self-report	OR 1.00 (1.00, 1.00) P=0.61	aOR 1.00 (1.00, 1.00) p=0.71	
Morin 2020[59]		Neighbourhood Income	Infective Endocarditis (diagnostic code in administrative data, but date/timing unclear)	OR 5 (highest): Ref 4: 0.9 (0.8–1.0) 3: 0.9 (0.8–1.0) 2: 0.9 (0.8–1.0) 1 (lowest): 0.9 (0.9–1.0)	aOR 5 (highest): Ref 4: 0.9 (0.8–1.0) 3: 1.0 (0.9–1.1) 2: 0.9 (0.9–1.1) 1 (lowest): 1.0 (0.9-1.1)	
Morin 2020[59]		Neighbourhood Income	Osteomyelitis (diagnostic code in administrative data, but date/timing unclear)	OR 5 (highest): Ref 4: 1.1 (0.9–1.4) 3: 1.0 (0.8–1.3) 2: 1.2 (0.9–1.5) 1 (lowest): 1.3 (1.1–1.6)	aOR 5 (highest): Ref 4: 4.2 (3.0–5.8) 3: 1.0 (0.8–1.3) 2: 1.2 (0.9–1.4) 1 (lowest): 1.3 (1.0–1.6)	
Morin 2020[59]		Neighbourhood Income	Septic Arthritis (administrative data, but date/timing unclear)	OR 5 (highest): Ref 4: 1.0 (0.7–1.4) 3: 1.1 (0.8–1.5) 2: 1.3 (0.9–1.7) 1 (lowest): 1.2 (0.9–1.6)	aOR 5 (highest): Ref 4: 1.0 (0.7–1.4) 3: 1.0 (0.7–1.4) 2: 1.1 (0.8–1.6) 1 (lowest): 1.0 (0.8–1.4)	
Marital status / relationship						
Noroozi 2019[257]		Marital status	Lifetime injection site infection	Single: 106/262 Married: 94/238 P=0.4		
Roux 2020[242]		Living in a couple	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 0.35 [0.17,0.71]	aOR 0.38 [0.17,0.85]	

Migration history						
Doran 2020[232] (UAM)		Born in UK (yes vs. no)	Past year SSTI	OR 1.2 (0.8 0 1.6)		
Hope 2015[75]		Migration, years lived in current area	Abscess, past 12 months, self-reported	<= 1: 11/101 (10.9%) 2-10: 50/198 (25%) 11-20: 19/99 (19%) >=21: 80/457 (18.7%) p=0.019		
Hope 2015[75]		Migration, years lived in current area	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"Not associated"		
Sex work						
Doran 2020[232]		Taken part in transactional sex (Yes in past year or Yes but not in past year, vs. never as ref)	Past year SSTI	Yes, in past year: OR 1.2 (1.0 – 1.1) Yest but not in past year: OR 1.4 (1.0-2.0)		
Hope 2015[75]		Sex, preceding year (paid)	Abscess, past 12 months, self-reported	No: 45/175 Yes, but not paid: 100/626 Yes, but paid: 15/54	No: Ref Yes, but not paid: 0.59 (0.39 – 0.90) Yes, but paid: 1.08 (0.53 – 2.20)	
Hope 2015[75]		Sex, preceding year (paid	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	No: 72/175 Yes, but not paid: 311/626 Yes, but paid: 31/54 p=0.054		
Lloyd-Smith 2005[235]		Sex trade involved, past 6 months	Self-report abscess ("lasting for more than 3 days"), past 6 months	OR 2.4 (1.9 – 3.1)	aOR 1.5 (1.1 – 2.1)	
Lloyd-Smith 2008[237]		Sex trade, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR 1.74 (1.24 – 2.45)	aOR 1.02 (0.67 – 1.56)	
Milloy 2010[240]		Sex-trade participation, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 60/447 Yes: 12/98 p=0.755 RR for number of ED visits for CIRI during follow-up: 1.40 (1.08–1.84)	aRR for number of ED visits for CIRI during follow-up: 1.48 (1.10–1.98)	

Pollini 2010[245]		Principal source of income was through sex work	Past 6-months abscess	Yes: 17/31 No: 110/592 P<0.01	aOR 4.56 (2.08 – 10.00)	
Pollini 2010[245]		Traded sex for money or drugs, past 6 mos.	Past 6-months abscess	Yes: 18/38 No: 109/585 P<0.01		
Saeland 2014[259]		Sex trade involvement (NOS)	Current abscess. Self-report and confirmed by physical examination.	"did not differ" (data not shown)		
Wurcel 2018[253]		Sex work	Abscess ever	OR Among females: 2.19 (0.83, 5.81) Among males: 0.60 (0.26, 1.37)	aOR Among females: 5.42 (1.27, 23.10) Among males: 0.49 (0.20, 1.21)	
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Incarceration history						
Doran 2020[232] (UAM)		Ever imprisoned	Past year SSTI	OR 1.2 (1.1 – 1.5)		
Dunleavy 2017[92]		Ever in prison	Past year SSTI	Yes: 356/1238 (29%) No: 175/622 (28%), p=0.780		
Hope 2014[125]		Imprisonment last year	Self-reported abscess "(a swelling containing pus)", past 28 days	"No associations found"		
Hope 2014[125]		Imprisonment last year	Self-reported "redness, swelling, and tenderness", past 28 days	"No associations found"		
Hope 2015[75]		Imprisonment (Never; Yes, not preceding year; Yes, preceding year)	Abscess, past 12 months, self-reported	"not associated"		
Hope 2015[75]		Imprisonment (Never; Yes, not preceding year; Yes, preceding year)	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"not associated"		
Hope 2010[101]		Ever imprisoned	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	No: 536/1570 (34%) Yes, not last year: 844/2289 (37%) Yes, in last year: 469/1315 (36%) p=0.22		
Hope 2008[104]		Having been imprisoned	Self-reported symptoms of injection site infections (abscess or open wound), past year	"…was not associated with…"		

Lloyd-Smith 2005[235]		Recent incarceration, past 6 months	Self-report abscess ("lasting for more than 3 days"), past 6 months	OR 1.7 (1.3 – 2.1)	aOR 1.7 (1.3 – 2.2)	
Milloy 2010[240]		Recent incarceration, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline: Yes: 31/187 No: 41/358 p=0.093 RR for number of ED visits for CIRI during follow-up: 1.56 (1.32 – 1.85)	aRR for number of ED visits for CIRI during follow-up: 1.56 (1.31-1.85)	
Pollini 2010[245]		Incarcerated, past 6 mos.	Past 6-months abscess	Yes: 72/320 No: 55/303 P=0.14		
Saeland 2014[259]		Imprisonment (NOS)	Current abscess. Self-report and confirmed by physical examination.	"did not differ" (data not shown)		
Injected during incarceration						
Pollini 2010[245]		Injected during incarceration, past 6 mos.	Past 6-months abscess	Yes: 22/86 No: 105/537 P=0.18		
Food insecurity						
Saeland 2014[259]		"Limited access to food" (NOS)	Current abscess. Self-report and confirmed by physical examination.	Limited access: 35/123 No limited access: 12/65 P=0.10		
Saeland 2014[259]		Number of meals last 24 hours	Current abscess. Self-report and confirmed by physical examination.	Median (IQR) Abscess: 2 (1,3) No abscess: 3 (2,4) P=0.01		
Health insurance						
Baltes 2020[254]		Health insurance	Past-year SSTI, self report	Private: 0/5 Medicaid: 9/43 Medicare: 2/2 Other: 1/2 Calculated OR (exposure is Medicaid) 0.79 (0.18-3.56)		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	

Overdose history						
Hope 2014[125]		Overdose history	Self-reported abscess "(a swelling containing pus)", past 28 days	Never: 20/479 (4.2%) Yes, not last year: 13/200 (6.5%) Yes, last year: 19.175 (11%) p=0.007	aOR Never: 1.00 Yes, not last year: 1.39 (0.65 – 2.99) Yes, last year: 2.41 (1.20 – 4.82)	
Hope 2014[125]		Overdose	Self-reported "redness, swelling, and tenderness", past 28 days	Never: 83/479 (17%) Yes, not last year: 43/200 (21%) Yes, last year: 52/175 (30%) p=0.003	Never: 1.00 Yes, not last year: 1.20 (0.76 – 1.88) Yes, last year: 1.84 (1.19 – 2.87)	
Hope 2015[75]		Overdose	Abscess, past 12 months, self-reported	Never: 68/479 Yes, not preceding year: 47/200 Yes, preceding year: 45/175 P=0.001	Never: Ref Yes, not preceding year: 1.50 (0.97 – 2.31) Yes, preceding year: 1.69 (1.09 – 2.63)	
Hope 2015[75]		Overdose	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	Never: 198/479 Yes, not preceding year: 105/200 Yes, preceding year: 110/175 P<0.001	Never: Ref Yes, not preceding year: 1.37 (0.98 – 1.93) Yes, preceding year: 2.00 (1.39 – 2.89)	
Saeland 2014[259]		Number of overdoses (NOS)	Current abscess. Self-report and confirmed by physical examination.	"did not differ" (data not shown)		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted/final effect estimate**	
Drug supply and acquisition						
Type of substance injected						
Heroin						
Baltes 2020[254]		Drug of choice: heroin	Past-year SSTI, self report	Heroin: 6/20 Other: 12/59		
Dahlman 2015[230]		Heroin as "main drug" vs. not"	Ever had an SSTI	OR 2.18 (0.88–5.43)		
Dahlman 2017[231]		Injected heroin, past 6 months	Past 30 day SSTI	OR 1.28 (0.48, 3.44)		
Fink 2013[100]		Type of drug injected: Heroin	Past 6 months SSTI, self-report	Heroin: 312/807 (39%), Not heroin: 8/51 p=0.001		
Hope 2014[125]		Injected heroin last 28 days	Self-reported abscess "(a swelling containing pus)", past 28 days	No: 0/48 (0%) Yes: 52/807 (6.4%) p=0.07		

Hope 2014[125]		Injected heroin last 28 days	Self-reported "redness, swelling, and tenderness", past 28 days	"No associations found"		
Hope 2015[75]		Injected heroin preceding year	Abscess, past 12 months, self-reported	"Not associated"		
Hope 2015[75]		Injected heroin preceding year	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"Not associated"		
Hope 2010[101]		Opiate use in past year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	Opiate, no stimulant: 688/2105 (33%) Stimulant, no opiate: 39/206 (19%) Stimulant and opiate: 1136/2898 (39%) p<0.001	aOR Opiate, no stimulant: 1.00 Stimulant, no opiate: 0.49 (0.34-0.71) Stimulant and opiate: 1.24 (1.09-1.40)	
Hope 2010[101]		Opiate use in past year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months (among subgroup reporting injecting in past 4 weeks)	Opiate, no stimulant: 484/1416 (34%) Stimulant, no opiate: 30/144 (21%) Stimulant and opiate: 861/2173 (40%) p<0.001	aOR Opiate, no stimulant: 1.00 Stimulant, no opiate: 0.47 (0.30-0.75) Stimulant and opiate: 1.06 (0.91-1.24)	
Lloyd-Smith 2005[235]		Heroin use, past 6 months	Self-report abscess ("lasting for more than 3 days"), past 6 months	OR Less than daily: Ref Daily use: 1.4 (1.1 – 1.8)		
Lloyd-Smith 2012[236]		Heroin injecting, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	OR Less than daily: Ref Daily use: 1.44 (1.00 – 2.07) Among females: HR 1.55 (1.01 – 2.37) Among males: HR 1.13 (0.85 – 1.51)	aHR, only separate models by sex/gender Among females: aHR 1.22 (0.79 – 1.90) Among males: Not reported (because not included in stepwise regression)	
Lloyd-Smith 2008[237]		Heroin injection, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Less than daily: Ref Daily use: 1.53 (1.14 – 2.04)	aOR Less than daily: Ref Daily use: 1.26 (0.93 – 1.72)	
Lloyd-Smith 2009[238]		Heroin injection, past six months	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR Less than daily: Ref Daily use: 1.41 (1.02 – 1.95) HR	aHR 1.52 (1.13 – 2.04)	

				Daily use: 1.82 (1.37 – 2.42)		
Milloy 2010[240]		>= Daily heroin use, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 40/302 Yes: 32/243 p=0.979 RR for number of ED visits for CIRI during follow-up: 0.82 (0.69–0.98)		
Murphy 2001[241]		Ever injected heroin	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Yes: 146/401 No: 5/18 p=0.06		
Phillips 2008[244]		Heroin use days in past month	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 1.00; 0.94–1.06	aOR 1.00; 0.94–1.06	
Phillips 2010[258]		Heroin injection days past month	Past year SSTI, self-report	OR 1.11; 1.04–1.18		
Pollini 2010[245]		Injected heroin (alone) past 6 months	Past 6-months abscess	Yes: 105/502 No: 22/121 P=0.35		
Roux 2020[242]		Heroin injection at least once in previous month	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 2.21 [1.14,4.30]		
Saeland 2014[259]		Heroin on a regular basis	Current abscess. Self-report and confirmed by physical examination.	Heroin: 44/155 No heroin: 3/36 P=0.012		
Shah 2020[247]		Heroin injected	Endocarditis	Heroin: 4/18 No heroin: 29/117 p=1.00		
Sierra 2006[248]		Heroin alone	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	Cases: 0 (n=15 total) Controls: 20 (n=58 total) P<0.001 Heroin alone: 0/20 Other: 15/53		
Smith 2015[249]		Heroin use	Current abscess	Other: 2/31		

				Every day: 25/121		
Wurcel 2018[253]		High heroin injection use in the past 30 days	Abscess ever	OR Among females: 1.50 (0.64, 3.51) Among males: 0.85 (0.49, 1.50)	aOR Among females: 2.33 (0.70, 7.78) Among males: 0.74 (0.37, 1.47)	
Type of heroin						
Ciccarone 2016[137]		Mexican "tar" heroin-dominant cities vs. Colombian powder heroin-dominant cities	Proportion of opiate-related hospital admissions comprised of skin and soft-tissue infections	10.7% in MHD cities vs. 5.2% in CHD cities (p<0.001)	Unclear / uninterpretable Figure 3 shows adjusted odds ratio of 2.05 (p<0.001) for "Percent Mexican-sourced dominant", but units and increments are not provided. Visually extracting from figure, 95%CI appears to be 1.75-2.40.	
Pollini 2010[245]		Form of heroin usually injected (Black tar)	Past 6-months abscess	Black tar: 127/618 Other: 0/5 p=0.25		
Summers 2017[260]		Form of heroin, black tar vs. powder	Past year abscess, self-report	OR 7.93 [3.73, 16.88]	aOR 7.68 [3.01,19.60] This is from "Final model" which was stepwise, after an intermediate model that included all covariates	
Cocaine						
Baltes 2020[254]		Drug of choice: Cocaine	Past-year SSTI, self report	Cocaine: 2/5 Other: 16/74		
Buchanan 2006[264]		Ever injected "crack" cocaine (vs. never injected crack cocaine)	Ever had abscess	OR 1.66 (1.05 – 2.63)	aOR 0.91 (0.53 – 1.57)	
Dahlman 2017[231]		Injected crack or rock cocaine, past 6 months	Past 30 day SSTI	OR 0.95 (0.37, 2.46)		
Dahlman 2017[231]		Injected powder cocaine, past 6 months	Past 30 day SSTI	OR 1.09 (0.38, 3.15)		
Fink 2013[100]		Type of drug injected: Cocaine (powder)	Past 6 months SSTI, self-report	Cocaine (powder): 40/108 (37%), Not cocaine (powder): 280/750 p=0.94		
Fink 2013[100]		Type of drug injected: Cocaine (rock)	Past 6 months SSTI, self-report	Cocaine (rock): 20/53 (38%) Not cocaine (rock): 280/785 p=0.95		

Hope 2014[125]		Injected cocaine last 28 days	Self-reported abscess "(a swelling containing pus)", past 28 days	No: 44/796 (5.5%) Yes: 8/59 (14%) p=0.013		
Hope 2014[125]		Injected crack last 28 days	Self-reported abscess "(a swelling containing pus)", past 28 days	No: 18/425 (4.2%) Yes: 33/430 (7.7%) p=0.034		
Hope 2014[125]		Injected cocaine last 28 days	Self-reported "redness, swelling, and tenderness", past 28 days	"No associations found"		
Hope 2014[125]		Injected crack last 28 days	Self-reported "redness, swelling, and tenderness", past 28 days	No: 78/425 (18%) Yes: 99/430 (23%) p=0.092		
Hope 2015[75]		Injected cocaine preceding year	Abscess, past 12 months, self-reported	No: 123/732 Yes: 37/123	1.78 (1.14 – 2.78)	
Hope 2015[75]		Injected cocaine preceding year	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	No: 334/732 Yes: 70/123		
Hope 2015[75]		Injected crack preceding year	Abscess, past 12 months, self-reported	No: 43/331 Yes: 117/524		
Hope 2015[75]		Injected crack preceding year	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"not associated"		
Hope 2008[104]		Inject crack last 4 weeks	Self-reported symptoms of injection site infections (abscess or open wound), past year	ORs No: 1.0 Yes: 1.7 (1.3 – 2.2)	aORs No: 1.0 Yes: 1.5 (1.1 – 2.0)	
Lloyd-Smith 2005[235]		Cocaine use, past 6 months	Self-report abscess ("lasting for more than 3 days"), past 6 months	OR Less than daily: Ref Daily use: 1.9 (1.5 – 2.5)	aOR Less than daily: Ref Daily use: 1.5 (1.2 – 2.0)	
Lloyd-Smith 2012[236]		Cocaine injecting, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	HR, only separate models by sex/gender Among females: Less than daily: Ref Daily: 1.37 (0.88 – 2.11) Among males: Less than daily: Ref Daily: 1.18 (0.87 – 1.60)		

Lloyd-Smith 2012[236]		Crack use, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	HR, only separate models by sex/gender Among females: Less than daily: Ref Daily: 1.42 (0.90 – 2.24) Among males: Less than daily: Ref Daily: 1.46 (1.10 – 1.94)	aHR, only separate models by sex/gender Among females: Not reported Among males: 1.30 (0.97 – 1.74)	
Lloyd-Smith 2008[237]		Cocaine injection, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Less than daily: Ref Daily use: 1.66 (1.23 – 2.25)	aOR Less than daily: Ref Daily use: 1.41 (1.02 – 1.95)	
Lloyd-Smith 2008[237]		Crack injection, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Less than daily: Ref Daily use: 1.54 (0.96 – 2.46)		
Lloyd-Smith 2009[238]		Cocaine injection, past six months	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR Less than daily: Ref Daily use: 1.57 (1.13 – 2.19) HR Daily use: 1.14 (0.82 - 1.58)		
Lloyd-Smith 2010[239]		Cocaine injection, past six months	Hospitalization for injecting-related infection (cellulitis, abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis)	HR Daily use: 1.75 (1.17 – 2.62)	aHR Daily use: 1.46 (0.94 – 2.25)	
Milloy 2010[240]		>= Daily cocaine use, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 49/381 Yes: 23/164 p=0.713 RR for number of ED visits for CIRI during follow-up: 1.05 (0.85–1.29)		

Murphy 2001[241]		Ever injected cocaine	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Yes: 113/305 No: 18/82 p=0.31		
Phillips 2017[243]		Cocaine use, past 90 days	Past year SSTI, self-report	OR 1.77 (0.83, 3.78)	aOR 1.39 (0.50, 3.91)	
Phillips 2008[244]		Cocaine use days in past month	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 0.97; 0.90–1.04	aOR 0.97; 0.90–1.04	
Roux 2020[242]		Stimulant injection at least once in previous month	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 1.60 [0.88,2.91]		
Shah 2020[247]		Cocaine injected	Endocarditis	Cocaine: 3/19 No cocaine: 30/116 p=0.41		
Shah 2020[247]		Crack injected	Endocarditis	Crack: 0/8 No cocaine: 33/127 p=0.20		
Sierra 2006[248]		Cocaine alone	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	OR 0 (0-1.26) P=0.94		
Smith 2015[249]		Cocaine use	Current abscess	Other: 14/98 Every day: 13/54		
Wurcel 2018[253]		High cocaine injection use in the past 30 days	Abscess ever	OR Among females: 0.47 (0.17, 1.29) Among males: 1.77 (0.89, 3.51)	aOR Among females: 0.27 (0.06, 1.23) Among males: 2.50 (1.06, 5.91)	
Illicit amphetamines / Methamphetamines						
Baltes 2020[254]		Drug of choice: Methamphetamine	Past-year SSTI, self report	Methamphetamine: 7/40 Other: 11/39		
Dahlman 2017[231]		Injected methamphetamine, past 6 months	Past 30 day SSTI	OR 0.70 (0.27, 1.76)		
Doran 2020[232]		Main drug injected in past year (opioids, cocaine, crack, and combinations vs. amphetamine-like drugs as ref)	Past year SSTI	OR 2.0 (1.3 – 3.0)	aOR 1.7 (1.1 – 2.8)	

Doran 2020[232]		Main drug injected in past year (opioids, cocaine, crack, and combinations vs. amphetamine-like drugs as ref)	Ever SSTI	OR 2.5 (0.9 – 6.8)		
Fink 2013[100]		Type of drug injected: Methamphetamines	Past 6 months SSTI, self-report	Methamphetamines: 14/69 (20%), Not methamphetamines: 306/789 (39%) p=0.002		
Hope 2014[125]		Injected amphetamine last 28 days	Self-reported abscess "(a swelling containing pus)", past 28 days	"No associations found"		
Hope 2014[125]		Injected amphetamine last 28 days	Self-reported "redness, swelling, and tenderness", past 28 days	"No associations found"		
Hope 2015[75]		Injected amphetamine preceding year	Abscess, past 12 months, self-reported	"Not associated"		
Hope 2015[75]		Injected amphetamine preceding year	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"Not associated"		
Hope 2008[104]		Injecting amphetamines	Self-reported symptoms of injection site infections (abscess or open wound), past year	"…was not associated with…"		
Lloyd-Smith 2008[237]		Crystal meth injection, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Less than daily: Ref Daily use: 1.48 (0.73 – 3.02)		
Lloyd-Smith 2008[237] #530		Crystal meth injection, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Less than daily: Ref Daily use: 1.48 (0.73 – 3.02)		
McMahan 2020[389]		Main drug is methamphetamine (vs. main drug is opioids)	Past-year injecting-related infection ("an abscess, skin infection such as cellulitis, blood clot or blood infection like sepsis, or endocarditis")	"A smaller proportion of participants whose main drug was methamphetamine… had an infection that was likely related to injection in the past 12 months (26 % vs 48 %, p < .001) compared to participants whose main drug was an opioid."		

				Methamphetamine: 36/140 Opioids: 214/443		
Murphy 2001[241]		Ever injected amphetamine	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Yes: 81/243 No: 70/111 p=0.27		
Noroozi 2019[257]		Methamphetamine injection during last 6 mo.	Lifetime injection site infection	ORs Yes: 1.7 (1.1-4.52) No: 1	aORs 1.6 (0.48-5.7)	
Pollini 2010[245]		Injected methamphetamine (alone) past 6 months	Past 6-months abscess	Yes: 19/88 No: 108/535 P=0.72		
Saeland 2014[259]		Amphetamine on a regular basis	Current abscess. Self-report and confirmed by physical examination.	Amphetamine: 21/88 No amphetamine: 26/104 P=0.890		
Shah 2020[247]		Crystal methamphetamine	Endocarditis	Crystal meth: 18/98 No: 15/37 p=0.07		
Pollini 2010[245]		Color of meth usually injected	Past 6-months abscess	Clear (crystal): 100/462 Other: 27/161 p=0.26		
Other/Combined stimulant use						
Hope 2010[101]		Stimulant use in past year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	Opiate, no stimulant: 688/2105 (33%) Stimulant, no opiate: 39/206 (19%) Stimulant and opiate: 1136/2898 (39%) p<0.001	aOR Opiate, no stimulant: 1.00 Stimulant, no opiate: 0.49 (0.34-0.71) Stimulant and opiate: 1.24 (1.09-1.40)	
Hope 2010[101]		Stimulant use in past year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months (among subgroup reporting injecting in past 4 weeks)	Opiate, no stimulant: 484/1416 (34%) Stimulant, no opiate: 30/144 (21%) Stimulant and opiate: 861/2173 (40%) p<0.001	aOR Opiate, no stimulant: 1.00 Stimulant, no opiate: 0.47 (0.30-0.75) Stimulant and opiate: 1.06 (0.91-1.24)	
Yeung 2017[139]		Self-reported use of ethylphenidate (a novel psychoactive substance / stimulant associated	Weekly rate of S. pyogenes or S. aureus infections among people who inject drugs		aRR 1.81 (1.12-2.93)	

		with high frequency of injecting)				
Speedball						
Dahlman 2017[231]		Injected speedball, past 6 months	Past 30 day SSTI	OR 0.78 (0.30, 2.01)		
Dahlman 2017[231]		Injected goofball, past 6 months	Past 30 day SSTI	OR 1.17 (0.45, 3.04)		
Fink 2013[100]		Type of drug injected: Speedball	Past 6 months SSTI, self-report	Speedball (heroin+cocaine): 88/211 (42%), Not speedball: 232/647 p=0.13		
Lloyd-Smith 2012[236]		Speedball injecting, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	OR Less than daily: Ref Daily use: 1.77 (1.12 – 2.79) Among females: HR 1.61 (0.97 - 2.65) Among males: HR 1.28 (0.82 – 2.02)		
Lloyd-Smith 2009[238]		Speedball injection, past six months	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR Less than daily: Ref Daily use: 1.96 (1.30 – 2.95) HR Daily use: 1.92 (1.21 – 3.05)	aHR 1.47 (0.95 – 2.26)	
Lloyd-Smith 2010[239]		Speedball injection, past six months	Hospitalization for injecting-related infection (cellulitis, abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis)	HR 1.90 (1.15 – 3.14)	aHR 1.19 (0.69 – 2.07)	
Milloy 2010[240]		>= Daily speedball use, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No speedball use: 63/483 Yes speedball use: 9/62 p=0.747		

				RR for number of ED visits for CIRI during follow-up: 1.24 (0.92–1.67)		
Murphy 2001[241]		Ever injected speedball	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Yes: 133/331 No: 18/75 p<0.001		
Phillips 2010[258]		Speedball injection days past month	Past year SSTI, self-report	OR 1.11; 1.04–1.18		
Pollini 2010[245]		Injected heroin and methamphetamine together, past 6 months	Past 6-months abscess	Yes: 70/318 No: 57/305 P=0.38		
Smith 2015[249]		Speedball	Current abscess	Other: 16/103 Every day: 11/49		
Other or unspecified polydrug use						
Binswanger 2000[99]		"Type of drug injected" (not defined)	Current abscess or cellulitis on physical examination	"did not differ significantly"		
Dunleavy 2017[92]		Poly-drug injection (Defined as use of more than one drug type in past 6 months (where drug type is Opiate, Stimulant or Other including Legal Highs).	Past year SSTI	Yes: 133/300 (44%) No: 399/1567 (26%), p<0.001		
Hope 2010[101]		Stimulant and opiate use, past year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	Opiate, no stimulant: 688/2105 (33%) Stimulant, no opiate: 39/206 (19%) Stimulant and opiate: 1136/2898 (39%) p<0.001	aOR Opiate, no stimulant: 1.00 Stimulant, no opiate: 0.49 (0.34-0.71) Stimulant and opiate: 1.24 (1.09-1.40)	
Hope 2010[101]		Stimulant and opiate use, past year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months (among subgroup reporting injecting in past 4 weeks)	Opiate, no stimulant: 484/1416 (34%) Stimulant, no opiate: 30/144 (21%) Stimulant and opiate: 861/2173 (40%) p<0.001	aOR Opiate, no stimulant: 1.00 Stimulant, no opiate: 0.47 (0.30-0.75) Stimulant and opiate: 1.06 (0.91-1.24)	
Noroozi 2019[257]		"Poly-drug use"	Lifetime injection site infection	Yes: 110/236 No: 90/264 P=0.01		

Roux 2020[242]		Polydrug use in past month (excluding cannabis)	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 1.53 [1.23,1.89]	aOR 1.41 [1.10,1.81]	
Prescription opioids - Injected methadone						
Baltes 2020[254]		Drug of choice: Methadone	Past-year SSTI, self report	Methadone: 1/2 Other: 17/77 Calculated OR 3.52 (0.21-59.43)		
Dahlman 2015[230]		Injected methadone liquid, ever	Ever had an SSTI	OR 1.41 (0.57–3.52)		
Dahlman 2015[230]		Injected methadone tablets, ever	Ever had an SSTI	OR 1.30 (0.42–4.00)		
Roux 2020[242]		Methadone injection at least once in previous month	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 0.32 [0.15,0.68]		
Prescription opioids - Injected buprenorphine						
Dahlman 2015[230]		Injected buprenorphine, ever	Ever had an SSTI	OR 0.95 (0.38–2.36)		
Dahlman 2015[230]		Injected buprenorphine-naloxone, ever	Ever had an SSTI	OR 1.21 (0.42–3.54)		
Prescription opioids (not OAT)						
Baltes 2020[254]		Drug of choice: Opiate pain killers	Past-year SSTI, self report	"Opiate pain killers": 0/2 Other: 18/77		
Shah 2020[247]		Oxycodone hydrochloride tablets (Oxycontin)	Endocarditis	Oxy: 10/53 No Oxy: 59/82 p=0.22 Calculated OR 0.83 (0.36-1.90)		
Shah 2020[247]		Hydromorphone controlled-release capsules (HydromorphContin)	Endocarditis	Hydromorph: 30/113 No Hydromorph: 3/22 p=0.20 Calculated OR 2.29 (0.63-8.29)		
Shah 2020[247]		Hydromorphone tablets (Dilaudid)	Endocarditis	Dilaudid: 21/97 No dilaudid: 12/38 p=0.43		

				Calculated OR 0.59 (0.26-1.38)		
Shah 2020[247]		Fentanyl patch	Endocarditis	Fentanyl patch: 3/4 No patch: 30/131 p=0.45 When I calculate: OR 10.1 (1.01 - 100.70)		
Shah 2020[247]		Fentanyl tablet	Endocarditis	Fentanyl tablet: 1/5 No fentanyl: 32 /130 p=1.00 When I calculate: OR 0.76 (0.08-7.10)	Not tested	
Silverman 2020[390]		Living in regions with high vs. low hydromorphone prescription rates	Endocarditis	"Within the matched cohort, we observed 254 (1·6%) of 16288 admissions with infective endocarditis related to injection drug use in sectors with high hydromorphone prescription rates and 113 (0·7%) of 16288 admissions in sectors with low prescription rates (adjusted OR 2·2, 95% CI 1·8–2·8, p<0·0001).		
Silverman 2020[390]		People who filled a prescription for hydromorphone vs. other opioids	Endocarditis	"Among the matched cohort, we observed 109 (2·8%) admissions with infective endocarditis among patients who filled prescriptions for hydromorphone compared with 41 (1·1%) admissions among those who filled prescriptions for non-hydromorphone opioids (adjusted OR 2·5, 95% CI 1·8–3·7, p<0·0001)."		
Silverman 2020[390]		People who filled a prescription for hydromorphone vs. other opioids	Endocarditis	"Among the matched cohort, we observed 109 (2·8%) admissions with infective endocarditis among patients who filled prescriptions for hydromorphone compared with 41 (1·1%) admissions among those who filled prescriptions for non-hydromorphone opioids (adjusted OR		

				2·5, 95% CI 1·8–3·7, p<0·0001).” “We observed 36 (1·8%) admissions with infective endocarditis among 1989 patients who filled prescriptions for immediate-release hydromorphone and 21 (1·1%) admissions among 1989 matched patients who filled prescriptions of non-hydromorphone opioids (adjusted OR 1·7, 95% CI 0·9–3·6, p=0·072). For controlled-release hydromorphone, we observed 73 (3·9%) admissions compared with 20 (1·1%) admissions among 1895 matched patients who filled prescriptions for nonhydromorphone opioids (adjusted OR 3·3, 95% CI 2·1–5·6, p <0·0001).		
Weir 2019[263]		Trend in proportion of prescription opioids that are hydromorphone	Trend in proportion of endocarditis admissions attributable to injection drug use	Visually compared. Hydromorphone was 16% of outpatient opioid prescriptions at the start of the study period and 53% by the end.		
Prescription stimulants						
Dahlman 2015[230]		Injected methylphenidate, ever	Ever had an SSTI	OR 0.80 (0.31–2.06)		
Shah 2020[247]		Bupropion (Wellbutrin)	Endocarditis	Bupropion: 1/1 No: 32/134 p=0.24 Calculated OR is Infinity.		
Shah 2020[247]		Methylphenidate (Ritalin)	Endocarditis	Methylphenidate: 4/22 No: 29/113 p=0.43 Calculated OR 0.64 (0.20-2.06)		
Other/multiple prescription drugs						

Baltes 2020[254]		Drug of choice: Prescription anxiety drugs	Past-year SSTI, self report	Prescription anxiety drugs: 1/5 Other: 17/74		
Baltes 2020[254]		Drug of choice: "Synthetics"	Past-year SSTI, self report	Synthetics: 0/2 Other: 18/79		
Baltes 2020[254]		Drug of choice: Other	Past-year SSTI, self report	Other: 1/3 Other-other: 17/76		
Dahlman 2015[230]		Injected prescribed drugs (crushed tablets/liquid), ever	Ever had an SSTI	OR 7.50 (2.52–22.32)	aOR 52.15 (5.17–525.67)	
Dahlman 2015[230]		Injected benzodiazepines, ever	Ever had an SSTI	OR 2.44 (0.98–6.04)		
Dahlman 2017[231]		Injected "nonpowder drugs", past 6 months "Nonpowder drugs" meant any of: "prescription pain relievers, prescription tranquilizers or sedatives, prescription stimulants, methadone, buprenorphine, or Suboxone"	Past 30 day SSTI	OR 3.57 (1.23, 10.35)	aOR 2.18 (0.66–7.18)	
Saeland 2014[259]		Flunitrazepam on a regular basis	Current abscess. Self-report and confirmed by physical examination.	Flunitrazepam: 39/130 No flunitrazepam: 8/61 P=0.009		
Saeland 2014[259]		Benzodiazepines (?other than flunitrazepam)	Current abscess. Self-report and confirmed by physical examination.	Benzos: 14/58 No benzos: 33/135 P=0.965		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted/final effect estimate**	
Drug policy change - Policy changes on unregulated drug supply						
DiGiorgio 2019[266]		Implementation of state-wide restrictions on opioid prescribing in Louisiana, USA	Monthly rate of injection drug use-associated spinal epidural abscess	0.54 cases per month to 1.15 cases per month (p = 0.017)		
Weir 2019[263]		Implementation of province-wide delisting of extended-release oxycodone	Quarterly proportion of endocarditis hospital admissions attributed to injection drug use	Non-significant step (p = 0.4) and slope (p = 0.8) change		

Yeung 2017[139]		Implementation of temporary class order on ethylphenidate (a novel psychoactive substance / stimulant associated with high frequency of injecting)	Weekly rate of S. pyogenes or S. aureus infections among people who inject drugs		level change: aRR 1.11 (95% CI 0.46 – 2.70) trend change: aRR 0.88 (95% CI 0.82– 0.94)	
Nagar 2015[267]		Implementation of House Bill 1 (July 2012) in Kentucky, USA, which restricted prescription opioids prescribing and dispensing	Annual rate of hospital admissions for spinal epidural abscess at one teaching hospital in Lexington, Kentucky	"The incidence of intraspinal abscess in subjects with drug abuse diagnosis remained constant between 2010 (n = 3) and 2012 (n = 3). However, it increased twofold (n = 7) in 2013 and then ninefold (n = 27) in 2014.		
Supply network - Person / place of purchase						
Sierra 2006[248]		Purchasing from one particular drug seller who was identified as high risk (likely colonized) during outbreak	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	OR 72 (8 – 3090)		
Sierra 2006[248]		Purchasing from one particular drug selling site, where suspected drug seller worked	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	OR 33.92 (7.44 – 174.93)		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Unstable housing						
Baltes 2020[254]		Homelessness (past 6 months)	Past-year SSTI, self report	Yes: 11/52 No: 7/28		
Betts 2016[229]		Unstable housing (vs. stable housing), self-report	Past-month abscess, self-report		aOR 1.39 (0.97, 1.99)	
Binswanger 2000[99]		Homelessness (not otherwise specified)	Current abscess or cellulitis on physical examination	"did not differ significantly"		
Dahlman 2017[231]		Homeless	Past 30-day skin and soft-tissue infections	OR 1.25 (0.49 – 3.23)		
Doran 2020[232]		Homeless (Street or Hostels)	Past year SSTI	Yes, in past year: OR 1.2 (1.0 – 1.1) *Note that OR is not in between CI… Yes, but not in past year: OR 1.2 (0.9 – 1.4)		

Doran 2020[232]		Ever Street Homeless	Ever SSTI	OR 1.2 (0.8 – 1.9)		
Dunleavy 2017[92]		Ever homeless	SSTI in past year	Yes: 414/1435 (29%) No: 118/430 (27%), p=0.57		
Dunleavy 2017[92]		Homeless in past 6 months	SSTI in past year	Yes: 143/529 (27%) No: 388/1333 (29%), p=0.371		
Fink 2013[100]		Homeless	Past 6-month abscess, self-report	Yes: 175/460 (38%) No: 140/384 (36%)		
Hope 2014[125]		Homelessness	Self-reported abscess "(a swelling containing pus)", past 28 days	"No associations found"		
Hope 2014[125]		Homelessness	Self-reported "redness, swelling, and tenderness", past 28 days	Never: 13/106 (12%) Yes, not last year: 64/319 (20%) Yes, last year: 101/430 (23%) p=0.036		
Hope 2015[75]		Homelessness	Abscess, past 12 months, self-reported	"not associated"		
Hope 2015[75]		Homelessness	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	Never: 33/106 Yes, not preceding year: 156/319 Yes, preceding year: 224/430 P=0.001	Never: 1.00 Yes, not preceding year: 2.01 (1.24 – 3.23) Yes, preceding year: 2.16 (1.36 – 3.45)	
Hope 2010[101]		Homeless last year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	No: 1022/3015 (34%) Yes: 841/2194 (38%) p value not reported	No: 1.00 Yes: 1.18 (1.05-1.33)	
Hope 2010[101]		Homeless last year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months (among subgroup of participants reporting injecting in past 4 weeks)	Yes: 629/1588 (40%) No: 746/2145 (35%) p= 0.002		
Hope 2008[104]		Homeless	Self-reported symptoms of injection site infections (abscess or open wound), past year	ORs Never: 1.0 Over a year ago: 1.7 (1.1 – 2.7) In last year: 1.9 (1.2 – 2.9)		

Lloyd-Smith 2005[235]		Unstable housing, past 6 months	Self-report abscess ("lasting for more than 3 days"), past 6 months	OR 1.3 (1.1 – 1.8)		
Lloyd-Smith 2012[236]		Unstable housing, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	Only separate models by sex/gender Among females: HR 1.68 (1.09 – 2.61) Among males: HR 1.60 (1.18 – 2.17)	Only separate models by sex/gender Among females: aHR 1.12 (0.69 – 1.82) Among males: aHR 1.37 (0.98 – 1.92)	
Lloyd-Smith 2008[237]		Unstable housing, current	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR 1.56 (1.15 – 2.12)	aOR 1.49 (1.10 – 2.03)	
Lloyd-Smith 2009[238]		Unstable housing, past 6 months	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR 1.19 (0.86 – 1.65) HR 1.61 (1.17 – 2.22)	aHR 1.39 (1.02 – 1.88)	
Lloyd-Smith 2010[239]		Unstable housing, current visit	Hospitalization for injecting-related infection (cellulitis, abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis)	HR 1.65 (1.08 – 2.53)	aHR 1.26 (0.79 – 2.02)	
Milloy 2010[240]		Unstable housing, current visit	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 12/168 Yes: 18/109 p=0.259 RR for number of ED visits for CIRI during follow-up: 1.23 (0.98–1.56)	aRR for number of ED visits for CIRI during follow-up: 1.30 (1.01–1.67)	
Noroozi 2019[257]		Housing	Lifetime injection site infection	Homeless: 150/300 Stable housing: 50/245 p=0.02		
Phillips 2017[243]		Homelessness (past 90 d)	Past year SSTI, self-report	OR 0.78 (0.39, 1.56)	aOR 0.52 (0.22, 1.27)	
Phillips 2008[244]		Homeless (how many nights they had spent on	ED visit or hospitalization for skin abscess, cellulitis,	OR 1.00; 0.43–2.32	aOR 1.00; 0.43–2.33	

		the street or in a shelter in the 6-months prior to baseline)	osteomyelitis, or endocarditis; self-report			
Phillips 2010[258]		Homeless	Past year SSTI, self-report	OR 1.22; 0.35–4.27		
Pollini 2010[245]		Homeless, past 6 months	Past 6-months abscess	Yes: 8/22 No: 119/482 p=0.07		
Roux 2020[242]		Slept in the street at least once in prior month	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 2.22 [1.19,4.15]		
Shah 2020[247]		Stable housing	Endocarditis	Stable housing: 12/57 No stable housing: 21/78 p=0.17		
Sierra 2006[248]		Homeless	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	4.22 (1.5-12.5)		
Smith 2015[249]		Housing	Current abscess	Unstable housing: 6/39 Stable housing: 21/113		
Summers 2017[260]		Stably housed	Past year abscess, self-report	OR 3.09 [1.53, 6.24]	aOR 1.28 [0.33, 4.94]	
Thønnings 2020[261]		Homeless	Bacteraemia, among hospitalised PWID	OR 0.74 (0.38–1.45)		
Wilson 2002[251]		Homeless	Infective endocarditis, self-report + medical chart review	OR 0.78 (0.46–1.32)		
Wright 2020[252]		Ever homeless	Lifetime SSTI, self-report	Yes: 231/355 No: 60/100 p=0.35		
Wurcel 2018[253]		Homeless ("Do you consider yourself homeless?")	Abscess ever	OR Among females: 2.33 (0.77, 7.12) Among males: 0.69 (0.30, 1.56)	aOR Among females: 1.99 (0.48, 8.27) Among males: 0.40 (0.16, 1.00)	
Social context of injecting						
Pollini 2010[245]		Injected drugs alone, past 6 mos.	Past 6-months abscess	Yes: 71/349 No: 56/274 p=0.99		
Pollini 2010[245]		Injected drugs with friends, past 6 mos.	Past 6-months abscess	Yes: 58/282 No: 69/341 p=0.79		

Pollini 2010[245]		Injected drugs with family member/spouse, past 6 mos.	Past 6-months abscess	Yes: 20/55 No: 107/568 P<0.01		
Roux 2020[242]		Context of injecting	At least one cutaneous abscess in the previous six months	OR Alone or did not inject: Ref With someone else: 0.90 [0.48,1.68] In group: 2.28 [0.90,5.80] 0.083		
Smith 2015[249]		With whom do you inject	Current abscess	OR Alone: Reference Friends: 1.37 (0.45–4.18) Family member or partner: 3.78 (1.38–10.31)	OR Alone: Reference Friends: 1.66 (0.42–6.47) Family member or partner: 4.06 (0.99–16.58)	
Public injecting						
Dahlman 2017[231]		Never injecting publicly vs. other response	Past 30 day SSTI	OR Never: Ref Other: 1.15 (0.44 – 2.96)		
Milloy 2010[240]		Public injection, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 62/506 Yes: 10/39 p=0.0.017 RR for number of ED visits for CIRI during follow-up: 1.40 (1.01–1.95)	aRR for number of ED visits for CIRI during follow-up: 1.35 (0.97–1.88)	
Roux 2020[242]		Injected in public settings	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 1.67 [0.94,2.97]		
Trayner 2020[391]		Public injecting	Past year SSTI, self-report	OR 1.67 (1.24 to 2.23)	aOR 1.42 (1.17 to 1.73)	
Assisted injecting / require help to inject						
Dahlman 2017[231]		Injected by another person, past 30 days	Past 30 day SSTI	OR 2.63 (1.02, 6.78)	aOR 2.08 (0.72–5.65)	
Lee 2013[268]		Requiring help injecting, past 6 moths	Past 6 month soft-tissue infections	OR 3.51 (1.43 – 8.64)	aOR 3.02 (1.14 – 7.72)	
Lloyd-Smith 2012[236]		Require assistance with injecting, past 6 months	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	OR No: Ref Yes: 2.01 (1.40 – 2.89) Among females:	aOR, only separate models by sex/gender Among females: aHR 1.40 (0.92 – 2.13)	

				HR 1.56 (1.03 – 2.37) Among males: HR 1.59 (1.16 – 2.17)	 Among males: 1.38 (1.01 – 1.90)	
Lloyd-Smith 2008[237]		Requiring help injecting, past 6 months	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR 1.85 (1.37 – 2.50)	aOR 1.42 (1.03 – 1.94)	
Lloyd-Smith 2009[238]		Require help to inject	Injecting-related infection cared for at supervised consumption site (from nursing notes)	OR 1.27 (0.91 – 1.77)		
Pollini 2010[245]		Sought someone to help you inject, past 6 mos.	Past 6-months abscess	Yes: 25/70 No: 102/553 P<0.01	aOR 2.06 (1.18 – 3.61)	
Robertson 2010[269]		Sought someone to help you inject, past 6 mos.	Past 6-months abscess	Yes: 123/260 No: 188/796 OR 2.90 2.17–3.89	aOR 2.59 (1.93–3.47)	
Roux 2020[242]		Injection by someone else	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 1.96 [1.08,3.57]	aOR 1.94 [0.96,3.92]	
Study	**Study**	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	**Notes**
Police contacts and arrests						
Cooper 2005[256]		Policing crackdowns on drug use and possession	Monthly rate of hospitalisation for abscess/cellulitis	IRR Preparation: 0.96 (0.90 – 1.02) Initiation month: aRR 0.99 (0.89 – 1.09) First crackdown quarter: 1.06 (0.98 – 1.15) Second crackdown quarter: 1.09 (0.98–1.22) Third crackdown quarter: 0.94 (0.87–1.02)	aIRR Preparation: aRR 0.94 (0.85 – 1.04) Initiation month: aRR 0.89 (0.78-1.00) First crackdown quarter: 0.88 (0.77–1.00) Second crackdown quarter: 0.86 (0.74–0.99)	

				Fourth crackdown quarter: 0.79 (0.71–1.15)	Third crackdown quarter: 0.80 (0.67–0.94) Fourth crackdown quarter: 0.72 (0.57–0.91)	
Cooper 2005[256]		Policing crackdowns on drug use and possession	Monthly rate of hospitalisation for endocarditis	Preparation: aRR 1.11 (0.88–1.40) Initiation month: aRR 0.92 (0.68–1.26) First crackdown quarter: 0.92 (0.73–1.16) Second crackdown quarter: 0.89 (0.73–1.09) Third crackdown quarter: 0.87 (0.66–1.15) Fourth crackdown quarter: 0.62 (0.44–0.89)	Preparation: aRR 1.21 (0.96 – 1.54) Initiation month: aRR 0.96 (0.66–1.41) First crackdown quarter: 0.91 (0.66–1.25) Second crackdown quarter: 0.81 (0.62–1.06) Third crackdown quarter: 0.74 (0.53–1.05) Fourth crackdown quarter: 0.57 (0.35–0.92)	
Hope 2014[125]		Arrested last year	Self-reported abscess "(a swelling containing pus)", past 28 days	"No associations found"		
Hope 2014[125]		Arrested last year	Self-reported "redness, swelling, and tenderness", past 28 days	Not in last year: 44/281 (16%) In last year: 133/574 (23%) p=0.011	Not in last year: 1.00 In last year: 1.61 (1.07 – 2.43)	
Hope 2015[75]		Arrested	Abscess, past 12 months, self-reported	Not in preceding year: 42/281 Yes in preceding year: 118/574		
Hope 2015[75]		Arrested	Cellulitis (redness, swelling, or tenderness), past 12 months, self-reported	"Not associated"		
Pollini 2010[245]		Arrested for sterile syringes, past 6 mos.	Past 6-months abscess	Yes: 14/59 No: 113/564 P=0.50		
Pollini 2010[245]		Arrested for used syringes, past 6 mos.	Past 6-months abscess	Yes: 11/71 No: 116/552 P=0.44		
Pollini 2010[245]		Arrested for track marks, past 6 mos.	Past 6-months abscess	Yes: 29/104 No: 98/519		

				P=0.03		
Pollini 2010[245]		Police asked you for money, past 6 mos.	Past 6-months abscess	Yes: 50/188 No: 77/435 P=0.02		
Pollini 2010[245]		Police affected where you use drugs, past 6 mos.	Past 6-months abscess	Yes: 19/54 No: 108/569 P=0.02	aOR 2.14 (1.15–3.96)	
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Needle and syringe programs						
Bhattacharya 2006[270]		Implementation of needle and syringe program in October 2000	Monthly prevalence of skin abscess in community-based cohort		Abscess rates were as high as 22.6% in September 2000, whereas they declined to very low levels (at times 0%; e.g. during October 2001), after the intervention started.	
Binswanger 2000[99]		Used syringe exchange program, past 30 days	Current abscess or cellulitis on physical examination	1.0 (0.4 – 2.20)		
Dunleavy 2017[92]		High needle and syringe uptake (>/=200% uptake) vs. low	SSTI past year	OR 0.65 (0.53-0.80), p<0.001 High: 270/1085 (25%) Low: 258/767 (34%)	aOR 0.72 (0.58-0.89), p=0.002	
Dunleavy 2017[92]		High paraphernalia uptake (>/=200% uptake) vs. low	SSTI past year	OR 0.71 (0.58–0.87), p=0.001 High: 270/1060 (25%) Low: 258/792 (33%)	aOR 0.77 (0.63–0.95), p=0.015	
Dunleavy 2017[92]		High injecting equipment uptake (>/=200% uptake) vs. low	SSTI past year	OR 0.706 (0.576–0.865), p=0.001 High: 246/979 (25%) Low: 280/869 (32%)	aOR 0.775 (0.628–0.956), p=0.017	
Fink 2013[100]		Syringe exchange program client	SSTI past six months, self-report	Yes: 220/587 (37%) No: 100/270 (37%), p=0.90	aOR 0.91 (0.65–1.27)	

Hope 2010[101]		Used needle exchange last year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	No: 150/566 (27%) Yes: 1713/4643 (37%) P<0.001	No: 1.00 Yes: 1.65 (1.35-2.01)	
Hope 2010[101]		Used needle exchange last year	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months (among subgroup who report injecting in past 4 weeks)	No: 75/270 (28%) Yes: 1300/3463 (38%) P<0.001	No: 1.00 Yes: 1.44 (1.07-1.93)	
Noroozi 2019[257]		NSP utilization during last 6 mo.	Lifetime injection site infection	ORs Yes: 0.4 (0.30-0.71) No: 1	aORs 0.5 (0.32-0.78)	
Tomolillo 2007[271]		Number of needle exchanged, per week	Number of abscesses treated at clinic associated with NSP, per week	"Analyses with ARIMA (p = 1) yielded a significant neg- ative relationship between number of needles exchanged and number of abscesses treated, b = −.001, t (109) = −3.1, p = .002"		
Tomolillo 2007[271]		Number of visits to needle exchange program, per week	Number of abscesses treated at clinic associated with NSP, per week	"ARIMA (p = 1) yielded a significant negative relationship be- tween number of needle exchange program visits and the number of abscesses treated in the community, b = −.12, t (109) = −3.7, p < .001 "		
Tomolillo 2007[271]		Self-report number of needles exchanged (timeline not specified)	Self-report occurrences of abscesses (timeline not specified)	"Regression analysis yielded a significant negative relationship between number of needles exchanged and occurrences of abscesses, R2 = .10, F (1, 60) = 6.41, p = .01, B = −.68 "		
Tomolillo 2007[271]		Self-reported "more use of sterile equipment" (timeline not specified)	Self-report occurrences of abscesses (timeline not specified)	"Use of sterile injecting equipment was not related to abscesses reported, R2 = .10, F (3, 58) = 2.23, p = .10 "		
Wurcel 2018[253]		Obtains needles at Needle Exchange Program	Abscess ever	OR Among females: 0.48 (0.19, 1.24) Among males: 1.43 (0.80, 2.56)	aOR Among females: 0.27 (0.07, 1.01) Among males: 1.31 (0.65, 2.63)	
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Barriers to needle/syringe access - Access to needles/syringes outside of NSP harm reduction programs						

Pollini 2010b [166]		Refused/overcharged syringes when trying to purchase at pharmacy	Abscess last 6 months	Refused/overcharged: 20/100 No: 108/527 P=0.91		
Pollini 2010b [166]		Refused/overcharged syringes when trying to purchase at pharmacy	Abscess ever	Refused/overcharged: 48/100 No: 240/527 P=0.65		
Pollini 2010b [166]		Refused/overcharged syringes when trying to purchase at pharmacy	Median # abscesses (lifetime)	Refused/overcharged: 0 (0-3) No: 0 (0-2) P=0.195	aOR 1.02 (1.00, 1.03)	
Tomolillo 2007[271]		Implementation of policy restricting the number of needles distributed per person and requiring appointment for access	Abscesses treated at clinic associated with needle exchange	Mean (SD) abscesses treated each week - Before policy change: 8.51 (3.18) - After policy change: 14.34 (5.95) Mean (SD) needles distributed each week - Before policy change: 3268.32 (965.25) - After policy change: 470.53 (320.75) No statistical test/p-value		
Supervised consumption site / overdose prevention site / SIF						
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Scherbaum 2010[275]		Attendance at SCS	Past-month skin abscess, self-reported during follow-up interview at SCS	Among 71 people with 1 month follow-up: - 3/71 (4.2%) at baseline vs. 6/71 (8.5%) at 1 month Among 38 people with 2 month follow-up: - 3/38 (7.9%) at baseline vs. 2/38 (5.3%) at 2 months Among 26 people with 3 month follow-up: - 2/26 (7.7%) at baseline vs. 3/26 (1.5%) at 3 months "There were no statistically significant intra-individual changes from M0 to		

				M1, M2, or M3; McNemar tests, all at p > 0.3 or greater"		
Lloyd-Smith 2008[237]		SIF use	Current injecting-related skin infection (self-report & confirmed by study nurse)	OR Less than always: Ref Always use: 0.47 (0.23 – 0.94)	aOR 0.58 (0.29 – 1.19)	
Milloy 2010[240]		>=75% of injections at supervised injection facility	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 49/367 Yes: 23/178 P=0.889 RR for number of ED visits for CIRI during follow-up: 1.25 (1.06–1.48) (yes vs. no)		
Shooting gallery						
Phillips 2008[244]		Shooting gallery use (item on the Risk Assessment Battery [RAB])	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 1.32; 0.31–5.58	aOR 1.33; 0.31–5.73	
Pollini 2010[245]		Locations injected drugs: Shooting gallery	Past 6-months abscess	Yes: 53/286 No: 74/337 P=0.33		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Opioid agonist treatment						
Bassetti 2002[272]		Enrolling in injection opiate maintenance program	Skin infections requiring hospitalisation (Abscesses, phlegmonous infections, erysipelas, ulcerations, and necrosis); frequency and incidence per 100 patient-years before and after	Before admission into program: 20 (3.8/100 patient-years[PY]) During program: 21 (4.6/100PY)		
Bassetti 2002[272]		Enrolling in injection opiate maintenance program	Bloodstream infections requiring hospitalisation; frequency and incidence per 100 patient-years, before and after	Before admission into program: 5 (0.9/100PY) During program: 3 (0.7/100PY)		
Bertin 2020[273]		Prescribed morphine sulfate as opioid	1-year risk of hospitalizations for bacterial infections	Crude incidence per 100,000 PY, by cohort	aHR 2.8 (1.8-4.4) vs. patients starting buprenorphine	

		maintenance, vs. buprenorphine and vs. methadone	associated with intravenous injecting	MS: 7.0 (4.7 – 10.6) Bupe: 2.2 (1.8 – 2.5) Methadone: 1.6 (1.2 – 2.0)	aHR 3.6 (2.2-5.9) vs. patients starting methadone	
Betts 2016[229]		NOT receiving OST treatment (vs. yes receiving)	Past-month abscess, self-report		aOR 0.97 (0.71 – 1.33) so inverse is 1.03 (0.75 - 1.41)	
Dunleavy 2017[92]		Opiate substitution treatment	Past year SSTI, self-report	Past: 139/380 (36%) Never: 42/162 (26%) Current: 352/1320 (27%) OR Past: 1 Never: 0.622 (0.413–0.936), p=0.023 Current 0.646 (0.508–0.822), p<0.001	aOR Past: 1 Never: 0.593 (0.386–0.910),p=0.017 Current: 0.672 (0.524–0.862), p=0.002	
Hope 2010[101]		"Prescribed treatment for their drug use"	Self-report, 'swelling containing pus (abscess), sore, or open wound' at an injection site during the previous 12 months	Never in treatment: 206/706 (29%) Currently scripted: 1321/3570 (37%) Previously scripted: 336/933 (36%) p<0.001		
Hope 2008[104]		Received prescribed substitute drug	Self-reported symptoms of injection site infections (abscess or open wound), past year	ORs Currently: 1.0 Previously: 1.6 (1.2 – 2.2) Never: 0.6 (0.4 – 0.9)	aORs Currently: 1.0 Previously: 1.7 (1.3 – 2.4) Never: 0.9 (0.5 – 1.3)	
Milloy 2010[240]		Current MMT	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	At baseline, ED visit in previous 6 month: No: 53/383 Yes: 19/159 p=0.577 RR for number of ED visits for CIRI during follow-up: 0.88 (0.72–1.08) (yes vs. no)	aRR for number of ED visits for CIRI during follow-up: 0.92 (0.75–1.13)	
Morin 2020[59]		Receiving OAT	Infective Endocarditis (diagnostic code in administrative data, but date/timing unclear)	OR 0.6 (0.5–0.9)	aOR 0.71 (0.55-0.93)	

Morin 2020[59]		Receiving OAT	Osteomyelitis (diagnostic code in administrative data, but date/timing unclear)	OR 0.7 (0.6–0.8)	aOR 0.94 (0.91–0.93)	
Morin 2020[59]		Receiving OAT	Septic Arthritis (administrative data, but date/timing unclear)	OR 0.6 (0.4–0.9)	aOR 0.93 (0.92–0.94)	
Oviedo-Joekes 2017[274]		Injectable OAT with hydromorphone vs. diacetylmorphine	Cellulitis or abscess	HDM: 7 episodes among 100 patients DAM: 17 episodes among 100 patients		
Roux 2020[242]		On opioid agonist treatment	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 0.73 [0.39,1.37]		
Sierra 2006[248] *#482*		Methadone program	Invasive soft-tissue Group A Strep (S. pyogenes) infections in Barcelona	OR 0.03 (0-0.19) Methadone: 0/12 No methadone: 15/46		
Stein 2020[250]		MOUD, past 3 months	Number of ED visits for injecting-related infections in 12 months following educational intervention		IRR 0.98 (0.61, 1.59)	
Stein 2020[250]		MOUD, past 3 months	Number of hospitalizations visits for injecting-related infections in 12 months following educational intervention		IRR 0.95 (0.58, 1.56)	
Thønnings 2020[261]		Opioid substitution treatment	Bacteraemia, among hospitalised PWID	OR 2.25 (0.90–5.60)		
Combined harm reduction interventions						
Dunleavy 2017[92]		Combined Injecting Equipment uptake & current OST Low = Low IE (<200% uptake), no OST; Medium = Low IE + OST, or High IE + no OST; High = High IE + OST (where No OST = never and in the past; OST = currently prescribed).	Past year SSTI, self-report	Low: 117/316 (37%) Medium: 225/777 (28%) High: 184/754 (24%) OR Low: 1 (ref) Medium: 0.693 (0.526–0.914), p=0.022 High: 0.549 (0.414–0.728), p=0.000	aOR Low: 1 (ref) Medium: 0.732 (0.551–0.973), p=0.032 High: 0.622 (0.463–0.834), p=0.002	

Other substance use treatment						
Binswanger 2000[99]		"Substance abuse treatment" (not defined)	Current abscess or cellulitis on physical examination	"did not differ significantly"		
Thønnings 2020[261]		"Contact to an addiction treatment center" (not defined)	Bacteraemia, among hospitalised PWID	OR 1.21 (0.64–2.26)		
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Unhealthy alcohol use						
Dunleavy 2017[92]		Excessive alcohol use (>14units/week for women and >21units per week for men)	Past year SSTI	Yes: 145/475 (30%) No: 385/1388 (28%), p=0.245		
Murphy 2001[241]		Had 1+ alcoholic drink in the past month	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	No: 64/161 Yes: 87/263 p=0.17		
Phillips 2017[243]		AUDIT-C positive "The 3-item Alcohol Use Disorders Identification Test Consumption (AUDIT-C) (Bradley et al., 2007) was used to assess hazardous alcohol use. Scores range from 0 to 12 and a total score above 3 for females"	Past year SSTI, self-report	OR 0.72 (0.36, 1.47)	aOR 0.47 (0.19, 1.17)	
Phillips 2008[244]		AUDIT (>=8)	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 0.83; 0.23–3.08	aOR 0.78; 0.20–3.08	
Phillips 2008[244]		Alcohol intoxication days in past month	ED visit or hospitalization for skin abscess, cellulitis, osteomyelitis, or endocarditis; self-report	OR 1.01; 0.94–1.08	aOR 1.01; 0.94–1.08	
Roux 2020[242]		Harmful alcohol consumption ("AUDIT C	At least one cutaneous abscess in the previous six months	OR No: Ref Yes: 0.89 [0.45,1.77]		

		score ≥3 for women or ≥4 for women")				
Safaeian 2000[246] *#936*		Alcohol use	Infective endocarditis, self-report confirmed through medical chart review	OR No: Ref Yes: 0.6 (0.4 – 1.2)		
Wilson 2002[251]		Alcohol consumption	Infective endocarditis, self-report + medical chart review	None: Ref 1-21 drinks/week: 0.61 (0.35–1.06) >21 drinks/week: 0.53 (0.26–1.09)	None: Ref 1-21 drinks/week: 0.43 (0.22–0.83) >21 drinks/week: 0.32 (0.13–0.78)	
Smoking						
Murphy 2001[241]		Current cigarette smoker	ED visit or hospitalization for injecting-related abscess, recruited for this case-control study	Yes: 142/388 No: 9/36 p=0.16		
Pollini 2010[245]		Smoked methamphetamine, past 6 months	Past 6-months abscess	Yes: 39/134 No: 88/489 p<0.01	aOR 1.65 (1.05–2.62)	
Saeland 2014[259]		Hashish/cannabis	Current abscess. Self-report and confirmed by physical examination.	Cannabis: 24/92 No cannabis: 23/99 P=0.647		
Safaeian 2000[246]		Cigarette smoking	Infective endocarditis, self-report confirmed through medical chart review	OR No: Ref Yes: 0.6 (0.3 – 1.2)		
Safaeian 2000[246]		Cigarette smoking	Abscess, self-report	OR No: Ref Yes: 2.4 (1.5-3.9)	aOR 1.8 (1.1-3.2)	
Study		**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	

8.18 Appendix 18. Narrative synthesis and meta-analyses of studies with outcomes occurring during treatment for injecting-related infections

Included studies assessed several different outcomes that occurred during treatment for injecting-related bacterial infections:

(a) healthcare-seeking for injecting-related infection;
(b) self-treatment of abscess;
(c) hospital admissions among people with an injecting-related SSTI;
(d) premature hospital discharges against medical advice, among people hospitalized with injecting-related infections;
(e) new/secondary bloodstream infections among people receiving antibiotic treatment;
(f) in-hospital death; and
(g) other outcomes (development of endogenous endophthalmitis, and respiratory failure among people with botulism).

Subsections below are orgniazed by outcome and then by each exposure assessed in association with that outcome. See Appendix 17 for a list of all extracted effect estimates in this section.

8.18.1.1 Healthcare-seeking for injecting-related infections

Four studies [Hope 2008; Hope 2015; Lloyd-Smith 2010; Lloyd-Smith 2012][75,104,236,239] assessed associations between seeking treatment for injecting-related infections (once they had developed) and the following exposures: gender/sex; age; income/employment; sex work; unstable housing; incarceration; overdose history; migration status; heroin use; crack and powder cocaine use; amphetamine use; opioid agonist treatment; and supervised consumption site use.

Results were mixed and none of these social-structural, substance use, or health services correlates were significantly associated with seeking treatment for injecting-related infections in more than one study (and for most "non-significant" associations, study authors did not report frequencies or statistics). Seeking medical advice about injection-site infections was associated with female sex in Hope 2015[75] (aOR 3.04, 95%CI 1.14-8.13) but not in Hope 2008[104] (no statistics provided). Recent incarceration was associated with decreased healthcare seeking in Hope 2015[75] for cellulitis (uOR 0.55; 95%CI 0.34- 0.88), but there was no evidence an association for abscess in Hope 2015[75] or for any SSTI in Hope 2008[104]. Seeking medical advice was not associated with age [Hope 2008[104]; Hope

2015[75]]; illicit/illegal work as main source of employment (uOR 1.50; 95%CI 0.99 – 2.78) [Hope 2015[75]]; sex work in the preceding year (uOR 0.45; 0.19-1.07) [Hope 2015[75]]; or unstable housing/homelessness [Hope 2008[104]; Hope 2015[75]].

Seeking medical advice for cellulitis was more likely in people who injected powder cocaine (aOR 2.37; 1.36-4.14, for cellulitis only) and crack cocaine (uOR 1.71; 1.12-2.63) in Hope 2015[75] (vs. people who did not inject cocaine), but not for abscesses in Hope 2015 and not for SSTI in Hope 2008[104]. Advice-seeking was not associated with overdose history [Hope 2008[104]; Hope 2015[75]]; heroin use [Hope 2015[75]]; or amphetamine use [Hope 2008[104]; Hope 2015[75]].

In one study [Hope 2008[104]], people who never received opioid agonist treatment (aOR 0.3; 95%CI 0.1-0.7) and people who previously received opioid agonist treatment (aOR 0.5; 95%CI 0.3-0.9) were less likely to seek health care for an injecting-site infection than people currently receiving opioid agonist treatment. In Lloyd-Smith 2012[236] and Lloyd-Smith 2010[239], people who received a referral from a nurse at a supervised consumption site were more likely to have ED visit or hospital admission (respectively) for an injecting-related infection – however, these analyses were confounded as people with infections would be referred more often than people without infections.

8.18.1.2 Self-treating abscess

Two studies [Fink 2013; Monteiro 2020][100,276] assessed factors associated with self-treatment of an abscess: gender/sex; age; race/ethnicity; unstable housing; heroin use; cocaine use; needle and syringe programs; and several measures of access to health care.

Self-treating abscesses was not associated with most of these, but effect estimates tended to be imprecise with wide confidence intervals. The only statistically significant findings were that self-treating abscess was more common among Latino vs. Black participants in Fink 2013[100] (aOR 2.83; 95%CI 1.65-5.10). Self-treating abscess was also less likely among people who reported having a "usual place" to access health care (aOR 0.61; 95%CI 0.40-0.92) [Fink 2013[100]], but self-treatment was not significantly associated with other measures of health care access (e.g., having a primary care provider or having health insurance). These analyses also had wide confidence intervals that could potentially include meaningful effects.

8.18.1.3 Hospital admission, among people presenting for healthcare with SSTI

Two studies [Hope 2015; Takahashi 2007][75,277] assessed associations between hospital admission (among people with injecting-related infections) and the following exposures: gender/sex; age;

race/ethnicity; education; income/employment; sex work; migration status; unstable housing/homelessness; incarceration history; overdose history; heroin; cocaine; amphetamines; alcohol use; needle and syringe program use; access to health care (e.g., insurance, having a primary care provider); self-treatment of infections; and hospital admission history.

Almost all exposures (e.g., education, income/employment, sex work, incarceration history, health insurance, self-treatment of infections, and others) were not significantly associated with risks of hospital admission, often in the context of small sample sizes and imprecise effect estimates. Reporting two or more hospitalizations in the past year was significantly associated with hospital admission for SSTI in the one study in which it was assessed (aOR 4.4; 95%CI 1.6-11.8) [Takahashi 2007[277]].

The following exposures were inconsistently associated with hospital admission, between multiple studies. Older age was associated with hospital admission in one study [Hope 2015[75]] (for age 35 years or older, uOR 3.71, 95%CI 1.77-7.81) for only those with abscesses (not those with cellulitis), and was not significantly associated with hospital admission in another study [Takahashi 2007[277]]. Similarly, female sex was associated with decreased likelihood (uOR 0.40, 95%CI 0.17-0.96) only for abscess, but not cellulitis, in one study [Hope 2015[75]] and not in a second [Takahashi 2007[277]]. In one study [Takahashi 2007[7]], "living in a shelter" was associated with increased risk of hospital admission (aOR 4.2, 95%CI 1.2–15.1), but "living on the street" was not (aOR 1.4, 95%CI 0.5–4.1). Housing status was not significantly associated with the outcome in a second study [Hope 2015[2]]. In one study [Hope 2015[75]], injecting crack was associated with a large positive effect (aOR 7.49, 2.50-22.50) only for people with injection-site abscesses, and was not significantly associated for people reporting injection-site cellulitis.

8.18.1.4 Against medical advice discharge

Ten studies assessed relationships between social, substance use, and health services exposures and risks of premature hospital discharges against medical advice (among people admitted to hospital with an injecting-related infection).[278–288] The exposures included gender/sex; age; race/ethnicity; income/employment; unstable housing; overdose history; opioid use; cocaine; alcohol; other substance use; health care access; opioid agonist treatment; in-hospital addiction treatment; hospital characteristics; hospital policy; surgery during hospitalization.

8.18.1.4.1 Gender/sex

Six studies assessed relationships between gender/sex and risk of premature hospital discharge against medical advice, among patients hospitalized with injecting-related infections.[278–283] Meta-analysis of two univariate effect estimates resulted in summary uOR 2.34 (95%CI 0.90-6.10; Figure 67). Meta-analysis of six fully-adjusted effect estimate resulted in aOR 1.22 (95%CI 0.99-1.50; Figure 68).

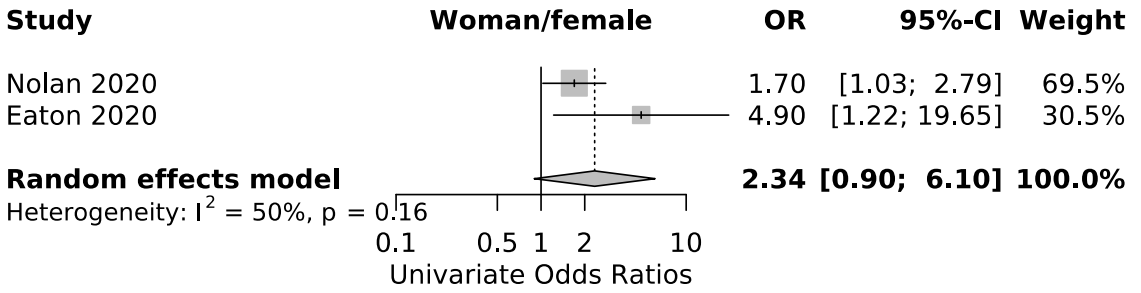

Figure 67. Meta-analysis of univariate effect estimates of relationship between woman/female gender/sex and premature hospital discharge against medical advice, among people hospitalized with injection drug use-associated bacterial infections.

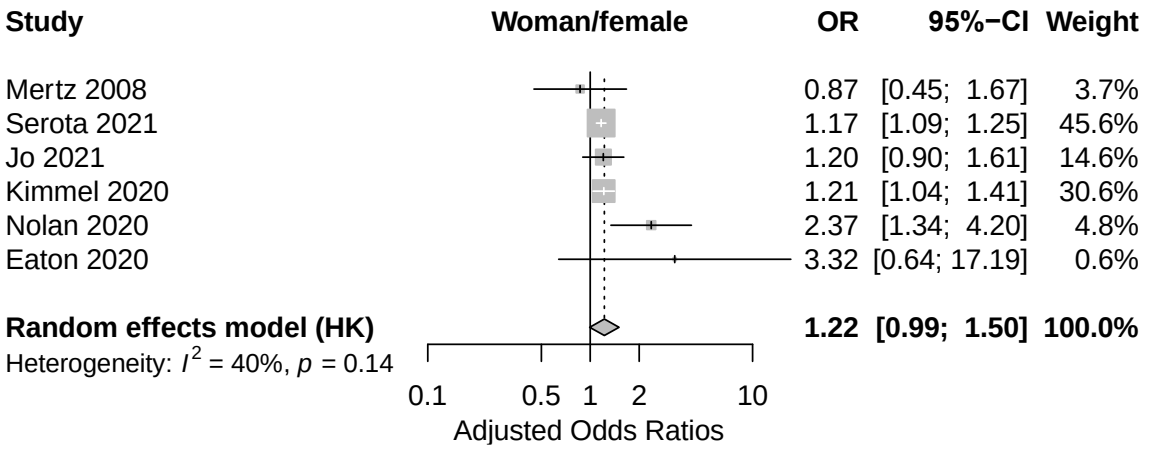

Figure 68. Meta-analysis of fully-adjusted effect estimates of relationship between woman/female gender/sex and premature hospital discharge against medical advice, among people hospitalized with injection drug use-associated bacterial infections.

8.18.1.4.2 Age

Four studies assessed risk of premature hospital discharge against medical advice in relation to age.[279–281,283] Younger age was associated with increased likelihood of premature discharge when measured categorically in two studies[280,283] (e.g., aOR 3.02; 95%CI 2.10-4.34 for age 18-24 vs. 56-65

years)[280]. Younger age was associated with premature hospital discharge when assessed linearly in one study [Jo 2021[279]] (but intervals not defined; aOR 1.04; 95%CI 1.03-1.06) but not in another [Mertz 2008[281]] (per 10-year intervals; aOR 1.25; 0.83-2.00).

8.18.1.4.3 Race/ethnicity

Three studies assessed relationships between race/ethnicity and risk of premature hospital discharge.[279,280,283] Associations were nonsignificant in two studies. In the third [Kimmel 2020][280], compared to white patients, Hispanic patients had a higher risk (aOR 1.31; 95%CI 1.03-1.69). Differences were nonsignificant for Black, Asian, Native American, and "Other" patients.

8.18.1.4.4 Income/employment

In the one study that assessed it [Kimmel 2020[280]], lower neighbourhood income quartile was associated with higher risk of premature hospital discharge (e.g., aOR 1.56; 95% 1.21, 1.99, for lowest income quartile vs. highest income quartile).

8.18.1.4.5 Unstable housing and homelessness

People with unstable housing or homelessness were more likely to have premature discharge against medical advice in one study [Cooksey 2020[284]] (uOR 4.6; 95%CI 1.4-15.0) but not in a second [Nolan 2020[282]] (aOR 1.39; 95%CI 0.62–3.12).

8.18.1.4.6 Overdose history

In one study [Serota 2021[283]], people with diagnostic codes for overdose were not more likely to have premature hospital discharge against medical advice (aOR 0.87; 95%CI 0.74-1.01). It was unclear if these overdose-related codes were during the same hospital admission, or a prior one.

8.18.1.4.7 Substance use (opioids, stimulants, alcohol, other substance use)

Five studies analyzed substance use and risk of premature hospital discharge against medical advice, among people hospitalized with injecting-related infections.[279–283] Compared to people who use only opioids, premature hospital discharge was more common among people who use only stimulants (aOR 1.09; 1.00-1.19) in one study [Serota 2021[283]]; differences were nonsignificant compared to people who use both stimulants and opioids (aOR 1.23, 0.85-1.77 in Jo 2021[279]; aOR 1.19, 95%CI 0.24-5.88 in Nolan 2020[282]). Risk of premature discharge was not associate with sedative or cannabis use in Kimmel 2020[280], and was not associated with alcohol use in Kimmel 2020[280] nor Mertz 2008[281].

8.18.1.4.8 Opioid agonist treatment

Six studies assessed relationships between receiving opioid agonist treatment in hospital and risk of premature discharge against medical advice.[278,279,282,285–287] Among four univariate effect estimates, meta-analysis summary was uOR 0.65 (95%CI 0.42-1.01; Figure 69). Among three fully-adjusted effect estimates, summary was aOR 0.69 (95%CI 0.31-1.56; Figure 70).

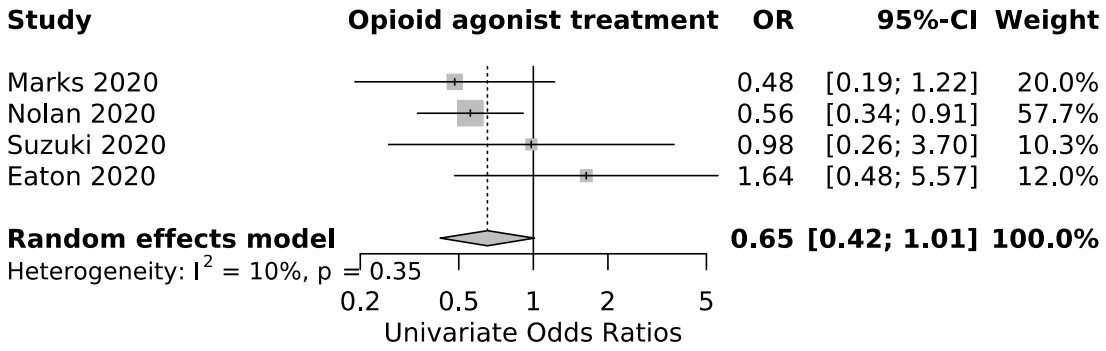

Figure 69. Meta-analysis of univariate effect estimates of relationship between opioid agonist treatment receipt and premature hospital discharge against medical advice, among people hospitalized with injection drug use-associated bacterial infections.

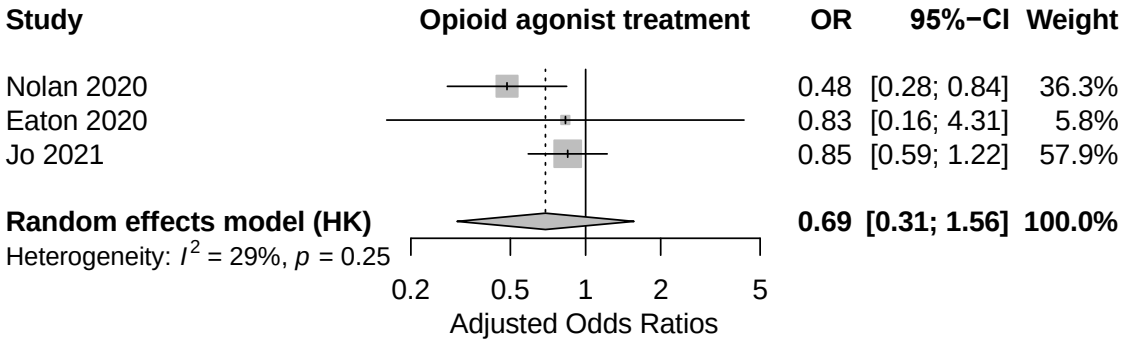

Figure 70. Meta-analysis of fully-adjusted effect estimates of relationship between opioid agonist treatment receipt and premature hospital discharge against medical advice, among people hospitalized with injection drug use-associated bacterial infections.

8.18.1.4.9 In-hospital addiction treatment

Hospital inpatient addiction medicine consultation was associated with lower risk of premature hospital discharge against medical advice (uOR 0.19, 95%CI 0.08–0.48), in one study [Marks 2020[285]].

8.18.1.4.10 Health care access (health insurance)

Increased risk of premature discharge was experienced among people without health insurance in all four studies that assessed it.[279,280,282,283] One univariate effect estimate was uOR 3.93 (95%CI 2.17-

7.13). Summary effect estimate for four adjusted effect estimates was aOR 2.06 (95%CI 1.09-3.91; Figure 71).

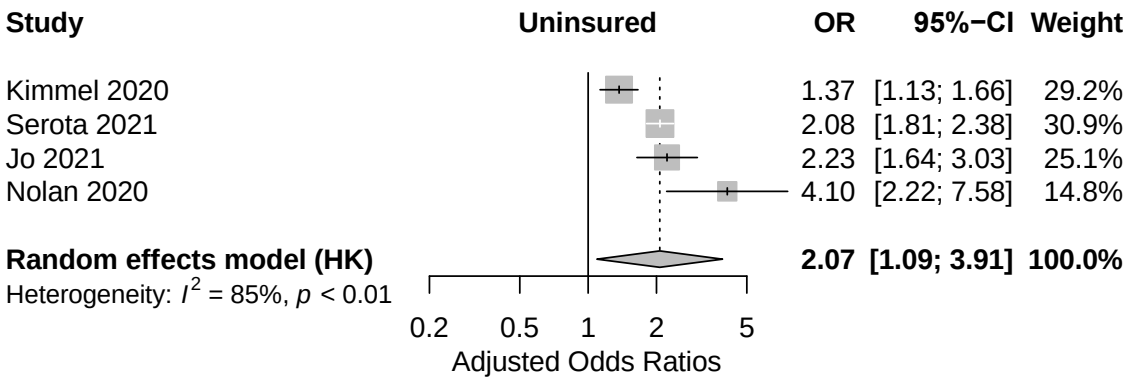

Figure 71. Meta-analysis of fully-adjusted effect estimates of relationship between lack of health insurance and premature hospital discharge against medical advice, among people hospitalized with injection drug use-associated bacterial infections.

8.18.1.4.11 Hospital characteristics

Risk of premature hospital discharge was not associated with hospital location/teaching status, nor hospital bed size, in Kimmel 2020.[280]

8.18.1.4.12 Hospital policies

In one study [Cooksey 2020[284]], following implementation of a new hospital-wide policy (to search patient's belongings, supervise and limit all visitation, restrict cell phone access, provide analgesics and sedatives only in liquid formulation, make patients who inject drugs wear self-identifying gowns, and flag their medical chart), premature hospital discharges increased from 6% to 35% (p<0.001).

In Wang 2020[287], before and after implementation of a hospital protocol to identify opioid use disorder and facilitate opioid agonist treatment, premature discharges were similar (from 42.2% to 40.8%, p=0.85).

8.18.1.4.13 Heart valve surgery during hospitalization

Among patients admitted to hospital with injecting-related endocarditis, having heart valve surgery during the hospital stay was associated with decreased risk of premature hospital discharges in two studies [Kimmel 2020[280]; Rudasill 2019[288]]. One univariate effect estimate was uOR 0.22 (95%CI 0.19-0.27; Rudasill 2019[288]) and one adjusted effect estimate was aOR 0.23 (95%CI 0.16-0.33; Kimmel 2020[280]).

8.18.1.5 New/secondary bloodstream infection during treatment

One study [Tan 2020[289]] assessed the following exposures in relation to developing a new (secondary) bloodstream infection during treatment for injection drug use-associated infective endocarditis: gender/sex; age; unstable housing and homelessness; substance use (heroin, stimulants, polysubstance use, other); substance use treatment; and insertion of peripherally-inserted intravenous central catheters (PICC lines) for parenteral antimicrobial treatment.

Increased risk of new bloodstream infections was seen among people who inject opiates (uOR 7.44; 95%CI 1.77-31.19, and 87% of participants injected opiates) and people who inject more than one substance (uOR 2.57; 1.27-5.21, and 76% injected more than one substance). Reduced risk weas seen among patients receiving an inpatient addiction medicine consultation (aHR 0.53l 95%CI 0.32-0.88).

Differences were nonsignificant for all other exposures, including experiencing homelessness (uOR 1.77; 95%CI 0.99-3.18), referral to outpatient addiction treatment (uOR 1.43; 95%CI 0.87-2.33), and PICC line insertion (aHR 0.60; 95%CI 0.14-2.56).

8.18.1.6 In-hospital death

Five studies assessed exposures associated with in-hospital mortality, during a hospital admission for injecting-related infection: gender/sex; age; race/ethnicity; overdose history; substance use (opioids, stimulants); health care access (insurance); hospital policies; and surgery during hospital admission.[60,281,283,290,291] Associations were nonsignificant for most exposures. Significant associations are highlighted below.

8.18.1.6.1 Race/ethnicity

Hispanic people had higher risk of in-hospital mortality than non-Hispanic white people in one study [Serota 2021[283]] (aOR 1.27; 95%CI 1.01-1.61), while Black people's risk of in-hospital death did not differ from white people (aOR 0.85; 95%CI 0.68-1.07). In another study [Saydain 2010[291]], the effect estimate for race and in-hospital mortality was imprecise and could include meaningful differences (uOR 1.33; 95%CI 0.28-6.30).

8.18.1.6.2 Substance use

In a U.S. nationwide study [Serota 2021[283]], higher risk of in-hospital death was associated with only-stimulant use (vs., only-opioid use; aOR 1.26, 95%CI 1.03-1.46), a history of overdose (aOR 1.26, 95%CI 1.01-1.59), and Medicaid insurance (publicly financed insurance, primarily for people with low

income; aOR 1.41, 95%CI 1.09-1.82 vs. private insurance). People who were uninsured had lower risk of in-hospital death (aOR 0.74, 95%CI 0.55-0.98).

8.18.1.6.3 Hospital policy

Two studies assessed policy change as exposures. Following implementation of a policy of searching, surveillance, and restricting movement of people admitted to hospital with injection drug use-associated endocarditis, in-hospital mortality rates decreased from 11% to 0% (p=0.003) [Cooksey 2020[284]]. Following implementation of a new U.S. nationwide policy of reporting outcomes of aortic valve replacement surgery, the in-hospital mortality rate for patients with injection drug use-associated endocarditis changed from 3.7% (95% CI 2.2%–6.2%) to 3.2% (95% CI 1.8%–5.4%) [Kimmel 2020[292]].

8.18.1.6.4 Heart valve surgery

In both the studies that assessed it [Martín-Dávila 2005[290]; Rudasill 2019[288]], receiving valve surgery during hospitalization with injection drug use-associated endocarditis was associated with decreased in-hospital mortality.

8.18.1.7 Other outcomes during treatment

One study [Uppuluri 2021[227]] on risk factors for endogenous endophthalmitis among patients with injecting-related infections found these associated with female sex, non-white race/ethnicity, and infection of a central intravenous catheter. Endophthalmitis was less common among people with diagnostic codes for alcohol use disorder. One study [Sandrock 2001[293]] on risk factors for respiratory failure among people who inject drugs with botulism, identified no significant differences by gender or age.

8.19 Appendix 19. List of exposure-outcome pair effect estimates for studies where outcome occurs during treatment of injecting-related bacterial infections drug use-associated bacterial and fungal infections, included in quantitative systematic review.

Study	Exposures	Outcomes	Unadjusted effect estimate	Adjusted effect estimate	
Outcome: healthcare seeking for injecting-related infections					
Exposures: Gender/sex					
Hope 2008[104]	Gender	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Hope 2015[75]	Gender	Seeking medical advice about an injection-site abscess, past 12 months	Male: 79/121 Female: 33/39 P=0.022	Male: Ref Female: 3.04 (1.14 – 8.13)	
Hope 2015[75]	Gender	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	Male: 105/306 Female: 54/109 P=0.005	Male: Ref Female: 2.41 (1.49 – 3.91)	
Age					
Hope 2008[104]	Age	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Hope 2015[75]	Age	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Age	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	"not associated"		
Income/employment					
Hope 2015[75]	Main source of income	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Main source of income	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	Licit: 95/272 Illicit: 63/141 P=0.053		
Sex work					
Hope 2015[75]	Sex preceding year (paid / sex work)	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Sex preceding year (paid / sex work)	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	No: 29/72 Yes, but not paid: 111/311 Yes, but paid: 18/30 P=0.03		
Housing					

Hope 2008[104]	Homelessness	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Hope 2015[75]	Homelessness	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Homelessness	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	"not associated"		
Incarceration					
Hope 2008[104]	Having been imprisoned	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Hope 2015[75]	Imprisonment	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Imprisonment	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	Never: 31/81 Yes, not preceding year: 88/202 Yes, preceding year: 39/131 P=0.04		
Overdose history					
Hope 2008[104]	Having had an overdose	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Migration status					
Hope 2015[75]	Migration, years lived in current area	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Migration, years lived in current area	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	"not associated"		
Heroin					
Hope 2015[75]	Injecting heroin, predecing year	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Injecting heroin, predecing year	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	"not associated"		
Cocaine					
Hope 2008[104]	Injecting crack-cocaine	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Hope 2015[75]	Injected cocaine preceding year	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		

Hope 2015[75]	Injected cocaine preceding year	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	No: 119/344 Yes: 40/71 P<0.001	No: Ref Yes: 2.37 (1.36 – 4.14)	
Hope 2015[75]	Injected crack preceding year	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Injected crack preceding year	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	No: 45/149 Yes: 113/265 P=0.012 1.71 (1.12-2.63)		
Amphetamines					
Hope 2008[104]	Injecting amphetamines	Seeking health care among those having had injection site infections in the previous year	"…was not associated with…"		
Hope 2015[75]	Injected amphetamines preceding year	Seeking medical advice about an injection-site abscess, past 12 months	"not associated"		
Hope 2015[75]	Injected amphetamines preceding year	Seeking medical advice about injection-site cellulitis ("redness, swelling, and tenderness"), past 12 months	"not associated"		
Opioid agonist treatment					
Hope 2008[104]	Received prescribed substitute drug	Seeking health care among those having had injection site infections in the previous year	ORs Currently: 1.0 Previously: 0.6 (0.4 – 0.9) Never: 0.2 (0.1 – 0.5)	aORs Currently: 1.0 Previously: 0.5 (0.3 – 0.9) Never: 0.3 (0.1 – 0.7)	
Supervised consumption site					
Lloyd-Smith 2012[236]	Referral from nurse at supervised consumption site	ED visit for cutaneous injecting-related infection (admin data) from SIF/community cohort	OR 4.69 (2.76 – 7.97) Among females: HR 5.06 (3.14 – 8.17) Among males: HR 3.28 (2.14 – 5.04)	Among females: aHR 4.48 (2.76 – 7.30) Among males: aHR 2.97 (1.93 – 4.57)	
Lloyd-Smith 2010[239]	Referral from nurse at supervised consumption site	Hospitalization for injecting-related infection (cellulitis, abscess, osteomyelitis, Staph infection, endocarditis, septic arthritis, ulcer, thrombophlebitis, myositis)	HR 2.41 (1.55 – 3.77)	aHR 5.38 (3.39 – 8.55)	
Outcome: self-treated abscess					
Gender/sex					

Fink 2013[100]	Age (years)	Self-treated last abscess, among people ever having an abscess requiring treatment	<30: 14/22 (64%) 30-39: 33/74 (45%) 40-49: 108/209 (52%) 50+: 105/234 (45%) P=0.21	aOR <30: 1 30-39: 0.91 (0.29 – 2.90) 40-49: 1.31 (0.44 – 3.90) 50+: 1.49 (0.49 – 4.56)	
Monteiro 2020[392]	Age (units unknown)	Self-treatment of SSTI among PWID who had SSTI in past year	OR 0.98 (0.95; 1.01)	aOR 0.95 (0.94; 1.01)	
Gender/sex					
Fink 2013[100]	Gender	Self-treated last abscess, among people ever having an abscess requiring treatment	Male: 177/380 Female: 84/164 P=0.67	Male: 1 Female: 1.21 (0.79 – 1.85)	
Monteiro 2020[392]	Sex (male)	Self-treatment of SSTI among PWID who had SSTI in past year	OR 0.60 (0.31; 1.70)	aOR 1.05 (0.40; 2.83)	
Race/ethnicity					
Fink 2013[100]	Race	Self-treated last abscess, among people ever having an abscess requiring treatment	White: 55/109 (50%) Black: 70/186 (38%) Latino: 116/208 (56%) Other: 15/32 (47%) P=0.004	White: 1 Black: 0.60 (0.34 – 1.04) Latino: 1.57 (0.95 – 2.60) Other: Not reported "Latino vs. Black" "Odds Ratio 2.6 (1.66-4.13)" (from table) "AOR 2.83, 1.6-5.1" (from text)	
Monteiro 2020[392]	Race (white)	Self-treatment of SSTI among PWID who had SSTI in past year	OR 1.16 (0.59; 2.28)	aOR 1.06 (0.34; 3.31)	
Monteiro 2020[392]	Hispanic (yes)	Self-treatment of SSTI among PWID who had SSTI	OR 0.92 (0.47; 1.80)	aOR 1.32 (0.55; 3.17)	
Housing					
Fink 2013[100]	Homelessness	Self-treated last abscess, among people ever having an abscess requiring treatment	Yes: 144/294 No: 114/242 P=0.67		
Needle and syringe program					
Fink 2013[100]	Syringe exchange program client	Self-treated last abscess, among people ever having an abscess requiring treatment	Yes: 174/362 No: 87/182	Yes: 0.88 (0.58 – 1.32) No: 1	
Access to healthcare					
Fink 2013[100]	Access to medical care	Self-treated last abscess, among people ever having an abscess requiring treatment	No usual place for care: 110/190 Have a usual place for care: 151/354	No: 1 Yes: 0.61 (0.40 – 0.92)	

			P=0.0007		
Fink 2013[100]	Usual place of care	Self-treated last abscess, among people ever having an abscess requiring treatment	Private doctor's office: 24/36 (67%) Community clinic: 42/97 (43%) Hospital outpatient clinic: 24/84 (29%) Emergency room: 44/93 (47%) Syringe exchange program: 4/4 Other: 19/42 Refuse to answer: 6/10 P<0.0001		
Monteiro 2020[392]	Has a primary care provider (yes)	Self-treatment of SSTI among PWID who had SSTI	OR 0.57 (2.29; 1.12)	aOR 1.14 (0.44; 2.95)	
Monteiro 2020[392]	Trust in the medical profession	Self-treatment of SSTI among PWID who had SSTI	OR 0.89 (0.59; 1.36)	aOR 0.96 (0.53; 1.71)	
Fink 2013[100]	Insurance	Self-treated last abscess, among people ever having an abscess requiring treatment	No insurance: 162/323 Insured: 98/220 P=0.20	No: 1 Yes: 0.92 (0.62 – 1.39)	
Heroin					
Monteiro 2020[392]	Days injecting heroin (past 3 months)	Self-treatment of SSTI among PWID who had SSTI	OR 1.00 (0.99; 1.01)	aOR 1.00 (0.99; 1.01)	
Cocaine					
Monteiro 2020[392]	Days injecting cocaine (past 3 months)	Self-treatment of SSTI among PWID who had SSTI	OR 1.00 (0.99; 1.01)	aOR 0.99 (0.97; 1.01)	
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Outcome: hospital admission for SSTI, among people reporting SSTI					
Age					
Hope 2015[75]	Age	Hospital admission for infection when had injection site abscess, past 12 months	<25: 0/5 25-29: 9/30 30-34: 15/31 >=35: 27/47 P=0.019		
Hope 2015[75]	Age	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	<25: 1/16 25-29: 18/49 30-34: 10/42 >=35: 18/51 P=0.077		

Takahashi 2007[277]	Age	Hospitalized for SSTI, among ED patients with injecting-related infection	Mean age, (SD), yrs Hospitalized: 41 (8) Discharged from ED: 43 (8) P=0.19		
Gender					
Hope 2015[75]	Gender	Hospital admission for infection when had injection site abscess, past 12 months	Male: 41/79 Female: 10/33 P=0.036		
Hope 2015[75]	Gender	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	Male: 36/105 Female: 11/53 P=0.079		
Takahashi 2007[277]	Female	Hospitalized for SSTI, among ED patients with injecting-related infection	Female: 24/52 Male: 31/84		
Race/ethnicity					
Takahashi 2007[277]	Non-Hispanic White	Hospitalized for SSTI, among ED patients with injecting-related infection	Non-Hispanic White: 36/85 Other: 19/51		
Housing					
Takahashi 2007[277]	Living situation	Hospitalized for SSTI, among ED patients with injecting-related infection	OR (95% CI) Owns or rents a home: Ref Lives in a shelter: 5.6 (1.6–19.0)	Owns or rents a home: Reference Lives in a shelter: 4.2 (1.2–15.1) Lives on the streets: 1.4 (0.5–4.1) Other: 1.1 (0.5–2.8)	
Hope 2015[75]	Homelessness (Never; Yes, not preceding year; Yes, preceding year)	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Homelessness (Never; Yes, not preceding year; Yes, preceding year)	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Education					
Takahashi 2007[277]	Graduated from high school/GED	Hospitalized for SSTI, among ED patients with injecting-related infection	Graduated: 42/104 Did not: 13/32 p=0.97		
Income/employment					
Takahashi 2007[277]	Currently employed	Hospitalized for SSTI, among ED patients with injecting-related infection	Employed: 6/15 Unemployed: 49/121 p=1.00		

Hope 2015[75]	Main source of income (licit vs. illicit)	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Main source of income (licit vs. illicit)	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Sex work					
Hope 2015[75]	Sex preceding year (sex work / paid)	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Sex preceding year (sex work / paid)	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Migration					
Hope 2015[75]	Migration, years lived in current area	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Migration, years lived in current area	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Incarceration					
Hope 2015[75]	Imprisonment	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Imprisonment	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	Never: 4/31 Yes, not preceding year: 29/89 Yes, preceding year: 15/39 P=0.052		
Takahashi 2007[277]	Reported time in jail, prison, or juvenile detention	Hospitalized for SSTI, among ED patients with injecting-related infection	History of incarceration: 41/112 Not: 14/24 p=0.18		
Health care access					
Takahashi 2007[277]	Two or more hospitalizations past year	Hospitalized for SSTI, among ED patients with injecting-related infection	OR 2.7 (0.9–7.7)	aOR 4.4 (1.6–11.8)	
Takahashi 2007[277]	Insurance	Hospitalized for SSTI, among ED patients with injecting-related infection	Medicare/Medicaid: 39/79 Self pay: 13/29		

			Other/unknown: 3/31 p=0.96		
Takahashi 2007[277]	Has a primary care provider	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 19/54 No: 36/80 p=0.26		
Takahashi 2007[277]	Considered coming in for the infection. Before today	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 43/106 No: 12/30 p=0.80		
Takahashi 2007[277]	One or more days of ANY symptoms	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 42/101 No: 13/35 p=0.30		
Takahashi 2007[277]	One or more days of SYSTEMIC symptoms	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 50/114 No: 5/22 p=0.30		
Takahashi 2007[7]	Self-treatment with oral antibiotics	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 14/35 No: 41/101 p=1.00		
Takahashi 2007[7]	Self-treatment with incision and drainage	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 22/55 No: 33/81 p=1.00		
Overdose history					
Hope 2015[75]	Overdose history (No; Yes, not preceding year; Yes, preceding year)	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Overdose history (No; Yes, not preceding year; Yes, preceding year)	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Heroin					

Takahashi 2007[277]	Most frequently used drug is heroin only	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 51/119 No: 4/17 p=0.07		
Hope 2015[75]	Injected heroin preceding year	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Injected heroin preceding year	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Cocaine					
Hope 2015[75]	Injected cocaine preceding year	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Injected cocaine preceding year	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Hope 2015[75]	Injected crack preceding year	Hospital admission for infection when had injection site abscess, past 12 months	No: 7/33 Yes: 44/80 P=0.001	No: Ref Yes: 7.49 (2.50 – 22.50)	
Hope 2015[75]	Injected crack preceding year	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	No: 9/45 Yes: 39/114 P=0.079		
Amphetamines					
Hope 2015[75]	Injected amphetamine preceding year	Hospital admission for infection when had injection site abscess, past 12 months	"Not associated"		
Hope 2015[75]	Injected amphetamine preceding year	Hospital admission for infection when had injection site cellulitis (redness, swelling, tenderness), past 12 months	"Not associated"		
Needle and syringe program					
Takahashi 2007[277]	Reported using a needle exchange program	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 51/121 No: 4/15 p=0.14		
Alcohol					
Takahashi 2007[277]	Hazardous drinking	Hospitalized for SSTI, among ED patients with injecting-related infection	Yes: 13/38 No: 42/98 p=0.34		

	(AUDIT-C score >4)				
Outcome: Against medical advice discharge					
Gender/sex					
Eaton 2020[278]	Gender (female)	Patient-directed discharge (among patients being treated for injecting-related infections)	OR 4.89 (1.22-19.65)	aOR 3.31 (0.64-17.19)	
Jo 2021[279]	Biological sex	Patient-directed discharge (among patients with untreated OUD and either endocarditis or osteomyelitis)		aOR Male: 0.83 (0.62 – 1.11) Female: Ref	
Kimmel 2020[280]	Sex	Discharge AMA (Among patients with IDU-IE)		aOR Female: 1.21 (1.04, 1.41) Male: Ref	
Mertz 2008[281]	Male gender	"Patient's non-compliance… "if the patient did not comply with diagnostic measures or adhere to therapeutic measures, left the hospital against medical advice, continued intravenous drug use during hospitalization, smoked in the room, or assaulted hospital staff.""		aOR 1.2 (0.6 – 2.2)	
Nolan 2020[282]	Female	AMA Discharge	OR 1.69 (1.03–2.79)	aOR 2.37 (1.34– 4.20)	
Serota 2021[283]	Biological sex	AMA Discharge		Female: Ref Male: 0.86 (.80, .92)	
Age					
Jo 2021[279]	Age (?continuous)	Patient-directed discharge (among patients with untreated OUD and either endocarditis or osteomyelitis)		aOR 0.96 (0.94, 0.97)	
Kimmel 2020[280]	Age	Discharge AMA (Among patients with IDU-IE)		aOR 18-24: 3.02 (2.10, 4.34) 25-34: 2.87 (2.08, 3.95) 35-44: 2.31 (1.66, 3.21) 45-55: 1.61 (1.16, 1.41) 56-65: Ref	
Mertz 2008[281]	Age (per 10 years older	"Patient's non-compliance… "if the patient did not comply with diagnostic measures or adhere to therapeutic measures, left the hospital against medical		aOR 0.8 (0.5 – 1.2)	

		advice, continued intravenous drug use during hospitalization, smoked in the room, or assaulted hospital staff.""			
Serota 2021[283]	Age	AMA Discharge		aRR 18–34: 4.87 (3.41, 6.96) 35–54: 3.97 (2.79, 5.63) 55–64: 2.20 (1.53, 3.15) 65–75: REF	
Race/ethnicity					
Jo 2021[279]	Ethnicity	Patient-directed discharge (among patients with untreated OUD and either endocarditis or osteomyelitis)		aOR White: 1.24 (0.82 – 1.87) Other: Ref	
Kimmel 2020[280]	Race/Ethnicity	Discharge AMA (Among patients with IDU-IE)		aOR White: Ref Black: 1.13 (0.89 – 1.45) Hispanic: 1.32 (1.03 – 1.69) Asian: 0.59 (0.18 – 1.94) Native American: 1.01 (0.42 – 2.46) Other: 0.99 (0.62 – 1.59)	
Serota 2021[283]	Race	AMA Discharge		aRR Hispanic: 0.97 (.85, 1.10) Non-Hispanic Black: 0.75 (.65, .86) Non-Hispanic White: Ref	
Unstable housing					
Cooksey 2020[284]	Homeless (not otherwise defined)	Hospital discharge against medical advice (among patients being treated for IDU-IE)	OR 4.6 (1.4-15.0)		
Nolan 2020[282]	Unstable housing (not otherwise defined)	AMA Discharge	OR 0.85 (0.54–1.32)	aOR 1.39 (0.62–3.12)	
Health insurance (?same as "access to health care" larger category)					
Jo 2021[279]	Insurance status	Patient-directed discharge (among patients with untreated OUD and either endocarditis or osteomyelitis)		aOR Govt funded insurance: 0.45 (0.33, 0.61)	

				Commercial insurance: 0.28 (0.16 – 0.48) Uninsured: Ref	
Kimmel 2020[280]	Payor	Discharge AMA (Among patients with IDU-IE)		aOR Medicaid: Ref Medicare: 0.75 (0.58 – 0.96) Commercial: 0.57 (0.44 – 0.74) Self: 1.37 (1.13 – 1.66) No charge: 1.24 (0.79 – 1.94) Other: 0.70 (.046 – 1.05)	
Nolan 2020[282]	Uninsured	AMA Discharge	OR 3.93 (2.17–7.13)	aOR 4.10 (2.22–7.58)	
Serota 2021[283]	Insurance	AMA Discharge		aRR Private: Ref Medicare: 1.09 (.93, 1.29) Medicaid 1.49 (1.29, 1.72) Uninsured 2.07 (1.81, 2.38)	
Income/employment					
Kimmel 2020[280]	Zip Code Income Quartile	Discharge AMA (Among patients with IDU-IE)		aOR Quartile 1 (lowest): 1.56 (1.21, 1.99) Quartile 2: 1.24 (0.96, 1.60) Quartile 3: 1.16 (0.89, 1.52) Quartile 4 (highest): Ref	
Inpatient addiction medicine consultation					
Marks 2020[285]	Inpatient addiction medicine consultation (during hospitalization with endocarditis, fungemia, bacteremia, necrotizing fasciitis or myositis, septic joint, epidural	"Elopement or discharged AMA"	0.19 (0.08 – 0.48)		

	abscess, osteomyelitis)				
Opioid agonist treatment					
Eaton 2020[278]	MOUD	Patient-directed discharge (among patients being treated for injecting-related infections)	OR 1.63 (0.48-5.57)	aOR 0.83 (0.16-4.31)	
Jo 2021[279]	Initiation of OAT (but maybe just for treatment of withdrawal, and/or at insufficient dose…)	Patient-directed discharge (among patients with untreated OUD and either endocarditis or osteomyelitis)	MOUD: 49 out of 269 No MOUD: 209 out of 1138 p value not tested	aOR 0.85 (0.59 – 1.22)	
Marks 2020[310]	MOUD prescription at discharge	AMA discharge	RR 0.49 (0.19 – 1.22) (Cannot find frequencies to generate 2X2 table, but 15% of sample experienced AMA discharge		
Nolan 2020[282]	Received MOUD in hospital	AMA Discharge	OR 0.55 (0.34–0.91)	0.49 (0.28–0.84)	
Suzuki 2020[286]	Initiated on MOUD	AMA Discharge (among patients with IDU-IE)	OR 0.98, 95%CI 0.26 to 3.7		
Wang 2020[287]	Any form of medication-assisted therapy (continuation, initiation and linkage, or detox/taper)	AMA discharge (among patients admitted to hospital with injecting-related infections)	No MAT: 59.7% AMA (out of n = 57) MAT: 30.0% (out of n = 90) relative risk [RR] 0.50; 95% confidence interval [CI], 0.34-0.74).		
Overdose history					
Serota 2021[283]	Overdose (NOS)… I think during same admission?	AMA Discharge		aRR 0.87 (.74, 1.01)	
Substance use					

Jo 2021[279]	Cocaine/amphetamine use	Patient-directed discharge (among patients with untreated OUD and either endocarditis or osteomyelitis)		aOR Yes: 1.23 (0.85 – 1.77) No: Ref	
Nolan 2020[282]	Opioid use alone (fentanyl or heroin) without stimulants vs. people who use opioids and stimulants	AMA Discharge	OR 0.54 (0.34–0.87)	aOR 0.84 (0.17–4.06)	
Nolan 2020[282]	Opioid use + methamphetamines (vs. patients using opioid alone or opioid + cocaine)	AMA Discharge	OR 1.86 (1.05–3.29)	aOR 1.83 (0.99–3.41)	
Nolan 2020[282]	Opioid use + cocaine (vs. patients using opioid alone or opioid + methamphetamines)	AMA Discharge	OR 1.35 (0.77–2.36)	aOR 1.38 (0.73–2.59)	
Kimmel 2020[280]	Alcohol	Discharge AMA (Among patients with IDU-IE)		aOR 0.92 (0.73, 1.16)	
Kimmel 2020[280]	Cannabis	Discharge AMA (Among patients with IDU-IE)		aOR 1.26 (0.96, 1.65)	
Kimmel 2020[280]	Sedative	Discharge AMA (Among patients with IDU-IE)		aOR 1.05 (0.64, 1.71)	

Mertz 2008[281]	Alcohol addiction	"Patient's non-compliance… "if the patient did not comply with diagnostic measures or adhere to therapeutic measures, left the hospital against medical advice, continued intravenous drug use during hospitalization, smoked in the room, or assaulted hospital staff.""		aOR 1.2 (0.4 – 1.7)	
Serota 2021[283]	Opioids, stimulants, or opioids+stimulants	AMA Discharge		Opioid only: Ref Opioid+stimulant: 1.28 (1.17, 1.40) Stimulant-only: 1.09 (1.00, 1.19)	
Valve surgery for IE					
Kimmel 2020[280]	CT Surgery	Discharge AMA (Among patients with IDU-IE)		aOR 0.23 (0.16, 0.33)	
Rudasill 2019[288]	Surgery (among patients with IDU-IE)	Discharge AMA	Medical treatment: 4,048/24,314 Surgical treatment: 131/3,073 p<0.001 Calculated OR 0.22 (0.19-0.27)		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Hospital characteristics					
Kimmel 2020[280]	Hospital location/teaching status	Discharge AMA (Among patients with IDU-IE)		aOR Rural: Ref Urban, non-teaching: 1.12 (0.82 – 1.53) Urban, teaching: 0.91 (0.67, 1.24)	
Kimmel 2020[280]	Hospital bed size	Discharge AMA (Among patients with IDU-IE)		aOR Small: Ref Medium: 0.96 (0.76, 1.22) Large: 0.76 (0.61, 0.94)	
Hospital policy					
Cooksey 2020[284]	Implementation of hospital-wide policy: search of patient's belongings, supervised and limited	Hospital discharge against medical advice (among patients being treated for IDU-IE)	6% pre-intervention vs. 35% post-intervention (p<0.001)		

	visitation, restricted cell phone access, analgesics and sedatives provided only in liquid formulation. Patients' wear self-identifying gowns, medical chart is flagged. Coerced (patient's must agree)				
Wang 2020[287]	Implementation of a hospital-wide policy to identify OUD and facilitate MOUD	AMA discharge (among patients admitted to hospital with injecting-related infections)	42.2% (out of 71 hospitalizations) prior to protocol rollout and 40.8% (out of 76 hospitalizations) after protocol (p=0.85)		
Outcome: New bloodstream infection during treatment					
Tan 2020[289]	Age	New bloodstream infection during treatment for IDU-IE	Mean (SD) New BSI: 34.5 (8.1) No new BSI: 36.0 (10.0)		
Tan 2020[289]	Male	New bloodstream infection during treatment for IDU-IE	Male: 38/213 Female: 44/207 Calculated OR 1.24 (0.76-2.02)		
Tan 2020[289]	No fixed address	New bloodstream infection during treatment for IDU-IE	NFA: 20/72 Other: 62/348 Calculated OR 1.77 (0.99-3.18)		
Tan 2020[289]	Injecting opiates	New bloodstream infection during treatment for IDU-IE	Opiates: 80/365 No opiates: 2/55 Calculated OR 7.44 (1.77-31.19)		

Tan 2020[289]	Injecting stimulants	New bloodstream infection during treatment for IDU-IE	Stimulants: 55/272 No stimulants: 27/148 Calculated OR 1.14 (0.68-1.89)		
Tan 2020[289]	Injecting antidepressant	New bloodstream infection during treatment for IDU-IE	Antidepressants: 6/46 No antidepressants: 76/374 Calculated OR 0.59 (0.24-1.44)		
Tan 2020[289]	Polysubstance injection	New bloodstream infection during treatment for IDU-IE	Polysubstance: 72/321 Mono-substance: 10/99 Calculated OR 2.57 (1.27-5.21)		
Tan 2020[289]	Inpatient prescription for opiates	New bloodstream infection during treatment for IDU-IE	Rx for opiates: 82/402 No rx: 0/18 Unable to calculate OR. With continuity correction, 0.11 (0.01-1.76)		
Tan 2020[289]	Consultation with inpatient addictions treatment	New bloodstream infection during treatment for IDU-IE	Consult: 35/156 No consult: 47/264 Calculated OR 1.34 (0.82-2.18)	aHR 0.53 (0.32 – 0.88)	
Tan 2020[289]	Referral to outpatient addictions treatment	New bloodstream infection during treatment for IDU-IE	Referral: 35/151 No consult: 47/269 Calculated OR 1.43 (0.87-2.33)		
Tan 2020[289]	PICC insertion	New bloodstream infection during treatment for IDU-IE		aHR 0.60 (0.14 – 2.56)	
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
In-hospital mortality					
Gender/Sex					
Martín-Dávila 2005[290]	Sex (male)	In-hospital mortality	OR 0.90 (0.10 – 7.70)		
Mertz 2008[281]	Male gender	In-hospital mortality		aOR 1.0 (0.4 – 2.6)	

Saydain 2010[291]	Sex (female)	In-hospital mortality (among patients with IDU-IE who were admitted to intensive care unit)	OR 0.50 (0.10 – 2.47)		
Serota 2021[283]	Biological sex	In-hospital mortality		aRR Male: 1.09 (0.95, 1.27) Female: REF	
Age					
Mertz 2008[281]	Age (per 10 years older)	In-hospital mortality		aOR 2.0 (1.0 – 3.8)	
Saydain 2010[291]	Age, per year	In-hospital mortality (among patients with IDU-IE who were admitted to intensive care unit)	OR 0.99 (0.92 – 1.07)	aOR 0.94 (0.83 – 1.07)	
Serota 2021[283]	Age	In-hospital mortality		aRR 18–34: 0.41 (.30, .56) 35–54: 0.62 (.48, .81) 55–64: 0.90 (.70, 1.15) 65–75: REF	
Meel 2018[60]	Age >/= 30 years	In-hospital mortality (among patients hospitalized with IE from IV nyaope use in South Africa)	OR 3.7 (0.95 – 14.7)	aOR 4.13 (0.89 – 19.17)	
Race					
Saydain 2010[291]	Race: "White/African American"	In-hospital mortality (among patients with IDU-IE who were admitted to intensive care unit)	OR 1.33 (0.28 - 6.30) Unclear which is ref…		
Serota 2021[283]	Race	In-hospital mortality		aRR Hispanic: 1.27 (1.01, 1.61) Non-Hispanic Black: 0.85 (.68, 1.07) Non-Hispanic White: REF	
Substance use					
Serota 2021[283]	Substance use	In-hospital mortality		aRR Opioid+stimulant: 0.99 (.78, 1.25) Stimulant-only: 1.26 (1.03, 1.46) Opioid-only: Ref	
Overdose history					

Serota 2021[283]	"Overdose" (NOS, I think diagnostic codes for overdose during the same hospitalization?	In-hospital mortality		aRR 1.26 (1.01, 1.59)	
Insurance					
Serota 2021[283]	Insurance	In-hospital mortality		aRR Medicare: 0.96 (.74, 1.25) Medicaid: 1.41 (1.09, 1.82) Uninsured: 0.74 (.55, .98) Private: REF	
Surgery in-patient					
Martín-Dávila 2005[290]	Surgery (among patients with IDU-IE)	In-hospital mortality	OR 0.95 (0.92 – 0.98)		
Rudasill 2019[288]	Surgery (among patients with IDU-IE)	In-hospital mortality	Medical treatment: 1,730/24,314 Surgical treatment: 145/3,073 p=0.007 Calculated OR 0.64 (95%CI 0.54-0.77)		
Hospital policies					
Cooksey 2020[284]	Implementation of hospital-wide policy: search of patient's belongings, supervised and limited visitation, restricted cell phone access, analgesics and	In-hospital mortality rate (among patients being treated for IDU-IE)	11% pre-intervention vs. 0% post-intervention (p=0.003)		

	sedatives provided only in liquid formulation. Patients' wear self-identifying gowns, medical chart is flagged. Coerced (patient's must agree)				
Other policies					
Kimmel 2020[292]	to investigate the effect of initiating public reporting of AVR outcomes in January 2013 on rates of valve surgery and in-hospital mortality in IDU and non–IDU-IE cases.	Inpatient mortality	"In the preintervention period, the in-hospital mortality rates were 7.9% (95% CI 6.8%–9.0%) for IDU-IE… In the postintervention period, the proportions of hospitalizations resulting in death were 7.8% (95% CI 7.0%–8.6%) of IDU-IE…"	"In adjusted segmented regression models following backwards selection… the odds of in-hospital mortality during the preintervention period decreased by 2% per quarter for both IDU-IE and non–IDU-IE cases (AOR 0.97, 95% CI 0.97–0.9)… Compared to projected preintervention trends, 2 years after the implementation of public reporting, the in-hospital mortality rate for IDU-IE cases changed from 3.7% (95% CI 2.2%–6.2%) to 3.2% (95% CI 1.8%–5.4%)… a decrease of 16%"	
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Outcome: Respiratory failure in botulism					
Sandrock 2001[293]	Gender	Respiratory failure	Male: 13/15 Female: 2/5 "p=NS"		
Sandrock 2001[293]	Age, yr	Respiratory failure	Average (unclear if mean or median) With RF: 47 Without RF: 40 "p=NS"	q	

Outcome: Injecting-related infection with endogenous endophthalmitis vs. without EE					
Uppuluri 2021[227]	Sex	EE (vs. infection without EE)	OR Women: Ref Men: 1.74 (1.39–2.18)	aOR 1.84 (1.44–2.34)	
Uppuluri 2021[227]	Age group	EE (vs. infection without EE)	OR 21-45: Ref 46-65: 1.23 (1.00–1.51)	aOR 1.12 (0.88–1.42)	
Uppuluri 2021[227]	Race	EE (vs. infection without EE)	OR White: Ref Black: 1.15 (0.86–1.55) Hispanic: 1.34 (1.00–1.81) Asian/Pacific Islander: 4.31 (1.93–9.66) Native American 0.27 (0.02–4.3) Other 0.59 (0.25–1.41)	aOR White: Ref Black: Not tested Hispanic: Not tested Asian/Pacific Islander: 4.41 (1.99–9.77) Native American: Not tested Other: Not tested	
Uppuluri 2021[227]	Cocaine use	EE (vs. infection without EE)	OR 0.57 (0.41–0.79)	aOR 0.80 (0.57–1.12)	
Uppuluri 2021[1,2227]	Amphetamine use	EE (vs. infection without EE)	OR 0.34 (0.15–0.79)	aOR 0.49 (0.21–1.13)	
Uppuluri 2021[227]	Alcohol use disorder	EE (vs. infection without EE)	OR 0.34 (0.22–0.53)	aOR 0.35 (0.22–0.56)	
Uppuluri 2021[227]	Marijuana use	EE (vs. infection without EE)	OR 0.50 (0.27–0.92)	aOR 0.80 (0.43–1.48)	
Uppuluri 2021[227]	Tobacco use	EE (vs. infection without EE)	OR 0.82 (0.66–1.01)	aOR Not tested	
Uppuluri 2021[227]	Infection of central venous line	EE (vs. infection without EE)	OR 4.46 (2.67–7.44)	aOR 1.90 (1.09–3.29)	

8.20 Appendix 20. Narrative synthesis and meta-analyses of studies with outcomes occurring after treatment for injecting-related infections

Included studies assessed several different outcomes that occurred after initial treatment for injecting-related infections:

(a) infection-related rehospitalization;
(b) all-cause rehospitalization;
(c) overdose-related rehospitalization;
(d) all-cause mortality;
(e) other outcomes (failure of outpatient parental antimicrobial therapy [OPAT] and change in visual acuity following treatment for endogenous endophthalmitis).

See Appendix 19 for a list of all extracted effect estimates in this section.

8.20.1.1 Infection-related rehospitalization

Eight studies assessed relationships between the following exposures and infection-related rehospitalization (after people were discharged from an initial hospital admission with injecting-related infections): gender/sex; age; race/ethnicity; rural residency; substance use (injecting prescription opioids); opioid agonist treatment; other substance use treatment; hospital policy; premature hospital discharge against medical advice; cardiac surgery during admission.[261,294–300] Most exposures (including gender/sex, race/ethnicity, rural residency, premature hospital discharge against medical advice, cardiac surgery during admission), were not significantly associated with risks of infection-related rehospitalization, though effect estimates often had wide confidence intervals that could include meaningful differences.

8.20.1.1.1 Age

Increasing age (measured continuously, in years) was associated with increased risk of infection related rehospitalization in one study [Barocas 2020[294]] (aOR 1.01; 95%CI 1.01–1.01), but not in two others [Huang 2018[295]; Thønnings 2020[261]].

8.20.1.1.2 Substance use (prescription opioids)

In one study [Huang 2018[295]], people who had multiple hospital admissions for endocarditis were more likely to inject prescription opioids compared to people who had only one single hospital admission for endocarditis.

8.20.1.1.3 Opioid agonist treatment

Four studies assessed relationships between opioid agonist treatment and infection-related rehospitalization.[261,294,297,300] In univariate analyses, people prescribed opioid agonist treatment had lower rates of rehospitalization (10.3 [95%CI 9.87-10.64] per 100 person-years vs. 18.7 [95%CI 18.53-18.78] per 100 person-years) in one study [Barocas 2020[294]], and rates did not differ between groups in three other studies [Hilbig 2020[297]; Suzuki 2020[300]; Thønnings *2020*[261]]. Two fully-adjusted effect estimates for opioid agonist treatment from the same study [Barocas 2020[294]], were aHR 0.49 (95%CI 0.18-1.23) for infection-related rehospitalization by 30 days and aHR 0.41 (95%CI 0.42–0.91) for infection-related rehospitalization by 1 year. A new hospital policy to identify opioid use disorder and facilitate opioid agonist treatment did not change 90-day rates of infection-related rehospitalization in one study [Ray 2020[299]].

8.20.1.1.4 Other addiction treatment

In two studies [Thønnings 2020[261]*;* Rodger 2019[298]], referrals to outpatient addiction treatment were not associated with risk of infection-related rehospitalization.

8.20.1.2 All-cause rehospitalization

Nine studies assessed factors associated with all-cause rehospitalization (following an initial hospital admission with injecting-related infections): gender/sex; age; race/ethnicity; unstable housing; access to healthcare (health insurance); substance use (heroin, cocaine, methamphetamine, other); opioid agonist treatment; other addiction treatment; hospital policies; antibiotic treatment models; surgery during hospital admission.[279,284,287,288,294,299,301–303] Several of the exposures (including age; unstable housing; health insurance; heroin cocaine; methamphetamine; benzodiazepine use) were not significantly associated with the outcome.

8.20.1.2.1 Gender/sex

Woman/female gender/sex was associated with increased risk of all-cause rehospitalization. Summary meta-analysis of three fully-adjusted effect estimates was aOR 1.22 (95%CI 1.08-1.38; Figure 72). One univariate effect estimate was nonsignificant at uOR 1.23 (95%CI 0.77-1.96).

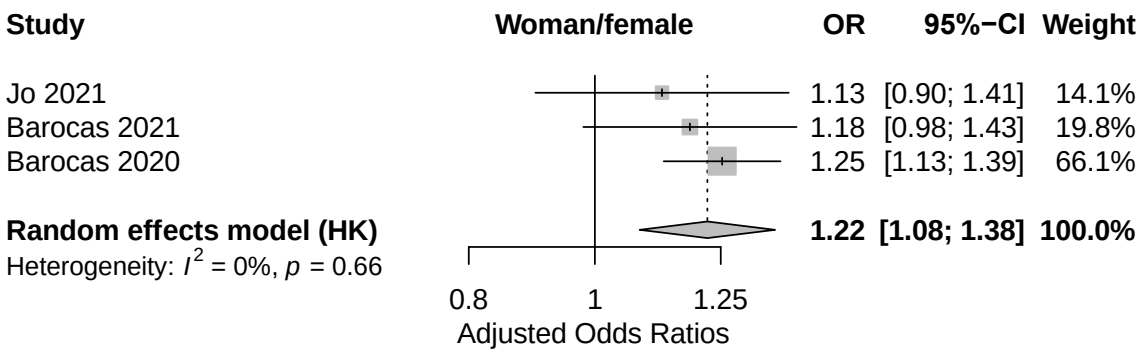

Figure 72. Meta-analysis of fully-adjusted effect estimates of relationship between woman/female gender/sex and all-cause rehospitalization, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

8.20.1.2.2 Substance use

People who had diagnostic codes for multiple substances (including alcohol, cannabis, hallucinogens, or sedatives), were at higher risk of all-cause rehospitalization in one study (aHR 1.29; 95%CI 1.11–1.50) [Barocas 2020[294]].

8.20.1.2.3 Opioid agonist treatment

Four studies assessed receipt of opioid agonist treatment and risk of all-cause rehospitalization; the studies measured opioid agonist treatment receipt in hospital or at discharge, or received within 30 days of hospital discharge.[279,287,294,301] Summary of two univariate effect estimates was uOR 0.82 (95%CI 0.42-1.60; Figure 73). Meta-analytic summary of three fully-adjusted effect estimates was aOR 0.98 (95%CI 0.75-1.29; Figure 74).

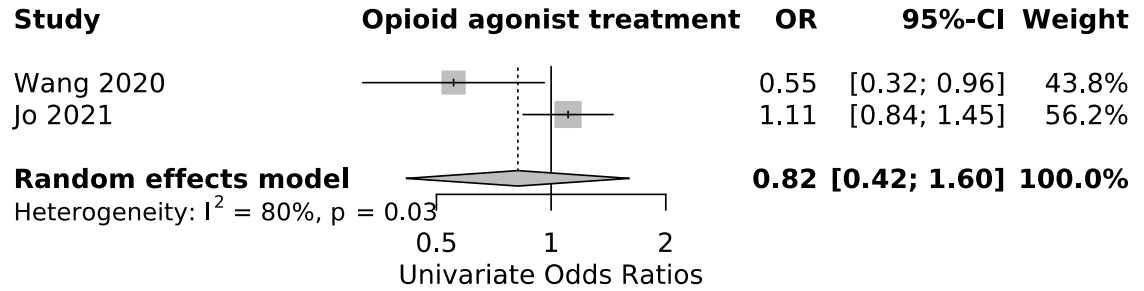

Figure 73. Meta-analysis of univariate effect estimates of relationship between receiving opioid agonist treatment (during hospitalization or at discharge) and all-cause rehospitalization, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

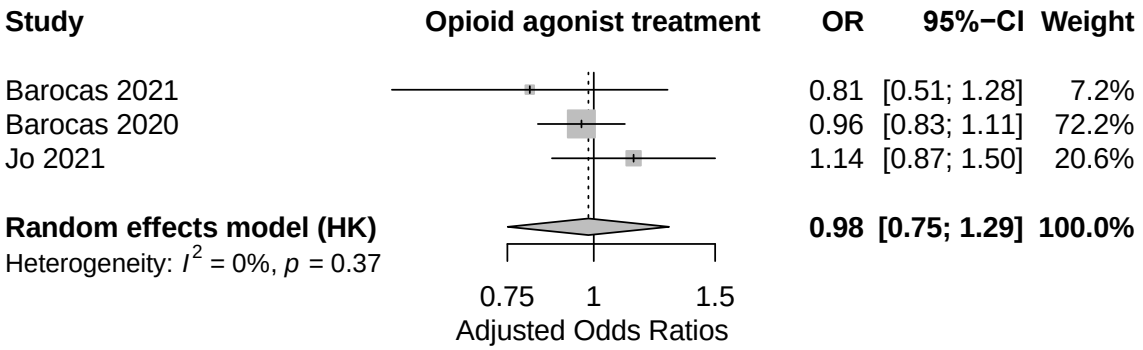

Figure 74. Meta-analysis of fully-adjusted effect estimates of relationship between receiving opioid agonist treatment (during hospitalization or within 30 days following discharge) and all-cause rehospitalization, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

8.20.1.2.4 In-hospital addiction medicine treatment

In two studies, receiving an inpatient addiction medicine consultation was associated with reduced risk of all-cause rehospitalization; summary of two univariate effect estimates was uOR 0.46 (95%CI 0.33-0.63; Figure 75) and one fully-adjusted effect estimate was aOR 0.57 (95%CI 0.38–0.86; Marks 2019[285]).

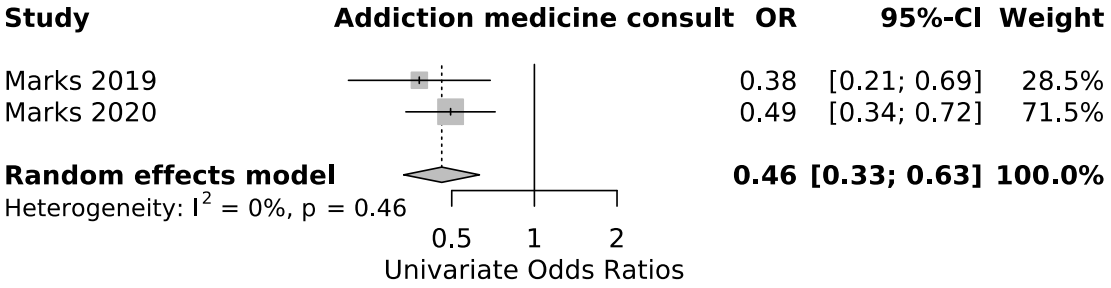

Figure 75. Meta-analysis of univariate effect estimates of relationship between receiving an addiction medicine consultation (during hospitalization) and all-cause rehospitalization, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

8.20.1.2.5 Hospital policy

Three studies assessed the impact of hospital policy change on all-cause readmission, following an initial hospital admission with an injecting-related infection.[284,287,299] In Cooksey 2020[284], implementation of a new hospital policy of searching, surveillance, and restricting movement of people who use drugs was associated with a decrease in 90-day all-cause readmissions (aOR 0.2,

95%CI 0.08-0.6; from 48% pre-implementation to 34% post-implementation). In two other studies [Ray 2020[299]; Wang 2020[287]], implementation of hospital policies to facilitate access to opioid agonist treatment were not associated with changes in readmission rates.

8.20.1.2.6 Antimicrobial treatment mode

One study [Marks 2020[302]] assessed whether patients with injecting-related bacterial infections who left hospital prematurely received oral antibiotics to finish out their course. Compared to completing a full inpatient course of intravenous antibiotics, people receiving partial intravenous/partial oral treatment courses had similar risk of all-cause readmission (aHR 0.99, 95%CI 0.62-1.62). People receiving partial intravenous/no oral treatment had higher risk of all-cause readmission (aHR 2.32, 95%CI 1.41 – 3.82).

8.20.1.2.7 Surgery during hospitalization

Three studies assessed the impact of surgical intervention during a hospital admission for injecting-related infections, on risk of all-cause rehospitalization.[288,302,303] Surgery was associated with decreased risks of readmission in the two studies that assessed it [Marks 2020[302]; Rudasill 2019[288]]. One study [Slaughter 2019[303]] compared different types of cardiac surgery in people with tricuspid valve endocarditis; valvectomy was associated with higher rates of all-cause readmission than repair or replacement (aOR 5.42, 95%CI 2.33–12.57, vs. repair).

8.20.1.3 Overdose-related rehospitalization

Two studies [Barocas 2021[301]; Wang 2020[287]] assessed factors associated with opioid overdose-related rehospitalization, following an initial hospital admission with injecting-related infections: gender/sex; age; substance use; opioid agonist treatment; hospital policy.[287,301] Risks of rehospitalization with overdose was associated with age (aHR 0.97; 95%CI 0.95–0.99) but not female sex (aHR 0.89; 95%CI 0.47–1.63) nor substance use (diagnostic codes related to alcohol, cannabis, hallucinogens, or sedatives; aHR 0.86; 95%CI 0.26–2.84) in one study.

Both studies assessed the impact of opioid agonist treatment. In one study [Barocas 2021[301]], receiving a prescription within 30 days of hospital discharge was not associated with rehospitalization for overdose (aHR 0.86; 95%CI 0.26–2.91), but the effect estimate was nonspecific and could include meaningful differences. In the second [Wang 2020[287]], having opioid agonist treatment continued at hospital discharge was associated with decreased risk of 30-day (uRR 0.34; 95% CI 0.16-0.74) and 90-day opioid-related readmission (uRR 0.46; 95%CI 0.24-0.88). Implementation of a hospital protocol to facilitate access to opioid agonist treatment did not lead to

significant changes in opioid-related readmission (e.g., uRR 0.83, 95% CI 0.44-1.57 at 30 days) [Wang 2020[287]].

8.20.1.4 All-cause mortality

Fourteen studies assessed the following exposures in relation to all-cause mortality after surviving an initial hospital admission with an injecting-related infection: gender/sex; age; unstable housing; substance use (opioid, stimulant, polysubstance use); premature hospital discharge against medical advice; opioid agonist treatment; other addiction medicine treatment; hospital policy; surgery during hospital admission.[284,287,289,296,300,303–311] All-cause mortality after hospital discharge was not associated with several outcomes (gender/sex, unstable housing, stimulant-only use, polysubstance use, and premature hospital discharge against medical advice). Risk of all-cause mortality was increased among people who use only opioids (vs. use other substances or multiple substances) in one study (uRR 1.72; 95%CI 1.06–2.80) [Rodger 2018[306]].

8.20.1.4.1 Opioid agonist treatment

Four studies assessed relationships between opioid agonist treatment and all-cause mortality after hospital discharge.[300,305,306,310] Three studies provided univariate effect estimates of the relationship between opioid agonist treatment prescriptions provided at hospital discharge and risk of all-cause mortality. Meta-analysis summary was uOR 0.58 (95%CI 0.24-1.45; Figure 76). In the only fully-adjusted effect estimate [Kimmel 2020[305]], opioid agonist treatment was associated with reduced risks of all-cause death in the month within which it was received (when treated as a time-varying exposure; aHR 0.30; 95% CI 0.10-0.89).

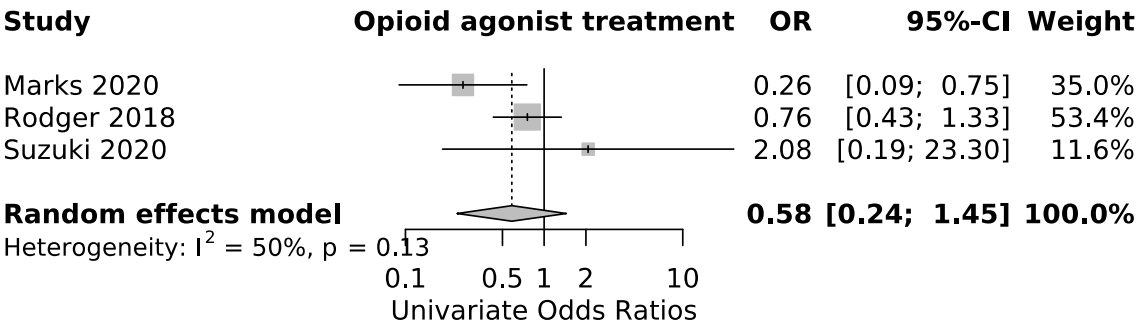

Figure 76. Meta-analysis of univariate effect estimates of relationship between receiving opioid agonist treatment at hospital discharge and all-cause mortality, following discharge from an initial hospital admission with injection drug use-associated bacterial infections.

8.20.1.4.2 In-hospital addiction medicine consultation

Three studies assessed risk of all-cause mortality after hospital discharge in relation to receiving other addiction treatment in hospital. In one study [Nguemeni Tiako 2020[311]], 0 out of 20 people with endocarditis who received "comprehensive addiction treatment" (defined as psychiatry and social work consultation and/or opioid agonist treatment during hospitalization) died at 24 months after hospital discharge, compared to 7 out of 22 who did not. In Tan 2020[289], receiving an inpatient addiction medicine consultation was not statistically significantly associated with all-cause mortality after discharge (aHR 0.64, 95%CI 0.32–1.29), though the confidence interval was wide and could include meaningful differences.

8.20.1.4.3 Other substance use treatment

In Rodger 2018[306], referral to outpatient addiction treatment at hospital discharge was associated with reduced all-cause mortality (aHR 0.29; 95%CI 0.12–0.73). However, it it seems as if the all-cause mortality outcome here included some patients who died in hospital, so this may have simply indicated those who survived to hospital discharge and reflect "immortal time".

8.20.1.4.4 Hospital policies

In Cooksey 2020[284], following implementation of a hospital policy of searching, surveillance, and restricting movement of people with injecting-related infections, all-cause mortality at 12 months decreased from 7% to 4% (aOR 0.25; 95%CI 0.07–0.89). In Wang 2020[287], following implementation of a hospital policy to facilitate access to opioid agonist treatment, all-cause mortality by 3 months changed from 2.8% (2/71) to 3.9% (3/76), and they concluded, "These numbers were too small to compare".

8.20.1.4.5 Surgery during hospitalization

Five studies assessed the impact of heart valve surgery during hospitalization with injecting-related endocarditis, and all-cause mortality following discharge. Meta-analysis summary of three univariate effect estimates was uOR 0.95 (95%CI 0.49-1.82; Figure 77), and for four fully-adjusted effect estimates was aOR 0.61 (95%CI 0.19-1.93; Figure 78).

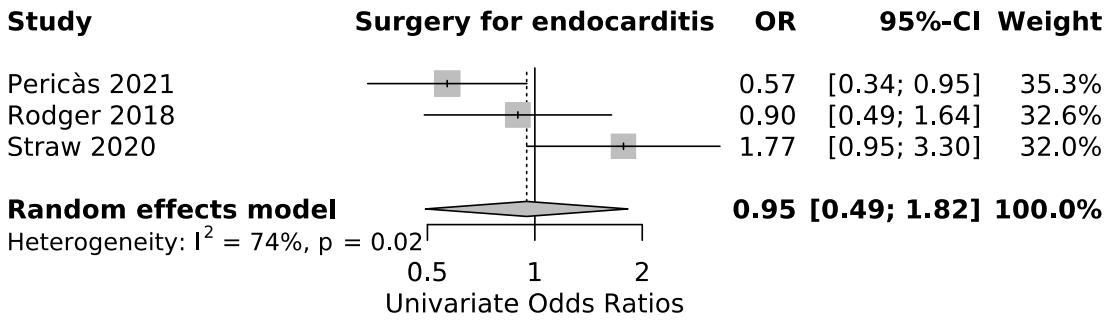

Figure 77. Meta-analysis of univariate effect estimates of relationship between receiving surgery and all-cause mortality following discharge from an initial hospital admission with injection drug use-associated endocarditis.

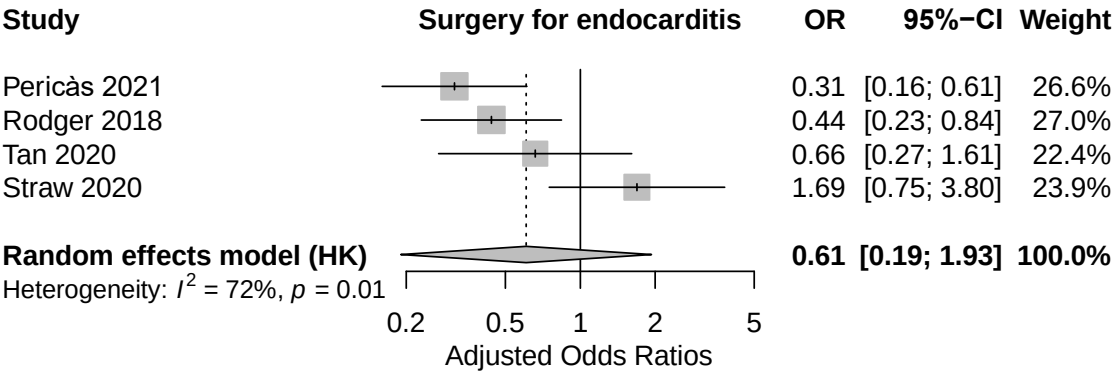

Figure 78. Meta-analysis of fully-adjusted effect estimates of relationship between receiving surgery and all-cause mortality following discharge from an initial hospital admission with injection drug use-associated endocarditis.

One of these studies compared types of heart valve surgery among people with injecting-related tricuspid valve endocarditis. Compared to valve repair, valvectomy (removal of the valve without replacement) was associated with higher risk of all-cause mortality (aOR 5.42; 95%CI 2.33–12.57), and valve replacement did not have significantly different risk (aOR 1.04; 95%CI 0.47–2.27).

8.20.1.5 Other outcomes

Studies assessed other outcomes after treatment for injecting-related bacterial infections, including outpatient parenteral antibiotic treatment ("OPAT") failure[312–314] and change in visual acuity after treatment for endogenous endophthalmitis.[228]

OPAT failure (after initial hospitalization with an injecting-related infection) was not associated with age[312] and did not differ according to whether patients were discharged home or to a post-acute care nursing facility.[313] In a pilot trial [Fanucchi 2020][314] that randomized 20 patients to either complete antibiotic treatment as a hospital inpatient vs. OPAT integrated with opioid agonist

treatment, all participants completed the recommended antibiotic treatment course. In one study [Connell 2010][228], improvement in visual acuity after treatment for endogenous endophthalmitis was seen more commonly among men than among women, but did not differ by age group.

8.21 Appendix 21. List of exposure-outcome pair effect estimates for studies where outcome occurs after treatment of injecting-related bacterial infections drug use-associated bacterial and fungal infections, included in quantitative systematic review.

Study	Exposures	Outcomes	Unadjusted effect estimate	Adjusted effect estimate	
Infection-related rehospitalization					
Age					
Barocas 2020[294]	Age (years) (after hospitalization for injecting-related SSTI)	1-year rehospitalization for SSTI		aHR 1.01 (1.01 – 1.01)	
Huang 2018[295]	Age, median (IQR)	Repeat episode of endocarditis (comparing features during first episode among people with single episode vs. repeat episode)	Single episode: 29 (24-38.5) Repeat episode: 28.5 (23-37.3) p=0.63		
Thønnings 2020[261]	Age, years	Recurrent bacteraemia after initial bacteremia (vs. no recurrence)	OR 0.93 (0.86–1.01)		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Gender/sex					
Barocas 2020[294]	Sex (female) (after hospitalization for injecting-related SSTI)	1-year rehospitalization for SSTI		aHR 1.10 (0.96 – 1.25)	
Huang 2018[295]	Male	Repeat episode of endocarditis (comparing features during first episode among people with single episode vs. repeat episode)	Single episode: 32 (49% male) Repeat episode: 11 (50% male) p=0.95		
Pericàs 2021[296]	Male (among PWID with IE)	6-month "relapse" (Readmission with same microbiology)	OR Female: Ref Male: 0.83 (0.37–1.88)		
Race					
Huang 2018[295]	Caucasian race	Repeat episode of endocarditis (comparing features during first episode among people with single episode vs. repeat episode)	Single episode: 62 (95.4%) Repeat episode: 22 (100%) p=0.57		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Rural/urban					

Huang 2018[295]	Nonmetro residency	Repeat episode of endocarditis (comparing features during first episode among people with single episode vs. repeat episode)	Single episode: 46 (71%) Repeat episode: 15 (68%) p=0.82		
Substances injected					
Huang 2018[295]	Prescription opioid injecting	Repeat episode of endocarditis (comparing features during first episode among people with single episode vs. repeat episode)	Single episode: 44 (68%) Repeat episode: 21 (95.4%%) p=0.01		
Opioid agonist treatment or naltrexone					
Barocas 2020[294]	Prescription for naltrexone or buprenorphine within 30 days of hospital discharge (after hospitalization for injecting-related SSTI)	30-day rehospitalization for SSTI	No MOUD group: 2.8 per 100 person-months (95% CI, 2.73-2.81) MOUD group: 1.13 per 100 person-months (95% CI, 1.02-1.24)	aHR = 0.49, 95% CI 0.18-1.23	
Barocas 2020[294]	Prescription for naltrexone or buprenorphine within 30 days of hospital discharge (after hospitalization for injecting-related SSTI)	1-year rehospitalization for SSTI	No MOUD group: 18.7 per 100 person-years (95% CI, 18.53-18.78) MOUD group: 10.3 per 100 person-years (95% CI, 9.87-10.64)	aHR 0.41 (0.42 – 0.91)	
Hilbig 2020[297]	Methadone vs. no methadone (among patient's hospitalized with first episode IDU-IE)	"Recurrence"	"No patients who were receiving methadone therapy on admission had a recurrence, compared with 25% of patients not receiving methadone therapy, but this difference was not statistically significant (p = 0.06)."		
Hilbig 2020[297]	Methadone vs. no methadone (among patient's hospitalized with first OR second episode IDU-IE)	"Recurrence"	"When analysis was extended to all primary and secondary episodes, there were some differences… The association with methadone therapy was no longer significant."		
Suzuki 2020[300]	MOUD	Repeat episode of endocarditis (among PWID with IE)	Buprenorphine: 4/8 Methadone taper and referral: 2/8 Declined MOUD: 4/10 P=NS		

Thønnings 2020[261]	Opioid substitution treatment	Recurrent bacteraemia after initial bacteremia (vs. no recurrence)	OR 5.88 (0.64–50.00)		
Other substance use treatment					
Thønnings 2020[261]	Contact to an addiction treatment center (not otherwise defined)	Recurrent bacteraemia after initial bacteremia (vs. no recurrence)	OR 1.39 (0.45–4.17)		
Rodger 2019[298]	Referral to addiction treatment	Recurrent endocarditis	OR 0.63; 0.32–1.24	aOR 0.54; 0.26–1.14	
Cardiac surgery during admission					
Pericàs 2021[296]	Cardiac surgery during first admission	6-month "relapse" (Readmission with same microbiology)	OR 1.73 (0.79–3.78)	aOR 1.96 (0.88–4.37)	
Rodger 2019[298]	Surgery during first admission	Recurrent endocarditis	OR 1.06; 0.50–2.22	aOR 0.90; 0.38–2.14	
AMA discharge					
Rodger 2019[298]	AMA discharge during first admission	Recurrent endocarditis	OR 0.56; 0.24–1.28	aOR 0.50; 0.21–1.20	
Hospital factors/policy					
Ray 2020[299]	Hospital initiative to improve pain and OUD management for patients with IDU-IE, including pain and addiction medicine consultation and new care pathway	90-day endocarditis readmission	Preintervention: 8/37 (22%) Postintervention: 9/33 (27%) p=0.58		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
All-cause rehospitalization					
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Age					
Barocas 2020[294]	Age (years) (after hospitalization for injecting-related SSTI)	30-day all-cause rehospitalization		aHR 1.0 (0.99 – 1.00)	
Jo 2021[279]	Age (?continuous) (among patients with untreated OUD and either endocarditis or osteomyelitis)	30-day all-cause rehospitalization		aOR 1.00 (0.99, 1.01)	
Barocas 2021[301]	Age (years)	1-year all-cause rehospitalization		aHR 1.01 (1.00 – 1.01)	

	(after hospitalization for injecting-related endocarditis)				
Marks 2020[302]	Age (>50 years) (after hospitalization with invasive infections: Endocarditis, septic arthritis, bacteremia, osteomyelitis, epidural abscess)	90-day all-cause readmission	OR 1.09 (0.59 – 2.02)		
Sex/Gender					
Barocas 2020[294]	Sex (female) (after hospitalization for injecting-related SSTI)	30-day all-cause rehospitalization		aHR 1.25 (1.13 – 1.39)	
Jo 2021[279]	Biological sex (among patients with untreated OUD and either endocarditis or osteomyelitis)	30-day all-cause rehospitalization		aOR Male: 0.89 (0.71 – 1.11) Female: Ref	
Barocas 2021[301]	Sex (female) (after hospitalization for injecting-related endocarditis)	1-year all-cause rehospitalization		aHR 1.18 (0.98 – 1.43)	
Marks 2020[302]	Sex (female) (after hospitalization with invasive infections)	90-day all-cause readmission	OR 1.23 (0.77 – 1.96)		
Race/Ethnicity					
Jo 2021[279]	Ethnicity (among patients with untreated OUD and either endocarditis or osteomyelitis)	30-day all-cause rehospitalization		aOR White: 0.69 (0.51 – 0.93) Other: Ref	

Marks 2020[302]	African American (extracted from medical chart review) (after hospitalization with invasive infections)	90-day all-cause readmission	OR 0.79 (0.49 – 1.27)		
Unstable housing					
Marks 2020[302]	Homeless (extracted from medical chart review) (after hospitalization with invasive infections)	90-day all-cause readmission	OR 0.92 (0.46 – 1.83)		
Insurance					
Cooksey 2020[284]	Lacking insurance on hospital admission for IDU-IE	90-day all-cause rehospitalization (after hospitalization for IDU-IE)	OR 1.3 (0.6 – 2.6)		
Jo 2021[279]	Insurance status (among patients with untreated OUD and either endocarditis or osteomyelitis)	30-day all-cause rehospitalization		aOR Govt funded insurance: 1.18 (0.90, 1.56) Commercial insurance: 1.08 (0.73 – 1.61) Uninsured: Ref	
Substances injected - heroin					
Marks 2020[302]	Heroin or fentanyl use (after hospitalization with invasive infections)	90-day all-cause readmission	OR 0.69 (0.32 – 1.46)		
Jo 2021[279]	Cocaine/amphetamine use (among patients with untreated OUD and either endocarditis or osteomyelitis)	30-day all-cause rehospitalization		aOR Yes: 0.86 (0.62 0 1.18) No: Ref	
Cocaine use					
Marks 2020[302]	Cocaine use (after hospitalization with invasive infections)	90-day all-cause readmission	OR 1.53 (0.90 – 2.60)		

Methamphetamine					
Marks 2020[302]	Methamphetamine use (after hospitalization with invasive infections)	90-day all-cause readmission	OR 1.32 (0.78 – 2.25)		
Other substance use					
Barocas 2020[294]	Other substance use disorder (ICD codes related to alcohol, cannabis, hallucinogens, or sedatives from hospital admin data) (after hospitalization for injecting-related SSTI)	30-day all-cause rehospitalization		aHR 1.29 (1.11 – 1.50)	
Marks 2020[302]	Benzodiazepine use (after hospitalization with invasive infections)	90-day all-cause readmission	OR 0.49 (0.09 – 2.45)		
Addiction medicine consultation					
Marks 2020[302]	Inpatient addiction medicine consultation (after hospitalization with invasive infections)	90-day all-cause readmission	OR 0.39 (0.24 – 0.64) HR 0.49 (0.34 – 0.72)	aHR 0.57 (0.38 – 0.86)	
Marks 2019[285]	Inpatient addiction medicine consultation (after hospitalization with invasive infections)	90-day all-cause readmission	HR 0.378 (0.21 – 0.69)		
OAT + naltrexone					
Barocas 2020[294]	Prescription for naltrexone or buprenorphine within 30 days of hospital discharge (after hospitalization for injecting-related SSTI)	30-day all-cause rehospitalization	no MOUD group: 27.5 per 100 person-months (95% CI 27.4-27.7) MOUD group: 35.9 (95% CI 35.3-36.6)	aHR 1.29 (1.05-1.59)	
Barocas 2020[294]	Prescription for naltrexone or buprenorphine within 30	1-year all-cause rehospitalization	no MOUD group: 192.9 per 100 person-years (95% CI, 192.5-193.3)	aHR = 0.96, 95% CI 0.83-1.11	

	days of hospital discharge (after hospitalization for injecting-related SSTI)		MOUD group: 169.4 per 100 person-years (95% CI, 167.9-171.0)		
Barocas 2021[301]	Prescription for naltrexone or buprenorphine within 30 days of hospital discharge (after hospitalization for injecting-related endocarditis	1-year all-cause rehospitalization		aHR 0.81 (0.51 – 1.28)	
Jo 2021[279]	OAT initiation (among patients with untreated OUD admitted with endocarditis or osteomyelitis)	30 days all-cause readmission	MOUD: 106/269 No MOUD: 421/1138 P value not tested	aOR 1.14 (0.87 – 1.50)	
Wang 2020[287]	MOUD in hospital AND continued on discharge (vs. no MOUD on discharge)	30-day all-cause readmission (among patients admitted to hospital with injecting-related infections)	RR 0.54; 95% CI, 0.32-0.96		
Wang 2020[287]	MOUD in hospital AND continued on discharge (vs. no MOUD on discharge)	90-day all-cause readmission (among patients admitted to hospital with injecting-related infections)	RR 0.64; 95% CI, 0.40-1.03;		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Hospital policy					
Cooksey 2020[284]	Implementation of hospital-wide policy: search of patient's belongings, supervised and limited visitation, restricted cell phone access, analgesics and sedatives provided only in liquid formulation. Patients' wear self-identifying gowns, medical chart is flagged. Coerced (patient's must agree)	90-day all-cause rehospitalization (after hospitalization for IDU-IE)	48% pre-intervention vs. 34% post-intervention (p=0.068)	aOR 0.2 (95% CI 0.08-0.6)	
Cooksey 2020[284]	Implementation of hospital-wide policy: search of patient's belongings,	12-month all-cause rehospitalization (after hospitalization for IDU-IE)	70% pre-intervention vs. 38% post-intervention (p<0.001)		

	supervised and limited visitation, restricted cell phone access, analgesics and sedatives provided only in liquid formulation. Patients' wear self-identifying gowns, medical chart is flagged. Coerced (patient's must agree)				
Ray 2020[299]	Hospital initiative to improve pain and OUD management for patients with IDU-IE, including pain and addiction medicine consultation and new care pathway	90-day all-cause readmission	Preintervention: 16/37 (43%) Postintervention: 13/33 (39%) p=0.74		
Wang 2020[287]	Implementation of a hospital-wide policy to identify OUD and facilitate MOUD	30-day all-cause readmission (among patients admitted to hospital with injecting-related infections)	The rate of 30-day all-cause readmissions was 29.6% prior to protocol rollout and 25.3% afterward (RR 0.86; 95% CI, 0.51-1.45; P = .56)		
Wang 2020[287]	Implementation of a hospital-wide policy to identify OUD and facilitate MOUD	90-day all-cause readmission (among patients admitted to hospital with injecting-related infections)	The rate of 90-day all-cause readmissions was 38.0% prior to protocol rollout and 32.9% afterward (RR 0.86; 95% CI, 0.55-1.35; P = .52)		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Antibiotic treatment mode					
Marks 2020[302]	Antibiotic treatment mode (after hospitalization with invasive infections)	90-day all-cause readmission	Completed inpatient IV antibiotics: Ref Partial IV, partial oral: OR 1.05 (0.58 – 1.83) Partial IV, no oral: OR 4.77 (2.55 – 8.92) Partial IV, partial OR: HR 0.92 (0.57 – 1.48) Partial IV, no oral: HR 3.17 (0.197 – 5.12)	Partial IV, partial oral: aHR 0.99 (0.62 – 1.62) Partial IV, no oral: aHR 2.32 (1.41 – 3.82)	
Surgery					

Marks 2020[302]	Received surgical procedure (after hospitalization with invasive infections)	90-day all-cause readmission	OR 0.38 (0.23 – 0.62) HR 0.44 (0.29 – 0.66)	aHR 0.57 (0.37 – 0.87)	
Rudasill 2019[288]	Surgery (among patients with IDU-IE)	Readmission within 30 days	Medical treatment: 5,507/24,314 (22.6%) Surgical treatment: 584/3,073 (19%) p=0.007		
Rudasill 2019[288]	Surgery (among patients with IDU-IE)	Readmission from 30 to 180 days	Medical treatment: 2,681/24,314 Surgical treatment: 405/3,073 p=0.044		
Slaughter 2019[303]	Type of cardiac surgery in tricuspid valve endocarditis	30 day readmission	Valvectomy: 10/119 (9.9%) Repair: 31/532 (5.9%) Replacement: 84/962 (8.9%) p=0.34	aOR Repair: Reference Replacement: 1.04 (0.47 – 2.27) Valvectomy: 5.42 (2.33 – 12.57)	
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	
Overdose Hospitalisation					
Barocas 2021[301]	Age (years) (after hospitalization for injecting-related endocarditis)	Opioid-related overdose hospitalization		aHR 0.97 (0.95 – 0.99)	
Barocas 2021[301]	Sex (female) (after hospitalization for injecting-related endocarditis)	Opioid-related overdose hospitalization		aHR 0.89 (0.47 – 1.63)	
Barocas 2021[301]	Other substance use disorder (ICD codes related to alcohol, cannabis, hallucinogens, or sedatives from hospital admin data)	Opioid-related overdose hospitalization		aHR 0.86 (0.26 – 2.84)	

	(after hospitalization for injecting-related endocarditis)				
Barocas 2021[301]	Prescription for naltrexone or buprenorphine within 30 days of hospital discharge (after hospitalization for injecting-related endocarditis	Opioid-related overdose		aHR 0.86 (0.26 – 2.91)	
Wang 2020[287]	MOUD in hospital and continued on discharge (vs. no MOUD on discharge)	30-day opioid-related readmission (among patients admitted to hospital with injecting-related infections)	The respective 30-day opioid-related readmission rate was 10.1% vs 29.9% (RR 0.34; 95% CI, 0.16-0.74; P = .003).		
Wang 2020[287]	MOUD in hospital and continued on discharge (vs. no MOUD on discharge)	90-day opioid-related readmission (among patients admitted to hospital with injecting-related infections)	The respective 90-day opioid-related readmission rate was 15.2% vs 33.3% (RR 0.46; 95% CI, 0.24-0.88; P = .01).		
Wang 2020[287]	Implementation of a hospital-wide policy to identify OUD and facilitate MOUD	30-day opioid-related readmission (among patients admitted to hospital with injecting-related infections)	The rate of 30-day opioid-related readmissions was 22.5% prior to protocol rollout and 18.7% afterward (RR 0.83; 95% CI, 0.437-1.57, P = .56).		
Wang 2020[287]	Implementation of a hospital-wide policy to identify OUD and facilitate MOUD	90-day opioid-related readmission (among patients admitted to hospital with injecting-related infections)	The rate of 90- day opioid-related readmissions was 26.7% prior to protocol rollout and 22.9% afterward (RR 0.95; 95% CI, 0.48-1.52; P = .59).		
All-cause mortality					
Sex/gender					
Clarelin 2021[304]	Sex (female)	Mortality, survival analysis After hospitalization with IDU-IE	HR 0.72 (0.50 – 1.03)	aHR 1.05 (0.71 – 1.56)	
Kimmel 2020[305]	Female	Mortality, survival analysis After hospitalization with IDU-IE		aHR 0.80 (0.45-1.43)	
Pericàs 2021[296]	Male	6-month mortality (among PWID with IE)	OR Female: Ref Male: 1.92 (1.06–3.46)	aOR 1.75 (0.89–3.48)	
Rodger 2018[306]	Sex	All-cause mortality (time undefined)	Unclear numerators and denominators and no reference		

			category for relative risk statistics? RR estimates for both categories… "p=0.12"		
Rohn 2020[307]	Gender	30-day mortality	Female: 2/28 Male: 4/34 p=>0.999		
Straw 2020[308]	Sex (male vs. female)	Survival		aHR 0.67 (0.30 – 1.5)	
Weymann 2014[309]	Female (among patients with IDU-IE undergoing surgery)	90-day mortality	Female: 1/7 Male: 1/13 p=0.639		
Age					
Clarelin 2021[304]	Age (per year)	Mortality, survival analysis After hospitalization with IDU-IE	OR 1.05 (1.04-1.07)	aOR 1.03 (1.01 – 1.05)	
Kimmel 2020[305]	Age	Mortality, survival analysis After hospitalization with IDU-IE		aHR 18-34: 0.26 (0.12-0.55) 35-49: 0.62 (0.35 – 1.10) 50-64: Ref	
Rodger 2018[306]	Age	All-cause mortality	Only presents age median (IQR) for those who died, but "p=0.04"		
Rohn 2020[307]	Age	30-day mortality	Mean (SD), Survivors: 29 (5.97) Non-survivors: 33.3 (26.5) P=0.0525		
Slaughter 2019[303]	Age, per year	"Operative mortality" which was death in hospital OR within 30 days of discharge		aOR 1.01 (0.98 – 1.04)	
Straw 2020[308]	Age, per year	Survival		aHR 1.1 (1.0-1.1)	
Weymann 2014[309]	Age, years (among patients with IDU-IE undergoing surgery)	90-day mortality	Survivors: 35.1 (7.7) Non-survivors: 34.5 (10.6) P=0.926 (I think mean, SD, but doesn't say?)		
Unstable housing					
Kimmel 2020[305]	Homelessness	Mortality, survival analysis After hospitalization with IDU-IE		aHR 0.60 (0.31 – 1.14)	
Specific substances					

Rodger 2018[306]	Opioid (alone)	All-cause mortality	RR 1.72 (1.06 – 2.80) Unclear reference category -- is it everyone else?		
Rodger 2018[306]	Stimulant (alone)	All-cause mortality	RR 0.79 0.30 – 2.11) Unclear reference category -- is it everyone else?		
Rodger 2018[306]	Polysubstance use	All-cause mortality	RR 0.81 (0.62 – 1.06) Unclear reference category -- is it everyone else?		
Against medical advice AMA discharge					
Rodger 2018[306]	Left against medical advice	All-cause mortality	RR 0.34 (0.14 – 0.84) HR 0.34 (0.14 – 0.85) But outcome included many (most?) people who died during hospitalization (e.g. sepsis, etc.) so really this is just an indicator that they survived the hospital admission…	aHR 0.47 (0.18 – 1.19) (adjusted for age and sex)	
Opioid agonist treatment at/after discharge					
Kimmel 2020[305]	Receipt of MOUD (buprenorphine, methadone, naltrexone)	Mortality, survival analysis After hospitalization with IDU-IE		aHR 0.30; 95% CI, 0.10-0.89	
Marks 2020[310]	MOUD prescription at discharge	All-cause mortality at 1 year	RR 0.26 (0.09 – 0.75) (Cannot find frequencies to generate 2X2 table, but 15% of sample died)		
Rodger 2018[306]	Opioid substitution treatment prescription at discharge	All-cause mortality (among PWID with IE)	RR 0.34 (0.43 – 1.33) Unclear if it includes OST received during hospitalization or only at discharge. Outcome seems to include in-hospital deaths, so may just be an indicator of who survived to discharge		

Suzuki 2020[300]	MOUD given in hospital	Mortality (among PWID with IE)	Buprenorphine: 0/8 Methadone taper and referral: 3/8 Declined MOUD: 1/10 P=NS		
Addiction medicine consultation/referral					
Nguemeni Tiako 2020[311]	"Comprehensive addiction treatment" as inpatient	24-month survival	Yes addiction treatment: 0/20 died No/partial addiction treatment 7/22 died	Not tested	
Rodger 2018[306]	Referral to addiction treatment (on discharge)	All-cause mortality (among PWID with IE)	RR 0.28 (0.12 – 0.69) HR 0.28 (0.12 – 0.69) Outcome seems to have included in-hospital deaths, so this is likely just an indicator of who survived to hospital discharge…	aHR 0.29 (0.12 – 0.73) (adjusted for age and sex)	
Tan 2020[289]	Consultation with inpatient addictions treatment	90 day all-cause mortality		aHR 0.64 (0.32 – 1.29)	
Hospital policy					
Cooksey 2020[284]	Implementation of hospital-wide policy: search of patient's belongings, supervised and limited visitation, restricted cell phone access, analgesics and sedatives provided only in liquid formulation. Patients' wear self-identifying gowns, medical chart is flagged. Coerced (patient's must agree)	12-month all-cause mortality (after hospitalization for IDU-IE)	7% pre-intervention vs. 4% post-intervention (p=0.73)	aOR 0.25 (95% CI 0.07 – 0.89)	
Wang 2020[287]	Implementation of a hospital-wide policy to identify OUD and facilitate MOUD	Mortality in 3 months after discharge (among patients admitted to hospital with injecting-related infections)	In the pre-protocol cohort, 2 of 71 patients died within 3 months. In the post-protocol cohort, 3 of 76 patients died within 3 months. The overall 3-month mortality rate was 3.4%. These numbers were too small to compare	Not tested	
Surgery during hospitalization					

Pericàs 2021[296]	Cardiac surgery during initial admissions (among PWID with IE)	6-month mortality	OR No: Ref Yes: 0.57 (0.34–0.95)	aOR 0.32 (0.16–0.61)	
Rodger 2018[306]	Cardiac surgery	All-cause mortality	Unclear numerators and denominators and no reference category for relative risk statistics? RR estimates for both categories… "p>0.99" HR 0.89 (0.49 – 1.64)	aHR 0.44 (0.23 – 0.84) (adjusted for age and sex)	
Slaughter 2019[303]	Type of cardiac surgery in tricuspid valve endocarditis	"Operative mortality" which was death in hospital OR within 30 days of discharge	Valvectomy: 19/119 (16%) Repair: 12/532 (2.3%) Replacement: 29/962 (3.0%) p<0.01	aOR Repair: Reference Replacement: 1.04 (0.47 – 2.27) Valvectomy: 5.42 (2.33 – 12.57)	
Straw 2020[308]	Surgery	Survival	HR 1.8 (0.95 – 3.3)	aHR 17 (0.75 – 3.8)	
Tan 2020[289]	Cardiac surgery	New bloodstream infection during treatment for IDU-IE		aHR 0.66 (0.27 – 1.61)	
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	**Notes**
Other post-hospital/outpatient outcomes					
Buehrle 2017[312]	Age (years) (while on OPAT after hospitalization for injecting-related infection)	OPAT failure as any of the following: worsening or ongoing infection requiring hospital readmission within 30 days, worsening or ongoing infection resulting in prolonged antibiotic therapy, antibiotic noncompliance, noncompliance with follow-up clinic appointments, or death during treatment course.	Median age in years (range) Success: 34 (25–62) Failure: 35 (19–63) P=0.82		
Connell 2010[228]	Male vs. female	Change in visual acuity after treatment for endogenous Candida endophthalmitis	Among males: mean visual acuity pre-treatment 6/48 vs. post-treatment 6/24 (p=0.04)		

			Among females: mean visual acuity pre-treatment 6/60 vs. post-treatment 6/48 (p=0.58)		
Connell 2010[228]	Age <= 35 years vs. >35 years	Change in visual acuity after treatment for endogenous Candida endophthalmitis	Among age <= 35: mean visual acuity pre-treatment 6/48 vs. post-treatment 6/36 (p=0.29) Among age >5: mean visual acuity pre-treatment 6/60 vs. post-treatment 6/36 (p=0.45)		
Study	**Exposures**	**Outcomes**	**Unadjusted effect estimate**	**Adjusted effect estimate**	**Notes**
Discharge location					
D'Couto 2018[313]	Discharge home vs. to skilled nursing facility (while on OPAT, after hospitalization for injecting-related infeciton	Any complication (including line complications, IDU relapse, loss to follow-up, death)	Discharged home: 4/21 Discharged to SNF: 11/31 P = 0.23		
Fanucchi 2020[314]	Discharge home (OPAT) vs. remaining in hospital [pilot randomized trial] (once hospitalized for injecting-related infection)	Antibiotic completion	All participants (100%) completed the recommended course of IV antibiotic therapy. OPAT participants completed 20.1 (SD ± 11.1) days of outpatient IV antibiotics compared 1.8 (SD ± 5.3) days for UC participants (t(17) = –4.5, P < .001).		
Buehrle 2017[312]	Discharged from hospital to residential treatment facility	OPAT failure as any of the following: worsening or ongoing infection requiring hospital readmission within 30 days, worsening or	Success: 1 (4%) out of 26 Failure: 0 (0%) out of 41 P = NA		

	(while on OPAT after hospitalization for injecting-related infection)	ongoing infection resulting in prolonged antibiotic therapy, antibiotic noncompliance, noncompliance with follow-up clinic appointments, or death during treatment course.			

8.22 Appendix 22. Narrative synthesis and meta-analyses of studies where outcome is colonization with pathogenic bacteria.

Five studies assessed factors associated with colonization with specific pathogenic bacteria among people who inject drugs, including *Staphylococcus aureus* and methicillin-resistant *S. aureus*: gender/sex; age; race/ethnicity; education; employment; relationship status; unstable housing and homelessness; incarceration; substance use (heroin, cocaine, crack, speedball, methamphetamines, prescription opioids; cannabis); public injecting; injecting in groups; opioid agonist treatment; other addiction treatment; recent hospital admission; and other (e.g. using public shower facilities).[315–319] See for all effect estimates extracted for this section.

Most exposures were not significantly associated with colonization. Several exposures had significant associations in some studies but not others. Meta-analysis for four univariate effect estimates on the relationship between homelessness and colonization with pathogenic bacteria was uOR 1.84 (95%CI 0.81-4.18; Figure 79), and I identified no fully-adjusted effect estimates. Recent hospital admission was significantly associated with colonization in one study (uOR 4.3; 95%CI 1.34-13.80) [Packer 2019[319]], but not in two others [Leung 2015[316]; Miller 2007[317]].

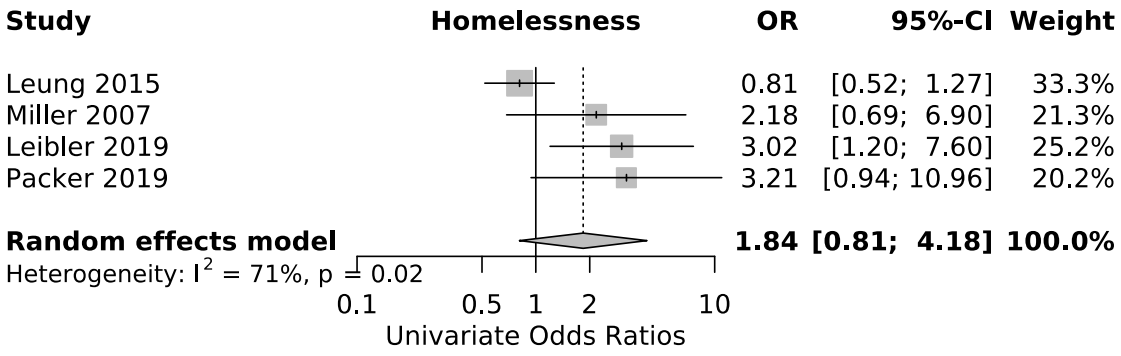

Figure 79. Meta-analysis of univariate effect estimates of relationship between homelessness and colonization with pathogenic bacteria among people who inject drugs.

Several other exposures has significant associations in single studies. In one study [Packer 2019[319]], public injecting (uOR 5.5; 95%CI 1.34-22.73) and frequently injecting in groups of three or more people (uOR 15.8; 95%CI 2.51-99.28) were both associated with colonization. In a second study [Leibler 2019[4]], positive associations were seen with sleeping at more than one place during the last week (uOR OR 3.1; 1.3-7.6), use of public shower facilities in the last week (uOR 13.7, 95%CI 1.4-132.8), and sharing bedding with other people (uOR 2.2; 95%CI 1.0 –4.7).

8.23 Appendix 23. List of exposure-outcome pair effect estimates for studies where outcome is colonization with pathogenic bacteria among people who inject drugs, included in quantitative systematic review.

Study	Exposures	Outcomes	Unadjusted effect estimate	Adjusted effect estimate	
Sociodemogaphic factors					
Gender/Sex					
Colombo 2012[315]	Sex (not defined)	MRSA-positive nose/throat or wound swabs (vs. MRSA-negative)	"no statistical differences"		
Leung 2015[316]	Sex	*S. aureus* nasal colonization *(76% MSSA, 24% MRSA)*	Male: 78/347 (22%) Female: 27/ 90 (30%) P value not reported	Male: Ref Female: 1.07 (0.98 – 1.18)	
Miller 2007[317]	Sex	*S. aureus* nasal colonization *(14% MRSA)*	Male: 36/166 Female: 29/116 P=0.52		
Age					
Colombo 2012[315]	Age (not defined)	MRSA-positive nose/throat or wound swabs (vs. MRSA-negative)	"no statistical differences"		
Leung 2015[316]	Age (mean, SD)	*S. aureus* nasal colonization	Colonized: 43.7, 12.6 Not colonized: 47.6, 11.1 "p<0.05"	aOR 0.99 (0.99-1.00)	
Miller 2007[317]	Age	*S. aureus* nasal colonization *(14% MRSA)*	<=30 years: 2/20 21-45 years: 44/188 >45 years: 19/74 p=0.3		
Race/Ethnicity					
Leung 2015[316]	Race	*S. aureus* nasal colonization	Hispanic/Latino: 18/72 White: 26/90 Black: 59/258 Other: 3/20 P value not reported		
Miller 2007[317]	Race/ethnicity	*S. aureus* nasal colonization *(14% MRSA)*	Hispanic: 43/200 Black: 11/53 Other: 11/29 P=0.13		
Education					
Leung 2015[316]	Education	*S. aureus* nasal colonization	Grades 1-11: 36/139 Grade 12 or GED: 44/185		

			Some college or more: 26/116 P value not reported		
Employment					
Leung 2015[316]	Employment	*S. aureus* nasal colonization	Employed: 24/104 Unemployed: 82/318 "Not currently in the workforce": 0/18 P<0.05	Employed: 0.96 (0.88 – 1.06) Unemployed: Ref "Not currently in the workforce": 0.78 (0.64 – 0.95)	
Miller 2007[317]	Employed	*S. aureus* nasal colonization *(14% MRSA)*	Employed: 15/73 Unemployed: 50/209 P=0.56		
Marital status					
Leung 2015[316]	Marital status	*S. aureus* nasal colonization	Married/common-law: 16/54 Separated: 11/54 Divorced: 27/122 Widowed: 2/23 Never married: 50/187 P value not reported	Married/common-law: 1.04 (0.99 – 1.00) *double-checked this one and must be a typo Separated: 0.94 (0.83 – 1.07) Divorced: 0.96 (0.87 – 1.05) Widowed: 0.83 (0.70 – 1.00) Never married: Ref	
Unstable housing					
Leung 2015[316]	History of homelessness	*S. aureus* nasal colonization	Yes homelessness: 63 colonized out of 278 homelessness No homelessness: 43 colonized out of 162 not homeless P value not reported OR 0.81 (0.52-1.27)		
Leibler 2019[318]	Sleeping in a homeless shelter in the last 3 months	MRSA-positive nasal swab	OR 3.0 (1.2, 7.6)		

Leibler 2019[318]	Sleeping on the street	MRSA-positive nasal swab	"No associations were observed…"		
Leibler 2019[318]	Sleeping at >1 place during the last week	MRSA-positive nasal swab	OR 3.1 (1.3, 7.6)		
Leibler 2019[318]	Use of public shower facilities in the last week ("Public restrooms are exclusive of restrooms in homeless shelters, day centers, or hospitals")	MRSA-positive nasal swab	OR 13.7 (1.4, 132.8)		
Leibler 2019[318]	Sharing bedding with other people	MRSA-positive nasal swab	OR 2.2 (1.0 – 4.7)		
Miller 2007[317]	Homeless during the past six months	*S. aureus* nasal colonization *(14% MRSA)*	Yes: 5/13 No: 60/269 p=0.19		
Miller 2007[317]	Spent time in a shelter during the past 6 months	*S. aureus* nasal colonization *(14% MRSA)*	Yes: 2/65 No: 63/275 P=0.66		
Packer 2019[319]	Homeless past year	*MRSA* colonization	OR 3.2 (0.94 – 10.96)		
Public injecting					
Packer 2019[319]	Most frequent injecting location	*MRSA* colonization	ORs House own/friend: Ref Hostel, squat, other: 1.7 (0.41 – 7.16) Public places: 5.5 (1.34 – 22.73)		
Inject in groups					
Packer 2019[319]	Frequently inject in groups	*MRSA* colonization	ORs Own: Ref		

			Less than three people: 1.5 (0.4 – 5.3) Three or more people: 15.8 (2.51 – 99.28)		
Incarceration					
Leung 2015[316]	Incarceration, past 12 months	*S. aureus* nasal colonization	Yes incarcerated: 37 colonized out of 165 incarceration Not incarcerated: 69 colonized out of 275 not incarcerated P value not reported. OR 0.86 (0.55-1.36)		
Miller 2007[317]	Spent time in prison during the past 6 months	*S. aureus* nasal colonization *(14% MRSA)*	Yes: 9/36 No: 56/246 p=0.77		
Recent hospitalization					
Leung 2015[316]	Hospitalized, past 6 months	*S. aureus* nasal colonization	Yes hospitalized: 20 colonized out of 79 hospitalized Not hospitalized: 86 colonized out of 361 not hospitalized P value not reported OR 1.08 (0.62-1.90)		
Miller 2007[317]	Hospitalized during the past 6 months	*S. aureus* nasal colonization *(14% MRSA)*	Yes: 6/39 No: 59/243 P=0.22		
Packer 2019[319]	Hospital contact past month	*MRSA* colonization	OR 4.3 (1.34 – 13.8)		
Drug treatment					
Leung 2015[316]	Drug treatment program, past 12 months	*S. aureus* nasal colonization	Yes drug treatment: 25 colonized out of 82 in drug treatment No drug treatment: 81 colonized out of 358 not in drug treatment	aOR 1.08 (0.97 – 1.19)	

			P value not reported		
Miller 2007[317]	Enrolled in a methadone program (but not limited to opioid users?)	*S. aureus* nasal colonization *(14% MRSA)*	Yes: 60/254 No: 5/28 P=0.49		
Substances injected					
Leung 2015[316]	Speedball, injection	*S. aureus* nasal colonization		aOR 1.02 (0.94 – 1.10)	
Leung 2015[316]	Heroin (alone), injection	*S. aureus* nasal colonization		aOR 1.10 (0.98 – 1.24) in full "Factors associated with" vs. QIC best-fit model aOR 1.13 (1.01-1.27) in second model specifically controlling for gender, employment status, HIV status, and ARV use, +/- other variables? (unclear)	
Leung 2015[316]	Cocaine (powder or crack), injection	*S. aureus* nasal colonization		aOR 0.98 (0.89 – 1.09)	
Leung 2015[316]	Crystal meth, injection	*S. aureus* nasal colonization		aOR 0.99 (0.89 – 1.10)	
Leung 2015[316]	Oxycontin, injection	*S. aureus* nasal colonization		aOR 1.01 (0.90–1.13)	
Other substance use					
Leung 2015[316]	Marijuana	*S. aureus* nasal colonization		aOR 0.98 (0.90 – 1.06)	
Leung 2015[316]	Heroin, non-injection use	*S. aureus* nasal colonization		aOR 0.93 (0.86-1.12) in full "Factors associated with" vs. QIC best-fit model aOR 0.90 (0.83 – 0.98) in second model specifically controlling for gender, employment status, HIV status, and ARV use, +/- other variables? (unclear)	

Leung 2015[316]	Cocaine (powder or crack), non-injection use	*S. aureus* nasal colonization		aOR 0.98 (0.90 – 1.06)	
Leung 2015[316]	Crystal meth, non-injection use	*S. aureus* nasal colonization		aOR 1.06 (0.96 – 1.18)	

8.24 Appendix 24. ICD-10 codes to define infections of interest.

Variable name	Codes	Diagnosis
Skin and soft tissue infections	A48.0	Gas gangrene
	L02.X	Cutaneous abscess, furnuncle and carbuncle
	L03.X	Cellulitis
	L08.8	Other specified local infections of skin and subcutaneous tissue
	L08.9	Local infection of skin and subcutaneous tissue, unspecified
	L97	Ulcer of lower limb, NEC
	L98.4	Chronic ulcer of skin, NEC
	L98.8	Other specified disorders of skin and subcutaneous tissue
	L98.9	Disorder of skin and subcutaneous tissue, unspecified
	M72.6	Necrotizing fasciitis
	R02	Gangrene, NEC
Sepsis and bacteraemia	A40.X	Streptococcal sepsis
	A41.X	Other sepsis
	R57.2	Septic shock
	B37.7	Candidal sepsis
Endocarditis	B37.6	Candidal endocarditis
	I33.0	Acute and subacute infective endocarditis
	I33.9	Acute endocarditis, unspecified
	I34.0	Mitral (valve) insufficiency
	I34.2	Nonrheumatic mitral (valve) stenosis
	I34.8	Other nonrheumatic mitral valve disorders
	I34.9	Nonrheumatic mitral valve disorder, unspecified
	I35.X	Nonrheumatic aortic valve disorders
	I36.X	Nonrheumatic tricuspid valve disorders
	I37.X	Pulmonary valve disorders
	I38	Endocarditis, valve unspecified
	I39.X	Endocarditis and heart valve disorders in diseases classified elsewhere
	T82.6	Infection and inflammatory reaction due to cardiac valve prosthesis
Septic arthritis	M00.X	Pyogenic arthritis
Osteomyelitis & vertebral discitis	M86.X	Osteomyelitis
	M46.2	Osteomyelitis of vertebra
	M46.3	Infection of intervertebral disc (pyogenic)
	M46.4	Discitis, unspecified
	M89.9	Disorder of bone, unspecified
Central nervous system infections	G06.0	Intracranial abscess and granuloma
	G06.1	Intraspinal abscess and granuloma
	G06.2	Extradural and subdural abscess, unspecified

8.25 Appendix 25. DAG describing hypothesized relationships between primary exposure, covariates, and outcomes in study on opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections.

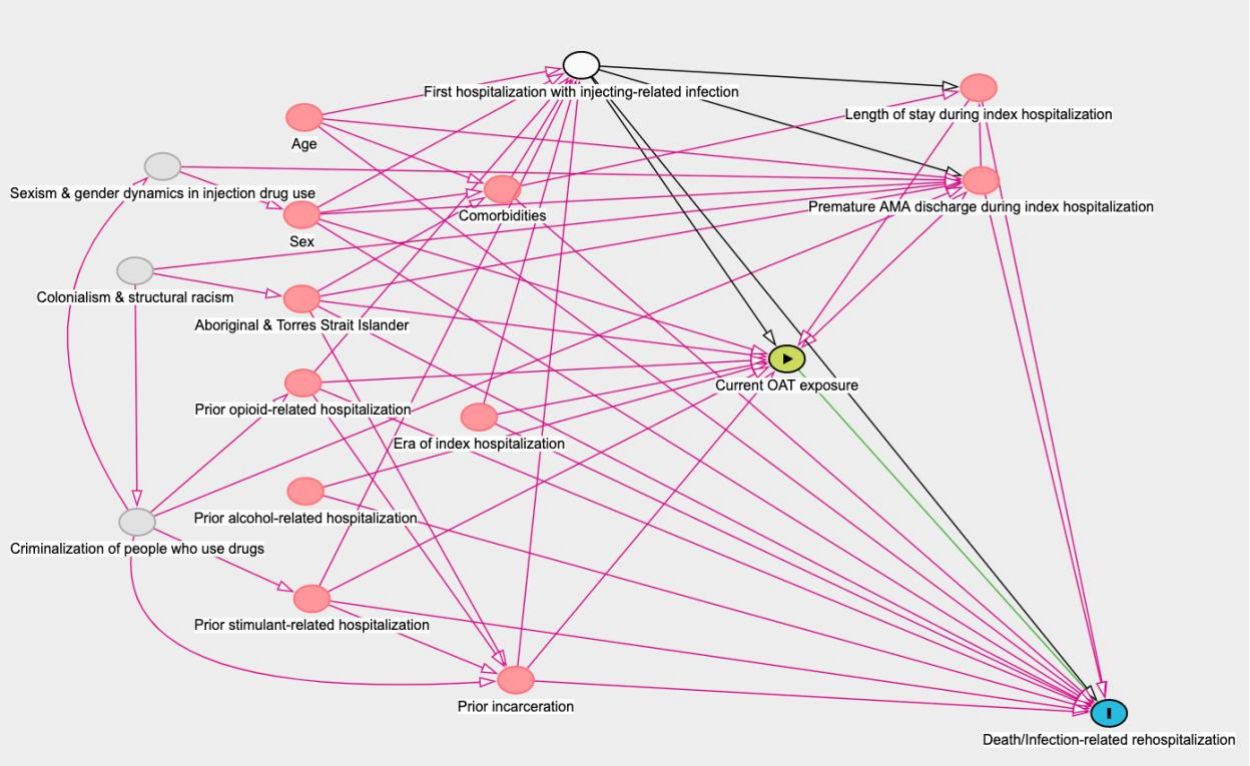

Figure 80. Directed Acyclic Graph (DAG) describing hypothesized relationships between primary exposure, covariates, and outcomes.

Figure generated with Daggity.net software. Temporal order of variables generally goes from the left to right. Blue circle is outcome. Green circle is the main exposure. Red circles are exposures that are ancestors of exposures and of outcomes; in this case, they are conceptualized and presented as confounders. White circles are other adjusted variables (in this case, conditioned-upon through study design and selection criteria). Grey circles are unobserved variables (in this case, macro-environmental influences on risk). The green line (from the green circle/main exposure, "Current OAT exposure", to the blue circle/outcome, all-cause death or injection-related infection) represents the causal relationship of interest. The pink lines represent potentially-biasing "backdoor" paths. Adjusting for all the exposures represented by red circles (in a multivariable regression model) blocks the potentially-biasing paths and is intended to improve the accuracy of the effect estimate for the relationship between the main exposure and the outcome.

8.26 Appendix 26. Pre-registered study protocol for self-controlled case series on time periods of altered risk of injecting-related infections.

Time periods of altered risk for severe injection drug use-associated skin and soft-tissue infections: protocol for a self-controlled case series in New South Wales, Australia, 2001-2018

PROTOCOL

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Thomas D. Brothers[1,2,3,*]; Dan Lewer[1,2]; Nicola Jones[1]; Samantha Colledge-Frisby[1]; Matthew Bonn[4]; Alice Wheeler[5]; Jason Grebely[5]; Michael Farrell[1]; Andrew Hayward[2]; Matthew Hickman[6]; Louisa Degenhardt[1]

[1]National Drug and Alcohol Research Centre (NDARC), UNSW Sydney
[2]UCL Collaborative Centre for Inclusion Health, Department of Epidemiology and Public Health, University College London
[3]Division of General Internal Medicine, Department of Medicine, Dalhousie University
[4]Canadian Association of People who Use Drugs
[5]Kirby Institute, UNSW Sydney
[6]Population Health Sciences, University of Bristol

*Address correspondence to: thomas.brothers@dal.ca (TDB)

INTRODUCTION

Injecting-related bacterial and fungal infections (e.g., skin and soft-tissue infections, endocarditis, osteomyelitis, etc.) are common health problems among people who inject drugs, associated with pain, disability, and death. The incidence of these infections is rising in the UK,[1,2] Australia,[3,4], Canada,[5–7] and the USA.[8–10] Individual injecting practices (e.g. intramuscular or subcutaneous injecting, skin cleaning, handwashing, more frequent injecting) have been identified as risk factors for injecting-related infections.[11] Individual-level behavioural and educational interventions have been developed to promote safer injecting techniques,[12–15] but these show inconsistent efficacy and have not made an impact on population incidence. Better understanding of the social and environmental factors that shape individual injecting practices and risk for injecting-related infections is urgently needed.[16,17]

Qualitative research has explored several social and structural factors contributing to risk for injecting-related infections through shaping individual injecting experiences and access to health care.[16,17] For example, people who are incarcerated often need to hide their injection drug use and reuse contaminated or blunted (dull) needles when they do not have access to harm reduction services like a needle and syringe program.[18–20] People without housing are less likely to have hygienic, well-lit, and safe spaces to prepare and inject their drugs using clean touch techniques, especially if they do not have access to a supervised consumption site.[21–23] Policing enforcement may lead people to rush their injection when injecting publicly, and inject in their muscle (a practice associated with increased risk of abscesses) to avoid being caught with drugs.[24] Many people who inject drugs delay or avoid accessing health care for superficial infections, because of previous experiences of discrimination and untreated pain and withdrawal in health care settings.[25]

While these social determinants of injecting-related infections have been explored in interview-based and ethnographic qualitative work, quantitative research on how social and structural exposures contribute to risk for injecting-related infections has been limited. For example, several quantitative studies have simply described positive associations between injecting-related infections with recent incarceration[18,26,27] and with current homelessness.[28] One ecological study found no association between police raids and hospital admissions for injection drug use-associated endocarditis among the same neighborhoods during those time periods.[29] These quantitative studies have not identified potential causal pathways or opportunities for risk-reduction interventions.

A potential value of quantitative studies would be to identify signals of specific time periods or transitions (e.g., immediately following release from incarceration) associated with increased risk for injecting-related infections. These findings could both explore the time-varying nature of social exposures (e.g. incarceration) that would require tailored responses (e.g. harm reduction programs within jails and prisons) and may reveal opportunities for "critical time interventions"[30,31] (i.e. time-specific interventions harm reduction, navigation, or liaison/linkage to care) at certain time points. This has been most robustly investigated in the relationship between release from incarceration and increased overdose risk,[30,32] but to our knowledge has not been explored in the context of risk for injecting-related infections.

Self-controlled study designs can be particularly useful for examining the effect of the timing of exposures. The self-controlled case series makes within-individual comparisons in the probability of an event occurring during different exposure periods. As such, self-controlled study designs inherently account for the effects of unmeasured confounding factors that do not vary over time. These methods are especially useful for studying exposures, such as incarceration or opioid agonist treatment (OAT) use, in which people who have these exposures likely differ from people who do not have these exposures in ways that are difficult to measure.[33–38] For example, a self-controlled study identified time periods of increased risk of non-fatal overdose on the day of admission to

prison, within 4 weeks after release from prison, and within 2 weeks after hospital discharge.[38] The same study identified lower risk of non-fatal overdose during use of opioid agonist treatment (OAT).[38] A case-crossover study identified increased risk for fatal overdose in the days after hospital discharge compared to other times.[37]

The excess risk of overdose seen during these time periods has been attributed to several potential factors. These include return to use following periods of abstinence and associated loss of tolerance, and a reduced capacity to use drugs more safely due to disconnection from social networks, housing and income support, and harm reduction and treatment services.[32,39] Some of these (e.g. reduced capacity to use drugs safely due to social disconnection) could be relevant to injecting-related infections but others (e.g. loss of tolerance) would not necessarily be relevant. We are not aware of any existing studies using self-controlled designs to understand associations between timing of exposures and risk for injecting-related infections.

Using a self-controlled study design, the aim of this proposed study is to quantify the risks of injecting-related bacterial and fungal infections associated with initiation of, exposure to, and discontinuation of incarceration and OAT among a sample of people with opioid use disorder.

METHODS

This study will involve several self-controlled case series. This method includes only cases (i.e., people who experienced the outcome of interest) and focuses on the timing of exposures in relation to the outcome.[33,34,36,40] Self-controlled study designs measure the effects of transient exposures; they were initially designed to understand the "triggering" effects of an exposure (e.g. MMR vaccination) on an outcome (e.g. aseptic meningitis) and now have been extended to time-varying exposures of longer duration.[33,34,41]

Setting and data sources

Data will come from the Opioid Agonist Treatment Safety (OATS) Study, which is an administrative data linkage cohort including every person in New South Wales, Australia, who accessed OAT (methadone or buprenorphine) for opioid use disorder from 2001 to 2018. OAT permit records are linked to vital statistics (mortality records), hospitalizations, emergency department visits, incarceration, and ambulatory mental health records databases. Every participant in the OATS Study has opioid use disorder and has accessed OAT at some point. The protocol and cohort profile for the OATS Study has been published.[42,43]

Sample

The sampling frame includes all OATS Study participants with linkage to hospital records. As self-controlled case series are a case-only study design, the analytic sample will include all OATS Study cohort participants who experienced at least one outcome of interest (i.e., hospitalization for injecting-related infection) after their first recorded use of OAT (which made them eligible for inclusion in the OATS Study).

Outcomes

Our primary outcome is hospital admission (unplanned, emergency) for skin and soft-tissue infection, defined using ICD-10 code groupings consistent with prior studies (See Table 1).[4,44]

Table 1. ICD-10 codes used to identify skin and soft-tissue infections.

Codes	Diagnosis
A48.0	Gas gangrene
L02.X	Cutaneous abscess, furnuncle and carbuncle
L03.X	Cellulitis
L08.8	Other specified local infections of skin and subcutaneous tissue
L08.9	Local infection of skin and subcutaneous tissue, unspecified
L97	Ulcer of lower limb, NEC
L98.4	Chronic ulcer of skin, NEC
L98.8	Other specified disorders of skin and subcutaneous tissue
L98.9	Disorder of skin and subcutaneous tissue, unspecified

M72.6	Necrotizing fasciitis
R02	Gangrene, NEC

NEC : Not elsewhere classified.

Prior research from our team has grouped together multiple types of injecting-related bacterial and fungal infections (including endocarditis, osteomyelitis, and septic arthritis) in addition to skin and soft-tissue infections, recognizing their shared pathophysiology.[4,44] These deeper infections are often caused by insufficiently treated skin and soft-tissue infections that progress and become more severe until they enter the bloodstream; so, there is likely a more a variable and longer duration between the timing of the initial infection and the timing of the hospitalization with deeper infections compared to skin and soft-tissue infections.

The self-controlled case-series method requires recurrent outcome events to be independent. Given that having had a previous injecting-related infection is associated with increased risk of subsequent infections, recurrent infections are likely to be dependent. Therefore, we plan to follow recommended practice and limit the analysis to the first hospitalization for injecting-related skin and soft-tissue infections during the study period.[35,45,46]

Exposures

In separate models, we will examine time periods (known as "focal windows" in guidance documents[40]) associated with initiation of, exposure to, and discharge from (a) incarceration and (b) use of OAT (methadone or buprenorphine). These will be compared to unexposed time periods (also known as "referent windows"[40]).

These exposures have been assessed in relation to risk of overdose in prior self-controlled studies.[37,38] We plan to assess time periods of up to 2 weeks, while these prior studies examining overdose risk included time periods as short as one day. Overdoses are immediate events occurring

over a timeline of minutes, so a risk period of one day may capture this entirely. Given that acute injecting-related infections may take days (and occasionally weeks) to progress in severity to the point of requiring hospitalization, we only consider risk periods in increments of two or more weeks.

We also added time periods preceding the exposure. If we observe an excess risk of injecting-related infections in the time period leading up to an exposure (e.g. incarceration), it may point to a third factor (e.g. life stressors associated with impoverishment or loss of housing) that are increasing risks for both the outcome and the exposure (e.g. infections and incarceration). This will also allow us to further explore the recent findings of Colledge-Frisby and colleagues that infection risk may be increased immediately before OAT initiation.[4] Similarly, if risk of hospitalization for injecting-related infections appears elevated immediately following incarceration or initiation of OAT, this may reflect a process of recognizing and facilitating treatment of pre-existing infections in these settings.

Primary exposure 1: Incarceration

Depending on the incarceration setting, people may have less or more access to unregulated drugs while incarcerated. People who use drugs who are incarcerated are forced to use drugs in unconventional and hidden ways, exposing them to greater harms and risks related to drug use.[47] At the same time, incarceration leads to heavily restricted access to harm reduction services, including no access to needle and syringe distribution programmes and lack of education on safer injecting technique. For example, a study on hepatitis C risks in Australian prisons found that of 1,926 study participants with any history of injection drug use, 1,134 (59%) reported injecting in prison.[48] Of the 797 who reported injecting in the previous month, 598 (75% of these) reported injecting at least once per week and 722 (91%) reported re-using injecting equipment after someone else had used it (a known risk factor for injecting-related infections). All Australian prisons in the study offered some harm reduction services, including OAT and access to an ammonium disinfectant to cleanse injecting equipment, but did not offer needle and syringe programmes.[48–50] The likelihood of injection during

prison may vary depending on length of imprisonment and availability of OAT. Therefore, risks for injecting-related infections may be higher while incarcerated or soon after release. As described above, the time immediately following release from incarceration is associated with excess risks of overdoses, which has been attributed to return to use following periods of abstinence and associated loss of tolerance, and a reduced capacity to use drugs more safely due to disconnection from social networks, housing and income support, and harm reduction and treatment services.[32,39]

Proposed risk periods for incarceration exposure:

1. Weeks -4 and -3 (days -30 to -16) before incarceration
2. Weeks -2 and -1 (days -15 to -1) before incarceration
3. Weeks 1 and 2 (days 0 to 14) of incarceration
4. Weeks 3 and 4 (days 15 to 29) of incarceration
5. Remainder of time incarcerated (day 30 onward)
6. Weeks 1 and 2 (day 0 to 14) after release
7. Weeks 3 and 4 (day 15 to 29) after release
8. Remainder of time not incarcerated (day 30 onward)

Primary exposure 2: Opioid agonist treatment (OAT)

Opioid agonist treatment (OAT; e.g. methadone, buprenorphine) allows people with opioid use disorder to inject less frequently and in a more controlled manner, and facilitates regular health care contacts. It is well-established that current use of OAT is associated with significantly reduced risks of overdose.[51,52] Prior research from the OATS Study found use of OAT was associated with reduced incidence[4] and recurrence[44] of injecting-related infections but this has not been studied using a self-

controlled study design. The time following OAT discontinuation has been associated with excess risks of death,[53] but this has not been previously studied in relation to injecting-related infections.

Consistent with prior OATS Study analyses, a new OAT episode will be defined as one starting more than six days after the end of a previous treatment episode.[4,39,44,54–56] The same definition will be used for defining the end of an OAT episode, interpreting the 6 days following the final day of the prescription exposed to OAT. This decision was originally based on consultation with clinicians and pharmacologists[56] and similar approaches (e.g., 3 to 6 days) have been used by other investigators outside the OATS Study.[57,58]

Proposed risk periods for OAT exposure:

1. Weeks -4 and -3 (days -30 to -16) before OAT initiation
2. Weeks -2 and -1 (days -15 to -1) before OAT initiation
3. Weeks 1 and 2 (days 0 to 14) on OAT
4. Weeks 3 and 4 (days 15 to 29) on OAT
5. Remainder of OAT treatment episode (day 30+)
6. Weeks 1 and 2 (day 0 to 14) after OAT discontinuation
7. Weeks 3 and 4 (day 15 to 29) after discontinuation
8. Remainder of time not using OAT (day 30+)

Covariates

Covariates that do not vary by time will be adjusted for by the self-controlled study design. We will incorporate the following time-varying exposures into multivariable regression models, described below:

- Calendar year: This could act as a proxy for policy and risk environment changes affecting exposures (e.g. availability and eligibility of OAT; changes in policing enforcement and incarceration) and outcomes (e.g. changes in unregulated drug supply influencing risk for injecting-related infections).
- Age

Analysis

We will calculate descriptive statistics for this case-only sample, including age at study entry, sex, and Aboriginal or Torres Strait Islander status.

We will then calculate incidence rate ratios (IRRs) of each outcome using conditional Poisson models, comparing the incidence of hospitalizations for skin and soft-tissue infections during defined exposure periods to the unexposed period. Only individuals who change exposure status during follow-up will contribute to these IRR estimates. However, all other individuals contributed indirectly to the multivariable models through the estimates of the other covariates.

See Figure 1, below for schematic illustrating separate analyses for one individual who has experienced each exposure at least once. Note that some of the exposure periods can occur simultaneously (e.g. initiation of OAT in the days following release from incarceration). Our primary analysis will consider each of these potential exposures in separate models without any interactions.

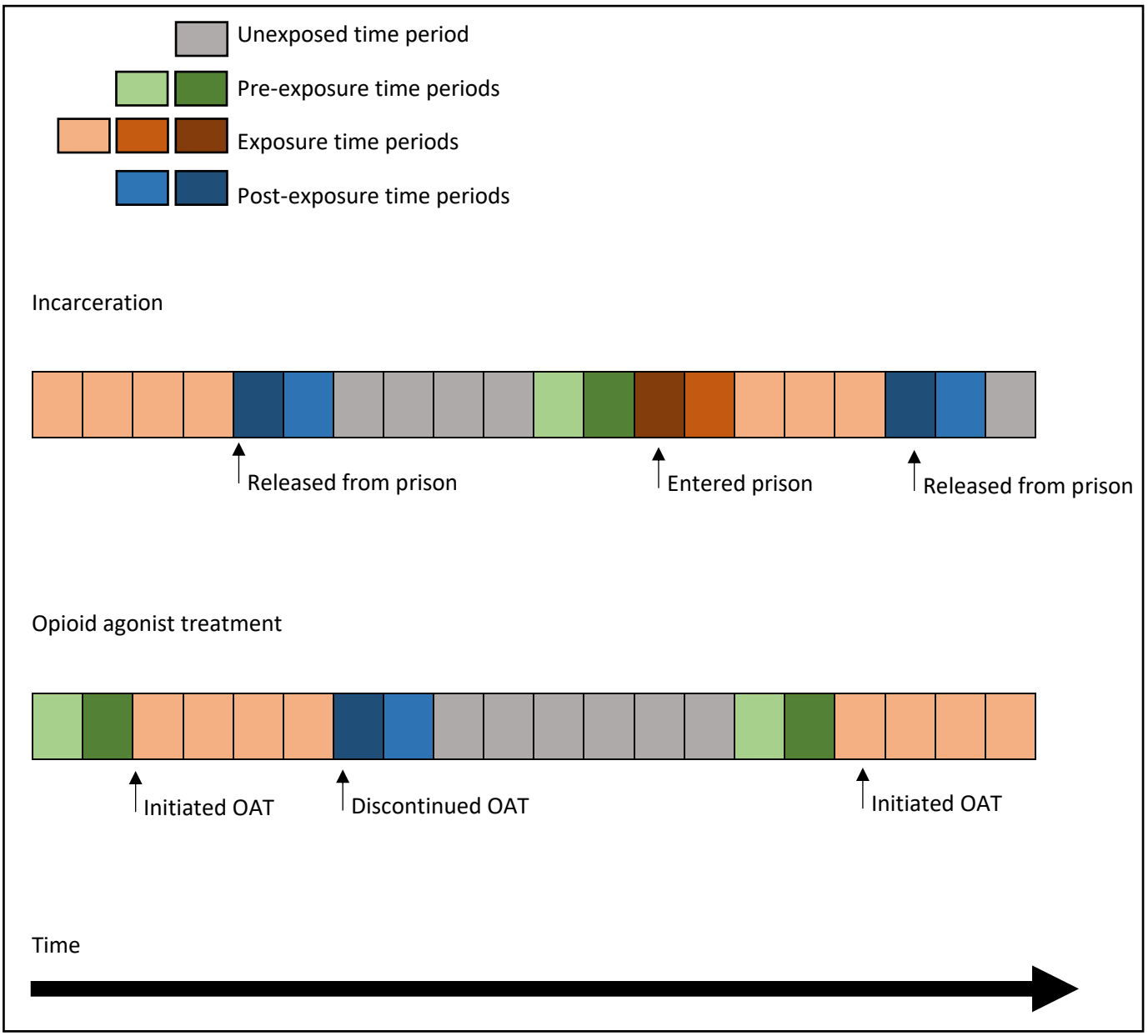

Figure 1. Time periods of potentially altered risk for outcomes in the self-controlled case series. Each horizontal bar represents a single study participant, which each shaded block representing a different risk time period. Figure adapted from Keen et al.[38] OAT: Opioid agonist treatment.

POTENTIAL RESULTS

Table 1. Shell table showing potential presentation of sample characteristics

Variable	Level	Value
Age at study entry	Median (IQR)	
Sex	N (%) female	
Aboriginal or Torres Strait Islander	N (%)	
Ever incarcerated	Yes, N(%)	
	No	
Ever on OAT	Yes, N(%)	
	No	

Table 2. Shell table showing potential presentation of association between time periods and the incidence of hospitalizations for injecting-related bacterial or fungal infections.

Exposure category	**N (%)**	**IRR (95% CI)**	**Adjusted IRR (95% CI)**
Incarceration			
Time out of incarceration	N (%)	1 (ref)	1 (ref)
Weeks 4-3 before incarceration	N (%)	IRR (95% CI)	aIRR (95% CI)
Weeks 2-1 before incarceration	…	…	…
Weeks 1-2 of incarceration	...	...	...
Weeks 3-4 of incarceration			
During remainder of incarceration	…	…	…
Weeks 1-2 post-release	…	…	…

Weeks 3-4 post-release	…	…	…
Opioid agonist treatment			
Time out of OAT	N (%)	1 (ref)	1 (ref)
Weeks 3-4 before OAT	N (%)	IRR (95% CI)	aIRR (95% CI)
Weeks 1-2 before OAT	…	…	…
Weeks 1-2 after OAT initiation	…	…	…
Weeks 3-4 after OAT initiation	…	…	…
Remainder of time on OAT	…	…	…
Weeks 1-2 after OAT discontinuation	…	…	…
Weeks 3-4 after OAT discontinuation	…	…	…

LIMITATIONS

1. **The self-controlled case series design does not produce estimates of absolute risk, only estimates of relative risk.** As this study design involves a case-only analytic sample, it cannot estimate the absolute risk of injecting-related infections in the population.[34] However, the estimates of relative risk in self-controlled study designs are applicable to the wider population from which the sample was drawn.[34,41]

2. **Some time-varying confounding will not be measurable.** The self-controlled case series design eliminates time-fixed confounders (since individuals serve as their own control), and we will account for measurable time-varying exposures like age and calendar year in regression models. However, some exposures that are not observable in this administrative data, including individual injecting behaviours, housing, income supports, and access to harm reduction services, may be important contributors to infection that vary over time. Some of these may act as unmeasured, time-varying confounders, e.g. if periods of extreme life stressors (e.g. loss of housing) lead to both increased risk of our main exposure (e.g. incarceration) and study outcome (i.e., injecting-related infections). We have included pre-exposure risk periods (e.g. 1-2 and 3-4 weeks prior to incarceration) as one way to identify potential time-varying confounding.
3. **The onset duration of injecting-related infections might vary from days to weeks between an initial abscess and hospitalization, so timing of "trigger" effects might differ from observations window.** To account for this we have designed the risk periods to comprise weeks instead of 1-2 days, but this could bias effect estimates towards the null, especially for acute risk periods (e.g. immediately after prison release).
4. **This analysis excludes people who were never on OAT.** Every participant in the OATS Study (from which our sample was derived) has used OAT for opioid use disorder at some point. Effect estimates (in this case, IRRs) from self-controlled case series only include people with varying exposure status, so for the OAT exposure analysis people who never accessed OAT would be excluded anyway. For the incarceration exposure analysis this could introduce some selection bias.
5. **Linkage to hospitalisations outside of New South Wales are not available**.

ETHICS AND APPROVALS

Approval for the OATS Study is provided by New South Wales Population & Health Services Research Ethics Committee (2018/HRE0205), the NSW Corrective Services Ethics Committee and the Aboriginal Health and Medical Research Council Ethics Committee (1400/18).

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8.27 Appendix 27. Modifications to pre-registered study protocol for self-controlled case series on time periods of altered risk for injecting-related skin and soft-tissue infections.

In the study protocol,[372] I had proposed as the outcome for our main analysis to assess only hospitalizations for injecting-related skin and soft-tissue infections, because I assumed that the timing between infection onset (e.g. injecting site abscess) and developing a severe infection requiring hospitalization would be shorter and more consistent for skin and soft-tissue infections compared to deeper infections. I had proposed to assess hospitalizations for any injecting-related bacterial infection (e.g., including skin and soft-tissue infections, endocarditis, osteomyelitis) as a supplementary analysis to see if effect estimates differ. I found the effect estimates did not meaningfully differ and we consider that these time periods of altered risk apply to all injecting-related infections (rather than only skin and soft-tissue infections). I chose to include all injecting-related infections in the main analysis to achieve a larger sample size, and given the shared pathophysiology and risk factors among multiple types of injecting-related bacterial infections.

Limiting the outcome to only participants' first hospitalization for skin and soft-tissue infections, resulted in 6,192 participants with at least one hospitalization (see Table 14). Regression results were similar to the main analyses. See Table 15 and, Table 16 below.

Table 14. Descriptive characteristics of sample in self-controlled case series of hospital admissions for injection drug use-associated bacterial infections, following original protocol.

Variable	Level	Value
Sample size	N (%)	6,192 (100%)
Age at study entry	Median (IQR)	37.9 (31.5 – 45.2)
Age at first hospital admission for injecting-related infection	Median (IQR)	39.3 (32.5 – 46.6)
Sex	Female, N (%)	2,142 (34.6%)
Aboriginal or Torres Strait Islander	Yes, N (%)	827 (13.4%)
Ever incarcerated during observation period	Yes, N(%)	3,177 (51.3%)
Ever on OAT during observation period	Yes, N(%)	6,192 (100%)
Infection type in first hospital admission for injecting-related infection	N (%)[a]	
	Skin and soft-tissue infections	6,192 (100%)
	Sepsis/bacteraemia	154 (2.5%)
	Endocarditis	58 (0.9%)
	Osteomyelitis	59 (1.0%)
	Septic arthritis	34 (0.5%)
	Central nervous system	8 (0.1%)

IQR: Interquartile range. OAT: Opioid agonist treatment.

[a]Values sum to greater than 100% because each hospital admission can have more than one infection diagnosis.

Table 15. Risk of hospitalization for injecting-related skin and soft tissue infections according to time period in relation to incarceration (results of self-controlled case series). Results of planned analysis with outcome limited to include participants' first hospitalization for injecting-related skin and soft-tissue infection.

Variable	Levels	Model 1 (Not including pre-exposure periods)	Model 2 (Including pre-exposure periods)
Incarceration	4 to 3 weeks before incarceration	–	1.45 (1.20 – 1.76)
	2 weeks before incarceration	–	1.31 (1.08 – 1.59)
	Incarcerated, first 2 weeks	1.24 (0.96 – 1.60)	1.25 (0.93 – 1.68)
	Incarcerated, weeks 3 and 4	0.22 (0.12 - 0.41)	0.24 (0.13 - 0.47)
	Incarcerated, weeks 5 to 52	0.23 (0.18 - 0.28)	0.23 (0.18 - 0.29)
	Incarcerated, beyond 52 weeks	0.14 (0.10 - 0.20)	0.15 (0.11 - 0.22)
	4 to 3 weeks before release from incarceration	–	0.25 (0.13 - 0.45)
	2 weeks before release from incarceration	–	0.53 (0.36 - 0.78)
	Community (after release), first 2 weeks	1.52 (1.26 - 1.82)	1.46 (1.18 - 1.80)
	Community, weeks 3 and 4	1.24 (1.01 – 1.52)	1.29 (1.03 – 1.60)
	Community, weeks 5 to 52	Reference (1.00)	Reference (1.00)
	Community, beyond 52 weeks	0.75 (0.69 - 0.82)	0.76 (0.69 - 0.83)
Opioid agonist treatment	1 day intervals	0.80 (0.72 – 0.87)	0.79 (0.73 – 0.88)
Age	10 year intervals	0.96 (0.85 - 1.09)	0.96 (0.85 - 1.09)
Calendar year	1 year intervals	1.01 (0.99 - 1.03)	1.01 (0.99 - 1.03)
Time since first OAT	1 year intervals	1.00 (0.97 – 1.02)	1.00 (0.97 - 1.02)

Table 16. Risk of hospitalization for injecting-related skin and soft tissue infections according to time period in relation to opioid agonist treatment (results of self-controlled case series). Results of planned analysis with outcome limited to include participants' first hospitalization for injecting-related skin and soft-tissue infection.

Exposure (all time-varying, by day)	Levels	Model 1 (Not including pre-exposure periods) aIRR (95% CI)	Model 2 (Including pre-exposure periods) aIRR (95% CI)
Opioid agonist treatment	4 to 3 weeks before starting OAT	–	2.36 (1.92 – 2.89)
	2 weeks before starting OAT	–	3.80 (3.23 – 4.47)
	On OAT, first 2 weeks	2.60 (2.18 – 3.11)	2.63 (2.15 – 3.22)
	On OAT, weeks 3 and 4	1.56 (1.24 – 1.97)	1.64 (1.28 - 2.10)
	On OAT, weeks 5 to 52	Reference (1.00)	Reference (1.00)
	On OAT, beyond 52 weeks	0.89 (0.81 – 0.98)	0.89 (0.81 – 0.98)
	4 to 3 weeks before stopping OAT	–	1.59 (1.27 – 1.99)
	2 weeks before stopping OAT	–	1.70 (1.39 – 2.08)
	Off OAT, first 2 weeks	1.75 (1.41 – 2.19)	1.72 (1.34 – 2.20)
	Off OAT, weeks 3 and 4	1.34 (1.04 – 1.73)	1.14 (0.85 – 1.54)
	Off OAT, weeks 5 to 52	1.30 (1.17 - 1.45)	1.18 (1.06 – 1.32)
	Off OAT, beyond 52 weeks	1.01 (0.91 – 1.13)	0.93 (0.83 – 1.04)
Incarcerated	1 day intervals	0.30 (0.26 – 0.35)	0.31 (0.26 - 0.36)
Age	10 year intervals	0.99 (0.91 – 1.09)	1.00 (0.92 – 1.09)
Calendar year	1 year intervals	1.02 (1.01 – 1.03)	1.01 (1.00 - 1.03)
Time since first OAT	1 year intervals	0.98 (0.97 – 1.00)	0.98 (0.97 – 1.00)

8.28 Appendix 28. Results of sensitivity analyses.

Table 17. Risk of hospitalization for injecting-related bacterial infections according to time period in relation to incarceration (results of self-controlled case series). Results of supplementary analysis with outcome expanded to include all of participants' hospitalizations for injecting-related infections.

Variable	Levels	Model 1 (Not including pre-exposure periods) aIRR (95% CI)	Model 2 (Including pre-exposure periods) aIRR (95% CI)
Incarceration	4 to 3 weeks before incarceration	–	1.31 (1.14 – 1.49)
	2 weeks before incarceration	–	1.18 (1.03 – 1.35)
	Incarcerated, first 2 weeks	0.94 (0.76 – 1.14)	0.93 (0.73 – 1.16)
	Incarcerated, weeks 3 and 4	0.24 (0.15 - 0.35)	0.24 (0.14 – 0.37)
	Incarcerated, weeks 5 to 52	0.20 (0.17 – 0.24)	0.21 (0.18 – 0.25)
	Incarcerated, beyond 52 weeks	0.14 (0.10 – 0.18)	0.14 (0.10 – 0.18)
	4 to 3 weeks before release from incarceration	–	0.25 (0.16 – 0.37)
	2 weeks before release from incarceration	–	0.41 (0.30 – 0.55)
	Community (after release), first 2 weeks	1.38 (1.21 – 1.57)	1.38 (1.19 - 1.60)
	Community, weeks 3 and 4	1.27 (1.10 – 1.46)	1.29 (1.10 – 1.50)
	Community, weeks 5 to 52	Reference (1.00)	Reference (1.00)
	Community, beyond 52 weeks	0.78 (0.74 – 0.83)	0.80 (0.75 – 0.85)
Opioid agonist treatment	1 day intervals	0.78 (0.74 – 0.83)	0.79 (0.73 - 0.83)
Age	10 year intervals	0.99 (0.91 – 1.07)	0.99 (0.91 - 1.07)
Calendar year	1 year intervals	1.08 (1.07 - 1.09)	1.07 (1.06 - 1.09)
Time since study entry	1 year intervals	0.98 (0.97 – 1.00)	0.98 (0.97 – 1.00)

Table 18. Risk of hospitalization for injecting-related bacterial infections according to time period in relation to opioid agonist treatment (results of self-controlled case series). Results of sensitivity analysis with outcome expanded to include all of participants' hospitalizations for injecting-related infections.

Exposure (all time-varying, by day)	Levels	Model 1 (Not including pre-exposure periods) aIRR (95% CI)	Model 2 (Including pre-exposure periods) aIRR (95% CI)
Opioid agonist treatment	4 to 3 weeks before starting OAT	–	2.49 (2.19 - 2.83)
	2 weeks before starting OAT	–	3.43 (3.07 - 3.83)
	On OAT, first 2 weeks	2.20 (1.93 - 2.50)	2.23 (1.92 - 2.59)
	On OAT, weeks 3 and 4	1.49 (1.26 - 1.75)	1.53 (1.27 - 1.81)
	On OAT, weeks 5 to 52	Reference (1.00)	Reference (1.00)
	On OAT, beyond 52 weeks	0.85 (0.80 – 0.91)	0.85 (0.80 - 0.91)
	4 to 3 weeks before stopping OAT	–	1.54 (1.32 - 1.77)
	2 weeks before stopping OAT	–	1.71 (1.49 - 1.94)
	Off OAT, first 2 weeks	1.50 (1.28 – 1.76)	1.45 (1.21 - 1.73)
	Off OAT, weeks 3 and 4	1.29 (1.08 – 1.53)	1.13 (0.92 - 1.37)
	Off OAT, weeks 5 to 52	1.28 (1.19 - 1.38)	1.16 (1.07 - 1.25)
	Off OAT, beyond 52 weeks	0.99 (0.92 – 1.06)	0.90 (0.83 - 0.97)
Incarcerated	1 day intervals	0.26 (0.23 - 0.29)	0.27 (0.24 – 0.30)
Age	10 year intervals	0.99 (0.93 – 1.06)	0.99 (0.94 – 1.05)
Calendar year	1 year intervals	1.08 (1.07 - 1.09)	1.08 (1.07 - 1.09)
Time since first OAT	1 year intervals	0.98 (0.96 – 0.99)	0.98 (0.97 – 0.99)

Table 19. Risk of hospitalization for injecting-related bacterial and fungal infections according to time period in relation to opioid agonist treatment (results of self-controlled case series). Results of sensitivity analysis with opioid agonist treatment exposure duration limited to two days after end date of treatment episode.

Exposure (all time-varying, by day)	Levels	Model 1 (Not including pre-exposure periods) aIRR (95% CI)	Model 2 (Including pre-exposure periods) aIRR (95% CI)
Opioid agonist treatment	4 to 3 weeks before starting OAT	–	2.54 (2.13 – 3.04)
	2 weeks before starting OAT	–	3.58 (3.09 – 4.15)
	On OAT, first 2 weeks	2.54 (2.15 - 2.99)	2.57 (2.13 – 3.09)
	On OAT, weeks 3 and 4	1.55 (1.25 - 1.91)	1.59 (1.26 - 1.99)
	On OAT, weeks 5 to 52	Reference (1.00)	Reference (1.00)
	On OAT, beyond 52 weeks	0.87 (0.79 – 0.94)	0.87 (0.79 - 0.95)
	4 to 3 weeks before stopping OAT	–	1.74 (1.43 – 2.11)
	2 weeks before stopping OAT	–	1.69 (1.40 – 2.04)
	Off OAT, first 2 weeks	1.97 (1.63 – 2.37)	2.12 (1.73 – 2.60)
	Off OAT, weeks 3 and 4	1.42 (1.14 – 1.77)	1.19 (0.91 - 1.55)
	Off OAT, weeks 5 to 52	1.31 (1.19 - 1.44)	1.19 (1.08 - 1.32)
	Off OAT, beyond 52 weeks	1.01 (0.92 – 1.11)	0.93 (0.84 – 1.02)
Incarcerated	1 day intervals	0.30 (0.26 - 0.34)	0.30 (0.26 – 0.35)
Age	10 year intervals	0.98 (0.90 – 1.06)	0.98 (0.90 – 1.06)
Calendar year	1 year intervals	1.02 (1.01 - 1.03)	1.02 (1.01 - 1.03)
Time since first OAT	1 year intervals	0.98 (0.96 – 0.99)	0.98 (0.97 – 0.99)