

# Social and structural determinants of injection drug use-associated bacterial and fungal infections: A qualitative systematic review and thematic synthesis

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## Abstract

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

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

**Results:** We screened 4841 abstracts and included 26 qualitative studies on experiences of injecting-related bacterial and fungal infections. We identified six descriptive themes organized into two analytical themes. The first analytical 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) restrictions on harm reduction programmes, including structural barriers to effective service provision. The second analytical theme, practices of care among people who use drugs, addressed protective strategies that people 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.

#### KEYWORDS

Endocarditis, epidural abscess, injecting drug use, injection drug use, risk environment, skin and soft-tissue infections, social determinants

## INTRODUCTION

Injection drug use-associated bacterial and fungal infections (e.g. skin and soft-tissue infections, endocarditis, epidural abscess, etc.) cause significant morbidity and mortality among people who inject drugs [1–6]. The incidence of hospitalizations for severe injecting-related infections is increasing in Australia [7], Canada [2, 8], the UK [9] and the USA [10–14].

Efforts to prevent injecting-related bacterial and fungal infections have focused upon individual-level behavioural interventions [15, 16], including education on hand-washing before drug preparation [17], skin-cleaning before injecting [18] and avoiding subcutaneous/intramuscular injecting [19]. While individual-level interventions may be helpful for people who can adopt these practices, evaluations of these interventions have shown mixed results [20–22] and the incidence of injecting-related infections continues to rise.

The 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 [23–26]. Identifying, measuring and ameliorating social-structural factors has informed clinical and public health responses to other drug-related harms, including HIV [27–29], hepatitis C virus (HCV) [30] and overdose [31, 32]. Understanding the influence of social context on health can broaden awareness of the causes of illness [33] and inform more appropriate prevention and treatment interventions [29, 34, 35].

## Objectives

To understand social-structural determinants of injecting-related bacterial and fungal infections and to identify opportunities for potential intervention, we 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.

## METHODS

Before conducting the search, we published our protocol [1] and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021231411). This manuscript follows Preferred Reporting Items for Systematic reviews and Meta-Analyses

(PRISMA) guidelines [36] and is informed by the ENTREQ statement [37] on qualitative systematic reviews. We modified the protocol after our search and full-text review. Our protocol specified a ‘mixed studies review’ of quantitative, qualitative and mixed-methods studies [38, 39]. As we identified more and richer qualitative sources than anticipated, we decided to consider qualitative and quantitative data separately. Here, we report the qualitative systematic review and thematic synthesis.

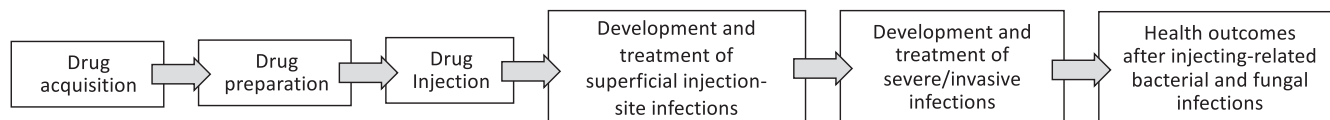
## Conceptual model and framework

The ‘risk environment’, as developed by Rhodes and others [27, 29, 40, 41], is a socio-ecological model describing how macro-environmental (e.g. criminalization; racism) and micro-environmental (e.g. local availability of needle and syringe programmes) factors interplay to influence health practices and outcomes [42]. 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) [43]. 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 [42].

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 [35, 44]. To conceptualize how environments create and perpetuate risk injecting-related infections at different moments, we developed a framework [1] (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.

## Eligibility criteria

A full description is in our published protocol [1]. Briefly, we included articles reporting qualitative studies in peer-reviewed journals. We followed the population, exposures, outcomes approach [45]. The population was people who inject drugs (i.e. any psychoactive



**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.

substance; excluding injecting only performance-enhancing or gender-affirming hormones). 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. re-using non-sterile equipment) or affecting treatment (e.g. leaving hospital before medically advised), we were interested in social-structural factors that influenced these practices. Outcomes included incidence, treatment or sequelae after injecting-related bacterial and fungal infections. Eligible studies were published in English or French between 1 January 2000 and 18 February 2021 (to capture contemporary research more likely to inform policy and clinical practice).

### Information sources and search strategy

We searched PubMed, EMBASE, Scopus, CINAHL and PsycINFO databases. We developed the search strategy in consultation with a librarian (see Supporting information, Table S1 for full search strategy). We supplemented searches with backward and forward citation chaining and with studies known to the review team (which included people with lived/past and living/current experience of injection drug use, researchers and clinicians).

### Data management and reference selection

We uploaded titles/abstracts into Covidence software, where they were automatically de-duplicated. Two reviewers (T.D.B. and either M.B., D.L., E.C. or I.K.) independently screened titles/abstracts, resolving discrepancies through consensus. We obtained full-text reports for sources that passed screening, and one reviewer (T.D.B.) assessed full-text reports.

### Quality assessment

We used the mixed methods appraisal tool (MMAT), which is a validated and commonly used appraisal tool for mixed studies reviews [46, 47]. For qualitative studies, five criteria questions focus on appropriateness of study methods and whether findings are supported by the data. We followed a 'user guide' provided by the MMAT developers [48]. We included studies meeting both MMAT screening

questions: 'Are there clear research questions?' and 'Do the collected data allow to address the research questions?'. We report MMAT results for each study, but this did not inform our qualitative synthesis beyond the screening questions. T.D.B. and E.C. independently appraised each study, resolving discrepancies through discussion.

### Data synthesis

Following Thomas & Harden [49–52], 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; and (3) translating descriptive themes and associated codes across studies to generate analytical themes. Coding and generation of descriptive themes focuses upon study authors' analysis and interpretation, because reviewers do not have full knowledge of the original study data [49, 50].

First, T.D.B. (physician and PhD student with qualitative methods training) familiarized himself with the included studies. Next, M.B. (researcher and drug policy activist with lived/living experience of injecting-related infections) and T.D.B. independently performed line-by-line coding on the same three purposefully selected, data-rich sources [53–55]. They compared and contrasted codes and revised them in an iterative, deductive-inductive process, informed by the risk environment model.

The whole review team met to provide feedback on these candidate codes: D.L. (public health specialist), E.C. and I.K. (medical students), D.W. (infectious diseases and addiction medicine physician), A.K. (infectious disease epidemiologist) and M.H. (health sociologist with lived experience of injection drug use). T.D.B. coded the remaining papers over several rounds, including adding and revising new candidate codes after discussing with the team and through collaborative on-line writing.

T.D.B. 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. T.D.B. then consolidated descriptive themes into conceptual categories to generate analytical themes that were finalized over several iterations and team meetings.

The pre-registered hypothesis can be accessed at: [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=231411](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=231411); the published protocol can be accessed at: <https://doi.org/10.1136/bmjopen-2021-049924>.

## RESULTS

Following de-duplication, we screened 4841 titles/abstracts and evaluated 631 full-text reports. After considering 16 additional reports identified outside the search, we identified 131 eligible studies (quantitative, qualitative and mixed-methods) for the 'mixed studies' review. Here, we report on the 26 studies with qualitative data and analysis (19 qualitative-only, seven mixed-methods); see Figure 2 for the PRISMA diagram. All 26 qualitative studies met quality criteria for inclusion (see Supporting information, Table S2 for full MMAT results).

### Study characteristics

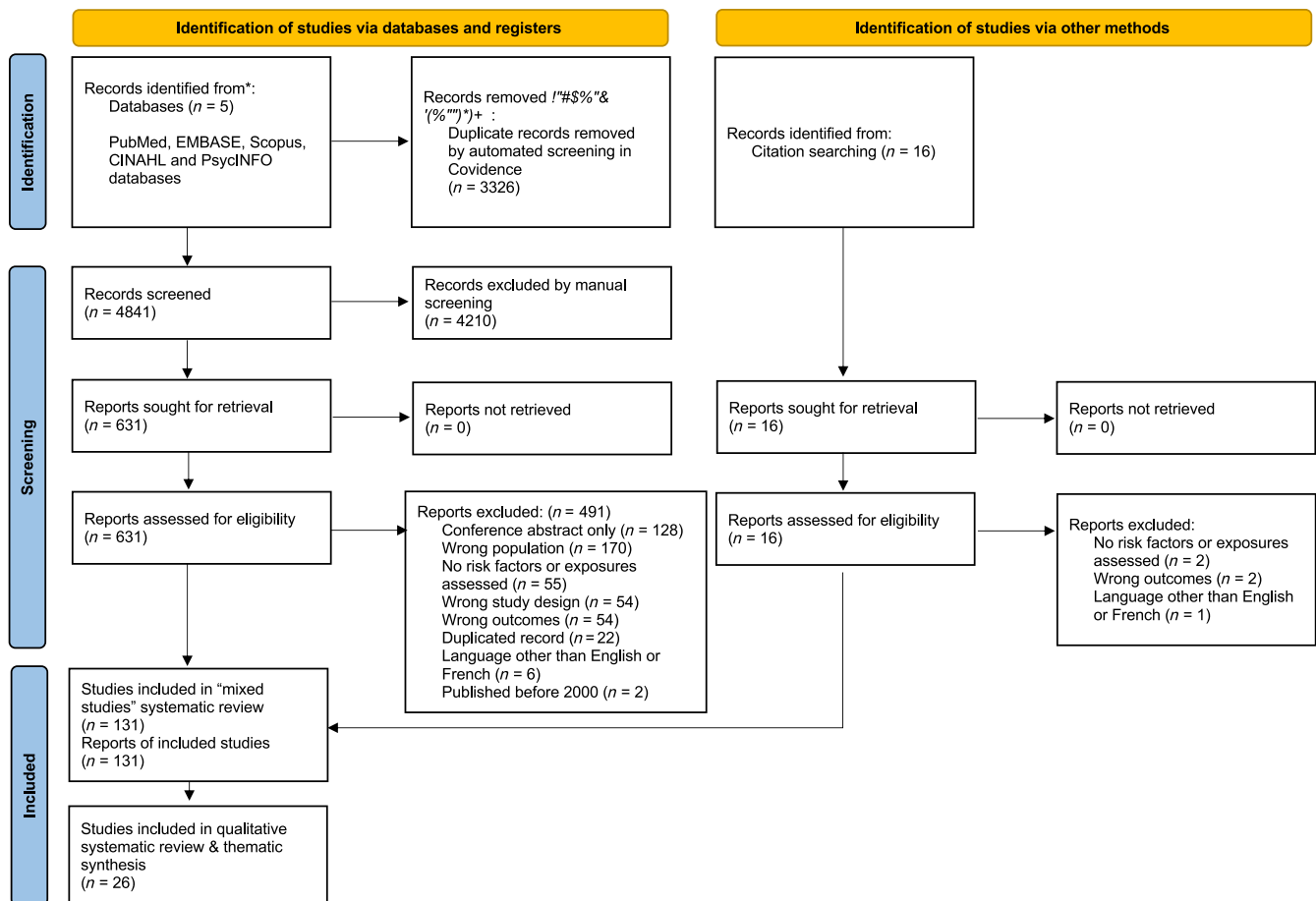
See Table 1 for summaries of individual studies. The majority ( $n = 20$  studies) were conducted in North America. Qualitative data came from individual interviews ( $n = 23$ ), observation/ethnography ( $n = 4$ ) and focus groups ( $n = 2$ ). Studies included experiences of injecting-related skin and soft-tissue infections ( $n = 22$ ), endocarditis ( $n = 7$ ),

bacteraemia ( $n = 3$ ) and osteomyelitis ( $n = 2$ ). All 26 studies included bacterial infections; only one study [66] included fungal infections (candidal ophthalmitis).

### Thematic synthesis

We identified six descriptive themes organized into two analytical themes (see Figure 3).

The first analytical 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) restrictions on harm reduction programmes, including structural barriers to effective service delivery.



**FIGURE 2** Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of included studies in systematic review and thematic synthesis of social and structural determinants of injection drug use-associated bacterial and fungal infections.

**TABLE 1** Summary of included studies in systematic review on social-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 [56]	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 [57]	USA	Secondary analysis of interview data from Bearnot 2019 [56] 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 re-hospitalizations with recurrent infections
Bodkin 2015 [58]	Canada	Individual interviews Qualitative descriptive analysis	14 people who inject drugs recruited from an outreach programme 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

(Continues)

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Bourgois 2006 [59]	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 white people who inject drugs	'... a social science theoretical understanding of the link between large-scale power relations and individual risky practices that shape the spread of blood-borne disease among injectors'	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
Case 2008 [60]	Mexico	Individual interviews Thematic content analysis	43 people who inject drugs recruited through street-based outreach, shooting galleries and drug treatment programmes in Tijuana ( $n = 20$ ) and Ciudad Juárez ( $n = 23$ ) 42% women; median age 30; 30% lived or slept 'on streets' in past 6 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 [61]	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 [53]	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	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

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Epele 2002 [62]	USA	Individual interviews, observations and participation in everyday life settings Analysis approach not specified	programme (Glasgow; $n = 14$ ) or drug treatment service (Edinburgh; $n = 8$ ) 32% women; median 36 years; 59% experienced homelessness during the past six months 35 people who inject drugs recruited through syringe service programme 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	equipment and safer injecting techniques. No participants had learned about infections and associated risks from harm reduction programmes. 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 Some women who inject drugs rely upon 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 [63]	USA	Secondary analysis of interview data from Summers 2018 [64] Thematic analysis	Same sample as qualitative sample in Summers 2018 [64] 12 clients of a syringe services programme 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 behaviours 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 (Continues)

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Harris 2018 [54]	USA	Individual interviews Analysis approach not specified	19 clients of a syringe services programme in Philadelphia [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 health-care 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 2018 [65]	USA	Individual interviews Thematic analysis	Same sample as Harris RE 2018a [54]. 19 clients of a syringe services programme in Philadelphia. 53% women; median 39 years; housing status not reported	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



TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Harris 2019 [66]	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 programmes
Harris 2020 [67]	England	Individual interviews Constructivist grounded theory	36 people who inject drugs, recruited through specialist drug services, homeless hostels and day centres across London, UK	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 (Continues)

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Harris 2020 [68]	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	<p>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</p> <p>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 programmes. 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</p>

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Jafari 2015 [69]	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-orientated medical respite programme Gender, age and current housing status not reported	Experiences of care for injecting-related infections	None specified	despite these environmental constraints, including filtering water through alcohol swabs or asking passers-by for bottled water Participants described past experiences of leaving hospital before completion of their medical treatment because of judgemental and stigmatizing care. Clients with severe injecting-related infections who were being cared for at a harm reduction-orientated medical respite describe receiving less judgemental and stigmatizing care compared to their experience in acute care hospitals
Krüsi 2009 [70]	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 [71]	USA	Ethnography and individual interviews Grounded theory	41 people who inject drugs recruited during ethnographic insertion in drug using community and	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

(Continues)

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
McNeil 2014 [72]	Canada	Individual interviews Thematic analysis	with snowball sampling in Philadelphia (n = 22) and San Francisco (n = 19) 49% women; age unknown; homelessness 'common'	Hospital care experiences	Rhodes' risk environment Social violence	<p>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 US heroin market</p> <p>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 experiences. These were influenced by hospital policies, written and unwritten</p>
Meyer 2020 [73]	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	<p>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 programme to people taking methadone (which was common among</p>

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Paquette 2018 [74]	USA	Individual interviews 'Mixed inductive and deductive approach'	46 people who attended syringe service programmes 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	people injecting diphenhydramine) and stigmatization and punishment of diphenhydramine users in the prison (which led people to delay seeking care for skin infections) 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 programme for sterile injecting equipment as this would 'out' them as a drug user to the small community
Phillips 2013 [55]	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-behavioural 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 re-using needles; and to not cleaning skin. Barriers to practising safer drug preparation and

(Continues)

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Pollini 2010 [75]	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	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 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 re-use being common practice. Participants did not spontaneously attribute risks for abscesses to needle and syringe re-use, until asked by a focus group facilitator
Pollini 2021 [76]	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

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Sheard 2008 [77]	England	Individual interviews Grounded theory	45 women who inject drugs recruited among clients of needle and syringe programmes and addiction treatment programmes in semi-rural North Nottinghamshire and urban Leeds, and through snowball sampling of participant contacts 100% women; age range 16–46 years	Assistance with injecting among women	None specified	cars with out-of-state licence 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 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 equipment. Cleanliness and hygiene were commonly raised as important reasons to avoid re-using or sharing of equipment
Small 2008 [78]	Canada	Individual interviews Thematic analysis	50 people who use supervised injection sites in Vancouver	Impact of the supervised consumption site on access	None specified, but motivated by exploration of 'social and structural barriers to care'	Participants described delaying or avoiding medical care because of previous (Continues)

TABLE 1 (Continued)

Study	Country	Qualitative study design	Sample	Focus of interviews/analysis	Conceptual or explanatory model(s)	Summary of findings
Summers 2018 [64]	USA	Mixed methods Individual interviews Thomas' general inductive approach	12 people who inject drugs recruited from needle and syringe programmes 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	negative experiences. By providing non-judgemental 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  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

The second analytical 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. Our analysis is supplemented by quotations from study authors and participants.

### Social production of risk

#### Unregulated drug supply

In five studies [53, 55, 66, 68, 71], authors presented perspectives from people with injecting-related infections who attributed infections to the quality of unregulated drugs, including adulterants [53, 55, 66, 71], poor solubility [53, 55, 66, 68, 71] and bacterial contamination [55], especially through precipitating skin abscesses and vein sclerosis. Phillips and colleagues [55] 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 are cooking it, it's an okay color, and then the next time you are doing it you have got all this shit floating up, and it's all burnt around the sides (USA) [55].

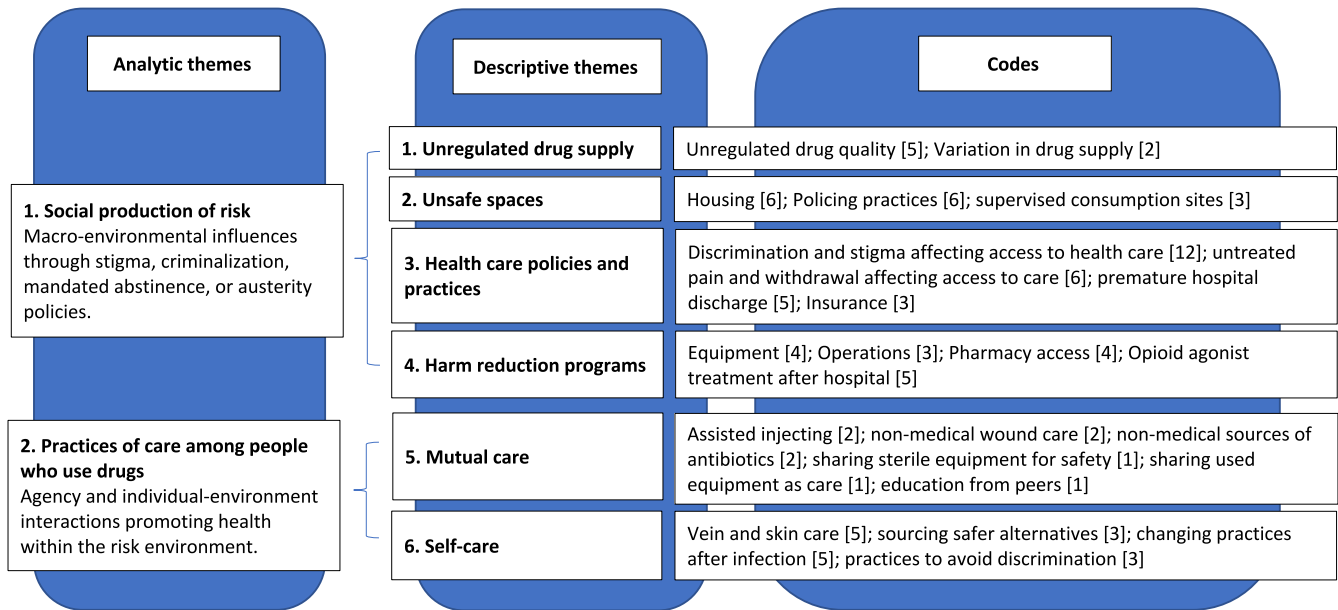
In two studies [66, 71], authors analysed drivers of variation in the unregulated drug supply and associated infection risks. Mars and co-authors [71] identified that participants in Philadelphia, USA, could purchase only tar heroin (less soluble than powder heroin and associated with greater bacterial infection risk) due to regional demarcation of supply networks. In London, UK, Harris and colleagues [66] 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.

#### Unsafe spaces

In eight studies [54, 55, 59, 62, 65, 67, 68, 76], 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 [54, 57, 62, 65, 67, 68], authors explored influences of being without housing. Lack of housing made it harder to prepare and inject drugs safely, including no





**FIGURE 3** Schematic summary of analytical and descriptive themes on social and structural determinants of injection drug use-associated bacterial and fungal infections.

hygienic surfaces to prepare drugs [54, 67, 68], inadequate lighting to find veins (leading to ‘missed hits’ and inadvertent subcutaneous injection) [54] and no clean, running water to wash hands/skin or to dissolve drugs (leading people to use unhygienic water alternatives) [62, 65, 67, 68]:

...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, UK) [68].

In research with people with injecting-related endocarditis, Bearnot and colleagues [56,57] noted that being unhoused interfered with participants’ follow-up care, including ineligibility for outpatient parenteral anti-microbial therapy and having no fixed address for clinic contacts.

In six studies [54, 55, 59, 65, 68, 76] 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 [65], and compromising injecting preparation practice when hurrying and not using filters or sterile water, and/or inadvertently injecting subcutaneously [54, 65, 68]:

I do not 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) [54].

In ethnographic research, Bourgois and colleagues [59] 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 programmes). Police evicted homeless encampments and confiscated possessions, causing participants to miss medical appointments.

Three studies [65, 70, 78] 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 [70] and access to wound/abscess care [70, 78].

#### Health-care policies and practices

In 13 studies [54–56, 58, 61–64, 67, 69, 72–74], 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 [54–56, 58, 61–64, 67, 72–74]) and of untreated pain and withdrawal (in six studies [54, 56, 57, 63, 64, 67]). 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 5 mg Percocet ain’t doing nothing for me. But they automatically think when you come in, ‘I got an abscess. I’m hurting’, ‘Oh, you are trying to get drugs’, this and that... it does prevent a lot of people from going (USA) [54].

Some negative experiences were driven by hospital policies. Harris [67] explains how a London, UK, hospital policy mandates that urine drug screens be obtained before methadone can be dispensed, even if doses are confirmed by pharmacies or treatment programmes. 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 did not [give] me methadone, like someone's said he [doctor] will not do it unless he would have to, and if you do not know your rights, but yeah, it was that that really scared me more than anything, was being sick [in withdrawal] in a hospital (England, UK) [67].

Four studies [61, 62, 67, 72] 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 [72] 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 [62] and fear of child apprehension if their substance use was reported by health professionals [61, 67].

In four studies [57, 58, 69, 72], participants described leaving hospital prematurely, before completing treatment for injecting-related infections. Explanations included leaving hospital in response to discrimination [69, 72] and because restrictions on their movements in hospital triggered post-traumatic stress [57]. Two studies [58, 72] highlighted participants being involuntarily discharged from hospital because of drug use, despite ongoing medical need. Jafari and colleagues [69] evaluated experiences with a care model in Vancouver, Canada, intending to overcome these issues: clients at a residential, harm-reduction orientated programme for people with severe injecting-related infections described receiving less judgemental and stigmatizing care compared to experiences in mainstream hospitals.

Only one study specifically explored insufficient health insurance as a barrier to care [61]. 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 [72], and Medicaid in the USA [56, 57]).

#### Restrictions on harm reduction programmes

In four studies [53, 63, 66, 68], authors analysed consequences of participants having insufficient or non-preferred drug preparation and injecting equipment distributed from harm reduction programmes. In their study of experiences of skin and soft-tissue infections in Glasgow, UK, Dunleavy and colleagues [53] 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 re-purposing alcohol swabs distributed by harm reduction programmes: to clean up blood after injecting [53, 63], to filter visible particulate matter from puddle water [68] and burning swabs to obtain an adequate flame to heat drug solutions [53]. In two studies, Harris and colleagues explored how legal/regulatory and funding restrictions on harm reduction programmes limited distribution of sterile water [68] or single-use ascorbic acid packets [66].

In three studies participants described structural barriers to needle and syringe programmes that limited effectiveness, including limited operating hours (e.g. closures at weekends [53]) and restricting eligibility [72, 73]. McNeil and colleagues [72] assessed consequences of participants being unable to access sterile equipment in hospital, leading to re-use of contaminated equipment:

[Nurses] do not give rigs [syringes] to us... I think that they should. If not, we are re-using our rigs or we are 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 did not have it in her to go and try and steal clean rigs (Canada) [72].

Four further studies focused upon places without needle and syringe programmes (in USA and Mexico), where pharmacists refused to sell syringes to participants [60, 74–76]:

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 do not care and borrow one from a friend, since it's a desperate feeling... (Mexico) [75].

Paquette and colleagues [74] explored how people would prefer having multiple access points for sterile injecting equipment, including pharmacies and needle and syringe programmes: '... 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]' [74].

Two studies highlighted how suboptimal delivery of opioid agonist treatment (OAT; e.g. methadone, buprenorphine) after hospital discharge could increase risks for recurrent infections, including involuntary discharge from OAT because of ongoing use [57], waiting lists [56, 57] and a lack of coordination [56]:

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) [56].

## Practices of care among people who use drugs

### Mutual care

Five studies [53, 54, 62, 63, 76] 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 [53], sharing sterile needles or injecting equipment in settings of scarcity [76] and offering or receiving assistance with injecting to reduce bacterial infection risks [54, 62]:

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) [62].

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 [54, 63].

While navigating risk environments, protective strategies for bacterial infections could precipitate other health risks. For example, three studies [62, 66, 77] assessed particular risks that women face when relying on injecting assistance in the context of gendered power dynamics. In their study, Epele [62] 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, non-medical abscess treatment or use of potentially inappropriate antibiotics from non-medical sources can lead to worsening infections, but participants described employing these strategies to avoid negative experiences in health-care settings [54, 63].

### Self-care

Twelve studies [53, 54, 56, 57, 62, 63, 65, 68, 70, 71, 74, 75] included analyses of participants' practices to prevent and self-treat bacterial infections. These included practices to promote vein and skin care, including staying hydrated [63], rotating injecting sites [62], taking time to access veins [54, 63, 71], asking for help to access veins [62, 77] and self-treating superficial abscesses (e.g. incision and drainage; non-medical sources of antibiotics) before they progressed [54, 63, 74]:

Little things like drink a lot of liquids,... make sure you get enough sleep,... eat regularly. (USA) [63].

In three of these studies [66, 68, 75], 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) [75], sourcing safer water by asking passers-by for bottled water [68] and using ascorbic acid (which is safer than citric acid or lemon juice) when preparing heroin [66].

In five studies [53, 56, 57, 66, 70], participants described changing their drug use practices after experiencing an infection in order to avoid another. This included applying new learnings on safer injecting techniques [53, 56, 70], switching from injecting to smoking [53], getting wounds assessed by a nurse [53], using minimum required acidifier to dissolve drugs [66] and seeking addiction treatment to reduce or abstain from injection use [57].

Three studies [54, 62, 65] 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 [53, 62], and using in unhygienic abandoned buildings to avoid being seen in public [65].

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 colonization). Considering unintended harms of inappropriate self-treatment of bacterial infections, Gilbert and colleagues [63] 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'.

## DISCUSSION

We 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. We identified two analytical 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; restrictions on harm reduction programmes; mutual care; and self-care. We 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 upon infection development, and fewer focused upon sequelae post-infection. While the importance of education on safer injecting technique arose in several studies [53, 54, 66, 75, 78], our findings suggest that individual-level behavioural interventions alone are probably 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 [34, 79, 80].

Several social-structural determinants of bacterial and fungal infections (as well as practices of mutual- and self-care [35, 81–83]) that we identified are consistent with prior research examining risk for HIV and HCV among people who inject drugs [27, 29, 42, 84–88]. Insecure housing, hurrying injections to avoid police, insufficient harm reduction services and laws restricting sterile injecting equipment are known to contribute to HIV [27, 86, 89–91] and HCV [84, 92] transmission. Stigmatizing and discriminatory health-care experiences similarly discourage HIV and HCV treatment access and exacerbate health inequities [30, 93]. Conversely, some factors confer different risks for bacterial and viral infections. Within our review, participants attributed abscesses to tar heroin entering the unregulated drug supply, as it was less soluble than powder heroin and damaged veins. However prior research suggests that tar heroin may be associated with a lower risk of HIV transmission at a population-level, because it requires thorough heating to sufficiently dissolve and this process kills viruses [94]. Compared to the literature on HIV and HCV among people who inject drugs [85, 87, 95], we identified relatively little published research considering intersectionality and risk for injecting-related bacterial or fungal infections [42].

Two qualitative studies were published after our search. Interviewing people admitted to hospital with injecting-related infections in New York, USA, Hrycko and colleagues [96] 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 [97, 98]. In their ethnography in Dhaka, Bangladesh, Khan and colleagues [99] 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 re-use 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 interfered with employment.

A key motivation for our 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’ [34], operating at micro-environmental (e.g. supervised consumption sites) and macro-environmental (e.g. decriminalization) levels. Many social-structural factors we identified are modifiable, and some have already been ameliorated in certain settings; however, 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 OAT [with liquid formulations of diacetylmorphine (also known as ‘heroin-assisted treatment’), hydromorphone and fentanyl] and through ‘safe supply’ prescribing programmes or compassion clubs [100–102]. Injectable OAT is associated with low risk for bacterial infections even when injected intramuscularly, as sterile, liquid formulations of drugs are provided in a hygienic and safe environment [103]. Prescribed safer supply programmes involve health professionals providing pharmaceutical-grade alternatives to unregulated drugs [104–107]. Patients/clients can take these home and consume them how they prefer (including crushing and injecting tablets) and/or consume under supervision (depending on the programme). Prescribed safer supply is often offered alongside primary care and other health and social services. One study found participants in a prescribed safer supply programme in London, Canada, were less likely to be hospitalized with injecting-related bacterial infections compared to before they entered the programme [108]. Social and supportive housing (including Housing First) can help people who use drugs access and maintain housing; some models combine housing with injectable OAT, safe supply and/or supervised consumption sites [109–111]. 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 [112]. Several initiatives have improved health-care experiences for people with injecting-related infections [113, 114], including incorporating harm reduction and cultural safety principles [67, 115], specialized addiction medicine consultation services [116–118], needle and syringe programmes [119, 120] and supervised consumption sites [121–123] into hospital care. Policy changes are needed at many hospitals to facilitate these initiatives [124, 125].

Our study has three key limitations. First, our review only included studies describing experiences of injecting-related infections and we did not include all studies investigating determinants of risky injecting practices (e.g. subcutaneous injecting; re-use of contaminated equipment) unless explicitly connected to infections. Second, we did not include grey literature that might have discussed further social-structural factors beyond those we identified in peer-reviewed papers. Third, some commentators [49, 126] 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. We 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 [38, 127].

## Conclusions

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.

## AUTHOR CONTRIBUTIONS

**Thomas D. Brothers:** Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). **Matthew Bonn:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); writing—review and editing (supporting). **Dan Lewer:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); writing—review and editing (supporting). **Emilie Comeau:** Data curation (supporting); formal analysis (supporting); investigation (supporting); writing—review and editing (supporting). **Inhwa Kim:** Data curation (supporting); formal analysis; investigation (supporting); writing—review and editing (supporting). **Duncan Webster:** Conceptualization (supporting); formal analysis; investigation (supporting); supervision (supporting); writing—review and editing (supporting). **Andrew Hayward:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); supervision (lead); writing—review and editing (supporting). **Magdalena Harris:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); supervision (supporting); writing—review and editing (supporting).

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## DECLARATION OF INTERESTS

M.B. reports personal fees from AbbVie, a pharmaceutical research and development company, and grants and personal fees from Gilead Sciences, a research-based biopharmaceutical company, outside of the submitted work. The other authors report no competing interests.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the manuscript and supporting information of this article.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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