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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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)

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199 *Primary exposure 2: Opioid agonist treatment (OAT)*

200 Opioid agonist treatment (OAT; e.g. methadone, buprenorphine) allows people with opioid use
201 disorder to inject less frequently and in a more controlled manner, and facilitates regular health
202 care contacts. It is well-established that current use of OAT is associated with significantly
203 reduced risks of overdose.[51,52] Prior research from the OATS Study found use of OAT was
204 associated with reduced incidence[4] and recurrence[44] of injecting-related infections but this has
205 not been studied using a self-controlled study design. The time following OAT discontinuation
206 has been associated with excess risks of death,[53] but this has not been previously studied in
207 relation to injecting-related infections.

208

209 Consistent with prior OATS Study analyses, a new OAT episode will be defined as one starting
210 more than six days after the end of a previous treatment episode.[4,39,44,54–56] The same definition
211 will be used for defining the end of an OAT episode, interpreting the 6 days following the final
212 day of the prescription exposed to OAT. This decision was originally based on consultation with
213 clinicians and pharmacologists[56] and similar approaches (e.g., 3 to 6 days) have been used by
214 other investigators outside the OATS Study.[57,58]

215

216 Proposed risk periods for OAT exposure:

217 1. Weeks -4 and -3 (days -30 to -16) before OAT initiation
218 2. Weeks -2 and -1 (days -15 to -1) before OAT initiation
219 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.

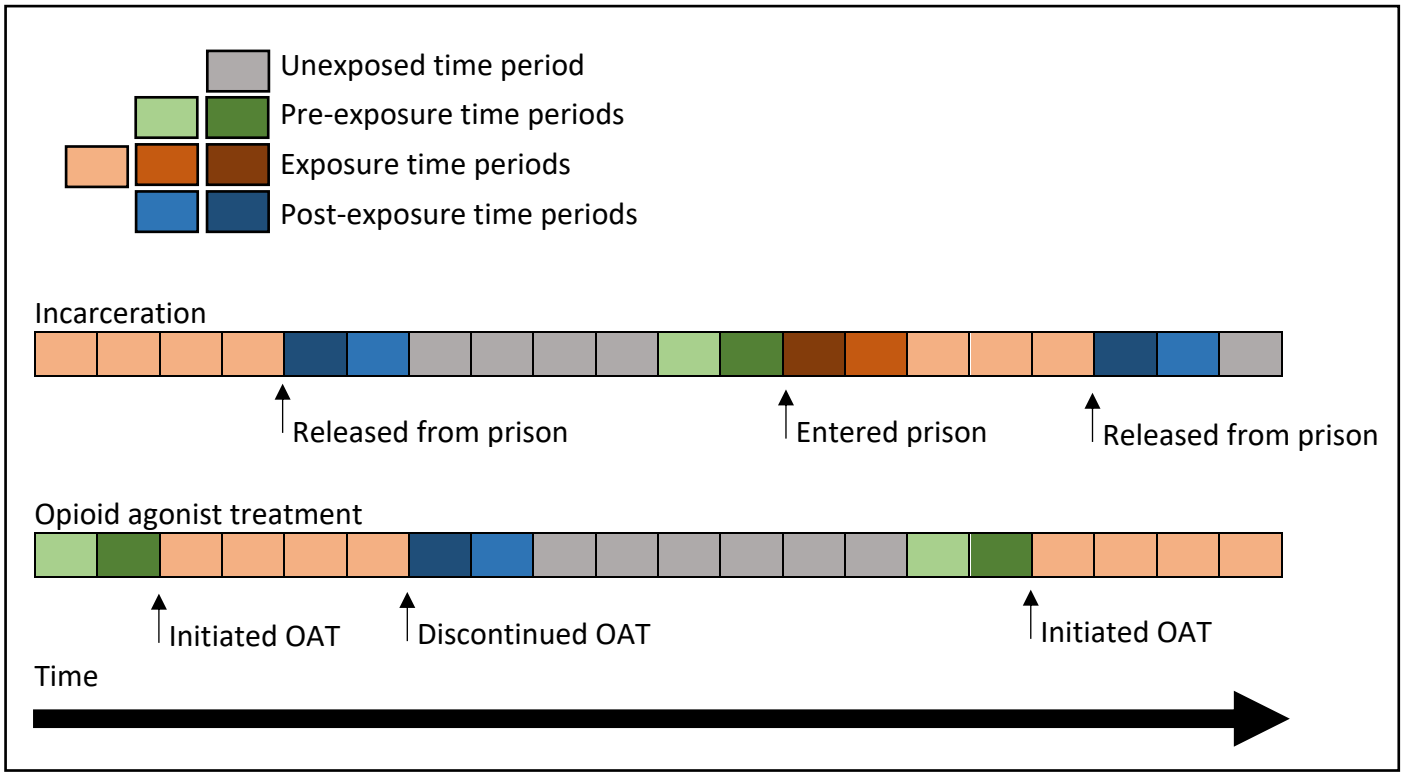

Figure 1. Time periods of potentially altered risk for outcomes in the self-controlled case series. Each horizontal bar represents a single study participant, which each shaded block

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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