European Monitoring Centre
for Drugs and Drug Addiction

TECHNICAL REPORT

Evidence for the effectiveness of interventions to prevent infections among people who inject drugs

Drug treatment, needle and syringe programmes and drug consumption rooms for preventing hepatitis C, HIV and injecting risk behaviour

From the package of technical documents published to accompany the joint ECDC and EMCDDA update of the guidance, 'Prevention and control of infectious diseases among people who inject drugs' (2023)

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About this report

This report was commissioned by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) through contract CT.19.EU4MD.0099.1.0 and was produced by Norah Palmateer (Glasgow Caledonian University [GCU] and Public Health Scotland [PHS]), Victoria Hamill (GCU), Harriet Bloomfield (GCU), Lara Gordon (University of Bristol [UoB]), Sharon Hutchinson (GCU and PHS), Matt Hickman (UoB), Peter Vickerman (UoB), Jack Stone (UoB), Hannah Fraser (UoB), Yueijiao Duan (GCU), Richard Tran (GCU), Kirsten Trayner (GCU and PHS), Christopher Biggam (GCU and PHS), Shanley Smith (GCU and PHS) and Tony Knox (GCU).

This technical report is complemented by a second technical report, commissioned by the EMCDDA, entitled *Evidence for the effectiveness of interventions to prevent infections among people who inject drugs: Review of mathematical modelling studies of opioid agonist treatment and needle and syringe programmes for preventing hepatitis C transmission.*

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Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews
aHR	Adjusted hazard ratio
aRR	Adjusted risk ratio
BBV	Blood-borne virus
CI	Confidence interval
CM	Contingency management
DCRs	Drug consumption rooms
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
HAT	Heroin-assisted treatment
HCV	Hepatitis C virus
HDSS	High dead space syringe
IECS	Information, education, counselling and/or skills training
IF	Injection frequency
IRB	Injecting risk behaviour
LDSS	Low dead space syringe
NSP	Needle and syringe programme
OAT	Opioid agonist treatment
OoR	Overview of reviews
OR	Odds ratio
OST	Opioid substitution treatment
PICO	Population, Intervention, Comparison and Outcome
PWID	People who inject drugs
RCT	Randomised controlled trial
RoR	Review of reviews
RR	Risk ratio
SMD	Standardised mean difference
UK	United Kingdom
WHO	World Health Organization
XR-NTX	Extended-release naltrexone

Executive summary

This report describes the methods and findings of systematic reviews of the literature undertaken to update the European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2011 joint guidance on 'Prevention and control of infectious diseases among people who inject drugs'. The aim of the work was to assess the latest evidence on the effectiveness of select interventions — specifically, drug treatment, needle and syringe programmes (NSPs), drug consumption rooms and the combination of opioid agonist treatment (OAT) and NSPs — in the prevention of hepatitis C virus (HCV) transmission, HIV transmission, injecting risk behaviour (IRB) and injection frequency (IF) among people who inject drugs.

Methods

We updated the 2011 review of reviews using an approach that involved an initial search for systematic reviews (i.e. an overview of reviews) and subsequent searches for primary studies where required. Where there was sufficient evidence for an intervention/outcome in the 2011 review of reviews, new evidence was not sought. MEDLINE, CINAHL, the Cochrane Library, EMBASE, PsycINFO and Web of Science were searched for the period from 2011 to 2020; the websites of key international agencies and conference abstracts from selected conferences were also searched for grey literature publications. Two independent reviewers screened papers for relevance and extracted data from the reviews; a third member of staff resolved any discrepancies. Screening and data extraction were undertaken using Covidence software. Two reviewers also independently graded each of the included studies/reviews. Systematic reviews were graded using an adapted version of the AMSTAR 2 tool. Primary studies were graded based on study design, with randomised controlled trials, non-randomised experimental studies and cohort studies considered to provide 'stronger' evidence and any other study designs considered to provide 'weaker' evidence. To synthesise the evidence from the relevant reviews and studies identified, we applied the same framework to derive evidence statements, as was used in the 2011 guidance, which classifies the evidence as 'sufficient', 'tentative', 'insufficient' or 'no evidence'. If the evidence from the reviews was deemed to be sufficient, then the primary studies were not consulted. However, if there was less than sufficient evidence from the reviews, the evidence statement was revised in accordance with the findings of the primary studies. Finally, evidence statements were combined with the evidence statements generated as part of the 2011 guidance to generate an overall updated evidence statement.

Findings

Systematic reviews of literature commissioned as part of this project found that the level of evidence with regard to OAT and combination interventions (OAT and NSPs) in preventing HCV is sufficient while the level of evidence with regard to NSPs in preventing HCV is tentative.

The level of evidence with regard to NSPs in prison and pharmacy settings and the provision of low dead space syringes remains insufficient (i.e. some reviews or studies were identified but the evidence is limited).

Regarding the prevention of HIV as an outcome, the level of evidence is sufficient for the effectiveness of both OAT and NSPs.

With regard to self-reported behavioural outcomes, namely, IRB and IF, the evidence is generally stronger than for serological outcomes (on HCV or HIV transmission). The level of evidence concerning OAT and NSPs in reducing IRB/IF is sufficient (in the case of NSPs, this relates primarily to reductions in sharing injecting equipment and, in the case of OAT, to decreases in IF).

In relation to IRB/IF as an outcome, the level of evidence is also sufficient for psychosocial interventions, pharmacy-based NSPs and provision of sterile drug preparation equipment, and provision of OAT in prison settings. The level of evidence remains insufficient for technology-based psychosocial interventions.

Regarding drug consumption rooms, the level of evidence is currently insufficient for serological outcomes (HCV and HIV transmission) and tentative for IRB as an outcome.

Conclusions and recommendations for future research

There is now a strong body of empirical evidence for the effectiveness of OAT and NSPs and for the combination of these two interventions in preventing HCV and HIV transmission and IRB. However, evidence on the effectiveness of these two interventions, when delivered in prisons, remains scarce.

With regard to infectious disease outcomes and IRB, there is a dearth of studies for many of the interventions reviewed. This clearly inhibits our ability to make assessment of their effects, whether positive or otherwise, and future research is recommended to establish the effectiveness of these interventions. This will be important both for community-based interventions and their implementation in prisons.

Background

In October 2011, the European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published joint guidance on 'Prevention and control of infectious diseases among people who inject drugs' (ECDC and EMCDDA, 2011). Seven key interventions were recommended based on scientific evidence endorsed by expert opinion and models of best practice of prevention within the European Union/European Economic Area. The guidance was supported by two technical reports (ECDC, 2011a, 2011b) summarising the evidence for the effectiveness of needle and syringe programmes (NSPs) and of drug treatment, respectively, for preventing hepatitis C virus (HCV), HIV and injecting risk behaviour (IRB). A stakeholder survey conducted in 2018 by the ECDC and EMCDDA suggested the need to update the evidence base underpinning the guidance recommendations in order to capture new evidence and to take cognisance of emerging public health topics and new regional/global infectious disease strategies. The ECDC and EMCDDA initiated the update process in 2019 and commissioned an update of the evidence base and a collection of evidence for several new areas.

In order to update the guidance, five packages of work were undertaken:

- an update of the review of reviews (RoR) on the effectiveness of NSPs (existing intervention), drug treatments (existing intervention) and drug consumption rooms (DCRs) (new intervention),
- a literature review of modelling studies of the population-level impacts of drug treatments and NSPs (new component),
- a systematic review of interventions that can improve linkage to care and adherence to treatment for hepatitis B virus, HCV, HIV and tuberculosis (new component of the infectious disease treatment intervention),
- a collection of models of practice about linkage to care, adherence to treatment, community-based testing and health promotion (new accompanying report), and
- updates to infectious disease testing, infectious disease treatment and health promotion (existing interventions).

The present technical report describes the literature reviews that were undertaken to identify and synthesise the evidence for the second package of work listed above. Closely related to this report is a second technical report (Technical report. Evidence for the effectiveness of interventions to prevent infections among people who inject drugs - Review of mathematical modelling studies of opioid agonist treatment and needle and syringe programmes for preventing hepatitis C transmission), which describes a systematic review of mathematical modelling studies of the effects of opioid agonist treatment (OAT) and NSPs on HCV transmission. The evidence generated from these two work packages was presented at a meeting of multidisciplinary experts, appointed by the ECDC/EMCDDA, who appraised the evidence, voted on draft recommendations and provided considerations based on practice. A summary report of the discussions from the expert panel meeting and the proposed changes to the draft recommendations arising from these discussions are presented in a separate report.

Methods

General overview of approach

Literature reviews were undertaken to answer the following research questions:

What is the effectiveness of a) drug treatment (for both opioid and stimulant dependence), b) NSPs and c) drug consumption rooms (DCRs) in the prevention of hepatitis C transmission, HIV transmission and IRB among people who inject drugs (PWID)?

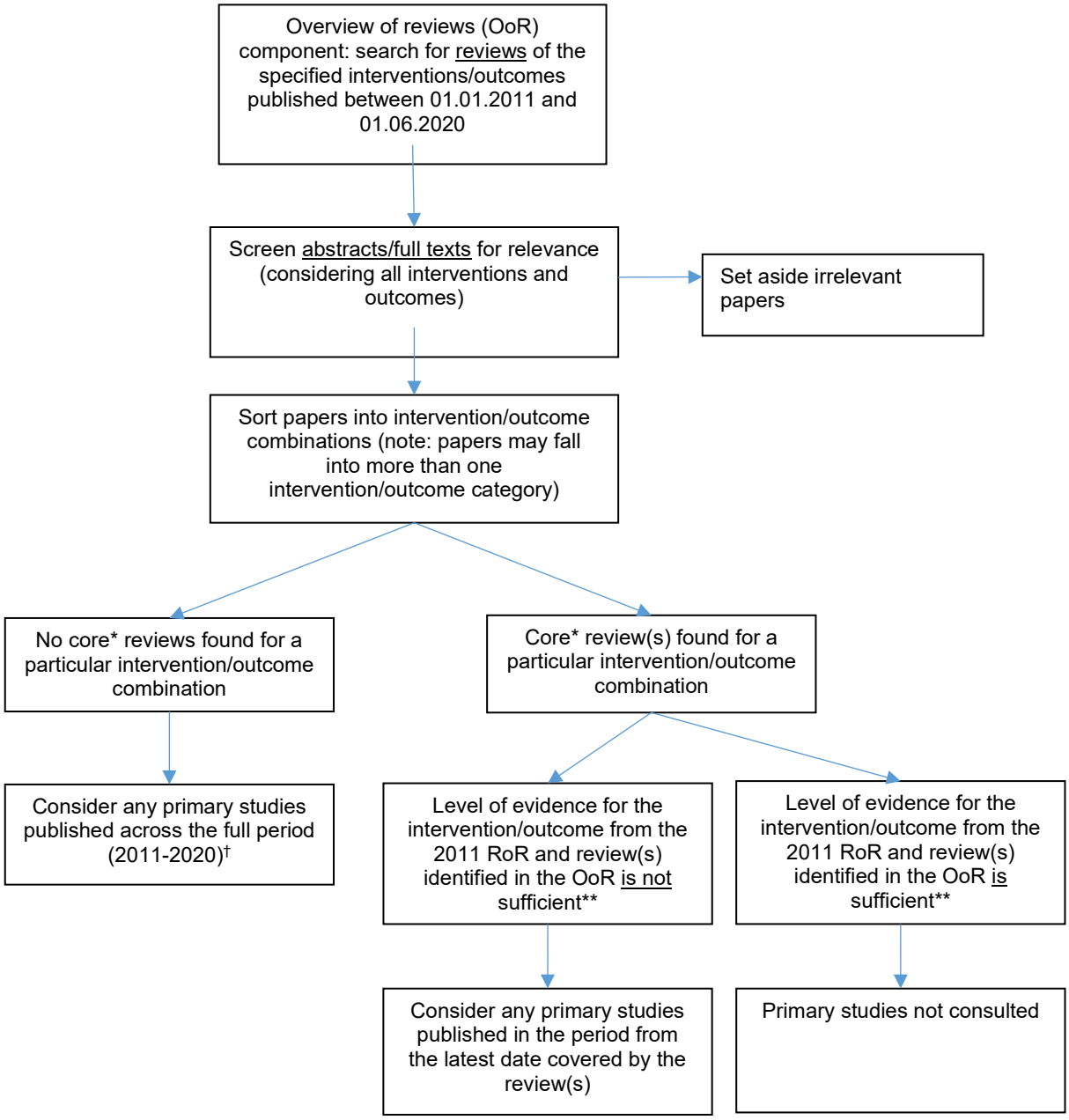
While the primary aim of the current review was to identify evidence relating to blood-borne viruses (BBVs) (i.e. HCV and HIV), IRB was also included as an outcome because it is on the causal pathway to BBV transmission. Furthermore, the RoR, that is, the reviews undertaken to inform the 2011 guidance, found a paucity of evidence relating to HCV and HIV and it was therefore important to examine the evidence on IRB as a proxy (ECDC, 2011a, 2011b; MacArthur et al., 2014). For drug treatment interventions, injection frequency ([1]) (IF) was also considered as an outcome because a reduction in IF will decrease the opportunities for equipment sharing and therefore BBV transmission.

We updated the 2011 RoR using an approach that involved an initial search for systematic reviews (i.e. an overview of reviews [OoR]) and subsequent systematic searches for primary studies where required (see Figure 1). First, an OoR was undertaken for the period from 2 January 2011 to 1 June 2020. Where there was already sufficient evidence (with 'sufficient' defined as per Table 4) for an intervention/outcome in the 2011 RoR, new evidence was not considered. Second, a search for primary studies was conducted, covering the period from 1 January 2011 to 27 October 2020. The evidence from primary studies was considered in certain cases: where no core reviews (with 'core' defined as per Section 2.6) for a particular intervention/outcome combination were identified, we considered primary studies published across the full period and, where one or more core reviews for a particular intervention/outcome were identified and the evidence for the intervention/outcome was not already sufficient (from the evidence identified in the 2011 RoR and the OoR), we considered relevant studies published after the latest date covered by the review(s).

A protocol was developed prior to commencement of the reviews and published on PROSPERO (https://www.crd.york.ac.uk/prospero, registration no.: CRD42020185487).

([1]) Terms 'injection frequency' and 'injecting frequency' are used interchangeably through this document.

FIGURE 1
Flow diagram illustrating the approach to the literature search ([2])



Abbreviations: OoR, overview of reviews; RoR, review of reviews.

*Where 'core' is defined as per the methods (Section 2.6).

**Where 'sufficient' is defined as per the methods (Section 2.7).

†Search for primary studies covering the period from 01.01.2011 to 27.10.2020

([2]) Exact numbers of titles, abstracts and articles reviewed for the RoR and primary literature are detailed in PRISMA flowcharts in Figures 2 and 3.

PICO and inclusion/exclusion criteria

The Population, Intervention, Comparison and Outcome (PICO) criteria, as well as any additional inclusion or exclusion criteria, are described below and summarised in Tables 1 and 2.

TABLE 1
Population, Intervention, Comparison and Outcome (PICO) criteria for the overview of reviews and primary literature review

Population	People who inject drugs
Interventions	1. Drug treatment, including pharmacological or psychosocial treatment for both opioid and stimulant dependence 2. Needle and syringe programmes, including the provision of sterile needles/syringes or other drug preparation equipment 3. Drug consumption rooms 4. Combination interventions (opioid agonist treatment and needle and syringe programmes)
Comparators	Any comparison/comparator as defined by the study authors
Outcomes	1. Biological measures of HIV 2. Biological measures of hepatitis C virus 3. Self-reported injecting risk behaviour, such as the borrowing, lending or reuse of needles/syringes or other drug preparation equipment 4. For drug treatment interventions only: any self-reported measure of injecting (e.g. frequency of injecting, abstinence from injecting, proportion of participants injecting)

Types of participants

The population of interest is PWID. Other subpopulations of interest (who must be related to PWID) are people in prison, young people (younger than 24 years of age), migrants, homeless people, polydrug injectors and people who inject synthetic opioids. While the literature was not specifically searched for these subpopulations, separate consideration was given to any evidence arising in relation to them. Reviews of individuals who inject drugs for a medical purpose (excluding drug treatment) were excluded. Reviews of non-injecting drug users were excluded (e.g. many reviews concerned people with opioid use disorder, which may include injecting and non-injecting drug users), unless results were presented separately specifically for the PWID subset of the study population. Reviews that did not explicitly state their study population were excluded.

Types of interventions

The following interventions were included:

- drug treatment, which may comprise
    - agonist or antagonist pharmacological treatment for opioid dependence,
    - psychosocial treatment for opioid dependence,

    - pharmacological treatment for stimulant dependence, and/or
    - psychosocial treatment for stimulant dependence;
- NSPs, which may comprise
    - provision of sterile needles/syringes, and/or
    - provision of sterile drug preparation equipment (e.g. cookers, filters, water ampoules); and
- DCRs, where individuals, who have purchased drugs elsewhere, may consume them in a clean environment under the supervision of medically trained staff, be provided sterile injecting equipment and be given information and advice on reducing the risk of BBVs and other infections.

Where literature on combinations of interventions was found, this evidence was considered separately. However, combination interventions had to be delivered at the individual level.

Comparators

Any comparators included in the studies cited by reviews or in studies were considered for inclusion.

Types of outcome measures

The outcomes of interest were HIV and HCV or, alternatively, IRB (which is defined as self-reported borrowing, lending or reuse of needles/syringes or other drug preparation equipment). Where the intervention was drug treatment, outcomes measuring the extent of injection (e.g. frequency of injecting, any injecting or abstinence/cessation of injecting) were included. The latter were self-reported; studies that reported urinalysis as the only measure of drug use were excluded, given that this approach cannot establish the route of drug taking. Any biological measure of HIV or HCV was considered relevant; studies or reviews that included self-reported measures of HIV or HCV were ineligible. Measures of HCV infection included primary infection or reinfection. Reviews examining other infections only (e.g. tuberculosis, bacterial infections or sexually transmitted infections) were excluded.

Types of study design

All systematic reviews (which may include meta-analyses) were considered eligible for inclusion, both published (i.e. in a peer-reviewed journal) and unpublished (grey literature). Given that a number of reviews labelled themselves ‘systematic’ when they were in fact not, it became apparent that we had to define ‘systematic’. Reviews were therefore considered systematic if they were transparent in their approach to reviewing the literature and included, at a minimum, a description of the study population and a statement of the databases searched. Systematic reviews of qualitative studies, cost-effectiveness studies or mathematical modelling studies were considered out of scope. OoRs were also excluded, although these were retained as potential sources of references.

For the primary literature review, eligible study designs included randomised controlled trials (RCTs), non-randomised trials, prospective and retrospective cohort studies, case-control studies, ecological studies, serial cross-sectional studies and cross-sectional studies. Qualitative studies, cost-effectiveness studies and mathematical modelling studies were

excluded, as were ecological studies where the impact of multiple interventions could not be separated.

Other criteria

There were no English-language restrictions.

Specific settings for the delivery of the interventions (e.g. prison, pharmacy, outreach) were considered. These were not searched as separate interventions per se but, where evidence was found that related to a given setting, it was considered separately and specific conclusions were drawn.

TABLE 2
Inclusion/exclusion criteria for the overview of reviews (OoR) and primary literature review

	Inclusion criteria	Exclusion criteria
Publication date	OoR: published from 1.1.2011 to 1.6.2020	OoR: published prior to 1.1.2011 or after 1.6.2020
	Primary literature review: dependent on OoR findings	Primary literature review: dependent on OoR findings
Language	No language restrictions	N/A
Publication type	Full study publication available; peer-reviewed or grey literature	Conference abstracts (unless full publication available from authors), study protocols, repeated/duplicate results
Study design/type	OoR: systematic reviews, where 'systematic' is defined as transparent and reproducible methods used to review the literature and includes, at a minimum, a description of the study population and a statement of the databases searched	OoR: systematic reviews of qualitative studies, cost-effectiveness studies or mathematical modelling studies; narrative reviews; OoRs. Additionally, reviews that did not meet the quality criteria were excluded (see Section 2.6)
	For primary literature review: randomised controlled trials, non-randomised trials, prospective and retrospective cohort studies, case-control studies, ecological studies, serial cross-sectional studies and cross-sectional studies	For primary literature review: qualitative studies, cost-effectiveness studies, mathematical modelling studies and ecological studies where the impact of multiple interventions could not be separated
Study population	PWID. May include 'subpopulations' of PWID, such as incarcerated PWID, young PWID (younger than 24 years of age), migrant PWID, homeless PWID, polydrug injectors and people who inject synthetic opioids	Individuals who inject drugs for a medical purpose (excluding drug treatment), non-injecting drug users (unless results were presented separately specifically for a PWID subset of the study population), reviews/studies that did not explicitly state their study population, reviews/studies where injecting risk

		could not be separated from sexual transmission risk (usually for HIV) ([3])
Interventions	Interventions as stated in the PICO criteria. With regard to combination interventions, these had to be delivered at the individual level	Combination interventions that were not delivered at the individual level (i.e. ecological studies)
Study outcomes	Outcomes as stated in the PICO criteria. Any biological measure of HIV or HCV was considered. Measures of HCV infection included primary infection or reinfection. IRB outcomes were self-reported. Where the intervention was drug treatment, outcomes that measured the extent of injection (e.g. frequency of injecting, any injecting or abstinence/cessation of injecting) were included	Self-reported HIV or HCV status; studies/reviews that reported urinalysis as the only measure of drug use (for studies/reviews of drug treatment interventions)
Study setting/mode of delivery of intervention	All settings for the delivery of the interventions (e.g. pharmacies, prisons, outreach, peers) were considered	No exclusions based on study setting/mode of delivery of intervention

Abbreviations: HCV, hepatitis C virus; IRB, injecting risk behaviour; N/A, not applicable; OoR, overview of reviews; PICO, Population, Intervention, Comparison and Outcome; PWID, people who inject drugs.

Data sources and search methods

Lists of search terms used for the OoR and primary literature review are included in Appendix 1 and Appendix 2, respectively. The following databases were searched for both the OoR and primary literature review: MEDLINE, CINAHL, the Cochrane Library, EMBASE, PsycINFO and Web of Science. The searches for the OoR and primary studies were run on 1 June 2020 and 27 October 2020, respectively. The websites of key international agencies were searched for grey literature publications: ECDC, Cochrane Database of Systematic Reviews, EMCDDA, National Institute on Drug Abuse (NIDA), US National Academy of Medicine (NAM), United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO). Conference proceedings at relevant conferences in 2019 and 2020 (International Network of Hepatitis in Substance Users [INHSU], European Conference on Addictive Behaviours and Dependencies – Lisbon Addictions, Harm Reduction International [HRI], Society for the Study of Addiction [SSA] and European Association for the Study of the Liver [EASL]) were searched and authors were contacted for full publications or papers in press based on featured abstracts. Finally, reference lists of all included reviews and studies were scanned for any additional relevant reviews or studies.

([3]) For example, where the study sample involved participants who were sexual and injecting partners.

Selection of reviews/studies

For both the OoR and the primary literature review, two independent reviewers screened titles and abstracts meeting PICO criteria for relevance. Papers thought to be relevant at this stage were retrieved, and the reviewers subsequently screened the full texts. In the case of disagreement, a third author made the final decision. Covidence software was used to screen abstracts and full texts.

Data extraction and management

Two reviewers extracted data from the reviews using a pre-defined form; a third senior member of staff reconciled the forms and resolved any discrepancies. Data extraction was undertaken using Covidence software. The following information was extracted from reviews:

- title and author(s),
- date of publication,
- objective(s)/research question(s),
- PWID subpopulation if applicable (e.g. young or migrant populations or people who are incarcerated or experiencing homelessness),
- definition of PWID, if stated,
- intervention(s),
- outcome(s),
- inclusion/exclusion criteria,
- comparisons, if applicable,
- databases searched,
- search dates,
- study period,
- number of included studies,
- locations where included studies were undertaken,
- number of participants in the studies and range,
- study designs of included studies,
- number of studies with positive, negative and equivocal results,
- summary effect measure (for meta-analyses),
- assessment of the quality/risk of bias of the primary studies, as presented in the review,
- strengths and limitations of the review, and
- a summary of the authors' conclusions.

The following information was extracted from primary studies:

- title and author(s),
- date of publication,
- objective(s)/research question(s),

- study location,
- study (recruitment) setting,
- study dates,
- description of study population,
- PWID subpopulation if applicable (e.g. young, migrant, prisons, homeless),
- inclusion/exclusion criteria,
- intervention(s),
- outcome(s),
- comparisons, if applicable,
- study design,
- number of participants (overall and in the groups being compared),
- duration of follow-up, if applicable,
- effect measurement (unadjusted and adjusted, if presented),
- confounding factors adjusted for,
- strengths and limitations, as described by the study authors, and
- the overall conclusions of the study authors.

Assessment of the methodological quality of the included reviews and studies

Two reviewers independently graded each of the included reviews; a third senior member of staff resolved any discrepancies. To critically appraise the included systematic reviews, we adapted the internationally recognised and validated AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) tool (Shea et al., 2017), which allows the assessment of reviews that include both randomised and non-randomised studies of interventions. The tool comprises 16 items, with 7 suggested as 'critical' for determining the quality of the review; our adaptation of the tool comprised 16 items and 5 critical domains (see Appendix 3). AMSTAR 2 does not generate an overall score but provides a broad assessment of review quality and generates a rating of 'high', 'moderate', 'low' or 'critically low'. We translated these assessments into 'core' or 'supplementary' reviews, a grading system that was used in the 2011 guidance, as per Table 3 below. Systematic reviews that had a high or moderate AMSTAR 2 rating were included as core reviews; these reviews were used to derive evidence-based statements on the effectiveness of the interventions. Systematic reviews with a low AMSTAR 2 rating were included as supplementary reviews and were not considered to be of sufficient quality to derive conclusions but were included as a potential source of primary studies when core reviews were lacking. Systematic reviews with a critically low AMSTAR 2 rating were excluded.

TABLE 3
AMSTAR 2: rating overall confidence in the results of the review and how this will guide the inclusion of systematic reviews in the overview of reviews

AMSTAR rating	Description (criteria for AMSTAR rating)	Inclusion/exclusion in this overview of reviews
High	*No or one non-critical weakness:* the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest	Included as a 'core review' to derive evidence-based statements on the effectiveness of interventions
Moderate	*More than one non-critical weakness*:* the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies included in the review	Included as a 'core review' to derive evidence-based statements on the effectiveness of interventions
Low	*One critical flaw with or without non-critical weaknesses:* the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest	Included as a 'supplementary review' to derive evidence-based statements on the effectiveness of interventions
Critically low	*More than one critical flaw with or without non-critical weaknesses:* the review has more than one critical flaw and should not be relied upon to provide an accurate and comprehensive summary of the available studies	*Excluded*

Abbreviation: AMSTAR, A MeaSurement Tool to Assess systematic Reviews.

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to downgrade the overall appraisal from moderate confidence to low.

To be consistent with the 2011 RoR — the evidence reviews undertaken to inform the 2011 guidance and described in the technical reports (ECDC, 2011a, 2011b) — the same approach to assessing primary study quality was applied: a systematic critical appraisal of the primary studies was not undertaken; rather, the study design was used as an indication of the inferences that could be drawn from the study findings, with RCTs, non-randomised experimental studies and cohort studies considered to be 'strong' and any other study designs considered to provide 'weaker' evidence (see Appendix 4 for a summary of study designs).

Synthesis of evidence and derivation of evidence statements

A flowchart describing the process of evidence synthesis is presented in Appendix 5. By intervention/outcome combination, summaries of the relevant reviews were first generated in tabular format. A judgement with regard to the strength of evidence was first made from the results of the reviews alone: we applied the same framework to derive 'evidence statements' that was used in the review to inform the 2011 guidance (Table 4).

TABLE 4
Types of evidence statements and the level of evidence required to support each statement

Evidence statement	Level of evidence
Sufficient evidence to either support or discount the effectiveness of an intervention	• Clear and consistent statement from one or more core reviews based on multiple robust studies, *or* • Consistent evidence across multiple robust studies within one or more core reviews, in the absence of a clear and consistent statement in the review(s)
Tentative evidence to either support or discount the effectiveness of an intervention	• A tentative statement from one or more core reviews based on consistent evidence from a small number of robust studies or multiple weaker studies, *or* • Consistent evidence from a small number of robust studies or multiple weaker studies within one or more core reviews, in the absence of a clear and consistent statement in the review(s), *or* • Conflicting evidence from one or more core reviews, with the stronger evidence weighted towards one side (either supporting or discounting effectiveness) and a plausible reason for the conflict, *or* • Consistent evidence from multiple robust studies within one or more supplementary reviews, in the absence of a core review
Insufficient evidence to either support or discount the effectiveness of an intervention	• A statement of insufficient evidence from a core review, *or* • Insufficient evidence to either support or discount the effectiveness of an intervention (either because there is too little evidence or the evidence is too weak), in the absence of a clear and consistent statement of evidence from (a) core review(s), *or* • Anything less than consistent evidence from multiple robust studies within one or more supplementary reviews
No evidence	• No core or supplementary reviews of the topic identified, possibly due to a lack of primary studies

If the evidence from the reviews was deemed to be sufficient, the primary studies were not consulted. However, if the evidence from the reviews was less than sufficient, the primary studies were summarised in tabular format, and the evidence statement was revised according to their findings. Finally, evidence statements were 'combined' with the evidence statements generated as part of the 2011 guidance reviews, as per the algorithm in Table 5.

TABLE 5
Algorithm for combining evidence statements from the 2011 guidance and from the 2020/2021 update

Evidence statement from 2011 review	Evidence statement from 2020/2021 update	Final evidence statement
Sufficient	N/A*	Sufficient (i.e. 2011 evidence statement stands)
Tentative or insufficient	Sufficient	Sufficient (i.e. 2020/2021 evidence statement stands)
	Tentative or insufficient	Evidence base across both 2011 and 2020/2021 reviews considered and statement derived accordingly to determine if evidence statement gets upgraded
	No evidence	2011 evidence statement stands (i.e. either 'tentative' or 'insufficient')
None	Sufficient, tentative, insufficient or none	2020/2021 evidence statement stands

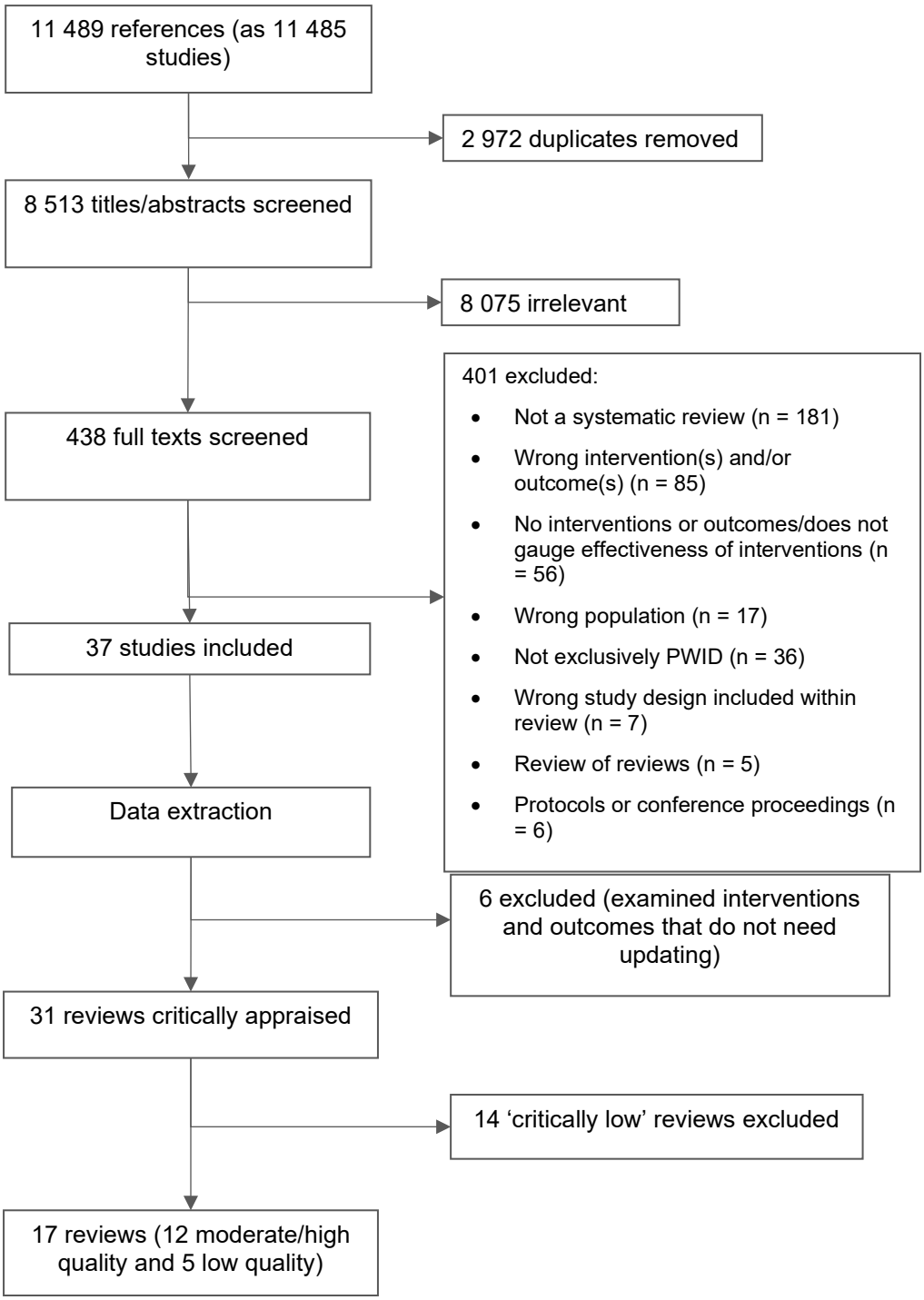
Abbreviation: N/A, not applicable.

*Review of evidence not updated in 2020/2021 due to the compelling level of evidence identified in the 2011 review of reviews.

Results

Figure 2 illustrates the OoR component of the review: 8 513 abstracts were screened in total, followed by 438 full texts, resulting in 31 relevant reviews. The reviews that were appraised as 'critically low' quality were excluded, leaving 17 reviews in total. Of these, 12 were rated as moderate or high quality (Aspinall et al., 2014; Bahji et al., 2019; ECDC, 2018; EMCDDA, 2016a; Gilchrist et al., 2017b; Hajarizadeh et al., 2020; Hedrich et al., 2012; Korownyk et al., 2019; Moore et al., 2019; Platt et al., 2017; Sacks-Davis et al., 2012; Sawangjit et al., 2017) and were thus considered core reviews and 5 were rated as low quality (Abdul-Quader et al., 2013; Crowley and Van Hout, 2017; Davis et al., 2017; Kennedy et al., 2017; WHO, 2012) and were thus considered supplementary reviews (and therefore used as a source of primary studies).

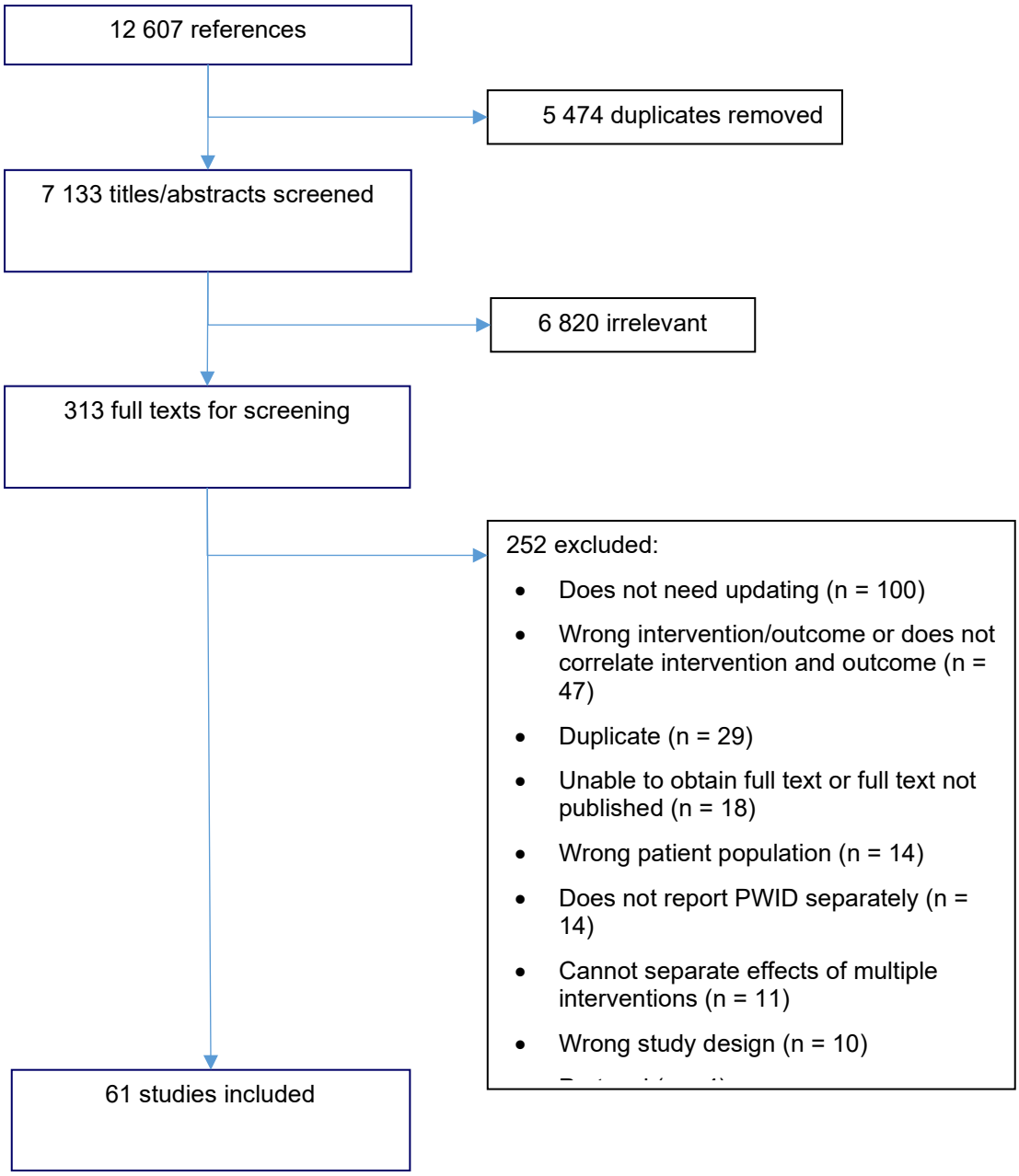
FIGURE 2
PRISMA flow diagram for the overview of reviews



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PWID, people who inject drugs.

The primary literature component of the review identified 61 potentially relevant studies (Figure 3). However, not all of these studies were necessarily included in the evidence base; this depended on the results of the OoR.

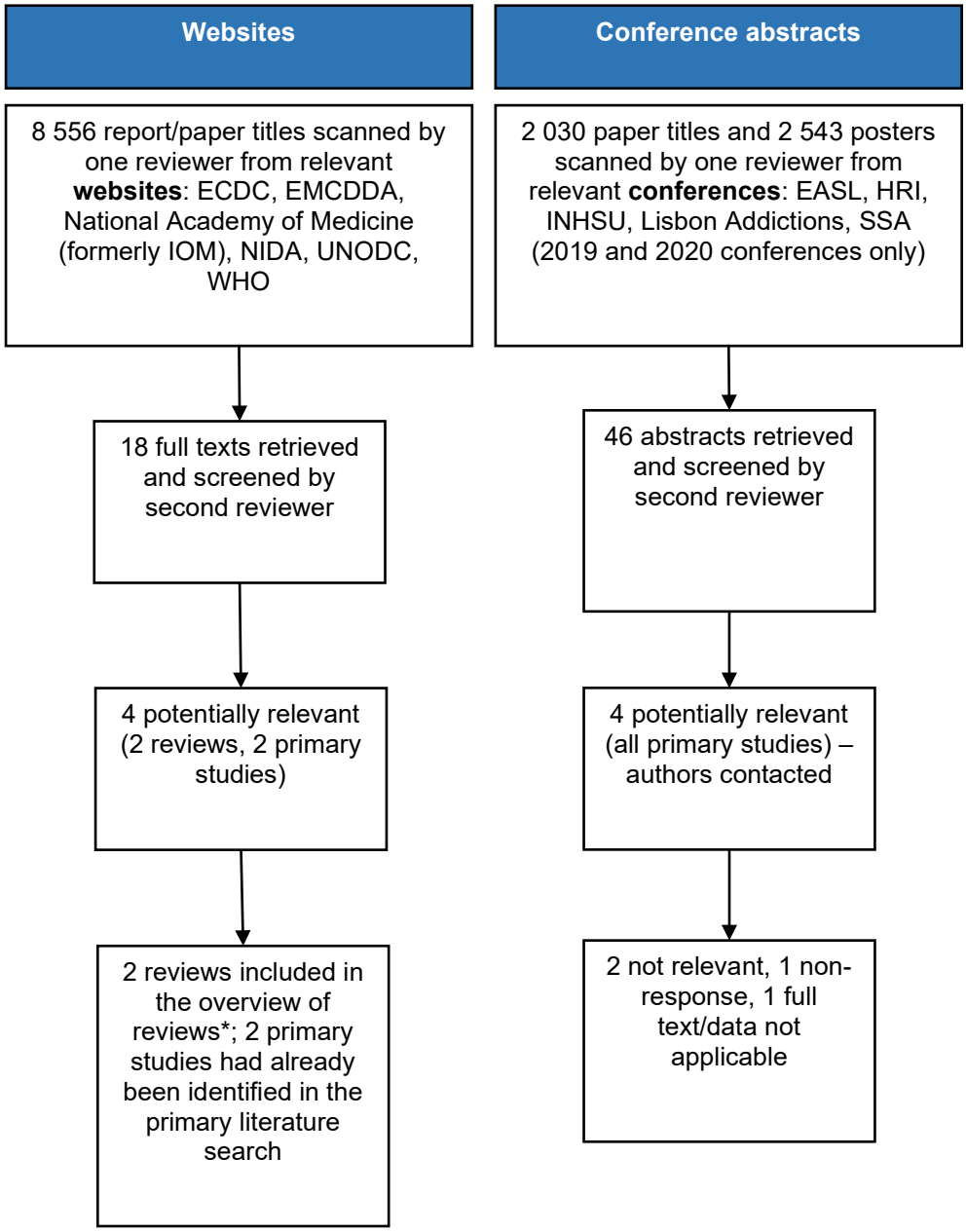
FIGURE 3
PRISMA flow diagram for the primary literature review



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PWID, people who inject drugs.

The outcomes of the grey literature search are indicated in the flow diagram in Figure 4.

FIGURE 4
PRISMA flow diagram for the grey literature review



Abbreviations: EASL, European Association for the Study of the Liver; ECDC, European Centre for Disease Prevention and Control; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; HRI, Harm Reduction International; INHSU, International Network of Hepatitis in Substance Users; IOM, Institute of Medicine; NIDA, National Institute on Drug Abuse; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SSA, Society for the Study of Addiction; UNODC, United Nations Office on Drugs and Crime; WHO, World Health Organization.

*The two reviews were added to the flowchart in Figure 2 and therefore factor into the total reviews identified in the OoR.

An overview of the reviews and studies identified for each intervention and outcome combination is presented in Table 6.

TABLE 6
Overview of studies identified in the overview of reviews and primary literature search by intervention and outcome

Intervention		Outcome	Overview of reviews findings	Primary literature review findings
Drug treatment	Agonist pharmacological treatment for opioid dependence (i.e. OAT)	HCV	Four reviews: all core reviews (ECDC, 2018; Hajarizadeh et al., 2020; Hedrich et al., 2012; Platt et al., 2017), two of which were specific to the prison setting (ECDC, 2018; Hedrich et al., 2012)	Sixteen studies: eight with strong designs (Aitken et al., 2017; Artenie et al., 2019; Cunningham et al., 2017, 2020; Islam et al., 2017; Minoyan et al., 2020; Molès et al., 2020; Rossi et al., 2018) and eight with weaker designs (Aye et al., 2018; Chen et al., 2018; Graham et al., 2017; Handanagic et al., 2017; Leyna et al., 2019; Valerio et al., 2021; Yi et al., 2019; Zietara et al., 2020)
		HIV	No update required given sufficient evidence from 2011 review of reviews	N/A
		IRB/IF	No update required given sufficient evidence from 2011 review of reviews	N/A
	Heroin-assisted treatment	HCV	0 reviews	0 studies
		HIV	0 reviews	0 studies
		IRB/IF	0 reviews	0 studies
	Antagonist pharmacological treatment	HCV	0 reviews	0 studies
		HIV	0 reviews	0 studies
		IRB/IF	Four reviews: three core (Bahji et al., 2019; Korownyk et al., 2019; Moore et al., 2019) and one supplementary (Crowley and Van Hout, 2017), two of which relate to prison (Bahji et al., 2019; Moore et al., 2019)	0 studies
		HCV	0 reviews	0 studies

Intervention		Outcome	Overview of reviews findings	Primary literature review findings
	Pharmacological treatment for stimulant dependence	HIV	0 reviews	0 studies
		IRB/IF	0 reviews	0 studies
Drug treatment (psychosocial)	Psychosocial interventions – information, education, counselling and/or skills training	HCV	Two reviews: one core (Sacks-Davis et al., 2012) and one supplementary (WHO, 2012)	One study: one with a strong design (Islam et al., 2017)
		HIV	No reviews	Four studies: three with strong designs (Booth et al., 2016; Go et al., 2013; Miller et al., 2018) and one with a weaker design (Hammett et al., 2012)
		IRB/IF	Four reviews: three core (ECDC, 2018; Gilchrist et al., 2017b; Sacks-Davis et al., 2012) and one supplementary (WHO, 2012), one of which is related to prison (ECDC, 2018)	21 studies: 17 with strong designs (Barak et al., 2020; Bertrand et al., 2015; Booth et al., 2011; Calvo et al., 2020; Gilchrist et al., 2017a, 2017c; Go et al., 2013; Hajebi et al., 2016; Hochstatter et al., 2020; Lea et al., 2017; Mateu-Gelabert et al., 2014; Mezaache et al., 2018; Owczarzak et al., 2019; Pitpitan et al., 2016; Roux et al., 2016, 2021; Smith et al., 2017) and four with weaker designs (Chen et al., 2018; Hammett et al., 2012; Mackesy-Amiti et al., 2017; Wang et al., 2015)
	Psychosocial treatment – contingency management	HCV	0 reviews	0 studies
		HIV	0 reviews	0 studies
		IRB/IF	Two reviews: two core (EMCDDA, 2016a; Korownyk et al., 2019)	0 studies
		HCV	0 reviews	0 studies
		HIV	0 reviews	0 studies

Intervention		Outcome	Overview of reviews findings	Primary literature review findings
	Psychosocial treatment – technology-based	IRB/IF	0 reviews	One study with a strong design (Calvo et al., 2020)
Needle and syringe programmes (NSPs)	Needle and syringe provision	HCV	Six reviews: three core (ECDC, 2018; Platt et al., 2017; Sawangjit et al., 2017) and three supplementary (Abdul-Quader et al., 2013; Davis et al., 2017; WHO, 2012). Of the core reviews, one was related to the pharmacy setting (Sawangjit et al., 2017) and one to the prison setting (ECDC, 2018)	Seven studies: one with a strong design (Minoyan et al., 2020) and six with weaker designs (Chen et al., 2018; Fatseas et al., 2012; Handanagic et al., 2017; Leyna et al., 2019; Panda et al., 2014; Salek et al., 2017)
		HIV	Five reviews: three core (Aspinall et al., 2014; ECDC, 2018; Sawangjit et al., 2017) and two supplementary (Abdul-Quader et al., 2013; WHO, 2012). Of the core reviews, one was related to the pharmacy setting (Sawangjit et al., 2017) and one to the prison setting (ECDC, 2018)	Nine studies: two with strong designs (Huang et al., 2014; Sypsa et al., 2017) and seven with weaker designs (Chen et al., 2018; Fatseas et al., 2012; Luo et al., 2015; Marotta and McCullagh, 2016; McAuley et al., 2019; Nghiem et al., 2018; Panda et al., 2014)
		IRB	No update required given sufficient evidence from the 2011 review of reviews	N/A
	Low dead space syringes	HCV	One supplementary review (WHO, 2012)	One study with a weaker design (Trickey et al., 2018)
		HIV	One supplementary review (WHO, 2012)	0 studies
		IRB	N/A	N/A
	Provision of sterile drug preparation	IRB	0 reviews	Eleven studies: one with a strong design (Patel et al., 2018) and 10 with weaker designs (Aspinall et al., 2012; Behrends et al., 2017; Fatseas et al., 2012; Kim et

Intervention		Outcome	Overview of reviews findings	Primary literature review findings
	equipment (paraphernalia)			al., 2015; Mehrabi et al., 2020; Naserirad and Beulaygue, 2020; Nazari et al., 2016; Noroozi et al., 2018; Rezaie et al., 2017; Welch-Lazoritz et al., 2017)
		HIV	0 reviews	Eleven studies: one with a strong design (Patel et al., 2018) and 10 with weaker designs (Aspinall et al., 2012; Behrends et al., 2017; Fatseas et al., 2012; Kim et al., 2015; Mehrabi et al., 2020; Naserirad and Beulaygue, 2020; Nazari et al., 2016; Noroozi et al., 2018; Rezaie et al., 2017; Welch-Lazoritz et al., 2017)
		HCV	0 reviews	One study with a weaker design (Fatseas et al., 2012)
Combination interventions (OAT and NSPs)		IRB	0 reviews	0 studies
		HIV	0 reviews	0 studies
		HCV	One core review (Platt et al., 2017)	One study with a strong design (Minoyan et al., 2020)
Drug consumption rooms		IRB	One supplementary review (Kennedy et al., 2017)	One study with a weaker design (Folch et al., 2018)
		HIV	0 reviews	Two studies with weaker designs (Folch et al., 2018; Kennedy et al., 2019a)
		HCV	0 reviews	Two studies with weaker designs (Folch et al., 2018; Kennedy et al., 2019a)

Abbreviations: HCV, hepatitis C virus; IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; NSP, needle and syringe programme; OAT, opioid agonist treatment.

Drug treatment (pharmacological)

This section considers pharmacological treatment for dependence on opioids and/or stimulants. The section is divided into treatment for opioid dependence, which includes agonist treatment, heroin-assisted treatment (HAT) and antagonist treatment, and treatment for stimulant dependence.

Agonist treatment for opioid dependence (OAT)

Agonist treatment for opioid dependence refers to pharmacological treatment using agonist medication to eliminate withdrawal symptoms and relieve drug cravings. The most commonly prescribed agonist medications are methadone and buprenorphine (Strang et al., 2020). Opioid agonist treatment is often abbreviated as OAT; this abbreviation will be used throughout this document, unless quoting a paper that uses another abbreviation. Another common abbreviation seen in the literature is OST, which stands for 'opioid substitution treatment'. While 'substitution' could technically include both agonist and antagonist treatment, the overwhelming majority of people receiving OST would likely be receiving methadone or buprenorphine; therefore, OST is considered equivalent to OAT for the purposes of this review.

Effects on hepatitis C virus transmission

Two core reviews were identified (Hajarizadeh et al., 2020; Platt et al., 2017): one examined primary infection and the other studied reinfection. Details of these reviews can be found in Appendix 6 and a summary of the evidence is presented in Table 7. In a meta-analysis of 12 studies, of mostly robust designs, Platt et al. (2017) (also published as a peer-reviewed paper (Platt et al., 2018)) found that OAT was associated with a 50 % reduction in the risk of primary HCV infection (risk ratio [RR] 0.50, 95 % confidence interval [CI] 0.40-0.63). Hajarizadeh et al. examined reinfection risk in a meta-regression of 22 studies, all with robust designs, and found that individuals on OAT (with no reported injecting) had a 73 % reduced risk of HCV reinfection (adjusted RR [aRR] 0.27, 95 % CI 0.13-0.56) relative to those not on OAT (with reported injecting) ([4]). When those on OAT without injecting were compared to those on OAT with injecting, the findings were consistent with an approximately 70 % reduction in HCV reinfection risk (aRR 0.29, 95 % CI 0.14-0.61). Given a clear and consistent statement from two core reviews, based on multiple robust studies, we conclude that the level of evidence is sufficient for the prevention of both primary HCV infection and HCV reinfection (Table 7). The level of evidence from the 2011 RoR had been classified as tentative and was therefore updated to give the following evidence statement.

Evidence statement: There is sufficient review-level evidence to conclude that OAT, delivered at a sufficient dose, is effective in preventing both primary HCV infection and HCV reinfection among PWID.

([4]) The inverse of the odds ratios is given here to facilitate comparison with the results of Platt et al.

TABLE 7
Evidence summary for opioid agonist treatment (OAT) and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	Two core: Hajarizadeh et al. (2020) and Platt et al. (2017)*	Hajarizadeh: 'Our finding of significantly lower reinfection risk among people receiving OAT who did not use drugs, indicates the importance of enhancing access to OAT as a strategy to prevent reinfection'. Platt: 'OST is associated with a reduction in the risk of HCV acquisition…'	Hajarizadeh: 22 in total (9 RCTs, 13 cohort). N = 2 772 (range, 11-909). Platt: 12 in total (10 cohort, 1 cross-sectional, 1 case-control). N = 6 361 (range, 80-2 788). Mean, 440.5 person-years follow-up	Hajarizadeh: relative to studies with participants on OAT and with no injecting during follow-up (i.e. OAT yes/IDU no – the reference category), the OAT yes/IDU yes studies had higher reinfection rates (aRR 3.47, 95 % CI 1.65-7.32, p = 0.002), as did the OAT no/IDU yes studies (aRR 3.74, 95 % CI 1.77-7.89, p = 0.001). Platt: relative to no OAT, current OAT was	Australia (6), Canada (9), China (1), Eastern Europe (1), multiple countries (2), United States (6), Western Europe (18)	Based on a clear and consistent statement from one or more core reviews or based on multiple robust studies, we conclude that the level evidence is **sufficient** for the prevention of both primary HCV infection and HCV reinfection	**Tentative:** 'Consistent evidence from multiple longitudinal studies within supplementary reviews shows a weak or absent association between OST and a reduction in HCV incidence. However, a recent meta-analysis of UK studies, taken together with primary studies, provides tentative evidence of the effectiveness of OST in reducing HCV incidence.'	Evidence from two core reviews demonstrates that there is **sufficient** review-level evidence to conclude that OAT, delivered at sufficient dose, is effective for preventing both primary HCV infection and HCV reinfection among PWID

				associated with a reduction in the risk of HCV infection (RR 0.5, 95 % CI 0.4-0.63, p < 0.001)				
Primary literature review*	N/A	N/A	N/A	N/A	N/A			

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; HCV, hepatitis C virus; IDU, intravenous drug user; N/A, not applicable; OAT, opioid agonist treatment; OoR, overview of reviews; OST, opioid substitution treatment; PWID, people who inject drugs; RR, risk ratio.

*The primary literature was not consulted given a statement of sufficient evidence from the reviews, as per the methods.

Effects on HIV transmission

In the 2011 RoR, the evidence for agonist pharmacological treatment for opioid dependence was deemed sufficient with regard to HIV and thus was not updated here, as per the methods. Therefore, the 2011 evidence statement stands, as follows.

Evidence statement: 'Evidence in three core reviews demonstrates that there is sufficient review-level evidence to conclude that OAT in community settings is effective in reducing HIV seroconversion, especially for those in continuous treatment.'

Effects on injecting risk behaviour/injection frequency

In the 2011 RoR, the evidence for agonist pharmacological treatment for opioid dependence was deemed sufficient with regard to IRB/IF and thus was not updated here, as per the methods. Therefore, the 2011 evidence statement stands, as follows.

Evidence statement: 'Consistent evidence from multiple robust studies in core reviews indicates that there is sufficient review-level evidence to support the effectiveness of OST in reducing the frequency of injection, the sharing of injecting equipment and injecting risk behaviour.'

Agonist treatment for opioid dependence in prison/criminal justice settings

Effects on hepatitis C virus transmission

Details of the relevant reviews and studies are given in Appendix 7. Two core reviews examined the provision of OAT in prison settings and its association with HCV (ECDC, 2018; Hedrich et al., 2012). Between them, these reviews identified three studies (one RCT and

two case-controls), two of which had non-significant findings and one that demonstrated an increased risk of HCV among those on OAT at enrolment, but this was attributed to disruptions in OAT continuity. An additional cohort study was also identified but this found no difference in time to HCV seroconversion among those on current OAT vs. not on OAT among incarcerated individuals (Cunningham et al., 2017). Based on statements of insufficient evidence from two core reviews, and only one additional robust primary study with an equivocal finding, we conclude that there is insufficient evidence to either support or discount the effectiveness of OAT in preventing HCV transmission in the prison setting (Table 8). There was insufficient evidence from the 2011 RoR and the updated evidence statement thus remains insufficient.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of OAT in preventing HCV in prison settings.

TABLE 8
Evidence summary for opioid agonist treatment (OAT) in prison/criminal justice settings and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	Two core: ECDC (2018) and Hedrich et al. (2012)	ECDC: 'The evidence on the effectiveness of [...] OST [...] in prison settings is limited...Existing UN-system guidelines recommend the implementation of OST [...] in prison settings.' Hedrich: 'There was insufficient evidence concerning HIV/HCV incidence...Disruption of OMT continuity, especially due to brief periods of imprisonment, was	ECDC: two studies (one RCT, one case-control). N = 471 (range, 218-253). Hedrich: three studies (one RCT, two case-control). N = 959 (range, 218-488)	ECDC: 4-month follow-up RCT – 12.5 % of OAT participants seroconverted vs. 11.4 % of controls (p = NS). Four-year follow-up results also NS Hedrich: same as ECDC, in addition to case-control with 12 months follow-up – OR for HCV incidence comparing those in	Australia (3)	Given statements of insufficient evidence from two core reviews and only one robust primary study with an equivocal finding, we conclude that there is **insufficient** evidence to either support or discount the effective	**Insufficient**: '...there is insufficient evidence in the prison setting to draw conclusions regarding the impact of OST in reducing...HCV transmission.' [Note: the statement was based on two of the three studies in the updated review]	The review-level evidence for the effectiveness of OAT in preventing HCV in prison settings is still **insufficient**

		associated with very significant increases in HCV incidence.'		OMT at enrolment vs. not = 3.1 (p < 0.001)		ness of OAT in the preventi on of HCV in prison settings		
Primary literature review	One strong: Cunningham et al. (2017)	N/A	One study (coho rt). N = 197; 433 perso n-years follow -up	Adjusted hazard ratios for time to HCV seroconv ersion 'on current OST' vs. 'not' = 1.27 (p = 0.386) among entire cohort and = 1.32 (p = 0.627) among those continuou sly imprisone d during follow-up	Australi a (1)			

Abbreviations: ECDC, European Centre for Disease Prevention and Control; HCV, hepatitis C virus; N/A, not applicable; NS, not significant; OAT, opioid agonist treatment; OMT, opioid maintenance treatment; OoR, overview of reviews; OST, opioid substitution treatment; RCT, randomised controlled trial.

Effects on HIV transmission

The two above-mentioned reviews that examined HCV also examined HIV as an outcome: both included the same two studies (one RCT and one case-control study) but there were too few HIV seroconversions in the studies for any conclusions to be drawn. No additional primary studies were identified. Given statements of insufficient evidence from two core reviews, we conclude that the level of evidence is insufficient (Table 9). The 2011 RoR also made a statement of insufficient evidence and the final combined evidence statement therefore remains insufficient.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of OAT in preventing HIV in prison settings.

TABLE 9
Evidence summary for opioid agonist treatment (OAT) in prison/criminal justice settings and HIV

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	Two core: ECDC (2018) and Hedrich et al. (2012)	ECDC: 'The evidence on the effectiveness of [...] OST [...] in prison settings is limited...Existing UN-system guidelines recommend the implementation of OST [...] in prison settings.' Hedrich: 'There was insufficient evidence concerning HIV/HCV incidence'	ECDC: two studies (one RCT, one case-control). N = 471 (range, 218-253). Hedrich: two studies (one RCT, one case-control). N = 471 (range, 218-253)	ECDC and Hedrich identified the same studies, which had no HIV seroconversions or too few to enable any conclusions to be made	Australia (2)	Given statements of insufficient evidence from two core reviews, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of OAT in the prevention of HIV in prison settings	**Insufficient**: 'There is insufficient review-level evidence to draw conclusions about the effect of OST on HIV... seroconversion in the prison setting'. [Note: the statement was based on one of the two studies identified in the updated review]	The review-level evidence for the effectiveness of OAT in preventing HIV in prison settings is **insufficient**
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: ECDC, European Centre for Disease Prevention and Control; HCV, hepatitis C virus; N/A, not applicable; OAT, opioid agonist treatment; OoR, overview of reviews; OST, opioid substitution treatment; RCT, randomised controlled trial.

Effects on injecting risk behaviour/injection frequency

One core review (Hedrich et al., 2012) investigated the association between OAT and IRB: six studies were included, four of which had robust designs (RCTs and cohorts). Five of the studies showed significant reductions in the sharing of injecting equipment associated with uptake of OAT and five showed significant reductions in injecting drug use associated with uptake of OAT. Given a statement of sufficient evidence from a core review that is based on multiple robust studies, we conclude that there is sufficient evidence to support the effectiveness of OAT in preventing IRB and IF (Table 10). The 2011 RoR had identified

tentative evidence of effectiveness; this has been superseded by the 2020 findings of sufficient evidence, as per the algorithm in Table 5.

Evidence statement: There is sufficient review-level evidence for the effectiveness of OAT in preventing IRB and IF in the prison setting.

TABLE 10
Evidence summary for opioid agonist treatment (OAT) in prison/criminal justice settings and injecting risk behaviour (IRB)/injection frequency (IF)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency								
Overview of reviews (OoR)	One core: Hedrich et al. (2012)	Hedrich: 'OMT was associated significantly with reduced heroin use, injecting and syringe-sharing in prison if doses were adequate'	Six studies (two RCTs, two cohort, one serial cross-sectional, one cross-sectional). N = 1 071 (range, 120-253)	Five studies showed significant ($p < 0.05$) reductions in the sharing of injecting equipment associated with OAT; five studies showed significant ($p < 0.05$) reductions in injecting drug use associated with OAT	Australia (2), Iran (2), Spain (2)	Given a statement of sufficient evidence from a core review, based on multiple robust studies, we conclude that there is **sufficient** evidence to support the effectiveness of OAT in preventing IRB and IF	**Tentative**: 'There is tentative evidence to support the effectiveness of prison-based OST in reducing injecting risk behaviour among PWID by significantly reducing the frequency of injection'. [Note: the statement is based on three of the five studies identified in the updated review that examined injecting drug use]	The review-level evidence for the effectiveness of OAT in preventing IRB/IF is **sufficient**
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; OAT, opioid agonist treatment; OMT, opioid maintenance treatment; OoR, overview of reviews; OST, opioid substitution treatment; PWID, people who inject drugs; RCT, randomised controlled trial.

Heroin-assisted treatment

HAT is a specific type of OAT involving the prescription of diamorphine (medical-grade heroin); HAT is also referred to as supervised injectable heroin. HAT is typically used to treat long-term refractory heroin-dependent individuals who have not responded to standard treatments (EMCDDA, 2012; Ferri et al., 2011; Strang et al., 2015).

Effects on hepatitis C virus transmission

No reviews or studies were identified that examined the effectiveness of HAT in preventing HCV in the updated reviews. No statement on HAT was given in the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of HAT in preventing HCV transmission among PWID.

Effects on HIV transmission

No reviews or studies were identified that examined the effectiveness of HAT in preventing HIV in the updated reviews. No statement on HAT was given in the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of HAT in preventing HIV transmission among PWID.

Effects on injecting risk behaviour/injection frequency

No reviews or studies were identified that examined the effectiveness of HAT in preventing IRB or IF in the updated reviews. No statement on HAT was given in the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of HAT in preventing IRB or IF among PWID.

Antagonist pharmacological treatment (naltrexone) for opioid dependence

Opioid antagonists block the effects of heroin and other opioids by binding to opioid receptors but not activating them (thereby preventing opioid-induced euphoria). The most common opioid antagonist treatment is naltrexone; all of the reviews identified here relate to naltrexone.

Effects on hepatitis C virus transmission

No reviews or studies were found to examine the effectiveness of naltrexone in preventing HCV in either the updated reviews or the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of antagonist treatment for opioid dependence in relation to prevention of HCV transmission.

Effects on HIV transmission

No reviews or studies were identified that examined the effectiveness of naltrexone in preventing HIV transmission in either the updated reviews or the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of antagonist treatment for opioid dependence in relation to prevention of HIV transmission.

Effects on injecting risk behaviour/injection frequency and other drug dependence outcomes

There were no reviews or studies identified that investigated the effectiveness of naltrexone in preventing IRB or IF in the updated review. In relation to other drug dependence

outcomes, one core review (Korownyk et al., 2019) conducted a meta-analysis of three robust studies (RCTs) and found a pooled RR of 1.48 (95 % CI 1.11-1.98) for opioid abstinence among individuals on naltrexone (oral or injectable extended-release) vs. placebo or usual care, suggesting an approximate 50 % increase in abstinence associated with naltrexone (range, 11 % to 98 %). Details of this review are outlined in Appendix 8. Given a tentative statement of evidence from a core review (based on consistent evidence from a small number of robust studies), we conclude that the evidence for the effectiveness of naltrexone regarding opioid abstinence as an outcome is tentative (Table 11). However, the review was not restricted to PWID and there is therefore no evidence regarding the effectiveness of naltrexone in reducing IRB or IF. The 2011 RoR made a statement of insufficient evidence concerning IRB outcomes. The updated statement therefore remains insufficient in this regard, but tentative for opioid abstinence outcomes.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of naltrexone in preventing IRB or IF. There is tentative evidence for the effectiveness of naltrexone with regard to opioid abstinence.

TABLE 11
Evidence summary for opioid antagonist treatment (OAT) and injecting risk behaviour (IRB)/injection frequency (IF)/other drug dependence outcomes

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency/other drug dependence outcomes								
Overview of reviews (OoR)	One core: Korownyk et al. (2019)	'Low quality evidence suggests that the use of injectable naltrexone in the management of opioid use disorder results in a statistically significant benefit vs. placebo or usual care for...abstinence...The largest barrier is the need for patients to undergo detox prior to initiation...We suggest naltrexone could be considered for patients who have been opioid free for at least 7-10 days who are unable or unwilling to use OAT.'	Three studies (all RCTs). N = 451 (range, 34-306)	Pooled risk ratio for confirmed abstinence among those on naltrexone (oral or injectable extended-release) vs. placebo or usual care = 1.48 (95 % CI 1.11-1.98)	Russia (1), United States (2)	Given a tentative statement of evidence from a core review (based on consistent evidence from a small number of robust studies), we conclude that the evidence for the effectiveness of naltrexone with regard to opioid abstinence as an outcome is **tentative**. However, the review was not restricted to PWID and we therefore cannot make	'There is **insufficient**... evidence regarding the effectiveness of naltrexone treatment in relation to...injecting risk behaviour. One meta-analysis reported a significant benefit of naltrexone alone or alongside psychosocial treatments compared to placebo in relation to a reduction in drug use. However, there is no evidence that naltrexone provides benefit with respect to relapse at follow-up...'	The evidence statement with regard to the effectiveness of naltrexone in preventing IRB remains **insufficient.** The evidence statement with regard to the effectiveness of naltrexone with regard to drug dependence outcomes (heroin use, abstinence) is **tentative**, given the conclusions of the 2011 review of reviews and the
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

						any statements with regard to the evidence for the effectiveness of naltrexone in reducing IRB or IF		updated review

Abbreviations: CI, confidence interval; IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; OAT, opioid agonist treatment; OoR, overview of reviews; PWID, people who inject drugs; RCT, randomised controlled trial.

Antagonist pharmacological treatment (naltrexone) for opioid dependence in prison/criminal justice settings

Effects on hepatitis C virus transmission

No reviews or studies were identified that examined the effectiveness of naltrexone in prison/criminal justice settings in preventing HCV in either the updated reviews or the 2011 RoR

Evidence statement: There is no evidence to either support or discount the effectiveness of antagonist treatment for opioid dependence in the prison/criminal justice setting in relation to the prevention of HCV transmission.

Effects on HIV transmission

No reviews or studies were identified that examined the effectiveness of naltrexone in prison/criminal justice settings in preventing HIV in either the updated reviews or the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of antagonist treatment for opioid dependence in the prison/criminal justice setting in relation to the prevention of HIV transmission.

Effects on injecting risk behaviour/injection frequency and other drug dependence outcomes

Two core reviews examined IRB/IF or other drug dependence outcomes (Appendix 9: Bahji et al., 2019; Moore et al., 2019). Only one study, an RCT, which looked at injecting outcomes, was identified by Moore et al. The study had an equivocal finding: there was no difference in post-prison release injecting between the intervention group that received extended-release naltrexone (XR-NTX) and the control group.

With regard to other drug dependence outcomes, Bahji et al. meta-analysed 11 studies (mostly RCTs) and found an approximate 40 % reduction in opioid relapse (pooled RR 0.63, 95 % CI 0.53-0.76) and a 40 % increase in opioid abstinence (pooled RR 1.38, 95 % CI 1.16-1.65) associated with naltrexone (Table 12). The latter effect was primarily seen in individuals on XR-NTX: subgroup analyses revealed a significant pooled RR for XR-NTX of 1.41 (95 % CI 1.12-1.78) compared with oral NTX (pooled RR 1.38, 95 % CI 0.92-2.08; Appendix 9).

Given a statement of insufficient evidence with regard to injecting outcomes from a core review (based on only one study with an equivocal outcome), we conclude that there is insufficient evidence to either support or discount the effectiveness of naltrexone in prison settings to prevent injecting drug use post-release. No statement about this specific intervention was made in the 2011 RoR. Therefore, the updated evidence statement is 'insufficient'. Regarding other drug dependence outcomes, given a statement of sufficient evidence from one core review (based on multiple robust studies), we conclude that there is sufficient evidence that naltrexone reduces opioid relapse and improves opioid abstinence among criminal justice-involved individuals post-prison release or in the community. The updated evidence statement also then becomes 'sufficient'.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of antagonist treatment for opioid dependence in prison/criminal justice settings in relation to the prevention of IRB or IF post-prison release. There is sufficient evidence to support the effectiveness of naltrexone in reducing opioid relapse and increasing opioid abstinence among criminal justice-involved individuals post-prison release or in the community.

TABLE 12
Evidence summary for opioid antagonist treatment and injecting risk behaviour/injection frequency/other drug dependence outcomes

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency								
Overview of reviews (OoR)	Two core: Bahji et al. (2019) and Moore et al. (2019)	Bahji: '...naltrexone... improved opioid abstinence and reduced opioid relapses. There were differences in the effect sizes and statistical significance of some outcomes by naltrexone formulation...including opioid abstinence, which generally favour XR-NTX over oral naltrexone.... Naltrexone	Bahji: Eleven studies (one quasi-experimental, 10 RCTs). N = 1 048 (range, 15-308). Moore: three studies (one quasi-experimental, two RCTs). N = 173 (range, 34-93). Note: all three	Bahji: pooled RR for opioid relapse = 0.63 (95 % CI 0.53-0.76) (10 studies). Pooled RR for opioid abstinence = 1.38 (95 % CI 1.16-1.65) (nine studies).	United States (10), Norway (1)	Given a statement of insufficient evidence from a core review (Moore), we conclude that there is **insufficient** evidence to either support or discount the effectiveness of naltrexone in	There was no 2011 statement specifically with regard to naltrexone in the prison/criminal justice setting	There is **insufficient** evidence to either support or discount the effectiveness of naltrexone in prison settings to prevent injecting drug use post-release. There is **sufficient** evidenc

		use—either oral or XR-NTX—was not significantly associated with reductions in the use of heroin'. Moore: '...naltrexone... [was] as effective as methadone in reducing illicit opioid use post-release...There was no evidence that...naltrexone reduced...health risk behaviours [i.e. injecting drug use], partly due to methodological quality of the studies examined....'	studies were included in Bahji et al.	Pooled RR for heroin use = 0.89 (95 % CI 0.7-1.14) (seven studies). Moore: study findings with regard to opioid use outcomes are detailed in the appendix (not detailed here as all included in Bahji meta-analysis). Injecting drug use as an outcome: one RCT found no significant differences at 1 month post-release between XR-NTX and control groups		prison settings to prevent injecting drug use post-release. Given a statement of sufficient evidence from one core review (Bahji), based on multiple robust studies, we conclude that there is **sufficient** evidence that naltrexone reduces opioid relapse and improves opioid abstinence among criminal justice-involved individuals post-prison release or in the community		e to support the effectiveness of naltrexone in reducing opioid relapse and increasing opioid abstinence among criminal justice-involved individuals post-prison release or in the community
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: CI, confidence interval; N/A, not applicable; OoR, overview of reviews; RCT, randomised controlled trial; RR, risk ratio; XR-NTX, extended-release naltrexone.

Pharmacological treatment for stimulant dependence

Effects on hepatitis C virus transmission

No reviews or studies were identified that examined the effectiveness of treatment for stimulant dependence in preventing HCV in either the updated reviews or the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of pharmacological treatment for stimulant dependence in preventing HCV transmission among PWID.

Effects on HIV transmission

No reviews or studies were identified that examined the effectiveness of treatment for stimulant dependence in preventing HIV in either the updated reviews or the 2011 RoR.

Evidence statement: There is no evidence to either support or discount the effectiveness of pharmacological treatment for stimulant dependence in preventing HIV transmission among PWID.

Effects on injecting risk behaviour/injection frequency

No reviews or studies ([5]) were identified that examined the effectiveness of treatment for stimulant dependence in preventing IRB or reducing IF in either the updated reviews or the 2011 RoR ([6]).

Evidence statement: There is no evidence to either support or discount the effectiveness of pharmacological treatment for stimulant dependence in preventing IRB or reducing IF among PWID.

Drug treatment (psychosocial)

For the purposes of this evidence review, psychosocial interventions were defined as any interventions that emphasise psychological or social factors rather than biological factors to promote behaviour change (EMCDDA, 2016b; Forsman et al., 2011). Because this definition can encompass a number of different types of interventions, we attempted to separate them into the following categories: (a) information, education, counselling and/or skills training (IECS), (b) contingency management (CM) (i.e. the use of incentives to promote behaviour change), and (c) technology-based psychosocial interventions. These categories were partly informed by the reviews identified because, in some instances, reviews examined 'psychosocial interventions' that comprised many of the interventions within these categories, for which it was not possible to isolate the individual intervention effects where pooled effect sizes had been generated.

([5]) One study was identified that examined the impact of treatment with methylphenidate on injecting outcomes among 24 intravenous methamphetamine users (Minařík et al., 2016). However, the study was designed as a case series and it therefore did not meet our PICO criteria for inclusion (see Section 2.2).

([6]) The 2011 technical report stated that ''Institute of Medicine (2007) [a core review] reported that no pharmacological treatments have been found to be consistently efficacious in treating individuals dependent on stimulants in relation to drug use or retention in treatment. However, the impacts of such treatments on the occurrence and/or risk of HCV or HIV were not discussed and whether such individuals were injectors of such stimulants was not specified'.

Psychosocial interventions involving information, education, counselling and/or skills training

Effects on hepatitis C virus transmission

With regard to HCV as an outcome, one core and one supplementary review were identified (Sacks-Davis et al., 2012; WHO, 2012) ([7]). Details of these reviews can be found in Appendix 10. Sacks-Davis et al. found three studies (all RCTs) that all showed no difference in HCV incidence between intervention and control groups (first study: RR 1.89 – no CIs or p-values were provided but the authors reported that the result was not significant; second study: RR 1.15, 95 % CI 0.72-1.82; and third study: an annual cumulative incidence of 7.2 % vs. 11.0 % in the intervention vs. control groups, p = 0.539). The WHO review identified two studies, both of which were already included in the Sacks review. An additional robust (cohort) study was identified from the primary literature review (Islam et al., 2017), which found that receipt of mental health counselling (vs. none) was significantly associated with a reduced risk of HCV reinfection (adjusted hazard ratio [aHR] 0.71, 95 % CI 0.54-0.92, p = 0.011). Given a statement of insufficient evidence from a core review, and only one further study identified from the primary literature, we conclude that there is insufficient evidence to either support or discount the effectiveness of psychosocial interventions alone (that include IECS) in preventing HCV transmission among PWID (Table 13). The statements of evidence from the 2011 RoR also indicated an insufficient level of evidence (Table 13) and the updated evidence statement remains insufficient when considering the evidence across the 2011 RoR and the updated review.

Evidence statement: There is insufficient evidence for the effectiveness of psychosocial interventions alone (that include IECS) in preventing HCV transmission among PWID.

TABLE 13
Evidence summary table for information, education, counselling and/or skills training (IECS) and hepatitis C virus (HCV)

Component	Reviews/studies identified		Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
	Hepatitis C virus								
Overview of reviews (OoR)	One core: Sacks-Davis et al. (2012). One supplementary: WHO (2012)/Walsh et al. (2014)		Sacks-Davis: 'Due to the small number of trials identified, the small number of participants involved... .it is difficult to assess whether	Sacks-Davis: three studies (all RCTs). N = 1 041 (range, 78-854). WHO/Walsh: two studies (both	Sacks-Davis: no studies showed differences in HCV incidence between intervention and control groups – RR =	Sacks-Davis: United Kingdom (1), United States (2). WHO/Walsh: United Kingdom (1), United	Given a statement of **insufficient** evidence from a core review, and only one further study identified from the	**Insufficient**: 'There is insufficient evidence to either support or discount the effectiveness of IEC in preventing HCV.' Statement based on	Considering the evidence across the 2011 review of reviews and updated review, we conclude that there is **insuffici**

([7]) The WHO review is also published in a peer-reviewed journal as Walsh et al. (2014).

			such interventions are effective means of reducing HCV incidence in PWID. However, the studies that were identified suggest that at least in isolation, behavioural interventions are unlikely to have a considerable impact on rates of HCV transmission.' WHO/Walsh: N/A (supplementary review)	RCTs). N = 372 (range, 95-277)	1.89 (no CIs or p-value provided but the result was reported to be non-significant); aRR = 1.15, 95 % CI 0.72-1.82; and annual cumulative incidence = 7.2 % vs. 11.0 % in intervention vs. control (p = 0.539). WHO/Walsh: pooled RR for HCV incidence in intervention vs. control = 0.75 (95 % CI 0.33-1.71). [Note: the two studies included in the WHO/Walsh review were captured in the Sacks-Davis review. Therefore, the evidence from WHO/Walsh will not be considered;	States (1)	primary literature, we conclude that there is insufficient evidence to either support or discount the effectiveness of psychosocial interventions alone (that include IECS) in preventing HCV transmission among PWID	one positive finding (cross-sectional). 'There is insufficient evidence to draw conclusions regarding the impact of psychosocial approaches alone in relation to HIV and HCV incidence'. [where psychosocial includes family therapy counselling and contingency management]. Statement based on no studies/reviews	**ent** review-level evidence to either support or discount the effectiveness of psychosocial interventions alone (that include IECS) in preventing HCV transmission among PWID

					however, it is consistent with the Sacks-Davis findings]				
Primary literature review	One strong: Islam et al. (2017)		N/A	One study (cohort). N = 1 604	Mental health counselling (vs. none) associated with reduced risk of HCV reinfection (adjusted hazard ratio 0.71, 95 % CI 0.54-0.92, p = 0.011)	Canada			

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; HCV, hepatitis C virus; IEC, information, education and counselling; IECS, information, education, counselling and/or skills training; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs; RCT, randomised control trial; RR, risk ratio; WHO, World Health Organization.

Effects on HIV transmission

With regard to HIV, no reviews were identified but four relevant primary studies (three RCTs and a cross-sectional study) were found in the evidence review (Appendix 10: Booth et al., 2016; Go et al., 2015; Hammett et al., 2012; Miller et al., 2018). One RCT showed a significant positive effect in terms of reduced HIV incidence in the intervention group (aHR 0.53, 95 % CI 0.38-0.75, p = 0.0003) but the remaining RCTs did not demonstrate significant differences in HIV incidence between intervention and control groups. The serial cross-sectional study (weaker design) identified decreasing HIV prevalence over time before and after introduction of the intervention, but the change cannot necessarily be attributed to the intervention given the limitations of the study design. Therefore, on the basis of a small number of primary studies with inconsistent findings, we conclude that there is insufficient evidence to either support or discount the effectiveness of psychosocial interventions alone with regard to HIV prevention. The 2011 RoR grouped the interventions slightly differently but 'insufficient' evidence statements were made. Thus, considering the evidence across the 2011 RoR and the updated review, the updated evidence statement remains insufficient (Table 14).

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of psychosocial interventions alone (that include IECS) in preventing HIV transmission among PWID.

TABLE 14
Evidence summary table for information, education, counselling and/or skills training (IECS) and HIV

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	On the basis of a small number of primary studies with inconsistent findings, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of psychosocial interventions alone (that include IECS) in preventing HIV transmission among PWID	**Insufficient:** 'There is insufficient evidence to either support or discount the effectiveness of IEC in preventing HIV.' Statement based on three positive findings (one cohort study, one cross-sectional, one ecological). 'There is insufficient evidence to draw conclusions regarding the impact of psychosocial approaches alone in relation to HIV and HCV incidence'. [where psychosocial includes family therapy counselling and contingency management]. Statement based on no	There is **insufficient** evidence to either support or discount the effectiveness of psychosocial interventions alone (that include IECS) in preventing HIV transmission among PWID
Primary literature review	Three strong: Booth et al. (2016), Go et al. (2015) and Miller et al. (2018); one weaker: Hammett et al. (2012)	N/A	Four studies (three RCTs, one serial cross-sectional). N = 9 103 (range, 810-5 695)	One RCT showed a significant positive effect in terms of reduced HIV incidence in the intervention group (adjusted hazard ratio 0.53, 95 % CI 0.38-0.75, p = 0.0003) but the two remaining RCTs did not demonstrate significant differences in HIV incidence between intervention and control groups. The serial cross-sectional study demonstrated decreasing HIV prevalence over time pre- vs. post-introducti	China, Indonesia, Ukraine and Vietnam			

				on of the interventi on, but the change cannot necessaril y be attributed to the interventi on			studies/revi ews	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; IEC, information, education and counselling; IECS, information, education, counselling and/or skills training; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs; RCT, randomised controlled trial.

Effects on injecting risk behaviour/injection frequency

Two core reviews (Gilchrist et al., 2017b; Sacks-Davis et al., 2012) and one supplementary review (WHO, 2012) examined IRB outcomes (Appendix 10). Gilchrist et al. calculated standardised mean differences (SMDs) ([8]) to compare individuals receiving psychosocial interventions vs. control groups. The pooled SMD was −0.29 (95 % CI −0.42 to −0.15, p < 0.01) for any IRB outcome (based on 22 studies) while the SMDs were −0.43 (95 % CI −0.69 to −0.18, p < 0.01) for sharing needles/syringes (based on 13 studies), −0.21 (95 % CI −0.34 to −0.09, p < 0.01) for sharing paraphernalia (based on 7 studies) and −0.17 (95 % CI −0.35 to 0.00, p = 0.05) for IF (based on 8 studies). Sacks-Davis et al. identified six studies, but five of these were already captured in the Gilchrist review and the supplementary review was not consulted as all four of the studies identified had also been included in the Gilchrist review. The Gilchrist findings were therefore primarily relied upon to generate the evidence statement, which was that there is sufficient evidence (given a statement of sufficient evidence from a core review, based on multiple robust studies; Table 15). The 2011 RoR made statements of tentative and insufficient evidence, but the interventions had been categorised slightly differently. Regardless, the updated evidence statement would become sufficient according to the algorithm (Table 5).

Evidence statement: There is sufficient evidence that psychosocial interventions involving IECS are effective in reducing IRB and IF, compared to control conditions, among PWID.

([8]) A SMD of 0.2 is considered to be small, while 0.5 is considered medium and 0.8 large.

TABLE 15

Evidence summary table for information, education, counselling and/or skills training (IECS) and injecting risk behaviour/injection frequency (IRB/IF)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency								
Overview of reviews (OoR)	Two core: Gilchrist et al. (2017b) and Sacks-Davis et al. (2012). One supplementary: WHO (2012)/Walsh et al. (2014)	Gilchrist: 'Overall, psychosocial interventions reduced some of the target injecting (sharing of needle and syringes and other injecting paraphernalia)... .outcomes among PWID when compared with control conditions…..The findings highlight the difficulty and complexity involved in attempting to examine the effectiveness of interventions that include different content and functions, modes of delivery, dosage and number of sessions….Our findings suggest that psychosocial interventions could boost the impact of current harm reduction interventions'. Sacks-Davis: no clear statement with regard to IRB. WHO/Walsh: N/A (supplementary)	Gilchrist: 31 studies (all RCTs). N = 12 480 (range, 40-1 123). Sacks-Davis: six studies (all RCTs). N = 2 472 (range, 109-851). WHO/Walsh: four studies (all RCTs). By intervention: for IECS – two RCTs, N = 1 111 (range, 260-851); for 'peer education and mentoring' – two RCTs, N = 1 272 (range, 418-854)	Gilchrist: all standardised mean differences (SMDs) compare psychosocial vs. control. For any IRB outcome: SMD −0.29, 95 % CI −0.42 to −0.15, p < 0.01 (22 studies). For sharing needles/syringes: SMD −0.43, 95 % CI −0.69 to −0.18, p < 0.01 (13 studies). For sharing paraphernalia: SMD −0.21, 95 % CI −0.34 to −0.09, p < 0.01 (7 studies). For IF, SMD −0.17, 95 % CI −0.35 to 0.00, p = 0.05 (8 studies). Sacks-Davis: out of three	Gilchrist: Australia (1), Canada (2), Georgia (1), Kazakhstan (1), Mexico (1), Puerto Rico (1), Russia (3), United Kingdom (1), United States (18), Vietnam (2). Sacks-Davis: Australia (1), United Kingdom (1), United States (4). WHO/Walsh: Canada (1), United States (3)	Given a statement of sufficient evidence from a core review (Gilchrist), based on multiple robust studies, we conclude that there is **sufficient** evidence that psychosocial interventions involving IECS are effective in reducing IRB and IF — compared to control conditions — among PWID	**Tentative:** 'There is tentative evidence to support the effectiveness of outreach which includes IEC in reducing IRB'. Statement based on 28 studies: 18 positive (7 RCTs, 10 cohort studies, 1 CS); 10 no association (8 RCTs, 2 CSs). 'No psychosocial intervention alone has been shown to be effective in relation to reducing injecting risk behaviour and	There is **sufficient** evidence that psychosocial interventions involving IECS are effective in reducing IRB and IF — compared to control conditions — among PWID*

				studies that examined IF – two positive, one equivocal. Out of six studies that examined IRB – two positive, four equivocal. WHO/Walsh: for IECS – pooled RR 0.75 (95 % CI 0.33-1.71). For peer education and mentoring – pooled RR 0.61 (95 % CI 0.48-0.85). [Note that five of the six studies in the Sacks-Davis and all four studies in the WHO/Walsh reviews were captured in the Gilchrist review. Given that these study findings have already been reflected in a pooled estimated, we have relied primarily on the Gilchrist findings to derive the evidence statement.]			further evidence is needed. There is **insufficient** evidence to draw conclusions regarding the effectiveness of any single psychosocial intervention alone in relation to treatment of opiate dependence' [where psychosocial includes family therapy counselling and contingency management]	
Primary literatur	N/A	N/A	N/A	N/A	N/A			

e review**								

Abbreviations: CI, confidence interval; CS, cross-sectional study; IEC, information, education and counselling; IECS, information, education, counselling and/or skills training; IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs; RCT, randomised controlled trial; RR, risk ratio; SMD, standardised mean difference.

*2011 review of review statements of evidence are not directly comparable here as a result of different categorisations of the interventions; for example, the 'tentative' statement relates to '*outreach* which includes IEC'. Regardless of the evidence from the 2011 review of reviews, the statement of sufficient evidence from the updated review would supersede the statements from 2011.

**Primary literature not consulted given sufficient evidence from the overview of reviews.

Psychosocial interventions involving contingency management

CM is a behavioural management technique that involves the use of incentives to reinforce behaviours (or disincentives/punishments to discourage them). The main goal of CM applied to the drug treatment field is to reinforce compliance with treatment and therefore abstinence from illicit drugs. The incentives can be money, vouchers, prizes or other kinds of privileges (EMCDDA, 2016a).

Effects on hepatitis C virus transmission

No reviews or studies examining the association between CM and HCV transmission were identified. The 2011 RoR stated 'there is insufficient evidence to draw conclusions regarding the impact of psychosocial approaches alone in relation to HIV and HCV incidence', but the intervention also included 'family therapy counselling', as well as CM, and the statement was also based on no studies/reviews identified.

Evidence statement: There is no evidence to either support or discount the effectiveness of CM interventions in the prevention of HCV among PWID.

Effects on HIV transmission

No reviews or studies examining the association between CM and HIV transmission were identified. Similar to HCV (stated above), the 2011 RoR made a statement of insufficient evidence, but the intervention also included 'family therapy counselling', as well as CM, and the statement was also based on no studies/reviews identified.

Evidence statement: There is no evidence to either support or discount the effectiveness of CM interventions in the prevention of HIV among PWID.

Effects on injecting risk behaviour/injection frequency and other drug dependence outcomes

No reviews or studies examining the association between CM and BBV transmission or IRB were identified. Two reviews (EMCDDA, 2016a; Korownyk et al., 2019) examined the impact of CM interventions on drug use, usually measured via urinalysis (Appendix 11). The EMCDDA review included RCTs that examined the impact of CM by substance used: opioids (20 studies), stimulants (4 studies) and stimulants and opioids (14 studies). Similarly, Korownyk et al. identified 14, 8 and 12 studies of the impact of CM on opioid dependence, stimulant dependence and dependence on both (or not specified), respectively; all were RCTs. There was an overlap of 17 studies between the two reviews. The overall findings from the studies included in the reviews were mixed: out of the 21 studies of CM and opioid use, 3 had positive findings, 3 had positive/equivocal findings, 1 had positive/negative findings and 14 had equivocal findings. Of the 4 studies of stimulant use, 2 were positive, 1

was equivocal and 1 was unclear. Of the 23 studies looking at stimulant and opioid use, 9 were positive, 8 were positive/equivocal, 5 were equivocal and 1 was equivocal/negative.

Given no evidence with regard to IRB, the specific statement relating to this outcome was therefore 'no evidence'. The 2011 RoR made a statement of insufficient evidence; the updated evidence statement therefore became 'insufficient' (applying the algorithm in Table 5).

With regard to other drug dependence outcomes, there was a tentative statement of evidence from one core review and a statement of insufficient evidence from a second core review. We therefore examined the primary study findings: although there were a large number of robust studies, the findings were mixed and many were equivocal. We therefore conclude that the evidence is insufficient to support the effectiveness of CM in reducing drug use among opioid and stimulant users (Table 16).

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of CM interventions in the prevention of IRB among PWID. There is insufficient evidence to support the effectiveness of CM interventions in reducing drug use among opioid and stimulant users.

TABLE 16
Evidence summary table for contingency management (CM) and injecting risk behaviour/injection frequency (IRB/IF) and other drug dependence outcomes

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency								
Overview of reviews (OoR)	Two core: EMCDDA (2016) and Korownyk et al. (2019). [Note: neither review was restricted to PWID]	'Although limited, the present analysis shows that contingency management is a feasible and promising adjunct to treatment interventions for drug users...Overall, the study results show that it can help keep people in treatment,	All RCTs. EMCDDA: no of studies by substance – opioids (20), stimulants (4), stimulants and opioids (14). Sample sizes by substance – opioids, N = 1 676 (range, 20-320); stimulants, N =	All results relate to use of the indicated substance, measured primarily via urine analysis. EMCDDA: opioids – 5 positive, 14 equivocal, 1 unclear; stimulants – two positive, one equivocal, one unclear; stimulants and opioids – eight positive, four mixed positive/equivocal, two equivocal.	EMCDDA: opioids – China (3), Malaysia (1), United States (15), not stated (1); stimulants – United States (4); stimulants and opioids – United States (14).	There was **no** evidence to either support or discount the effectiveness of CM in reducing IRB. Given a tentative statement of evidence from one core review and a statement of insufficient evidence	**Insufficient** for IRB and opiate dependence: 'No psychosocial intervention alone has been shown to be effective in relation to reducing injecting risk behaviour and further evidence is needed. There is	There is **insufficient** evidence to either support or discount the effectiveness of CM interventions in the prevention of IRB among PWID. There is **insufficient** evidence to support the

		and promote a reduction of opioid and cocaine problems in patients in OST.' 'Evidence for reductions in opioid use with CM in patients on OAT is heterogeneous and inconsistent.….. These results suggest that positive reinforcement strategies should be used whenever possible. We recommend against punitive measures involving OAT (i.e. reduction in dose or loss of carries [decreasing medication doses or revoking take home privileges for non-compliance]), unless safety is a concern.'	676 (range, 87-229); stimulants and opioids, N = 1 604 (range, 42-240). Korownyk: no of studies by substance – opioid dependence (14); stimulant dependence (8); both or not specified (12). Sample sizes by substance – opioids, N = 2 116 (range, 16-388); stimulants, N = 1 268 (range, 57-388); both or not specified, N = 921 (range, 29-160)	Korownyk: opioids – nine positive, five equivocal; stimulants – five positive, three equivocal; both or not specified – five positive, six equivocal, one negative. Note that there was an overlap of 17 studies between the reviews. Combined: opioids – 21 studies (3 positive, 3 positive/equivocal, 1 positive/negative, 14 equivocal); stimulants – four studies (two positive, one equivocal, one unclear); stimulants and opioids – 23 studies (9 positive, 8 positive/equivocal, 5 equivocal, 1 equivocal/negative)	Korownyk: opioids – China (3), United States (10), not stated (1); stimulants – United States (8); both or not specified – United States (10), not stated (2)	from a second core review, we consulted the primary studies, which were numerous and robust but showed a mixture of positive and equivocal findings. We conclude that the evidence is **insufficient** to support the effectiveness of CM in reducing drug use among opioid and stimulant users	insufficient evidence to draw conclusions regarding the effectiveness of any single psychosocial intervention alone in relation to treatment of opiate dependence' [where psychosocial includes family therapy counselling and CM]	effectiveness of CM interventions in reducing drug use among opioid and stimulant users
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: CM, contingency management; IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; OAT, opioid agonist treatment; OoR, overview of reviews; OST, opioid substitution treatment; PWID, people who inject drugs; RCT, randomised controlled trial.

Technology-based psychosocial interventions

Effects on hepatitis C virus transmission

No reviews or studies were identified in relation to the effect of technology-based psychosocial interventions on HCV transmission, which resulted in a statement of 'no evidence'. No statement was made with regard to technology-based psychosocial interventions in the 2011 RoR. Therefore, the updated evidence statement remains 'no evidence'.

Evidence statement: There is no evidence to either support or discount the effectiveness of technology-based psychosocial interventions in the prevention of HCV transmission among PWID.

Effects on HIV transmission

No reviews or studies were identified in relation to the effect of technology-based psychosocial interventions on HIV transmission, leading to a statement of 'no evidence'. As above for HCV, no statement was made with regard to technology-based psychosocial interventions in the 2011 RoR. Therefore, the updated evidence statement remains 'no evidence'.

Evidence statement: There is no evidence to either support or discount the effectiveness of technology-based psychosocial interventions in the prevention of HIV transmission among PWID.

Effects on injecting risk behaviour/injection frequency

Only one study was identified that investigated technology-based psychosocial interventions and IRB. That cohort study (Calvo et al., 2020) examined the impact of a psychosocial intervention delivered through WhatsApp and found significant declines in risk assessment battery scores from pre- to 1 month post-intervention ($p < 0.001$) (Appendix 12). However, with only one primary study, we conclude that the level of evidence is insufficient. No statement was given in the 2011 RoR. Therefore, the updated evidence statement is 'insufficient'.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of technology-based psychosocial interventions in the prevention of HIV transmission among PWID.

TABLE 17
Evidence summary tables for technology-based psychosocial interventions and injecting risk behaviour/injection frequency (IRB/IF)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	We found only one study of technology-based psychosocial interventions with regard to IRB/IF. Therefore, we conclude that the evidence is **insufficient**	No statement	There is **insufficient** evidence to either support or discount the effectiveness of technology-based psychosocial interventions in the prevention of IRB/IF among PWID
Primary literature review	One strong: Calvo et al. (2020)	N/A	One study (cohort). N = 105	There were significant declines in risk assessment battery scores from pre- to 1 month post-intervention ($p < 0.001$)	Spain			

Abbreviations: IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs.

Psychosocial interventions in prison/criminal justice settings

Effects on hepatitis C virus transmission

No reviews or studies were identified in relation to the impact of any psychosocial interventions on HCV transmission in the prison setting. No statement was made in the 2011 RoR. Therefore, the updated evidence statement is 'no evidence'.

Evidence statement: There is no evidence to either support or discount the effectiveness of psychosocial interventions (involving IECS) in the prison setting for the prevention of HCV transmission among PWID.

Effects on HIV transmission

No reviews or studies were identified in relation to the impact of any psychosocial interventions on HIV transmission in the prison setting. No statement was made in the 2011 RoR. Therefore, the updated evidence statement is 'no evidence'.

Evidence statement: There is no evidence to either support or discount the effectiveness of psychosocial interventions (involving IECS) in the prison setting for the prevention of HIV transmission among PWID.

Effects on injecting risk behaviour/injection frequency

One core review was identified that examined the impact of IECS interventions on IRB (ECDC, 2018) (Appendix 13). This review retrieved two studies (both RCTs), one of which showed greater improvement in the intervention group (compared to usual care) in avoiding

risky drug use and risk reduction skills; the other study found no significant differences in the sharing of used drug injecting equipment. Given a statement of insufficient evidence from a core review (Table 18), we conclude that the level of evidence is insufficient. There was no statement of evidence from the 2011 RoR. Therefore, the updated evidence statement is 'insufficient'.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of psychosocial interventions alone (involving IECS) in the prison setting with regard to reducing IRB or IF.

TABLE 18
Evidence summary table for psychosocial interventions involving information, education, counselling and/or skills training (IECS) — prison setting — and injecting risk behaviour (IRB) or injection frequency (IF)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour/injection frequency								
Overview of reviews (OoR)	One core: ECDC (2018)	'Two RCTs investigated a combination of [group] health promotion and skills-building interventions and their impact on HIV knowledge and behaviour outcomes. They showed conflicting results.'	Two studies (both RCTs). N = 1 347 (range, 90-1 257)	No effect sizes presented. One study showed greater improvement in the intervention group (compared to usual care) in avoiding risky drug use and risk reduction skills. The other found no significant differences in the sharing of used drug injecting equipment	United States (2)	Given a statement of insufficient evidence from a core review, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of psychosocial interventions alone (involving IECS) in the prison setting with regard to IRB/IF	No statement	There is **insufficient** evidence to either support or discount the effectiveness of psychosocial interventions alone (involving IECS) in the prison setting with regard to reducing IRB or IF
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: IECS, information, education, counselling and/or skills training; IF, injection frequency; IRB, injecting risk behaviour; N/A, not applicable; OoR, overview of reviews; RCT, randomised controlled trial.

Needle and syringe programmes

NSPs are divided into the following interventions, which are described in subsequent sections: sterile needle and syringe provision, provision of low dead space syringes (LDSSs) and provision of sterile drug preparation equipment (often referred to as 'paraphernalia').

Sterile needle and syringe provision

While 'NSP' is usually an abbreviation for needle and syringe programme, and could therefore include services that provide a range of types of injecting and drug preparation equipment, in this review, it was taken to refer to the provision of sterile needle/syringes (unless it was otherwise specified that different types of equipment were supplied).

Effects on hepatitis C virus transmission

With regard to the prevention of HCV, one core review and two supplementary reviews were identified (Appendix 14: Abdul-Quader et al., 2013; Davis et al., 2017; Platt et al., 2017) ([9]). The Platt core review and meta-analysis found a pooled effect size that was consistent with a 76 % reduction in the risk of HCV associated with high NSP coverage (RR 0.24, 95 % CI 0.09-0.62, when restricted to two studies conducted in Europe), where high coverage was defined as regular attendance at a NSP or all injections covered by a new needle/syringe. Additional primary studies that were identified since the publication of the review (Chen et al., 2018; Handanagic et al., 2017; Leyna et al., 2019; Minoyan et al., 2020; Salek et al., 2017) were primarily of weaker designs and did not change the conclusions. Given a tentative statement of evidence from a core review, and additional primary studies that did not change the evidence base in either direction, we conclude that the level of evidence is tentative. Considering the evidence base across the 2020 OoR and the 2011 RoR, we conclude that the updated level of evidence is tentative (Table 19).

Evidence statement: There is tentative evidence to support the effectiveness of NSPs in reducing HCV transmission.

TABLE 19
Evidence summary table for sterile needle and syringe provision and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	One core: Platt et al. (2017). Two supplementary: Abdul-Quader et al. (2013) and Davis et al. (2017). [Note: supplementa	Platt: 'There was greater heterogeneity between studies and weaker evidence for the impact of NSP on	Platt: 15 studies (11 cohort, 1 case-control, 3 cross-sectional). N = 7 684 (range,	Platt: pooled RR = 0.79 (95 % CI 0.39-1.61) from five studies of high NSP covera	Platt: Australia (2), Canada (3), Netherlands (1), United Kingdom (3), United States (6)	The core review made a tentative statement of evidence that was based on a meta-analysis of findings from a	'There is **insufficient** review-level evidence to either support or discount the effectiveness of needle and syringe	Considering the evidence base across the updated and 2011 reviews, with the balance of evidence from the

([9]) The review by Platt et al. (2017) was also published in a peer-reviewed journal as Platt et al. (2018).

	ry studies were not relied upon because Davis et al. identified primarily the same studies as Platt et al. and because Abdul-Quader et al. only examined studies with weaker designs]	HCV acquisition. High NSP coverage was associated with a reduction in the risk of HCV acquisition in studies in Europe.'	46-2 788)	ge vs. no/low coverage (10); European studies only (two studies) had a RR of 0.24 (95 % CI 0.09-0.62)		small number of cross-sectional studies (n = 2).* The primary literature did not change the evidence in either direction (inconsistent findings, mainly based on weaker designs). Therefore, given a tentative statement of evidence from a core review, based on consistent evidence from a small number of robust studies, we conclude that there is **tentative** evidence to support the effectiveness of NSPs in reducing HCV	exchange programmes in reducing HCV transmission among PWID, although ecological investigations have demonstrated stable or declining HCV prevalence in the context of needle and syringe exchange programmes.' This statement was based on 17 studies: 9 positive (1 case-control study, 6 CSs, 2 ecological), 2 negative (2 COHs), 6 no association (3 COHs, 3 CSs). [Note: one study that was included in the Platt pooled RR was also included in the 2011 review of reviews]	2011 review of reviews tipped in favour of positive studies, we conclude that there is **tentative** evidence to support the effectiveness of NSPs in reducing HCV transmission
Primary literature review	One strong: Minoyan et al. (2020); four weaker: Chen et al. (2018), Handanagic et al. (2017), Leyna et al. (2019) and Salek et al. (2017)	N/A	Five studies (one cohort, three cross-sectional, one serial cross-sectional). N = 105 754 (range, 130-101 032)	Cohort: equivocal. Cross-sectional: negative (3). Serial cross-sectional: positive (1)	Canada (1), China (1), Croatia (1), Tanzania (1), United States (1)			

Abbreviations: CI, confidence interval; COH, cohort study, CS, cross-sectional study; HCV, hepatitis C virus; N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews; PWID, people who inject drugs; RR, risk ratio.

([10]) Where high coverage was defined as regular attendance at a NSP or all injections covered by a new needle/syringe.

*The cross-sectional studies included here examined the incidence of HCV infection (as opposed to the prevalence of infection, which is ordinarily what cross-sectional studies would measure) by identifying individuals in the short 'window period' before HCV antibody seroconversion (i.e. individuals who are HCV antibody negative and HCV RNA positive). These studies can therefore be considered as robust as cohort studies (and arguably more robust because they will not be subject to the attrition bias that affects cohort studies). We are placing greater weight on the European studies here because they used a stronger measure of exposure (NSP coverage: percentage of injections covered by clean needles/syringes), as opposed to the North American studies, which measured frequency of NSP attendance.

Effects on HIV transmission

For prevention of HIV, a core review and a supplementary review were identified (Abdul-Quader et al., 2013; Aspinall et al., 2014) (Appendix 14). The core review found a pooled effect size consistent with a 58 % reduction in the risk of HIV associated with the use of a NSP (RR 0.42, 95 % CI 0.22-0.81, when restricted to high-quality studies), although measures of NSP coverage or uptake differed among the meta-analysed studies. Given a statement of sufficient evidence from a core review (based on several robust studies), we conclude that the level of evidence is sufficient (Table 20). The 2011 RoR made a statement of tentative evidence. Therefore, the updated evidence statement becomes 'sufficient' (Table 5).

Evidence statement: There is sufficient evidence that NSPs effectively reduce the risk of HIV transmission.

TABLE 20
Evidence summary table for sterile needle and syringe provision and HIV

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	One core: Aspinall et al. (2014). One supplementary (Abdul-Quader et al., 2013). [Note: the supplementary review was not consulted because of sufficient statement from the core review]	Aspinall: 'There is evidence to support the effectiveness of NSP in reducing the transmission of HIV among PWID, although it is likely that other harm reduction interventions have also contributed to the observed reduction	Aspinall: 12 studies (10 cohort, 1 cross-sectional, 1 case-control). N = 12 023 (range, 226-2 505). Total, 11 984 person-years follow-up	Aspinall: pooled effect sizes = 0.66 (95 % CI 0.43-1.01) across all (12) studies and 0.42 (95 % CI 0.22-0.81) across six higher-quality	Australia (1), Canada (5), China and Vietnam (2), Sweden (1), United States (9), Western Europe (3)	As the core review identified made a statement of sufficient evidence based on pooled evidence from a reasonable number of robust studies, we conclude that there is **sufficient** evidence to support the	'There is **tentative** review-level evidence that NSP is effective in reducing HIV incidence...However...an often-cited cohort study found that high-level NSP in combination with high-level OST statistically significantly reduced the risk of HIV transmission.' This statement was based on 16 studies: 10 positive (2 COHs, 4 ecological, 4 case studies), 2 negative (2 COHs) and 4 with no association (2	There is **sufficient** evidence that NSPs are effective in reducing the risk of HIV transmission

		in HIV risk.'		studies		effectiveness of NSPs in reducing HIV incidence	COHs, 2 case-control). [Note: seven studies that were included by Aspinall et al. were also included in the 2011 review of reviews]	
Primary literature review	N/A	N/A	N/A	N/A	N/A			

Abbreviations: CI, confidence interval; COH, cohort study, N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews; OST, opioid substitution treatment; PWID, people who inject drugs.

Effects on injecting risk behaviour

In the 2011 RoR, the evidence for NSPs was deemed sufficient with regard to IRB and thus was not updated here, as per the methods. Therefore, the 2011 evidence statement stands, as below.

Evidence statement: 'There is sufficient review-level evidence to support the effectiveness of needle and syringe exchange programmes in reducing self-reported injecting risk behaviour among PWID.'

Sterile needle and syringe provision in prison/criminal justice settings

Effects on hepatitis C virus transmission

One high-quality review was identified (ECDC, 2018) that included three studies of in-prison NSPs and HCV transmission (Appendix 15): the studies had mixed findings, with two cohort studies observing no or too few HCV seroconversions to draw any conclusions and one ecological study (weaker design) demonstrating a decline in HCV prevalence over time during an expansion of an in-prison NSP. Given a statement of insufficient evidence from this core review (based on a small number of studies), we conclude that the level of evidence is insufficient (Table 21). The 2011 RoR did not make a statement with regard to NSP in the prison setting. Therefore, the updated evidence statement becomes 'insufficient'.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of NSPs in reducing HCV transmission in the prison setting.

TABLE 21
Evidence summary table for sterile needle and syringe provision and hepatitis C virus (HCV) – prison setting

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	One core: ECDC (2018)	ECDC: 'The evidence on the effectiveness of [...] NSP [...] measures to control BBVs transmission in prison settings is limited'	Three studies (one ecological, two cohort). N = 405 (range, 174-231)	Cohort studies: 1) incidence rate = 18/100 person-years (four seroconversions) after NSP implementation, possibly due to front-loading or spoon sharing; 2) no seroconversions after syringe vending machine installed. Ecological: HCV prevalence declined from 48.6 % in 1998 to 20 % in 2014 during a period of in-prison NSP expansion	Germany (2), Spain (1)	Given a statement of insufficient evidence from a core review, based on a small number of studies, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of NSPs in the prevention of HCV in the prison setting	There was no statement with regard to NSPs for the prevention of HCV in the prison setting	There is **insufficient** evidence to either support or discount the effectiveness of NSPs in reducing HCV transmission in the prison setting
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: BBV, blood-borne virus; ECDC, European Centre for Disease Prevention and Control; HCV, hepatitis C virus; N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews.

Effects on HIV transmission

The above-mentioned review (ECDC, 2018) also examined in-prison NSPs and HIV, and the studies within the review also showed mixed findings, with the two cohort study findings being equivocal and one ecological study observing a decline in HIV prevalence over time during an expansion of an in-prison NSP (Appendix 15). Therefore, given a statement of insufficient evidence from a core review (based on a small number of studies), we conclude that the level of evidence is insufficient (Table 22). As above for HCV, there was no statement with regard to NSPs in prison and the updated evidence statement therefore becomes 'insufficient'.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of NSP in reducing HIV transmission in the prison setting.

TABLE 22
Evidence summary table for sterile needle and syringe provision and HIV – prison setting

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	One core: ECDC (2018)	ECDC: 'The evidence on the effectiveness of [...] NSP [...] measures to control BBVs transmission in prison settings is limited'	Three studies (one ecological, two cohort). N = 405 (range, 174-231)	Both cohort studies found no HIV seroconversions during the study period. Ecological: HIV prevalence in prisons decreased from 12.1 % in 2003 to 5.8 % in 2014 during a period of in-prison NSP expansion	Germany (2), Spain (1)	Given a statement of insufficient evidence from a core review, based on a small number of studies, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of NSPs in the prevention of HIV in the prison setting	There was no statement with regard to NSPs for the prevention of HIV in the prison setting	There is **insufficient** evidence to either support or discount the effectiveness of NSPs in reducing HIV transmission in the prison setting
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: BBV, blood-borne virus; ECDC, European Centre for Disease Prevention and Control; N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews.

Effects on injecting risk behaviour

No evidence was found regarding the impact of prison NSPs on IRB and no statement was given in the 2011 RoR. The updated evidence statement is therefore 'no evidence'.

Evidence statement: There is no evidence to either support or discount the effectiveness of prison NSPs in preventing IRB.

Sterile needle and syringe provision in pharmacy settings

Effects on hepatitis C virus transmission

One high-quality review that examined the association between pharmacy NSP uptake and all three outcomes (HCV, HIV, IRB) was identified (Sawangjit et al., 2017); details of the review are available in Appendix 16. The studies within the review were meta-analysed and found significantly lower odds of HCV associated with pharmacy-based NSPs vs. no NSP but this was based on only two studies. A comparison of pharmacy-based vs. other types of NSPs showed no significant difference in HCV, based on four studies. No additional primary studies were identified. Given a statement of insufficient evidence from a core review, based on small numbers of studies with mostly weaker designs, we conclude that the level of evidence is insufficient (Table 23). No evidence was identified in the 2011 RoR and the updated level of evidence is therefore 'insufficient'.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of pharmacy-based NSPs in reducing HCV transmission.

TABLE 23
Evidence summary table for sterile needle and syringe provision and hepatitis C virus (HCV) – pharmacy setting

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	One core: Sawangjit et al. (2017)	'For...HCV prevalence, the evidence for pharmacy-based NSPs compared with other NSP or no NSP was unclear, as few studies reported this and most of them had a serious risk of bias.'	Six studies (five cross-sectional, one cohort). N = 2 628 (range, 128-1 020)	Pooled ORs: pharmacy vs. no NSP = 0.26 (95 % CI 0.18-0.38, two studies) and pharmacy vs. other NSP = 0.63 (95 % CI 0.27-1.45, four studies)	Australia (3), Canada (1), Estonia (1), United States (1)	Given a statement of insufficient evidence from a core review, based on studies with mostly weaker designs, we conclude that the evidence is **insufficient** to either support or discount the effectiveness of pharmacy NSPs in preventing HCV among PWID	**No** evidence: 'There is no review-level evidence to either support or discount the effectiveness of pharmacy access to needles/syringes on reducing the transmission of HCV among PWID.'	There is **insufficient** evidence to either support or discount the effectiveness of pharmacy NSPs in preventing the transmission of HCV among PWID
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews; OR, odds ratio; PWID, people who inject drugs.

Effects on HIV transmission

With regard to HIV, the meta-analysis conducted by Sawangjit et al. found no significant difference between pharmacy-based NSPs and no NSP (based on three studies) and a significantly reduced odds of HIV when comparing pharmacy-based NSPs vs. other types of NSPs, again based on three studies (Appendix 16, Table 24). Given a statement of insufficient evidence from a core review, based on studies with mostly weaker designs, we conclude that the evidence is insufficient. The 2011 RoR also made a statement of insufficient evidence. When considering the evidence across the 2011 RoR and 2020 OoR, the evidence statement remains insufficient (Table 24).

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of pharmacy-based NSPs in reducing HIV transmission.

TABLE 24
Evidence summary table for sterile needle and syringe provision and HIV – pharmacy setting

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	One core: Sawangjit et al. (2017)	'For...HIV prevalence, the evidence for pharmacy-based NSPs compared with other NSP or no NSP was unclear, as few studies reported this and most of them had a serious risk of bias.'	Six studies (two cohort, four cross-sectional). N = 2 273 (range, 328-1 020)	Pooled ORs: pharmacy vs. no NSP = 0.56, (95 % CI 0.18-1.77, three studies) and pharmacy vs. other NSP = 0.55 (95 % CI 0.41-0.76, three studies)	Australia (2), Canada (1), Estonia (1), United States (2)	Given a statement of insufficient evidence from a core review, based on studies with mostly weaker designs, we conclude that the evidence is **insufficient** to either support or discount the effectiveness of pharmacy NSPs in preventing HIV among PWID	Insufficient: 'There is **insufficient** review-level evidence to either support or discount the effectiveness of pharmacy access to needles/syringes in reducing HIV prevalence among PWID.' Statement based on four studies: four positive (all cross-sectional). [Note: the Sawangjit review included one study that had also been included in the 2011	There is **insufficient** evidence to either support or discount the effectiveness of pharmacy NSPs in preventing the transmission of HIV among PWID
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

							review of reviews]	

Abbreviations: CI, confidence interval; N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews; OR, odds ratio; PWID, people who inject drugs.

Effects on injecting risk behaviour

The meta-analysis undertaken by Sawangjit et al. found an approximately 50 % reduction in the odds of IRB associated with the use of pharmacy-based NSPs, compared to no NSP, based on a moderate number of studies (pooled OR 0.50, 95 % CI 0.34-0.73, six studies). A comparison of the use of pharmacy-based NSPs with other types of NSPs revealed no significant difference in IRB (pooled OR 1.46, 95 % CI 0.78-2.73, seven studies). Given a statement of sufficient evidence from a core review (based on a large number of studies, many with robust designs), we conclude that the evidence is sufficient to support the conclusion that pharmacy-based NSPs are at least as effective as other types of NSPs. Similarly, we also conclude that there is sufficient evidence that pharmacy-based NSPs, relative to no NSP, are effective in reducing IRB (Table 25). The evidence statement was 'tentative' in the 2011 RoR. Therefore, the updated evidence statement becomes 'sufficient', as per the algorithm in Table 5.

Evidence statement: There is sufficient evidence to support the conclusion that pharmacy-based NSPs are at least as effective in the prevention of IRB as other settings/modalities for NSP delivery. There is also sufficient evidence to support the effectiveness of pharmacy-based NSPs (relative to no NSP) in preventing IRB.

TABLE 25
Evidence summary table for sterile needle and syringe provision and injecting risk behaviour (IRB) – pharmacy setting

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour								
Overview of reviews (OoR)	One core: Sawangjit et al. (2017)	'Pharmacy-based needle/syringe exchange programmes appear to be effective for reducing risk behaviours among people who inject drugs'	11 studies (6 cross-sectional, 5 cohort). N = 5 455 (range, 128-1 181)	Pooled ORs: pharmacy vs. no NSP = 0.50 (0.34-0.73, six studies) and pharmacy vs. other NSP = 1.46 (95 % CI 0.78-2.73, seven studies)	Australia (3), Canada (1), Estonia (1), United Kingdom, (1), United States (5)	Given a statement of **sufficient** evidence from a core review, based on a large number of studies, of which numerous are robust, we conclud	**Tentative**: 'There is tentative review-level evidence to support that pharmacy access is at least as effective as dedicated needle and syringe programmes in reducing self-	There is **sufficient** evidence to support the conclusion that pharmacy-based NSPs are at least as effective as other types of NSPs in the preventi

Primary literature review	0 studies	N/A	N/A	N/A	N/A	e that the evidence is sufficient to support the conclusion that pharmacy-based NSPs are at least as effective as other types of NSPs in reducing IRB. Similarly, there is sufficient evidence that pharmacy-based NSPs, relative to no NSP, are effective in reducing IRB	reported injecting risk behaviour among PWID'. Statement based on 13 studies: 9 positive (1 CC, 6 CSs, 2 ecological), 2 negative (2 COHs) and 4 with no association (2 COH, 2 CC). [Note: Sawangjit et al. included two studies that were also included in the 2011 review of reviews]	on of IRB. There is also **sufficient** evidence that pharmacy-based NSPs, relative to no NSP, are effective in reducing IRB

Abbreviations: CC, case-control study; CI, confidence interval; COH, cohort study, CS, cross-sectional study; IRB, injecting risk behaviour; N/A, not applicable; NSP, needle and syringe programme; OoR, overview of reviews; OR, odds ratio; PWID, people who inject drugs.

Low dead space syringe provision

LDSSs are a particular design of syringe with a lower volume of 'dead space' between the syringe and needle when the plunger is completely depressed. By contrast, in high dead space syringes (HDSSs), which consist of a detachable needle connected to a syringe, the volume of dead space is substantially higher when the plunger is completely depressed; this results in more residual blood left in the syringe after injecting, which can pose a potentially higher risk of BBV transmission during needle/syringe sharing.

Effects on hepatitis C virus transmission

A supplementary systematic review (WHO, 2012) (Appendix 17) suggested a reduced risk of HCV associated with the use of LDSSs (compared to HDSSs) but was based on only two studies, which were cross-sectional (and therefore weaker) in design. An additional primary study found a lower likelihood of prevalent HCV associated with LDSS use, although this also had a cross-sectional design (Trickey et al., 2018). Therefore, given three studies with positive findings but weak designs, we conclude that the level of evidence is insufficient. LDSSs were not considered in the 2011 RoR. Therefore, the updated evidence statement is 'insufficient'.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of LDSS provision in reducing HCV transmission among PWID.

TABLE 26
Evidence summary table for low dead space syringes (LDSSs) and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	One supplementary: WHO (2012)/Walsh et al. (2014)	N/A (supplementary reviews not consulted for their evidence statements)	Two studies (both cross-sectional). N = 1 366 (range, 515-851)	Pooled analysis of the likelihood of being HCV infected having used LDSSs vs. HDSSs: risk ratio = 0.49 (0.44 to 0.55)	Hungary/Lithuania (1), United States (1)	Although the supplementary review found a pooled result in favour of LDSS use, this was based on only two weaker studies and only one additional primary study, also with a weaker design, was identified. Therefore, there is **insufficient** evidence to either support or discount the effectiveness of LDSS provision in the prevention of HCV	There was no statement with regard to LDSSs for the prevention of HCV	There is **insufficient** review-level evidence to either support or discount the effectiveness of LDSS provision in reducing HCV transmission among PWID
Primary literature review	One weaker: Trickey et al. (2018)	N/A	Cross-sectional. N = 2 174	Positive: LDSS use associated with lower odds of prevalent HCV (adjusted odds ratio 0.77, 95 % CI 0.64-0.93)	United Kingdom			

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HDSS, high dead space syringe; LDSS, low dead space syringe; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs.

Effects on HIV transmission

The above-mentioned supplementary review (WHO, 2012) (Appendix 17) also examined HIV as an outcome and found a pooled effect size that suggested a reduced risk of HIV associated with the use of LDSSs (compared to HDSSs), based on two cross-sectional studies (Table 27). No additional primary studies were found. Therefore, based on only two studies with weaker designs, we conclude that the level of evidence is insufficient. There

was no statement of evidence in the 2011 RoR. Therefore, the updated evidence statement is 'insufficient'.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of LDSS provision in reducing HIV transmission among PWID.

TABLE 27
Evidence summary table for low dead space syringes (LDSSs) and HIV

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	One supplementary: WHO (2012)/Walsh et al. (2014)	N/A (supplementary reviews not consulted for their evidence statements)	Two studies (both cross-sectional). N = 1 366 (range, 515-851)	Pooled analysis of the likelihood of being HIV infected having used LDSSs vs. HDSSs: risk ratio = 0.29 (95 % CI 0.18-0.46)	Hungary/Lithuania (1), United States (1)	Although the supplementary review found a pooled result in favour of LDSS use, as only two weaker studies were pooled and no further primary studies were identified, there is **insufficient** evidence to either support or discount the effectiveness of LDSS provision in the prevention of HIV	There was no statement with regard to LDSS for the prevention of HIV	There is **insufficient** review-level evidence to either support or discount the effectiveness of LDSS provision in reducing HIV among PWID
Primary literature review	0 studies	N/A	N/A	N/A	N/A			

Abbreviations: CI, confidence interval; HDSS, high dead space syringe; LDSS, low dead space syringe; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs.

Provision of sterile drug preparation equipment (paraphernalia)

Sterile drug preparation equipment (often also called 'paraphernalia') is equipment, other than needles and syringes, that is used to prepare drugs for injection. For the purposes of this review, we defined drug preparation equipment/paraphernalia as cookers or spoons (for heating or mixing drugs), cottons or filters (to remove particles when drugs are drawn into a syringe) or water (to rinse syringes or mix with drugs). In the reviews and studies identified here, some studies examined each item individually; others grouped multiple items into one

measure (e.g. ‘any paraphernalia’). While the provision of sterile paraphernalia was not always specifically stated in the included reviews/studies, we made an implicit assumption (for the IRB section) that a NSP provided sterile drug preparation equipment if one of the outcomes of the review/study was the sharing of any of these items of equipment.

Effects on hepatitis C virus transmission

We identified no reviews and only one study that examined the association between sterile drug preparation equipment provision and HCV/HIV (Fatseas et al., 2012) but it employed a weaker study design (Appendix 18; Table 28). Therefore, given one weaker study with an equivocal result, we conclude that the level of evidence is insufficient. The 2011 RoR made a statement of ‘insufficient’ evidence, also based on one study (albeit with a positive result). However, the combined level of evidence across the 2011 RoR and the 2020 OoR remains insufficient.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of providing sterile drug preparation equipment in reducing HCV transmission among PWID.

TABLE 28
Evidence summary table for sterile drug preparation equipment and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	On the basis of one weaker study with an equivocal result, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of the provision of sterile drug preparation equipment in preventing HCV transmission	**Insufficient:** ‘There is insufficient review-level evidence to either support or discount the effectiveness of providing drug injecting equipment other than needles/syringes in reducing the transmission of HCV among PWID’. The statement was based on one positive cross-sectional study	Considering the evidence across the updated review and the 2011 review of reviews, the evidence is **insufficient** to either support or discount the effectiveness of sterile drug preparation equipment in preventing HCV
Primary literature review	One weaker: Fatseas et al. (2012)	N/A	One study (serial cross-sectional). N = 648	Equivocal: non-significant decrease in HCV prevalence from 81.3 % in 1994-1995 to 73.7 % in 1996-1999 to 71.1 % in 2000-2004 (Z = −1.4, p = 0.1). [1994-1995 is pre-harm reduction; 1996-1999 is when kits	France (1)			

				were made available that included syringes, water, swabs and condoms; 2000-2004 is when the kits additionally included sterile spoons and sterile cotton filters]				

Abbreviations: HCV, hepatitis C virus; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs.

Effects on HIV transmission

As above for HCV, we identified no reviews and only one primary study, which had a weaker study design (Appendix 18; Table 29: Fatseas et al., 2012). The evidence was thus graded as 'insufficient'. Given no evidence in the 2011 RoR, the updated evidence statement is therefore 'insufficient'.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of providing sterile drug preparation equipment in reducing HIV transmission among PWID.

TABLE 29
Evidence summary table for sterile drug preparation equipment and HIV

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	On the basis of one weaker study, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of the	'There is **no** review-level evidence to either support or discount the effectiveness of providing drug injecting equipment other than needles/syringes in reducing the transmission of HIV	Considering the evidence across the updated review and the 2011 review of reviews, the evidence is **insufficient** to either support
Primary literature review	One weaker: Fatseas et al. (2012)	N/A	One study (serial cross-sectional). N = 648	Positive: HIV prevalence decreased significantly from 43.2 % in 1994-1995 to 17.8 % in 1996-	France (1)			

				1999 to 12.4 % in 2000-2004 (Z = −5.3, p < 0.0001). [see HCV studies above for description of the availability of equipment during the different periods]		provision of sterile drug preparation equipment in relation to the impact on HIV incidence	among PWID'	or discount the effectiveness of sterile drug preparation equipment in preventing HIV

Abbreviations: HCV, hepatitis C virus; N/A, not applicable; OoR, overview of reviews; PWID, people who inject drugs.

Effects on injecting risk behaviour

No reviews were identified. However, we found 11 studies that examined the association between the provision of sterile drug preparation equipment and IRB (Aspinall et al., 2012; Behrends et al., 2017; Fatseas et al., 2012; Kim et al., 2015; Mehrabi et al., 2020; Naserirad and Beulaygue, 2020; Nazari et al., 2016; Noroozi et al., 2018; Patel et al., 2018; Rezaie et al., 2017; Welch-Lazoritz et al., 2017). Details of the studies are provided in Appendix 18. While the effect measures and the definition of sharing varied across studies, those that reported on the sharing of any items of drug preparation equipment (i.e. cookers, filters or water as a combined measure, as opposed to separately) reported a 50 % to 70 % reduction in the sharing of such items (see summary of effect sizes table in Appendix 18). Although most of these studies had weaker designs, the conclusion, on the basis of the balance of evidence combined with that from the 2011 RoR, is that the evidence is sufficient (Table 30).

Evidence statement: There is sufficient evidence to support the effectiveness of sterile drug preparation equipment in preventing IRB.

TABLE 30
Evidence summary table for sterile drug preparation equipment and injecting risk behaviour (IRB)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	On the basis of consistent	'There is **tentative** review-level evidence to	Considering the evidence across

Primary literature review	One strong: Patel et al. (2018). Ten weaker: Aspinall et al. (2012), Behrends et al. (2017), Fatseas et al. (2012), Kim et al. (2015), Mehrabi et al. (2020), Naserirad and Beulaygue (2020), Nazari et al. (2016), Noroozi et al. (2018), Rezaie et al. (2017), Welch-Lazoritz et al. (2017). [Note: Nazari, Noroozi and Rezaie were different analyses of the same study]	N/A	Nine studies (one cohort, one cohort and cross-sectional [same publication], five cross-sectional, two serial cross-sectional). N = 6 644 (range, 148-2 037)	Cohort: positive. Cohort/cross-sectional [same publication]: positive. Cross-sectional: positive (two), mixed positive and equivocal results (one), equivocal (two). Serial cross-sectional: positive (two). Reported odds ratios range from 0.22 (0.12-0.40) to 0.71 (0.55-1.01) for sharing cookers, 0.25 (0.13-0.5) to 0.77 (0.55-1.27) for sharing filters, 0.33 (0.18-0.63) to 0.93 (0.79-1.12) for sharing water and 0.31 (0.21-0.53) to 0.40 (0.27-0.60) for sharing paraphernalia	Iran (3), United States (4), Western Europe (2)	evidence from a small number of robust studies or multiple weaker studies (in the absence of a review), we conclude that there is **tentative** evidence to support the effectiveness of the provision of sterile drug preparation equipment in reducing IRB	support the effectiveness of providing injecting paraphernalia other than needles/syringes in reducing injecting risk behaviour among PWID.' Statement was based on 15 studies: 10 positive (6 COHs, 4 CSs) and 5 with no association (2 COHs, 3 CSs). Adding the studies from the updated review brings the total to 24 studies: 16 positive (8 COHs, 6 CSs, 2 single-case studies), 7 with no association (2 COHs, 5 CSs) and 1 mixed positive/equivocal (CS)	the updated review and the 2011 review of reviews, the balance of the evidence is weighted heavily towards the positive studies, of which a considerable proportion have robust designs. Furthermore, the studies with equivocal findings are mostly of weaker designs. Thus, we conclude that there is **sufficient** evidence to support the effectiveness of sterile drug preparation equipment in preventing IRB

Abbreviations: COH, cohort study; CS, cross-sectional study; IRB, injecting risk behaviour; N/A, not applicable; OoR, overview of reviews.

Combination interventions (opioid agonist treatment and needle and syringe programmes)

The provision of interventions in combination (also called ‘parallel provision’) refers to interventions that are delivered in combination to achieve synergistic effects. Studies used different measures of combination interventions, but typically compared individuals on ‘full’ or ‘complete’ harm reduction (defined as those receiving OAT and also a NSP, although measures of each intervention vary) compared to those with less than full or complete harm reduction.

Effects on hepatitis C virus transmission

One review and meta-analysis examined the impact of combined OAT and NSPs on HCV (Platt et al., 2017) and found a 74 % reduction in the risk of HCV associated with the uptake of combined OAT and a high-coverage NSP vs. no OAT and low or no NSP coverage (RR 0.26, 95 % CI 0.07-0.89, based on three studies that presented adjusted effect sizes). This effect is larger than that found for OAT or NSP alone (RR 0.50 [95 % CI 0.40-0.63] and RR 0.79 [95 % CI 0.39-1.61], respectively). One further primary study (Minoyan et al., 2020) with a strong design was identified but the finding was not statistically significant (RR 0.37, 95 % CI 0.12-1.12, comparing full vs. minimal harm reduction coverage). The reviews and studies are detailed in Appendix 19. Given a tentative statement from a core review, based on consistent evidence from a small number of robust studies (and, additionally, only one robust primary study with an equivocal result, which does not change the level of evidence in either direction), we conclude that there is tentative evidence (Table 31). The 2011 RoR did not make an explicit statement, whether ‘sufficient’ or ‘tentative’, for example. However, given the pooled evidence across both the 2011 RoR and updated review and because there are two meta-analyses with statistically significant findings in favour of combined OAT and NSPs, which between them are based on 10 studies, 4 of which have robust designs, we conclude that the overall level of evidence is sufficient.

Evidence statement: There is sufficient evidence that participation in full harm reduction programmes involving OAT and NSPs in combination is effective in reducing HCV transmission among PWID.

TABLE 31

Evidence summary table for combination interventions (opioid agonist treatment and needle and syringe programmes) and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	One core: Platt et al. (2017)	'…. suggested a strong intervention effect for combined high coverage of NSP and OST…. The evidence is considered low quality because it was derived from observational studies with serious risk of bias'. 'OST is associated with a reduction in the risk of HCV acquisition, which is strengthened in studies that assess the combination of OST and NSP.'	Four studies (two cohort, two cross-sectional). N = 8 706 (range, 168-7 954)	Among studies that presented an adjusted estimate (n = 3), the pooled RR comparing combined OAT plus high coverage NSP (vs. no OAT and low or no NSP coverage) ([11]) was 0.26 (95 % CI 0.07-0.89). Including all four studies, the RR became 0.29 (95 % CI 0.13-0.65)	Canada (1), Netherlands (1), United Kingdom (2)	Given a tentative statement from a core review, based on consistent evidence from a small number of robust studies (and, additionally, only one robust primary study with an equivocal result, which does not change the level of evidence in either direction), we conclude that there is **tentative** evidence that participation in full harm reduction programmes involving OAT and	'Evidence from one meta-analysis and two cohort studies indicates that participation in full harm reduction programmes involving OST and high coverage of NSP are associated with reductions in HIV and HCV incidence and reduced injecting risk behaviour.' Statement based on two studies, both positive (one cohort and one meta-analysis of six UK studies involving	Based on evidence from two meta-analyses of 10 studies, including 4 robust studies, we conclude that there is **sufficient** evidence that participation in full harm reduction programmes involving OAT and NSPs in combination is associated with a reduction in HCV incidence

([11]) Where high coverage was defined as regular attendance at a NSP or all injections covered by a new needle/syringe.

Primary literature review	One strong: Minoyan et al. (2020)	N/A	One study (cohort). N = 3 327	Equivocal: adjusted HRs for partial and full harm reduction coverage vs. minimal ([12]) – partial, 1.27 (95 % CI 0.55-2.92); full, 0.37 (95 % CI 0.12-1.12)	Canada (1)	NSPs in combination is associated with a reduction in HCV incidence	two COHs and four CSs). [Note: the cohort study was also included in the Platt review] Considering the evidence across the 2011 review of reviews and updated reviews, there are therefore two positive meta-analyses, one involving six studies (two COHs, four CSs) and the other involving four studies (two COHs, two CSs)	

Abbreviations: CI, confidence interval; COH, cohort study; CS, cross-sectional study; HCV, hepatitis C virus; N/A, not applicable; NSP, needle and syringe programme; OAT, opioid agonist treatment; OoR, overview of reviews; OST, opioid substitution treatment; RR, risk ratio.

Effects on HIV transmission

No reviews or studies examining the effects of combined interventions on HIV were identified. The 2011 RoR did not make an explicit statement of evidence ('Evidence from one meta-analysis and two cohort studies indicates that participation in full harm reduction programmes involving OST and high coverage of NSP are associated with reductions in HIV and HCV incidence and reduced injecting risk behaviour') but this statement was based on two studies with mixed designs (one cohort and one single-case study). In the absence of a clear and consistent statement of the level of evidence from the 2011 RoR, based on only two studies, we conclude that the evidence regarding the effectiveness of harm reduction

([12]) Where 'full', 'partial' and 'minimal' are defined as follows: full = high OAT plus complete NSP coverage; partial = no or low OAT plus complete NSP coverage (i.e. 100 % needles/syringes from safe sources) or high OAT plus incomplete NSP coverage; minimal = no OAT and incomplete NSP coverage.

programmes involving OAT and high-coverage NSPs in relation to HIV incidence is insufficient.

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of full harm reduction programmes involving OAT and NSPs in reducing HIV transmission among PWID.

Effects on injecting risk behaviour

No reviews or studies examining the effects of combined interventions on IRB were identified. Again, the 2011 RoR did not make an explicit statement of evidence ('Evidence from one meta-analysis and two cohort studies indicates that participation in full harm reduction programmes involving OST and high coverage of NSP are associated with reductions in HIV and HCV incidence and reduced injecting risk behaviour'). This statement was based on a meta-analysis that found a pooled effect size of 0.52 (95 % CI 0.32-0.83), based on six studies, two of which had robust designs (two cohort studies and four cross-sectional studies). Our assessment of the underlying evidence (i.e. no clear and consistent statement of evidence but consistent evidence from a small number of robust studies) therefore leads to the conclusion that the level of evidence is tentative.

Evidence statement: There is tentative evidence to support the effectiveness of full harm reduction programmes involving OAT and NSPs in reducing IRB among PWID.

Drug consumption rooms

DCRs are healthcare settings where individuals (who have purchased drugs elsewhere) can go to consume their drugs in a clean environment, typically under the supervision of medically trained staff. Staff can provide sterile injecting equipment, give information and advice on reducing the risk of BBVs and other infections, and intervene in the case of overdose.

Effects on hepatitis C virus transmission

Only two studies with weaker (cross-sectional) designs were identified that examined an association between DCR use and HCV (Folch et al., 2018; Kennedy et al., 2019a) (Appendix 20). Both found no significant difference in HCV prevalence among groups with varying levels of DCR use. Given the lack of reviews, and only two weaker primary studies with equivocal results, we conclude that there is insufficient evidence. The 2011 RoR also made a statement of insufficient evidence and, considering the evidence base across both the 2011 RoR and the 2020 review, the evidence remains 'insufficient' (Table 32).

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of DCRs in preventing HCV transmission among PWID.

TABLE 32
Evidence summary table for drug consumption rooms (DCRs) and hepatitis C virus (HCV)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Hepatitis C virus								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	Based on no reviews, and only two weaker primary studies with equivocal results, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of DCRs in preventing HCV transmission	'There is **insufficient** review-level evidence to either support or discount the effectiveness of supervised injecting facilities with respect to HCV incidence.' Statement based on one cross-sectional study that showed no association	Considering the evidence base across the 2011 review of reviews and the updated review, there is **insufficient** evidence to either support or discount the effectiveness of DCRs in preventing HCV transmission
Primary literature review	Two weaker: Folch et al. (2018) and Kennedy et al. (2019a)	N/A	Two studies (both cross-sectional). N = 1 321 (range, 510-811)	Folch: prevalence of HCV in low and medium vs. frequent DCR users = 61.8 %, 71.5 % and 68.3 %, respectively (p = 0.128). Kennedy: at least weekly supervised injection facility use in 6 months prior to baseline vs. regular but not at least weekly = unadjusted OR 1.34 (95 % CI 0.91-1.98)	Canada (1), Spain (1)			

Abbreviations: CI, confidence interval; DCR, drug consumption room; HCV, hepatitis C virus; N/A, not applicable; OoR, overview of reviews; OR, odds ratio.

Effects on HIV transmission

The two studies mentioned above (Folch et al., 2018; Kennedy et al., 2019a) examined the association between DCR use and HIV: one found a significantly lower prevalence of HIV among those who used DCRs at least weekly in the last 6 months as compared to those who used them less frequently, whereas the other study found no significant difference in HIV prevalence between groups who used DCRs with different frequencies. Therefore,

based on the lack of reviews and only two weaker studies with mixed findings, we conclude that the evidence is insufficient. The 2011 RoR also made a statement of insufficient evidence based on one weaker study. Considering the evidence base across the two reviews (still a small number of studies with weaker designs), we therefore conclude that the updated evidence statement remains 'insufficient' (Table 33).

Evidence statement: There is insufficient evidence to either support or discount the effectiveness of DCRs in preventing HIV transmission among PWID.

TABLE 33
Evidence summary table for drug consumption rooms (DCRs) and HIV

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
HIV								
Overview of reviews (OoR)	0 reviews	N/A	N/A	N/A	N/A	Based on no reviews, and only two weaker primary studies with mixed results, we conclude that there is **insufficient** evidence to either support or discount the effectiveness of DCRs in preventing HIV transmission	'There is **insufficient** review-level evidence to either support or discount the effectiveness of supervised injecting facilities with respect to HIV incidence.' Statement based on one cross-sectional study that showed no association	Considering the evidence base across the 2011 review of reviews and the updated review, there is **insufficient** evidence to either support or discount the effectiveness of DCRs in preventing HIV transmission
Primary literature review	Two weaker: Folch et al. (2018) and Kennedy et al. (2019a)	N/A	Two studies (both cross-sectional). N = 1 321 (range, 510-811)	Folch: the prevalence of HIV in low, medium and frequent DCR users = 24.8 %, 25.0 % and 36.5 %, respectively (p = 0.062). Kennedy: at least weekly supervised injection facility use in 6 months prior to baseline vs. regular but not at least weekly = unadjusted OR 0.6 (95 % CI 0.44-0.81)	Canada (1), Spain (1)			

Abbreviations: CI, confidence interval; DCR, drug consumption room; N/A, not applicable; OoR, overview of reviews; OR, odds ratio.

Effects on injecting risk behaviour

Details of the review and study identified are presented in Appendix 20. One supplementary review examined the association between DCRs and IRB (Kennedy et al., 2017): out of six studies included within the review, three cross-sectional studies showed evidence of lower odds of IRB associated with DCR use (ORs ranging from 0.14 [95 % CI 0.00-0.78] to 0.30 [95 % CI 0.11-0.82]) and one cohort found no significant change in the 'use of non-sterile equipment or equipment sharing' over time (since baseline) among PWID who started using a DCR. Two of the studies, which were cross-sectional in design, demonstrated positive associations (i.e. a reduction in the particular risk behaviour under study) between DCR use and the reuse of syringes and the use of clean water for injecting. An additional study identified in the primary literature review (Folch et al., 2018) found a lower odds of sharing needles/syringes and other injecting equipment among those who frequently attended DCRs (vs. low/medium attendance). Therefore, given a supplementary review with positive evidence from studies with mostly weaker designs, and an additional positive study with a weak design, we conclude that the level of evidence is insufficient. The 2011 RoR had made a statement of tentative evidence; considering the evidence across both the RoR and updated review, we conclude that the evidence is tentative (Table 34).

Evidence statement: There is tentative evidence to support the effectiveness of DCRs in preventing injecting risk behaviour among PWID.

TABLE 34
Evidence summary table for drug consumption rooms (DCRs) and injecting risk behaviour (IRB)

Component	Reviews/studies identified	Review statements of evidence	No of studies and study designs	Range of effect sizes	Countries where studies took place	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Injecting risk behaviour								
Overview of reviews (OoR)	One supplementary: Kennedy et al. (2017)	N/A (supplementary)	Six studies (one cohort, five cross-sectional). N = 2 192 (range, 41-760)	Four of the six studies examined syringe sharing: three (cross-sectional) showed evidence of a positive association (ORs ranging from 0.14 [95 % CI 0.00-0.78] to 0.30 [95 % CI 0.11-0.82]);	Canada (3), Denmark (1), Germany (1), Spain (1)	Only one supplementary review was identified – it included five weaker primary studies with positive results, and one cohort study with an equivocal result. Similarly, only one weaker	'There is **tentative** review-level evidence to support the effectiveness of supervised injecting facilities in reducing injecting risk behaviour...' Statement based on seven	Considering the evidence base across the 2011 RoR and the updated review, the evidence to support the effectiveness of DCRs in reducing IRB remains **tentative**

				one (cohort) found no significant change in 'use of non-sterile equipment or equipment sharing' over time (since baseline) among PWID who initiated use of a DCR. Two of the studies (cross-sectional) demonstrated (positive) associations between DCR use and likelihood of other risk behaviours, including reusing of syringes, and using clean water for injecting		primary study was identified, although its result was also positive. Thus, based on 'less than consistent evidence from multiple robust studies within one or more supplementary reviews', we conclude that there is **insufficient** evidence to support the effectiveness of DCRs in reducing IRB	studies: four positive (two COHs, two CSs), three with no association (three CSs) [six further studies document that clients' report of positive changes to their injecting practices can be attributed to DCRs] [Note overlap of three studies between the 2011 RoR and update; these are not added below] Considering the evidence across the 2011 RoR and updated review, the number of studies becomes seven positive (two COHs, five CSs) and four with no association (one COH, three CSs)	
Primary literature review	One weaker: Folch et al. (2018)	N/A	One study (cross-sectional). N = 510	Frequent attendance at a DCR vs. medium or low attendance: adjusted OR for sharing needles and/or injecting equipment = 0.39 (95 % CI 0.2-0.78, p < 0.05)	Spain (1)			

Abbreviations: CI, confidence interval; COH, cohort study, CS, cross-sectional study; DCR, drug consumption room; IRB, injecting risk behaviour; N/A, not applicable; OoR, overview of reviews; OR, odds ratio; RoR, review of reviews.

Discussion and conclusions

Summary of evidence

Evidence statements from the 2011 RoR and the updated evidence statements for each intervention and outcome combination are presented in Table 35. Notably, the level of evidence with regard to HCV prevention has increased since the 2011 RoR for the 'mainstay' harm reduction interventions: from tentative to sufficient for OAT, from insufficient to tentative for NSP and from tentative to sufficient for combination OAT and NSP interventions. For the first time, the evidence for OAT also incorporates evidence on HCV reinfection as an outcome. Other interventions where the level of evidence was upgraded since 2011 include NSPs in prison and pharmacy settings and provision of LDSSs, all of which went from no evidence (or no statement of evidence) to insufficient evidence.

Regarding the prevention of HIV, there was already sufficient evidence for the effectiveness of OAT in 2011, but the level of evidence increased from tentative to sufficient for NSPs. Other interventions where the level of evidence increased for HIV are NSPs in prison, provision of LDSSs and provision of sterile drug preparation equipment, all of which went from no evidence (or no statement of evidence) to insufficient evidence.

With regard to IRB (+/- IF) outcomes, the evidence is generally stronger than for HCV or HIV. The level of evidence was already sufficient from the 2011 RoR for OAT and NSPs in reducing IRB/IF (in the case of NSPs, this primarily relates to reductions in the sharing of injecting equipment and, in the case of OAT, to decreases in the frequency of injection). The level of evidence increased from tentative to sufficient for in-prison OAT, psychosocial (IECS) interventions, pharmacy-based NSPs and provision of sterile drug preparation equipment. There was no statement on technology-based psychosocial interventions in the 2011 RoR, whereas this became 'insufficient evidence' in the current review.

Despite the expansion of the evidence base for these intervention/outcome combinations, it is apparent from Table 35 that there is still no or insufficient evidence for many of the interventions across all of the outcomes, including for HAT, antagonist treatment for opioid dependence, treatment for stimulant dependence, CM, technology-based psychosocial interventions and LDSSs. There is also less evidence for OAT and NSPs when delivered in specific settings, such as in prison. Regarding the latter finding, the lack of evidence in the prison setting reflects the fact that fewer studies have been conducted in this setting. Given that these interventions are delivered outside of prisons, their implementation in prison is justified based on the principle of equivalence of care. Future research should focus on how these interventions can be implemented in a way that maximises their effectiveness in the prison setting.

TABLE 35
Summary of evidence statements from the 2011 review of reviews and updated evidence statements

Intervention		Outcome	Level of evidence from 2011 RoR*	Updated level of evidence
Drug treatment	Agonist pharmacological treatment for opioid dependence (i.e. OAT)	HCV	Tentative	Sufficient (for preventing HCV primary infection and reinfection)
		HIV	Sufficient	Sufficient
		IRB/IF	Sufficient	Sufficient
	Agonist pharmacological treatment for opioid dependence – prison	HCV	Insufficient	Insufficient
		HIV	Insufficient	Insufficient
		IRB/IF	Tentative	Sufficient
	Heroin-assisted treatment	HCV	No statement	No evidence
		HIV	No statement	No evidence
		IRB/IF	No statement	No evidence
	Antagonist pharmacological treatment for opioid dependence	HCV	No evidence	No evidence
		HIV	No evidence	No evidence
		IRB/IF	Insufficient	Insufficient regarding IRB. Tentative regarding drug dependence outcomes (heroin use/abstinence)
	Antagonist pharmacological treatment for opioid dependence – prison	HCV	No evidence	No evidence
		HIV	No evidence	No evidence
		IRB/IF	No statement	Insufficient regarding IRB/Injecting drug use. Sufficient regarding opioid relapse/abstinence
	Pharmacological treatment for stimulant dependence	HCV	No evidence	No evidence
		HIV	No evidence	No evidence
		IRB/IF	No evidence	No evidence
Drug treatment (psychosocial)	Psychosocial interventions – IECS	HCV	Insufficient	Insufficient
		HIV	Insufficient	Insufficient
		IRB/IF	Tentative/insufficient	Sufficient
	Psychosocial interventions – contingency management	HCV	No evidence	No evidence
		HIV	No evidence	No evidence
		IRB/IF	Insufficient	Insufficient (regarding both IRB and injecting drug use)
	Psychosocial interventions – technology-based	HCV	No statement	No evidence
		HIV	No statement	No evidence
		IRB/IF	No statement	Insufficient
Needle and syringe programmes (NSPs)	Needle and syringe provision	HCV	Insufficient	Tentative
		HIV	Tentative	Sufficient
		IRB	Sufficient	Sufficient
	Needle and syringe provision – prison	HCV	No statement	Insufficient
		HIV	No statement	Insufficient
		IRB	No statement	No evidence
	Needle and syringe provision – pharmacy	HCV	No evidence	Insufficient
		HIV	Insufficient	Insufficient
		IRB	Tentative	Sufficient
	Low dead space syringes	HCV	No statement	Insufficient
		HIV	No statement	Insufficient
		IRB	N/A	N/A
	Provision of sterile drug	HCV	Insufficient	Insufficient
		HIV	No evidence	Insufficient

Intervention		Outcome	Level of evidence from 2011 RoR*	Updated level of evidence
	preparation equipment (paraphernalia)	IRB	Tentative	Sufficient
Combination interventions (OAT and NSP)		HCV	Tentative	Sufficient
		HIV	Insufficient	Insufficient
		IRB	Tentative	Tentative
Drug consumption rooms		HCV	Insufficient	Insufficient
		HIV	Insufficient	Insufficient
		IRB	Tentative	Tentative

Abbreviations: HCV, hepatitis C virus; IECS, information, education, counselling and/or skills training; IF, injection frequency; IRB, injecting risk behaviour; NSP, needle and syringe programme; OAT, opioid agonist treatment; RoR, review of reviews.

*Statements of evidence in the 2011 technical reports were not always clearly expressed as one of the four categories and, therefore, in some instances, a judgement was made to interpret the statement as either no, tentative, insufficient or sufficient evidence.

Strengths and limitations

General limitations of the methodology

The general limitations of the RoR/OoR methodologies have been described previously (Baker et al., 2014; Ellis et al., 2003) and some of these limitations are also applicable here: in particular, that the quality of the reporting of the review has to be used as a proxy for the quality of the review itself, meaning that good-quality reviews that do not explicitly report all aspects of their methods may be downgraded. A strength of our methodology, as compared to literature reviews that only undertake an OoR, is that we performed searches of the primary literature to supplement the evidence where there were gaps. The approach that we took to updating the 2011 RoR specified that interventions and outcome combinations with level of evidence already deemed ‘sufficient’ in the RoR did not need to be updated (this applied to OAT and HIV, OAT and IRB/IF, and NSPs and IRB). It is therefore possible, but unlikely, that evidence published since 2011 that was not considered might otherwise have resulted in a downgrading in the level of evidence.

Inclusion of relevant papers

Relevant reviews or studies may have been missed in our literature searches. We took steps to reduce this risk: we included non-English-language papers, as well as undertook a search of the grey literature and hand searches of the reference lists of included papers. Double screening of abstracts and studies by reviewers will also have reduced the likelihood of missed relevant studies/reviews.

Critical appraisal

We updated the tool used to critically appraise the reviews in the 2011 RoR to an internationally recognised and validated tool. In general, critical appraisal tools have been designed for robust reviews and study designs (e.g. for systematic reviews and meta-analyses that have been conducted on RCTs or for RCTs in the case of critical appraisal tools for primary studies). Studies and reviews of public health interventions tend not to be as rigorous as those conducted for clinical interventions, and we therefore felt that the critical appraisal tools should be adapted to account for this. When conducting critical appraisal, it should be recognised that an element of subjectivity remains. We attempted to reduce the effect of subjectivity by having two reviewers critically appraise each study independently

and a third reviewer resolve discrepancies. We did not perform a full critical appraisal of the primary studies and instead used the study designs as a proxy, in order to be consistent with the 2011 RoR.

Interventions

The interventions included in this evidence review were as defined in the reviews or studies themselves. In some cases, these definitions were not explicitly stated and it is therefore not known exactly what the intervention comprised, at what dose or level of coverage, and for how long. For example, studies of NSPs often did not state whether these services also distributed other drug preparation equipment. In other cases, reviews may have been hampered by a lack of detail in the underlying primary studies because the level of exposure is rarely measured in the same way between studies. Some reviews, for example, simply categorised individuals as on or off OAT during the study period.

Outcomes

The evidence is generally stronger for behavioural outcomes (e.g. IRB and IF) than for biological outcomes (HCV and HIV), and this has consistently been observed across previous reviews (ECDC, 2011a; MacArthur et al., 2014; Palmateer et al., 2010). One explanation for this could be a non-linear relationship between injecting equipment sharing (associated with NSP uptake) and BBV acquisition. Particularly for HCV, where there tends to be larger pools of infected PWID and the transmissibility of HCV is greater (compared with HIV), comparatively few sharing events may still result in a high probability of HCV acquisition. Thus, substantial reductions in the levels of IRB may be needed to reduce the risk of HCV acquisition. A further limitation of the behavioural outcomes is that they are generally self-reported and therefore potentially associated with reporting biases (such as social desirability bias and recall bias). Although self-reported behaviour by PWID has been suggested to be reliable (Darke, 1998), it is uncertain whether this applies to all behaviours. For example, syringe sharing may be a more stigmatised behaviour and may therefore be underreported relative to other IRBs. For PWID who seek out services such as NSPs, it is conceivable that, through their interactions with the service, they become more aware of the risks of sharing and therefore more reluctant to report this behaviour compared with those who do not interact (or do not interact on a regular basis) with such services. If this is the case, it would result in an overestimate of the effect size associated with the intervention.

Conclusions and recommendations for future research

There is now a strong body of empirical evidence for the effectiveness of OAT in preventing HCV, HIV and IRB. There is also a strong body of evidence for the effectiveness of NSPs in preventing HIV and IRB, and the combination of these two interventions, in preventing HCV. However, there is still a lack of studies on many interventions, including HAT, pharmacological treatment for stimulant dependence, CM, technology-based interventions, LDSSs and DCRs in respect of the outcomes of interest in this review. For all of these interventions, this was not because of the existence of evidence demonstrating lack of effectiveness, but rather an absence of reviews and studies that have been undertaken to summarise their effectiveness. Future research to establish the effectiveness of these interventions is recommended, especially in relation to HCV and HIV incidence, which will require pooling across multiple studies. New, well-powered trials are unlikely and, for many interventions, no longer ethical. Therefore, it is critical that observational studies consistently measure exposure to single interventions or the intensity of harm reduction interventions.

References

Abdul-Quader, A. S., Feelemyer, J., Modi, S., Stein, E. S., Briceno, A., Semaan, S., Horvath, T., Kennedy, G. E. and Des Jarlais, D. C. (2013), 'Effectiveness of structural-level needle/syringe programs to reduce HCV and HIV infection among people who inject drugs: a systematic review', *AIDS and Behavior* 17, pp. 2878-2892, doi:10.1007/s10461-013-0593-y.

Aitken, C. K., Agius, P. A., Higgs, P. G., Stoové, M. A., Bowden, D. S. and Dietze, P. M. (2017), 'The effects of needle-sharing and opioid substitution therapy on incidence of hepatitis C virus infection and reinfection in people who inject drugs', *Epidemiology and Infection* 145, pp. 796-801, doi:10.1017/S0950268816002892.

Artenie, A. A., Minoyan, N., Jacka, B., Høj, S., Jutras-Aswad, D., Roy, É., Gauvin, L., Zang, G. and Bruneau, J. (2019), 'Opioid agonist treatment dosage and patient-perceived dosage adequacy, and risk of hepatitis C infection among people who inject drugs', *CMAJ : Canadian Medical Association Journal* 191:E462-E468, doi:10.1503/cmaj.181506.

Aspinall, E., Hutchinson, S. J., Taylor, A., Palmateer, N., Hellard, M., Allen, E. and Goldberg, D. (2012), 'Uptake of paraphernalia from injecting equipment provision services and its association with sharing of paraphernalia among injecting drug users in Scotland', *Drug and Alcohol Dependence* 126, pp. 340-346, doi:10.1016/j.drugalcdep.2012.05.041.

Aspinall, E. J., Nambiar, D., Goldberg, D. J., Hickman, M., Weir, A., Van Velzen, E., Palmateer, N. et al. (2014), 'Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis', *International Journal of Epidemiology*, 43, pp. 235-248, doi:10.1093/ije/dyt243.

Aye, N. S., Oo, M. M., Harries, A. D., Mon, M. M., Hone, S., Oo, H. N. and Wan, N. M. A. (2018), 'HIV, HBV and HCV in people who inject drugs and are placed on methadone maintenance therapy, Yangon, Myanmar', *Public Health Action* 8, pp. 202-210, doi:10.5588/pha.18.0050.

Bahji, A., Carlone, D. and Altomare, J. (2019), 'Acceptability and efficacy of naltrexone for criminal justice-involved individuals with opioid use disorder: a systematic review and meta-analysis', *Addiction* 115, pp. 1413-1425, doi:10.1111/add.14946.

Baker, P. R. A., Costello, J. T., Dobbins, M. and Waters, E. B. (2014), 'The benefits and challenges of conducting an overview of systematic reviews in public health: a focus on physical activity', *Journal of Public Health* 36, pp. 517-521, doi:10.1093/pubmed/fdu050.

Barak, I., Adelson, M., Sason, A., Livnat, Y., Schreiber, S. and Peles, E. (2020), 'Educational lectures enhance knowledge about the human immunodeficiency virus (HIV) and reduce risky behavior and fear among methadone maintenance treatment patients', *Substance Abuse* 41, pp. 14-18, doi:10.1080/08897077.2018.1528492.

Behrends, C. N., Li, C.-S. and Gibson, D. R. (2017), 'Decreased odds of injection risk behavior associated with direct versus indirect use of syringe exchange: evidence from two California cities', *Substance Use and Misuse* 52, pp. 1151-1159, doi:10.1080/10826084.2017.1299182.

Bertrand, K., Roy, É., Vaillancourt, É., Vandermeerschen, J., Berbiche, D. and Boivin, J.-F. (2015), 'Randomized controlled trial of motivational interviewing for reducing injection risk behaviours among people who inject drugs', *Addiction* 110, pp. 832-841, doi:10.1111/add.12867.

Booth, R. E., Davis, J. M., Dvoryak, S., Brewster, J. T., Lisovska, O., Strathdee, S. A. and Latkin, C. A. (2016), 'HIV incidence among people who inject drugs (PWIDs) in

Ukraine: results from a clustered randomised trial', *The Lancet. HIV* 3:e482-9, doi:10.1016/S2352-3018(16)30040-6.

Booth, R. E., Lehman, W. E. K., Latkin, C. A., Dvoryak, S., Brewster, J. T., Royer, M. S. and Sinitsyna, L. (2011), 'Individual and network interventions with injection drug users in 5 Ukraine cities', *American Journal of Public Health* 101, pp. 336-343, doi:10.2105/AJPH.2009.172304.

Calvo, F., Turró-Garriga, O. and Carbonell, X. (2020), 'Evaluation of the efficacy of WhatsApp through a harm reduction intervention group for injecting drug users', *Adicciones* 0, pp. 201-216, doi:10.20882/adicciones.1329.

Chen, Y., Tang, Z., Tang, S., Shen, Z., Zhu, Q., Li, R., Huang, W. et al. (2018), 'Decreasing HIV, syphilis, and hepatitis C infection after a decade of harm reduction implementation among drug users in southwestern areas of China', *Journal of Studies on Alcohol and Drugs* 79, pp. 248-257, doi:10.15288/jsad.2018.79.248.

Crowley, D. and Van Hout, M. C. (2017), 'Effectiveness of pharmacotherapies in increasing treatment retention and reducing opioid overdose death in individuals recently released from prison: a systematic review', *Heroin Addiction and Related Clinical Problems* 19, pp. 1592-1638.

Cunningham, E. B., Hajarizadeh, B., Amin, J., Hellard, M., Bruneau, J., Feld, J. J., Cooper, C. et al. (2020), 'Reinfection following successful direct-acting antiviral therapy for hepatitis C infection among people who inject drugs', *Clinical Infectious Diseases* 72, pp. 1392-1400, doi:10.1093/cid/ciaa253.

Cunningham, E. B., Hajarizadeh, B., Bretana, N. A., Amin, J., Betz-Stablein, B., Dore, G. J., Luciana, F. et al. (2017), 'Ongoing incident hepatitis C virus infection among people with a history of injecting drug use in an Australian prison setting, 2005-2014: The HITS-p study', *Journal of Viral Hepatitis* 24, pp. 733-741, doi:10.1111/jvh.12701.

Darke, S. (1998), 'Self-report among injecting drug users: a review', *Drug and Alcohol Dependence* 51, pp. 253-263, doi:10.1016/s0376-8716(98)00028-3.

Davis, S. M., Daily, S., Kristjansson, A. L., Kelley, G. A., Zullig, K., Baus, A., Davidov, D. and Fisher, M. (2017), 'Needle exchange programs for the prevention of hepatitis C virus infection in people who inject drugs: a systematic review with meta-analysis', *Harm Reduction Journal* 14, pp. 25, doi:10.1186/s12954-017-0156-z.

ECDC (2011a), *Evidence for the effectiveness of interventions to prevent infections among people who inject drugs, Part 1: Needle and syringe programmes and other interventions for preventing hepatitis C, HIV and injecting risk behaviour*, ECDC, Stockholm.

ECDC (2011b), *Evidence for the effectiveness of interventions to prevent infections among people who inject drugs, Part 2: Drug treatment for preventing hepatitis C, HIV and injecting risk behaviour*, ECDC, Stockholm.

ECDC (2018), *Systematic review on the prevention and control of blood-borne viruses in prison settings* (https://www.ecdc.europa.eu/en/publications-data/systematic-review-prevention-and-control-blood-borne-viruses-prison-settings).

ECDC and EMCDDA (2011), *Prevention and control of infectious diseases among people who inject drugs*, ECDC, Stockholm.

Ellis, S., Barnett-Page, E., Morgan, A., Taylor, L., Walters, R. and Goodrich, J. (2003), *HIV prevention: a review of reviews assessing the effectiveness of interventions to reduce the risk of sexual transmission*, London: Health Development Agency, London (https://wellcomecollection.org/works/h3e32e9k).

EMCDDA (2012), *New heroin-assisted treatment. Recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond,* EMCDDA Insights, EMCDDA, Lisbon (https://www.emcdda.europa.eu/publications/insights/heroin-assisted-treatment_en).

EMCDDA (2016a), *How can contingency management support treatment for substance use disorders? A systematic review*, EMCDDA, Lisbon (https://www.emcdda.europa.eu/publications/papers/contingency-management-systematic-review_sl).

EMCDDA (2016b), *The role of psychosocial interventions in drug treatment,* Perspectives on Drugs, EMCDDA, Lisbon.

Fatseas, M., Denis, C., Serre, F., Dubernet, J., Daulouède, J.-P. and Auriacombe, M. (2012), 'Change in HIV-HCV risk-taking behavior and seroprevalence among opiate users seeking treatment over an 11-year period and harm reduction policy', *AIDS and Behavior* 16, pp. 2082-2090, doi:10.1007/s10461-011-0054-4.

Ferri, M., Davoli, M. and Perucci, C. A. (2011), 'Heroin maintenance for chronic heroin-dependent individuals', *Cochrane Database of Systematic Reviews* 12, pp.1465-1858, doi:10.1002/14651858.CD003410.pub4.

Folch, C., Lorente, N., Majó, X., Parés-Badell, O., Roca, X., Brugal, T., Brugal, T. et al. (2018), 'Drug consumption rooms in Catalonia: A comprehensive evaluation of social, health and harm reduction benefits', *The International Journal on Drug Policy* 62, pp. 24-29, doi:10.1016/j.drugpo.2018.09.008.

Forsman, A. K., Nordmyr, J. and Wahlbeck, K. (2011), 'Psychosocial interventions for the promotion of mental health and the prevention of depression among older adults', *Health Promotion International* 26 Suppl 1, pp. i85-107, doi:10.1093/heapro/dar074.

Gilchrist, G, Swan, D., Widyaratna, K., Marquez-Arrico, J. E., Hughes, E., Mdege, N. D., Martyn-St James, M. and Tirado-Munoz, J. (2017), 'A systematic review and meta-analysis of psychosocial interventions to reduce drug and sexual blood borne virus risk behaviours among people who inject drugs', *AIDS and Behavior* 21, pp. 1791-1811, doi:10.1007/s10461-017-1755-0.

Gilchrist, G, Tirado-Munoz, J., Taylor, A., Fischer, G., Moskalewicz, J., Köchl, B., Giammarchi, C. et al. (2017), 'An uncontrolled, feasibility study of a group intervention to reduce hepatitis C transmission risk behaviours and increase transmission knowledge among women who inject drugs', *Drugs: Education, Prevention and Policy* 24, pp. 179-188, doi:10.1080/09687637.2016.1197885.

Gilchrist, G., Swan, D., Shaw, A., Keding, A., Towers, S., Craine, N., Munro, A. et al. (2017), 'Preventing blood-borne virus infection in people who inject drugs in the UK: systematic review, stakeholder interviews, psychosocial intervention development and feasibility randomised controlled trial', *Health Technology Assessment* 21, pp. 1-312, doi:10.3310/hta21720.

Go, V. F., Frangakis, C., Le Minh, N., Latkin, C. A., Ha, T. V., Mo, T. T., Sripaipan, T. et al. (2013), 'Effects of an HIV peer prevention intervention on sexual and injecting risk behaviors among injecting drug users and their risk partners in Thai Nguyen, Vietnam: a randomized controlled trial', *Social Science and Medicine* 96, pp. 154-164, doi:10.1016/j.socscimed.2013.07.006.

Go, V. F., Frangakis, C., Minh, N. L., Latkin, C., Ha, T. V., Mo, T. T., Sripaipan, T. et al. (2015), 'Efficacy of a multi-level intervention to reduce injecting and sexual risk behaviors among HIV-infected people who inject drugs in Vietnam: a four-arm randomized controlled trial', *Plos One* 10:e0125909, doi:10.1371/journal.pone.0125909.

Graham, S., Maher, L., Wand, H., Doyle, M. and Iversen, J. (2017), 'Trends in hepatitis C antibody prevalence among Aboriginal and Torres Strait Islander people attending Australian needle and syringe programs, 1996-2015', *The International Journal on Drug Policy* 47, pp. 69-76, doi:10.1016/j.drugpo.2017.06.007.

Hajarizadeh, B., Cunningham, E. B., Valerio, H., Martinello, M., Law, M., Janjua, N. Z., Midgard, H. et al. (2020), 'Hepatitis C reinfection after successful antiviral treatment

among people who inject drugs: a meta-analysis', *Journal of Hepatology* 72, pp. 643-657, doi:10.1016/j.jhep.2019.11.012.

Hajebi, A., Naserbakht, M. and Noroozi, A. (2016), 'Adding-on a brief skill-based HIV prevention psychoeducation to needle and syringe programs: a randomized controlled trial', *Iranian Journal of Psychiatry and Behavioral Sciences* 10:e7411, doi:10.17795/ijpbs-7411.

Hammett, T. M., Des Jarlais, D. C., Kling, R., Kieu, B. T., McNicholl, J. M., Wasinrapee, P., McDougal, J. S. et al. (2012), 'Controlling HIV epidemics among injection drug users: eight years of Cross-Border HIV prevention interventions in Vietnam and China', *Plos One* 7:e43141, doi:10.1371/journal.pone.0043141.

Handanagic, S., Sevic, S., Barbaric, J., Dominkovic, Z., Dakovic Rode, O., Begovac, J. and Bozicevic, I. (2017), 'Correlates of anti-hepatitis C positivity and use of harm reduction services among people who inject drugs in two cities in Croatia', *Drug and Alcohol Dependence* 171, pp. 132-139, doi:10.1016/j.drugalcdep.2016.11.028.

Hedrich, D., Alves, P., Farrell, M., Stöver, H., Møller, L. and Mayet, S. (2012), 'The effectiveness of opioid maintenance treatment in prison settings: a systematic review', *Addiction* 107, pp. 501-517, doi:10.1111/j.1360-0443.2011.03676.x.

Hochstatter, K. R., Hull, S. J., Sethi, A. K., Burns, M. E., Mundt, M. P. and Westergaard, R. P. (2020), 'Promoting safe injection practices, substance use reduction, hepatitis C testing, and overdose prevention among syringe service program clients using a computer-tailored intervention: pilot randomized controlled trial', *Journal of Medical Internet Research* 22:e19703, doi:10.2196/19703.

Huang, Y.-F., Yang, J.-Y., Nelson, K. E., Kuo, H.-S., Lew-Ting, C.-Y., Yang, C.-H., Chen, C.-H., Chang, F.-Y. and Liu, H.-R. (2014), 'Changes in HIV incidence among people who inject drugs in Taiwan following introduction of a harm reduction program: a study of two cohorts', *PLoS Medicine* 11:e1001625, doi:10.1371/journal.pmed.1001625.

Institute of Medicine. 2007. *Preventing HIV Infection Among Injecting Drug Users in High-Risk Countries: An Assessment of the Evidence*. Washington, DC: The National Academies Press. https://doi.org/10.17226/11731.

Islam, N., Krajden, M., Shoveller, J., Gustafson, P., Gilbert, M., Buxton, J. A., Wong, J. et al. (2017), 'Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study', *The Lancet. Gastroenterology and Hepatology* 2, pp. 200-210, doi:10.1016/S2468-1253(16)30182-0.

Kennedy, M. C., Hayashi, K., Milloy, M. J., Wood, E. and Kerr, T. (2019a), 'Supervised injection facility use and all-cause mortality among people who inject drugs in Vancouver, Canada: a cohort study', *PLoS Medicine* 16:e1002964, doi:10.1371/journal.pmed.1002964.

Kennedy, M. C., Karamouzian, M. and Kerr, T. (2017), 'Public health and public order outcomes associated with supervised drug consumption facilities: a systematic review', *Current HIV/AIDS Reports* 14, pp. 161-183, doi:10.1007/s11904-017-0363-y.

Kennedy, M. C., Klassen, D. C., Dong, H., Milloy, M. J. S., Hayashi, K. and Kerr, T. H. (2019b), 'Supervised injection facility utilization patterns: a prospective cohort study in Vancouver, Canada', *American Journal of Preventive Medicine* 57, pp. 330-337, doi:10.1016/j.amepre.2019.04.024.

Kim, N. J., Jin, H., McFarland, W. and Raymond, H. F. (2015), 'Trends in sources and sharing of needles among people who inject drugs, San Francisco, 2005-2012', *The International Journal on Drug Policy* 26, pp. 1238-1243, doi:10.1016/j.drugpo.2015.08.013.

Korownyk, C., Perry, D., Ton, J., Kolber, M. R., Garrison, S., Thomas, B., Allan, G. M. et al. (2019), 'Managing opioid use disorder in primary care: PEER simplified guideline', *Canadian Family Physician* 65, pp. 321-330.

Lea, T., Kolstee, J., Lambert, S., Ness, R., Hannan, S. and Holt, M. (2017), 'Methamphetamine treatment outcomes among gay men attending a LGBTI-specific treatment service in Sydney, Australia', *Plos One*, 12:e0172560, doi:10.1371/journal.pone.0172560.

Leyna, G. H., Makyao, N., Mwijage, A., Ramadhan, A., Likindikoki, S., Mizinduko, M., Leshabari, M. T., Moen, K. and Mmbaga, E. J. (2019), 'HIV/HCV co-infection and associated risk factors among injecting drug users in Dar es Salaam, Tanzania: potential for HCV elimination', *Harm Reduction Journal* 16, 68, doi:10.1186/s12954-019-0346-y.

Luo, W., Wu, Z., Poundstone, K., McGoogan, J. M., Dong, W., Pang, L., Rou, K., Wang, C. and Cao, X. (2015), 'Needle and syringe exchange programmes and prevalence of HIV infection among intravenous drug users in China', *Addiction* 110 Suppl, pp. 61-67, doi:10.1111/add.12783.

MacArthur, G. J., van Velzen, E., Palmateer, N., Kimber, J., Pharris, A., Hope, V., Taylor, A. et al. (2014), 'Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness', *The International Journal on Drug Policy* 25, pp. 34-52, doi:10.1016/j.drugpo.2013.07.001.

Mackesy-Amiti, M. E., Boodram, B., Spiller, M. W., Paz-Bailey, G., Prachand, N., Broz, D. and NHBS Study Group. (2017), 'Injection-related risk behavior and engagement in outreach, intervention and prevention services across 20 US cities', *JAIDS Journal of Acquired Immune Deficiency Syndromes* 75 Suppl 3, pp. S316-S324, doi:10.1097/QAI.0000000000001406.

Marotta, P. L. and McCullagh, C. A. (2016), 'A cross-national analysis of the effects of methadone maintenance and needle and syringe program implementation on incidence rates of HIV in Europe from 1995 to 2011', *The International Journal on Drug Policy* 32, pp. 3-10, doi:10.1016/j.drugpo.2016.02.007.

Mateu-Gelabert, P., Gwadz, M. V., Guarino, H., Sandoval, M., Cleland, C. M., Jordan, A., Hagan, H., Lune, H. and Friedman, S. R. (2014), 'The staying safe intervention: training people who inject drugs in strategies to avoid injection-related HCV and HIV infection', *AIDS Education and Prevention* 26, pp. 144-157, doi:10.1521/aeap.2014.26.2.144.

McAuley, A., Palmateer, N. E., Goldberg, D. J., Trayner, K. M. A., Shepherd, S. J., Gunson, R. N., Metcalfe, R. et al. (2019), 'Re-emergence of HIV related to injecting drug use despite a comprehensive harm reduction environment: a cross-sectional analysis', *The Lancet. HIV* 6:e315-e324, doi:10.1016/S2352-3018(19)30036-0.

Mehrabi, Y., Etemad, K., Noroozi, A., Higgs, P., Nasirian, M., Sharhani, A., Khademi, N. et al. (2020), 'Correlates of injecting paraphernalia sharing among male drug injectors in Kermanshah, Iran: implications for HCV prevention', *Journal of Substance Use* 25, pp. 330-335, doi:10.1080/14659891.2019.1698670.

Mezaache, S., Protopopescu, C., Debrus, M., Morel, S., Mora, M., Suzan-Monti, M., Carrieri, P. and Roux, P. (2018), 'Changes in supervised drug-injecting practices following a community-based educational intervention: a longitudinal analysis', *Drug and Alcohol Dependence* 192, pp. 1-7, doi:10.1016/j.drugalcdep.2018.07.028.

Miller, W. C., Hoffman, I. F., Hanscom, B. S., Ha, T. V., Dumchev, K., Djoerban, Z., Rose, S. M. et al. (2018), 'A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): a randomised, controlled phase 3 feasibility and efficacy study', *The Lancet* 392, pp. 747-759, doi:10.1016/S0140-6736(18)31487-9.

Minařík, J., Gabrhelík, R., Malcolm, R., Pavlovská, A. and Miller, P. (2016), 'Methylphenidate substitution for methamphetamine addiction and implications for future randomized clinical trials: a unique case series', *Journal of Substance Use* 21, pp. 435-438, doi:10.3109/14659891.2015.1045047.

Minoyan, N., Artenie, A. A., Zang, G., Jutras-Aswad, D., Turcotte, M.-È. and Bruneau, J. (2020), 'Harm reduction coverage and hepatitis C incidence: findings from a cohort of people who inject drugs', *American Journal of Preventive Medicine* 58, pp. 845-853, doi:10.1016/j.amepre.2020.01.024.

Molès, J.-P., Vallo, R., Khue, P. M., Huong, D. T., Oanh, K. T. H., Thoa, N. T., Giang, H. T. et al. (2020), 'HIV control programs reduce HIV incidence but not HCV incidence among people who inject drugs in HaiPhong, Vietnam', *Scientific Reports* 10, pp. 6999, doi:10.1038/s41598-020-63990-w.

Moore, K. E., Roberts, W., Reid, H. H., Smith, K. M. Z., Oberleitner, L. M. S. and McKee, S. A. (2019), 'Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review', *Journal of Substance Abuse Treatment* 99, pp. 32-43, doi:10.1016/j.jsat.2018.12.003.

Naserirad, M. and Beulaygue, I. C. (2020), 'Accessibility of needle and syringe programs and injecting and sharing risk behaviors in high hepatitis C virus prevalence settings', *Substance Use and Misuse* 55, pp. 900-908, doi:10.1080/10826084.2019.1710210.

Nazari, S. S. H., Noroozi, M., Soori, H., Noroozi, A., Mehrabi, Y., Hajebi, A., Sharifi, H., Higgs, P. and Mirzazadeh, A. (2016), 'The effect of on-site and outreach-based needle and syringe programs in people who inject drugs in Kermanshah, Iran', *The International Journal on Drug Policy* 27, pp. 127-131, doi:10.1016/j.drugpo.2015.10.011.

Nghiem, V. T., Bui, T. C., Nadol, P. P., Phan, S. H., Kieu, B. T., Kling, R. and Hammett, T. M. (2018), 'Prevalence and correlates of HIV infection among men who inject drugs in a remote area of Vietnam', *Harm Reduction Journal* 15, pp. 8, doi:10.1186/s12954-018-0210-5.

Noroozi, M., Marshall, B. D. L., Noroozi, A., Armoon, B., Sharifi, H., Farhoudian, A., Ghiasvand, H. et al. (2018), 'Do needle and syringe programs reduce risky behaviours among people who inject drugs in Kermanshah City, Iran? A coarsened exact matching approach', *Drug and Alcohol Review* 37 Suppl 1, pp. S303-S308, doi:10.1111/dar.12646.

Owczarzak, J., Nguyen, T. Q., Mazhnaya, A., Phillips, S. D., Filippova, O., Alpatova, P., Zub, T. and Aleksanyan, R. (2019), 'Outcome evaluation of a "common factors" approach to develop culturally tailored HIV prevention interventions for people who inject drugs', *Drug and Alcohol Dependence* 199, pp. 18-26, doi:10.1016/j.drugalcdep.2019.02.015.

Palmateer, N., Kimber, J., Hickman, M., Hutchinson, S., Rhodes, T. and Goldberg, D. (2010), 'Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews', *Addiction* 105, pp. 844-859, doi:10.1111/j.1360-0443.2009.02888.x.

Panda, S., Roy, T., Pahari, S., Mehraa, J., Sharma, N., Singh, G., Joseph, F., Singh, S. and Sharma, N. M. (2014), 'Alarming epidemics of human immunodeficiency virus and hepatitis C virus among injection drug users in the northwestern bordering state of Punjab, India: prevalence and correlates', *International Journal of STD and AIDS* 25, pp. 596-606, doi:10.1177/0956462413515659.

Patel, M. R., Foote, C., Duwve, J., Chapman, E., Combs, B., Fry, A., Hall, A., Roseberry, J., Brooks, J. T. and Broz, D. (2018), 'Reduction of injection-related risk behaviors after emergency implementation of a syringe services program during an HIV outbreak',

JAIDS Journal of Acquired Immune Deficiency Syndromes 77, pp. 373-382, doi:10.1097/QAI.0000000000001615.

Pitpitan, E. V., Patterson, T. L., Abramovitz, D., Vera, A., Martinez, G., Staines, H. and Strathdee, S. A. (2016), 'Policing behaviors, safe injection self-efficacy, and intervening on injection risks: moderated mediation results from a randomized trial', *Health Psychology* 35, pp. 87-91, doi:10.1037/hea0000241.

Platt, L., Minozzi, S., Reed, J., Vickerman, P., Hagan, H., French, C., Jordan, A. et al. (2017), 'Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs', *Cochrane Database of Systematic Reviews* 9, pp. CD012021, doi:10.1002/14651858.CD012021.pub2.

Platt, L., Minozzi, S., Reed, J., Vickerman, P., Hagan, H., French, C., Jordan, A. et al. (2018), 'Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis', *Addiction* 113, pp. 545-563, doi:10.1111/add.14012.

Rezaie, F., Farhadi, M. H., Farhoudian, A., Najafi, M., Bazrafshan, A., Higgs, P., Shahboulagh, F. M. et al. (2017), 'Access to needle and syringe programs and the relationship to equipment sharing among people who inject drugs in Kermanshah, Iran', *Journal of Substance Use* 22, pp. 397-402, doi:10.1080/14659891.2016.1227384.

Rossi, C., Butt, Z. A., Wong, S., Buxton, J. A., Islam, N., Yu, A., Darvishian, M. et al. (2018), 'Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort', *Journal of Hepatology* 69, pp. 1007-1014, doi:10.1016/j.jhep.2018.07.025.

Roux, P., Donadille, C., Magen, C., Schatz, E., Stranz, R., Curado, A., Tsiakou, T. et al. (2021), 'Implementation and evaluation of an educational intervention for safer injection in people who inject drugs in Europe: a multi-country mixed-methods study', *The International Journal on Drug Policy* 87, pp. 102992, doi:10.1016/j.drugpo.2020.102992.

Roux, P., Le Gall, J.-M., Debrus, M., Protopopescu, C., Ndiaye, K., Demoulin, B., Lions, C. et al. (2016), 'Innovative community-based educational face-to-face intervention to reduce HIV, hepatitis C virus and other blood-borne infectious risks in difficult-to-reach people who inject drugs: results from the ANRS-AERLI intervention study', *Addiction* 111, pp. 94-106, doi:10.1111/add.13089.

Sacks-Davis, R., Horyniak, D., Grebely, J. and Hellard, M. (2012), 'Behavioural interventions for preventing hepatitis C infection in people who inject drugs: a global systematic review', *The International Journal on Drug Policy* 23, pp. 176-184, doi:10.1016/j.drugpo.2011.08.002.

Salek, T. P., Katz, A. R., Lenze, S. M., Lusk, H. M., Li, D. and Des Jarlais, D. C. (2017), 'Seroprevalence of HCV and HIV infection among clients of the nation's longest-standing statewide syringe exchange program: A cross-sectional study of Community Health Outreach Work to Prevent AIDS (CHOW)', *The International Journal on Drug Policy* 48, pp. 34-43, doi:10.1016/j.drugpo.2017.06.009.

Sawangjit, R., Khan, T. M. and Chaiyakunapruk, N. (2017), 'Effectiveness of pharmacy-based needle/syringe exchange programme for people who inject drugs: a systematic review and meta-analysis', *Addiction* 112, pp. 236-247, doi:10.1111/add.13593.

Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D. et al. (2017), 'AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both', *BMJ* 358, pp. j4008, doi:10.1136/bmj.j4008.

Smith, L. R., Strathdee, S. A., Metzger, D. and Latkin, C. (2017), 'Evaluating network-level predictors of behavior change among injection networks enrolled in the HPTN 037 randomized controlled trial', *Drug and Alcohol Dependence* 175, pp. 164-170, doi:10.1016/j.drugalcdep.2017.02.007.

Strang, J., Groshkova, T., Uchtenhagen, A., van den Brink, W., Haasen, C., Schechter, M. T., Lintzeris, N. et al. (2015), 'Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction', *The British Journal of Psychiatry* 207, pp. 5-14, doi:10.1192/bjp.bp.114.149195.

Strang, J., Volkow, N. D., Degenhardt, L., Hickman, M., Johnson, K., Koob, G. F., Marhsall, B. D. L., Tyndall, M. and Walsh, S. L. (2020), 'Opioid use disorder', *Nature Reviews. Disease Primers* 6, pp. 3, doi:10.1038/s41572-019-0137-5.

Sypsa, V., Psichogiou, M., Paraskevis, D., Nikolopoulos, G., Tsiara, C., Paraskeva, D., Micha, K. et al. (2017), 'Rapid decline in HIV incidence among persons who inject drugs during a fast-track combination prevention program after an HIV outbreak in Athens', *The Journal of Infectious Diseases* 215, pp. 1496-1505, doi:10.1093/infdis/jix100.

Trickey, A., May, M. T., Hope, V., Ward, Z., Desai, M., Heinsbroek, E., Hickman, M. and Vickerman, P. (2018), 'Usage of low dead space syringes and association with hepatitis C prevalence amongst people who inject drugs in the UK', *Drug and Alcohol Dependence* 192, pp. 118-124, doi:10.1016/j.drugalcdep.2018.07.041.

Valerio, H., Alavi, M., Silk, D., Treloar, C., Martinello, M., Milat, A., Dunlop, A. et al. (2021), 'Progress towards elimination of hepatitis C infection among people who inject drugs in Australia: the ETHOS engage study', *Clinical Infectious Diseases* 73:e69–e78, doi:10.1093/cid/ciaa571.

Walsh, N., Verster, A., Rodolph, M. and Akl, E. A. (2014), 'WHO guidance on the prevention of viral hepatitis B and C among people who inject drugs', *The International Journal on Drug Policy* 25, pp. 363-371, doi:10.1016/j.drugpo.2014.01.009.

Wang, M., Mao, W., Zhang, L., Jiang, B., Xiao, Y., Jia, Y., Wu, P., Cassell, H. and Vermund, S. (2015), 'Methadone maintenance therapy and HIV counseling and testing are associated with lower frequency of risky behaviors among injection drug users in China', *Substance Use and Misuse* 50, pp. 15-23, doi:10.3109/10826084.2014.957768.

Welch-Lazoritz, M., Habecker, P., Dombrowski, K., Rivera Villegas, A., Davila, C. A., Rolón Colón, Y. and Miranda De León, S. (2017), 'Differential access to syringe exchange and other prevention activities among people who inject drugs in rural and urban areas of Puerto Rico', *The International Journal on Drug Policy* 43, pp. 16-22, doi:10.1016/j.drugpo.2016.12.011.

WHO (2012), *Guidance on prevention of viral hepatitis B and C among people who inject drugs*. (World Health Organization, ed.) (p. 52). Geneva: World Health Organization (https://www.who.int/hiv/pub/guidelines/hepatitis/en/).

Yi, S., Mun, P., Chhoun, P., Chann, N., Tuot, S. and Mburu, G. (2019), 'Prevalence of and risk factors for hepatitis C virus antibody among people who inject drugs in Cambodia: a national biological and behavioral survey', *Harm Reduction Journal* 16, pp. 29, doi:10.1186/s12954-019-0299-1.

Zietara, F., Crotty, P., Houghton, M., Tyrrell, L., Coffin, C. and Macphail, G. (2020), 'Sociodemographic risk factors for hepatitis C virus infection in a prospective cohort study of 257 persons in Canada who inject drugs', *Canadian Liver Journal* 3, pp. 276-285, doi:10.3138/canlivj.2019-0023.

Appendix 1. Search terms used in the overview of reviews

MEDLINE (via OVID)

1. exp Hepatitis C, Chronic/ or exp Hepatitis C/ or exp Hepacivirus/
2. ("Hepatitis C" or HCV or "Hep C" or hepacivirus).ti,ab.
3. exp HIV/ or exp Acquired Immunodeficiency Syndrome/
4. (HIV or "Human Immunodeficiency Virus" or "acquired immunodeficiency syndrome" or "acquired immune deficiency syndrome" or AIDS).ti,ab.
5. exp Risk Reduction Behavior/ or exp Health Risk Behaviors/ or exp Needle Sharing/ or exp Risk-Taking/
6. ((injecting or injection) adj3 (risk or frequency)).ti,ab.
7. ((needle$ or syringe$ or equipment or paraphernalia) adj3 (shar$ or reus$ or borrow$)).ti,ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Substance Abuse, Intravenous/ or exp Drug Users/ or exp Heroin Dependence/ or exp Opioid-Related Disorders/ or exp Substance-Related Disorders/ or exp Drug Misuse/ or exp Amphetamine-Related Disorders/ or exp Cocaine-Related Disorders/
10. ("people who inject drugs" or PWID).ti,ab.
11. exp Crack Cocaine/ or exp Cocaine/ or exp Synthetic Drugs/ or exp Amphetamine/
12. (amphetamine or cocaine or stimulant or opiate or opioid or heroin or synthetic).ti,ab.
13. (substance$ or drug$).ti,ab.
14. (abus$ or depend$ or us$ or misus$ or addict$ or disorder or inject$ or intravenous).ti,ab.
15. 9 or 10 or (11 and 14) or (12 and 14) or (13 and 14)
16. exp Harm Reduction/ or exp Needle-Exchange Programs/ or exp Preventative Health Services/ or exp Community Health Services/ or exp Primary Prevention/
17. ((needle$ or syringe$ or equipment) adj3 (exchange or suppl$ or program$ or service or facility or distribut$ or dispens$ or provision or provider)).ti,ab.
18. ((outreach or peer) adj3 (exchange or suppl$ or program$ or service or facility or distribut$ or dispens$ or provision or provider)).ti,ab.
19. 16 or 17 or 18
20. exp Buprenorphine/ or exp Buprenorphine, Naloxone Drug Combination/ or exp Methadone/ or exp Naltrexone/ or exp Substance Abuse Treatment Centers/ or exp Opiate Substitution Treatment/
21. (methadone or buprenorphine or suboxone or naltrexone or subutex or OST).ti,ab.
22. ((opiate or opioid or agonist or antagonist) adj2 (substitut$ or replac$ or maint$ or treatment or therapy)).ti,ab.
23. ((heroin or hydromorphone or diacetylmorphine or dilaudid or diamorphine) adj2 (assisted or treatment or maintenance)).ti,ab.
24. 20 or 21 or 22 or 23
25. exp Cognitive Behavioral Therapy/ or exp Behavior Therapy/ or exp Counseling/ or exp Psychosocial Support Systems/ or exp Reimbursement, Incentive/
26. (counselling or counseling or therapy or psycho-social or psychosocial or "contingency management" or incentiv$ or monetary or reward).ti,ab.
27. 25 or 26
28. ("drug consumption" adj2 (room or site or space or facilit$)).ti,ab.
29. (safe$ inject$ adj2 (room or site or space or facilit$)).ti,ab.
30. (supervised inject$ adj2 (room or site or space or facilit$)).ti,ab.
31. "overdose prevention site$".ti,ab.
32. 28 or 29 or 30 or 31
33. 19 or 24 or 27 or 32
34. 8 and 15 and 33
35. exp “Systematic Review”/ or exp Review/ or exp Meta-analysis/
36. (systematic review or review or meta-analysis).pt
37. ((review$ or overview$) adj2 (systematic or methodologic$ or quantitative or literature)).ti,ab.
38. (meta-analysis or meta-synthesis).ti,ab.
39. 35 or 36 or 37 or 38

EMBASE (via OVID)

1. exp Hepatitis C virus/ or exp hepatitis C/ or exp Hepacivirus/
2. (“Hepatitis C” or HCV or "Hep C" or hepacivirus).ti,ab
3. exp Human immunodeficiency virus/ or exp acquired immune deficiency syndrome/

4. (HIV or “Human Immunodeficiency Virus ” or “acquired immunodeficiency syndrome” or “acquired immune deficiency syndrome” or AIDS).ti,ab
5. exp high risk behavior/ or exp risk reduction/ or exp needle sharing/
6. ((injecting or injection) adj3 (risk or frequency)).ti,ab
7. ((needle$ or syringe$ or equipment or paraphernalia) adj3 (shar$ or reus$ or borrow$)).ti,ab
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp injection drug user/ or exp intravenous drug abuse/ or exp drug dependence/ or exp cocaine dependence/ or exp heroin dependence/ or exp drug misuse/ or exp drug abuse/ or exp opiate addiction/
10. (“people who inject drugs” OR PWID).ti,ab
11. exp amphetamine/ or exp cocaine/ or exp street drug/ or exp opiate/
12. (amphetamine or cocaine or stimulant or opiate or opioid or heroin or synthetic).ti,ab
13. (substance$ or drug$).ti,ab
14. (abus$ or depend$ or us$ or misus$ or addict$ or disorder or inject$ or intravenous).ti,ab
15. 9 or 10 or (11 and 14) or (12 and 14) or (13 and 14)
16. exp harm reduction/ or exp preventive health service/
17. ((needle$ or syringe$ or equipment) adj3 (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)).ti,ab.
18. ((outreach or peer) adj3 (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)).ti,ab.
19. 16 or 17 or 18
20. exp opiate substitution treatment/ or exp drug dependence treatment/ or exp narcotic antagonist/
21. (methadone or buprenorphine or suboxone or naltrexone or subutex or OST).ti,ab
22. ((opiate or opioid or agonist or antagonist) adj2 (substitute$ or replac$ or maint$ or treatment or therapy)).ti,ab
23. ((heroin or hydromorphone or diacetylmorphine or dilaudid or diamorphone) adj2 (assisted or treatment or maintenance)).ti,ab
24. 20 or 21 or 22 or 23
25. exp cognitive therapy/ or exp therapy/ or exp behavior therapy/ or exp counseling/
26. (counseling or counselling or therapy or psycho-social or psychosocial or "contingency management" or incentiv$ or monetary or reward).ti,ab.
27. 25 or 26
28. ("drug consumption" adj2 (room or site or space or facilit$)).ti,ab.
29. (safe$ inject$ adj2 (room or site or space or facilit$)).ti,ab.
30. (supervised inject$ adj2 (room or site or space or facilit$)).ti,ab.
31. “overdose prevention site$”.ti,ab.
32. 28 or 29 or 30 or 31
33. 19 or 24 or 27 or 32
34. 8 and 15 and 33
35. exp systematic review/ or exp meta analysis/ or exp review/
36. (systematic review or review or meta-analysis).pt
37. (review$ or overview$) adj2 (systematic or methodologic$ or quantitative or literature).ti,ab
38. (meta-analysis or meta-synthesis).ti,ab
39. 35 or 36 or 37 or 38

<u>PsycINFO (via OVID)</u>

1. exp Hepatitis/
2. ("Hepatitis C" or HCV or "Hep C" or hepacivirus).ti,ab.
3. exp HIV/ or exp AIDS/
4. (HIV or "Human Immunodeficiency Virus" or “acquired immunodeficiency syndrome” or “acquired immune deficiency syndrome” or AIDS).ti,ab.
5. exp Risk Taking/ or exp Risk Factors/ or exp Needle Sharing/
6. ((injecting or injection) adj3 (risk or frequency)).ti,ab
7. ((needle$ or syringe$ or equipment or paraphernalia) adj3 (shar$ or reus$ or borrow$)).ti,ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Intravenous Drug Usage/ or exp Drug Addiction/ or exp Drug Dependency/ or exp Drug Abuse/ or exp Heroin Addiction/
10. (“people who inject drugs” or PWID).ti,ab

11. exp Amphetamine/ or exp Opiates/ or exp Methamphetamine/ or exp Cocaine/ or exp Crack Cocaine/
12. (amphetamine or cocaine or stimulant or opiate or opioid or heroin or synthetic).ti,ab
13. (substance$ or drug$).ti,ab
14. (abus$ or depend$ or us$ or misus$ or addict$ or disorder or inject$ or intravenous).ti,ab
15. 9 or 10 or (11 and 14) or (12 and 14) or (13 and 14)
16. exp Harm Reduction/ or exp Prevention/ or exp Needle Exchange Programs/
17. ((needle$ or syringe$ or equipment) adj3 (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)).ti,ab.
18. ((outreach or peer) adj3 (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)).ti,ab.
19. 16 or 17 or 18
20. exp Methadone/ or exp Methadone Maintenance/ or exp Buprenorphine/ or exp Naltrexone/ or exp Narcotic Antagonists/ or exp Narcotic Agonists/
21. (methadone or buprenorphine or suboxone or naltrexone or subutex or OST).ti,ab
22. ((opiate or opioid or agonist or antagonist) adj2 (substitut$ or replac$ or maint$ or treatment or therapy)).ti,ab
23. ((heroin or hydromorphone or diacetylmorphine or dilaudid or diamorphone) adj2 (assisted or treatment or maintenance)).ti,ab
24. 20 or 21 or 22 or 23
25. exp Behavior Therapy/ or exp Cognitive Behavior Therapy/ or exp Cognitive Therapy/ or exp Counseling/ or exp Contingency Management/
26. (counseling or counselling or therapy or psycho-social or psychosocial or "contingency management" or incentiv$ or monetary or reward).ti,ab.
27. 25 or 26
28. ("drug consumption" adj2 (room or site or space or facilit$)).ti,ab.
29. (safe$ inject$ adj2 (room or site or space or facilit$)).ti,ab.
30. (supervised inject$ adj2 (room or site or space or facilit$)).ti,ab.
31. "overdose prevention site$".ti,ab.
32. 28 or 29 or 30 or 31
33. 19 or 24 or 27 or 32
34. 8 and 15 and 33
35. exp Systematic Review/ or exp Meta Analysis or exp Literature review/
36. (systematic review or review or meta-analysis).pt
37. (review$ or overview$) adj2 (systematic or methodologic$ or quantitative or literature).ti,ab
38. (meta-analysis or meta-synthesis).ti,ab
39. 35 or 36 or 37 or 38

CINAHL (via EBSCO)

1. (MH “Hepatitis C+”) OR (MH “Hepatitis C, Chronic”)
2. TI,AB: “Hepatitis C” OR HCV OR “Hep C” OR “hepacivirus”
3. (MH “Human Immunodeficiency Virus+”) OR (MH “HIV Infections+”) OR (MH “Acquired Immunodeficiency Syndrome”)
4. TI,AB: HIV OR “Human Immunodeficiency Virus” OR “acquired immunodeficiency syndrome” OR “acquired immune deficiency syndrome” OR AIDS
5. (MH “Risk Taking Behavior+”) OR (MH “Needle Sharing”)
6. TI,AB: (injecting or injection) N3 (risk OR frequency)
7. TI,AB: (needle* or syringe* or equipment or paraphernalia) N3 (shar* or reus* or borrow*)
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. (MH "Intravenous Drug Users") OR (MH “Substance Abuse, Intravenous) OR (MH “Substance Use Disorders+”) OR (MH “Substance Dependence”) OR (MH “Substance Abuse+”) OR (MH “Substance Abusers+”)
10. TI,AB: “people who inject drugs” OR PWID
11. (MH "Crack Cocaine") OR (MH “Cocaine+”) OR (MH "Synthetic Drugs") OR (MH “Amphetamine+”) OR (MH “Amphetamines+”) OR (MH “Street Drugs”) OR (MH “Heroin”)
12. TI,AB: amphetamine OR cocaine OR stimulant OR opiate OR opioid OR heroin OR synthetic
13. TI,AB: substance* OR drug*
14. TI,AB: abus* or depend* or us* or misus* or addict* OR disorder OR inject* or intravenous
15. 9 OR 10 OR (11 AND 14) OR (12 AND 14) OR (13 AND 14)
16. (MH “Needle-Exchange Programs”) OR (MH “Preventative Health Care) OR (MH “Community Health Services+”)

17. TI,AB: (needle* OR syringe* OR equipment) N3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)
18. TI,AB: (outreach or peer) N3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)
19. 16 OR 17 OR 18
20. (MH "Buprenorphine") OR (MH “Methadone”) OR (MH “Naltrexone”) OR (MH “Narcotic Antagonists”) OR (MH “Substance Use Rehabilitation Programs”)
21. TI,AB: methadone OR buprenorphine OR suboxone OR naltrexone OR subutex OR OST
22. TI,AB: (opiate OR opioid OR agonist OR antagonist) N2 (substitut* or replac* or maint* or treatment or therapy)
23. TI,AB: (heroin OR hydromorphone OR diacetylmorphine OR dilaudid OR diamorphine) N2 (assisted OR treatment OR maintenance)
24. 20 OR 21 OR 22 OR 23
25. (MH “Cognitive Therapy+”) OR (MH “Behavior Therapy+”) OR (MH “Counseling”) OR (MH “Support, Psychosocial+”) OR (MH “Rehabilitation, Psychosocial”) OR (MH “Contingency Management”)
26. TI,AB: counselling OR counseling OR therapy OR psycho-social OR psychosocial OR “contingency management” OR incentiv* or monetary or reward
27. 25 OR 26
28. TI,AB: "drug consumption" N2 (room or site or space or facilit*)
29. TI,AB: “safe* inject*” N2 (room or site or space or facilit*)
30. TI,AB: “supervised inject*” N2 (room or site or space or facilit*)
31. TI,AB: “overdose prevention site*”
32. 28 OR 29 OR 30 OR 31
33. 19 OR 24 OR 27 OR 32
34. 8 AND 15 AND 33
35. PT “systematic review” OR PT “review” OR PT “meta-analysis”
36. (MH “Literature Review+”) OR (MH “Meta-analysis”) OR (MH “Systematic Review”)
37. TI,AB: (review* OR overview*) N2 (systematic OR methodologic* OR quantitative OR literature)
38. TI,AB: meta-analysis OR meta-synthesis
39. 35 OR 36 OR 37 OR 38

Web of Science

1. TS=(HIV OR “Human Immunodeficiency Virus” OR “acquired immunodeficiency syndrome” OR “acquired immune deficiency syndrome” OR AIDS)
2. TS=(HCV OR “Hepatitis C” OR “Hep C” OR hepacivirus)
3. TS=((injecting or injection) NEAR/3 (risk or frequency))
4. TS=((needle* OR syringe* OR equipment or paraphernalia) NEAR/3 (shar* OR reus* OR borrow*))
5. 1 OR 2 OR 3 OR 4
6. TS=(“people who inject drugs” OR PWID)
7. TS=amphetamine OR cocaine OR stimulant OR opiate OR opioid OR heroin OR synthetic
8. TS=(substance* or drug*)
9. TS=(abus* OR depend* OR misus* OR addict* OR disorder OR inject* OR intravenous OR use*)
10. #6 OR (#7 AND #9) OR (#8 AND #9)
11. TS=(harm NEAR/2 reduc*)
12. TS=(needle* OR syringe* OR equipment) NEAR/3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)
13. TS=(outreach or peer) NEAR/3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)
14. #11 OR #12 OR #13
15. TS=(methadone OR buprenorphine OR suboxone OR naltrexone OR subutex OR OST)
16. TS=((opiate OR opioid OR agonist OR antagonist) NEAR/2 (substitut* OR replac* OR maint* OR treatment OR therapy))

17. TS=((heroin OR hydromorphone OR diacetylmorphine OR dilaudid OR diamorphine) NEAR/2 (assisted OR treatment OR maintenance))
18. #15 OR #16 OR #17
19. TS=(counselling OR counseling OR therapy OR psycho-social OR psychosocial OR “contingency management” OR incentiv* or monetary or reward)
20. #19
21. TS=(("drug consumption" NEAR/2 (room or site or space or facilit*))
22. TS=((safe* inject*) NEAR/2 (room or site or space or facilit*))
23. TS=((supervised inject*) NEAR/2 (room or site or space or facilit*))
24. TS=(“overdose prevention site*”)
25. #21 OR #22 OR #23 OR #24
26. #14 OR #18 OR #20 OR #25
27. #5 AND #10 AND #26
28. TS=((systematic or literature) NEAR/2 (review or overview))
29. TS=(“meta-analysis” OR “meta-synthesis”)
30. #28 OR #29

Cochrane Library

1. (inject):ti,ab,kw or (intravenous):ti,ab,kw
2. (HCV):ti,ab,kw or ("Hepatitis C"):ti,ab,kw or ("Hep C"):ti,ab,kw or (hepacivirus):ti,ab,kw
3. (HIV):ti,ab,kw or ("Human Immunodeficiency Virus"):ti,ab,kw or (“acquired immunodeficiency syndrome”):ti,ab,kw or (“acquired immune deficiency syndrome”):ti,ab,kw or (AIDS):ti,ab,kw
4. (risk NEXT behav*):ti,ab,kw
5. (#2 or #3 or #4)
6. (#1 and #5)

Appendix 2. Search terms used in the primary literature review

MEDLINE (via OVID)

1 Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/
2 ("hepatitis c" or HCV or "hep c" or hepacivirus).ti,ab.
3 HIV/
4 (HIV or Human Immunodeficiency Virus).ti,ab.
5 Risk Reduction Behavior/ or Health Risk Behaviors/ or Needle Sharing/ or Risk-Taking/

6 ((injecting or injection) adj (risk or frequency)).ti,ab.
7 ((needle* or syringe* or equipment or paraphernalia) adj (shar* or reus* or borrow*)).ti,ab.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 Substance Abuse, Intravenous/
10 ("people who inject" or "person who injects" or PWID or "injecting drug user" or "injection drug user" or "intravenous drug user" or IDU or IDUs or IVDU or IVDUs).ti,ab.
11 Crack Cocaine/ or Cocaine/ or Synthetic Drugs/ or Amphetamine/ or Heroin/
12 (amphetamine or cocaine or stimulant or opiate or opioid or heroin or synthetic).ti,ab.

13 (substance* or drug*).ti,ab.
14 (inject* or intravenous).ti,ab.
15 9 or 10 or (11 and 14) or (12 and 14) or (13 and 14)
16 Harm Reduction/ or Needle-Exchange Programs/ or Preventative Health Services/ or Primary Prevention/
17 (((needle* or syringe* or equipment) adj (exchange or suppl* or program* or service or facility or distribut* or dispens* or provision or provider)) or foil).ti,ab.
18 ((outreach or peer) adj (exchange or suppl* or program* or service or facility or distribut* or dispens* or provision or provider)).ti,ab.
19 16 or 17 or 18
20 Buprenorphine/ or Buprenorphine, Naloxone Drug Combination/ or Methadone/ or Naltrexone/ or Substance Abuse Treatment Centers/ or Opiate Substitution Treatment/
21 (methadone or buprenorphine or suboxone or naltrexone or subutex or OST).ti,ab.

22 (((opiate or opioid or agonist or antagonist) adj (substitut* or replac* or maint* or treatment or therapy or implant or slow-release or "slow release" or extended-release or "extended release")) or (stimulant adj3 (treatment or therapy))).ti,ab.
23 ((heroin or hydromorphone or diacetylmorphine or dilaudid or diamorphine) adj (assisted or treatment or maintenance)).ti,ab.
24 20 or 21 or 22 or 23
25 Cognitive Behavioral Therapy/ or Behavior Therapy/ or Counseling/ or Psychosocial Support Systems/ or Reimbursement, Incentive/
26 (counselling or counseling or therapy or psycho-social or psychosocial or contingency management or incentiv* or monetary or reward).ti,ab.
27 25 or 26
28 ("drug consumption" adj2 (room or site or space or facilit*)).ti,ab.
29 (safe* inject* adj2 (room or site or space or facilit*)).ti,ab.
30 (supervised inject* adj2 (room or site or space or facilit*)).ti,ab.
31 overdose prevention site*.ti,ab.
32 28 or 29 or 30 or 31
33 19 or 24 or 27 or 32
34 8 and 15 and 33
35 34
36 limit 35 to yr="2011 -Current"

EMBASE (via OVID)

1 Hepatitis C virus/ or hepatitis C/ or Hepacivirus/
2 ("hepatitis c" or HCV or "hep c" or hepacivirus).ti,ab.
3 Human immunodeficiency virus/
4 (HIV or "Human Immunodeficiency Virus").ti,ab.
5 high risk behavior/ or risk reduction/ or needle sharing/

6 ((injecting or injection) adj (risk or frequency)).ti,ab.
7 ((needle$ or syringe$ or equipment or paraphernalia) adj (shar$ or reus$ or borrow$)).ti,ab.

8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 injection drug user/ or intravenous drug abuse/
10 ("people who inject" or "person who injects" or PWID or "injection drug user" or "injecting drug user" or "intravenous drug user" or IDU or IDUs or IVDU or IVDUs).ti,ab.
11 amphetamine/ or cocaine/ or street drug/ or opiate/ or heroin/
12 (amphetamine or cocaine or stimulant or opiate or opioid or heroin or synthetic).ti,ab.

13 (substance$ or drug$).ti,ab.
14 (inject$ or intravenous).ti,ab.
15 9 or 10 or (11 and 14) or (12 and 14) or (13 and 14)
16 harm reduction/
17 (((needle$ or syringe$ or equipment) adj (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)) or foil).ti,ab.
18 ((outreach or peer) adj (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)).ti,ab.
19 16 or 17 or 18
20 opiate substitution treatment/ or drug dependence treatment/ or narcotic antagonist/

21 (methadone or buprenorphine or suboxone or naltrexone or Subutex or OST).ti,ab.

22 (((opiate or opioid or agonist or antagonist) adj (substitut$ or replac$ or maint$ or treatment or therapy or implant or slow-release or "slow release" or extended-release or "extended release")) or (stimulant adj3 (treatment or therapy))).ti,ab.
23 ((heroin or hydromorphone or diacetylmorphine or dilaudid or diamorphine) adj (assisted or treatment or maintenance)).ti,ab.
24 20 or 21 or 22 or 23
25 cognitive therapy/ or behavior therapy/ or counselling/
26 (counseling or counselling or "behaviour$ therapy" or "behavior$ therapy" or psycho-social or psychosocial or "contingency management" or incentiv$ or monetary or reward).ti,ab.

27 25 or 26
28 ("drug consumption" adj2 (room or site or space or facilit$)).ti,ab.
29 (safe$ inject$ adj2 (room or site or space or facilit$)).ti,ab.
30 (supervised inject$ adj2 (room or site or space or facilit$)).ti,ab.
31 overdose prevention site$.ti,ab.
32 28 or 29 or 30 or 31
33 19 or 24 or 27 or 32
34 8 and 15 and 33
35 34
36 limit 35 to yr="2011 -Current"

PsycINFO (via OVID)
1 Hepatitis/
2 ("Hepatitis C" or HCV or "Hep C" or hepacivirus).ti,ab.
3 HIV/
4 (HIV or "Human Immunodeficiency Virus").ti,ab.
5 Risk Taking/ or Risk Factors/ or Needle Sharing/
6 ((injecting or injection) adj (risk or frequency)).ti,ab.
7 ((needle$ or syringe$ or equipment or paraphernalia) adj (shar$ or reus$ or borrow$)).ti,ab.

8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 Intravenous Drug Usage/
10 ("people who inject" or "person who injects" or PWID or "injecting drug user" or "injection drug user" or "intravenous drug user" or IDU or IDUs or IVDU or IVDUs).ti,ab.
11 Amphetamine/ or Opiates/ or Methamphetamine/ or Cocaine/ or Crack Cocaine/ or Heroin/

12 (amphetamine or cocaine or stimulant or opiate or opioid or heroin or synthetic).ti,ab.

13 (substance$ or drug$).ti,ab.

14 (inject$ or intravenous).ti,ab.
15 9 or 10 or (11 and 14) or (12 and 14) or (13 and 14)
16 Harm Reduction/ or Prevention/ or Needle Exchange Programs/
17 (((needle$ or syringe$ or equipment) adj (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)) or foil).ti,ab.
18 ((outreach or peer) adj (exchange or suppl$ or program$ or service or facilit$ or distribut$ or dispens$ or provision or provider)).ti,ab.
19 16 or 17 or 18
20 exp Methadone/ or exp Methadone Maintenance/ or exp Buprenorphine/ or exp Naltrexone/ or exp Narcotic Antagonists/ or exp Narcotic Agonists/
21 (methadone or buprenorphine or suboxone or naltrexone or Subutex or OST).ti,ab.

22 (((opiate or opioid or agonist or antagonist) adj (substitut$ or replac$ or maint$ or treatment or therapy or implant or slow-release or "slow release" or extended-release or "extended release")) or (stimulant adj3 (treatment or therapy))).ti,ab.
23 ((heroin or hydromorphone or diacetylmorphine or dilaudid or diamorphine) adj (assisted or treatment or maintenance)).ti,ab.
24 20 or 21 or 22 or 23
25 Behavior Therapy/ or Cognitive Behavior Therapy/ or Cognitive Therapy/ or Counseling/ or Contingency Management/
26 (counseling or counselling or "behaviour$ therapy" or "behavior$ therapy" or psycho-social or psychosocial or "contingency management" or incentiv$ or monetary or reward).ti,ab.

27 25 or 26
28 ("drug consumption" adj2 (room or site or space or facilit$)).ti,ab.
29 (safe$ inject$ adj2 (room or site or space or facilit$)).ti,ab.
30 (supervised inject$ adj2 (room or site or space or facilit$)).ti,ab.
31 "overdose prevention site$".ti,ab.
32 28 or 29 or 30 or 31
33 19 or 24 or 27 or 32
34 8 and 15 and 33
35 limit 34 to yr="2011 -Current"

CINAHL (via EBSCO)
S1 MH Hepatitis C OR MH Hepatitis C, Chronic
S2 TI (“Hepatitis C” OR HCV OR “Hep C” OR hepacivirus) OR AB (“Hepatitis C” OR HCV OR “Hep C” OR hepacivirus)
S3 MH Human Immunodeficiency Virus OR MH HIV Infections
S4 TI (HIV OR “Human Immunodeficiency Virus”) OR AB (HIV OR “Human Immunodeficiency Virus”)
S5 MH Risk Taking Behavior OR MH Needle Sharing
S6 TI ((injecting OR injection) N3 (risk OR frequency)) OR AB ((injecting OR injection) N3 (risk OR frequency))
S7 TI ((needle* or syringe* or equipment or paraphernalia) N3 (shar* or reus* or borrow*)) OR AB ((needle* or syringe* or equipment or paraphernalia) N3 (shar* or reus* or borrow*))
S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S9 MH Intravenous Drug Users OR MH Substance Abuse, Intravenous
S10 TI ("people who inject" or "person who injects" or PWID or "injecting drug user" or "injection drug user" or "intravenous drug user" or IDU or IDUs or IVDU or IVDUs) OR AB ("people who inject" or "person who injects" or PWID or "injecting drug user" or "injection drug user" or "intravenous drug user" or IDU or IDUs or IVDU or IVDUs)
S11 MH Crack Cocaine OR MH Cocaine OR MH Synthetic Drugs OR Amphetamine OR MH Amphetamines OR MH Street Drugs OR MH Heroin
S12 TI (amphetamine OR cocaine OR stimulant OR opiate OR opioid OR heroin OR synthetic) OR AB (amphetamine OR cocaine OR stimulant OR opiate OR opioid OR heroin OR synthetic)
S13 TI (substance* OR drug*) OR AB (substance* OR drug*)
S14 TI (inject* or intravenous) OR AB (inject* or intravenous)
S15 S9 OR S10 OR (S11 AND S14) OR (S12 AND S14) OR (S13 AND S14)
S16 MH Needle Exchange Programs OR MH Preventive Health Care OR MH Community Health Services

S17 TI ((needle* OR syringe* OR equipment) N3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)) OR AB ((needle* OR syringe* OR equipment) N3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)) OR TI foil OR AB foil
S18 TI ((outreach or peer) N3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider)) OR AB ((outreach or peer) N3 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider))
S19 S16 OR S17 OR S18
S20 MH Buprenorphine OR MH Methadone OR MH Naltrexone OR MH Narcotic Antagonists OR MH Substance Use Rehabilitation Programs
S21 TI (methadone OR buprenorphine OR suboxone OR naltrexone OR subutex OR OST) OR AB (methadone OR buprenorphine OR suboxone OR naltrexone OR subutex OR OST)
S22 TI ((opiate OR opioid OR agonist OR antagonist) N2 (substitut* OR replac* OR maint* OR treatment OR therapy OR implant OR slow-release OR "slow release" OR extended-release OR "extended release")) OR AB ((opiate OR opioid OR agonist OR antagonist) N2 (substitut* OR replac* OR maint* OR treatment OR therapy OR implant OR slow-release OR "slow release" OR extended-release OR "extended release")) OR TI (stimulant adj3 (treatment or therapy)) OR AB (stimulant adj3 (treatment or therapy))
S23 TI ((heroin OR hydromorphone OR diacetylmorphine OR dilaudid OR diamorphine) N2 (assisted OR treatment OR maintenance)) OR AB ((heroin OR hydromorphone OR diacetylmorphine OR dilaudid OR diamorphine) N2 (assisted OR treatment OR maintenance))
S24 S20 OR S21 OR S22 OR S23
S25 MH Cognitive Therapy OR MH Behavior Therapy OR MH Counseling OR MH Support, Psychosocial OR MH Rehabilitation, Psychosocial OR MH Contingency Management
S26 TI (counselling OR counseling OR "behaviour* therapy" OR "behavior* therapy" OR psycho-social OR psychosocial OR “contingency management” OR incentiv* or monetary or reward) OR AB (counselling OR counseling OR "behaviour* therapy" OR "behavior* therapy" OR psycho-social OR psychosocial OR “contingency management” OR incentiv* or monetary or reward)
S27 S25 OR S26
S28 TI ("drug consumption" N2 (room or site or space or facilit*)) OR AB ("drug consumption" N2 (room or site or space or facilit*))
S29 TI (“safe* inject*” N2 (room or site or space or facilit*)) OR AB (“safe* inject*” N2 (room or site or space or facilit*))
S30 TI (“supervised inject*” N2 (room or site or space or facilit*)) OR AB (“supervised inject*” N2 (room or site or space or facilit*))
S31 TI "overdose prevention site*" OR AB "overdose prevention site*"
S32 S28 OR S29 OR S30 OR S31
S33 S19 OR S24 OR S27 OR S32
S34 S8 AND S15 AND S33
S35 S8 AND S15 AND S33

Web of Science

27 #25 AND #10 AND #5
Refined by: PUBLICATION YEARS: (2020 OR 2011 OR 2019 OR 2018 OR 2017 OR 2016 OR 2015 OR 2014 OR 2013 OR 2012)
26 #25 AND #10 AND #5
25 #24 OR #19 OR #18 OR #14
24 #23 OR #22 OR #21 OR #20
23 TOPIC: (“overdose prevention site*”)
22 TOPIC: ((supervised inject*) NEAR/2 (room or site or space or facilit*))
21 TOPIC: ((safe* inject*) NEAR/2 (room or site or space or facilit*))
20 TOPIC: ("drug consumption" NEAR/2 (room or site or space or facilit*))
19 TOPIC: (counselling OR counseling OR "behaviour* therapy" OR "behavior* therapy" OR psycho-social OR psychosocial OR “contingency management” OR incentiv* or monetary or reward)
18 #17 OR #16 OR #15
17 TOPIC: ((heroin OR hydromorphone OR diacetylmorphine OR dilaudid OR diamorphine) NEAR/2 (assisted OR treatment OR maintenance))

16 TS=(((opiate OR opioid OR agonist OR antagonist) NEAR/2 (substitut* OR replac* OR maint* OR treatment OR therapy OR implant OR slow-release OR "slow release" OR extended-release OR "extended release")) OR (stimulant adj3 (treatment or therapy)))
15 TOPIC: ((methadone OR buprenorphine OR suboxone OR naltrexone OR subutex OR OST))
14 #13 OR #12 OR #11
13 TS=((outreach or peer) NEAR/1 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider))
12 TS=((needle* OR syringe* OR equipment) NEAR/1 (exchange OR suppl* OR program* OR service OR facility OR distribut* OR dispens* or provision or provider))
11 TS=(harm NEAR/1 reduc*)
10 #6 OR (#7 AND #9) OR (#8 AND #9)
9 TOPIC: (inject* OR intravenous)
8 TOPIC: (substance* or drug*)
7 TS=(amphetamine OR cocaine OR stimulant OR opiate OR opioid OR heroin OR synthetic opioid or synthetic heroin)
6 TS=("people who inject" or "person who injects" or PWID or "injection drug user" or "injecting drug user" or "intravenous drug user" or IDU or IDUs or IVDU or IVDUs)
5 #4 OR #3 OR #2 OR #1
4 TOPIC: ((needle* OR syringe* OR equipment or paraphernalia) NEAR/3 (shar* OR reus* OR borrow*))
3 TOPIC: ((injecting or injection) NEAR/3 (risk or frequency))
2 TOPIC: (HCV OR “Hepatitis C” OR “Hep C” OR hepacivirus)
1 TOPIC: ((HIV OR "Human Immunodeficiency Virus"))

Cochrane Library (trials only)

#1 (HCV):ti,ab OR ("Hepatitis C"):ti,ab OR ("Hep C"):ti,ab
#2 (HIV):ti,ab OR ("Human Immunodeficiency Virus"):ti,ab
#3 ("injecting risk");ti,ab OR ("injection risk");ti,ab OR ("injecting frequency");ti,ab OR ("injection frequency");ti,ab OR ("*needle* shar*");ti,ab OR ("*needle* borrow*");ti,ab OR ("*needle* reus*");ti,ab OR ("*syringe shar*");ti,ab OR ("*syringe borrow*");ti,ab OR ("*syringe reus*");ti,ab OR ("paraphernalia shar*");ti,ab OR ("paraphernalia borrow*");ti,ab OR ("paraphernalia reus*");ti,ab OR ("equipment shar*");ti,ab OR ("equipment borrow*");ti,ab OR ("equipment reus*");ti,ab
#4 #1 OR #2 OR #3
#5 ("people who inject");ti,ab OR ("person who injects");ti,ab OR (PWID);ti,ab OR ("injection drug users");ti,ab OR ("injecting drug users");ti,ab OR ("intravenous drug users");ti,ab OR (IDU);ti,ab OR (IDUs);ti,ab OR (IVDU);ti,ab OR (IVDUs);ti,ab
#6 (amphetamine);ti,ab OR (cocaine);ti,ab OR (stimulant);ti,ab OR (opiate);ti,ab OR (opioid);ti,ab OR (heroin);ti,ab OR (synthetic);ti,ab
#7 (substance*);ti,ab OR (drug*);tiab
#8 (inject*);ti,ab OR (intravenous);ti,ab
#9 #5 OR (#6 AND #8) OR (#7 AND #8)
#10 (needle*);ti,ab OR (syringe*);ti,ab OR (outreach);ti,ab OR (peer);ti,ab OR ("harm reduction");ti,ab OR (foil);ti,ab
#11 (methadone);ti,ab OR (buprenorphine);ti,ab OR (suboxone);ti,ab OR (naltrexone);ti,ab OR (Subutex);ti,ab OR (OST);ti,ab
#12 (opiate);ti,ab OR (opioid);ti,ab OR (agonist);ti,ab OR (antagonist);ti,ab or (stimulant);ti,ab
#13 (substitut*);ti,ab OR (replac*);ti,ab OR (maint*);ti,ab OR (treatment);ti,ab OR (therapy);ti,ab OR (implant);ti,ab OR (slow-release);ti,ab OR ("slow release");ti,ab OR (extended-release);ti,ab OR ("extended release");ti,ab
#14 (heroin);ti,ab OR (hydromorphone);ti,ab OR (diacetylmorphine);ti,ab OR (dilaudid);ti,ab or (diamorphine);ti,ab
#15 (assisted);ti,ab OR (treatment);ti,ab OR (maintenance);ti,ab
#16 #11 OR (#12 AND #13) OR (#14 AND #15)
#17 (counseling);ti,ab OR (counselling);ti,ab OR ("behaviour* therapy");ti,ab OR ("behavior* therapy");ti,ab OR (psycho-social);ti,ab OR (psychosocial);ti,ab or ("contingency management");ti,ab OR (incentiv*)ti,ab OR (monetary);ti,ab OR (reward);ti,ab
#18 ("drug consumption");ti,ab OR ("safe* inject*");ti,ab OR ("supervised inject*");ti,ab
#19 (room*);ti,ab OR (site*);ti,ab OR (space);ti,ab OR (facility*);ti,ab
#20 ("overdose prevention site*");ti,ab
#21 (#18 AND #19) OR #20
#22 #10 OR #16 OR #17 OR #21

#23 #4 AND #9 AND #22

Appendix 3. Original and adapted AMSTAR 2 tool

Differences between the two sets of tools are highlighted in red font. Rows highlighted in orange indicate 'critical' domains.

AMSTAR 2		Adapted AMSTAR 2	
1. Did the research questions and inclusion criteria for the review include the components of PICO?	For Yes, a study has to have indicated the: -population -intervention -comparator group -outcome	1. Did the research questions and inclusion criteria for the review include the components of PICO?	For Yes, a study has to have indicated the: -population -intervention -outcome
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	**For Partial Yes:** The authors state that they had a written protocol or guide that included ALL of the following: -review question(s) -a search strategy -inclusion/exclusion criteria -a risk of bias assessment **For Yes:** as for partial yes, the protocol should also be registered and have specified: - a meta-analysis/synthesis plan, if appropriate -a plan for investigating causes of heterogeneity -justification for any deviations from the protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review?	**For Partial Yes:** The authors state that they had a written protocol or guide that included, for example: -review question(s) -a search strategy -inclusion/exclusion criteria -a risk of bias assessment **For Yes:** as for partial yes, plus the protocol should be registered
3. Did the review authors explain their selection of the study designs for inclusion in the review?	For Yes, the review should satisfy one of the following: -an explanation for including only RCTs, -an explanation for including only NRSIs, or -an explanation for including both RCTs and NRSIs	3. Did the review authors explain their selection of the study designs for inclusion in the review?	For Yes, the review should satisfy one of the following: -an explanation for including only RCTs, -an explanation for including only NRSIs, or -an explanation for including both RCTs and NRSIs

AMSTAR 2		Adapted AMSTAR 2	
4. Did the review authors use a comprehensive literature search strategy?	**For Partial Yes** (all of the following): -searched at least two databases -provided key word and/or search strategy -justified publication restrictions (e.g. language) **For Yes**, should also have (all of the following): -searched the reference lists of included studies -searched trial/study registries -included/consulted content experts in the field -where relevant, searched for grey literature -conducted search within 24 months of completion of the review	4. Did the review authors use a comprehensive literature search strategy?	**For Partial Yes** (all of the following): -searched at least two databases -provided key word and/or search strategy **For Yes**, should also have (all of the following): -searched the reference lists of included studies -included/consulted content experts in the field -where relevant, searched for grey literature
5. Did the review authors perform study selection in duplicate?	For Yes, either one of the following: -at least two reviewers independently agreed on the selection of eligible studies and achieved consensus on which studies to include, or -two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 %), with the remainder selected by one reviewer	5. Did the review authors perform study selection in duplicate?	For Yes, -at least two reviewers independently agreed on the selection of eligible studies and achieved consensus on which studies to include
6. Did the review authors perform data extraction in duplicate?	For Yes, either one of the following: -at least two reviewers achieved consensus on which data to extract from included studies, or -two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 %), with the remainder extracted by one reviewer	6. Did the review authors perform data extraction in duplicate?	For Yes, -at least two reviewers achieved consensus on which data to extract from included studies
7. Did the review authors provide a list of excluded studies and justify the exclusions?	**For Partial Yes:** -provided a list of all potentially relevant studies that were read in full-text form but excluded from the review **For Yes**, must also have: -justified the exclusion from the review of each potentially relevant study	7. Did the review authors provide a flow diagram that gives details on the number of abstracts that were screened and excluded, the number of full texts that were screened and excluded and the final number of included studies?	For Yes, must have included a detailed flow diagram

AMSTAR 2		Adapted AMSTAR 2	
8. Did the review authors describe the included studies in adequate detail?	**For Partial Yes** (all of the following): -described populations -described interventions -described comparators -described outcomes -described research designs **For Yes,** should also have all of the following: -described population in detail -described intervention in detail (including doses where relevant) -described comparator in detail (including doses where relevant) -described the study setting -stated timeframe for follow-up	8. Did the review authors describe the included studies in adequate detail?	**For Partial Yes** (all of the following): -described populations -described interventions -described comparators (if applicable) -described outcomes -described research designs **For Yes,** should also have all of the following: -stated the study sample size -described the study setting -stated timeframe for follow-up (if applicable)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	**RCTs** **For Partial Yes**, must have assessed RoB from: -unconcealed allocation, and -lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) **For Yes**, must also have assessed RoB from: -allocation sequence that was not truly random, and -selection of the reported result from among multiple measurements or analyses of a specified outcome **NRSIs** **For Partial Yes**, must have assessed RoB from: -confounding, and -selection bias **For Yes**, must also have assessed RoB from: -methods used to ascertain exposures and outcomes, and -selection of the reported result from among multiple measurements or analyses of a specified outcome	9. Did the review authors use a satisfactory technique or tool for assessing study quality or risk of bias (RoB) in individual studies that were included in the review?	For Yes, must have indicated the use of a known tool for assessing RoB

AMSTAR 2		Adapted AMSTAR 2	
10. Did the review authors report on the sources of funding for the studies included in the review?	For Yes: -must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	10. Did the review authors report on the sources of funding for the studies included in the review?	For Yes: -must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies
11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?	**RCTs** **For Yes:** -the authors justified combining the data in a meta-analysis, -used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present, and -investigated the causes of any heterogeneity **NRSIs** **For Yes:** -the authors justified combining the data in a meta-analysis, -used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present, -statistically combined effect estimates from NRSIs that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not applicable, and -reported separate summary estimates for RCTs and NRSIs when both were included in the review	11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results from the RCTs?	**RCTs** **For Yes:** -the authors used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present, and -investigated the causes of any heterogeneity **NRSIs** **For Yes:** -the authors used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present, -statistically combined effect estimates from NRSIs that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not applicable, and -reported separate summary estimates for RCTs and NRSIs when both were included in the review
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	For Yes: -included only low-RoB RCTs -or, if the pooled estimate was based on RCTs and/or NRSIs at variable RoB, the authors performed analyses to investigate the possible impact of RoB on summary estimates of effect	12. If meta-analysis was performed, did the review authors assess the potential impact of study quality/RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	For Yes: -included only low-RoB RCTs -or, if the pooled estimate was based on RCTs and/or NRSIs at variable quality/RoB, the authors performed analyses to investigate the possible impact of quality/RoB on summary estimates of effect

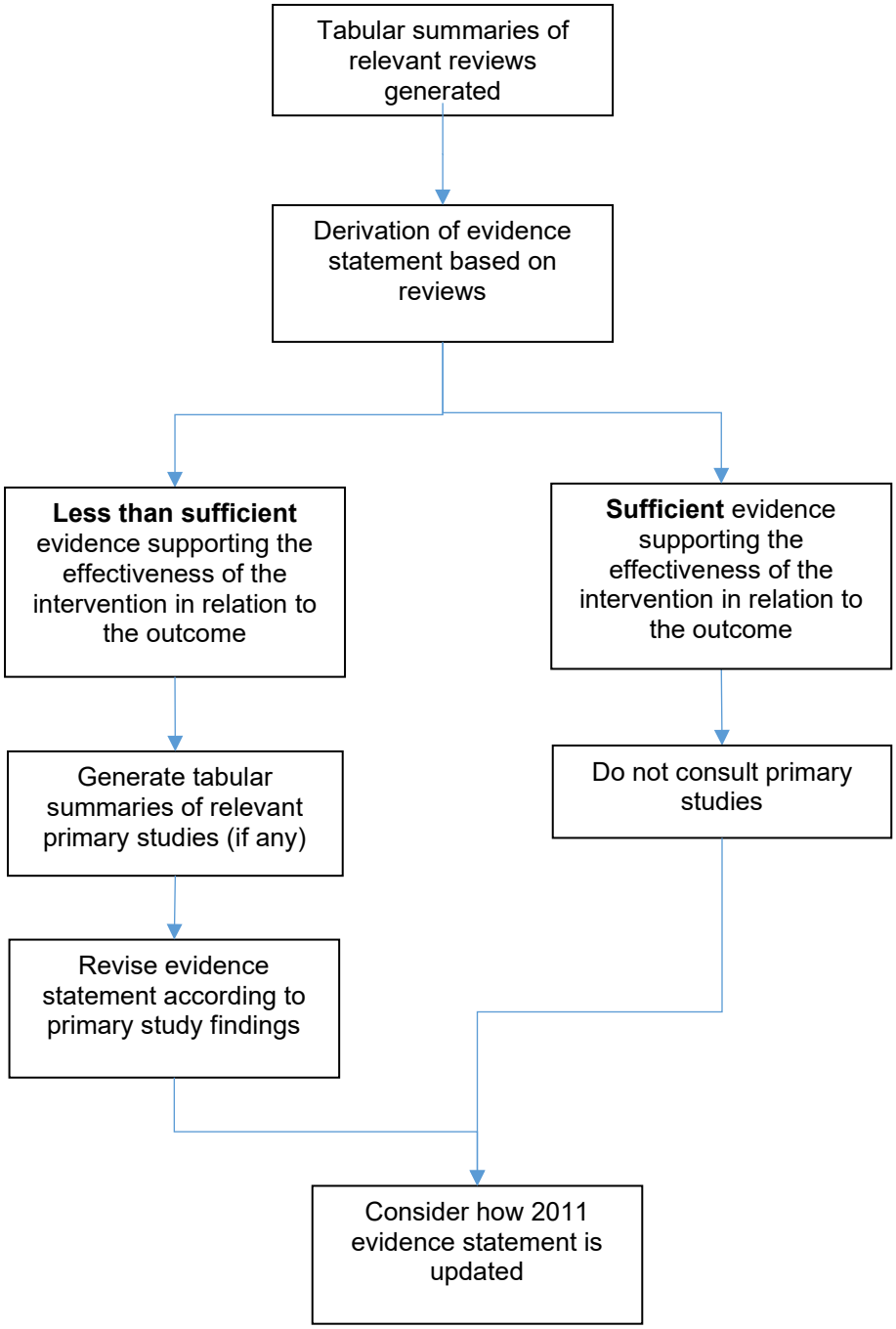
AMSTAR 2		Adapted AMSTAR 2	
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	For Yes: -included only low-RoB RCTs -or, if the RCTs had moderate or high RoB or NRSIs were included, the review provided a discussion of the likely impact of RoB on the results	13. Did the review authors account for quality/RoB in individual studies when interpreting/discussing the results of the review?	For Yes: -included only low-RoB/high-quality RCTs -or, if the RCTs had moderate or high RoB/low quality or NRSIs were included, the review provided a discussion of the likely impact of study quality/RoB on the results
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	For Yes: -there was no significant heterogeneity in the results -or, if heterogeneity was present, the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	For Yes: -there was no significant heterogeneity in the results -or, if heterogeneity was present, the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	For Yes: -performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of its impact of publication bias	15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	For Yes: -performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of its impact of publication bias, or -provided a justification for why they were not able to examine publication bias
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	For Yes: -the authors reported no competing interests, or -the authors described their funding sources and how they managed potential conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	For Yes: -the authors reported no competing interests, or -the authors described their funding sources and how they managed potential conflicts of interest

Abbreviations: NRSI, non-randomised study of intervention; RCT, randomised controlled trial; RoB, risk of bias.

Appendix 4. Summary of study designs used to assess the effectiveness of harm reduction interventions

	Randomised controlled trial	Cohort (with non-randomised control group)	Cohort (pre- vs. post-intervention comparison)	Case-control	Ecological	Serial cross-sectional	Cross-sectional
Type	Experimental	Observational					
Description	Researchers control which individuals are exposed to the intervention by random assignment. Individuals are then followed over time to see who develops the outcome of interest	Individuals with and without the exposure of interest (i.e. exposed vs. not exposed to a harm reduction intervention) are followed over time and compared to see if they develop the outcome	The outcome of interest is compared among a single group of individuals before and after (and sometimes during) the implementation of an intervention	Individuals who have the condition of interest (cases) are identified and their past exposure to the intervention is compared with that of patients who do not have the condition (controls)	The association is measured between exposure and outcome variables at the population or community level	The prevalence (or incidence) is measured of the exposure and outcome at multiple points in time in comparable samples drawn from the same population	The prevalence is measured of the exposure and outcome at one particular point in time
Weight of evidence	Strongest	Stronger	Stronger	Stronger	Weaker	Weaker	Weaker
Establishes temporal sequence between exposure and outcome	Yes	Yes	Yes	Yes	Usually	Yes	No

Appendix 5. Summary of the process for synthesising evidence and generating evidence statements



Appendix 6. Summary of reviews of opioid agonist treatment (OAT)

First author and year of publication	Dates covered	Outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence	Additional context
Hajarizadeh et al., 2020 (core review)	To June 2019	HCV reinfection following treatment	Total, 22: RCTs (9), cohort (13)	Total, 2 772; range, 11-909	Australia (1), Canada (5), Eastern Europe (1), multiple countries (2), United States (3), Western Europe (10)	Relative to studies with participants on OAT and with no injecting during follow-up (i.e. OAT yes/IDU no – the reference category), the OAT yes/IDU yes studies had higher reinfection rates (aRR 3.47, 95 % CI 1.65-7.32, p = 0.002), as did the OAT no/IDU yes studies (aRR 3.74, 95 % CI 1.77-7.89, p = 0.001)	Effect sizes are from a meta-regression of study-level factors associated with the HCV reinfection rate	'Our finding of significantly lower reinfection risk among people receiving OAT who did not use drugs, indicates the importance of enhancing access to OAT as a strategy to prevent reinfection'	The increased risk of reinfection in studies with participants on OAT but with recent injecting indicate that OAT dosing is important for HCV prevention

Platt et al., 2017 (core review)	To 16 November 2015	HCV incidence	Total, 12: cohort (10), cross-sectional (1), case-control (1). Mean, 440.5 person-years follow-up	Total, 6 361; range, 80-2 788	Australia (2), Canada (2), France (1), Italy (1), United Kingdom (3), United States (3)	Relative to no OAT, OAT was associated with a reduction in the risk of HCV infection (RR 0.50, 95 % CI 0.4-0.63, p < 0.001)	Random-effects meta-analysis of multivariable estimates presented by 12 of the primary studies was used to determine the RR of HCV infection	'OST is associated with a reduction in the risk of HCV acquisition, which is strengthened in studies that assess the combination of OST and NSP.'	With each 10 % increase in female participants in the sample, the effect of OAT was reduced; however, geographical region, main drug used and history of homelessness/imprisonment had no significant impact. Five of the studies included by Platt et al. had been included in the 2011 review of reviews

Abbreviations: aRR, adjusted risk ratio; HCV, hepatitis C virus; IDU, intravenous drug user; NSP, needle and syringe programme; OAT, opioid agonist treatment; OST, opioid substitution treatment; RCT, randomised controlled trial; RR, risk ratio.

Appendix 7. Summary of reviews and primary studies of opioid agonist treatment (OAT) – prison setting

Reviews

First author and year of publication	Dates covered	Outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Setting	Review statement of evidence	Additional context
ECDC, 2018 (core review)	From 1980 to 2017	HCV incidence	Hepatitis C virus				Prison setting	'The evidence on the effectiveness of [...] OST [...] in prison settings is limited...Existing UN-system guidelines recommend the implementation of OST [...] in prison settings.'	In the 4-year follow-up analysis, individuals incarcerated < 2 months and those on OAT < 5 months had a significantly increased risk of HCV seroconversion
			Total, two: RCT (one), case-control (one)	Total, 471; range, 218-253	Australia (2)	Four-month follow-up RCT: 12.5 % of OAT participants seroconverted vs. 11.4 % of controls (p = NS). Four-year follow-up case-control study: results also NS			
			HIV						
			Total, two (same as the above studies)	Total, 471; range, 218-253	Australia (2)	No difference in HIV seroconversion between the OAT and control group after 4 months in the RCT. The other study documented only two seroconversions (incidence rate of 0.28 per 100 person-years)			
Hedrich et al., 2012		HCV incidence,	Hepatitis C virus				Prison setting	'OMT was associated significantly with	The 4-year follow-up of the RCT

(core review)	To January 2011	HIV incidence, injecting risk behaviour, injecting drug use	Total, three: RCT (one), case-control (two)	Total, 959; range, 218-488	Australia (3)	Four-month follow-up RCT: 12.5 % of OAT participants seroconverted vs. 11.4 % of controls (p = NS). Four-year follow-up case-control study: results also NS. Case-control with 12 months follow-up: OR for OAT at enrolment vs. not = 3.1 (p < 0.001)		reduced heroin use, injecting and syringe-sharing in prison if doses were adequate.....There was insufficient evidence concerning HIV/HCV incidence...Disruption of OMT continuity, especially due to brief periods of imprisonment, was associated with very significant increases in HCV incidence.'	showed that longer, uninterrupted periods of OMT were associated with reduced risk of HCV seroconversion. One of the possible explanations for the OR of 3.1: differences in the continuity of OMT treatment – most incident cases among subjects not continuously in prison
			HIV							
			Total, two : RCT (one), case-control (one)	Total, 471; range, 218-253	Australia (2)	There were insufficient HIV seroconversions to draw any conclusions in either study (zero in the RCT and two in the case-control)				
			Injecting risk behaviour							
			Total, five: RCTs (two), cohort (one), serial cross-sectional (one), cross-sectional (one)	Total, 948; range, 120-253	Australia (2), Iran (2), Spain (1)	All studies reported significant reductions in sharing injection equipment associated with OAT. In particular, the two RCTs both found reductions in N/S sharing between baseline and follow-up from 24 % to 8 % (p < 0.05) and 53 % to 20 % (p < 0.001) in the treated group. In both, N/S sharing increased in the control group				
			Injection frequency							

			Total, five: RCTs (2), cohort (one), serial cross-sectional (one), cross-sectional (one)	Total, 900; range, 120-253	Australia (2), Iran (2), Spain (1)	All studies reported significant reductions in injection drug use associated with OAT. In particular, the two RCTs both demonstrated reductions in injecting between baseline and follow-up from 47 % to 11 % ($p < 0.0004$) and 64 % to 34 % ($p < 0.001$) in the treated group. In both of these RCTs, injection frequency increased in the control group			

Abbreviations: HCV, hepatitis C virus; N/S, needle/syringe; NS, not significant; NSP, needle and syringe programme; OAT, opioid agonist treatment; OMT, opioid maintenance treatment; OR, odds ratio; OST, opioid substitution treatment; RCT, randomised controlled trial.

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Finding	Results	Notes
Cunningham et al., 2017	Australia	Cohort	2005-2014	197 (433 person-years follow-up); 99 of whom were continuously imprisoned (221 person-years follow-up)	Equivocal	Adjusted hazard ratios showed no significant association between being on current OAT (relative to not) and time to HCV seroconversion in (a) the entire cohort (aHR 1.27, 95 % CI 0.74-2.20, p = 0.386) and (b) those who were continuously imprisoned during follow-up (aHR 1.32, 95 % CI 0.43-4.10, p = 0.627)	Prison setting

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, hepatitis C virus; OAT, opioid agonist treatment.

Appendix 8. Summary of reviews of opioid antagonist treatment (naltrexone)

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence	Additional context
Korownyk et al., 2019 (core review)	Up to June 2018 but generally limited to past 5 to 10 years	Intervention: naltrexone. Outcome: abstinence from opioids confirmed via urine screen	Total, three: all RCTs	Total, 451; range, 34-306	Russia (1), United States (2)	Pooled risk ratio for confirmed abstinence on naltrexone (oral or injectable extended-release) vs. placebo or usual care = 1.48 (95 % CI 1.11-1.98)	Population is individuals with OUD. Review does not specify that participants are PWID. Studies completed within a prison setting were excluded	'Low quality evidence suggests that the use of injectable naltrexone in the management of opioid use disorder results in a statistically significant benefit vs. placebo or usual care for...abstinence...The largest barrier is the need for patients to undergo detox prior to initiation...We suggest naltrexone could be considered for patients who have been opioid free for at least 7-10 days who are unable or unwilling to use OAT.'	'Due to injectable naltrexone mostly contributing to the positive effect, the overall benefit for this treatment may not apply to the oral formulation. However, the test for subgroup differences did not show a significant difference between groups.'

Abbreviations: CI, confidence interval; OAT, opioid agonist treatment; OUD, opioid use disorder; PWID, people who inject drugs.

Appendix 9. Summary of reviews of opioid antagonist treatment (naltrexone) – prison/criminal justice settings

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence	Additional context
Bahji et al., 2019 (core review)	To July 2019	Intervention: naltrexone (NTX) or extended-release naltrexone (XR-NTX) (vs. placebo or other treatment). Outcomes, as determined by self-report and/or urine drug screen: (1) opioid abstinence, (2) opioid relapse, (3) heroin use	Total, 11: quasi-experimental (1), RCTs (10)	Total, 1 048: range, 15-308	United States (10), Norway (1)	Pooled RR for opioid relapse = 0.63 (95 % CI 0.53-0.76) (10 studies). Pooled RR for opioid abstinence = 1.38 (95 % CI 1.16-1.65) (9 studies). Pooled RR for heroin use = 0.89 (95 % CI 0.7-1.14) (7 studies)	Note: population is 'criminal justice-involved' individuals with OUD. Setting is therefore not always prison (e.g. parolees, probationers, offenders). There is no information on whether the outcomes were specifically through injection	'...naltrexone...improved opioid abstinence and reduced opioid relapses. There were differences in the effect sizes and statistical significance of some outcomes by naltrexone formulation,...including opioid abstinence, which generally favour XR-NTX over oral naltrexone....Naltrexone use—either oral or XR-NTX—was not significantly associated with reductions in the use of heroin'	Subgroup analysis showed a significant association with opioid abstinence among those on XR-NTX (pooled RR 1.41, 95 % CI 1.12-1.78; six studies) but not on oral NTX (pooled RR 1.38, 95 % CI 0.92-2.08; three studies)

Moore et al., 2019 (core review)	To December 2017	Intervention: XR-NTX. Outcomes (self-report): opioid use, injecting drug use	Total, three: quasi-experimental (one), RCTs (two) [same studies identified in Bahji et al. (2009)]	Total, 173; range, 34-93	Norway (1), United States (2)	Opioid use: the quasi-RCT and one RCT found no difference in self-reported opioid use post-release between those given NTX implants/injections in prison and those on methadone/placebo. The other RCT found that those who received XR-NTX injection in prison were less likely to use opioids at 1 and 3 months post-release compared to controls (OR 0.08, 95 % CI 0.01-0.48). Injecting drug use: the latter RCT found no significant differences at 1 month post-release between XR-NTX group and controls	Prison setting	'...naltrexone.... [was] as effective as methadone in reducing illicit opioid use post-release...There was no evidence that...naltrexone reduced...health risk behaviours [i.e. injecting drug use], partly due to methodological quality of the studies examined....'	There were too few studies of naltrexone to conduct meta-analyses. The intervention and control groups for the three studies were as follows: (1) XR-NTX implants vs. methadone, (2) XR-NTX injections + TAU (counselling, 12-step) vs. placebo + TAU, (3) XR-NTX injection + motivational enhancement vs. TAU (motivational enhancement + referral to community treatment)

Abbreviations: CI, confidence interval; NTX, naltrexone; OR, odds ratio; OUD, opioid use disorder; RCT, randomised controlled trial; RR, risk ratio; TAU, treatment as usual; XR-NTX, extended-release naltrexone.

Appendix 10. Summary of reviews and primary studies of psychosocial interventions for drug dependence: information, education, counselling and/or skills training (IECS)

Reviews

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence
Gilchrist et al., 2017b (core)	2000 to 2016	Intervention: IECS. Outcomes: any IRB, including sharing needles/syringes or other injecting paraphernalia (reported separately or aggregated), and injection frequency	31 in total, all RCTs	Total, 12 480; range. 40-1 123	Australia (1), Canada (2), Georgia (1), Kazakhstan (1), Mexico (1), Puerto Rico (1), Russia (3), United Kingdom (1), United States (18), Vietnam (2)	All SMDs compare psychosocial vs. control. For any IRB outcome: SMD −0.29, 95 % CI −0.42 to −0.15, p < 0.01 (22 studies). For sharing needles/syringes: SMD −0.43, 95 % CI −0.69 to −0.18, p < 0.01 (13 studies). For sharing paraphernalia: SMD −0.21, 95 % CI −0.34 to −0.09, p < 0.01 (7 studies). For injection frequency, SMD −0.17, 95 % CI −0.35 to 0.00, p = 0.05 (8 studies)	Not specified whether interventions targeted opioid- or stimulant-dependent patients. Not all of the studies were meta-analysed as a result of heterogeneity in interventions or outcomes. Many of the control groups received interventions of lesser time or intensity	'Overall, psychosocial interventions reduced some of the target injecting (sharing of needle and syringes and other injecting paraphernalia)....outcomes among PWID when compared with control conditions…..The findings highlight the difficulty and complexity involved in attempting to examine the effectiveness of interventions that include different content and functions, modes of delivery, dosage and number of sessions….Our findings suggest that psychosocial interventions could boost the impact of current harm reduction interventions'
Sacks-Davis et al., 2012 (core)		Intervention: IECS.	Hepatitis C virus					

	To October 2010	Outcomes: HCV incidence, frequency of injecting, needle sharing or sharing of other injecting equipment (studies used different measures of IRB)	Total, three: all RCTs	Total, 1 041; range, 78-854	United Kingdom (1), United States (2)	No studies showed a difference in HCV incidence between intervention and control groups: RR 1.89 (no CIs or p-value provided but the result was NS); aRR 1.15 (95 % CI 0.72-1.82); and annual cumulative incidence of 7.2 % vs. 11.0 % in intervention vs. control (p = 0.539)	One intervention was a peer-educator training intervention; the other two interventions were counselling. Control groups received a lesser intensity of intervention (hand outs, video screenings or 10-min educational session)	'Due to the small number of trials identified, the small number of participants involved....it is difficult to assess whether such interventions are effective means of reducing HCV incidence in PWID. However, the studies that were identified suggest that at least in isolation, behavioural interventions are unlikely to have a considerable impact on rates of HCV transmission.'
			Injecting risk behaviour					
			Total, six: all RCTs	Total, 2 472; range, 109-851	Australia (1), United Kingdom (1), United States (4)	Out of three studies examining injection frequency: two were positive and one was equivocal. Out of six studies examining IRB: two were positive and four were equivocal	Five of the six included studies were already captured in the Gilchrist review	'There is a tendency towards larger trials (n>400) observing significant reductions in self-reported injecting risk behaviours in the intervention group compared to the control group, and smaller trials (n<150) observing significant reductions in self-reported risk behaviours in both the intervention and control groups over time.'
WHO, 2012/ Walsh et al., 2014 (supplementary)	Unclear but possibly to February 2011	Intervention: IECS, 'peer education and mentoring'. Outcomes: HCV incidence, needle sharing	Hepatitis C virus					
			Total, two: both RCTs	Total: 372; range, 95-277	United Kingdom (1), United States (1)	For IECS: combined RR of two RCTs examining psychosocial interventions for the prevention of HCV = 0.75 (95 % CI 0.33-1.71)	Both studies were included in the Sacks-Davis review	N/A (supplementary review)

			Injecting risk behaviour					
			Total, four: all RCTs. By intervention: IECS – two; peer education and mentoring – two	IECS: total, 1 111; range, 260-851 Peer education and mentoring: total, 1 272; range, 418-854	Canada (1), United States (3)	For IECS: RR 0.75 (95 % CI 0.33-1.71). For peer education and mentoring: RR 0.61 (95 % CI 0.48-0.85)	All of the studies were captured in other reviews	N/A (supplementary review)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; HCV, hepatitis C virus; IECS, information, education, counselling and/or skills training; IRB, injecting risk behaviour; N/A, not applicable; NTX, naltrexone; PWID, people who inject drugs; RCT, randomised controlled trial; RR, risk ratio; SMD, standardised mean difference; XR-NTX, extended-release naltrexone.

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Study population	Intervention detail	Outcome detail	Finding	Results	Notes
Hepatitis C virus studies										
Islam et al., 2017	Canada	Cohort	1992-2013	5 915 (1 604 PWID)	HCV-positive individuals who cleared their primary infection spontaneously or achieved SVR after treatment	At least one mental health counselling visit between date of HCV clearance and last day of follow-up	Incidence of HCV reinfection	Positive	Adjusted HR comparing mental health counselling vs. none = 0.71 (95 % CI 0.54-0.92, p = 0.011)	
HIV studies										

Booth et al., 2016	Ukraine	RCT	2010-2013	1 200 (1 085 with follow-up data)	Index participants (peer educators) who were HIV negative and injected drugs in the past 30 days and network members of index participants (exact criteria unclear)	Five training sessions delivered in small groups over a 2-week period designed to motivate peer leaders to become educators within their injection network and provide them with skills training in how to teach HIV risk reduction behaviours to network members	HIV incidence	Positive	Adjusted HR 0.53 (95 % CI 0.38-0.75, p = 0.0003) comparing network intervention vs. no further intervention after counselling	
Go et al., 2015	Vietnam	RCT	2009-2013	455 indices; 355 network members	Male HIV-infected 'index' PWID and their HIV negative injecting network members (network members had injected with index in last 6 months)	Two-stage randomisation: first, subdistricts were randomised to either a community video screening and house-to-house visits or standard-of-care educational pamphlets. Second, within each subdistrict, participants were randomised to receive either enhanced individual level post-test counselling and group support sessions or standard-of-care HIV testing and counselling. This resulted in four arms (see Notes)	HIV incidence	Equivocal	HIV incidence rates were 10/1 000 person-years (Arm 1), 5/1 000 person-years (Arm 2), 18/1 000 person-years (Arm 3) and 0/1 000 person-years (Arm 4). No significant difference in seroconversions between intervention and control arms over 24 months (Cox-regression p-value = 0.261)	Arm 1, control; Arm 2, community intervention only; Arm 3, individual intervention only; Arm 4, combined intervention

Hammett et al., 2012	Vietnam and China	Serial cross-sectional study	2002-2011	5 695	At least 18 years of age and injected heroin in the past 6 months	Intervention ('peer outreach') comprised peer educators regularly contacting other PWID in community, providing them with information on reducing drug use- and sex-related HIV risks, verbally and through distribution of brochures. They also distributed new N/S, sterile water for injection, and condoms and vouchers redeemable for these items at participating pharmacies. The peer educators also collected and disposed of used N/S	HIV prevalence	Positive	HIV prevalence decreased from 17 % to 11 % ($p = 0.003$) in Ning Ming, from 46 % to 23 % ($p < 0.001$) in Lang Son and from 51 % to 18 % ($p < 0.001$) in Ha Giang. In the comparison provinces in Northern Vietnam, the overall estimated change was a reduction of 1.2 % with a standard error of 2.44 %, which is statistically indistinguishable from no change	Comparisons were between baseline (2002/2003; when the Cross Border HIV Prevention Project was set up) and up to 8 years post-baseline at 6-month intervals initially (then, 12-month). Also compared trends over the same time periods in 'comparison provinces' where these interventions were not implemented

Miller et al., 2018	Ukraine, Vietnam and Indonesia	RCT	2015-2018	502 indices; 806 network members	HIV-infected injecting drug users and their uninfected injecting network members	Intervention was a minimum of two counselling sessions for index participants focusing on ART and adherence and MAT. Booster sessions were offered about 1 and 3 months post-enrolment. Intervention for network members comprised a standardised harm reduction package with referral for MAT (which the control group also received). Those in the intervention group did not directly receive any counselling but were the network members of index participants in the intervention group	HIV incidence	Equivocal	No injection partners in the intervention group acquired HIV infection (0 per 100 person-years, 95 % CI 0.0-1.7) vs. 7 in the control group (1.0 cases per 100 person-years, 95 % CI 0.4-2.1), for an incidence difference of 1.0 cases per 100 person-years (95 % CI −2.1 to 1.1)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; MAT, medication-assisted treatment; N/S, needle/syringe; RCT, randomised controlled trial; SVR, sustained virological response.

Appendix 11. Summary of reviews of psychosocial interventions for drug dependence: contingency management (CM)

Reviews

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence
EMCDDA, 2016a (core)	To September 2014	Intervention: CM. Outcomes: use of the main substance of abuse or another substance (based on self-reported data and urine analysis or other biochemical markers)	38 total: all RCTs. By substance: stimulant (i.e. cocaine or amphetamines)-dependent patients (4), stimulant- and opioid-dependent patients (14), opioid-dependent patients (20)	Stimulants: total, 676; range, 87-229. Stimulants and opioids: total, 1 604; range, 42-240. Opioids: total, 1 676; range, 20-320	Stimulants: United States (4). Stimulants and opioids: United States (14). Opioids: China (3), Malaysia (1), United States (15), not stated (1)	Stimulants: four total – two positive, one equivocal, one unclear. Stimulants and opioids: eight positive, four mixed positive/equivocal, two equivocal. Opioids: 5 positive, 14 equivocal, 1 unclear	Not restricted to PWID. 17 of the 38 studies identified were also included in the Korownyk review. The review also examined other outcomes (retention in treatment, cost-effectiveness outcomes, relapse prevention, participation in screening programmes for HIV, hepatitis B virus and HCV, mortality and overdose) that are not considered here. Note also that many of the interventions were delivered alongside pharmacological treatment (usually for opioid dependence)	'Although limited, the present analysis shows that contingency management is a feasible and promising adjunct to treatment interventions for drug users...Overall, the study results show that it can help keep people in treatment, and promote a reduction of opioid and cocaine problems in patients in OST.'

Korownyk et al., 2019 (core)	To June 2018 but generally limited to past 5 to 10 years	Intervention: CM. Outcomes: opioid use and stimulant use, usually measured via urine sample	All RCTs. No of studies by substance: CM for opioids (14), CM for stimulants (8), CM for both or not specified (12)	CM for opioids: total, 2 116; range, 16-388. CM for stimulants: total, 1 268; range, 57-388. CM for both or not specified: total, 921; range, 29-160	CM for opioids: China (3), United States (10), not stated (1). CM for stimulants: United States (8). CM for both or not specified: United States (10), not stated (2)	CM for opioids: 14 studies – 9 positive, 5 equivocal. CM for stimulants: 8 studies – 5 positive, 3 equivocal. CM for both or not specified: 12 studies – 5 positive, 6 equivocal, 1 negative	Not restricted to PWID. Note also that many of the interventions were delivered alongside pharmacological treatment for drug dependence	CM: 'Evidence for reductions in opioid use with CM in patients on OAT is heterogeneous and inconsistent… These results suggest that positive reinforcement strategies should be used whenever possible. We recommend against punitive measures involving OAT (i.e. reduction in dose or loss of carries [decreasing medication doses or revoking take home privileges for non-compliance]), unless safety is a concern.'

Abbreviations: CM, contingency management; HCV, hepatitis C virus; OAT, opioid agonist treatment; OST, opioid substitution treatment; PWID, people who inject drugs; RCT, randomised controlled trial.

Appendix 12. Summary of primary studies of psychosocial interventions for drug dependence: technology-based interventions

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Study population	Intervention detail	Outcome detail	Finding	Results
Calvo et al., 2020	Spain	Cohort	Not specified	105	PWID who had injected in the last year and possessed a smartphone	Eight-week group intervention designed to reduce the impact of the harm associated with injecting drug use via a mobile instant messaging service (WhatsApp). Participants were distributed across seven WhatsApp groups with the aim of facilitating discussion. The intervention featured a weekly thematic proposal based on some of the issues most relevant to reducing the risk of HIV infection. In the WhatsApp groups, participants interacted with each other or addressed professionals directly by asking questions, making suggestions, explaining experiences, clarifying doubts among themselves and interacting. Researchers intervened minimally in an attempt to have the group mediate in answering questions to enable peer support in discussion groups	RAB scores	Positive	Adjusted change in RAB scores from pre- to 1 month post-intervention: F = 4.57 (95 % CI 3.29-5.85, p < 0.001). Change in RAB score from immediately post-intervention to 1 month post-intervention: F = 0.76 (95 % CI −0.52 to 2.04, p = 0.241)

Abbreviations: CI, confidence interval; PWID, people who inject drugs; RAB, risk assessment battery.

Appendix 13. Summary of reviews of psychosocial interventions – prison setting

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Review statement of evidence
ECDC, 2018 (core)	From 1980 to 2017	Interventions: group health promotion and skills-building (IECS). Outcomes: 'risky drug use', 'risk reduction skills', sharing of drug injecting equipment	Two total: both RCTs	Total, 1 347: range, 90-1 257	United States (2)	One of the studies had positive results, as 'A greater improvement in the intervention group was found for all...measured outcomes' including avoiding risky drug use and risk reduction skills. The other had equivocal results: 'No significant differences for many...outcomes such as...the sharing of used drug injecting equipment...'	'Two RCTs investigated a combination of [group] health promotion and skills-building interventions and their impact on HIV knowledge and behaviour outcomes. They showed conflicting results.'

Abbreviations: IECS, information, education, counselling and/or skills training; RCT, randomised controlled trial.

Appendix 14. Summary of reviews and primary studies of sterile needle and syringe provision

Reviews*

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence	Additional context
Aspinall et al., 2014 (core)	1980-2012	Intervention: NSP (measures differ between studies). Outcome: HIV incidence	12 total: cross-sectional (1), cohort (10), case-control (1)	Total, 12 023; range, 226-2 505. Total, 11 984 person-years follow-up	United States (5), Canada (5), Holland (1), Sweden (1)	Pooled effect sizes = 0.66 (95 % CI 0.43-1.01) across all (12) studies and 0.42 (95 % CI 0.22-0.81) across six higher-quality studies	Of the 12 studies, 7 were included in the 2011 review of reviews	'There is evidence to support the effectiveness of NSP in reducing the transmission of HIV among PWID, although it is likely that other harm reduction interventions have also contributed to the reduction in HIV risk'	There was some evidence of publication bias; however, the use of a funnel plot where different types of outcomes measures have been calculated (OR, HR, RR) may have been misleading
Platt et al., 2017 (core)	To March 2017	Intervention: high NSP coverage (regular attendance at a NSP or all injections covered by a new needle/syringe) vs. low or no coverage. Outcome: HCV incidence	15 total: case-control (1), cohort (11), cross-sectional (3)	Total, 7 864; range, 46-2 788	Australia (2), Canada (3), Netherlands (1), United Kingdom (3), United States (6)	Pooled RR 0.79 (95 % CI 0.39-1.61) from five studies of those with high NSP coverage vs. no/low coverage. When restricted to Europe (two studies), high NSP coverage was associated with a 76 % reduction in	For 10 studies that examined low-level NSP coverage vs. no coverage, the pooled RR was 1.41 (95 % CI 0.95-2.09)	'There was greater heterogeneity between studies and weaker evidence for the impact of NSP on HCV acquisition. High NSP coverage was associated with a reduction in the risk of HCV acquisition in	The measure of heterogeneity among the five studies contributing to the pooled RR was I^2 = 77 %. Heterogeneity among the two European studies was 0 %. [Note: one of the five studies contributing to

						HCV acquisition risk (RR 0.24, 95 % CI 0.09-0.62)		studies in Europe.'	the RR formed part of the evidence base in the 2011 review of reviews]

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; NSP, needle and syringe programme; OR, odds ratio; RR, risk ratio.

*Note: two supplementary reviews (Abdul-Quader et al., 2013; Davis et al., 2017) were also identified but were not relied upon.

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Finding	Results	Notes
Hepatitis C virus studies							
Chen et al., 2018	China	Serial cross-sectional	2009-2015	101 032	Positive	HCV prevalence: 68.0 % in 2009 to 50.5 % in 2015 (p < 0.001)	Needle exchange service use in the last year increased from 52.0 % to 56.6 % (p < 0.001)
Handanagic et al., 2017	Croatia	Cross-sectional	2014-2015	654	Negative	Adjusted OR for ever used NSP vs. not = 3.9 (95 % CI 1.9-8.2, p < 0.001) in Rijeka sample of 255	Split sample size too small for equivalent analysis
Leyna et al., 2019	Tanzania	Cross-sectional	2017	611	Negative	Adjusted prevalence ratio for access to clean needles vs. not = 1.76 (95 % CI 1.44-12.74, p = 0.006)	N/A
Minoyan et al., 2020	Canada	Cohort	2010-2017	3 327	Equivocal	Adjusted HR for complete NSP coverage vs. incomplete NSP coverage = 1.2 (0.62-2.31)	

First author and year	Country	Study design	Date study carried out	Sample size	Finding	Results	Notes
Salek et al., 2017	United States	Cross-sectional	2012	130	Negative	Adjusted prevalence ratios vs. < 16.75 months exchanging: 16.75-39 months = 1.98 (95 % CI 1.23-3.48), 39-120 months = 2.18 (95 % CI 1.41-3.79), > 120 months exchanging = 2.72 (95 % CI 1.81-4.65) (p < 0.0001)	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; NSP, needle and syringe programme.

Appendix 15. Summary of reviews of sterile needle and syringe provision – prison setting

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size
ECDC, 2018	To January 2017	Intervention: NSP. Outcomes: HCV, HIV	Hepatitis C virus			
			Total, three: ecological (one), cohort (two)	Total, 405: range, 174-231; the ecological study did not report the sample size	Germany (2), Spain (1)	Cohort studies: 1) incidence rate = 18/100 person-years, possibly due to front-loading or spoon sharing; 2) no seroconversions after syringe vending machine installed. Ecological: HCV prevalence declined from 48.6 % in 1998 to 20 % in 2014 during a period of in-prison NSP expansion
			HIV			
			Total, three: ecological (one), cohort (two)	Total, 405: range, 174-231; the ecological study did not the report sample size	Germany (2), Spain (1)	Both cohort studies found no HIV seroconversions during the study period. Ecological: HIV prevalence in prisons decreased from 12.1 % in 2003 to 5.8 % in 2014 during a period of in-prison NSP expansion

Abbreviations: HCV, hepatitis C virus; NSP, needle and syringe programme.

Appendix 16. Summary of reviews of sterile needle and syringe provision – pharmacy setting

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size
Sawangjit et al., 2017	To January 2016	Intervention: NSP. Outcomes: HCV, HIV, syringe sharing	Hepatitis C virus			
			Six total: cross-sectional (five), cohort (one)	Total, 2 628; range, 128-1 020	Australia (3), Canada (1), Estonia (1), United States (1)	Pooled ORs: pharmacy NSP vs. no NSP = 0.26 (95 % CI 0.18-0.38, two studies) and pharmacy NSP vs. other NSP = 0.63 (95 % CI 0.27-1.45, four studies)
			HIV			
			Six total: cross-sectional (four), cohort (two)	Total, 2 273; range, 328-1 020	Australia (2), Canada (1), Estonia (1), United States (2)	Pooled ORs: pharmacy vs. no NSP = 0.56, (95 % CI 0.18-1.77, three studies) and pharmacy vs. other NSP = 0.55 (95 % CI 0.41-0.76, three studies)
			Injecting risk behaviour			
			11 total: cross-sectional (6), cohort (5)	Total: 5 455; range, 128-1 181	Australia (3), Canada (1), Estonia (1), United Kingdom, (1), United States (5)	Pooled ORs: pharmacy vs. no NSP = 0.50 (0.34-0.73, six studies) and pharmacy NSP vs. other NSP = 1.46 (95 % CI 0.78-2.73, seven studies)

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; NSP, needle and syringe programme; OR, odds ratio.

Appendix 17. Summary of reviews and studies of provision of low dead space syringes (LDSSs)

Reviews

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size
WHO, 2012/Walsh et al., 2014 (supplementary)	Unclear, possibly to February 2011	Intervention: LDSSs. Outcomes: HCV, HIV	Hepatitis C virus			
			Two total: both cross-sectional	Total, 1 366; range, 515-851	Hungary/Lithuania (1), United States (1)	Pooled analysis of the likelihood of being HCV infected having used LDSSs vs. high dead space syringes: RR 0.49 (0.44-0.55)
			HIV			
			Two total: both cross-sectional	Total, 1 366; range, 515-851	Hungary/Lithuania (1), United States (1)	Pooled analysis of the likelihood of being HIV infected having used LDSSs vs. high dead space syringes: RR 0.29 (95 % CI 0.18-0.46)

Abbreviations: HCV, hepatitis C virus; LDSS, low dead space syringe; RR, risk ratio.

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Finding	Results	Notes
Hepatitis C virus studies							
Trickey et al., 2018	United Kingdom	Cross-sectional	2014-2015	2 174	Positive	100 % LDSS use was associated with lower prevalent HCV among all PWID (aOR 0.77, 95 %CI 0.64-0.93) vs. those with 0-99 % LDSS use	The association between LDSS use and prevalent HCV was stronger among recent initiates (aOR 0.53, 95 % CI 0.30-0.94) than among experienced PWID (aOR 0.81, 95 % CI 0.66-0.99)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus; LDSS, low dead space syringe; PWID, people who inject drugs.

Appendix 18. Summary of primary studies of sterile drug preparation equipment provision

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Study population	Finding	Results	Notes
Hepatitis C virus studies								
Fatseas et al., 2012	France	Serial cross-sectional	1994-2004	648 (not all PWID)	Out-of-treatment opiate-dependent people seeking treatment (analyses related to participants who reported having injected drugs in previous 6 months)	Equivocal	Among injectors, HCV prevalence decreased from 81.3 % in 1994-1995 to 73.7 % in 1996-1999 to 71.1 % in 2000-2004 ($Z = -1.4$, $p = 0.1$)	1994-1995 is a pre-harm reduction period; 1996-1999 is when sterile syringe kits were made available that included syringes, water, swabs and condoms; 2000-2004 is when the sterile syringe kits additionally included sterile spoons and sterile cotton filters
HIV studies								
Fatseas et al., 2012	France	Serial cross-sectional	1994-2004	648 (not all PWID)	Out-of-treatment opiate-dependent people seeking treatment (analyses related to participants who reported having injected drugs in previous 6 months)	Positive	Among injectors, HIV prevalence decreased significantly from 43.2 % in 1994-1995 to 17.8 % in 1996-1999 to 12.4 % in 2000-2004 ($Z = -5.3$, $p < 0.0001$)	1994-1995 is a pre-harm reduction period; 1996-1999 is when sterile syringe kits were made available that included syringes, water, swabs and condoms; 2000-2004 is when the sterile syringe kits additionally included sterile spoons and sterile cotton filters
Injecting risk behaviour studies								

Aspinall et al., 2012	United Kingdom	Cross-sectional	2008-2009	2 037	Clients attending the participating injecting equipment provision services (for equipment and/or other harm reduction services) who had injected in previous 6 months	Positive (positive for obtaining ≥ 30 filters in average week, positive for any number of spoons obtained, positive for water)	Adjusted OR for sharing filters in relation to no of filters obtained in an average week in previous 6 months vs. none: 1-15 filters = 0.80 (95 % CI 0.59-1.08), 16-30 filters = 0.88 (95 % CI 0.64-1.23), more than 30 filters = 0.50 (95 % CI 0.32-0.79). Adjusted OR for sharing spoons in relation to no of spoons obtained in an average week in previous 6 months vs. none: 1-15 spoons = 0.61 (95 % CI 0.45-0.82), 16-30 spoons = 0.56 (95 % CI 0.39-0.79), more than 30 spoons = 0.46 (95 % CI 0.28-0.74). Adjusted OR for sharing water among those who collected sterile water in previous 6 months vs. not: yes = 0.36 (95 % CI 0.22-0.61)	All behaviours related to previous 6 months. Sharing filters was defined as having used a filter already used by someone else, sharing spoons was defined as having used a spoon already used by someone else and sharing water was defined as having used a water ampoule already used by someone else
Behrends et al., 2017	United States	Study 1: cohort. Study 2: cross-sectional	Study 1: 1995-1997. Study 2: 1999-2000	Study 1: 207. Study 2: 502	Active (untreated) PWID aged ≥ 18 years who reported any injection of heroin (alone or in combination with cocaine) during the previous 30 days	Positive	Study 1: 56 % of direct users of syringe exchange programmes, 62.1 % of indirect users and 67 % of non-users reported sharing filter/cooker/rinse water in last 30 days ($p < 0.05$). Study 2: 34.8 % of direct users, 75.3 % of indirect users and 75.8 % of non-users reported sharing filter/cooker/rinse water in last 30 days ($p < 0.01$)	
Fatseas et al., 2012	France	Serial cross-sectional	1994-2004	648 (not all PWID)	Out-of-treatment opiate-dependent people seeking treatment but analyses related to participants who reported having injected drugs in previous 6 months	Positive (higher odds of sharing all types of equipment in 1994-1995 vs. 2000-2004)	All adjusted ORs compared to baseline group (2000-2004). Sharing of water: 1994-1995 = OR 3.0 (95 % CI 1.6-5.6, $p < 0.001$); 1996-1999 = OR 1.4 (95 % CI 0.8-2.5, NS). Sharing of cotton wool: 1994-1995 = OR 4.0 (95 % CI 2.0-8.0, $p < 0.0001$); 1996-1999 = OR 1.7 (95 % CI 0.9-3.0, NS). Sharing of spoons: 1994-1995 = OR 4.5 (95 % CI 2.5-8.2, $p < 0.0001$); 1996-1999 = OR 2.4 (95 % CI 1.4-4.2, $p < 0.001$)	1994-1995 is a pre-harm reduction period; 1996-1999 is when sterile syringe kits were available that included syringes, water, swabs and condoms; 2000-2004 is when the sterile syringe kits also included sterile spoons and sterile cotton filters

Kim et al., 2015	United States	Serial cross-sectional	2005-2012	2005 = 565. 2009 = 535. 2012 = 570	18 years of age or older, reported injecting illicit drugs in the past 12 months. If not a seed subject, then given a referral coupon by another participant	Positive (for cookers and filters, equivocal for cottons)	Sharing cookers declined from 46.5 % (95 % CI 39.1-54.1) in 2005 to 37.9 % (95 % CI 31.8-44.1) in 2012 – chi-square test for trend p = 0.003. Sharing cottons declined from 2005 = 34.4 % (95 % CI 28.2-41.1) to 2012 = 30.2 % (95 % CI 24.3-36.4) – chi-square test for trend p = 0.124. Sharing water declined from 2005 = 38.3 % (95 % CI 31-46) to 2012 = 25.5 % (95 % CI 20.3-31.3) – chi-square test for trend p < 0.001	Over the study period, an increased proportion of PWID received their needles from pharmacies and NSPs and shifted away from buying needles from dealers and friends
Mehrabi et al., 2020	Iran	Cross-sectional	2017	606	Male, reported at least one drug injection in the past month, aged 18 years or over, lived in Kermanshah	Positive	Adjusted OR of paraphernalia sharing among those with regular attendance at NSPs vs. not = 0.4 (95 % CI 0.27-0.6, p < 0.001)	It is assumed that the NSP provided paraphernalia. Paraphernalia sharing not explicitly defined but possibly sharing of tourniquets, swabs, cookers and mixing water, as listed in the Introduction
Naserirad and Beulaygue, 2020	Iran	Cross-sectional	2018-2019	634	Alert at the time of the interview, proficient in Persian, aged 18 years or older, resided in the study area, injected drugs within the last 60 days (track marks verified)	Equivocal	All adjusted ORs compared to baseline group: high access to NSP (>67 %). Shared cookers: low access = OR 1.4 (95 % CI 0.99-1.82); middle access = OR 1.32 (95 % CI 0.92-1.73). Shared cotton: low access = OR 1.3 (95 % CI 0.79-1.81); middle access = OR 1.48 (95 % CI 1.05-1.91). Shared water: low access = OR 1.07 (95 % CI 0.89-1.26); middle access = OR 1.19 (95 % CI 0.9-1.48)	Sharing relates to last 2 months. The participants were stratified into subgroups according to their accessibility of NSP services during the last 2 months as low access (<34 %), middle access (34-67 %) and high access (>67 %)
Nazari et al., 2016/ Noroozi et al., 2018/ Rezaie et al., 2017 [different analyses of same study]	Iran	Cross-sectional	2014	455/ 500/ 500	Male, ≥ 18 years of age; drug injection within the last month	Equivocal when looking at type of NSP and 'ability to access NSP'; positive when looking at having used NSPs as main syringe source	Nazari: unadjusted ORs for sharing a cooker in the past month by type of NSP (vs. no NSP use): outreach NSP use = 0.94 (95 % CI 0.43-2.04); facility-based NSP use = 0.86 (95 % CI 0.42-1.75). Noroozi: unadjusted OR for sharing paraphernalia in the past 2 months among those with low NSP use vs. high NSP use = 3.24 (95 % CI 1.9-4.86). Rezaie: adjusted ORs for paraphernalia sharing by level of NSP access (vs. high NSP access): low = 2.5 (95 % CI	Nazari and Noroozi also generated adjusted ORs on a 'matched sample' using a Coarsened Exact Matching (CEM) approach but results were also equivocal. Noroozi: high NSP = having received 60 % or more of their syringes from a NSP in the previous 2 months. Rezaie: ability to access NSPs was calculated as the no of syringes received from NSPs to the total number of syringes obtained in the

							0.6-4.6, p = 0.3); medium = 1.8 (95 % CI 0.2-4.5, p = 0.6)	previous month and categorised as low (<40 %), medium (40-70 %) and high (>70 %)
Patel et al., 2018	United States	Cohort	2015	148	Individuals with at least two visits to the NSP, at least 7 days apart, between 4.4.2015 and 30.8.2015; must be 14 years or older to use service	Positive	Sharing other injection equipment (such as cookers, filters and water): 24 % at first visit to NSP vs. 5 % at most recent visit (19 % decrease, p < 0.001)	
Welch-Lazoritz et al., 2017	United States	Cross-sectional	Urban: 2012. Rural: 2015	Urban: 512. Rural: 315	Rural: 18 years of age or older; alert at the time of the interview; active injection drug user (injected drugs within the last 30 days). Urban: not stated	Equivocal	For received free works kits in past 12 months vs. did not: frequency of sharing a used cooker: beta = 0.063, p ≥ 0.1. frequency of sharing a used cotton: beta = 0.055, p ≥ 0.1	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; NSP, needle and syringe programme; OR, odds ratio; PWID, people who inject drugs.

Summary of effect sizes in studies reporting odds ratios

Injecting equipment item	**First author and year**	**Effect size (odds ratio)**	**Comparison**
Paraphernalia	Mehrabi et al., 2020	0.40 (0.27-0.60)	Regular attendance at NSP vs. not
	Noroozi et al., 2018	0.31 (0.21-0.53)	High NSP use vs. low NSP use
	Rezaie et al., 2017	0.40 (0.22-1.67)	High NSP access vs. low NSP access
Cookers	Aspinall et al., 2012	0.46 (0.28-0.74)	≥30 cookers vs. none
	Fatseas et al., 2012	0.22 (0.12-0.40)	2000-2004 vs. 1994-1995
	Naserirad and Beulaygue, 2020	0.71 (0.55-1.01)	High NSP access vs. low NSP access
	Nazari et al., 2016	0.86 (0.42-1.75)	Facility-based NSP use vs. no NSP use
Filters	Aspinall et al., 2012	0.50 (0.32-0.79)	≥30 filters vs. none
	Fatseas et al., 2012	0.25 (0.13-0.5)	2000-2004 vs. 1994-1995
	Naserirad and Beulaygue, 2020	0.77 (1.27-0.55)	High NSP access vs. low NSP access

Water	Aspinall et al., 2012	0.36 (0.22-0.61)	Obtained sterile water vs. not
	Fatseas et al., 2012	0.33 (0.18-0.63)	2000-2004 vs. 1994-1995

Abbreviation: NSP, needle and syringe programme.

Appendix 19. Summary of reviews and primary studies of combined interventions (opioid agonist treatment [OAT] and needle and syringe programmes [NSPs])

Reviews

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Review statement of evidence	Additional context
Platt et al., 2017 (core)	To 16 November 2015	Intervention: combined OAT and high coverage NSP (vs. no OAT and no/low NSP coverage). Outcome: HCV incidence	Four total: cohort (two), cross-sectional (two)	Total, 8 706: range, 168-7 954	Canada (1), Netherlands (1), United Kingdom (2)	Among studies that presented an adjusted estimate (three studies), the pooled RR was 0.26 (95 % CI 0.07-0.89). Including all four studies, the RR became 0.29 (95 % CI 0.13-0.65)	'…. suggested a strong intervention effect for combined high coverage of NSP and OST…. The evidence is considered low quality because it was derived from observational studies with serious risk of bias'. 'OST is associated with a reduction in the risk of HCV acquisition, which is strengthened in studies that assess the combination of OST and NSP.'	An analysis of exposure to OAT plus low NSP coverage (relative to the same reference group) showed a weaker effect (RR 0.87, 95 % CI 0.44-1.68, two studies)

Abbreviations: CI, confidence interval; NSP, needle and syringe programme; OAT, opioid agonist treatment; OST, opioid substitution treatment; RR, risk ratio.

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Study population	Finding	Results	Notes

Minoyan et al., 2020	Canada	Cohort	2010-2017	3 327	Aged ≥ 18 years; reported drug injection in the previous 6 months; reported opioid use or OAT in the previous 6 months, or initiated these during follow-up; tested HCV negative (or HCV Ab^+/RNA^-) at least once and returned for at least one subsequent HCV test; if HCV Ab^+/RNA^-, met clinical definitions of previous viral clearance	Equivocal	Adjusted HRs for partial and full harm reduction coverage vs. minimal: partial, 1.27 (95 % CI 0.55-2.92); full, 0.37 (95 % CI 0.12-1.12)	Full = high OAT plus complete NSP coverage. Partial = no or low OAT plus complete NSP coverage (i.e. 100 % needles/syringes from safe sources) *or* high OAT plus incomplete NSP coverage. Minimal = no OAT and incomplete NSP coverage. Effect size estimates were also generated separately for primary HCV infection and HCV reinfection, but these were very similar to the overall estimate

Abbreviations: Ab^+, antibody-positive; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; NSP, needle and syringe programme; OAT, opioid agonist treatment.

Appendix 20. Summary of reviews and primary studies of drug consumption rooms (DCRs)

Review

First author and year of publication	Dates covered	Intervention and outcome detail	No of studies and study designs	No of participants	Countries where studies took place	Range of effect sizes or pooled effect size	Additional considerations	Review statement of evidence
Kennedy et al., 2017 (supplementary)	To 1 May 2017	Intervention: DCRs. Outcomes: syringe sharing, borrowing/lending a used syringe, reusing syringes, using clean water for injecting, sharing injection equipment (not defined), use of non-sterile equipment	Six total: cohort (one), cross-sectional (five)	Total, 2 192: range, 41-760	Canada (3), Denmark (1), Germany (1), Spain (1)	Four of the six studies examined syringe sharing: three (cross-sectional) showed evidence of a positive association (ORs ranging from 0.14 [95 % CI 0.00-0.78] to 0.30 [95 % CI 0.11-0.82]); one (cohort study) found no significant change in 'use of non-sterile equipment or equipment sharing' over time (since baseline) among PWID who initiated use of the DCR; two of the studies (cross-sectional) demonstrated (positive) associations between DCR use and likelihood of other risk behaviours, including reusing of syringes, and using clean water for injecting	Studies also used different measures of DCR exposure: self-reported DCR use for all, most or some vs. few or no injections; self-reported exclusive DCR use for injection drug use in the previous month vs. not; consistent DCR use for ≥ 25 % of injections vs. < 25 %; any use of at least one of five DCRs since last interview; changes over time at 1, 2 and 3 months after first use of DCR vs. first use of DCR; behaviours after opening of DCR vs. before	N/A (supplementary review)

Abbreviations: CI, confidence interval; DCR, drug consumption room; N/A, not applicable; OR, odds ratio; PWID, people who inject drugs.

Primary studies

First author and year	Country	Study design	Date study carried out	Sample size	Study population	Finding	Results	Notes
Hepatitis C virus studies								
Folch et al., 2018	Spain	Cross-sectional	2014-2015	510	≥18 years; reported injecting drugs in the previous 6 months; attended one of the 15 participating harm reduction centres; and with a DCR located near their home or near to where they injected or purchased drugs, which they had attended in the previous 6 months	Equivocal	Chi-square test used to compare the prevalence of HCV in low, medium vs. frequent DCR users: 61.8 %, 71.5 % and 68.3 %, respectively (p = 0.128)	HCV seropositivity was based on an oral fluid sample
Kennedy et al., 2019a	Canada	Cross-sectional (effectively)	2006-2017	811	PWID enrolled in either the Vancouver Injection Drug Users Study (VIDUS) or the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study and who had completed at least one baseline or follow-up interview between 1.12.2006 and 30.6.2017 at which they reported having injected drugs and having used a supervised injection facility at least once in at least 50 % of their available study visits in the previous 6 months	Equivocal	At least weekly supervised injection facility use in the 6 months prior to baseline vs. regular but not at least weekly: unadjusted OR of HCV seropositivity = 1.34 (95 % CI 0.91-1.98)	Analysis of HCV seropositivity related to baseline interview
HIV studies								
Folch et al., 2018	Spain	Cross-sectional	2014-2015	510	≥18 years; reported injecting drugs in the previous 6 months; attended one of the 15 participating harm reduction centres; and with a DCR located near their home or near to where they injected or purchased drugs, which they had attended in the previous 6 months	Equivocal	Chi-square tests used to compare the prevalence of HIV in low, medium and frequent DCR users: 24.8 %, 25.0 % and 36.5 %, respectively (p = 0.062)	HIV seropositivity was based on an oral fluid sample

Kennedy et al., 2019b	Canada	Cross-sectional (effectively)	2006-2017	811	PWID enrolled in either the Vancouver Injection Drug Users Study (VIDUS) or the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study and who had completed at least one baseline or follow-up interview between 1.12.2006 and 30.6.2017 at which they reported having injected drugs and having used a DCR at least once in at least 50 % of their available study visits in the previous 6 months	Positive	At least weekly DCR use in 6 months prior to baseline vs. regular but not at least weekly: unadjusted OR of HIV seropositivity = 0.6 (95 % CI 0.44-0.81)	Analysis of HIV seropositivity related to baseline interview
Injecting risk behaviour studies								
Folch et al., 2018	Spain	Cross-sectional	2014-2015	510	≥18 years; reported injecting drugs in the previous 6 months; attended one of the 15 participating harm reduction centres; and with a DCR located near their home or near to where they injected or purchased drugs, which they had attended in the previous 6 months	Positive	Compared frequent attendance at a DCR vs. medium/low attendance: adjusted OR for sharing needles and/or injecting equipment = 0.39 (95 % CI 0.2-0.78, $p < 0.05$)	

Abbreviations: CI, confidence interval; DCR, drug consumption room; OR, odds ratio; PWID, people who inject drugs.