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Review

Interventions to prevent HIV and Hepatitis C among people who inject drugs: Latest evidence of effectiveness from a systematic review (2011 to 2020)

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ABSTRACT

Background: Hepatitis C virus (HCV) and HIV remain prevalent among people who inject drugs (PWID) and transmission is usually associated with injecting risk behaviour (IRB). We update a 2011 review of reviews (RoR) to assess the latest evidence on the effectiveness of harm reduction interventions – drug treatment (including opioid agonist therapy [OAT]), needle and syringe programmes (NSP) and other interventions – in the prevention of HCV and HIV transmission, and related measures of infection risk (IRB and injecting frequency [IF]), among PWID.

Methods: We undertook an initial search for systematic reviews (i.e. an Overview of Reviews [OoR]) and subsequent systematic searches for primary studies where required. Where there was sufficient evidence based on synthesis of multiple robust studies for an intervention effect in the 2011 RoR, new evidence was not sought. Medline, CINAHL, The Cochrane Library, EMBASE, PsycINFO and Web of Science were searched (2011-2020). Two reviewers screened papers, extracted data, and graded reviews/studies. We classified evidence as 'sufficient', 'tentative', 'insufficient', or 'no evidence'.

Results: We screened 8513 reviews and 7133 studies, with 27 and 61 identified as relevant, respectively. The level of evidence increased since the 2011 RoR and is now 'sufficient' for OAT (regarding all outcomes), NSP (for reducing HIV transmission and IRB), and combination OAT/NSP (for reducing HCV transmission). There is also now sufficient evidence for in-prison OAT, psychosocial interventions, pharmacy-based NSP and provision of sterile drug preparation equipment for reducing IRB.

Conclusion: There is now a strong body of empirical evidence for the effectiveness of OAT and NSP, alone and in combination, in reducing IRB, and HCV and HIV transmission. However, there is still a relative lack of evidence for other interventions, including heroin-assisted treatment, pharmacological treatment for stimulant dependence, contingency management, technology-based interventions, low dead space syringes and drug consumption rooms on HCV or HIV risk.

Introduction

Globally, there are an estimated 15.6 million (95% confidence interval [CI] 10.2–23.7 million) people who inject drugs (PWID) who are at risk of acquiring blood-borne infections, particularly hepatitis C virus (HCV) and HIV, through the sharing of needles/syringes or other drug preparation equipment (Degenhardt et al., 2017). These behaviours, usually referred to collectively as injecting risk behaviour (IRB), are highly prevalent among PWID globally, with an estimated 23.9% (95% CI: 21.2%–26.5%) reporting receptive sharing of needles/syringes and

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30.5% (95% CI: 21.2%-39.8%) reporting receptive sharing of other equipment within the past month (Tran et al., 2020). As a consequence, the prevalence of blood-borne viruses (BBV) among PWID is high, with an estimated 17.8% (95% CI 10.8%–24.8%) of PWID infected with HIV – equating to 2.8 million individuals – and 52.3% (95% CI 42.4%–62.1%) positive for HCV antibodies – equating to 8.2 million people (Degenhardt et al., 2017).

In 2014, UNAIDS set global targets for ending the AIDS epidemic by 2030: the '95-95-95' targets aim to diagnose 95% of all people living with HIV, provide antiretroviral therapy to 95% of those diagnosed, and achieve viral suppression in 95% of those treated (UNAIDS, 2014). Similarly, the World Health Organization (WHO), in 2016, adopted a global strategy to eliminate viral hepatitis as a public health threat by 2030, with targets of a 80% reduction in incident cases of HCV and a 65% reduction in mortality compared to 2015 (World Health Organization, 2016). To reach these targets, many countries will have to scale up evidence-based interventions to prevent HCV and HIV transmission (Larney et al., 2017). There is evidence of effectiveness for some harm reduction interventions – mainly needle and syringe programmes (NSP) and opioid agonist therapy (OAT) (ECDC & EMCDDA, 2011b, 2011c; MacArthur et al., 2014; Palmateer et al., 2010). In our most recent Review of Reviews (RoR), undertaken in 2011, while there was sufficient/tentative evidence that interventions – NSP, OAT, drug consumption rooms (DCRs) and providing non-needle drug preparation equipment – are effective in reducing IRB, the evidence was weaker for HIV, and especially HCV, prevention.

Here, we update the evidence from the 2011 RoR to answer the following research questions: What is the effectiveness of: a) drug treatment (for both opioid and stimulant dependence); b) NSP (including provision of clean needles/syringes, low dead space syringes (LDSS), and other drug preparation equipment); c) combined NSP and OAT, d) psychosocial interventions and e) DCRs, in the prevention of HCV transmission, HIV transmission and IRB among PWID? This work has informed updated European guidance for the prevention of infectious diseases among PWID published by the European Centre for Disease Prevention and Control (ECDC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2022.

Methods

A protocol was developed prior to commencement of the reviews and published on PROSPERO (https://www.crd.york.ac.uk/prospero, registration no.: CRD42020185487). 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 supplementary Fig. S1). First, an OoR was undertaken for the period 01/01/2011 to 01/06/2020. Where there was already sufficient evidence (where 'sufficient' is defined as per the Data synthesis section and Table 1) for an intervention/outcome in the 2011 RoR, new evidence was not considered; this applied to OAT and HIV, OAT and IRB, and NSP and IRB. The latter decision was based on scrutiny of the reviews identified for these intervention/outcome combinations, which we deemed would not change the level of evidence. Secondly, a search for primary studies was conducted, covering the period 01/01/2011 to 27/10/2020. The evidence from primary studies was considered in certain cases: where no core reviews ('core' reviews were those that received a high or moderate rating using the AMSTAR2 critical appraisal tool – see the Quality assessment section of the methods for more detail) 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 across the 2011 RoR and the OoR), we considered relevant studies published after the latest date covered by the review(s).

Inclusion criteria

Inclusion and exclusion criteria are summarised in supplementary Table S1. Systematic reviews, published and unpublished, were considered eligible for the OoR component. Systematic reviews of qualitative studies, cost-effectiveness studies or mathematical modelling studies were considered out-of-scope. Overviews of reviews 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.

Studies/reviews evaluating the following interventions were included: a) drug treatment (including pharmacological treatment for opioid dependence – i.e. OAT – or stimulant dependence); b) NSP (including provision of clean needles/syringes, LDSS, and other drug preparation equipment - e.g. cookers, filters, water ampoules, or provision of foil for smoking); c) combined NSP and OAT; d) psychosocial interventions; and e) DCRs. OAT refers to pharmacological treatment using agonist medication to eliminate withdrawal symptoms and relieve drug cravings - most commonly methadone or buprenorphine (Strang et al., 2020). Antagonist treatment for opioid dependence (e.g.naltrexone) was not considered. While 'NSP' is usually an abbreviation for needle and syringe programmes, and therefore could include services that provide a range of types of injecting and drug preparation equipment, in this review it was taken to refer to provision of sterile needle/syringes (unless it was otherwise specified that different types of equipment were supplied). LDSS are a particular design of syringe with a lower volume of "dead space" between the syringe and needle when the plunger is completely depressed; this results in less residual blood left in the syringe after injecting, which can potentially reduce the risk of BBV transmission during needle/syringe sharing. The provision of interventions in combination (in this case NSP and OAT) refers to interventions that are delivered in combination to achieve synergistic effects. Sterile drug preparation equipment (often also called "paraphernalia") is equipment that is used to prepare drugs for injection and usually consists of the following items: cookers or spoons (to heat or mix drugs in), cottons or filters (to remove particles when drawing drugs into a syringe), or water (to rinse syringes or mix with drugs). 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 an NSP provided sterile drug preparation equipment if one of the outcomes of the review/study was sharing any of these items of equipment. Psychosocial interventions were defined as any interventions that emphasize psychological or social factors rather than biological factors to promote behaviour change (EMCDDA, 2016b; Forsman, Nordmyr, & Wahlbeck, 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 skills training (IECS); (b) contingency management (CM), i.e. the use of incentives to promote behaviour change; and (c) technology-based psychosocial interventions. The evidence for interventions delivered in combination had to be evaluated at the individual level. For all interventions, where information on specific settings was provided, the evidence was considered separately (for example, prisons and pharmacies).

The outcomes of interest were HCV and HIV infection, and IRB (defined as self-reported borrowing, lending or reuse of needles/syringes or other drug preparation equipment). For drug treatment and psychosocial interventions, outcomes that measured the extent of injecting drug use (e.g. frequency of injecting, any injecting, or abstinence/cessation of injecting) were included. These behaviours have been abbreviated as 'injection frequency' (IF). Risk behaviours had to be self-reported; studies that reported urinalysis as the only measure of drug use were excluded

Table 1
Types of evidence statement 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

* Framework adapted from the Health Development Agency (Ellis et al., 2003), as described in our previous reviews (MacArthur et al., 2014; Palmateer et al., 2010).

given this cannot establish the route of drug taking. Studies/reviews that included biological measures of either incident or prevalent HIV/HCV infection were eligible; self-reported measures of infection were ineligible. Additionally, both primary HCV infection and HCV re-infection were considered eligible outcomes.

Studies/reviews had to relate to PWID (currently or formerly injecting). Papers where the study population was individuals who inject drugs for a medical purpose (with the exception of drug treatment) were excluded. Reviews of non-injecting drug users (for example, many reviews related to people with opioid use disorder, which may include injecting and non-injecting drug users) were excluded, unless results were presented separately for the PWID subset of the study population. Reviews that did not explicitly state their study population were excluded. There were no English language restrictions.

Study selection and data extraction

The following databases were searched for both the OoR (on 1st June 2020) and primary literature review (on 27th October 2020): Medline, CINAHL, The Cochrane Library, EMBASE, PsycINFO and Web of Science. Search terms for the OoR and primary literature review are listed in Appendices S1 and S2, respectively.

The websites of key international agencies were searched for grey literature publications: ECDC, EMCDDA, National Institute on Drug Abuse, National Academy of Medicine, United Nations Office on Drugs and Crime, and the World Health Organisation. Conference proceedings at relevant conferences in 2019/2020 (International Network of Health and Hepatitis in Substance Users, The European Conference on Addictive Behaviours and Dependencies (Lisbon Addictions), Harm Reduction International, Society for the Study of Addiction, and The European Association for the Study of the Liver) 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.

For both the OoR and the primary literature review, two independent reviewers screened titles and abstracts for relevance. Papers that were thought to be relevant were retrieved, and the reviewers subsequently screened the full texts. In the case of disagreement, a third review author made the final decision. 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.

Quality assessment

To critically appraise the included systematic reviews, we adapted the internationally recognised and validated AMSTAR2 (A MeaSurement Tool to Assess systematic Reviews) tool (Shea et al., 2017). AMSTAR2 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 RoR (supplementary Table S2). Systematic reviews that had a high or moderate AMSTAR2 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 AMSTAR2 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, where core reviews were lacking. Systematic reviews with a critically low AMSTAR2 rating were excluded. Two reviewers independently graded each of the included reviews; a third senior member of staff resolved any discrepancies. We used Covidence software for screening, data extraction, and critical appraisal.

As stated in the PROSPERO protocol, the Cochrane Collaboration’s Risk of Bias 2 tool and the ROBINS-I tool were originally intended for the critical appraisal of primary studies (Sterne et al., 2016, 2019). However, it became apparent that it was going to be problematic to synthesise the evidence from the updated review (2011-2020) in conjunction with that generated in the 2011 RoR, using the same framework. Therefore, to be consistent with the RoR, the same approach to assessing primary study quality was applied, and 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’s findings, with randomised controlled trials, non-randomised experimental studies and cohort studies considered to be “robust” and any other study designs considered to provide “weaker” evidence.

Data synthesis

By intervention and outcome combination, summaries of the relevant reviews were generated in tabular format. A judgment about 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 2011 RoR (Table 1).

If there was deemed to be sufficient evidence from the reviews in terms of synthesised evidence of an intervention effect from multiple robust studies, then the primary studies were not consulted. However,

Table 2
Algorithm for combining evidence statements from the 2011 guidance and from the 2020/21 update.

Evidence statement from 2011 review	Evidence statement from 2020/21 update	Final evidence statement
Sufficient	N/A*	Sufficient (i.e. 2011 evidence statement stands)
Tentative or insufficient	Sufficient	Sufficient (i.e. 2020/21 evidence statement stands)
	Tentative or insufficient	Evidence base across both 2011 and 2020/21 reviews considered and statement derived accordingly to see if evidence statement gets upgraded
	No evidence	2011 evidence statement stands (i.e. either 'tentative' or 'insufficient')**
None	Sufficient, tentative, insufficient or none	2020/21 evidence statement stands

* Review of evidence not updated in 2020/21 due to the compelling level of evidence identified in the 2011 Review of Reviews.
** Except for a specific case where the level of evidence from 2011 was labelled as 'insufficient' (for psychosocial interventions involving contingency management). There were, however, no studies relating to contingency management and the statement should therefore have been 'no evidence'. Thus, the evidence appears to have been downgraded (i.e. from insufficient in the 2011 RoR to no evidence).

if there was less than sufficient evidence from the reviews, 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 in the 2011 RoR, as per Table 2.

Results

Fig. 1 presents a flowchart for the OoR component of the review: 8513 abstracts were screened, followed by 438 full texts, resulting in 27 relevant reviews. The reviews that were appraised as 'critically low' quality were excluded, leaving 13 reviews in total (nine of which were rated as moderate or high quality (Aspinall et al., 2014; Bahji, Carlone, & Altomare, 2019; ECDC, 2018; Gilchrist et al., 2017; Hajarizadeh et al., 2020; Hedrich et al., 2012; Platt et al., 2017; Sacks-Davis, Horyniak, Grebely, & Hellard, 2012; Sawangjit, Khan, & Chaiyakunapruk, 2017), and thus considered core reviews, and four that were rated as low quality (Abdul-Quader et al., 2013; Davis et al., 2017; Kennedy, Karamouzian, & Kerr, 2017; WHO, 2012), and thus considered supplementary reviews.

For the primary literature component, 7133 abstracts and 313 full texts were screened, leading to the identification of 61 potentially relevant studies (Fig. 2); however, not all of these studies were necessarily included in the evidence base, dependent on the results of the OoR.

The outcomes of the grey literature search are presented in supplementary Fig. S2. An overview of which reviews and studies were identified for each intervention and outcome combination is presented in supplementary Table S3. Tables S4 and S5 present details of the individual reviews and primary studies, respectively.

Agonist treatment for opioid dependence (OAT)

Effects on HCV transmission

Two core reviews (Hajarizadeh et al., 2020; Platt et al., 2017) looked at reinfection and primary infection, respectively (Table S4). In a meta-analysis of 12 studies, of mostly robust designs, Platt et al. (also published as (Platt et al., 2018)) found that OAT was associated with a 50% reduction in risk of primary HCV infection (RR 0.50, 95% CI 0.40-0.63). Hajarizadeh et al. looked at reinfection risk (following treatment-induced HCV clearance) in a meta-regression of 22 studies, all with robust designs. They found that those not on OAT (with reported injecting) had a 3.7-fold increased risk of HCV reinfection (ARR 3.74, 95% CI 1.77-7.89) relative to those on OAT (with no reported injecting). In other words, OAT was associated with a reduction in HCV reinfection by approximately 73% (44-87%). Given a clear and consistent statement from two core reviews, based on multiple robust studies, we concluded that the level of evidence is sufficient for prevention of both primary HCV infection and HCV reinfection. The level of evidence from the 2011 RoR had been classified as tentative, and therefore was updated (as per Table 2) to give a statement of sufficient evidence (Table 3).

Effects on HIV transmission and injecting risk behaviour/injection frequency

In the 2011 RoR, the evidence for OAT was deemed sufficient regarding HIV, IRB/IF and thus was not updated here, as per the methods. Therefore, the 2011 evidence statement stands (Table 3).

Agonist treatment for opioid dependence (OAT) in prison/criminal justice settings

Effects on HCV transmission

Two core reviews looked at the provision of OAT in prison settings and its association with HCV (ECDC, 2018; Hedrich et al., 2012) (supplementary Table S4). Between them, these reviews identified three studies (one RCT, two case-controls), two of which had non-significant findings, and one that demonstrated an increased risk of HCV among those on OAT at the time of interview, but this was attributed by the review authors to disruptions in OAT continuity in prison (Hedrich et al., 2012). An additional cohort study was also identified through the primary literature search but this study of incarcerated individuals found no difference in time to HCV seroconversion among those on current OAT vs. not (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 concluded that there is insufficient evidence to either support or discount the effectiveness of OAT for preventing HCV transmission in the prison setting. There was insufficient evidence from the 2011 RoR, and so the updated evidence statement remains insufficient (Table 3).

Effects on HIV transmission

ECDC and Hedrich et al. also looked at HIV as an outcome: both included the same two studies (one RCT, one case-control) 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 concluded that the level of evidence was insufficient. The 2011 RoR also made a statement of insufficient evidence, and therefore the final combined evidence statement remains insufficient (Table 3).

Effects on injecting risk behaviour/injection frequency

One core review (Hedrich et al., 2012) identified six studies, four of which had robust designs. Five of the studies (three with robust designs) showed significant reductions in sharing of injecting equipment associated with uptake of OAT and five (three with robust designs) showed statistically significant reductions in injecting drug use associated with uptake of OAT. Given a statement of sufficient evidence from a core review, based on multiple robust studies, we concluded that there is sufficient evidence to support the effectiveness of OAT in reducing IRB and IF in prison settings (Table 3). The 2011 RoR had identified tentative evidence of effectiveness; this was superseded by the 2020 findings of sufficient evidence as per the algorithm in Table 2.

Table 3
Evidence for drug treatment interventions.

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Opioid agonist treatment (OAT)	HCV	OoR: Hajarizadeh et al., 2020 (core); Platt et al., 2017 (core) Primary literature: not consulted as a result of sufficient evidence from the OoR.	Hajarizadeh et al. provide a statement of evidence in support of OAT re HCV reinfection Platt et al. provide a statement of evidence in support of OAT re HCV infection	Hajarizadeh: 22 total (9 RCT, 13 COH). $N = 2772$ (range 11-909). Platt: 12 total (10 COH, 1 CS, 1 CC). $N = 6361$ (range 80-2788).	Hajarizadeh: Positive finding from pooled analysis Platt: Positive finding from pooled analyis	Given a clear and consistent statement from one or more core reviews, based on multiple robust studies, the level of evidence is sufficient regarding both primary HCV infection and HCV reinfection	Tentative	There is **sufficient** review-level evidence to support the effectiveness of OAT, delivered at sufficient dose, in the prevention of primary HCV infection and HCV reinfection among PWID.
	HIV	No update undertaken since level of evidence already sufficient from 2011 RoR	N/A	N/A	N/A	N/A	Sufficient	"Evidence in three core reviews demonstrates that there is **sufficient** review-level evidence to conclude that OST in community settings is effective in the prevention of HIV seroconversion, especially for those in continuous treatment" (from 2011 RoR)
	IRB/IF	No update undertaken since level of evidence already sufficient from 2011 RoR	N/A	N/A	N/A	N/A	Sufficient	"Consistent evidence from multiple robust studies in core reviews indicates that there is **sufficient** review-level evidence to support the effectiveness of OST in the prevention of the frequency of injection, the sharing of injecting equipment and injecting risk behaviour."
OAT in prison/ criminal justice settings	HCV	OoR: ECDC, 2018 (core); Hedrich et al., 2012 (core) Primary literature: Cunningham et al., 2017 (robust design)	ECDC provide a statement of insufficient evidence Hedrich et al provide a statement of insufficient evidence	ECDC: 2 studies (1 RCT, 1 CC). $N = 471$ (range 218-253). Hedrich: 3 studies (1 RCT, 2 CC). $N = 959$ (range 218-488). Primary literature: 1 study (COH) $N = 197$	ECDC: 2 equivocal (1 RCT, 1 CC); Hedrich: Same as ECDC plus 1 negative (1 CC) Primary literature: equivocal finding	Given statements of insufficient evidence from two core reviews, and only one robust primary study with an equivocal finding, we conclude there is insufficient evidence	Insufficient [Note: statement was based on 2 out of the 3 studies in the updated review]	There is **insufficient** evidence to either support or discount the effectiveness of OAT in the prevention of HCV among PWID in prison settings.
	HIV	OoR: ECDC, 2018 (core); Hedrich et al., 2012 (core) Primary literature: no studies	ECDC provide a statement of insufficient evidence Hedrich et al provide a statement of insufficient evidence	ECDC: 2 studies (1 RCT, 1 CC). $N = 471$ (range 218-253). Hedrich: 2 studies (1 RCT, 1 CC). $N = 471$ (range 218-253).	ECDC and Hedrich (same studies): 2 equivocal (1 RCT, 1 CC)	Given statements of insufficient evidence from two core reviews, we conclude that there is insufficient evidence	Insufficient [Note: the statement was based on 1 of the 2 studies identified in the updated review]	There is **insufficient** evidence to either support or discount the effectiveness of OAT in the prevention of HIV among PWID in prison settings.
	IRB/IF	OoR: Hedrich et al., 2012 (core) Primary literature: no studies	Hedrich et al. provide a statement of insufficient evidence	Hedrich: 6 studies (2 RCT, 2 COH, 1 serial CS, 1 CS). $N = 1071$ (range 120-253).	5 positive re IRB; 5 positive re IF	Given a statement of sufficient evidence from a core review, based on multiple robust studies, there is therefore sufficient evidence	Tentative [Note: statement is based on 3 of the 5 studies in the updated reviews that looked at IF]	There is **sufficient** review-level evidence to support the effectiveness of OAT in the prevention of IRB and IF among PWID in prison settings.

(*continued on next page*)

Table 3 (*continued*)

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Heroin-assisted treatment (HAT)	HCV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	No statement	There is **no evidence** to either support or discount the effectiveness of HAT in the prevention of HCV transmission among PWID.
	HIV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	No statement	There is **no evidence** to either support or discount the effectiveness of HAT in the prevention of HIV transmission among PWID.
	IRB/IF	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	No statement	There is **no evidence** to either support or discount the effectiveness of HAT in the prevention of IRB or IF among PWID.
Treatment for stimulant dependence	HCV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	No evidence	There is **no evidence** to either support or discount the effectiveness of pharmacological treatment for stimulant dependence in the prevention of HCV transmission among PWID.
	HIV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	No evidence	There is **no evidence** to either support or discount the effectiveness of pharmacological treatment for stimulant dependence in the prevention of HIV transmission among PWID.
	IRB/IF	OoR: no reviews Primary literature: no studies*	N/A	N/A	N/A	No evidence	No evidence**	There is **no evidence** to either support or discount the effectiveness of pharmacological treatment for stimulant dependence in the prevention of IRB or IF among PWID.

CC = case-control; COH = cohort; CI = confidence interval; CS = cross-sectional; EC = ecological; HCV = hepatitis C virus; IF = injection frequency; IRB = injecting risk behaviour; LDSS = low dead space syringes; NSP = needle and syringe programme; N/A = not applicable; OR = odds ratio; OoR = overview of reviews; PWID = people who inject drugs; py = person years; RoR = review of reviews; RR= risk ratio; SCS = serial cross-sectional; SC = seroconversion;

* One study was identified that looked at the impact of treatment with methylphenidate on injecting outcomes among 24 intravenous methamphetamine users (Minařík, Gabrhelík, Malcolm, Pavlovská, & Miller, 2016). The study design, however, was deemed to be a case series and it therefore did not meet our PICO criteria for inclusion (see methods).

** The 2011 technical report stated that "Tilson et al. (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."

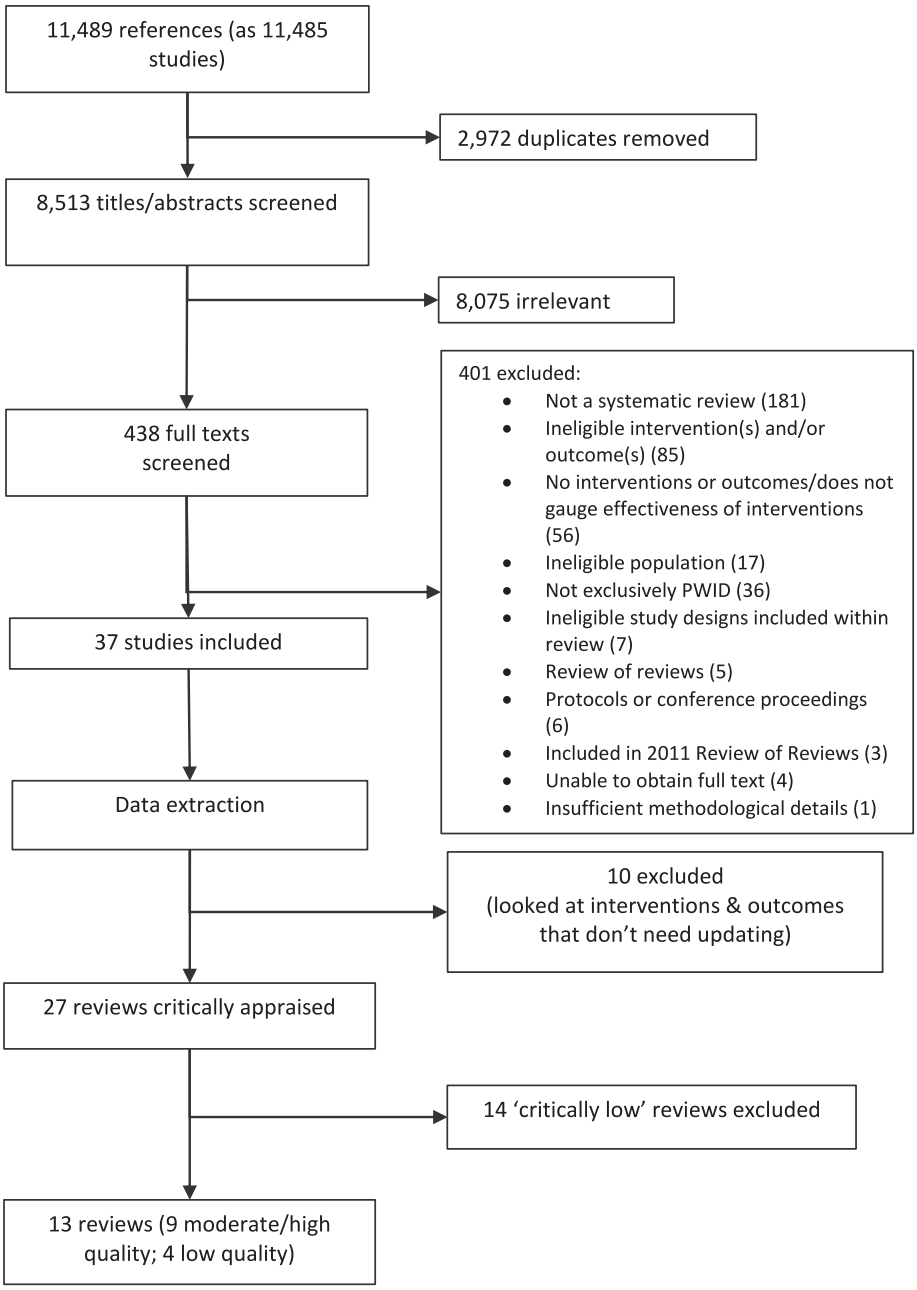

Fig. 1. PRISMA flow diagram for the Overview of Reviews (OoR) component.

Heroin-assisted treatment (HAT)

Effects on HCV transmission, HIV transmission and injecting risk behaviour/injection frequency

No reviews or studies were identified that looked at the effectiveness of HAT in preventing HCV, HIV or IRB/IF in the updated reviews. No statement of evidence was given in the 2011 RoR, therefore the updated evidence statement is that there is no evidence for all three outcomes (Table 3).

Pharmacological treatment for stimulant dependence

Effects on HCV transmission, HIV transmission and IRB/IF

No reviews or studies were identified that looked at the effectiveness of treatment for stimulant dependence in preventing HCV, HIV, or IRB/IF in either the updated reviews or the 2011 RoR. The updated evidence statement is therefore "no evidence" for all three outcomes (Table 3).

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

Effects on HCV transmission

With regard to HCV as an outcome, one core and one supplementary review were identified (Sacks-Davis et al., 2012; WHO, 2012) (supplementary Table S4). The WHO review is also published in a peer-reviewed journal (Walsh, Verster, Rodolph, & Akl, 2014). Sacks-Davis et al. found three studies (all RCTs) that all showed no difference in HCV incidence between intervention and control groups. The WHO review identified two studies, both of which were already included in the Sacks-Davis et al. review. An additional robust (cohort) study was identified from the primary literature review (Islam et al., 2017) (Table S5), which found

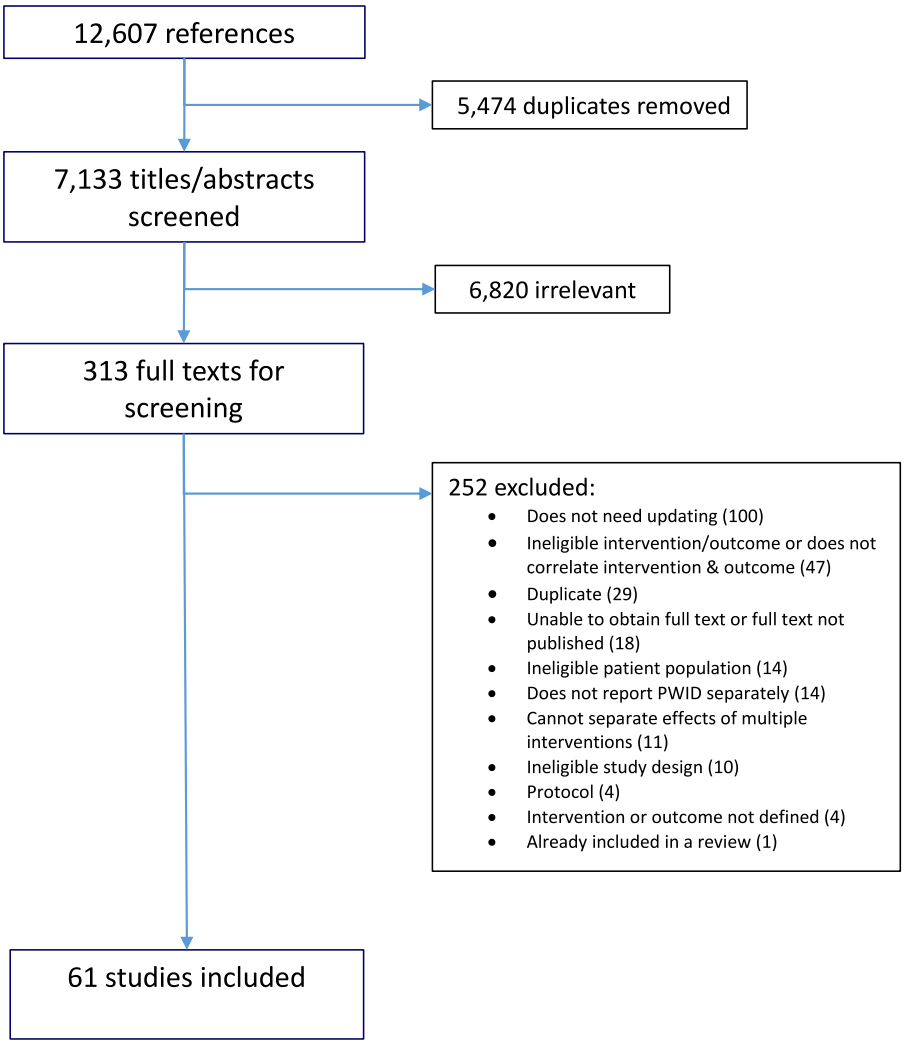

Fig. 2. PRISMA flow diagram for the primary literature review.

that receipt of mental health counselling (vs. none) was significantly associated with reduced risk of HCV reinfection (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 (albeit with a positive finding), we conclude that there is insufficient evidence to either support or discount the effectiveness of IECS interventions alone in reducing HCV transmission among PWID. The updated evidence statement therefore remained insufficient when considering the evidence across the 2011 RoR and the updated review (Table 4).

Effects on HIV transmission

With regard to HIV, no reviews were identified but four relevant primary studies were found in the evidence review (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 two RCTs did not demonstrate significant differences in HIV incidence between intervention and control groups. A serial cross-sectional study (weaker design) demonstrated decreasing HIV prevalence over time pre vs. post-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 concluded that there is insufficient evidence. Considering the evidence across the 2011 RoR and the updated review, the updated evidence statement remains insufficient (Table 4).

Effects on injecting risk behaviour/injection frequency

Two core reviews (Gilchrist et al., 2017; Sacks-Davis et al., 2012) and one supplementary review (WHO, 2012) looked at IRB outcomes (Table S4). Gilchrist et al. calculated standard mean differences (SMDs) in the outcome to compare those receiving psychosocial interventions vs. control groups. The pooled SMD for: any IRB outcome was -0.29, 95% CI -0.42 to -0.15, $p < 0.01$ (based on 22 studies); for sharing needles/ syringes the SMD was -0.43, 95% CI -0.69 to -0.18, $p < 0.01$ (based on 13 studies); for sharing paraphernalia the SMD was -0.21, 95% CI -0.34 to -0.09, $p < 0.01$ (based on 7 studies); and for IF the SMD was -0.17, 95% CI -0.35 to 0.00, $p = 0.05$ (based on 8 studies). Sacks-Davis et al. identified 6 studies, but five of these were already captured in the Gilchrist et al. 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 4). The updated evidence statement was "sufficient".

Psychosocial interventions involving information, education, counselling and/or skills training (IECS) in the prison setting

Effects on HCV transmission, HIV transmission and injecting risk behaviour/injection frequency

There was no or insufficient evidence for effectiveness of IECS interventions in the prison setting (detail in supplementary Appendix S3).

Table 4
Evidence for psychosocial interventions.

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement*	Updated evidence statement
Psychosocial interventions involving information, education, counselling and/or skills training (IECS)	HCV	OoR: Sacks-Davis et al., 2012 (core); WHO, 2012 (supplementary) Primary literature: Islam et al., 2017 (robust design)	Sacks-Davis et al. provide a statement of insufficient evidence WHO/Walsh: N/A (supplementary review)	Sacks-Davis: 3 studies (3 RCTs). *N* = 1041 (range 78-854) WHO/Walsh: 2 studies (2 RCTs). *N* = 372 (range 95-277) Primary literature: 1 study (COH) *N* = 1604	Sacks-Davis: 3 equivocal (3 RCTs) WHO/Walsh: pooled effect is equivocal Primary literature: positive finding	Given a statement of insufficient evidence from a core review, and only one further study identified from the primary literature, the evidence is insufficient	Insufficient [Statement based on 1 positive finding (CS)]	There is **insufficient** evidence for the effectiveness of IECS interventions **alone** in the prevention of HCV transmission among PWID.
	HIV	OoR: no reviews Primary literature: Booth et al., 2016 (robust); Go et al., 2015 (robust); Miller et al., 2018 (robust); Hammett et al., 2012 (weaker)	N/A	4 studies (3 RCTs, 1 SCS). *N* = 9103 (range 810-5695).	2 positive (1 RCT, 1 SCS); 2 equivocal (2 RCTs)	On the basis of a small number of primary studies with inconsistent findings, we conclude that there is insufficient evidence	Insufficient [Statement based on 3 positive findings (1 COH, 1 CS, 1 EC)]	There is **insufficient** evidence to either support or discount the effectiveness of IECS interventions **alone** in the prevention of HIV transmission among PWID.
	IRB/IF	OoR: Gilchrist et al., 2017 (core); Sacks-Davis et al., 2012 (core); WHO 2012 (supplementary) Primary literature: not consulted given sufficient evidence from OoR	Gilchrist et al provide a statement of sufficient evidence Sacks-Davis: No clear statement with regard to IRB WHO/Walsh: N/A (supplementary)	Gilchrist: 31 studies (31 RCTs). *N* = 12,480 (range 40-1123). Sacks-Davis: 6 studies (6 RCTs). *N* = 2472 (range 109-851). WHO/Walsh: 4 studies (4 RCTs). By intervention: for IECS: 2 RCTs, *N* = 1111 (range 260-851); for 'peer education & mentoring': 2 RCTs, *N* = 1272 (range 418-854).	Gilchrist: Positive pooled effect sizes for any IRB outcome (22 studies), for sharing needles/ syringes (13 studies), for sharing paraphernalia (7 studies), and for IF (8 studies). Sacks-Davis: Out of 3 studies that looked at IF: 2 positive, 1 equivocal. Out of 6 studies that looked at IRB: 2 positive, 4 equivocal‡ WHO/Walsh: Equivocal pooled effect for IECS. Positive pooled effect for peer education & mentoring‡	Given a statement of sufficient evidence from a core review (Gilchrist), based on multiple robust studies, we conclude that there is sufficient evidence that IECS interventions are effective compared to control conditions	Tentative [Statement based on 28 studies: 18 positive (7 RCT, 10 COH, 1 CS); 10 no association (8 RCT, 2 CS)]	There is **sufficient** evidence that IECS interventions are effective in the prevention of IRB and IF - compared to control conditions - among PWID.

(*continued on next page*)

Table 4 (*continued*)

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement*	Updated evidence statement
Psychosocial interventions involving contingency management (CM)	HCV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	Insufficient [where psychosocial includes family therapy counselling and CM. Statement based on no studies/ reviews.]	There is **no evidence** to either support or discount the effectiveness of CM interventions in the prevention of HCV among PWID.
	HIV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	Insufficient [where psychosocial includes family therapy counselling and CM. Statement based on no studies/ reviews.]	There is **no evidence** to either support or discount the effectiveness of CM interventions in the prevention of HIV among PWID.
	IRB/IF	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	Insufficient for both IRB and opioid dependence [where psychosocial includes family therapy counselling and CM]	There is **insufficient** evidence to either support or discount the effectiveness of CM interventions in the prevention of IRB or IF among PWID.

CC = case-control; COH = cohort; CI = confidence interval; CS = cross-sectional; EC = ecological; HCV = hepatitis C virus; IF = injection frequency; IRB = injecting risk behaviour; LDSS = low dead space syringes; NSP = needle and syringe programme; N/A = not applicable; OR = odds ratio; OoR = overview of reviews; PWID = people who inject drugs; py = person years; RoR = review of reviews; RR= risk ratio; SCS = serial cross-sectional; SC = seroconversion;

* 2011 RoR statements of evidence are not directly comparable here as a result of different categorisation of the interventions; for example, the 'tentative' statement relates to 'outreach which includes IEC'. However, regardless of the evidence from the 2011 RoR, the statement of sufficient evidence from the updated review would supersede the statements from 2011.**Note: the 2 studies included in the WHO/Walsh review were captured in the Sacks-Davis review, therefore the evidence from WHO/Walsh will not be considered; however, it is notable that it is consistent with the Sacks-Davis findings.†A SMD of 0.2 is considered to be small, 0.5 medium and 0.8 large

‡ Note that 5 of the 6 studies in the Sacks-Davis and all 4 of the studies in the WHO/Walsh reviews were captured in the Gilchrist review. Given that these study findings have already been reflected in a pooled estimate, we have relied primarily on the Gilchrist findings to derive the evidence statement.

Psychosocial interventions involving contingency management (CM)

Effects on HCV transmission, HIV transmission and IRB/IF

No reviews or studies examining the association between CM and HCV or HIV transmission were identified. The 2011 RoR made a statement of insufficient evidence but this was based on no studies/reviews identified. The updated evidence statement is therefore that there is "no evidence" for all outcomes (Table 4).

Technology-based psychosocial interventions

Effects on HCV transmission, HIV transmission and injecting risk behaviour/injection frequency

There was no or insufficient evidence for effectiveness of technology-based psychosocial interventions (see supplementary Appendix S4).

Sterile needle and syringe provision (NSP)

Effects on HCV transmission

One core review and two supplementary reviews were identified (Abdul-Quader et al., 2013; Davis et al., 2017; Platt et al., 2017). The Platt et al. core review meta-analysed five studies that compared high coverage NSP (where high coverage was defined as regular attendance at an NSP at least once per week, obtaining most needles/syringes from an NSP, or ≥100% of injections using a new needle/syringe) to either non-attendance or low coverage NSP, in respect of HCV incidence. The resulting pooled effect (RR 0.79, 95% CI 0.39-1.61) was indicative of weak evidence that there was no association between high coverage NSP and HCV infection. Restricting the meta-analysis to two studies conducted in Europe (a subset of the five studies included in the aforementioned meta-analysis), however, the pooled effect size was consistent with a 76% reduction in HCV incidence (RR 0.24, 95% CI 0.09-0.62). The rationale for restricting to European studies was that they more directly measured NSP coverage (i.e. the percentage of an individual's injections where a clean needles/syringe was used) as compared to the remaining studies (all from North America), which tended to use proxy measures such as frequency of attendance at NSP. We are therefore placing greater weight on the European studies here, given they used more precise and sensitive measures of exposure. The European studies, while both cross-sectional in design, examined incidence of HCV infection (as opposed to prevalence of infection, which is typical of cross-sectional studies) 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. Additional primary studies that were identified since the publication of the Platt review (supplementary Table S5: Chen et al., 2018; Handanagic et al., 2017; Leyna et al., 2019; Minoyan et al., 2020; Salek et al., 2017) had mixed findings (two studies showed evidence of an effect): one serial cross-sectional study had a positive finding (a significant reduction in HCV prevalence over time), one cohort was equivocal, and three cross-sectional studies had negative findings (higher odds of prevalent HCV infection among those who had accessed NSP or had used NSP for longer). Given these inconsistent findings, mainly based on weaker designs, we concluded that the primary studies did not change the evidence in either direction. Therefore, on the basis of a tentative statement of evidence from a core review, grounded in consistent evidence from a small number of robust studies, we concluded that the level of evidence is tentative. Considering the evidence base across the 2020 OoR and the 2011 RoR, with the balance of evidence from the 2011 RoR tipped in favour of positive studies, we concluded that the updated level of evidence is tentative (Table 5).

Effects on HIV transmission

For prevention of HIV, a core review and a supplementary review were identified (Abdul-Quader et al., 2013; E. J. Aspinall et al., 2014) (Table S4). The Aspinall et al. core review found an equivocal pooled effect size across all 12 studies (10 cohort, 1 case-control, 1 cross-sectional) identified in the review (RR 0.66, 95% CI 0.43-1.01). Restricting the meta-analysis to six studies that were graded as 'high quality' resulted in a pooled effect that was consistent with a 58% reduction in risk of HIV associated with use of NSP (RR 0.42, 95% CI 0.22-0.81), although measures of NSP coverage or uptake differed between the meta-analysed studies. Given a statement of sufficient evidence from a core review (based on multiple robust studies), we concluded that the level of evidence is sufficient. The 2011 RoR made a statement of tentative evidence, therefore the updated evidence statement is "sufficient" (Table 5).

Sterile needle and syringe provision in prison/criminal justice settings

Effects on HCV transmission

One high quality review was identified (ECDC, 2018) (Table S4) that included three studies of in-prison NSP and HCV transmission: 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 in-prison NSP. Given a statement of insufficient evidence from this core review (based on a small number of studies), we concluded that the level of evidence is insufficient (Table 5).

Effects on HIV transmission

The same review above (ECDC, 2018) also looked at in-prison NSP 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 in-prison NSP. Therefore, given a statement of insufficient evidence from a core review (based on a small number of studies), we concluded that the level of evidence is insufficient (Table 5).

Effects on injecting risk behaviour

No evidence was found with regard to the impact of prison NSP on IRB and there was no statement given in the 2011 RoR. The updated evidence statement is therefore "no evidence" (Table 5).

Sterile needle and syringe provision in pharmacy settings

Effects on HCV transmission

One core review (Sawangjit et al., 2017) meta-analysed their identified studies and found significantly lower odds of HCV associated with pharmacy-based NSP vs. no NSP (0.26, 95% CI 0.18-0.38), but this was based on only two studies (Table S4). Comparing pharmacy-based vs. other types of NSP showed no significant difference in HCV, based on four studies (OR 0.63, 95% CI 0.27-1.45). 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 concluded that the level of evidence is insufficient. There was no evidence identified in the 2011 RoR, and therefore the updated level of evidence is "insufficient" (Table 5).

Effects on HIV transmission

The meta-analysis conducted by Sawangjit et al. found no significant difference between pharmacy-based vs. no NSP (OR 0.56, 95% CI 0.18-1.77, based on 3 studies), and a significantly reduced odds of HIV when comparing pharmacy-based vs. other types of NSP (OR 0.55, 95% CI 0.41-0.76), again based on 3 studies. Given a statement of insufficient evidence from a core review, based on studies with mostly weaker designs, we concluded that the evidence is insufficient. The 2011 RoR also made a statement of insufficient evidence; when considering the

Table 5
Evidence for injecting equipment provision interventions.

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
Needle and syringe (NSP)	HCV	OoR: Platt et al., 2017 (core); Abdul-Quader et al., 2013 (supplementary); Davis et al., 2017 (supplementary)* Primary literature: Minoyan et al., 2020 (robust); Chen et al., 2018 (weaker); Handanagic et al., 2017 (weaker); Leyna et al., 2019 (weaker); Salek et al., 2017 (weaker)	Platt et al. provide a statement of tentative evidence	Platt: 15 studies (11 COH, 1 CC, 3 CS). $N = 7684$ (range 46-2788). Primary lit: 5 studies (1 COH, 3 CS, 1 SCS). $N = 105{,}754$ (range 130-101,032).	Platt: Equivocal pooled effect (5 studies: 3 COH, 2 CS). Positive pooled effect (2 European studies – both CS**) Primary literature: 1 positive (1 SCS), 1 equivocal (1 COH), 3 negative (CS)	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	Insufficient Statement was based on 17 studies: 9 positive (1 CC, 6 CS, 2 EC); 2 negative (2 COH); 6 no association (3 COH, 3 CS). [Note: 1 study that was included in the Platt et al. pooled RR was also included in the 2011 RoR].	Considering the evidence base across the updated and 2011 reviews, with the balance of evidence from the 2011 RoR tipped in favour of positive studies, we conclude that there is **tentative** evidence to support the effectiveness of NSP in the prevention of HCV transmission among PWID.
	HIV	OoR: Aspinall et al., 2014 (core); Abdul-Quader et al., 2013 (supplementary)† Primary literature: not consulted given sufficient evidence from OoR	Aspinall et al. provide a statement of sufficient evidence	Aspinall: 12 studies (10 COH, 1 CS, 1 CC). $N = 12{,}023$ (range 226-2505).	Aspinall: Equivocal effect size across all (12) studies, and positive pooled effect across 6 higher quality studies	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	Tentative Statement based on 16 studies: 10 positive (2 COH, 4 EC, 4 CS); 2 negative (2 COH); 4 equivocal (2 COH, 2 CC) [overlap of 7 studies with Aspinall et al.]	There is **sufficient** evidence that NSP is effective in the prevention of HIV transmission among PWID.
	IRB	No update undertaken since level of evidence already sufficient from 2011 RoR	N/A	N/A	N/A	N/A	Sufficient	"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."
NSP (prison setting)	HCV	OoR: ECDC, 2018 (core) Primary literature: no studies	ECDC provide a statement of insufficient evidence	3 studies (1 EC, 2 COH). $N = 405$ (range 174-231).	1 positive (1 EC); 2 equivocal (2 COH)	Given a statement of insufficient evidence from a core review, based on a small number of studies, we conclude that there is insufficient evidence	No statement	There is **insufficient** evidence to either support or discount the effectiveness of NSP in reducing HCV transmission among PWID in the prison setting.
	HIV	OoR: ECDC, 2018 (core) Primary literature: no studies	ECDC provide a statement of insufficient evidence	3 studies (1 EC, 2 COH). $N = 405$ (range 174-231).	1 positive (1 EC); 2 equivocal (2 COH)	Given a statement of insufficient evidence from a core review, based on a small number of studies, we conclude that there is insufficient evidence	No statement	There is **insufficient** evidence to either support or discount the effectiveness of NSP in the prevention of HIV transmission among PWID in the prison setting.

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Table 5 (*continued*)

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
	IRB	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	No statement	There is **no evidence** to either support or discount the effectiveness of prison NSP in the prevention of IRB among PWID.
NSP (pharmacy settings)	HCV	OoR: Sawangjit et al., 2016 (core) Primary literature: no studies	Sawangjit et al. provide a statement of insufficient evidence	6 studies (5 CS, 1 COH). *N* = 2628 (range 128-1020).	Pooled effects were positive for pharmacy NSP vs no NSP and equivocal for pharmacy vs. other NSP	Given a statement of insufficient evidence from a core review, based on studies with mostly weaker designs, we conclude that the evidence is insufficient.	No evidence	There is **insufficient** evidence to either support or discount the effectiveness of pharmacy NSP in the prevention of the transmission of HCV among PWID.
	HIV	OoR: Sawangjit et al., 2016 (core) Primary literature: no studies	Sawangjit et al. provide a statement of insufficient evidence	6 studies (2 COH, 4 CS). *N* = 2273 (range 328-1020).	Pooled effects were equivocal for pharmacy vs no NSP and positive for pharmacy vs other NSP	Given a statement of insufficient evidence from a core review, based on studies with mostly weaker designs, we conclude that the evidence is insufficient	Insufficient Statement based on 4 studies: 4 positive (4 CS). [overlap of one study with the Sawangjit et al. review]	There is **insufficient** evidence to either support or discount the effectiveness of pharmacy NSP in the prevention of the transmission of HIV among PWID.
	IRB	OoR: Sawangjit et al., 2016 (core) Primary literature: no studies	Sawangjit et al. provide a statement of sufficient evidence	11 studies (6 CS, 5 COH). *N* = 5455 (range 128-1181).	Pooled effect was positive for pharmacy NSP vs no NSP and equivocal for pharmacy NSP vs other NSP	Given a statement of sufficient evidence from a core review, based on a large number of studies of which numerous are robust, we conclude that the evidence is sufficient to support that pharmacy-based NSP is at least as effective as other types of NSP. Similarly, there is sufficient evidence that pharmacy-based NSP, relative to no NSP, is effective	Tentative Statement based on 13 studies: 9 positive (1 CC, 6 CS, 2 EC); 2 negative (2 COH); 4 no association (2 COH, 2 CC) [Note: Sawangjit et al included 2 studies that were also included in the 2011 RoR]	There is **sufficient** evidence to support that pharmacy-based NSP is at least as effective as other types of NSP in the prevention of IRB. There is also **sufficient** evidence that pharmacy-based NSP, relative to no NSP, is effective in the prevention of IRB.
Low dead space syringes (LDSS)	HCV	OoR: WHO, 2012 (supplementary) Primary literature: Trickey et al., 2018 (weaker)	N/A (supplementary reviews not consulted for their evidence statements)	WHO: 2 studies (2 CS). *N* = 1366 (range 515-851). Trickey: CS. *N* = 2174	WHO: positive pooled effect Trickey: positive finding	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	No statement	There is **insufficient** review-level evidence to either support or discount the effectiveness of LDSS provision in the prevention of HCV transmission among PWID.

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Table 5 (*continued*)

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement	Updated evidence statement
	HIV	OoR: WHO, 2012 (supplementary) Primary literature: no studies	N/A (supplementary reviews not consulted for their evidence statements)	2 studies (2 CS). $N = 1366$ (range 515-851).	Positive pooled effect	Although the supplementary review found a result in favour of LDSS use, as only two weaker studies were pooled, and no further primary studies were identified, there is insufficient evidence	No statement	There is **insufficient** review-level evidence to either support or discount the effectiveness of LDSS provision in the prevention of HIV among PWID.
	IRB	N/A‡	N/A	N/A	N/A	N/A	N/A	N/A
Drug preparation equipment	HCV	OoR: no reviews Primary literature: Fatseas et al., 2012 (weaker)	N/A	1 study (1 SCS). $N = 648$.	Equivocal finding	On the basis of one weaker study with an equivocal result, we conclude that there is insufficient evidence	Insufficient [statement was based on 1 positive CS study]	The evidence is **insufficient** to either support or discount the effectiveness of sterile drug preparation equipment in the prevention of HCV.
	HIV	OoR: no reviews Primary literature: Fatseas et al., 2012 (weaker)	N/A	1 study (1 serial CS). $N = 648$.	Positive finding	On the basis of one weaker study, albeit with a positive result, we conclude that there is insufficient evidence	No evidence	The evidence is **insufficient** to either support or discount the effectiveness of sterile drug preparation equipment in the prevention of HIV.
	IRB	OoR: no reviews Primary literature: Patel et al., 2018 (robust) 10 weaker: Aspinall et al., 2012; Behrends et al., 2017; Fatseas et al., 2012; Kim et al., 2015; Mehrabi et al., 2020; Naserirad et al., 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 and so counted as 1 study]	N/A	9 studies (1 COH, 1 COH and CS [same publication], 5 CS, 2 SCS). $N = 6644$ (range 148-2037).	6 positive (1 COH, 1 COH/CS, 2 CS, 2 SCS); 1 mixed positive and equivocal results (1 CS); 2 equivocal (2 CS)	On the basis of consistent 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	Tentative Statement based on 15 studies: 10 positive (6 COH, 4 CS); 5 no association (2 COH, 3 CS). Adding the studies from the updated review brings the total to 24 studies: 16 positive (8 COH, 6 CS, 2 SCS); 7 no association (2 COH, 5 CS); 1 mixed positive/equivocal (CS)	Considering the evidence across the updated review and the 2011 RoR, the balance of the evidence is weighted heavily towards the positive studies, of which a good proportion have robust designs. Furthermore, the studies with equivocal findings are mostly of weaker designs. We conclude that there is **sufficient** evidence to support the effectiveness of sterile drug preparation equipment in the prevention of IRB.

CC = case-control; COH = cohort; CI = confidence interval; CS = cross-sectional; EC = ecological; HCV = hepatitis C virus; IF = injection frequency; IRB = injecting risk behaviour; LDSS = low dead space syringes; NSP = needle and syringe programme; N/A = not applicable; OR = odds ratio; OoR = overview of reviews; PWID = people who inject drugs; py = person years; RoR = review of reviews; RR= risk ratio; SCS = serial cross-sectional; SC = seroconversion;

* Note: supplementary studies were not relied upon because Davis et al. identified mainly the same studies as Platt et al. and Abdul-Quader et al. only looked at studies with weaker designs

** The cross-sectional studies included here examined incidence of HCV infection (as opposed to 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, given they used a stronger measure of exposure (coverage of NSP – i.e. percentage of injections covered by clean needles/syringes), as opposed to the North American studies, which measured frequency of attendance at NSP.

† Supplementary review was not consulted because of sufficient statement from the core review.

‡ Low dead space syringes do not impact on injecting risk behaviour.

evidence across the 2011 RoR and 2020 OoR, the evidence statement remains "insufficient" (Table 5).

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 use of pharmacy-based NSP, compared to no NSP, based on several studies (pooled OR 0.50, 95% CI 0.34-0.73, 6 studies). Comparing use of pharmacy-based with other types of NSP showed no significant difference in IRB (pooled OR 1.46, 95% CI 0.78-2.73, 7 studies). Given a statement of sufficient evidence from a core review (based on a large number of studies of which numerous had robust designs), we concluded that the evidence is sufficient to support that pharmacy-based NSP is at least as effective as other types of NSP. Similarly, we also concluded that there is sufficient evidence that pharmacy-based NSP, relative to no NSP, is effective in reducing IRB. The evidence statement was "tentative" from the 2011 RoR, therefore the updated evidence statement becomes "sufficient" (Table 5).

Low dead space syringe provision

Effects on HCV transmission

A supplementary systematic review (WHO, 2012) (supplementary Table S4) suggested a reduced risk of HCV associated with use of LDSS compared to HDSS (pooled RR 0.49, 95% CI 0.44-0.55) but was based on only two studies, which were cross-sectional in design and based on differences in prevalent HCV infections (i.e. not new/incident infections). An additional primary study found a lower likelihood of prevalent HCV associated with LDSS use (AOR 0.77, 95% CI 0.64-0.93), although this was also a cross-sectional design (Trickey et al., 2018). Therefore, given three studies with positive findings but weak designs, we concluded that the level of evidence is insufficient. LDSS were not considered in the 2011 RoR.

Effects on HIV transmission

The same supplementary review as above (WHO, 2012) also looked at HIV as an outcome, and found a pooled effect size that suggested a reduced risk of HIV associated with use of LDSS (RR 0.29, 95% CI 0.18-0.46), based on two cross-sectional studies. No additional primary studies were found. Therefore, based on only two studies with weaker designs, we concluded that the level of evidence was insufficient. There was no statement of evidence from the 2011 RoR.

Provision of sterile drug preparation equipment (paraphernalia)

Effects on HCV transmission

We identified no reviews and only one study that looked at the association between sterile drug preparation equipment provision and HCV/HIV (Fatseas et al., 2012), which had an equivocal finding (a non-significant decline in HCV prevalence over time) and employed a weaker study design (supplementary Table S5). Therefore, given one weaker study with an equivocal result, we concluded that the level of evidence was insufficient. The 2011 RoR made a statement of "insufficient" evidence, also based on one study (albeit with a positive result). The combined level of evidence across the 2011 RoR and the 2020 OoR, however, remains insufficient (Table 5).

Effects on HIV transmission

We identified no reviews and only one primary study that had a weaker study design (Fatseas et al., 2012). The evidence was therefore graded as "insufficient". Given no evidence in the 2011 RoR, the updated evidence statement is therefore "insufficient".

Effects on injecting risk behaviour

No reviews were identified; however, we found eleven studies looking at the association between provision of sterile drug preparation equipment and injecting risk behaviour (Aspinall et al., 2012; Behrends, Li, & Gibson, 2017; Fatseas et al., 2012; Kim, Jin, McFarland, & Raymond, 2015; Mehrabi et al., 2020; Naserirad & Beulaygue, 2020; Nazari et al., 2016; Noroozi et al., 2018; Patel et al., 2018; Rezaie et al., 2017; Welch-Lazoritz et al., 2017) (Table S5). Studies reporting ORs ranged 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 (0.22-1.67) for sharing any items of drug preparation equipment (Table S6). Although the majority of these studies had weaker designs, the conclusion – on the basis of the balance of evidence combined with that from the 2011 RoR – was that the evidence was sufficient (Table 5).

Combination interventions (OAT and NSP)

Effects on HCV transmission

One review and meta-analysis looked at the impact of combined OAT and NSP on HCV (Platt et al., 2017) and found a 74% reduction in risk of HCV associated with uptake of combined OAT plus high coverage NSP vs. no OAT and low or no NSP coverage (RR 0.26, 95% CI 0.07-0.89, based on 3 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 robust 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). 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 concluded that there is tentative evidence. The 2011 RoR did not make an explicit statement of "sufficient", or "tentative", etc. However, considering the pooled evidence across both the 2011 RoR and updated review, there are two meta-analyses that have statistically significant findings in favour of combined OAT and NSP, which between them are based on 10 studies, 4 of which have robust designs. We therefore concluded that the overall level of evidence is sufficient (Table 6).

Effects on HIV transmission

No reviews or studies looking at the effect of combined interventions on HIV were identified. The 2011 RoR did not make an explicit statement of evidence, but our assessment of the underlying evidence (i.e. no clear and consistent statement of evidence, based on a very small number of studies ($n = 2$) with mixed designs) leads to the conclusion that the level of evidence is insufficient (Table 6).

Effects on injecting risk behaviour

No reviews or studies looking at combined interventions on injecting risk behaviour were identified. Again, the 2011 RoR did not make an explicit statement of evidence; however, a meta-analysis identified in the 2011 RoR found a pooled effect size of 0.52 (95% CI 0.32-0.83), based on 6 studies, 2 of which had robust designs. 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 (Table 6).

Drug consumption rooms

Effects on HCV transmission

Only two studies with weaker (cross-sectional) designs were identified that looked at an association between DCR use and HCV (Folch et al., 2018; Kennedy, Hayashi, Milloy, Wood, & Kerr, 2019) (Table S5). Both found no significant difference in HCV prevalence among

Table 6
Evidence for opioid agonist therapy and needle and syringe programmes in combination.

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement*	Updated evidence statement
Combination OAT and NSP	HCV	OoR: Platt et al., 2017 (core) Primary literature: Minoyan et al., 2020 (robust)	Platt et al. provide a tentative statement of evidence	Platt: 4 studies (2 COH, 2 CS). *N* = 8706 (range 168-7954). Minoyan: COH. *N* = 3327.	Platt: Positive pooled effect among all 4 studies, as well as among subset of 3 studies that presented an adjusted effect Minoyan: Equivocal: finding	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	Statement unclear Statement based on 2 positive studies: 1 COH and 1 meta-analysis of 6 UK studies involving 2 COH and 4 CS [the cohort study overlapped with the Platt et al review] Considering the evidence across the 2011 RoR and updated reviews, there are therefore 2 positive meta-analyses: one involving 6 studies (2 COH, 4 CS) and the other involving 4 studies (2 COH, 2 CS)	There is **sufficient** evidence that participation in full harm reduction programmes involving OAT and NSP, in combination, is effective in the prevention of HCV transmission among PWID.
	HIV	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	Statement unclear Statement was based on 2 studies: 2 positive (1 COH, 1 SCS)	There is **insufficient** evidence that participation in full harm reduction programmes involving OAT and NSP, in combination, is effective in the prevention of HIV transmission among PWID.
	IRB	OoR: no reviews Primary literature: no studies	N/A	N/A	N/A	No evidence	Statement unclear Statement based on 1 positive study: a meta-analysis of 6 UK studies involving 4 CS and 2 COH	There is **tentative** evidence that participation in full harm reduction programmes involving OAT and NSP, in combination, is effective in the prevention of IRB among PWID.

groups with varying levels of DCR use. Given no reviews, and only two weaker primary studies with equivocal results, we concluded 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 remained 'insufficient' (Table 7).

Effects on HIV transmission

The same two studies above (Folch et al., 2018; Kennedy et al., 2019) looked at 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 frequency. Therefore, based on only two weaker studies with mixed findings, we concluded that the evidence was 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 concluded that the updated evidence statement remains "insufficient" (Table 7).

Effects on injecting risk behaviour

One supplementary review looked at 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 injecting risk behaviour 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 'use of non-sterile equipment or equipment sharing' over time (since baseline) among PWID who initiated use of the 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 other risk behaviours including reuse of syringes, and using 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 concluded 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 concluded that the evidence is tentative (Table 7).

Discussion

The level of evidence has increased since the 2011 review of reviews (RoR) with now sufficient evidence for the effectiveness of OAT (for preventing HIV, HCV and IRB), NSP (for preventing HIV and IRB), and combination OAT and NSP (for preventing HCV). There is also sufficient evidence for the effectiveness of OAT in prison settings (for preventing IRB/IF), NSP in pharmacy settings (for preventing IRB), IECS interventions (for preventing IRB/IF), and provision of sterile drug preparation equipment (for preventing IRB). For the first time, the evidence for OAT also incorporates evidence on HCV reinfection as an outcome. There is still no or insufficient evidence for many of the interventions – including for HAT, treatment for stimulant dependence, CM, technology-based psychosocial interventions, LDSS and DCRs. There is also a lower level of evidence for OAT and NSP when delivered in specific settings, such as in prison. The previous and updated evidence statements are presented in Table 8.

Even though there is a robust evidence base for NSP and OAT, levels of provision of these interventions are still inadequate in most countries, with global coverage estimated at an average of 33 (21–50) needle/syringes distributed via NSP per PWID annually, and 16 (10–24) OAT recipients per 100 PWID (Larney et al., 2017). The scale-up to, and maintenance of, high coverage NSP and OAT are required in order for countries to reduce HIV and HCV incidence, and thereby make progress against global elimination targets (United Nations, 2015; World Health Organization, 2016).

This work underpins updated guidance for the prevention of infectious diseases among PWID (ECDC & EMCDDA, 2022). The original guidance, published in 2011, was translated into 15 languages, was widely disseminated and reached a significant group of decision makers and practitioners in the field of infectious diseases, public health, and drug misuse services, both in Europe and internationally (ECDC & EMCDDA, 2011a). While many countries have scaled up the coverage of services, progress is still incomplete and considerable gaps in intervention coverage exist. The availability of authoritative information on effective interventions among PWID is a critical tool for policy makers and practitioners to leverage in order to improve service coverage and achieve a reduction in blood-borne viruses at population level.

It should be noted that when we refer to 'sufficient' evidence, this does not necessarily mean that there is global evidence for effectiveness, as most of the included studies were conducted in high income countries (Western Europe, North America and Australia). Therefore, a major limitation of the reviews is that the evidence is not necessarily applicable to low and middle income countries.

We acknowledge the general limitations of the RoR/OoR methodologies (Baker, Costello, Dobbins, & Waters, 2014; Ellis et al., 2003) applied to mostly observational studies: in particular, that the quality of reporting of the review has to be used as a proxy for the quality of the review itself, and thus 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. It is possible that relevant reviews or studies were missed in our literature searches. We took steps to reduce this risk: we included non-English language papers, as well as undertaking 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.

Our approach for updating the 2011 RoR specified that, for interventions and outcome combinations where the level of evidence was already deemed "sufficient" in the RoR, these did not need to be updated (this applied to OAT and HIV, OAT and IRB/IF, and NSP and IRB). We based this decision on the reviews we identified between 2011-2020 for these intervention/outcome combinations: these reviews were not formally appraised and extracted, but it was evident from an inspection that they would not lead to a change in the levels of evidence. It is possible that additional primary studies published since 2011 might have resulted in a downgrading in the level of evidence. However, there are additional justifications for not updating the evidence base. While we accept that estimates of intervention effectiveness may change with temporal changes in drug types and BBV epidemiology (for example, a shift to cocaine injection may increase injection frequency and the levels of circulating virus in a population affect BBV transmission risk), NSP and OAT have nevertheless been shown to be efficacious in reducing IRB (and HIV in the case of OAT) and we propose that there is not a lot to be gained from continually updating the evidence base for interventions that already have sufficient evidence of effectiveness. Rather, we recommend trying to identify and better understand factors that mediate effectiveness and therefore recommend that future research stratify effect estimates by drug type and epidemic trends.

When conducting critical appraisal, it should be recognised that there remains an element of subjectivity. We attempted to reduce the effect of subjectivity by having two reviewers critically appraise each study independently and a third reviewer resolve discrepancies. 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

Table 7
Evidence for drug consumption rooms.

Intervention	Outcomes	Reviews/studies identified	Review statements of evidence	No of studies & study designs	Range of effect sizes	Evidence statement based on OoR and primary literature	2011 evidence statement*	Updated evidence statement
Drug consumption rooms (DCRs)	HCV	OoR: no reviews Primary literature: Folch et al., 2018 (weaker); Kennedy et al., 2019 (weaker)	N/A	2 studies (2 CS). *N* = 1321 (range 510-811).	2 equivocal (2 CS)	Based on no reviews, and only two weaker primary studies with equivocal results, we conclude that there is insufficient evidence	Insufficient Statement based on 1 CS study that showed no association.	There is **insufficient** evidence to either support or discount the effectiveness of DCRs in the prevention of HCV transmission among PWID.
	HIV	OoR: no reviews Primary literature: Folch et al., 2018 (weaker); Kennedy et al., 2019 (weaker)	N/A	2 studies (2 CS). *N* = 1321 (range 510-811).	1 positive (1 CS); 1 equivocal (1 CS)	Based on no reviews, and only two weaker primary studies with mixed results, we conclude that there is insufficient evidence	Insufficient Statement based on 1 CS study that showed no association.	There is **insufficient** evidence to either support or discount the effectiveness of DCRs in the prevention of HIV transmission among PWID.
	IRB	OoR: Kennedy et al., 2017 (supplementary) Primary literature: 1 weaker: Folch et al., 2018	N/A (supplementary review)	Kennedy: 6 studies (1 COH, 5 CS). *N* = 2192 (range 41-760). Folch: CS. *N* = 510.	Kennedy: 4 studies examined syringe sharing: 3 positive (3 CS); 1 equivocal (1 COH). 2 studies looked at other risk behaviours: 2 positive (2 CS) Folch: Positive finding	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 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	Tentative Statement based on 7 studies: 4 positive (2 COH, 2 CS), 3 no association (3 CS) [6 further studies document that clients' report of positive changes to their injecting practices can be attributed to DCRs] [overlap of 3 studies between the 2011 RoR and update; these are not added below] Considering the evidence across the 2011 RoR and updated review, the no. of studies becomes 7 positive (2 COH, 5 CS), 4 no association (1 COH, 3 CS)	There is **tentative** evidence to support the effectiveness of DCRs in the prevention of IRB among PWID.

Table 8
Summary of evidence statements from the 2011 Review of Reviews and updated level of evidence.

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
	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 - CM	HCV	Insufficient	No evidence
		HIV	Insufficient	No evidence
		IRB/IF	Insufficient	No evidence
	Psychosocial interventions - technology-based	HCV	No statement	No evidence
		HIV	No statement	No evidence
		IRB/IF	No statement	Insufficient
Needle and syringe programmes (NSP)	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 (LDSS)	HCV	No statement	Insufficient
		HIV	No statement	Insufficient
		IRB	N/A	N/A
	Provision of sterile drug preparation equipment (paraphernalia)	HCV	Insufficient	Insufficient
		HIV	No evidence	Insufficient
		IRB	Tentative	Sufficient
Combination interventions (OAT & NSP)		HCV	Tentative	Sufficient
		HIV	Insufficient	Insufficient
		IRB	Tentative	Tentative
Drug consumption rooms (DCRs)		HCV	Insufficient	Insufficient
		HIV	Insufficient	Insufficient
		IRB	Tentative	Tentative

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. Similarly, we did not perform a full critical appraisal of the primary studies (which was a deviation from the protocol), and instead used study design as a proxy for study quality, with trials and cohort studies providing 'robust' evidence and all other study designs providing 'weaker' evidence. This approach was based on the premise that stronger causal inferences can be derived from designs that have the lowest risk of bias. There are, however, clear limitations to this approach as bias can emerge in the design, implementation, and analysis stage in every type of study (for example, trials and cohort studies can have small sample sizes and samples that are not representative of the wider target population, and be at risk of attrition bias). Furthermore, as we have described in the section on NSP/HCV, designs that would traditionally be considered weaker can have innovative modifications that strengthen their causal inference.

As described above, our approach to grading and synthesising evidence differs to that used in Cochrane reviews, which may generate apparently discrepant statements of evidence: for example, Platt et al. rated the quality of evidence as 'very low' with regard to the impact of NSP on HCV acquisition, whereas our assessment (based mainly on the Platt review) was 'tentative evidence'. While they rated the evidence as very low, they nevertheless concluded that "high NSP coverage was associated with a reduction in the risk of HCV acquisition in studies in Europe", which we considered to be a tentative statement of evidence and translates into a final 'tentative' evidence statement according to our framework.

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 therefore it is not known exactly what the intervention comprised, at what dose or level of coverage, and for how long. For example, studies of NSP 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, as the level of exposure to an intervention 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.

For some of the interventions considered here, the lower level of evidence is likely attributable to a general absence of studies, and/or that studies are underpowered to detect differences in BBV outcomes. Given the barriers to conducting trials of public health interventions, future observational studies will require pooling across multiple studies to achieve power. Additionally, future studies need to consistently measure the intensity or coverage of interventions, which could be facilitated via the development of a standardised means of reporting/collecting information on intervention uptake.

We only included studies of PWID, which necessarily restricted the number of relevant reviews and studies. For some drug treatment/psychosocial interventions, there may be stronger evidence in relation to broader drug use outcomes, not just injecting – such as for CM in relation to opioid and stimulant use (EMCDDA, 2016a; Korownyk et al., 2019). (Notably, while the focus of some studies was not on BBV as the outcome of interest, outcomes such as a reduction in drug use may have positive indirect benefits in reducing risk of BBV acquisition.) Similarly, a lack of studies may be because BBV prevention is not the main objective of the intervention; there is existing evidence some interventions are effective in preventing other drug-related harms – for HAT in reducing street heroin use (Strang et al., 2015) and for DCRs in preventing fatal overdoses (Potier, Laprévote, Dubois-Arber, Cottencin, & Rolland, 2014) – and their implementation may be justified on this basis alone. Equally, despite the lack of data from studies conducted in prisons, their implementation may be justified based on the principle of equivalence of care (UN, 1991).

The evidence is generally stronger for behavioural outcomes which are more common (e.g. IRB and IF), as compared to biological outcomes (HCV and HIV), and this has consistently been observed across previous reviews (ECDC, 2011; MacArthur et al., 2014; Palmateer et al., 2010). One explanation for this could be that the relationship between injecting equipment sharing (associated with uptake of NSP) and BBV acquisition is not linear. Particularly for HCV, where there tend to be larger pools of infected PWID and the transmissibility of HCV is greater (as compared to HIV), comparatively few sharing events may still result in a high probability of HCV acquisition. Thus, it is possible that substantial reductions in levels of injecting risk behaviour 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 and recall biases. Although it has been suggested that self-reported behaviour by PWID can 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 injecting risk behaviours. For PWID who seek out services such as NSP or services that provide information/education/counselling interventions, 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 as compared to those who do not interact (or do not interact on a regular basis) with services. If this is the case, it would result in an overestimate of the effect size associated with the intervention.

In conclusion, there is now a stronger body of empirical evidence for the effectiveness of OAT and NSP, and the combination of these two interventions, in preventing injecting risk behaviour, HCV and HIV. However, there is still a relative lack of evidence for many interventions including HAT, treatment for stimulant dependence, contingency management, technology-based interventions, LDSS 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 in relation to the outcome of interest of this review. 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 can measure consistently, exposure to single interventions, or the intensity of harm reduction interventions.

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Ethics approval

The authors declare that the work reported herein did not require ethics approval because it did not involve animal or human participation.

Declarations of Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2022.103872.

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