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European Monitoring Centre for Drugs and Drug Addiction

TECHNICAL REPORT

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

Part 1:
Needle and syringe programmes and other interventions for preventing hepatitis C, HIV and injecting risk behaviour

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ECDC AND EMCDDA TECHNICAL REPORT

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Part 1: Needle and syringe programmes and other interventions for preventing hepatitis C, HIV and injecting risk behaviour

European Monitoring Centre
for Drugs and Drug Addiction

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The report was produced under contract ECDC/10/2246 with the Strathclyde Consortium by Eva van Velzen (University of Strathclyde/Health Protection Scotland (HSP)), Norah Palmateer (HPS), Sharon Hutchinson (University of Strathclyde/HPS), Hamish Innes (University of Strathclyde/HPS), Esther Aspinall (HPS), Matthew Hickman (University of Bristol), Kirsty Roy (HPS), Vivian Hope (London School of Hygiene and Tropical Medicine), Avril Taylor (University of West of Scotland), Alex Sanchez-Vivar (HPS), and David Goldberg (HPS).

This report builds on previous work of Norah Palmateer, Jo Kimber, Matthew Hickman, Sharon Hutchinson, Tim Rhodes and David Goldberg (2008).

This technical report is complemented by another technical report titled 'Evidence for the effectiveness of interventions to prevent infections among people who inject drug, Part 2: Drug treatment for preventing hepatitis C, HIV and injecting risk behaviour among people who inject drugs'. Both technical reports accompany the 'ECDC-EMCDDA Guidance: Prevention and control of infectious diseases among people who inject drugs' which is also published 'In brief'.

Errata
The following corrections were made on 27 September 2012:
Page 44: the first three lines were deleted.
Pages 46–56: the list of references was corrected and expanded.

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Contents

Abbreviations and glossary

BBV	Blood-borne viruses
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU	European Union
Harm reduction	Policies, programmes, and interventions seeking to reduce the health, social and economic harms of drug use to individuals, communities and societies
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IEC	Information, education, and counselling
IRB	Injecting risk behaviour
Low-threshold services	Low-threshold services are social and health services for people who use drugs, including counselling, needle and syringe programmes, drug treatment, and shelter. The low-threshold approach aims to reach more users with problematic use patterns earlier and to remain in contact with this highly problematic group of drug users in order to prevent health damage while at the same time not requesting abstinence.
MMT	Methadone maintenance treatment
NSP	Needle and syringe exchange programmes
OR	Odds ratio
OST	Opioid substitution treatment
PWID	People who inject drugs
RCT	Randomised controlled trial
RoR	Review of reviews
VCT	Voluntary counselling and testing

Executive summary

Introduction

This report presents the results of two literature reviews. The aim of the reviews was to provide evidence to inform the recommendations made by ECDC and the EMCDDA in the 2011 publication 'Guidance on the prevention and control of infectious diseases among people who inject drugs'.

The evidence presented here focuses on the effectiveness (and in some cases the cost-effectiveness) of the following interventions: the provision of needles and syringes; the provision of other (non-needle and syringe) drug preparation equipment; the provision of foil to stimulate route transition; the provision of information, education and counselling; knowledge of hepatitis C status; disease treatment; modes of service delivery including supervised injecting facilities; and access to, retention in, and combination of interventions. Additional evidence on the effectiveness of drug treatment is covered in a companion technical report 'Evidence for the effectiveness of interventions to prevent infections among people who inject drugs, Part 2: Drug treatment for preventing hepatitis C, HIV and injecting risk behaviour'.

The evidence included in this report is based on published research and does not present exhaustive evidence for the effectiveness of public health interventions, as different types of evidence may be considered, for example expert opinion or 'best implementation practices'. There are also other reasons for providing some of the interventions reviewed here, such as to attract and attach users to services and, while such outcomes were out of the scope of this review, these factors may provide rationale to include certain interventions as part of successful multi-component intervention programmes, even in the absence of their effectiveness in decreasing hepatitis C, HIV, and injecting-risk behaviour.

Methods

Two literature reviews were conducted for this report. For the first review, a 'review of reviews' method was applied: only reviews (published between 2000 and 2011) were included. Reviews are considered high-level evidence because they summarise and collate findings from the primary literature. In this review of reviews we investigated the effectiveness of a number of (established) interventions, including the provision of needles and syringes; the provision of other (non-needle and syringe) drug preparation equipment; the provision of foil to stimulate route transition; the provision of information, education and counselling; knowledge of hepatitis C status; modes of service delivery including drug consumption rooms. Effectiveness was defined as the reduction in transmission of the human immunodeficiency virus (HIV), the hepatitis C virus (HCV), and the reduction of injecting risk behaviour among people who inject drugs.

Reviewing reviews is an efficient method of bringing high-level evidence together but, like any method, it has limitations. An absence of high-level evidence for effectiveness does not necessarily equate to evidence for the lack of effectiveness; instead it might signify that not enough research has been undertaken or published in reviews to sufficiently prove (in-)effectiveness. Another limitation is the lag time between the publication of a primary study and subsequent inclusion of a paper in a published review.

In addition to collating review-level evidence for effectiveness of interventions, we also reviewed papers published in the primary literature. In this second review, findings from primary research papers were summarised that related to access to, retention in, and combination of interventions covered in the review of reviews.

Main findings of the review of reviews

Provision of sterile needles and syringes, and models of delivery

The review-level evidence for the effectiveness of needle and syringe programme interventions is modest but improving. There is sufficient review-level evidence to show that needle and syringe programmes are effective in reducing injecting risk behaviour among people who inject drugs, and moderate evidence to show that they are effective in reducing HIV transmission. However, there is a lack of published reviews demonstrating that needle and syringe programmes are also effective in reducing hepatitis C (HCV) transmission. Nevertheless, ecological studies examining HCV transmission rates in the context of needle and syringe programmes have demonstrated stable or declining HCV rates, and a recently published meta-analysis indicates that needle and syringe programmes in combination with the provision of opioid substitution treatment are effective in reducing HCV transmission. We also found moderate evidence to indicate that distributing sterile needles/syringes through pharmacies is at least as effective as distributing them through other services. The available reviews did not provide evidence for the effectiveness of other models of distributing sterile needles/syringes; this was attributable

to a lack of reviews addressing the defined outcomes, but also to a lack of robust primary studies with comparable study designs.

Distribution of non-needle/syringe drug injecting equipment

There was moderate evidence for the effectiveness of the distribution of injecting equipment besides needles and syringes in reducing injecting risk behaviour among people who inject drugs, but we found no or insufficient evidence for the effectiveness in reducing HCV or HIV; only one primary paper, included in one review, had addressed these outcomes.

Information, education and counselling

Generally, the evidence was stronger for the reduction of injecting risk behaviour than for the reduction of HCV and HIV. For instance, we found relatively good evidence to support the effectiveness of outreach interventions, involving the provision of information, education and counselling to people who inject drugs, in reducing injecting risk behaviour. We found no or insufficient evidence in reviews, however, to show effectiveness in the reduction of HIV or HCV, because the reviews had not included these outcomes.

Provision of foil to stimulate route transition

The provision of foil as a method to stimulate 'route transition' from injecting to safer modes of using drugs is a recent intervention, documented in Europe since the end of the 1990s. No review-level evidence was found, but as mentioned before, this does not necessarily mean that providing foil is not effective; it does indicate, however, that there is a lack of published reviews on this topic.

Knowledge of HCV status

Based on a limited number of primary studies included in only one review, we concluded that there was insufficient evidence to indicate the effectiveness or the ineffectiveness of knowing one's HCV status (i.e. having been tested for HCV) on HCV transmission or reduction of injecting risk behaviour.

Supervised injecting facilities

We found moderate evidence to indicate the effectiveness of attending supervised injecting facilities in reducing injecting risk behaviour among people who inject drugs. There was a lack of reviews that had investigated the effectiveness of supervised injecting facilities on the reduction of HCV or HIV.

Cost-effectiveness of the provision of sterile needles/syringes and other equipment

We included reviews in this report which investigated evidence for cost-effectiveness of NSP and drug preparation equipment, but did not undertake a full economic evaluation. Based on the findings of two reviews, we concluded that there was not enough evidence to support or discount the cost-effectiveness of needle and syringe programmes in relation to HCV transmission. Much more evidence was available, however, in relation to the cost-effectiveness regarding HIV. Based on the findings of three reviews that support the cost-effectiveness of the provision of needles/syringes, we concluded that there is sufficient evidence for the cost-effectiveness of needle and syringe programmes for preventing the transmission of HIV, assuming that these programmes are effective in reducing HIV. We found no reviews that assessed cost-effectiveness of the provision of injecting equipment besides needles and syringes to people who inject drugs.

Main findings of the review of primary literature

The second review, which summarised findings from the primary literature, resulted in the following key findings.

- Low prices, geographical proximity, encouraging staff attitudes and the option to receive additional services from an NSP were facilitating factors for people who inject drugs to visit needle and syringe programmes. Conversely, geographical distance, a fear of being caught by the police whilst attending a needle and syringe programme, opening hours, and a lack of privacy can act as barriers.
- Based on recently published studies, there is now considerable evidence that higher levels of coverage of interventions (i.e. receiving adequately dosed opiate substitution treatment and at least one sterile needle/syringe per injection) are more effective than lower levels of coverage per person who injects drugs. The literature also indicates that offering a combination of interventions rather than offering them separately has benefits in terms of HCV and HIV transmission and in terms of increased access to care for people who inject drugs.
- Vaccination for infectious diseases may be offered to people who inject drugs from general healthcare providers, or through specialised low-threshold and outpatient facilities which offer needle and syringe programme and other services to drug users. The venue may influence uptake and completion of

vaccination courses. The included studies that looked at the advantages and disadvantages of these venues lacked coherence due to great differences in study design, setting and outcomes, but implied that offering vaccination in combination with other drug services at specialist facilities could result in higher uptake than through referral to general healthcare facilities.

- When considering the effect of offering diagnostic testing for HCV and HIV from the site of a needle and syringe programme, we found no studies that directly compared uptake of diagnostic testing provided from needle and syringe programme and non-programme sites. The results of two studies indirectly indicated that it may be effective to offer testing for blood-borne viruses at the site of a needle and syringe programme because many people who inject drugs already access these programmes.
- In relation to the merits of diagnostic testing and referral on the uptake of treatment for HCV by people who inject drugs, the literature suggests that active involvement of drug services and medical staff in the referral of people who inject drugs may be beneficial in increasing the uptake of HCV treatment among people who inject drugs.
- Studies included in the review in relation to HCV treatment outcomes among people who inject drugs could not be formally compared. A number of studies reported that despite chaotic lifestyles good treatment responses can be achieved in people who inject drugs, but the literature also indicated considerable treatment drop-out rates.

Recommendations for further research

Both reviews have resulted in a collation of evidence from the literature. They show that the evidence for effectiveness of many interventions reviewed is increasing but remains limited, and that most of the evidence stems from observational studies. They also indicate a great variety of types of research papers that investigated different ways of implementing services that provide interventions.

Additional (robust) research into effectiveness and modes of implementation of services to prevent infections among people who inject drugs is required to provide a clear scientific evidence base that can complement evidence based on expert opinion and practical experiences from drug services in a meaningful way.

In particular, additional attention to research that allows comparison of combinations and modes of delivery of interventions as well as levels of coverage of these interventions is crucial in order to determine the most effective manner and level at which to delivery services to prevent infections among people who inject drugs.

1 Background and aim

In 2011, the European Centre for Disease Prevention and Control (ECDC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) sought to review the scientific evidence base for the ECDC–EMCDDA Guidance on the prevention of infectious disease among people who inject drugs. The aim of this report was to provide an up-to-date body of scientific evidence to enable decision-making on topics to be included in the guidance by:

- synthesising the available (review-level) research evidence on the effectiveness (and in some cases the cost-effectiveness) of the following interventions: the provision of needles and syringes; the provision of other (non-needle and syringe) drug preparation equipment; the provision of foil to stimulate route transition; the provision of information, education and counselling; knowledge of hepatitis C status; modes of service delivery including supervised injecting facilities in reducing the transmission of HCV, HIV and injecting risk behaviour; and
- reviewing primary literature pertaining to topics relating to (the implementation of) these interventions.

2 Methods

In 2008, in the context of a significant number of people infected with HCV in the UK, a collaboration was established to review and summarise the available research evidence on the effectiveness of harm reduction interventions in the prevention of HCV among PWID. As time and resources did not permit a full systematic review of the range of potential interventions, a 'review of reviews' (RoR) approach was used. The RoR method is a method of systematically bringing together the evidence captured in reviews which themselves have captured evidence from primary studies. Results of this original RoR exercise have been published previously in peer-reviewed journals and grey literature reports (Kimber et al., 2010; Palmateer et al., 2010; Palmateer et al., 2008). The existing review, carried out by a consortium including the original RoR authors (see p. ii), was to serve as the basis of this evidence report, but required updating. Thus, in this report the results of the update of the RoR and an additional literature review on topics related to the interventions covered by the RoR are presented.

2.1 Review of reviews

The RoR approach is based on methods developed by the Health Development Agency (Kelly et al., 2002). Given the increasing number of reviews of the effectiveness of public health interventions in the literature, the goal of the RoR methodology is to bring together the evidence from such reviews, rather than undertake a systematic review of the primary literature in itself. Briefly, the RoR methodology entails the following steps:

- a systematic search of the literature for published reviews;
- a selection of relevant systematic, meta-analytic, and narrative reviews;
- a critical appraisal of the selected reviews; and
- a synthesis of the findings into an evidence briefing.

Previously, we had applied the RoR methodology to a report titled 'Evidence for the effectiveness of harm reduction interventions in preventing hepatitis C transmission among injecting drug users: a review of reviews' generated for the Prevention Working Groups of the Advisory Council on the Misuse of Drugs and the Hepatitis C Action Plan for Scotland (Palmateer et al., 2010). In the RoR component of this report, we have updated our previous work by Palmateer et al. (2010) to include newly published review-level evidence up to March 2011. In updating the RoR, the same methods were applied as in the original RoR with some minor adaptations, as detailed below.

Topics

The topics included in the RoR were:

- provision of sterile needle and syringes (NSP);
- models of service delivery for NSP; NSP through pharmacies, vending machines, outreach, supervised injecting facilities;
- the provision of (non-needle and syringe) drug preparation equipment;
- information, education, and counselling (IEC);
- diagnostic testing;
- provision of foil[1]; and
- cost-effectiveness of NSP and distribution of other drug preparation equipment.

All topics included in the RoR related to the following outcomes in PWID:

- Transmission of HCV
- Transmission of HIV
- Injecting risk behaviour

In addition, all included core reviews were screened for the following two outcomes:

- Reduction in number of BBV outbreaks
- Maintaining low prevalence of BBV in a given population

[1] This topic was not included in the original RoR (2000–2007); the literature for this topic was thus only searched for 2007–2011 as opposed to all other topics. This however was not deemed to add bias to the results, as the provision of foil is a new intervention and will therefore not have been covered in reviews published prior to 2007.

However as it was found that only one review had included these outcomes, its results have been included in the narrative summary (see effects on HIV incidence/prevalence in the NSP, section 3.1) rather than as separate outcomes.

Identification of the reviews and period covered

The literature search focused on the selected harm reduction interventions and outcomes listed above. A list of the search terms used in the ROR can be found in Appendix A-1 (relating to the original RoR) and A-2 (relating to the updated RoR). Databases were searched with principally identical search terms in both the original and the updated RoR. However, due to changed profiles of, and access rights to, databases, some of these databases were searched through different portals for the updated RoR (summarised below and detailed in Appendix A-1 and A-2). To maximise the retrieval rate, the search strategies combined Medical Subject headings (MeSH terms) with textual words.

The following electronic databases were searched:

- Cochrane Library (through Wiley InterScience in the original RoR and OVID gateway in the updated RoR)
- EMBASE (through OVID gateway in both the original and updated RoR)
- MEDLINE (through OVID gateway in both the original and updated RoR)
- CINAHL (through OVID gateway in the original RoR and EBSCOhost in the updated RoR)
- PsycINFO (through WebSPIRS 5 in the original RoR and EBSCOhost in the updated RoR)
- IBSS (through WebSPIRS 5 in the original RoR and CSA Illumina).

We also searched grey literature publications listed on the websites of key international agencies for harm reduction. These included: the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA), the National Institute on Drug Abuse (NIDA), the US Institute of Medicine, the United Nations Office on Drugs and Crime Prevention (UNDCP), and the World Health Organization (WHO).

In the original RoR, databases were searched from January 1980 to the end of February 2007 with the exception of CINAHL, which was searched from January 1982 to the end of February 2007. At the screening stage it became apparent that the relevant reviews from the 1980s and 1990s had been superseded or updated by more recent reviews; consequently, the period was restricted to 2000 onwards. For the updated RoR, the aforementioned databases were searched again from March 2007 to the end of March 2011. The literature search was limited to English language reviews only.

Selection of relevant reviews

The criteria for inclusion of a review were:

- systematic review, synthesis, meta-analysis, or literature review;
- consideration of the effectiveness, or the cost-effectiveness, of one or more of the interventions listed above in the topics (see section 2.1); and
- relevance to the prevention of HCV, HIV, or injecting risk behaviour among PWID[2].

The criteria for exclusion of a review were:

- review about interventions targeting the sexual transmission of HCV or HIV;
- RoR, i.e. reviews that did not include primary studies.

In the original RoR, screening of abstracts of the retrieved papers was undertaken by two independent reviewers. If there was disagreement between the two reviewers regarding the relevance of an abstract, or it was unclear from the abstract whether it should be included, the full paper was retrieved for a more detailed evaluation by both researchers until consensus was established. For the update of the RoR, this process was largely repeated, but one reviewer undertook the initial screening of titles and abstracts for relevance; thereafter, two reviewers further screened the articles for inclusion in the critical appraisal process (see flowchart, section 3).

Critical appraisal

Critical appraisal was undertaken by two independent reviewers. In both the original and the updated RoR, the reviews selected for inclusion were critically appraised using a tool developed by the HDA, included in Appendix B (Kelly et al., 2002). The tool provides a guide to assess the reviews according to the strength of the methods used to identify, select, and appraise the relevant literature; the quality of methodological analysis (in the case of meta-analyses); the appropriateness of the conclusions; and the relevance to the EU population.

[2] This was expanded to include all drug users in the case of the provision of non-injection drug preparation equipment (e.g. crack pipes) as an intervention.

The tool does not assign a score. Rather, it directs the reviewer to consider criteria that are important in judging the quality and relevance of a review. Upon consideration of these criteria, the reviewer then categorises the papers as one of the following:

1. To be included as data where the whole of the review is judged to be of high quality
2. To be included as data where only part of the review is judged to be of high quality
3. To be included only as potential background or contextual material

Papers that were categorised as 1 or 2 were included here as 'core' reviews: the evidence from these reviews would form the basis from which to derive evidence statements about the effectiveness of harm reduction interventions. The remaining papers were retained as 'supplementary' reviews: these reviews were not considered to be of sufficient quality to rely on the authors' conclusions, but were seen as a source of useful references for primary review or as providing complementary information on the effectiveness of the interventions.

Appraisal of primary literature retrieved through reviews

The design of a study has significant bearing on the causal inferences that can be derived from it, and hence on its contribution to the evidence base. In this report, when we refer to the primary literature included in the reviews, we frequently refer to studies being more or less 'robust', or providing 'strong' versus 'weak' evidence. This appraisal is based on study design rather than on systematic critical appraisal of primary studies. Appendix C includes a summary of the types of study designs (and their limitations) that have typically been used to investigate the effectiveness of harm reduction interventions and how they were graded based on study design.

Allocation of evidence statements

Subsequent to the presentation and discussion of the evidence, an 'evidence statement' is made: the process for deriving and the format of evidence statements are based on the HDA RoR methodology (Kelly et al., 2002). Table 1 outlines the four types of evidence statements and the level of evidence that is required to support each statement.

It should be noted that a lack of evidence at review-level, indicated by the evidence statement, may reflect a lack of primary research undertaken or published, rather than evidence for a lack of effectiveness.

Table 1. Types of evidence statements and the level of evidence that was required to support each statement*

Evidence statement	Level of evidence
Sufficient review-level 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 review-level 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 review-level 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 review-level evidence	• No core or supplementary reviews of the topic identified, possibly due to a lack of primary studies

** Modified from Ellis et al.*

2.2 Methods of the review of primary literature

The second part of this report consists of the results of a review of the primary literature, relating to a number of specific topics (detailed below). The literature was searched systematically, but due to time and resource constraints, we did not apply a systematic method of appraising and grading the literature.

Topics

In March 2011, additional gaps in the existing evidence base were identified by ECDC and the EMCDDA. Eight additional topics were subsequently selected in April 2011 to be included in a review of the primary literature. These topics all related to access to, retention in, and combinations of services providing the interventions included in the review of reviews. The following eight topics were included in this review:

- Factors pertaining to (the environment of) a needle and syringe provider that encourage people who inject drugs to visit the NSP again, i.e. that increase client satisfaction.
- Combinations of models of service delivery ('mix of services') effective in reducing HCV/HIV transmission and injecting risk behaviour.
- The level of coverage of services required to reduce HCV/HIV transmission in people who inject drugs.
- Vaccination uptake and completion rates of HBV, HAV and tetanus vaccines in people who inject drugs when vaccination is offered at an NSP site.
- Uptake of diagnostic testing for HCV/HIV when offered on site at an NSP site.
- Association between diagnostic testing and referral on uptake of treatment for HCV by people who inject drugs.
- Response to treatment of HCV in people who inject drugs.
- Association between the provision of IEC and occurrence of bacterial skin infections.

Retrieval of publications

For each topic, separate search terms were used (Appendix L). Searches were undertaken in the Medline, Embase (including in-process and other non-indexed citations) and Cochrane Reviews databases through OVID. We applied two limits:

- Time period January 2000–March 2011 (with the exception of topic 4, for which the time period was January 1980–March 2011)
- Papers written in English.

The criteria for inclusion of a publication in the summary tables were:

- The paper considered the exposure and outcomes as stipulated in the list of topics.
- The paper was relevant to PWID and the opinions or characteristics of PWID (e.g. not those of policy makers).

The exclusion criteria were:

- The publication pertained to interventions targeting sexual transmission of blood-borne viruses (BBV).

No restrictions on study design were applied.

The literature searches were run by one researcher who thereafter screened the abstracts for relevance. This resulted in the selection of papers whose methods and main results were summarised in a number of tables. A number of papers were added after a review of references in included papers. Per topic, a concise narrative was added to summarise the papers' findings.

2.3 Format of the report

The RoR results section of this report is divided into chapters, each considering the evidence for a specific intervention with regard to three outcomes: (i) HCV transmission, (ii) HIV transmission, and (iii) injecting risk behaviour. Appendices D to K provide summaries of conclusions of primary studies that were included in the core reviews. These conclusions were based on the reviewers' summaries of findings in the primary papers.

The evidence statements for all interventions and outcomes have been summarised and included in Appendix M.

The second section of the results section of this report (section 4) is dedicated to the review of primary literature papers. For each topic, research papers were summarised in tables and accompanied by a narrative summary.

3 Results: Review of reviews

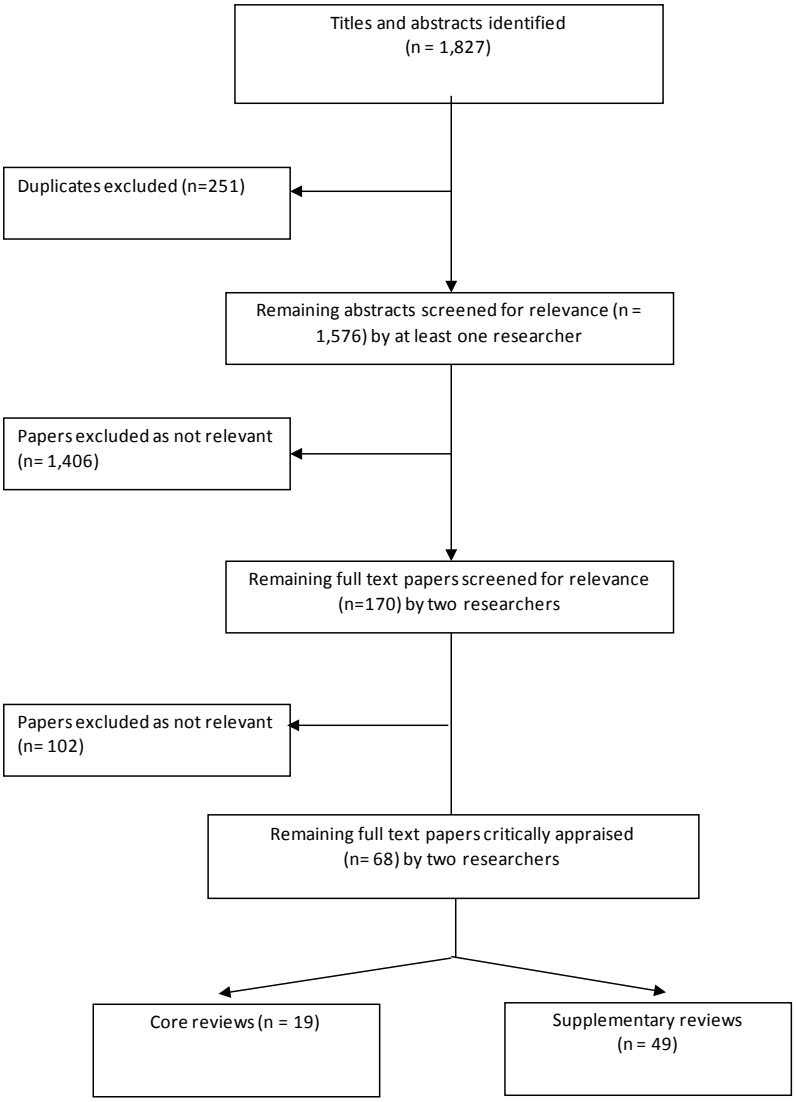
3.1 Number of reviews retrieved for the review of reviews

The search (up to March 2011) generated 1576 unique references (excluding duplicates). After screening, a total number of 19 core reviews and 49 supplementary reviews were included (see Figure 1 and Appendix K for further details).

In the updated RoR (see Appendix K), the reviewers concluded that four reviews met the criteria for inclusion as core reviews (Gillies et al., 2010; Jones et al., 2008; Jones et al., 2010; Medley et al., 2009) and four reviews were judged to be supplementary reviews (Hong and Li, 2009; Islam et al., 2008; Kerr et al., 2007; Nacopoulos et al., 2010). Two of the core reviews were by the same authors: the earlier grey literature report (Jones et al., 2008) reviewed both the effectiveness and cost-effectiveness of NSP, and the later peer-reviewed publication (Jones et al., 2010), stemming from the earlier grey literature report, reviewed the effectiveness of models of delivery of NSP. In the RoR, we extracted information on cost-effectiveness from the earlier grey literature report, and information on effectiveness of models of NSP provision from the later peer-reviewed publication (Jones et al., 2010).

Figure 1: Flow chart of reviews retrieved in the RoR (covering the period January 2000 to March 2011)*

* See Appendix K for further details.



3.1 Needle and syringe programmes (NSP)

The goal of needle and syringe provision is to reduce the sharing and reuse of needles/syringes and the transmission of blood-borne viruses among PWID by increasing access to sterile needles/syringes and removing potentially contaminated ones from circulation. This section begins with a consideration of the effectiveness of needle and syringe exchange programmes (NSP), which may exist as dedicated needle and syringe programmes, or in accident and emergency departments, genito-urinary medicine clinics, or primary care settings . Alternative means of providing needles/syringes – pharmacies, vending machines, and outreach – are addressed in the next section.

Three of the core review papers that met our critical appraisal criteria were of some relevance to NSP and were primarily drawn upon for the evidence of effectiveness of this intervention:

Gibson DR, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. AIDS. 2001 Jul 27; 15(11):1329-41.

Tilson H, Aramrattana A, Bozzette S, Celentano D, Falco M, Hammett T, et al. Preventing HIV Infection among Injecting Drug Users in High Risk Countries: An Assessment of the Evidence. Washington DC: Institute of Medicine; 2007.

Wodak A, Cooney A. Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users. Geneva: World Health Organization; 2004. Available from: http://www.who.int/hiv/pub/prev_care/effectivenesssterileneedle.pdf.
[Also published as: Wodak A, Cooney A. Do needle syringe programs reduce HIV infection among injecting drug users: a comprehensive review of the international evidence. Subst Use Misuse. 2006;41(6-7):777-813.]

A summary of these review papers is presented in Appendix D. Where appropriate, evidence from other reviews that did not meet our critical appraisal criteria ('supplementary reviews') was considered. The following supplementary reviews were considered:

Dolan KA, Niven H. A review of HIV prevention among young injecting drug users: A guide for researchers. Harm Reduct J. 2005 Mar 17;2(1):5

Dolan K, Rutter S, Wodak AD. Prison-based syringe exchange programmes: a review of international research and development. Addiction. 2003 Feb;98(2):153-8.

Stöver H, Nelles J. Ten years of experience with needle and syringe exchange programmes in European prisons, Int J Drug Policy. 2003 14, 437-44.

Wright NM, Tompkins CN. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. Harm Reduct J. 2006 Sep 6;3:27

Nacopoulos AG, Lewtas AJ, Ousterhout MM. Syringe exchange programs: Impact on injection drug users and the role of the pharmacist from a U.S. perspective. J Am Pharm Assoc (2003). 2010 Mar-Apr 1;50(2):148-57.

Hong Y, Li X. HIV/AIS behavioural interventions in China: a literature review and recommendations for future research. AIDS Behav. 2009 Jun;13(3):603-13.

Effects on HCV incidence/prevalence

Three core reviews considered HCV incidence or prevalence as an outcome in the assessment of the effectiveness of needle and syringe exchange programmes (NSP). The Institute of Medicine review (Tilson et al., 2007) was primarily concerned with HIV; the evidence considered in relation to HCV was not obtained through a dedicated literature search, but rather through studies that arose in the search for HIV prevention interventions. The review refers to the results of five studies, which led to the authors' conclusions that 'five studies provide moderate evidence that HIV prevention programs that include needle and syringe exchange have significantly less impact on transmission and acquisition of hepatitis C virus (HCV) than on HIV, although one case-control study shows a dramatic decrease in HCV and HBV acquisition.'

Wodak and Cooney (2004) referred to one HCV study, which is addressed by the two other reviews, but they did not make any statements on the effectiveness of NSP in this regard.

The Gibson et al. (2001) review included HCV and HBV seroconversion as outcomes and was therefore more likely to comprise the relevant literature; however, the review covered the period from 1989 to 1999 and many of the findings relating to HCV have been published subsequently. This review identified three studies: the results were mixed, with one study showing a decreased risk of HCV seroconversion associated with NSP and the two other studies showing no association. The authors did not formulate any conclusions with regard to the effectiveness of NSP in reducing HCV seroconversion, and it is apparent that there was insufficient evidence at the time the review was carried out.

Table D-2 (Appendix D) lists the primary studies included in each of the reviews. The three reviews covered a total of seven primary studies (only one of which was common to all); however, from a supplementary review that focused exclusively on HCV outcomes, it became apparent that there were more relevant papers upon which to build the evidence base. As part of the RoR update, a further two supplementary reviews were identified (Hong and Li, 2009; Nacopoulos et al., 2010) which covered primary studies published up to 2010.

The Wright and Tompkins review covered studies published up until the end of 2002. The results of these studies, together with the studies identified by the core reviews and the two added supplementary reviews discussed above, are listed in Table D-3. From this table, it becomes apparent that the few positive findings are mainly from studies with weaker designs. The findings from stronger study designs (cohort and case-control) for the most part showed no association between NSP and HCV seroconversion. Ecological and serial cross-sectional studies undertaken in various locations (USA, Scotland, Spain, India, and Australia) mainly documented evidence of stable or decreasing trends in HCV prevalence in the presence of NSP. However, given an absence of clear statements from the core reviews, and inconsistent evidence from the studies identified by a supplementary review, we concluded that there is insufficient evidence that NSP are effective in reducing HCV transmission.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of needle and syringe exchange programmes in reducing HCV transmission among PWID, although ecological investigations have demonstrated stable or declining HCV prevalence in the context of needle and syringe exchange programmes.

Effects on HIV incidence / prevalence

Three core reviews assessed the evidence with respect to HIV prevalence and incidence outcomes, covering 16 primary studies (see Table D-2, Appendix D). This summary will primarily focus on the Tilson et al. (2007) review, which is the most up-to-date of the three. This review identified 13 studies with HIV incidence or prevalence outcomes: four prospective cohort studies (Bruneau et al., 1997; Mansson et al., 2000; Schechter et al., 1999; Strathdee et al., 1997), two case-control studies (Patrick et al., 1997; van Ameijden et al., 1992), three ecological studies (Des Jarlais et al., 2005; Hurley et al., 1997; MacDonald et al., 2003), and two serial cross-sectional studies (Des Jarlais et al., 2005(a); Hammett et al., 2006). Prospective cohort and case-control study designs were considered to provide the strongest evidence. Other studies that did not form part of their evidence base, but were nevertheless included in their discussion were Des Jarlais et al. (1995) and Coutinho (2005). A summary of the results of the primary studies is presented in Table D-4 in the Appendix. In the presence of three core reviews, supplementary reviews (including the two supplementary reviews retrieved as part of the update of the RoR and mentioned in relation to HCV) are not described as their evidence did not alter the level of evidence.

The authors highlighted the findings of two prospective cohort studies conducted in Montreal and Vancouver (Bruneau et al., 1997; Strathdee et al., 1997) that associated NSP participation with a higher risk of HIV seroconversion. However, they acknowledged that the following could have contributed to, or accounted for, these results:

High-risk individuals being more likely to use the NSP:

- In both Vancouver and Montreal, the majority of NSP attendees were cocaine injectors, who inject much more frequently than heroin users and are therefore at higher risk of HIV infection.
- In Montreal, NSP users had higher baseline rates of HIV and HBV infection.

Operational characteristics of the NSPs:

- In both Vancouver and Montreal, there were limits on the number of needles/syringes users could obtain during a given visit, therefore many PWID accessing NSP may still have been engaging in risky injecting.

The availability of clean injecting equipment from other sources:

- Clean injecting equipment was also readily available through pharmacies in Montreal, and thus PWID who were classified as 'non-users' of NSP might nevertheless have had access to clean injecting equipment.

Moreover, Tilson et al. reported that declines in HIV prevalence among NSP users have since been documented: in Montreal, there was a decrease in HIV incidence from 6.1 per 100 person-years in 1995 to 4.7 per 100 person-years in 2004, after the limits on needles/syringes were increased and the provision of other injection equipment was commenced. Similarly, in Vancouver, HIV incidence among PWID fell following the implementation of a needs-based approach to NSP and the introduction of a variety of distribution methods, including mobile and home delivery. The reviewers also noted that a study conducted in the same setting found no association between NSP and HIV incidence (Patrick et al., 1997).

Tilson et al. (2007) highlighted several studies conducted in Amsterdam, where no relationship between NSP and HIV incidence was established (Coutinho, 2005; van Ameijden et al., 1992). They also made specific reference to ecological studies conducted in cities that had 'averted HIV epidemics' in which NSP was pursued as part of wider harm reduction programmes: Des Jarlais et al. demonstrated stable HIV prevalence (1995) and reductions in HIV prevalence and incidence (2005). Two other ecological studies compared HIV prevalence in cities with and without

NSP (Hurley et al., 1997; MacDonald et al., 2003): both found that prevalence fell in cities with NSP and rose in cities without NSP over the period examined. Lastly, (Ljungberg et al., 1991) found that HIV seroprevalence in a Swedish city where NSP had been introduced remained at 1%, whereas prevalence was higher in other Scandinavian regions with comparable drug using population.

Tilson et al. acknowledged the following limitations to the primary studies: (i) cohort studies were not randomised (i.e. randomly assigned to treatment and control groups), creating a risk of selection bias, and (ii) the study designs generally did not allow separate examination of programme elements, therefore making it difficult to attribute findings to NSP alone.

In drawing conclusions from the evidence, the authors considered the findings from ecological studies separately:

> 'Four ecological studies have associated implementation or expansion of HIV prevention programs that include needle and syringe exchange with reduced prevalence of HIV in cities over time and after considering the local prevalence of HIV at the time of program implementation or expansion – although a causal link cannot be made based on these studies. The evidence of the effectiveness of [NSP] in reducing HIV prevalence is considered modest, based on the weakness of these study designs.'

With respect to the remaining evidence the authors concluded that:

> 'Evidence regarding the effect of needle and syringe exchange on HIV incidence is limited and inconclusive.'

Wodak and Cooney (2004) assessed the evidence for whether NSPs fulfill the nine Bradford Hill criteria (strength of association, replication of findings, specificity of association, temporal sequence, biological plausibility, biological gradient, experimental evidence, coherence of the evidence, and reasoning by analogy) as well as five additional criteria (cost-effectiveness, absence of negative consequences, feasibility of implementation, expansion and coverage, unanticipated benefits, and special populations). With respect to strength of association, the authors referred to 10 studies involving HIV seroconversion or seropositivity as outcomes, among which five report a positive (protective) effect, two report a negative association, and three report no association (see Tables D-2 and D-4).

As did Tilson et al. (2007), the authors discussed possible explanations for the negative results observed in Vancouver and Montreal, including that NSPs may attract high-risk PWID, and that PWID may obtain sterile needles/syringes from sources other than NSP. In particular, they reiterate the arguments put forth by Gibson et al. (2001), which are described in further detail below.

The authors stated that there is convincing evidence that six of the Bradford Hill criteria (strength of association, replication of findings, temporal sequence, biological plausibility, coherence of the evidence, reasoning by analogy) and all of the additional criteria are fulfilled and hence conclude that 'there is compelling evidence that increasing the availability and utilization of sterile injecting equipment by PWID reduces HIV infection substantially.' A limitation of this review is that it does not consider separately the effects of NSP on HIV transmission versus injecting risk behaviour: it is possible that the evidence of effectiveness of NSP in reducing injecting risk behaviour had a bearing on conclusions drawn with respect to HIV. Indeed, the majority of the positive findings in the primary studies reviewed relate to an effect on injecting risk behaviour. Therefore, the statement that NSPs 'reduce HIV infection substantially' seems disproportionate to the evidence presented.

Gibson et al. (2001) reviewed studies published up until 1999; all of the studies they reviewed were also covered in the later reviews discussed above. Again, the authors postulated that negative and null findings are likely explained by bias, and cite examples of studies that have confirmed the presence of 'selection bias' (that NSP attracts high-risk users) and 'dilution bias' (the availability of other sources of syringes). Moreover, they noted that the negative and null findings were concentrated in studies conducted with PWID community samples (i.e. that compared users with non-users of NSP), whereas the studies conducted with NSP clients only (i.e. pre vs. post-intervention comparisons) all found positive associations. They also noted that a large number of the negative findings were conducted in settings where PWID have legal access to needles/syringes from pharmacies. Particular consideration of potential bias was given for the studies with negative results, but not for the studies which showed a protective effect of NSP. Other general limitations of the primary studies were noted: inconsistent controlling for confounders and crude measurements of NSP use.

Gibson et al. (2001) arrived at the overall conclusion that there is 'substantial evidence that syringe exchange programs are effective in preventing [HIV risk behaviour and] HIV seroconversion among PWID'. However, similar to Wodak and Cooney (2004), they considered the evidence relating to HIV in concurrence with the evidence relating to injecting risk behaviour. Given that they identified six studies of HIV with conflicting results – two showed an increased risk of HIV infection associated with NSP (Bruneau et al., 1997; Strathdee et al., 1997), one showed a protective effect of NSP (Des Jarlais et al., 1996), and three showed no association (Patrick et al., 1997; Schechter et al., 1999; van Ameijden et al., 1992) – it appears that the evidence was over-interpreted.

It is difficult to reconcile the somewhat conflicting conclusions of the three core reviews described above. The Tilson et al. (2007) review appeared to undertake the most rigorous evaluation of the primary studies, and was the only review to consider HIV incidence/prevalence as a separate outcome. Table D-5 presents the studies identified

in all of the core reviews, listed by direction of association (positive, negative or no association between NSP and HIV prevalence/incidence) and study design. The most rigorous studies (cohort and case-control) seem to provide conflicting evidence: two of the six cohort studies had positive findings, two had negative findings, and two had null findings. Neither of the two case-control studies established an association between NSP and HIV transmission. The equivocal results from cohort and case-control studies would appear to be consistent with the conclusions of Tilson et al. There is consistency in the evidence from ecological studies, but this must be considered in light of the weakness of this study design; again, this is consistent with Tilson and colleagues' conclusions. Given our assessment of the Tilson et al. review as the most rigorous, and the apparent consistency of their statements with the primary evidence, we based the evidence statements upon this review. Thus, on the basis of a tentative statement from one core review, supported by consistent evidence from less robust primary studies included in the original RoR and in the absence of robust new evidence stemming from the update of the RoR, we conclude that the level of evidence is tentative.

Evidence statement: There is tentative review-level evidence to support the effectiveness of needle and syringe exchange programmes in reducing HIV transmission among PWID although ecological investigations have demonstrated stable or declining HIV prevalence in the context of needle and syringe exchange programmes.

Effects on injecting risk behaviour

Injecting risk behaviour has been studied more frequently than biological outcomes such as HCV and HIV, and this is reflected in the numbers of primary studies identified by the core reviews. The three core reviews covered a total of 43 primary studies, 26 of which appeared in at least two of the reviews (see Tables D-2 and D-6 in the Appendix). In the presence of three core reviews, supplementary reviews are not described here, as their evidence did not alter the level of evidence.

Tilson et al. (2007) identified 14 prospective cohort studies that found participation in multi-component harm reduction programmes, which included NSP, resulted in reductions in self-reported needle sharing (defined as lending or borrowing needles/syringes). They also discussed studies that examined changes in injection frequency, but these will not be considered here. The reviewers highlighted the results of selected studies: Ouellet et al., Buthenthal et al. (2000), Schoenbaum et al. (1996), Gibson et al. (2002), and Vlahov et al. (1997) all demonstrated reductions in needle sharing; Hagan et al. (1993) found a decline in the frequency of 'unsafe injection'; whereas Hartgers et al. (1992) did not find an effect of NSP on needle sharing.

In addition to the limitations of the primary studies of HIV seroconversion outcomes (see previous section), Tilson et al. acknowledged an additional limitation of studies of injecting risk behaviour: that the measurement of risk behaviour relies on self-reported data, which can introduce bias if respondents tend to underestimate risky practices or overestimate protective practices.

Based on the evidence, the reviewers concluded that

> 'moderate evidence from a large number of studies and review papers – most from developed countries – shows that participation in multi-component HIV prevention programs that include needle and syringe exchange is associated with a reduction in drug-related HIV risk behaviour. Such behaviour includes self-reported sharing of needles/syringes, safer injecting and disposal practices, and frequency of injection.'

Wodak and Cooney (2004) identified 28[3] primary studies of injecting risk behaviour (defined as needle/syringe borrowing, lending, or reuse). Among these studies, there were 24 positive, one negative, and three indeterminate results relating to the association between NSP and injecting risk behaviour. As stated in the previous section, the review did not separately consider the effects of NSP on HIV transmission versus injecting risk behaviour, therefore, the discussion above of the evidence in fulfilling the Bradford Hill (and additional) criteria and the limitations of the primary studies also applies here. The reviewers did not formulate any conclusions specifically regarding injecting risk behaviour.

The 23 studies identified by Gibson et al. (2001) were covered in the later core reviews, with the exception of Broadhead et al. (1999), and Hagan et al. (1994). Both studies were suggestive of a protective effect of NSP: Broadhead et al. noted an increase in the reported reuse and sharing of syringes after the closure of an NSP, and Hagan et al. observed a decline in the proportion borrowing used syringes among NSP attendees (pre vs. post-intervention comparison). The limitations of the primary studies and the issues of bias highlighted by the reviewers are as discussed in the preceding section. The authors concluded that 'there is substantial evidence that syringe exchange programs are effective in preventing HIV risk behaviour [and HIV seroconversion] among PWID.'

Given the somewhat incompatible statements from two core reviews (with the third not formulating a conclusion related to injecting risk behaviour), we considered the evidence from the primary studies. Table D-7 in the Appendix lists collectively the studies included in the three core reviews by study design. For most study designs,

[3] Wodak and Cooney cited 29 studies, but one of these (Gibson DR, Flynn NM (2001) AIDS Research Institute, University of California, San Francisco) is not a primary research study.

the numbers of studies showing positive results are the overwhelming majority. Moreover, all of the studies which Tilson et al. considered to be strong in design and relevance, most notably cohort studies, demonstrated positive associations. Thus, based on consistent evidence across multiple robust studies, as well as moderate to strong statements of evidence in support of an effect of NSP on injecting risk behaviour from two core reviews included in the original RoR, and in the absence of robust new evidence stemming from the update of the RoR, we judged there to be sufficient review-level evidence.

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

Discussion and conclusions: Needle and syringe programmes

We concluded that evidence from the literature shows NSP to be effective in reducing self-reported injecting risk behaviour, but that the evidence relating to an effect of NSP in reducing HIV and HCV transmission is less conclusive. Ecological and serial cross-sectional studies have documented declines in HIV and HCV prevalence subsequent to implementation or expansion of NSP (although notably more consistently for HIV), suggesting that NSP may be effective as a component of a more comprehensive programme that includes a range of harm reduction interventions. Conversely, the more robust studies (i.e. cohort and case-control) that have examined the effect of NSP on HCV and HIV transmission have found a mixture of positive, negative, and null effects.

Notwithstanding the potential limitations of self-reported risk behaviour (see the final discussion for coverage of this issue), the balance of evidence tends to suggest that the impact of NSP on self-reported injecting risk behaviour does not necessarily translate into a reduction in blood-borne virus transmission. However, it is important to emphasise that lack of evidence of effectiveness should not be equated with evidence for lack of effectiveness: the lack of evidence may be attributable to the limitations of the primary studies that have been undertaken to evaluate the effectiveness of NSP. Criticisms that have been levelled at the primary studies (and which are mainly relevant to prospective cohort studies) include: lack of power, lack of adjustment for confounding variables, crude assessments of the exposure variable (i.e. participants' use of NSP) and inadequate study designs. Also, primary studies that were published recently may not have been included yet in reviews and thus not appear in the RoR. For instance, two recently published robust studies provide strong evidence that high coverage of NSP per PWID, in combination with adequately dosed OST, is statistically significantly associated with reduced transmission of HCV ((Turner et al., 2011)) and HIV ((Van Den Berg et al., 2007)) (see also section 5 of this report).

In relation to measurements of NSP use, studies have been criticised for using oversimplified categories: for example, 'frequent NSP attendees' (those attending at least once weekly) vs. 'infrequent attendees' . Thus, individuals who were classified as attendees were likely still engaging in injecting risk behaviour despite having access to NSP. Such residual behaviour may be sufficient to propagate the transmission of blood-borne viruses; particularly HCV, for which low levels of injecting risk behaviour may be sufficient to maintain transmission. Consideration needs to be given to the intervention coverage or intensity that is necessary to produce sustained changes in blood-borne virus transmission (see section 6 for a complete discussion of intervention coverage and intensity).

Bastos and Strathdee (2000) suggested other reasons why evaluations of NSP have not been conclusive. They contend that evaluations of NSP have not taken into account the numerous contextual factors, for example, NSP infrastructure and policies and local environmental conditions that may mediate their effectiveness. The probability of infection depends on the underlying prevalence and incidence of blood-borne infections, the duration of infection and the nature of syringe distribution networks among PWID, all of which vary by location. In evaluating the evidence, we have considered the international literature; however, aggregating the evidence in this way may conceal differences that were operating at a local level to affect the transmission of blood-borne viruses. Indeed, great differences in setting, models of service provision and policies relating to NSP were identified through the primary literature review included in section 4 of this report.

3.2 Provision of sterile drug preparation equipment

The sharing of drug preparation equipment other than needles/syringes is prevalent among PWID (Judd et al., 2005; Vickerman et al., 2007; Hagan et al., 2001) and there is growing evidence that blood-borne viruses may be transmitted through the sharing of such equipment (Thiede et al., 2007). For the purposes of this review, drug preparation equipment was defined as 'equipment for injecting or preparing drugs other than needles/syringes'.

Drug preparation equipment may consist of such items as cookers or spoons to heat and/or prepare drugs, cottons or filters to remove particles when drawing drugs up into a syringe, water to rinse syringes or mix with drugs, and citric acid to dissolve drugs. A number of studies have associated HCV prevalence/incidence with self-reported sharing of drug preparation equipment (Denis et al., 2000; Hagan et al., 2001; Hahn et al., 2002; Thorpe et al., 2002).

The reviews that provided the evidence in this section are summarised in Table F-1 of the Appendix. Two core reviews were consulted for evidence with respect to drug preparation equipment:

Tilson H, Aramrattana A, Bozzette SA, Celentano DD, Falco M, Hammett TM, et al. Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence. Washington: The National Academies Press; 2007.

Gillies M, Palmeteer N, Hutchinson SJ, Ahmed S, Taylor A, Goldberg D. The provision of non-needle/syringe drug injection paraphernelia in the primary prevention of HCV among IDU: a systematic review. BMC Public Health. 2010(10):721.

Effects on HCV incidence / prevalence

The objective of the Gillies systematic review was to look at the effect of providing drug preparation equipment in relation to HCV prevention and injecting risk behaviour. Out of thirteen included studies, however, only one cross-sectional study (Morissette et al., 2007) had 'self-reported HCV status' as an outcome; the authors found that PWID who frequently used sterile cookers and water (but not filters) were more likely to be self-reported HCV negative (see Table F-2). This was a cross-sectional study thus no inferences about temporality (let alone causality) of this effect could be made. Based on the statement of insufficient evidence from one core review we conclude:

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of providing drug injecting equipment other than needles/syringes in reducing the transmission of HCV among PWID.

Effects on HIV incidence / prevalence

We did not identify any reviews that looked at the effects of providing injecting equipment on HIV incidence or prevalence.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of providing drug injecting equipment other than needles/syringes in reducing the transmission of HIV among PWID.

Effects on injecting risk behaviour

Tilson et al. (2007) stated that few studies have looked at the effects of providing drug preparation equipment, possibly because few NSPs actually provide such equipment. They identified four relevant studies (Hagan and Thiede, 2000; Huo et al., 2005; Longshore et al., 2001; Ouellet et al., 2004), although it was not clear whether these were identified through a dedicated search. These studies are summarised in Table F-3 of the Appendix. Ouellet et al. (2004) and Longshore et al. (2001) both found that the provision of paraphernalia was associated with declines in sharing. Hagan and Thiede (2000) and Huo et al. (2005) found no association between use of NSP (which presumably provided drug preparation equipment, although this was not explicitly stated) and reductions in the sharing of drug preparation equipment.

Gillies et al. (2010) included 13 primary studies in relation to injecting risk behaviour, two of which were also included in the Tilson review (Hagan and Thiede, 2000) (Longshore et al., 2001). Studies were included in the review if the exposure was distribution of cookers, filters and/or water, or (as proxy measures) the self-reported use of these paraphernalia or attendance at an NSP or safer injecting facility providing the paraphernalia. The results of these studies are summarised in Table F-3 of the Appendix. The review's authors conclude that a number of studies (including four cohort studies) present data suggestive of reduced odds of sharing injecting paraphernalia (i.e. injecting risk behaviour) associated with attendance of NSPs or other drug services where paraphernalia were provided. The authors report that it was not possible to report an overall effect size, because there was too much heterogeneity in study design of the included primary studies. They do however tentatively claim that 'current evidence suggests that attendance at NSP providing sterile N/S injecting paraphernalia may be associated with reduced sharing of non-N/S injecting paraphernalia'. Based on the tentative statement of one core review, based on consistent evidence from a small number of robust studies, we concluded there was tentative evidence.

Evidence statement: There is tentative review-level evidence to support the effectiveness of providing injecting paraphernalia other than needles/syringes in reducing injecting risk behaviour among PWID.

3.3 Models of service delivery of NSP: alternative access

Alternatives to NSP aim to increase access to, and uptake of, sterile needles/syringes by PWID. In this section, we consider pharmacies, vending machines, and outreach as alternative means of needle and syringe provision. Community pharmacies in the UK are an important source of syringes for PWID: in a 2005 survey of needle exchange facilities in England and Scotland, 80% and 72%, respectively, were operating from pharmacies (Abdulrahim et al., 2007; Griesbach et al., 2006). In the context of needle and syringe provision, we define 'outreach NSP' as the distribution of sterile needles/syringes to 'hard-to-reach' populations of PWID; for example, mobile vans that visit areas where drug users are known to frequent. Outreach NSP may be particularly useful in

rural and remote areas, where PWID have difficulty accessing fixed site NSP or are reluctant to use such sites due to concerns over anonymity . Note that outreach is also addressed later in this report, with regard to the provision of information, education, and counselling (IEC) via outreach methods.

Three core reviews formed the basis for the evidence in this section:

Tilson H, Aramrattana A, Bozzette SA, Celentano DD, Falco M, Hammett TM, et al. Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence. Washington: The National Academies Press; 2007.

Wodak A, Cooney A. Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users. Geneva: World Health Organization; 2004. Available from: http://www.who.int/hiv/pub/prev_care/effectivenesssterileneedle.pdf.
[Also published as: Wodak A, Cooney A. Do needle syringe programs reduce HIV infection among injecting drug users: a comprehensive review of the international evidence. Subst Use Misuse. 2006;41(6-7):777-813.]

Jones L, Pickering L, Sumnall H, McVeigh J, Bellis MA. Optimal provision of needle and syringe programmes for PWID: a systematic review. Int J Drug Policy. 2010 Sep;21(5):335-42. [Review derived from a larger review published by NICE in 2008 (Jones et al., 2008).]

Two supplementary reviews provided supporting evidence:

Islam MM, Conigrave KM. Assessing the role of syringe dispensing machines and mobile van outlets in reaching hard-to-reach and high-risk groups of injecting drug users (IDUs): a review, Harm Reduct J. 2007 Oct 24;4:14.

Islam M, Wodak A, Conigrave KM. The effectiveness and safety of syringe vending machines as a component of needle syringe programmes in community settings. Int J Drug Policy. 2008 Dec;19(6):436-41.

Pharmacy access

Effects on HCV incidence/prevalence

We did not identify any reviews that looked at the effects of pharmacy access to needles/syringes on HCV incidence or prevalence.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of pharmacy access to needles/syringes on reducing the transmission of HCV among PWID.

Effects on HIV incidence/prevalence

Two core reviews examined the effectiveness of pharmacy access to needles/syringes in reducing HIV prevalence (Wodak and Cooney, 2004, Jones et al., 2010); both included two primary papers with this outcome related to pharmacy access. Table E-2 presents the results of the primary studies which both reviews included. The first was a serial cross-sectional study conducted in the UK (Hunter et al., 1995), which demonstrated declines in HIV prevalence that coincided with a period of increased access to needles/syringes through pharmacies and NSP. The second study was a cross-sectional survey that found a lower HIV prevalence in diabetic PWID, who had ready access to sterile syringes through pharmacies, compared with non-diabetic PWID (Nelson et al., 1991). Although the serial cross-sectional study demonstrated a temporal association, causation cannot be inferred, and the effects of pharmacy access cannot be isolated from other harm reduction interventions that were implemented during the same period. Cross-sectional studies have even more limited causal interpretations, and a lower HIV prevalence among diabetic PWID may be attributable to differing risk practices between diabetic and other PWID. They also referred to two studies as evidence towards the 'replication of findings' criterion: Des Jarlais et al. (1995) found that pharmacy exchange was a common characteristic of cities that had maintained HIV prevalence rates of less than 5% over the previous five years, and De Jong et al. (1999) attributed a low HIV infection rate in Georgia in part to the availability of syringes in pharmacies. The Jones review included two cross-sectional studies in relation to the effect of pharmacy distribution of needles/syringes on HIV. Miller et al. (2002) compared characteristics of PWID attending three types of NSP: pharmacies, fixed site NSP and mobile vans. HIV prevalence was lower among pharmacy users than among PWID who used another type of NSP. No significance levels were included in the review however and the 'pharmacy group' was much smaller than the other groups. Singer et al. (1997) described reduced HIV prevalence (and injecting risk behaviours) over different time periods in which the availability of sterile needles/syringes was increased, distributed from pharmacy and non-pharmacy NSP. The Jones review concludes that the results of these and other cross-sectional studies that were included (with a different outcome indicator, i.e. injecting risk behaviour) 'lacked coherence due to the differences in setting and populations examined'.

Wodak and Cooney (2004) did not separately evaluate the evidence with respect to HIV and injecting risk behaviour outcomes. They claim that the evidence demonstrated sufficient temporality (based on the serial cross-sectional studies), replication, and coherence, as well as fulfilling two further Bradford Hill criteria, and four of the five additional criteria (see the sections on needle syringe provision and effects on HIV incidence/prevalence for a full list of criteria). They concluded that 'there is reasonable evidence that pharmacy availability of sterile injecting equipment does provide specific benefits in addition to those derived from NSPs.'

Despite a tentative statement of effectiveness from one of the two core reviews, the evidence is based on a small number of primary studies with weak designs, and we therefore consider the evidence to be insufficient.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of pharmacy access to needles/syringes in reducing HIV prevalence among PWID.

Effects on injecting risk behaviour

Tilson et al. (2007) and Wodak and Cooney (2004) examined a total of seven studies on the effects of pharmacy access to needles/syringes on injecting risk behaviour. Jones et al. (2010) included another six primary studies, which were not covered by the aforementioned core reviews. Table E-3 in the Appendix presents a collective summary of the results of the studies from these three core reviews.

Tilson et al. (2007) identified two studies that compared injecting risk behaviour before and after liberalisation of the laws permitting syringe sale from pharmacies in New York (Pouget et al., 2005) and Connecticut (Groseclose et al., 1995): both found that reports of syringe sharing among PWID declined. The authors concluded that a 'few studies have examined the impact on drug-related HIV risk, and found suggestive evidence of a reduction.'

Wodak and Cooney (2004) reported the results of six studies – five cross-sectional and one serial cross-sectional – that looked at injecting risk behaviour in the context of increasing pharmacy access. All cross-sectional studies demonstrated that access to needles/syringes through pharmacies was associated with lower levels of injecting risk behaviour. The serial cross-sectional study was also identified by Tilson et al. and is discussed above. These results were interpreted by the authors as fulfilling the criterion of 'strength of association'. As HIV and injecting risk outcomes were considered together, the fulfilment of the remaining criteria and the authors' conclusions are as outlined in the preceding section on HIV.

Jones et al. (2008) included six new primary papers relating to the effectiveness of pharmacy access on injecting risk behaviours. Five cross-sectional studies related to injecting risk behaviour; one RCT related to injection frequency (the latter is generally not considered as injecting risk behaviour but included here as additional material in absence of robust studies). Fisher et al. (2003) undertook an RCT to examine the difference in injecting frequency between two groups of PWID: one group attending a pharmacy where needles and syringes were sold, one attending an NSP with pharmacy sales. They found that all participants reduced their injection frequency over time without a difference between the groups. The five cross-sectional studies included in the review gave varied outcomes; two studies (Khoshnood et al., 2000; Obadia et al., 1999) found no difference in injecting risk behaviour between pharmacy distribution and other types of needle/syringe distribution; two other cross-sectional studies (Bluthenthal et al., 2004; Rhodes et al., 2004 (a)) found a negative association. It should be noted however that the Bluthenthal study undertook an unequal comparison by comparing unlimited access through non-pharmacy NSP to limited access through pharmacy-based NSP. The Singer study (Singer et al., 1997) found that injecting risk behaviour statistically significantly reduced over time as the number of sterile needles/syringes provided increased; PWID not accessing the pharmacy and non-pharmacy NSP were twice as likely to report using pre-used needles/syringes than PWID who had accessed either. The Jones review did not make a clear statement in relation to effectiveness, the authors conclude that 'currently, it is difficult to draw conclusions on "what works best" within the range of harm reduction services available to PWID'.

All of the evidence relating to injecting risk behaviour is based on cross-sectional or serial cross-sectional study designs, from which one can only infer association, and not causation. As mentioned previously, the observed effects cannot necessarily be attributed to pharmacy access as the effects of other interventions cannot be excluded. Given overall consistent evidence from multiple weaker studies and one more robust study indicating 'no difference', identified within three core reviews, we conclude the following:

Evidence statement: There is tentative review-level evidence to support that pharmacy access is at least as effective as dedicated needle and syringe programmes in reducing self-reported injecting risk behaviour among PWID.

Vending machines

Effects on HCV incidence/prevalence

We did not identify any reviews that looked at the effects of vending machines on HCV incidence or prevalence.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of needle/syringe vending machines in reducing HCV transmission among PWID.

Effects on HIV incidence/prevalence

Both Wodak and Cooney (2004) and Jones (2010) included one cross-sectional study relating to effects of vending machines on HIV incidence or prevalence. Wodak and Cooney reported the results of the Obadia et al. (1999) study which found that primary users of vending machines were less likely to be HIV positive, although this was not significant after adjustment (Obadia, 1999). The review's authors stated that 'access to sterile needles and syringes [from community pharmacies and] syringe vending machines was shown in all nine studies to be effective in [reducing risk behaviour] and HIV seroprevalence', but this assessment was based on one study of vending

machines hampered by weak design, and we therefore concluded that there was insufficient evidence. The Jones review did not draw any conclusion on the effectiveness of vending machines in relation to HIV (see section on 'mobile vans').

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of needle/syringe vending machines in reducing HIV transmission among PWID.

Effects on injecting risk behaviour

Tilson et al. (2007) and Wodak and Cooney (2004) both mentioned a pilot study of vending machines in a German prison (Heinemann and Gross, 2001), although their interpretation of the study's results differ: while Wodak and Cooney saw a significant decrease in needle-sharing subsequent to the introduction of the programme, Tilson et al. stated that this study showed that PWID would use vending machines as a source of sterile needles/syringes.

One supplementary review (Islam et al., 2008) looked specifically at the effectiveness of vending machines, defined as (amongst other outcomes) increased access to sterile needles/syringes and reduced sharing of needles/syringes. The authors included 14 papers but did not provide details about study type or effect size. They concluded that all 14 studies increased PWID's access to sterile injecting equipment. Also, according to a table in the review which summarised the included studies' results, 12 out of 14 papers found that sharing was reduced, but no effect sizes or further details on study design were included. At the same time the review's authors state that 'the impact of the addition of syringe vending machines to NSP on sharing has not been directly studied'. Given conflicting statements of evidence from two core reviews based on one primary study and conflicting information on the results of studies included in one supplementary review, we conclude the following:

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of needle/syringe vending machines in reducing injecting risk behaviour among PWID.

Other findings from studies of vending machines

Studies of vending machines have mainly focused on the characteristics of PWID who access the machines. Both Tilson et al. (2007) and Wodak and Cooney (2004) reported the results of two reasonably large cross-sectional studies conducted in Germany and France (Obadia et al. 1999; Stark et al. 1994). Stark et al. found that 77% of PWID used vending machines more than four times per week. Obadia et al. reported that 21.3% of PWID interviewed reported using vending machines as their primary source of needles/syringes: these individuals were significantly more likely to be younger than 30 years, and significantly less likely to have been in drug treatment or to have shared needles or injection paraphernalia in the past six months. They were also less likely to be HIV positive, although this was not significant after adjustment (odds ratio 0.5; 95% CI 0.2-0.9). The Jones (2010) review also noted that the results of three cross-sectional studies, including the aforementioned Obadia study (Miller et al., 2002; Obadia et al., 1999; Riley et al., 2000) suggested that mobile vans and vending machines may attract a different population from other NSP: PWID who are younger and PWID who have higher risk profiles.

Outreach needle and syringe exchange (mobile vans)

Effects on HCV incidence/prevalence

No reviews were identified that examined the effects of the provision of needles/syringes through mobile vans on HCV transmission.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of the provision of sterile needle and syringes through mobile vans in reducing the transmission of HCV among PWID.

Effects on HIV incidence/prevalence

The (Jones et al., 2010) review was the only core review that included a primary paper (Miller et al., 2002) that compared characteristics of PWID using pharmacy-distributed needles/syringes to characteristics of PWID attending fixed-site NSP/mobile vans that distribute sterile needles/syringes. HIV prevalence was lower among pharmacy users than among PWID who used the other types of NSP (see section 3.3.1.) In the absence of a clear statement from the review and insufficient evidence from papers included in the review, we conclude the following:

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of the provision of sterile needle and syringes through mobile vans in reducing the transmission of HIV among PWID.

Effects on injecting risk behaviour

No reviews were identified that examine the effects of the provision of needles/syringes through mobile vans on reduction of injecting risk behaviour.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of the provision of sterile needle and syringes through mobile vans in reducing injecting risk behaviour among PWID.

3.4 Provision of foil to stimulate route transition

A number of NSPs in European countries have started to distribute sheets of aluminium foil to drug users who want to smoke or 'chase' drugs (Bridge, 2010). The goal of the provision of 'foil' is to stimulate 'route transition', i.e. to encourage drug users to smoke heroin and other drugs instead of injecting them.

This topic was not included in the original RoR but included in the update of the RoR (2007–2011 – see Methods section). We found no reviews assessing the effectiveness of the provision of foil in the reduction of HCV/HIV transmission or injecting risk behaviour. This lack of review-level evidence was anticipated, because the provision of foil is a relatively new intervention and primary papers may thus not have been published yet or included in reviews. It should be noted however that in the UK the Advisory Council on the Misuse of Drugs (ACMD) has advised the UK Government to endorse the intervention: the committee concluded that 'the ACMD finds that there is evidence of the benefits of foil provision, but can find no evidence of the dis-benefits.' (Advisory Council on the Misuse of Drugs (ACMD), 2010).

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of the provision of foil in reducing the transmission of HCV or HIV or injecting risk behaviour among injecting drug users.

3.5 Information, education and counselling and outreach

Information, education and counselling (IEC) seeks to change the behaviour of PWID through educating them on the risks associated with injecting drugs (particularly HIV/AIDS-related risks) and providing them with training in skills required for harm reduction, such as accessing clean needles/syringes, safer injecting methods, etc. (Aggleton et al., 2005). Many IEC programmes use motivational enhancement techniques to achieve these aims (Hunt et al., 2005).

Outreach is one method of delivering IEC and has the objective of reaching 'hidden' populations of PWID in order to bring them into contact with services and to modify their risk behaviour. Outreach may involve a peer-based approach, whereby current or former drug users are used to engage with their peers and convey risk reduction information (Needle et al., 2005). Outreach usually involves the provision of some sort of information or counselling and is thus considered in conjunction with IEC in this section. However, as IEC may take place in contexts and settings that are not outreach-based; any evidence regarding this will also be noted.

Six of the core review papers that met our critical appraisal criteria were of some relevance to IEC and/or outreach (see Table G-1 of the Appendix) and are primarily drawn upon for the evidence of effectiveness of these interventions:

Copenhaver MM, Johnson BT, Lee IC, Harman JJ, Carey MP. Behavioral HIV risk reduction among people who inject drugs: meta-analytic evidence of efficacy. J Subst Abuse Treat. 2006 Sep; 31(2):163-71.

Herbst JH, Kay LS, Passin WF, Lyles CM, Crepaz N, Marin BV. A systematic review and meta-analysis of behavioral interventions to reduce HIV risk behaviors of hispanics in the United States and Puerto Rico. AIDS & Behavior. 2007; 11(1):25-47.

Needle RH, Burrows D, Friedman SR, Dorabjee J, Touzé G, Badrieva L, et al. Effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users. Int J Drug Policy. 2005; 16(SUPPL. 1):S45-S57.

[See also: Needle RH, Burrows D, Friedman SR, Dorabjee J, Touzé G, Badrieva L, et al. Evidence for Action: Effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users. World Health Organization: Geneva; 2004.]

Prendergast ML, Urada D, Podus D. Meta-analysis of HIV risk-reduction interventions within drug abuse treatment programs, J Consult Clin Psychol. 2001 Jun;69(3):389-405.

Tilson H, Aramrattana A, Bozzette SA, Celentano DD, Falco M, Hammett TM, et al. Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence. Washington: The National Academies Press; 2007.

Medley A, Kennedy C, O'Reilly K, Sweat M. Effectiveness of peer education interventions for HIV prevention in developing countries: a systematic review and meta-analysis. AIDS Educ Prev. 2009 Jun; 21(3):181-206.

Evidence from the following supplementary reviews was also considered:

Aggleton P, Jenkins P, Malcolm A. HIV/AIDS and injecting drug use: Information, education and communication. Int J Drug Policy. 2005; 16(SUPPL. 1):S21-S30.

Coyle SL, Needle RH, Normand J. Outreach-based HIV prevention for injecting drug users: a review of published outcome data. Public Health Rep. 1998 Jun; 113 Suppl 1:19-30.

Dolan KA, Niven H. A review of HIV prevention among young injecting drug users: A guide for researchers. Harm Reduct J. 2005 Mar 17;2(1):5.

Jürgens R. HIV/AIDS and HCV in prisons: A select annotated bibliography (part 3). Int J Prison Health. 2006 Nov;2(3): 219-36.

Lines R, Jurgens R, Betteridge G, Stover H, Laticevschi D, Nelles J. Prison needle exchange: Lessons from a comprehensive review of international evidence and experience. 2nd edition. Canadian HIV/AIDS Legal Network: Toronto, 2006.

Hong Y, Li X. HIV/AIDS behavioral interventions in China: a literature review and recommendation for future research. AIDS Behav. 2009 Jun; 13(3):603-13.

Effects on HCV incidence/prevalence

We did not identify any reviews that examined the effects of IEC and/or outreach on HCV transmission.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of information, education and counselling and/or outreach in reducing HCV transmission among PWID.

Effects on HIV incidence/prevalence

Among the core reviews that considered the effects of outreach on HIV transmission (Needle et al., 2005; Tilson et al., 2007), one relevant study was identified by both reviews. Wiebel et al. (1996) conducted a prospective study of a street-based outreach intervention among 641 PWID who were HIV seronegative at baseline. The incidence of HIV infection among study participants declined from 8.4 to 2.4 per 100 person-years over the four year follow-up period. The Needle et al. review also discussed a study by Des Jarlais et al. (1998), which demonstrated that a range of prevention activities, including community outreach to disseminate AIDS information and risk reduction supplies, were able to maintain low HIV prevalence in several cities. However, they acknowledged that the effects of outreach/IEC could not be separated from other intervention components. Needle et al. concluded that 'community-based outreach…provides credible risk reduction information and the means for behaviour change to enable PWID populations to reduce drug use, to reduce reuse of syringes and other drug injecting equipment…' and that 'reducing risk behaviours greatly reduces HIV transmission.' Tilson et al. did not draw any conclusions with respect to HIV and IEC/outreach.

Based on the lack of clear statements from the core reviews, and a small number of corresponding primary studies, we conclude that the evidence is insufficient.

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of information, education and counselling and/or outreach in reducing HIV transmission among PWID.

Effects on injecting risk behaviour

All six core reviews examined studies on injecting risk behaviour outcomes. The reviews covered a total of 41 studies. Only one study was covered by more than one review (see Appendix, Table G-2). However, it should be noted that the reviews varied slightly in their respective remits, which may explain the lack of overlap. The studies covered by Copenhaver et al. (2006) are not presented here as the authors did not list the studies which looked at injecting risk behaviour. A summary of the results of the primary studies included in the core reviews could not be included in the Appendix as the reviews (with the exception of the review by Medley et al. (2009)) did not provide sufficient information.

As opposed to reviewing the primary literature, Tilson et al. (2007) mainly recounted the findings of two earlier reviews: Coyle et al. (1998) and Needle et al. (2005) (an update of the Coyle review). Although the Coyle et al. (1998) review was conducted prior to 2000, we included it in the current discussion since it is referred to in two core reviews.

Coyle et al. (1998) identified a total of 36 studies, 20 of which looked at injecting risk behaviour outcomes. All studies were conducted in the United States. The outreach interventions evaluated in the studies usually consisted of, at minimum, provision of literature on HIV prevention and services, the distribution of condoms and bleach, and referrals to services. These interventions were often followed-up by off-street HIV testing and counselling, and condom and bleach demonstrations. Most of the studies employed a one-group design, in which behaviours reported at baseline were compared with behaviours reported at a later follow-up date, after exposure to the intervention (pre vs. post-intervention studies). A few studies used an experimental design, whereby participants were randomised to receive basic or enhanced outreach.

The studies demonstrated declines in injecting risk behaviour associated with outreach interventions: 16 out of 20 studies showed a decline in the reuse of needles/syringes, and eight of 12 studies showed a decline in the reuse of drug preparation equipment such as cookers, cotton, and rinse water. For studies which used common outcome measures, Coyle et al. combined the results in order to estimate the magnitude of programme effects. Based on four studies of needle/syringe reuse (combined sample size = 2830), they calculated a 19% median reduction in the proportion of PWID who reported syringe reuse in the last 30 days (the median proportion at baseline was 37%). Similarly, based on four studies (combined sample size = 2554), the median reduction in the proportion of participants who reported reuse of drug preparation equipment was 27%. 'Reuse' was not defined, but the authors used it interchangeably with sharing. No confidence intervals were given for the median estimates. They concluded that 'accumulated evidence from observational and quasi-experimental studies strongly indicate that outreach-

based interventions have been effective in…providing the means for behaviour change and inducing behaviour change in the right direction.'

Needle et al. (2005) updated the evidence gathered in the Coyle review by identifying studies published since 1998: a further five studies confirmed Coyle and colleagues' findings that outreach results in reductions in HIV-related risk behaviour. They examined the overall body of evidence in relation to Hill's criteria and concluded that it satisfies the criteria of temporality, consistency of findings, specificity of association, and biological plausibility, although not the dose-response criterion. They concluded that evidence from more than 40 studies indicate that community-based outreach provides the means for behaviour change to enable PWID populations to reduce reuse of syringes and other drug injecting equipment.

Tilson et al. (2007) considered the aforementioned two reviews, but also pointed out the uncertainties in attributing the observed effects to a particular intervention, namely:

- that it is difficult to discern the effects of individual intervention components when multiple interventions occur simultaneously; and
- that secular trends can also account for observed changes in risk behaviour.

This is particularly relevant to studies that do not employ a comparison group. They concluded that 'modest evidence from several studies and reviews from developed countries – most with weak study designs – shows a degree of consistency in finding that outreach and education reduces self-reported drug-related risk behaviour' and that 'there is moderate evidence that outreach is an effective strategy for providing education on preventing HIV transmission, and referrals to services, for hard-to-reach populations of PWID.'

Herbst et al. (2007) conducted a systematic review and meta-analysis of the effectiveness of various behavioural interventions, some of which consisted of IEC and/or outreach. The inclusion criteria stipulated studies that were conducted in Latino populations and evaluated an intervention group relative to a control group. They identified four studies that considered injecting risk behaviour as an outcome (see Table G-2). The meta-analysis revealed no significant intervention effect on needle sharing (OR = 0.92, 95% CI: 0.81 to 1.04), but a statistically significant reduced odds of sharing cotton or cookers (OR = 0.73, 95% CI: 0.63 to 0.85). However, due to the small number of studies, stratified analyses could not be carried out to explore potential confounders. By reason of the inclusion criteria of this review, the generalisability of the results is uncertain and this review will not weigh heavily towards our conclusions.

Copenhaver et al. (2006) conducted a meta-analysis of randomised studies with PWID-related behavioural outcomes. The large majority of interventions included HIV/AIDS education, condom-use skills, self-management skills, and drug and sex-related risk reduction. A smaller proportion of interventions may also have included drug treatment, the provision of bleach, and the provision of condoms. A range of control conditions were used: brief HIV risk reduction interventions, HIV/AIDS education only, wait-list treatment/no treatment, substance abuse treatment only, and interventions with non-HIV content. They identified 37 relevant studies, although only 16 of these looked at injecting risk outcomes. It was not stated whether any of the interventions evaluated used outreach. Although the meta-analysis revealed significant reductions in injecting drug use among those who received the intervention versus those who were exposed to control conditions, there were no significant reductions in the sharing of needles or equipment. The authors stated that this could be a result of control conditions that are very similar to the intervention being evaluated.

Prendergast et al. (2001) conducted a meta-analysis of HIV risk reduction interventions that occurred within drug treatment programmes, all of which included some form of information, education, or counselling. The review was limited to studies that used an intervention and comparison group (randomised or non-randomised). The studies are listed in Table G-2 of the Appendix: since the interventions took place in a treatment setting, there was no overlap with the reviews that included primary studies of outreach interventions. Effect sizes (the mean difference between treatment and comparison group outcomes) were significant for 'risk reduction skills' (d = 0.62, 95% CI: 0.45 to 0.79; a 30% improvement in the intervention group), but not for 'injection practices' (d = 0.04, 95% CI: –0.14 to 0.22; a 2% improvement in the intervention group). 'Risk reduction skills' and 'injection practices' were not defined. The authors concluded that IEC interventions 'targeted specifically at HIV risk behaviours delivered within a drug treatment program can have an impact over and above that produced by drug treatment alone.'

Medley et al. (Medley et al., 2009) undertook a systematic review and meta-analysis into the effectiveness of peer education interventions for HIV prevention in developing countries (whereby 'developing countries' was broadly defined; the relevant studies for this review were set in China and Russia). They defined peer education interventions as 'the sharing of HIV/AIDS information in small groups or one-to-one by a peer'. The review included papers if their design included a pre-post intervention comparison or a 'multi-arm study design' and covered several populations at risk, such as youth, sex workers and PWID. A separate meta-analysis was undertaken for studies pertaining to PWID; four primary studies were included (see table G-2). Their study design is summarised by the authors as one before/after study (Broadhead et al., 2006), two serial cross-sectional designs (Hammett et al., 2006) (Li et al., 2001) and a 'time series study without comparison arm' (Sergeyev et al., 1999). Based on the information in the review it is difficult to assess the quality of these studies.

The review's authors report that three out of four primary studies showed a statistically significant reduction in injecting risk behaviour (equipment sharing) after receiving the educational intervention. The fourth study (Li et al., 2001) showed a non-significant reduction in needle sharing. The meta-analysis included six effect sizes (odds ratios) of the four studies (one study compared two interventions (Broadhead et al., 2006), one study compared interventions in two countries (Hammett et al., 2006)). This resulted in an overall statistically significant reduction in equipment sharing after implementation of the interventions (OR 0.37, 95% CI 0.20 – 0.67). The review's authors conclude that, despite the generally weak study designs of the included studies, 'peer education interventions were associated with (...) and reduced equipment sharing among PWID'.

Conclusions in relation to outreach IEC

One core review provided a tentative statement of the effectiveness of IEC/outreach (Tilson et al., 2007), whereas a second core review provided a clear statement of effectiveness (Needle et al., 2005). One more recent meta-analysis (Medley et al., 2009) provided a clear statement of the effectiveness of peer-delivered IEC (i.e. through outreach). Based on these clear statements from three core reviews, which based their conclusions on multiple weaker studies, we conclude:

Evidence statement: There is tentative review-level evidence to support the effectiveness of outreach, which includes information, education and counselling, in reducing injecting risk behaviour among PWID.

Conclusions in relation to non-outreach IEC

Two meta-analyses examined the effects of IEC in non-outreach settings (Copenhaver et al., 2006; Prendergast et al., 2001). Although Prendergast et al. found a small improvement in risk reduction skills, conclusions are limited by the lack of clarity regarding the outcome variable, and Copenhaver et al. did not find any reduction in injecting risk behaviour. Based on insufficient evidence to either support or discount the effectiveness and in the absence of clear statements from the core reviews, we conclude:

There is insufficient review-level evidence to either support or discount the effectiveness of information, education and counselling in non-outreach settings in reducing injecting risk behaviour among PWID.

Other findings related to IEC/outreach

Prendergast et al. (2001) also investigated the characteristics of IEC programmes that were associated with increased reduction in HIV risk behaviour. These were: interventions delivered later in the course of treatment, separate sessions for men and women, the use of didactic lectures, the provision of training in self-control and coping skills, and the conduct of peer group counselling and discussion.

Tilson et al. (2007) reviewed additional evidence that outreach maybe be an important means of facilitating PWID entry into other services. They cited numerous studies that showed outreach increases drug users' entry into treatment programmes, and at least one study that showed it was particularly effective in reaching newly initiated users. This led them to conclude that 'there is moderate evidence that outreach is an effective strategy for providing education on preventing HIV transmission, and referrals to services, for hard-to-reach populations of PWID.' Moreover, based on this evidence, they recommended that outreach services should be made available to provide education and links to other services.

3.6 Knowledge of HCV status

Gaining knowledge of HCV status through testing is hypothesised to change risk behaviour, such that those who test negative undertake to avoid becoming infected, and those who test positive can undertake to prevent transmission to others. PWID may seek testing or be offered a test as part of a screening programme which targets high risk groups. Voluntary counselling and testing (VCT) refers to the process of giving people professional counselling before and after their HCV (or HIV) test. VCT is widely available in many parts of the EU through medical clinics, drug treatment services, and prison health services.

One review that met our criteria as a core review examined the effect of knowledge of HCV status on injecting risk behaviour:

Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, et al. Screening for hepatitis C among PWID and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. Health Technol Assess. 2002;6(31):1-122.

This review only included studies published up to 2001 and only included four primary studies (Table I-1).

Effects on HCV incidence/prevalence

We did not identify any reviews that examined the effects of knowledge of HCV status on HCV incidence or prevalence.

Evidence statement: There is no review or primary level evidence to either support or discount the impact of gaining knowledge of HCV status on HCV incidence or prevalence.

Effects on injecting risk behaviour

The primary studies included in the Stein (2002) review, which comprised one cohort [4] and three cross-sectional studies , suggest that knowledge of HCV status has little impact on injecting risk behaviour (Table I-2).

Three studies found no statistically significant differences in recent injecting risk behaviours (e.g. sharing needles, syringes, spoons, filters and other drug preparation equipment) between PWID who had had a previous HCV test and those who had not ; those known to be HCV positive and those who reported a negative HCV test in the past; and among HCV-positive and non-HCV groups pre and post testing. Contrarily, the fourth study found that those who knew they were HCV negative were more likely to employ used equipment than those known to be HCV positive or of unknown HCV status, while those with unknown HCV status were more likely not to disinfect used equipment than those known to be HCV negative.

Stein et al. (2002) concluded:

> 'There was no compelling evidence to support the idea that behavioural changes would occur as a result of learning HCV status, either among those shown to be HCV positive (who may be encouraged to reduce the risk of infecting others) or those shown to be HCV negative (who might consider protecting themselves from infection), although the evidence base was insufficient to reject the possibility that such effects exist.' (p. 10).

Evidence statement: There is insufficient review-level evidence to either support or discount the impact of knowledge of HCV status on injecting risk behaviour.

3.7 Supervised injecting facilities

Supervised injecting facilities (sometimes also called 'drug consumption rooms' or 'safe injecting facilities') are professionally supervised healthcare facilities where drug users can use drugs in safer and more hygienic conditions. These facilities are typically located near illicit drug markets and target those who: inject in public places; are at high risk of injecting-related harms; and who are difficult to engage with other drug services. Supervised injecting facilities aim to reduce the incidence of blood-borne viruses and injecting-related infections through the provision of a hygienic and regulated injecting environment, clean injecting equipment, targeted safer injecting education, and wound care. These facilities currently operate in several European countries, Australia and Canada.

There were no reviews on the effectiveness of supervised injecting facilities which met our critical appraisal criteria as core reviews. In the absence of core reviews, we drew on one supplementary review which refers to HCV, HIV and injecting risk behaviour outcomes up to 2002 and one supplementary review addressing (among other outcomes such as access) injecting risk behaviour up to 2007. We also drew on a recent summary paper of the published findings of a Canadian supervised injecting facility evaluation that used a prospective cohort design, the most rigorous body of supervised injecting facility-related research to date. Notably, the majority of the literature on the impact of supervised injecting facilities published prior to 1999 was in German, Dutch and French. We thus considered the following supplementary reviews (Table J-1):

Hedrich D. European report on drug consumption rooms. Lisbon: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA); 2004.
[An update of this supplementary review was published in the EMCDDA 2010 Monograph (Hedrich et al., 2010) and has also been included.]

(Summary paper, no review) Wood E. Summary of findings from the evaluation of a pilot medically supervised safer injecting facility. Canadian Medicial Association Journal. 2006; 175(11):1399-404.

Kerr T, Kimber J, Debeck K, Wood E. The role of safer injection facilities in the response to HIV/AIDS among injection drug users. Curr HIV/AIDS Rep. 2007 Dec; 4(4):158-64.

Effects on HCV incidence / prevalence

Hedrich (2004) reports on an ecological and a serial cross-sectional study (Table J-2) from the Sydney supervised injecting facility evaluation. Trends in notifications of newly diagnosed HCV (and HIV and HBV) infections for the supervised injecting facilities' locality were compared to other control localities. No evidence of an increase or decrease in the incidence of notifications of HCV (or HIV and HBV) in the locality of the supervised injecting facility was found to be attributable to the operation of the facility.

However, it was acknowledged a priori that the low population prevalence of HCV and HIV in the Australian context made it unlikely that any changes in the number of cases would be sufficient to detect any statistically

[4] Stein cited findings from a conference presentation by Ompad et al.

significant trends (MSIC Evaluation Committee, 2001, p. 27). Subsequently they also concluded that the limited injection coverage of the facility was also unlikely to produce a detectable community impact on BBV incidence.

Additionally, data on HCV incidence from a nearby PWID primary care clinic and data on HCV prevalence from serial cross-sectional PWID surveys in the supervised injecting facility locality suggested that HCV incidence remained stable and that a trend towards increased HCV prevalence was consistent with national trends among PWID (MSIC Evaluation Committee, 2003).

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of supervised injecting facilities with respect to HCV incidence.

Effects on HIV incidence/prevalence

The review by Kerr et al. (Kerr et al., 2007) looked at the role of supervised injecting facilities in response to HIV/AIDS in PWID. They did not stipulate (biological) outcome indicators for inclusion of papers in their review; rather the review is a narrative summary of published literature. They did not include papers which looked at reduction in HIV transmission, but the authors concluded that 'a growing body of evidence suggests that supervised injecting facilities can complement other mainstream HIV-prevention strategies, in particular, supervised injecting facilities have been shown to attract individuals at heightened risk for HIV infection, act as locations for the provision of safer injecting education, reduce syringe sharing, and promote enrolment into abstinence-based withdrawal management and addiction treatment programmes.'

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of supervised injecting facilities with respect to HIV incidence.

Effects on injecting risk behaviour

Hedrich (2004) referred to findings from 12 studies on the impact of supervised injecting facility use on injecting risk behaviour, based on PWID self-report and/or staff observations (see Table J-3). These studies tended not to have high quality research designs, had small sample sizes and were subject to other possible confounders. These studies, however, consistently suggest supervised injecting facilities have a positive impact on injecting-related risk behaviour.

Pre-post studies showed increased knowledge of injecting hygiene and safer drug use. Serial cross-sectional surveys showed: decreases in the proportion of supervised injecting facility clients reporting syringe and equipment sharing; increases in the proportion saying they would never accept used equipment; and trends toward being more likely than non-supervised injecting facility clients to use sterile syringes for all injections and less likely to share syringes or other equipment.

Retrospective cross-sectional surveys showed: self-reported improvements by large proportions of supervised injecting facility clients in injecting-related risk behaviour, injecting practices and hygiene since using a supervised injecting facility. Staff also report positive changes in injecting hygiene in a majority of clients.

Hedrich (2004) concludes:

> 'The research evidence on the impact of consumption rooms, although still incomplete, suggests that consumption rooms …reach a population of long-term problem drug users with various health and social problems. They provide a hygienic environment for drug use and, for regular attendees at least, decrease exposure to risks of infectious diseases. They contribute to a reduction in levels of risk-taking among their clients and increase access for specific 'hard-to reach' target populations of drug users to health, welfare and drug treatment services.' (p. 83).

In relation to reduction of injecting risk behaviour, a small number of additional primary studies were added to the review in the 2010 update (Hedrich et al., 2010). Hedrich concludes:

> 'Collectively these studies provide clear evidence that (supervised injecting facility) use is associated with reduced self-reported and observed injecting risk behaviour, including the risk of overdose, and improvements in reported and observed injecting hygiene, especially among those who use the facilities consistently'.

Wood et al. (2006) reported on three different analyses undertaken in Vancouver using data from a community-recruited prospective PWID cohort.

One analysis compared the rate of syringe sharing among regular and irregular users of a supervised injecting facility. Supervised injecting facility use was found to be independently associated with reduced syringe sharing in the previous six months. Examination of data obtained before and after the supervised injecting facility opened revealed that the rate of syringe sharing decreased after the facility opened, but only among supervised injecting facility users. A subsequent analysis demonstrated that greater exposure to the facility was associated with reduced syringe lending by HIV-infected PWID and reduced syringe borrowing by HIV-negative PWID. Finally, in a study of the risk of injecting-related bacterial infections among supervised injecting facility users, supervised

injecting facility use was independently associated with other safe injection practices, including decreased reuse of syringes, increased use of sterile water and increased use of alcohol swabbing of injection sites.

Wood et al. (2006) conclude:

> 'Evaluations of the Vancouver safer injecting facility have shown that the program has been successful in attracting PWID in the community who have a number of characteristics associated with an increased risk of HIV infection and overdose, as well as PWID who were more likely to inject drugs in public. In turn, there have been large reductions in public drug use, publicly discarded syringes and syringe sharing after the facility opened. Use of the facility has also been associated with increased uptake of detoxification services; the facility has been a central referral mechanism to a range of other community and medical resources and a key venue for education about safer injecting. Research has indicated that the facility has not resulted in increases in drug dealing in the facility's vicinity, in drug acquisition crime or in rates of new PWID or relapse into injection drug use among former PWID.' (p. 1403)

Kerr et al. (2007) included 13 papers in relation to injecting risk behaviour, published up to 2007. A summary of these papers is not included in Table J-3, because the review did not provide sufficient information on the individual papers. Eight out of the 13 included papers had however been included by the other supplementary reviews (marked in Table J-3). Based on the reviews, the robustness of the included studies could not be assessed.

The review's authors state that a 'growing body of quantitative data point to the impact of SIF use in syringe sharing.' They also mention that supervised injecting facilities may play an indirect role in reducing injecting risk behaviour by reducing the need for unsafe injecting environments (e.g. 'shooting galleries'), and by reducing unsafe infecting practices other than sharing (e.g. not using sterile water to dissolve drugs) and increasing hygienic practices through the delivery of health education at supervised injecting facilities.

Based on one tentative statement for effectiveness of a supplementary review and one clear statement for effectiveness of a second (recently updated) supplementary review which included a number of robust studies and the positive result of one primary paper with robust design, but in the absence of a core review, we conclude:

Evidence statement: There is tentative review-level evidence to support the effectiveness of supervised injecting facilities in reducing injecting risk behaviour and improving injecting hygiene, particularly for injections that take place on supervised injecting facility premises.

3.8 Cost-effectiveness of NSP

We identified four core reviews that looked at the cost-effectiveness of NSP (De Wit and Bos, 2004; Jones et al., 2008; Pinkerton et al., 2002; Wodak and Cooney, 2004) (Table K-1). Three reviews were included in the original RoR; the Jones/NICE grey literature review (Jones et al., 2008) was added during the update of the RoR.

HCV prevention

De Wit and Bos identified only one study of cost-effectiveness of NSP in preventing HCV: the Commonwealth Department of Health and Ageing study (Health Outcomes International, 2002) used modelling to estimate the number of HCV (and HIV) infections averted by NSP, as compared with having no NSP. This study did not look at HCV in isolation, but found that the incorporation of HCV into the cost analysis further increased the net savings accrued due to HIV infections averted as a result of investment in NSP (from AUS $6,896 million to AUS $7,678 with an estimated 21,000 HCV infections averted). They noted that the savings related to HCV are less than those for HIV due to the lower costs of treatment associated with HCV. On the other hand, although it did not meet their inclusion criterion of a 'full economic review', De Wit and Bos pointed out a theoretical modelling study that concluded that NSPs are not cost-effective as a tool to prevent HCV (Pollack, 2001). They highlighted an important point made by Pollack, who states that analyses may overestimate the effectiveness of NSP in populations with a high prevalence of the disease of interest, as is the case for HCV. This is because, at the time of first contact with NSP, a large proportion of PWID may already have contracted the infection, at which point it is too late for these infections to be 'averted'. Among HCV-uninfected PWID who use NSP, the infection may be delayed, but over the average duration of injecting, very high proportions of PWID will become infected. De Wit and Bos concluded on the basis of the above evidence that it is 'difficult to draw firm conclusions with respect to the cost-effectiveness of NSPs for HCV prevention.'

The Jones review (Jones et al., 2008) included the same two analyses in its review of cost-effectiveness of NSP on the transmission of HCV. Contrary to De Wit and Bos, they judged the Pollack analysis of relatively good quality, but they highlighted the same points from the Pollack paper as described above. The review did not draw a clear conclusion, other than pointing out that one cost-effectiveness study (Pollack, 2001) implied that NSP are not cost-effective in reducing HCV incidence and prevalence, but that one cost-benefit analysis (Health Outcomes International, 2002) (i.e. expressing both costs and outcomes in monetary values) indicated that NSP provided net savings (see above).

Based on statements of insufficient evidence from two core reviews, we conclude the following:

Evidence statement: There is insufficient review-level evidence to either support or discount the cost-effectiveness of needle and syringe exchange programmes in preventing HCV transmission among PWID.

HIV prevention

The four core reviews that examined cost-effectiveness with respect to HIV covered fifteen relevant primary studies, eight of which were included in at least two reviews (see Table J-2 in Appendix). A summary of the study results is presented in Table J-3 of the Appendix.

Wodak and Cooney (2004) provided a brief summary of each of the studies they examined and concluded that 'there is sufficient evidence to consider that the criterion of cost-effectiveness has been fulfilled.' They did not discuss the limitations of the studies. The two reviews below concentrated exclusively on cost-effectiveness studies, and will thus form the bulk of the evidence in this section.

De Wit and Bos (2004) examined the results of seven full economic analyses; 'result' was defined as including an effect measure, and comparing at least one intervention to another; thus, theoretical models, reviews, and cost-only studies were excluded. All seven studies used epidemiological models, based on either published or empirical data, to estimate the number of HIV infections averted by NSP. All of the studies concluded that NSP is cost saving (i.e. that the costs per infection averted are lower than the costs of treatment of HIV infection). De Wit and Bos discussed the following limitations of these studies:

- Cost-effectiveness may be overestimated because most studies do not take into account that many PWID will never have access to the full range of possible treatments for HIV (i.e. costs averted for HIV treatment may not be as high as estimated).
- Since it is difficult to separate the effects of NSP from other interventions, studies of NSP effectiveness may overestimate the benefits and hence cost-effectiveness of NSP may be overestimated.
- Most studies do not consider the combined effect on the transmission of all blood-borne viruses, thereby underestimating cost-effectiveness.
- Not including the effects of secondary exchange of clean needles to PWID who do not directly access NSP would underestimate cost-effectiveness.
- Only one study included infections averted via secondary transmission of HIV to sex partners.
- Incorporation of productivity losses could have further improved cost-effectiveness.

They concluded that 'the economic evaluations in general show NSPs to be cost-effective or even cost-saving in HIV prevention.'

Pinkerton et al. (2002) identified studies of community-level interventions (either cost-effectiveness analyses, cost-utility analyses, or threshold analyses), including NSP (4 studies), and NSP and pharmacy distribution of needles/syringes (two studies). All studies demonstrated a lower cost per HIV infection averted than the estimated cost of treating a case of HIV/AIDS, suggesting that NSP is cost-saving. The authors noted that differences in key parameter values (for example, medical care costs saved when an infection is prevented), modelling assumptions (for example, the duration of intervention effectiveness), modelling techniques, and local epidemiological conditions (for example, HIV prevalence) should be taken into consideration when comparing cost-effectiveness studies. Other general limitations of cost-effectiveness studies were highlighted:

- Treatment for HIV is evolving, which can affect the cost of treatment, and hence cost-effectiveness.
- Other community-level factors affect intervention effectiveness and hence cost-effectiveness, for example, local mixing patterns and the extent to which potential participants are integrated into the community.
- The reliance on mathematical models to estimate HIV transmission as opposed to measuring actual HIV incidence.
- A lack of well-developed methods for assessing the statistical significance of cost-effectiveness results.

Pinkerton et al. concluded that 'the reviewed studies of cost-effectiveness of community-level HIV prevention interventions indicate that investing in such programs can yield economic benefits to society in the form of averted HIV/AIDS medical care costs, as well as saving many lives.'

The Jones/NICE report (2008) includes 12 economic analyses (11 cost-effectiveness analyses and one cost-benefit analysis) relating to cost-effectiveness of NSP on HIV transmission. Six of these had been included in the other three core reviews, six were new (see Tables K-2 and K-3). The report includes extensive structured and technical descriptions of each economic study which give insight into the applied methods, but do not always make clear (to the non-economist reader) what definition of cost-effectiveness is used and how the different time periods used for the calculations influence the results.

The review's authors drew the conclusion that all 12 studies showed that NSP was cost-effective in reducing HIV and state: 'There is evidence from 11 cost-effectiveness analyses and one cost-benefit analysis that in terms of reducing HIV incidence and prevalence among PWID, NSPs are cost-effective.'

In addition to the limitations cited by the above two studies, the generalisability of these cost-effectiveness studies to the European countries must be given special consideration. Most of the studies covered by the above reviews were undertaken in the United States, where many aspects of the cost-effectiveness models may differ, including the costs of HIV treatment, the costs of running NSP, the epidemiological parameters that are used to inform the cost models (HIV prevalence, prevalence of injecting risk behaviour, number of syringes returned to needle exchanges, etc.), and the level of ancillary services offered by an NSP. Nevertheless, studies conducted in Australia, Canada, and different parts of the US consistently demonstrated NSP to be cost-effective.

Based on statements of evidence in support of the cost-effectiveness from three core reviews, and consistent evidence from the corresponding primary economic studies, we conclude that the evidence is sufficient. This statement may appear to be at odds with the tentative evidence of effectiveness of NSP on HIV prevention presented in this report. We have not found sufficient evidence to conclude that NSP is effective in reducing HIV transmission, yet based on cost analyses, we have concluded that NSP is cost-effective in preventing HIV. This discrepancy is due to the fact that the cost-effectiveness studies reviewed here are mathematical models based on a number of estimated parameters, which are usually derived from selected studies or unpublished data that demonstrate a treatment effect (i.e. a reduction in the incidence of HIV associated with NSP). This is a significant caveat that must be taken into account when interpreting evidence of cost-effectiveness. We acknowledge that including such evidence can be misleading, but we felt that it would be informative for the purposes of this review.

Evidence statement: There is sufficient review-level evidence to support the cost-effectiveness of needle and syringe exchange programmes in preventing HIV transmission among PWID, assuming a treatment effect of such programmes in reducing HIV transmission.

3.9 Cost-effectiveness of provision of drug injection equipment

HCV and HIV prevention

We did not identify any review that looked at cost-effectiveness of the provision of paraphernalia in preventing HCV or HIV transmission in PWID.

Evidence statement: There is no review-level evidence to support the cost-effectiveness of the provision of paraphernalia in preventing HCV or HIV transmission among PWID.

4 Results of the review of primary literature

4.1 Number of papers retrieved

Table 2 gives the result of the literature search into the eight topics included in the review of primary papers. The last column shows the results of the selection of relevant papers, based on screening of titles and (where relevant) abstracts of the papers.

Table 1. Number of papers retrieved and selected in primary literature search

	Research topic	# papers retrieved in literature search	# papers included in review after screening of titles and abstracts
1	Factors that influence the retention of PWID in NSPs	197	8
2	Effectiveness of combinations of models of service delivery	41	4
3	Effectiveness of various levels of coverage of drug services	20	5
4	Uptake and completion of HBV vaccination offered on- site of NSP	9	6
5	Uptake of diagnostic testing for HCV/HIV when offered on-site at an NSP	71	2
6	Effect of testing and referral on uptake of treatment for HCV in PWID	5	4
7	Effectiveness of HCV treatment in PWID	140	6
8	Association between provision of IEC and occurrence of bacterial skin infections in PWID	26	0

4.2 Factors that influence the retention of people who inject drugs in needle and syringe programmes

In the RoR, we looked at the effectiveness of NSP in reducing BBV and injecting risk behaviour in PWID, mainly in terms of biological outcomes. One essential aspect of a healthcare provider's effectiveness is the ability to attract clients or patients to the offered services. Therefore we undertook a literature search into the factors pertaining to (the environment of) an NSP that would encourage PWID to visit the NSP and to visit again. Table Q1 summarises eight papers that were retrieved in the systematic search. The studies' designs, objectives and methods all varied significantly, but a number of facilitating factors and barriers for NSP use could be distilled from the papers. Low prices (Trubnikov et al., 2003), geographical proximity, supportive NSP staff attitudes, homelessness (Green et al., 2010) and the option to receive additional services were reported as facilitating factors for NSP use. In terms of barriers for NSP attendance the studies reported: distance to the NSP (Williams and Metzger, 2010), a lack of privacy (Voytek et al., 2003), a fear of being identified by the police as a drug user, and limited or unpredictable opening hours of the NSP (Sarang et al., 2008).

Table Q1: Which factors, pertaining to (the environment of) an NSP, encourage PWID to visit the NSP again?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Outcome / intervention covered	Facilitating factors for use of NSP by PWID	Barriers for use of NSP	Notes
Latkin et al., 2001	United States (Baltimore)	Cross-sectional survey (interview administered) in which characteristics of PWID who always obtained sterile n/s* from NSP were compared to characteristics of PWID who did not always use safe sources for n/s (multivariable analysis applied).	741 PWID recruited through snowball sampling in areas with high drug use.	'Safe sources of n/s' were defined as obtaining n/s from NSP, pharmacy or hospitals, or from a patient with diabetes.	Not reported	PWID who did not obtain n/s from safe sources were twice as likely to have shared n/s in the past month and three times as likely to report injecting in a shooting gallery within the previous six months.	Only 8% of all interviewed PWID obtained n/s exclusively from safe sources.
Trubnikov et al., 2003	Russia	Cross-sectional survey (questionnaire administered) describing PWID's drug injecting behaviours in the previous month.	232 PWID recruited through snowball sampling by staff of an NGO NSP in Moscow	N/A	Low price of sterile n/s	Risk of being examined by police when visiting NSP, opening hours.	

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Outcome / intervention covered	Facilitating factors for use of NSP by PWID	Barriers for use of NSP	Notes
Voytek et al., 2003	United States (Baltimore)	Qualitative interviews	10 PWID (recruited as part of a larger study)	The respondents obtained sterile n/s through secondary exchange (i.e. through PWID who visited NSP) but did not visit NSP themselves.	Not reported	Distance to NSP, opening hours, reluctance to carry around drugs and injecting equipment and hassle, standing in line and lack of privacy associated with NSP.	Small sample size
Sarang et al., 2008	Russia (three large cities)	Multi-method study combining the findings of a qualitative study (applying semi-structured interviews) and quantitative findings of a survey (structured interviews) amongst PWID recruited outside services	Qualitative interviews: 209 PWID	Access to sterile n/s through pharmacies and dedicated NSP	Geographical proximity; good relations with regular pharmacist; range of n/s available	Fear of police interference; cost of buying n/s (minority)	
			Survey: 1,473 PWID from same cities		Services free of charge; option to receive additional services (especially BBV testing); supportive attitude of staff.	Unpredictability of opening hours; the rules of n/s exchange (PWID preferred distribution alone, carrying used n/s carried risk of being exposed as PWID by family or police)	
Kerr et al., 2010	Thailand	Cross-sectional survey (interview administered) among community-recruited PWID to investigate whether there were differences between PWID accessing a multi-service drug centre and those who did not access the centre.	252 PWID of whom 30% had accessed the drug services (30%).	New PWID support centre providing sterile n/s, food, information and education.	Difficulty assessing syringes in the community (AOR 4.05); midazolam injection (AOR 3.25); having had more education than primary school only (AOR 1.88).	Female gender (AOR 0.20)	Among the 178 PWID who had not visited the centre before, the main reasons for not visiting were: not knowing about the existence of the centre, not knowing where to find it, the centre being too far from home, and a fear that data on drug use would be disclosed to the police.
Gindi et al., 2009	United States (Baltimore)	Retrospective analysis of secondary data (administrative client data of PWID attending 17 NSPs that belong to one organisation) to identify factors associated with retention in an NSP. Multivariable analysis was applied to compare the characteristics of PWID returning and PWID not returning to the NSP.	12,388 PWID who enrolled in any of the 17 NSPs between 1994 and 2006 (12 years). Each PWID had a unique identifier code.	Multi-visit usage of the NSP was defined as returning to any NSP within 12 months of first enrolment; PWID not returning within 12 months were considered single-visit clients.	Factors associated with repeated visits to NSP were: age above 30; white race; having high school diploma; not being married, 20+ years injecting history; living close to NSP.	Not reported	64% of all PWID returned to an NSP within 12 months. Up to 2002, younger PWID (aged < 30) were significantly less likely to return to NSP than older PWID; this difference disappeared after 2002.
Green et al., 2010	United States	Prospective cohort study investigating the characteristics of PWID who were not using NSP with PWID (who started) using NSPs by following them up for one year and undertaking multiple assessments including self-reported use of NSPs.	538 PWID	Transition from non-NSP user to NSP user	Factors associated with starting to use NSP were: city of recruitment; homelessness, injecting speedballs during past month, having been stopped by police.		Half of the participants in the initial sample were lost to follow up.

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Outcome / intervention covered	Facilitating factors for use of NSP by PWID	Barriers for use of NSP	Notes
Williams et al., 2010	United States	Geo-behavioural study into the association between distances relevant to PWID (i.e. distances between home, drug purchase and drug-use locations) and injecting risk behaviour. PWID were interviewed about their geographical whereabouts and about risk behaviour. Spatial analysis techniques where applied to calculate average distances; these were entered into multivariable models.	2,599 PWID recruited from social networks	Distances from home of PWID to the closest NSP, distance from drug buying location to NSP, and distance from drug using location to NSP.	Not reported	For each mile of increased distance between the PWID's home and NSP, the likelihood of using non-NSP n/s increased with 6%. Distance from the buying and using location to NSP had at least a similar effect. Effects varied by race of participants.	

** n/s = needles/syringes*

4.3 Effectiveness of combinations of models of service delivery

Four studies relating to the effectiveness of combinations of drug services and combinations of models of service delivery were included in this review (Table Q2).Two studies and one review/meta-analysis (Des Jarlais et al., 2010; Hagan et al., 2011; Hallinan et al., 2007) found low or reduced HCV transmission when PWID were enrolled in combined services; one RCT – unsurprisingly – reported higher access to medical care when referrals were offered in a hospital-based NSP. Thus, all studies indicated positive effects from offering combined prevention services to PWID. A recently published meta-analysis (Hagan et al., 2011) pooled data from two studies that had reported on combined services and found that the risk of HCV transmission was reduced by 75% when PWID were enrolled in OST programmes in combination with additional services. This result should be interpreted with caution however, since it was based on only two studies; both looked at OST and additional (but different) interventions.

Table Q2: Which combinations of models of service delivery ('mix of services') are effective in reducing HCV/HIV transmission and injecting risk behaviour?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Description of model of service delivery	Results	Notes
Hallinan et al., 2007	Australia	Review of HCV prevention and treatment practices in a Sydney-based addiction clinic which offers OST and additional services. The review included a small retrospective cohort study.	54 HCV seronegative PWID	Integrated care for HCV: regular (six months) HCV testing with post-test counselling, flexible dosing of OST (including high doses), distribution of take-away OST doses and flexible referral for HCV treatment.	Low transmission of HCV in 54 HCV negative PWID receiving OST and other services at the clinic compared to rates reported in the literature: the incidence of HCV was 3.8/100 person years (95% CI 1.2–9.8/100 person years), after a mean follow up time of 2.4 years.	This was a review of practical experience and study results from small scale studies and audits. Authors argued for 'integrated HCV prevention and treatment services within the setting of OST' and a minimum standard of HCV care including testing, flexible dosage OST and flexible referral for HCV treatment.

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Description of model of service delivery	Results	Notes
Masson et al., 2007	US (San Francisco)	RCT comparing NSP effectiveness in two different settings: community-based NSP vs. hospital-based NSP (participants were randomly assigned to receive community or hospital-based NSP).	166 PWID recruited from in- and outpatient departments of a hospital setting (none on OST).	All participants were offered testing for BBV. The community-NSP participants received sterile n/s and paraphernalia; the hospital-NSP participants received these and additional information, education and counselling and hospital referrals.	No difference in injecting risk behaviour or self-reported NSP use between participants in the two settings. Hospital-NSP participants made more in- and outpatients visits to the hospital (main reason: skin and soft-tissue infections) suggesting that this setting increased accessibility to medical services.	Small sample size, large number of (multiple) analyses. Authors mentioned the following operational factors from NSP from the literature: location, distribution policies, opening hours, law enforcement practices and attitude of staff.
Des Jarlais et al., 2010	USA (New York City)	Serial cross-sectional study from secondary data collected in drug treatment centre where policies have changed over time. This study compared HIV status and injecting risk behaviour in PWID attending the centre during two phases of (increasing) service provision.	1,414 PWID were included: 261 from the 'early prevention phase', 1153 during the 'integrated services phases'. The onset of injecting was taken into account for allocation in groups; an individual PWID could only be included in one phase but could be included more than once during that phase in the study period study.	Two time periods defined as onset of injecting 1984–1994 initial HIV prevention programmes and onset of injecting 1995–2008 combined services were combined (legal provision of sterile n/s and HIV treatment).	HIV prevalence in PWID in initial prevention programmes was 21% vs. 6 % in combined services PWID. The derived estimated incidence showed a statistically significant difference (P<0.0001).	General limitations of serial cross-sectional design apply (study design has limited power to show causality).
* Hagan et al., 2011	US	Meta-analysis of interventions to prevent HCV in PWID	Inclusion criteria: paper included the association between intervention and HCV seroconversion in HCV as outcome indicator. Twenty-six papers published between 1989 and 2010 were included.	Analysis of 'multicomponent programmes' included two papers: Abou-Saleh (2008) combined OST with extensive counselling, Van den Berg (2007) combined OST with NSP (see table of question 3).	Meta-analysis of results of two studies found a substantial reduction in HCV incidence in PWID enrolled in a combination programme which included OST(pooled RR 0.25, 95 % CI 0.07-0.83).	The two included studies in the 'multicomponent programmes analysis' both investigated OST plus another, different, intervention. Heterogeneity in the pooled analysis was just above the threshold for reasonable heterogeneity in included studies but not statistically significant.

** Added to the review after completion of the search; paper was published during review period.*

4.4 Effectiveness of various levels of coverage of drug services

The question of what level of coverage of services is required to reduce HCV and HIV transmission partly overlaps with the question pertaining to the effectiveness of various models of service delivery (see above). The term 'coverage' has many meanings in the literature (Sharma et al., 2007); therefore we included the definitions for coverage used in the five included papers (Table Q3). Our review included two papers with robust study designs: a prospective cohort study (Van Den Berg et al., 2007) and a meta-analysis (Turner et al., 2011). These papers showed that considerable evidence now exists that higher levels of harm reduction intervention coverage (i.e. PWID receiving adequately dosed OST and at least one sterile needle/syringe per injection) are more effective than lower levels of coverage of services per PWID. A cross-sectional study (Bluthenthal et al., 2007) and an ecological analysis (Wiessing et al., 2009) confirmed these findings. Lastly, the Harvard (Harvard et al., 2008) ecological study showed that even in an area where drug services have long been established (British Columbia, Canada), coverage of needle/syringe per injection is still low.

Table Q3: What level of coverage of services is required to reduce HCV/HIV transmission and IRB in PWID?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Definition of coverage of services	Services provided and their level of coverage	Results	Notes
Van den Berg et al., 2007	The Netherlands	Prospective cohort study (Amsterdam Cohort Study) in which seronegative PWID were followed up until seroconversion for HIV or HCV (or end of study); data on usage of harm reduction services were collected.	714 ever PWID, HCV and HIV negative, recruited through Amsterdam health centre.	The authors applied five levels of coverage which included a measure of current drug use and of uptake harm reduction (HR) services: no HR, incomplete HR, full HR, limited dependence on HR or no dependence on HR (i.e. no methadone use and no injecting drug use in past six months).	Full HR was defined as: methadone daily dose at least 60 mg/day AND (no injecting in past six months OR injecting and always use of NSP in past six months).	Multivariable analysis showed that methadone use or NSP use alone were not associated with decreased HIV/HCV transmission, but when used in combination, transmission for HIV was statistically significantly lowered (IRR 0.43, 95% CI 0.21-0.87); reduction in HCV transmission almost reached statistical significance (IRR 0.36, 95% CI 0.13-1.03).	
* Bluthenthal, Anderson et al., 2007	US (California)	Cross-sectional study in which PWID from 24 out of 25 of California's NSPs participated. Participants completed an interviewer-administered interview and were tested for HIV.	1,577 PWID recruited from NSPs.	'Individual syringe coverage' was defined as the monthly number of syringes retained from the last NSP visit, divided by the estimated number of monthly drug injections.	NSP: all participants were allocated to a category of individual syringe coverage of <50% coverage, 50-99% coverage, 100–149% coverage (this was the baseline in the analyses) and >150% coverage.	Participants with coverage <50% were statistically significantly more likely to re-use n/s and to share n/s (both receptive and distributive sharing) compared to participants with adequate coverage of 100–149%. Participants with coverage above 150% were statistically significantly less likely to re-use n/s, to share n/s or to share cookers (all results from multivariable analysis).	The authors also looked at unsafe n/s disposal and found no differences between the participants' level of coverage and unsafe n/s disposal, i.e. higher coverage was not associated with more unsafe disposal of n/s.
Harvard et al., 2008	Canada (British Columbia)	Ecological study in which administrative data (three years) were analysed to compare pharmacy distribution data (sterile n/s distribution-to-drugs centres) to population need data (estimates of the numbers of PWID and number of injections per geographical area in BC).	N/A	Coverage was defined as the number of sterile n/s (from pharmacy records) per area divided by the estimated number of drug injections per area (using PWID cohort data from two large cities).	N/A	Provision of injecting equipment was inequitable; there was marked variation in coverage across BC areas. The authors estimated that in BC, only 21.5% of all injections were covered by supply of sterile n/s.	The authors mentioned that the estimates of both the number of PWID and the number of daily injections may have been too low which may have led to an overestimation of coverage.
Wiessing et al., 2009	EU and four other countries	Ecological study in which intervention coverage data were compared with HIV incidence data in PWID per country.	N/A	NSP coverage was defined as the number of sterile n/s distributed divided by estimated number of PWID per country; OST coverage was defined as the number of PWID in OST divided by estimated number of PWID per country.	NSP and OST	The results of the coverage comparison with HIV incidence suggested that higher levels of NSP and OST were associated with lower incidence of HIV in PWID.	This was an ecological study using country level data; data collection in these countries may have been very different leading to difficulties in direct country comparisons.

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Definition of coverage of services	Services provided and their level of coverage	Results	Notes
Turner et al., 2011 (in press)	UK	Meta analysis to determine if OST and NSP, alone or in combination, could reduce HCV transmission among PWID. In total, 919 PWID were included in the analysis of OST and NSP combined.	Systematic review resulted in six UK studies with individual level data on NSP and / or OST coverage and data on newly acquired HCV infection.	OST was defined as 'currently being on OST or having been on OST for six months in past year' (yes/no), NSP coverage was defined as 'number of sterile needles obtained from NSP is at least 100% injections reported by PWID' (yes/no). 'Full harm reduction' coverage was subsequently defined as OST+NSP, 'partial harm reduction' as OST or NSP, 'minimal harm reduction' as no OST and NSP coverage below 100%.	NSP and OST	Compared to the PWID on minimal harm reduction, PWID on full harm reduction (OST and NSP) had an almost 80% reduced risk of a new HCV infection (AOR 0.21, 95% CI 0.08–0.52). The differences in risk between PWID on partial harm reduction compared to no harm reduction were smaller and did not reach statistical significance.	

** Derived from follow up of references of papers retrieved through the systematic literature search.*

4.5 Uptake and completion of HBV vaccination offered at an NSP site

Table Q4 includes six papers relating to uptake and completion rates of vaccination in PWID when offered on-site of an NSP. The literature search, which included search terms for hepatitis A, HBV and tetanus vaccinations (Appendix L), resulted in papers relating only to HBV vaccination. The efficacy of the HBV vaccine or of the various vaccine administering regimes were beyond the scope of this report, but one paper was included that showed that PWID were much more likely to complete the accelerated regime than the normal regime (Wright et al., 2002).

Rather, we looked to find an effect of offering the vaccination in combination with NSP instead of through referral to a health clinic. The included studies generally had weak study designs; only two studies applied some form of comparator group, albeit with great limitations in the comparison (see under 'notes' in Table Q4). Des Jarlais et al. (2001) found that the completion rate of HBV vaccination was much higher in an NSP than after referral to medical clinic. Morrison (Morrison et al., 2002) looked at the feasibility of introducing vaccination to existing drug services and comparing uptake; the authors suggested that drug services that have a continuing relationship with clients may achieve higher uptake than an NSP that clients only attend very briefly. Two papers described uptake and completion of the HBV vaccination without comparator groups: Altice et al. (2005) found that 66% of PWID who were offered vaccination from a mobile NSP completed the full course. When offered in an OST clinic, a completion rate of 83% was found (Ramasamy et al., 2010). The evidence was thus not conclusive, but the results described earlier for 'combining services', in combination with the findings from a number of studies, imply that offering vaccination in combination with drug services could result in higher uptake than through referral to regular healthcare.

Prison health services are out of scope of this report, but it should be noted that prison is an important venue for administering HBV vaccination to PWID. Hope et al. (2007) found that among PWID in England, a history of imprisonment was associated with having been vaccinated for HBV; almost 40% of PWID with completed HBV vaccinations had received at least one dose in prison.

Table Q4: What is the effect on vaccination uptake and completion rates of HBV, HAV and tetanus vaccines if offered at an NSP site?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Vaccine	Intervention	Results	Notes
* Des Jarlais, Fisher et al., 2001	US	Comparison of two cohort studies that assessed uptake of HBV vaccination among PWID using two models: through referral to a health centre and through an NSP.	Referral cohort: 350 eligible PWID (set in a major city in Alaska), NSP cohort: 36 eligible PWID (set in new York City).	HBV	HBV regime of three vaccinations at 0, 1 and 4 months after serological testing for HBV.	In the referral cohort, 31% received all three doses despite financial incentives of up to $50 per vaccination. In the NSP cohort, 83% received all three doses (incentive $10 per dose).	Study indicates that NSP may be a suitable venue for offering HBV vaccination. A direct comparison between the vaccination venues cannot be made: paper mentioned neither individual data nor results of multivariable analysis to correct for confounders; sample sizes varied greatly.
Wright et al., 2002	UK (England)	Serial cross-sectional: study compared completion rates of HBV vaccination in two samples of homeless PWID who were vaccinated in primary care centre for homeless people.	First year (1999): 54 PWID vaccinated with regular HBV scheme, second year (2000): 90 PWID vaccinated in accelerated HBV regime.	HBV	Regular regime: three doses at 0, 1 and 6 months. Accelerated regime: 3 doses at 0, 7 and 21 days. Vaccination was offered after serological screening for HBV.	Homeless PWID were seven times more likely to complete the accelerated HBV regime than PWID who were offered the regular regime.	The efficacy of accelerated regime was assumed to be comparable with the regular regime and not investigated further in this small study. Note that the vaccines were given in a primary care centre which provided services to PWID (and was linked to an NSP**).
Morrison et al., 2002	UK (Scotland)	Cross-sectional: these are the results of a pilot programme that looked at the effectiveness of delivery of HBV vaccinations through a number of drug agencies that previously did not provide vaccinations to PWID.	Total sample size: 1,000 PWID (drug crisis centre including NSP: 500; regular NSP: 250; specialised OST centre: 250).	HBV	Rapid HBV regime defined as four doses at 0, 1, 2 months, with booster at 12 months (course considered complete after three doses).	Only 20% of sample size target was met in 1.5 years; this was caused by failure to offer vaccination rather than refusal of clients. The regular NSP achieved the lowest vaccination rates of the three agencies (attributed to brief interaction time with service and absence of client case notes). The authors conclude that there was a higher uptake in services where clients had a continuing relationship with the service.	This study achieved a small sample size (thus there was a greater potential for inclusion bias); no individual data was collected thus no correction for confounding factors was undertaken.
Altice et al., 2005	USA	Service evaluation assessing the effectiveness of HBV screening and subsequent vaccination offered on-site at an NSP.	134 PWID attending the mobile NSP.	HBV	Three doses vaccination regime at 0, 1 and 6 months offered after serological screening for HBV.	The majority of PWID screened were eligible for vaccination; 94% of them accepted vaccination; 66% of those starting vaccination completed the full regime (three doses). Multivariable analysis identified three correlates of completing the full regime: being older, injecting every day and being homeless.	No monetary incentives were provided to participants.
Hope et al., 2007	UK (England)	Cross-sectional study (paper reports on two surveys, one of which was relevant); participants were interviewed about HBV vaccination and injecting risks and tested for HBV.	852 PWID recruited from drugs services and the street at five locations in England.	HBV	HBV vaccination offered at various locations.	Of those PWID who were eligible for vaccination and those who had self-reported at least three doses of HBV vaccine, 38% had received a vaccine in prison, 31% in a drug service, 14% through an NSP, 17% through the GP and 5% through a hospital. PWID who had been imprisoned were statistically significantly more likely to have been vaccinated for HBV.	PWID could indicate multiple venues for receiving the vaccine doses; hence the total exceeded 100%.

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Vaccine	Intervention	Results	Notes
Ramasamy et al., 2010	Australia	Service evaluation assessing the feasibility of HBV vaccination in an OST clinic and the seroconversion rate following an accelerated HBV regime.	143 PWID attending an out-patient OST clinic in Sydney who were eligible for HBV vaccination after serological testing.	HBV	HBV vaccine (accelerated regime: 0, 1 and 2 months) offered in methadone clinic. Booster offered in case of non-response, but complete regime defined as three doses)	62% eligible for HBV vaccination; of eligible PWID, 83% completed complete regime; 75% seroconverted, thus overall effectiveness of programmes was 63%.	This paper is about vaccination from an OST clinic, not NSP. Authors suggested that a normal HBV vaccination regime might be more effective for PWID attending OST, i.e. for PWID who are attending drug services long term and regularly. There was no conclusion on efficacy of the booster vaccination due to missing data.

** Derived from follow up of references of papers retrieved through the systematic literature search.*

*** Not mentioned in paper, but upon consultation a needle exchange programme has been attached to the homeless centre for >10 years.*

4.6 Uptake of diagnostic testing for HCV/HIV when offered on-site at needle and syringe programmes

We included two papers that related to offering diagnostic testing for BBV on-site at an NSP (Table Q5). (Liebman et al., 2002) compared client data of HIV tests undertaken in a mobile van (which operated together with a mobile NSP) to client data of other public HIV testing sites. They found that the proportion of PWID among the van's clientele was much higher than among the clientele of the non-mobile van testing sites. This is an indication that PWID could access testing in the van more easily than in other locations.

In a survey among PWID undertaken by Heinzerling et al. (2006), participants were asked about their receipt of 'additional' BBV prevention services which included testing and counselling for BBVs, STIs and TB. Many needs were unmet, but amongst those that had received HIV and HCV testing, the majority of PWID had been tested at an NSP.

No formal analysis based on two studies is possible, but both papers give an indication that it may be effective to offer testing for BBV on-site at an NSP because PWID already access NSPs. Nevertheless, a general limitation of many drug-related studies should be taken into account. Many studies applied a non-random method of sampling, which may have resulted in a selection bias favouring PWID who already had access to services such as NSP. For instance, Heinzerling et al. (2006) only recruited PWID from NSPs; PWID who did not attend NSP may well have had better access to testing from a non-NSP, but this could not be reported in the study.

Table Q5: What is the effect on uptake of diagnostic testing for HCV/HIV when offered on-site at an NSP?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Intervention	Results	Notes
* Liebman et al., 2002	US (Connecticut)	Cross-sectional study linking HIV testing data to data on demographics of PWID visiting a mobile medical van and comparing the characteristics of people tested for HIV in the mobile van to those of people tested in other public test centres.	247 patients (not all PWID) tested for HIV during study.	The mobile medical van offers testing and screening for STDs including HIV to deprived populations. The van covers poor neighbourhoods in conjunction with a mobile NSP.	HIV tests in mobile van accounted for 11.5% of all HIV tests in city. Among those tested for HIV in the mobile van, 32% of men and 19% of women were PWID, compared to 14% and 6%, respectively, for all other public test sites (difference in % of PWID was statistically significant).	
Heinzerling et al., 2006	US (California)	Cross-sectional study using standardised face to face interviews.	560 PWID recruited from 23 NSP across California, which varied in size and remit (some were stand-alone NSP, others were part of OST or social services).	Participants were asked about receipt of ten preventative services, including testing for HIV, HCV, HBC, TB, STIs, and receipt of counselling services.	On average, NSP clients received only 13% of 'needed' NSP services (need based on self-reported health history and use of preventative services). HIV testing was received most often from all services (by 35% of PWID who needed it); of those who were tested for HIV, 70% were tested at an NSP. Corresponding proportions for HCV were 17% and 55% respectively. Correlates (after multivariable analysis) associated with receipt of prevention services were OST and recent NSP attendance.	Unmet need was based on six months' history (to reduce recall bias) but according to the authors, several tests were recommended yearly; the need may thus have been overestimated.

** Derived from follow up of references of papers retrieved through the systematic literature search.*

4.7 Effect of testing and referral on uptake of treatment for HCV among people who inject drugs

After a PWID has been tested for HCV and is found HCV positive, adequate referral would ensure follow up and – if required – treatment for HCV. In practise, however, PWID may not be referred to treatment centres for various reasons, for example PWID's incompatible lifestyles or staff prejudice in assessing PWID's eligibility for treatment.

A number of papers that focussed on the important 'referral' step were included in the present review (Table Q6). Two papers with relatively strong study designs (one prospective cohort study and a prospective audit analysis) reported on projects which aimed to actively refer PWID to treatment centres (Hallinan et al., 2007; Lindenburg et al., 2011). The Lindenburg study found that active referral to a treatment centre, with extensive medical screening for treatment included in the process, could result in a relatively high uptake of testing, screening and treatment for drug users (see also 5.7). The authors remarked on the clear benefits of integrated care, although the study did not include a non-integrated care comparator programme. Hallinan et al. reported on their extensive experience with integrated care in a Sydney-based addiction clinic and argued for the stronger integration of prevention and care for drug users; they noted however that despite very flexible referral procedures, there remained a substantial delay between referral and actual decision-making about treatment.

A Scottish study (Anderson et al., 2009) investigated whether general practitioners could identify undiagnosed chronic HCV patients by screening all middle-aged adults in an area with high rates of drug use. They found that by establishing a dedicated screener in the practice, a higher proportion of people were screened for HCV than in a comparator practise and that a number of former PWID with chronic HCV were indeed identified through this intervention. A targeted approach however, targeting ever drug users, would have been more efficient. It is also of note that four years after the study was conducted, only two out of 11 former users referred for HCV treatment had actually received treatment. A minority of diagnosed patients dropped out because of alcohol misuse. The authors concluded that additional psychological and social services could play a role in supporting PWID through the process of testing and referral to treatment.

Lastly, Stoove et al. (2005) undertook a survey among a large sample of HCV-positive adults, 80% of whom had ever injected drugs. They found that having seen a general practitioner specifically for HCV was positively associated with being referred for treatment. Among those referred, there was a negative association between having used drugs and receiving treatment.

The results of the studies suggest that active involvement of drug services and medical staff in referral of PWID may be beneficial in increasing the uptake of treatment. As mentioned before, no robust evidence is available to

show this, but it can be assumed that the easier it is made for PWID to access treatment and care (both physically and in terms of flexibility of healthcare staff in relation to PWID's lifestyle), the better their uptake of treatment will be. Setting up additional services for PWID however, such as establishing a dedicated multidisciplinary treatment team like in Amsterdam (Lindenburg et al., 2011) will require additional resources for healthcare providers.

Table Q6: What is the association between diagnostic testing and referral on uptake of treatment for HCV by people who inject drugs?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Intervention	Results	Notes
Stoove et al., 2005	Australia	Cross-sectional study; self-administered questionnaire into factors associated with the impact of drug use status on HCV treatment enrolment.	659 HCV-positive adults recruited from treatment and community settings; more than 80% reported a history of injecting drug use.	N/A	After a multivariable analysis, a number of factors were independently associated with referral to a HCV treatment centre: having seen a GP specifically for HCV, not being a current PWID, having had a PCR test and a longer time since diagnosis. Among those referred, current PWID were statistically significantly less likely to receive HCV treatment than former PWID or non-PWID (15% vs. 38% and 50% received treatment, respectively).	
* Hallinan et al., 2007	Australia	Review of HCV prevention and treatment practices in Sydney addiction clinic where OST and additional services including referral for treatment where offered. Review included a small prospective clinical audit .	121 PWID with chronic HCV	Patients that met clinical criteria of high risk were systematically referred to an HCV treatment clinic with flexible treatment entry criteria (current drug and alcohol use were not exclusion criteria).	Preliminary results: 63 (52%) of PWID with chronic HCV met the treatment criteria. Despite flexible entry criteria, there remained a long delay between referral and treatment decision. Initial treatment results of 25 patients: 80% reached a successful virological response.	This was a review of practical experience and study results from small scale studies and audits. Authors argued for 'integrated HCV prevention and treatment services within the setting of OST' and a minimum standard of HCV care including testing, flexible dosage OST and flexible referral for HCV treatment.
Anderson et al., 2009	UK (Scotland)	Service evaluation comparing HCV testing uptake and referral to hepatology centres for HCV treatment across two GP practices. Practices were located in deprived areas of Glasgow with high rates of (history of) drug use amongst its inhabitants.	2,079 patients of GP practices (1,165 in intervention practice, 914 in comparison practice), aged 30 to 54 years.	In the intervention practice, all attending eligible patients (independently of risk factors) were actively offered HCV testing by the GP or practice nurse; they could then directly be counselled and tested by a trained counsellor in the practice.	In the intervention GP practice, 72% of eligible patients were offered testing; 29% of those offered were tested for HCV vs. none in the comparator practice. 14 out of 15 people who tested HCV positive had ever injected drugs. Eleven out of 15 were referred to a hepatology clinic; all attended at least one appointment but four years after the end of the study only two out of 11 patients had received HCV treatment. Alcohol misuse played a role in the drop-out of four diagnosed patients.	The doctor-to-patient ratio in the intervention practice was 1.5 times higher than in comparison practice, which may have biased the testing rate (doctor simply had more time for additional efforts such as testing); nevertheless the study indicates that screening of the general population in an area with known high drug use may identify HCV-positive patients, but that a targeted approach targeting ever PWID among the general population would have been more a more efficient case-finding strategy.

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Intervention	Results	Notes
Lindenburg et al., 2011	Netherlands	Prospective cohort study (analysis is part of Amsterdam Cohort Studies). This study presents results of a project that aimed to offer screening and subsequent treatment to PWID in Amsterdam by introducing a multidisciplinary treatment team.	497 drug users from the existing Amsterdam Cohort Study (i.e. who are tested for HIV twice yearly and are followed up as part of an ongoing study) and 81 PWID who were not yet in the cohort, but referred by other addiction services.	Establishment of a multidisciplinary referral and treatment team consisting of (medical and case managing) drug treatment staff and hospital-based virologist, liver specialist and psychiatrist. All HIV-negative but HCV-(RNA) positive PWID were offered extensive additional screening to determine treatment eligibility. Psychiatric illness and active drug/alcohol use were no exclusion criteria.	Willingness to be tested was above 90% and positively influenced by methadone use. Of HIV negative and HCV positive patients 63% was willing to undergo extensive additional screening for treatment eligibility. Final uptake of treatment was high (73%); overall uptake of all HCV-positive patients was 16%, which was considered high. Authors attribute the successful referral and treatment uptake to extensive counselling, which also involved the family (see Table Q7 for treatment effect).	The DU included in this study comprised mainly of non-injecting drug users (28% had injected in last six months). Amsterdam cohort population may not be representative of all drug users, as the cohort drug users are familiar with drug services and their staff.

4.8 Effectiveness of HCV treatment among people who inject drugs

Clinicians have often expressed reluctance to treat PWID (particularly current injectors), partly on the grounds that such patients are presumed less likely to be compliant to therapy, and so less likely to be treated successfully (i.e. to attain sustained virologic response (SVR) indicating the persistent absence of serum HCV RNA for six months or longer after therapy). We included a number of papers in this review that related to HCV treatment outcomes in injecting (and non-injecting) drug users (Table Q7). The included studies cannot be easily compared, as they included different populations of drug users with different genotypes of HCV (some of which are more difficult to treat than others), different levels of co-morbidity and investigated different treatment regimes.

Nevertheless, a number of papers from our review highlighted that response rates akin to those from large registration trials of pegylated interferon and ribavirin (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001) could be achieved in cohorts of chaotic PWID. For example, Lindenburg (Lindenburg et al., 2011) reported genotype-specific response rates that were broadly in line with the aforementioned trials. In addition, they found no evidence that response to therapy differed according to whether or not patients were engaging in active injecting drug use at the time of treatment (albeit based on a sample of only 11 active injectors, and 58 treatment initiates overall). Further, in an analytical review, Hellard (Hellard et al., 2009) reported that of ten studies formally comparing the response in PWID to non-PWID, none reported a statistically significant difference.

However, two studies in our review (Gigi et al., 2007; Zanini et al., 2010) reported rates of premature treatment discontinuation, considerably beyond that seen in the larger clinical trials. In a study by Gigi et al, 53% of patients discontinued therapy prematurely, for reasons unrelated to response. As a consequence only 33% of all treatment initiates attained a SVR. Further in the Zanini meta-analysis, the mean SVR rate in studies including active ongoing drug users (39%, 95% CI 30-49%) was lower than in studies involving a mandatory absence period before study entry (55%, 95% CI: 45-64%).

It must be pointed out that several studies in this review adopted extensive pre-treatment assessment criteria which will likely have selected only the most compliant of injectors (Grebely et al., 2010; Lindenburg et al., 2011; Litwin et al., 2009). Some studies reported excluding patients if their active injecting drug use was deemed unstable/unsuitable for treatment (Grebely et al., 2010; Lindenburg et al., 2011). Thus, their response rates are not necessarily applicable to all PWID (both current and former) but likely a more compliant subgroup. Differences in pre-treatment assessment criteria may to some extent explain the inconsistent messages proffered by these studies.

Table Q7: What is the response to antiviral treatment of HCV in PWID?

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Intervention covered	Results	Notes
Gigi et al., 2007	Greece	Patients derived from a retrospective cohort of treated former PWID of selected Greek treatment clinics	Analysis included 163 former PWID with chronic HCV treatment initiates who attended a drug detox programme without methadone substitution therapy. 30% of the cohort had been abstinent from drugs for more than 12 months. Patients were not treated if self-reporting current alcohol use.	IFN monotherapy (40% patients), PEG-RIB combination therapy (30% patients) and IFN–RIB combination (30% patients)	(1) Overall, 54/163 (33%) attained a SVR on an intention to treat basis, in a cohort where 32% of patients were genotype 1/4, and the 67% were GT2/3. (2) 53% of patients discontinued therapy prematurely; main reasons were relapse to drug use (62% of patients who stopped) and side effects (32%).	
Hellard et al., 2009	Australia	Review	(1) Nine studies were identified reporting SVR outcomes among PWID treated with pegylated interferon and ribavirin, (2) ten studies for which SVR attainment could be compared between PWID and non-PWID were identified, and (3) ten studies reporting treatment completion data among PWID and non-PWID were identified	Studies reporting treatment with any type of IFN therapy (with or without ribavirin) were included	(1) Median SVR rate among PWID receiving peg IFN + ribavirin was 54.3%, which is consistent with results from large trials, (2) among studies in which PWID were compared with non-PWID, none reported a statistically significant difference between the rate of SVR among PWID and non-PWID, (3) in terms of treatment compliance, 70.9% (median 71.9%) PWID completed treatment, compared to 79.4% (median 92.3%) of non-PWID.	(1) Patient was considered PWID whether actively using drugs, currently abstaining or in drug treatment. (2) Data were not combined to generate pooled comparisons of treatment completion/response, thus interpretation of data is limited.
Litwin et al., 2009	US (NYC)	Retrospective cohort study	Seventy-three methadone maintained patients recruited from eight methadone clinics.	Treatment delivered on site at US methadone maintenance clinics. Patients treated with PEG−IFN combination therapy.	33/73 (45%) patients attained a SVR, in a population of almost 70% GT1/4 patients. Treatment response rates were nearly equivalent to previously published response rates, despite high prevalence of ongoing drug use (49%), psychiatric co-morbidity (67%) and HIV co-infection (32%).	(1) PWID for whom adherence was predicted to be poor were not initiated onto therapy. The number of persons who were considered for treatment, but ultimately not offered (broken down by reason not offered) is not reported.
Zanini et al., 2010	Studies selected internationally (predominantly from Europe)	Meta-analysis	Sixteen studies were selected collectively comprising data on 953 PWID. Studies were included only if (1) they were prospective studies, (2) they were published in the last ten years, (3) had a homogenous treatment schedule and (4) had a sample size >15	Any type of IFN (pegylated or non-pegylated) in combination with ribavirin.	(1) Active ongoing drug use negatively affected treatment success: the mean SVR rate in active ongoing drug users was 39% (95% CI 30–49%), compared to 55% (95% CI 45–64%) in 'non active drug users' from studies involving a mandatory absence period before study entry (p=0.02). (2) The proportion of PWID patients discontinuing therapy prematurely for reasons not related to response or psychiatric adverse effects was 26% (95% CI. 18–35%).	

First author, publication year	Country	Study design	Number of participants (inclusion criteria)	Intervention covered	Results	Notes
Grebely et al, 2010	Australia	Follow-up study from prospective cohort study.	Number of treated patients analysed was 58.	PEG IFN alpha 2a or 2b + ribavirin, or IFN alpha 2b + ribavirin. Patients also received education regarding risks of re-infection.	Among 58 patients, 60% (38/58) attained a SVR.	(1) Participants whose active injecting drug use was not deemed suitable (in this case non suitability was defined as daily injecting in an unstable house setting) were not considered for treatment. (2) Although data were collected, the effect of active drug use variables (injecting in six months preceding therapy, and illicit drug use during treatment) on SVR attainment was not reported.
Lindenburg et al., 2011	The Netherlands	Prospective cohort study. Treatment patients were recruited from two sources: (1) a prospective cohort study of drug users in Amsterdam, and (2) drug users identified retrospectively to have been referred (from methadone and addiction clinics) to treatment clinics as part of routine clinical practice.	All HIV negative, HCV Ab + ve/RNA + ve were initially considered for therapy. Drug users were not considered for therapy if they failed to complete an array of medical screens (including physical examination, liver ultrasound, standard chest radiograph, psychiatric evaluation). Further, active drug use was only considered an exclusion criteria if it was deemed to interfere with schedule visits and was considered unstable. Overall 58 treatment initiates were considered in this analysis.	Patients were treated with peg interferon alpha 2a or alpha 2b + ribavirin.	(1) SVR attained among 76% (31/41) in PWID with genotype 2/3 HCV, and 38% (6/16) in PWID with genotype ¼. (2) No statistically significant difference in treatment outcome was found between drug users who injected and drug users who did not inject (OR 1.07 (95% CI 0.27–4.2)). (3) Treatment was never interrupted or stopped because of psychiatric events.	Due to lengthy pre-treatment assessment criteria, active drug users considered in this analysis may be not be representative of all active drug users, i.e. their response rates may be superior.

4.9 Association between provision of information, education and counselling and occurrence of bacterial skin infections in people who inject drugs

The literature review did not identify any relevant papers pertaining to the association between the provision of information, education and counselling and the occurrence of bacterial skin infections in PWID.

5 Summary of findings

Below the findings from the updated RoRs and from the review of primary literature have been summarised.

Evidence for interventions in reducing HCV transmission

There are still low levels of evidence at the level of reviews for the effectiveness of interventions to reduce HCV transmission. We found insufficient review-level evidence to either support or discount the effectiveness of NSP in reducing HCV, the most extensively implemented harm reduction intervention. The balance of evidence from the primary studies into NSP included in the reviews was mixed; however, ecological studies have demonstrated stable and declining HCV prevalence associated with NSP. We found no or insufficient review-level evidence for the effectiveness of alternative NSP access (i.e. pharmacy, vending machines, mobile vans), provision of sterile drug preparation equipment, IEC and outreach, knowledge of HCV status through testing, use of supervised injecting facilities or provision of foil with respect to HCV incidence.

This lack of review-level evidence does not equate to a lack of evidence for effectiveness, however. Recently published primary studies – not yet included in the reviews but included in the review of primary literature - have highlighted robust evidence for the effectiveness of NSP in reducing HCV transmission. For instance, pooling of data from small studies in a meta-analysis (Turner et al., 2011) showed that high NSP coverage (i.e. sufficient sterile needles/syringes per injection) reduced the risk of HCV transmission by more than 50%. The study also showed that high coverage NSP in combination with adequately dosed OST could reduce the transmission of HCV by nearly 80%.

Evidence for interventions in reducing HIV transmission

There is more review-level evidence for the effectiveness of interventions in reducing HIV transmission, although review-level evidence for many interventions other than NSP is still lacking. In the updated RoR, we found tentative review-level evidence that NSP is effective in reducing HIV incidence (although, similar to HCV, ecological studies have demonstrated declines in HIV prevalence associated with NSP). We found no or insufficient review-level evidence that alternative NSP access (pharmacy, vending machines, mobile vans), provision of sterile drug preparation equipment, IEC and outreach, knowledge of HCV status through testing, use of supervised injecting facilities or provision of foil have an impact on HIV incidence.

The primary literature review however included an often-cited cohort study (Van Den Berg et al., 2007) which found – in line with the aforementioned Turner paper – that high-level NSP in combination with high-level OST statistically significantly reduced the risk of HIV transmission in PWID.

Evidence for interventions in reducing injecting risk behaviour

The largest body of evidence for the effectiveness of interventions targeting PWID relates to self-reported reductions in injecting risk behaviour. We found sufficient review-level evidence that NSP is effective in reducing self-reported injecting risk behaviour. We found tentative review-level evidence that pharmacy access to sterile needles/syringes, IEC and behavioural outreach, and supervised injecting facilities are effective in reducing injecting risk behaviour. The update of the RoR resulted in an increase of evidence for the effectiveness of the provision of drug preparation equipment besides needles and syringes in reducing injecting risk behaviour: the evidence for this intervention is now tentative at review-level. We found no or insufficient review-level evidence to assess whether access to sterile needles/syringes through vending machines or mobile vans, IEC and outreach, knowledge of HCV status through testing, use of supervised injecting facilities or provision of foil was effective in reducing injecting risk behaviour.

Evidence for cost-effectiveness

The quality of cost-effectiveness studies was intrinsically related to the quality of the primary outcome studies and the economic methods and the mathematical models used. We found sufficient review-level evidence to support the cost-effectiveness of NSP in averting HIV infection, although cost-effectiveness estimates were based on assumed reductions in HIV incidence or prevalence associated with NSP. We found insufficient review-level evidence for the cost-effectiveness of NSP on HCV transmission, and no review-level evidence for the cost-effectiveness of the provision of paraphernalia on either HCV or HIV infection.

Evidence from the primary literature review

Our primary literature review aimed to provide a broader context of factors that may influence access to and uptake of services. The papers included in this review have been summarised below.

Factors pertaining to (the environment of) a needle/syringe provider that encourage PWID to visit the NSP again, i.e. that increase client satisfaction:

We found that low prices, geographical proximity, encouraging staff attitudes and the option to receive additional services from an NSP were facilitating factors to visit the NSP. Conversely, geographical distance, a fear of being caught by the police whilst attending an NSP, opening hours and a lack of privacy could act as barriers.

Combinations of models of service delivery ('mix of services') effective in reducing HCV/HIV transmission and injecting risk behaviour:

Four included studies described combinations of different programmes of integrated care for PWID. All found positive effects of combining services in either reducing HCV transmission in PWID enrolled in integrated care, or providing better access to services. A recently published meta-analysis (Hagan et al., 2011) found that HCV transmission was reduced by 75% when PWID were enrolled in OST programmes in combination with additional services.

Level of coverage of services required to reduce HCV/HIV transmission in PWID:

Based on recently published studies, there is now considerable evidence that higher levels of harm reduction coverage (i.e. PWID receiving adequately dosed OST and at least one sterile needle/syringes per injection) are more effective in reducing transmission of HCV and HIV than lower levels of coverage of services per PWID.

Vaccination uptake and completion rates of HBV, HAV and tetanus vaccines in PWID when vaccination is offered at an NSP site:

We found a number of studies whose results lacked coherence due to great differences in study design, setting and outcomes. Their findings, in combination with the results described earlier for 'combining services', however imply that offering vaccination in combination with drug services could result in higher uptake than through referral to regular healthcare.

Uptake of diagnostic testing for HCV/HIV when offered on site at an NSP:

We found no studies that directly compared uptake of diagnostic testing provided from NSP and non-NSP. Indirectly, two studies' results indicated that in terms of increasing test uptake it may be effective to offer testing for BBV on site of an NSP because PWID already access NSPs. One study showed that relatively more PWID were being tested for HIV in a mobile van offering testing and NSP; another study showed that amongst the minority of PWID who had ever been tested for HCV or HIV, most PWID had been tested at an NSP.

Association between diagnostic testing and referral on uptake of treatment for HCV by people who inject drugs:

The results of the included studies suggest that active involvement of drug services and medical staff in referral of PWID may be beneficial in increasing the uptake of HCV treatment among PWID. No robust evidence (including comparator referral programmes) was available to show this advantage, but it can be assumed that the easier it is made for PWID to access treatment and care (both physically and in terms of flexibility of healthcare staff in relation to their lifestyle), the better their uptake of treatment will be.

Response to treatment of HCV in PWID:

The results of the studies included in this review could not be formally compared; they included differently selected PWID populations, carrying different genotypes of HCV (associated with potential efficacy of treatment) and undergoing different treatment regimes. Nevertheless a number of studies have reported that good treatment responses can be achieved in PWID despite chaotic lifestyles. The literature, however, also indicated considerable treatment drop-out rates.

Association between provision of IEC and occurrence of bacterial skin infections:

No studies were identified in relation to this topic.

6 Limitations

6.1 Limitations of RoR method

A general discussion of the limitations of this methodology has previously been undertaken (Ellis et al., 2003) and these limitations are also applicable here:

The subjective element to the critical appraisal of the reviews, despite the use of a tool, may have affected reviews that were included or excluded

The evidence was limited by the decision to look at review-level evidence only; it is not known whether gaps in the evidence might have been filled by primary research, in particular primary research carried out since the date of the last review.

This evidence briefing only covers the type of evidence that is traditionally included within systematic reviews of the evidence (i.e. quantitative evaluations); although other types of evidence, such as qualitative and expert opinion are increasingly represented in reviews, we are not aware of a formal framework for considering this type of evidence.

We also acknowledge that we may have missed potentially relevant reviews due to our inclusion criteria. We limited our search to English language reviews, and consequently may have excluded potentially relevant reviews published in other languages. We did not undertake hand searches of the literature; nevertheless, we did search the English language grey literature (based on 'review' reports published on websites of key international drug agencies) to reduce the potential bias arising from inclusion of published reviews only. Our decision to include only reviews published from 2000 onwards may have resulted in the exclusion of relevant reviews; however, based on our literature search, we found that reviews published prior to this date had been updated or superseded by more recent reviews.

Since this evidence briefing is based on review-level evidence, it is hence subject to the limitations of the reviews themselves, as well as the primary studies on which these are based. The limitations of the primary studies have been discussed in the main body of this document, although it should be noted that these limitations are primarily those identified by the reviews.

The specific limitations of the reviews that were incorporated into our evidence base included: incomplete identification of all relevant studies, the absence of a formal critical appraisal tool or process to determine study quality, a lack of consideration of study quality in generating the evidence base, and a lack of transparency as to how conclusions were drawn from the evidence. Although the papers that we deemed to be core reviews were the highest quality reviews we could find, they were also subject to some of the aforementioned limitations. Moreover, we found discrepancies between core reviews in the studies they identified, their reports of study designs, their reports of study findings, and the conclusions they drew for the same harm reduction interventions. Given these discrepancies, we felt that for some interventions we could not solely rely on statements of evidence from the core reviews, and statements of evidence were not always given in the reviews. Therefore statements of evidence, where present, were required to be supported by the evidence from the primary literature. Due to time constraints, this usually required an assessment based on the reviews' accounts of the primary studies, and thus most of the primary findings presented here were secondary accounts.

6.2 Intervention intensity and coverage

Our review of the evidence focuses on 'direct' evidence of effectiveness of harm reduction interventions, i.e. evaluations that have sought to measure changes in biological or behavioural outcomes. Many of the reviews included within the RoR emphasise that it is often difficult to study the effects of a single intervention in isolation from other interventions that may occur at the same time or be part of the intervention under investigation. This is a limiting feature of many of the study designs that have been used to investigate the effectiveness of harm reduction interventions, particularly ecological study designs. Although not able to attribute the observed findings to any one intervention, Tilson et al. (2007) stressed that particular harm reduction interventions may be effective as components of an overall harm reduction programme. Other authors have even postulated that harm reduction measures may act synergistically to reinforce each other's effects. Fortunately, papers included in the review of primary studies included in this report now show that the evidence base for the combination of interventions, at different levels of coverage, is increasing (see also accompanying technical report 'Evidence for the effectiveness of interventions to prevent infections among people who inject drug, Part 2: Drug treatment for preventing hepatitis C, HIV and injecting risk behaviour among people who inject drugs' for a review of the effects produced by drug treatment interventions.

6.3 HCV and HIV prevention

The strength of evidence for the selected interventions is much greater for behavioural measures (i.e. self-reported sharing, see below) than for biological measures (HIV or HCV incidence or prevalence).

HCV control among PWID in many European countries will be more difficult to achieve than for HIV. There is a larger pool of PWID infected with HCV (for instance, 50% or more in several cities in the UK (Health Protection Agency, 2006)) and 44% among young PWID in Amsterdam (van de Laar et al., 2005); the transmissibility of HCV by syringe sharing or needle stick is a magnitude greater than for HIV (approximately 3% vs. 0.3% (Bell, 1997; Gerberding, 1995)). Thus, comparatively few sharing events may result in a high probability of HCV transmission: it is therefore not surprising that the evidence for effectiveness of interventions on reduction of HCV infection is relatively weak.

6.4 Self-reported injecting risk behaviour

The reliability and reliance on self-reported injecting behaviour is a problem for epidemiological and evaluation studies that needs to be considered when interpreting the evidence. First, as highlighted above, evaluation studies of NSP tend to report a larger treatment effect on syringe sharing and other risk behaviours than on biological outcomes. Second, cross-sectional and longitudinal observational studies often find no or only weak associations between reported syringe sharing and HCV infection. Third, though it has been suggested that self-reported behaviour by PWID in general can be reliable (Darke, 1998; Goldstein et al., 1995), it is uncertain whether we can assume this applies to all behaviours – in particular syringe sharing. A Welsh study found a substantial difference in reported sharing behaviour from a questionnaire delivered by a service as compared with an interview conducted by peers, with the latter recording a substantially higher frequency of sharing (Craine et al., 2006).

The implication is that studies and evidence that rest solely on self-reported behaviour are weak, unless alternative hypotheses for any association can be ruled out. For example, syringe sharing is strongly associated with sharing of other injecting equipment. If information on syringe sharing is more likely to be under-reported and less reliable than information on other drug injection equipment sharing, then the relationship between HCV infection and syringe sharing will be diluted, and an adjusted statistical model may suggest that injection equipment sharing poses a greater and independent risk than direct syringe sharing (because other injection equipment sharing is measured better and reported preferentially, as opposed to syringe sharing). In addition, for injectors exposed to harm reduction interventions such as NSP, it is conceivable that they become more sensitised to the risks of 'sharing' and more reluctant to report this behaviour in contrast to the unexposed population.

Finally, infectious disease models of HIV and HCV transmission suggest that incidence may be reduced in a stepwise fashion – that is, the impact of an intervention or change in behaviour on incidence occurs not in a pure linear relationship or simple dose-response but after a certain threshold amount has been achieved. Thus, some change in injecting risk behaviour or increase in coverage of an intervention may have no impact on HIV/HCV incidence; whereas other changes in the context of other factors may lead to reductions in incidence. Thus, a change in self-reported behaviour may be no guarantee of a reduction in blood-borne virus transmission.

6.5 Limitations of the review of primary literature

A number of limitations should also be taken into account when interpreting the results of the review of primary literature. In the systematic literature search, we only included papers published in English. Given time constraints, three databases were searched instead of the six databases searched for the RoR. However, given the very low yield of relevant papers from the other three databases in the RoR update, we expect to have retrieved most relevant primary papers following this method. Selection of relevant papers was undertaken by one reviewer, which may have resulted in the subjective inclusion of papers; but we are convinced that we have included a sufficient number of topical and relevant papers. A more important limitation is that we did not perform a full critical appraisal, involving the use of a standardised appraisal tool. This was not feasible given the time restraints, but would also have required substantial work in developing a systematic framework to summarise results of papers that varied greatly in their topics, study designs and included outcomes. Rather, we summarised all retrieved papers systematically and in tables, indicating obvious limitations or observations regarding the interpretation of each paper. This review should therefore not be interpreted as a systematic review (which would systematically grade the strength of evidence from each paper, and weigh these strengths to make a judgement on the overall strength of the evidence) but rather as an overview of existing relevant literature.

7 Suggestions for future evaluation research

Much of the evidence for harm reduction interventions, with the exception of OST (which is not examined in detail here), is based on observational study designs. Exposure to the interventions has not been randomised as this would be considered unethical given the obvious benefits of, for example, injecting with a sterile needle. Rather, PWID who were unexposed or exposed to different levels of the intervention under investigation have been followed up. Unfortunately, the level of exposure in these observational studies is rarely measured in the same way, which makes a direct comparison of the studies' results complex. Our review of primary studies indicated that services such as NSP are offered in many different shapes and forms. The mode of delivery (for instance, the opening hours of an NSP, which influences patronage by PWID) may be a confounding factor and thus influence the effectiveness outcomes of interventions. For instance, if we were to know that certain hard-to-reach (risk) groups consistently preferred pharmacies over fixed sites (a hypothetical example), then a worse result for effectiveness of the fixed-site NSP could in fact be due to high-risk PWID avoiding the fixed site. More evidence about e.g. access to services could help policy makers to better design their services. It is, therefore, recommend that more research should be focused in this area.

Also, as indicated by the review into primary literature, qualitative studies examining non-biological outcomes, such as client satisfaction, are more difficult to summarise in a systematic way. Given their potential value to improve service delivery, however, we recommend that more work should be undertaken into the development of a method to systematically appraise these studies.

Observational studies, in general, are at risk of confounding and selection bias that, under certain circumstances, can give precise but misleading results. One – assumed to be very common – form of bias in many papers is selection bias: PWID who are in touch with drug services are overrepresented in studies compared to PWID who do not access the services at all. This would result in over- or under-estimation of the effects found. Many authors refer to this risk and try to minimise it by sampling not only from NSP or OST services, but also from communities.

A second common problem is that individual exposure to interventions is often not measured, e.g. individual uptake of NSP or OST. We therefore recommend that public health surveillance systems should be strengthened to measure both uptake of interventions and outcomes such as HCV or HIV infection. Surveys of PWID are needed to monitor changes in prevalence and incidence of these infections over time, but also to determine the direct association between uptake of interventions and biological outcomes. Services would benefit from having systems in place to monitor and audit provision of interventions to PWID and enable ongoing needs assessment at a local level, but these data would also inform policymakers at regional and national levels on the extent of intervention coverage, and thus the need for future service development.

Although RCTs are the 'gold standard' to provide unbiased estimates of effect in epidemiology, they are often not feasible for public health interventions. For instance, it would be unethical to conduct a trial with no treatment as an arm for interventions which have multiple outcomes and with good evidence of effectiveness (such as OST); and it has been suggested that it would be unethical to conduct a trial for interventions that have face validity (such as NSP) or that already have been introduced widely (such as the distribution of some forms of drug preparation and injecting equipment). Instead, in line with the Amsterdam Cohort Study and the Tilson review and following recently published meta-analyses (Hagan et al., 2011; Turner et al., 2011), we recommend that more research be conducted within the EU which focuses on understanding the effectiveness of combinations of services and determining the appropriate level of coverage of services.

The evidence from the Netherlands and the UK – demonstrating that the combination of interventions (namely OST and high NSP coverage) can substantially reduce BBV transmission – needs further corroboration. The population impact of different levels of intervention exposure and combinations of interventions, in terms of making sustained and substantial reductions in BBV transmission, needs to be monitored. Among the combination of interventions, treatment of these infectious diseases needs to be considered; particularly in light of recent modelling work which illustrated that modest rates of HCV treatment among PWID could effectively reduce transmission (Martin et al., 2011). Further modelling work is also recommended to help inform on what sustained levels of intervention coverage are required to reduce prevalence of BBVs among PWID in the short to medium term.

References

Abdulrahim D, Gordon D, Best D. The NTA's 2005 survey of needle exchange in England. London; 2007.

Advisory Council on the Misuse of Drugs (ACMD). Consideration of the use of foil, as an intervention, to reduce the harms of injecting heroin. London: ACMD; 2010. Available from http://www.homeoffice.gov.uk/publications/agencies-public-bodies/acmd1/foil-report.

Aggleton P, Jenkins P, Malcolm A. HIV/AIDS and injecting drug use: Information, education and communication. Int J Drug Policy. 2005; 16(Suppl. 1):S21-S30.

Altice FL, Bruce RD, Walton MR, Buitrago MI. Adherence to hepatitis B virus vaccination at syringe exchange sites. 2005(1):151-61.

Anderson EM, Mandeville RP, Hutchinson SJ, Cameron SO, Mills PR, Fox R, et al. Evaluation of a general practice based hepatitis C virus screening intervention. Scott Med J. 2009 Aug; 54(3):3-7.

Bastos FI, Strathdee SA. Evaluating effectiveness of syringe exchange programmes: current issues and future prospects. Soc Sci Med. 2000 Dec; 51(12):1771-82.

Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med. 1997 May 19; 102(5B):9-15.

Benninghoff F, Dubois-Arber F. Résultats de l'étude de la clientèle du Cactus BIEL/BIENNE 2001. Lausanne: Institut universitaire de médecine sociale et préventive2002.

Benninghoff F, Solai S, Huissoud T, Dubois-Arber F. Evaluation de Quai 9 'Espace d'acceuil et d'injection' à Genéve: période 12/2001–12/2000. Lausanne: Institut universitaire de médecine sociale et preventive; 2003.

Bluthenthal RN, Anderson R, Flynn NM, Kral AH. Higher syringe coverage is associated with lower odds of HIV risk and does not increase unsafe syringe disposal among syringe exchange program clients. Drug Alcohol Depend. 2007 Jul 10; 89(2-3):214-22.

Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. The effect of syringe exchange use on high-risk injection drug users: a cohort study. AIDS. 2000 Mar 31; 14(5):605-11.

Bluthenthal RN, Malik MR, Grau LE, Singer M, Marshall P, Heimer R. Sterile syringe access conditions and variations in HIV risk among drug injectors in three cities. Addiction. 2004 Sep; 99(9):1136-46.

Bridge J. Route transition interventions: potential public health gains from reducing or preventing injecting. Int J Drug Policy. 2010 Mar; 21(2):125-8.

Broadhead RS, van Hulst Y, Heckathorn DD. The impact of a needle exchange's closure. Public Health Rep. 1999 Sep-Oct; 114(5):439-47.

Broadhead RS, Volkanevsky VL, Rydanova T, Ryabkova M, Borch C, van Hulst Y, et al. Peer-driven HIV interventions for drug injectors in Russia: First year impact results of a field experiment. Int J Drug Policy. 2006 SEP; 17(5):379-92.

Bruneau J, Lamothe F, Franco E, Lachance N, Desy M, Soto J, et al. High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: results of a cohort study. Am J Epidemiol. 1997 Dec 15; 146(12):994-1002.

Calsyn DA, Saxon AJ, Freeman G, Whittaker S. Needle-use practices among intravenous drug users in an area where needle purchase is legal. AIDS. 1991 Feb;5(2):187-93.

Center for Disease Control. Recommendations for follow-up of healthcare workers after occupational exposure to hepatitis C virus. MMWR: Morbidity and Mortality Weekly Report. 1997; 46(26):603-6.

Cohen DA, Wu SY, Farley TA. Comparing the cost-effectiveness of HIV prevention interventions. J Acquir Immune Defic Syndr. 2004 Nov 1;37(3):1404-14.

Cohen DA, Wu SY, Farley TA. Structural interventions to prevent HIV/sexually transmitted disease: are they cost-effective for women in the southern United States? Sex Transm Dis. 2006 Jul;33(7 Suppl):S46-9.

Colon HM, Finlinson HA, Negron J, Sosa I, Rios-Olivares E, Robles RR. Pilot trial of an intervention aimed at modifying drug preparation practices among injection drug users in Puerto Rico. AIDS Behav. 2009 Jun;13(3):523-31. Epub 2009 Mar 24.

Cook PA, McVeigh J, Syed Q, Mutton K, Bellis MA. Predictors of hepatitis B and C infection in injecting drug users both in and out of drug treatment. Addiction. 2001 Dec; 96(12):1787-97.

Copenhaver MM, Johnson BT, Lee IC, Harman JJ, Carey MP. Behavioral HIV risk reduction among people who inject drugs: meta-analytic evidence of efficacy. J Subst Abuse Treat. 2006 Sep; 31(2):163-71.

Coutinho R. Needle exchange: The Amsterdam experience: Institute of Medicine workshop on the prevention of HIV among injecting drug users in high-risk countries (20 December 2005).

Cox GM, Lawless MC, Cassin SP, Geoghegan TW. Syringe exchanges: a public health response to problem drug use. Ir Med J. 2000 Jul-Aug;93(5):143-6.

Coyle SL, Needle RH, Normand J. Outreach-based HIV prevention for injecting drug users: a review of published outcome data. Public Health Rep. 1998 Jun; 113 Suppl 1:19-30.

Craine N, Walker M, Williamson S, Bottomley T. Reducing the risk of exposure to HCV amongst injecting drug users: lessons from a peer intervention project in Northwest Wales. Journal of substance Use. 2006; 11(3):217-27.

Darke S. Self-report among injecting drug users: a review. Drug Alcohol Depend. 1998 Aug 1; 51(3):253-63; discussion 67-8.

De Jong W, Tsagarelli T, Schouten E. Rapid assessment of injection drug use and HIV in the Republic of Georgia. Journal of Drug Issues. 1999; 29(4):843-60.

De Wit A, Bos J. Cost-effectiveness of needle and syringe programmes: a review of the literature. EMCDDA Monographs. Hepatitis C and injecting drug use: impact, costs and policy options. Luxembourg: Office for Official Publications of the European Communities; 2004. p. 329-43.

Denis B, Dedobbeleer M, Collet T, Petit J, Jamoulle M, Hayani A, et al. High prevalence of hepatitis C virus infection in Belgian intravenous drug users and potential role of the 'cotton-filter' in transmission: the GEMT Study. Acta Gastroenterol Belg. 2000 Apr-Jun; 63(2):147-53.

Des Jarlais D, Hagan H, Friedman S, Friedmann P, Goldberg D, Frischer M. Preventing epidemics of HIV-1 among injecting drug users. In: Stimson G, Des Jarlais DC, Ball A, editors. Drug injecting and HIV infection: Global dimensions and local responses. London: University College of London Press; 1998.

Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Torian LV, et al. HIV infection during limited versus combined HIV prevention programs for IDUs in New York City: The importance of transmission behaviors. 2010 2010(1-3):154-60.

Des Jarlais DC, Fisher DG, Newman JC, Trubatch BN, Yancovitz M, Paone D, et al. Providing hepatitis B vaccination to injection drug users: referral to health clinics vs on-site vaccination at a syringe exchange program. Am J Public Health. 2001 Nov; 91(11):1791-2.

Des Jarlais DC, Hagan H, Friedman SR, Friedmann P, Goldberg D, Frischer M, et al. Maintaining low HIV seroprevalence in populations of injecting drug users. Jama. 1995 Oct 18; 274(15):1226-31.

Des Jarlais DC, Marmor M, Paone D, Titus S, Shi Q, Perlis T, et al. HIV incidence among injecting drug users in New York City syringe-exchange programmes. Lancet. 1996 Oct 12; 348(9033):987-91.

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Beatrice S, Milliken J, et al. HIV incidence among injection drug users in New York City, 1990 to 2002: use of serologic test algorithm to assess expansion of HIV prevention services. Am J Public Health. 2005 (a) Aug; 95(8):1439-44.

Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Hagan H, Beatrice S, et al. Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990-2001. AIDS. 2005 (b) Oct; 19 Suppl 3:S20-5.

Dolan KA, Niven H. A review of HIV prevention among young injecting drug users: A guide for researchers. Harm Reduct J. 2005 Mar 17;2(1):5.

Donoghoe MC, Dolan KA, Stimson GV. Life-style factors and social circumstances of syringe sharing in injecting drug users. Br J Addict. 1992 Jul;87(7):993-1003.

Donoghoe MC, Stimson GV, Dolan K, Alldritt L. Changes in HIV risk behaviour in clients of syringe-exchange schemes in England and Scotland. AIDS. 1989 May;3(5):267-72.

Ellis S, Barnett-Page E, Morgan A, Taylor L, Walters R, Goodrich J. HIV prevention: a review of reviews assessing the effectiveness of interventions to reduce the risk of sexual transmission: Health Development Agency2003.

Fisher DG, Fenaughty AM, Cagle HH, Wells RS. Needle exchange and injection drug use frequency: a randomized clinical trial. J Acquir Immune Defic Syndr. 2003 Jun 1; 33(2):199-205.

Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26; 347(13):975-82.

Frischer M, Elliott L, Taylor A, Goldberg D, Green S, Gruer L, et al. Do needle exchanges help to control the spread of HIV among injecting drug users? AIDS. 1993 Dec;7(12):1677-8.

Gerberding JL. Management of occupational exposures to blood-borne viruses. N Engl J Med. 1995 Feb 16; 332(7):444-51.

Gibson DR, Brand R, Anderson K, Kahn JG, Perales D, Guydish J. Two- to sixfold decreased odds of HIV risk behavior associated with use of syringe exchange. J Acquir Immune Defic Syndr. 2002 Oct 1; 31(2):237-42.

Gibson DR, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. AIDS. 2001 Jul 27; 15(11):1329-41.

Gigi E, Sinakos E, Lalla T, Vrettou E, Orphanou E, Raptopoulou M. Treatment of intravenous drug users with chronic hepatitis C: treatment response, compliance and side effects. Hippokratia. 2007 Oct; 11(4):196-8.

Gillies M, Palmeteer N, Hutchinson SJ, Ahmed S, Taylor A, Goldberg D. The provision of non-needle/syringe drug injection paraphernelia in the primary prevention of HCV among IDU: a systematic review. BMC Public Health. 2010(10):721.

Gleghorn AA, Jones TS, Doherty MC, Celentano DD, Vlahov D. Acquisition and use of needles and syringes by injecting drug users in Baltimore, Maryland. J Acquir Immune Defic Syndr Hum Retrovirol. 1995 Sep 1;10(1):97-103.

Gleghorn AA, Wright-De Agüero L, Flynn C. Feasibility of one-time use of sterile syringes: a study of active injection drug users in seven United States metropolitan areas. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18 Suppl 1:S30-6.

Gold M, Gafni A, Nelligan P, Millson P. Needle exchange programs: an economic evaluation of a local experience. CMAJ. 1997 Aug 1;157(3):255-62.

Goldberg D, Cameron S, McMenamin J. Hepatitis C virus antibody prevalence among injecting drug users in Glasgow has fallen but remains high. Commun Dis Public Health. 1998 Jun;1(2):95-7.

Goldberg D, McIntyre PG, Smith R, Appleyard K, Dunlop J, Taylor A, et al. Hepatitis C virus among high and low risk pregnant women in Dundee: unlinked anonymous testing. BJOG. 2001 Apr;108(4):365-70.

Goldstein MF, Friedman SR, Neaigus A, Jose B, Ildefonso G, Curtis R. Self-reports of HIV risk behavior by injecting drug users: are they reliable? Addiction. 1995 Aug; 90(8):1097-104.

Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol. 2010 Jul; 25(7):1281-4.

Green TC, Bluthenthal RN, Singer M, Beletsky L, Grau LE, Marshall P, et al. Prevalence and predictors of transitions to and away from syringe exchange use over time in 3 US cities with varied syringe dispensing policies. 2010:September 2010.

Griesbach D, Abdulrahim D, Gordon D, Dowell K. Needle Exchange Provision in Scotland: A Report of the National Needle Exchange Survey. Edinburgh: Scottish Executive2006.

Groseclose SL, Weinstein B, Jones TS, Valleroy LA, Fehrs LJ, Kassler WJ. Impact of increased legal access to needles and syringes on practices of injecting-drug users and police officers–Connecticut, 1992-1993. J Acquir Immune Defic Syndr Hum Retrovirol. 1995 Sep 1; 10(1):82-9.

Guydish J, Bucardo J, Clark G, Bernheim S. Evaluating needle exchange: a description of client characteristics, health status, program utilization, and HIV risk behavior. Subst Use Misuse. 1998 Apr;33(5):1173-96.

Guydish J, Clark G. Evaluation of needle exchange using street-based survey methods. J Drug Issues, 1995, 25: 33-41.

Hadziyannis SJ, Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004 Mar 2; 140(5):346-55.

Hagan H, Campbell J, Thiede H, Strathdee S, Ouellet L, Kapadia F, et al. Self-reported hepatitis C virus antibody status and risk behavior in young injectors. Public Health Rep. 2006 Nov-Dec; 121(6):710-9.

Hagan H, Des Jarlais DC, Friedman S. Risk for human immunodeficiency virus and hepatitis B virus in users of the Tacoma syringe exchange program. Washington D.C.: National Academy Press, 1994.

Hagan H, Des Jarlais DC, Purchase D, Friedman SR, Reid T, Bell TA. An interview study of participants in the Tacoma, Washington, syringe exchange. Addiction. 1993 Dec; 88(12):1691-7.

Hagan H, Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. Am J Public Health. 1995 Nov; 85(11):1531-7.

Hagan H, McGough JP, Thiede H, Weiss NS, Hopkins S, Alexander ER. Syringe exchange and risk of infection with hepatitis B and C viruses. Am J Epidemiol. 1999 Feb 1; 149(3):203-13.

Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. J Infect Dis. 2011 Jul; 204(1):74-83.

Hagan H, Thiede H. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. J Urban Health. 2000 Sep; 77(3):369-82.

Hagan H, Thiede H, Weiss NS, Hopkins SG, Duchin JS, Alexander ER. Sharing of drug preparation equipment as a risk factor for hepatitis C. Am J Public Health. 2001 Jan; 91(1):42-6.

Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis. 2002 Dec 1; 186(11):1558-64.

Hallinan R, Byrne A, Dore GJ. Harm reduction, hepatitis C and opioid pharmacotherapy: An opportunity for integrated hepatitis C virus-specific harm reduction. 2007 2007(4):437-43.

Hammett TM, Kling R, Johnston P, Liu W, Ngu D, Friedmann P, et al. Patterns of HIV prevalence and HIV risk behaviors among injection drug users prior to and 24 months following implementation of cross-border HIV prevention interventions in northern Vietnam and southern China. AIDS Educ Prev. 2006 Apr; 18(2):97-115.

Hart GJ, Carvell AL, Woodward N, Johnson AM, Williams P, Parry JV. Evaluation of needle exchange in central London: behaviour change and anti-HIV status over one year. AIDS. 1989 May;3(5):261-5.

Hartgers C, van Ameijden EJ, van den Hoek JA, Coutinho RA. Needle sharing and participation in the Amsterdam Syringe Exchange program among HIV-seronegative injecting drug users. Public Health Rep. 1992 Nov-Dec; 107(6):675-81.

Harvard SS, Hill WD, Buxton JA. Harm reduction product distribution in British Columbia. 2008 2008(6):446-50.

Haydon, E. and B. Fischer. Crack use as a public health problem in Canada: call for an evaluation of 'safer crack use kits'. Canadian Journal of Public Health, 2005, 96(3): 185-8.

Health Outcomes International. Return on investment in needle and syringe exchange programs in Australia. Canberra: Commonwealth Department of Health and Ageing; 2002.

Health Protection Agency. Shooting Up: Infections among injecting drug users in the United Kingdom 2005. London: Health Protection Agency; 2006.

Hedrich D, Kerr T, Dubois-Arber F. Drug consumption facilities in Europe and beyond. Chapter 11. In: European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA). Monograph 10. EMCDDA: Lisbon; 2010.

Heimer, R. Syringe exchange programs: lowering the transmission of syringe-borne diseases and beyond. [Review]. Public Health Rep. 1998 Jun;113 Suppl 1:67-74.

Heimer R, Clair S, Grau LE, Bluthenthal RN, Marshall PA, Singer M. Hepatitis-associated knowledge is low and risks are high among HIV-aware injection drug users in three US cities. Addiction. 2002 Oct;97(10):1277-87.

Heimer R, Kaplan EH, Khoshnood K, Jariwala B, Cadman EC. Needle exchange decreases the prevalence of HIV-1 proviral DNA in returned syringes in New Haven, Connecticut. Am J Med. 1993 Aug;95(2):214-20.

Heinemann A, Gross U. Prevention of blood-brone virus infections among drug users in an open prison by syringe vending machines. Sucht. 2001; 47(2):57-65.

Heinzerling KG, Kral AH, Flynn NM, Anderson RL, Scott A, Gilbert ML, et al. Unmet need for recommended preventive health services among clients of California syringe exchange programs: implications for quality improvement. 2006 Feb 1(2):167-78.

Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009 Aug 15; 49(4):561-73.

Herbst JH, Kay LS, Passin WF, Lyles CM, Crepaz N, Marin BV. A systematic review and meta-analysis of behavioral interventions to reduce HIV risk behaviors of Hispanics in the United States and Puerto Rico. AIDS & Behavior. 2007; 11(1):25-47.

Hernandez-Aguado I, Ramos-Rincon JM, Aviñio MJ, Gonzalez-Aracil J, Pérez-Hoyos S, de la Hera MG. Measures to reduce HIV infection have not been successful to reduce the prevalence of HCV in intravenous drug users. Eur J Epidemiol. 2001;17(6):539-44.

Holtgrave DR, Pinkerton SD, Jones TS, Lurie P, Vlahov D. Cost and cost-effectiveness of increasing access to sterile syringes and needles as an HIV prevention intervention in the United States. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18 Suppl 1:S133-8.

Holtzman D, Barry V, Ouellet LJ, Des Jarlais DC, Vlahov D, Golub ET, et al. The influence of needle exchange programs on injection risk behaviors and infection with hepatitis C virus among young injection drug users in select cities in the United States, 1994-2004. Prev Med. 2009 Aug;49(1):68-73. Epub 2009 May 4.

Hong Y, Li X. HIV/AIDS behavioral interventions in China: a literature review and recommendation for future research. AIDS Behav. 2009 Jun; 13(3):603-13.

Hope VD, Ncube F, Hickman M, Judd A, Parry JV. Hepatitis B vaccine uptake among injecting drug users in England 1998 to 2004: Is the prison vaccination programme driving recent improvements? J Viral Hepat. 2007 Sep;14(9):653-60.

Hunt N, Trace M, Bewley-Taylor D. Reducing drug related harms to health: An overview of the global evidence, Report 4. London: The Beckley Foundation; 2005.

Hunter GM, Donoghoe MC, Stimson GV, Rhodes T, Chalmers CP. Changes in the injecting risk behaviour of injecting drug users in London, 1990-1993. AIDS. 1995 May; 9(5):493-501.

Huo D, Bailey SL, Garfein RS, Ouellet LJ. Changes in the sharing of drug injection equipment among street-recruited injection drug users in Chicago, Illinois, 1994–1996. Subst Use Misuse. 2005; 40(1):63-76.

Huo D, Ouellet LJ. Needle exchange and injection-related risk behaviors in Chicago: a longitudinal study. J Acquir Immune Defic Syndr. 2007 May 1;45(1):108-14.

Hurley SF, Jolley DJ, Kaldor JM. Effectiveness of needle-exchange programmes for prevention of HIV infection. Lancet. 1997 Jun 21; 349(9068):1797-800.

Hutchinson SJ, McIntyre PG, Molyneaux P, Cameron S, Burns S, Taylor A, et al. Prevalence of hepatitis C among injectors in Scotland 1989-2000: declining trends among young injectors halt in the late 1990s. Epidemiol Infect. 2002 Jun;128(3):473-7.

Ingold FR, Ingold S. The effects of the liberalisation of syringe sales on the behaviour of intravenous drug users in France. Bull Narc. 1989;41(1-2):67-81.

Islam M, Wodak A, Conigrave KM. The effectiveness and safety of syringe vending machines as a component of needle syringe programmes in community settings. Int J Drug Policy. 2008 Dec; 19(6):436-41.

Islam MM, Conigrave KM. Assessing the role of syringe dispensing machines and mobile van outlets in reaching hard-to-reach and high-risk groups of injecting drug users (IDUs): a review. Harm Reduct Journal. 2007 Oct 24; 4(14).

Jacob J, Rottman J, Stöver H. Entstehung und Praxis eines Gesundheitsraumangebotes für Drogenkonsumierende. Abschlußbericht der einjährigen Evaluation des 'drop-in Fixpunkt', Hannover. Oldenburg: Bibliotheks -und Informationssystem der Universität Oldenburg; 1999.

Jacobs P, Calder P, Taylor M, Houston S, Saunders LD, Albert T. Cost effectiveness of Streetworks' needle exchange program of Edmonton. Can J Public Health. 1999 May-Jun;90(3):168-71.

Jones L, Pickering L, Sumnall H, McVeigh J, Bellis MA. A review of the effectiveness and cost-effectiveness of needle and syringe programmes for injecting drug users. Liverpool: Centre for Public Health, Liverpool John Moores University; 2008. Available from: http://www.nice.org.uk/nicemedia/pdf/PH18EffectivenessReviewRevised.pdf

Jones L, Pickering L, Sumnall H, McVeigh J, Bellis MA. Optimal provision of needle and syringe programmes for injecting drug users: A systematic review. Int J Drug Policy. 2010 Sep; 21(5):335-42.

Judd A, Hutchinson S, Wadd S, Hickman M, Taylor A, Jones S, et al. Prevalence of, and risk factors for, hepatitis C virus infection among recent initiates to injecting in London and Glasgow: cross sectional analysis. J Viral Hepat. 2005 Nov; 12(6):655-62.

Jürgens R. HIV/AIDS and HCV in prisons: A select annotated bibliography (part 3). Int J Prison Health, 2006; 2(3): 219-236.

Kahn J. Are NEPs cost-effective in preventing HIV infection? In: Lurie P, Reingold AL (eds) Public health impact of needle exchange programmes in the United States and Abroad. Berkeley, CA; 1993. p 473-509.

Kahn JG. Economic evaluation of primary HIV prevention in injection drug users. In: DR Holtgrave. Handbook of Economic Evaluation HIV Prevention Programmes. New York: Plenum Press; 1998

Kahn JG, DeCarlo P. Is HIV prevention a good investment? Center for AIDS Prevention Studies at the University of California San Francisco (CAPS). San Francisco: CAPS; 1995.

Kahn JG, Sanstad KC. The role of cost-effectiveness analysis in assessing HIV-prevention interventions. AIDS Public Policy J. 1997 Spring;12(1):21-30.

Kahn JG, Washington AE, Showstack J. Updated estimates of the impact and cost of HIV prevention in injecting drug users. Prepared for the Centers for Disease Control. Institute for Health Policy Studies, School of Medicine, University of California San Francisco: San Francisco; 1992

Kaplan EH. Back-of-the-envelope estimates of needle exchange effectiveness. Unpublished working paper, 1993.

Kaplan EH. Economic analysis of needle exchange. AIDS. 1995 Oct;9(10):1113-9.

Keene J, Stimson GV, Jones S, Parry-Langdon N. Evaluation of syringe-exchange for HIV prevention among injecting drug users in rural and urban areas of Wales. Addiction. 1993 Aug;88(8):1063-70.

Kelly M, Swann C, Killoran A, Naidoo B, Barnett-Page E, Morgan A. Methodological problems in constructing the evidence base in public health. London: Health Development Agency; 2002.

Kerr T, Kimber J, Debeck K, Wood E. The role of safer injection facilities in the response to HIV/AIDS among injection drug users. Curr HIV/AIDS Rep. 2007 Dec; 4(4):158-64.

Kerr T, Tyndall M, Li K, Montaner J, Wood E. Safer injection facility use and syringe sharing in injection drug users. Lancet. 2005; 366(9482):316-8.

Khoshnood K, Blankenship KM, Pollack HA, Roan CT, Altice FL. Syringe source, use, and discard among injection-drug users in New Haven, Connecticut. AIDS Public Policy J. 2000 Fall-Winter; 15(3-4):88-94.

Kimber J, Palmateer N, Hutchinson S, Hickman M, Goldberg D, Rhodes T. Harm reduction among injecting drug users – evidence of effectiveness. In: European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA). Monograph 10. EMCDDA: Lisbon; 2010.

Kipke M, Unger J, Palmer R, Edgington R. Drug injecting street youth: a comparison of HIV risk-injection behaviors between needle exchange users and non-users. AIDS Behav. 1997 1(4): 225-232.

Klee H, Faugier J, Hayes C, Morris J. The sharing of injecting equipment among drug users attending prescribing clinics and those using needle-exchanges. Br J Addict. 1991 Feb;86(2):217-23.

Klee H, Morris J. The role of needle exchanges in modifying sharing behaviour: cross-study comparisons 1989-1993. Addiction. 1995 Dec;90(12):1635-45.

Kumaranayake L. The cost-effectiveness of HIV preventive measures among injecting drug users in Svetlogorsk, Belarus. Geneva: UNAIDS; 2000. [Draft]

Kumaranayake L, Vickerman P, Walker D, Samoshkin S, Romantzov V, Emelyanova Z, et al. The cost-effectiveness of HIV preventive measures among injecting drug users in Svetlogorsk, Belarus. Addiction. 2004 Dec;99(12):1565-76.

Kwiatkowski CF, Fortuin Corsi K, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug users. Addiction. 2002 Oct;97(10):1289-94.

Lamden KH, Kennedy N, Beeching NJ, Lowe D, Morrison CL, Mallinson H, et al. Hepatitis B and hepatitis C virus infections: risk factors among drug users in Northwest England. J Infect. 1998 Nov; 37(3):260-9.

Laufer FN. Cost-effectiveness of syringe exchange as an HIV prevention strategy. J Acquir Immune Defic Syndr. 2001 Nov 1;28(3):273-8.

Li J, Luo J, Yang F. Evaluation on peer education program among injecting drug users. Zhonghua Liu Xing Bing Xue Za Zhi. 2001 Oct; 22(5):334-6.

Liebman J, Pat Lamberti M, Altice F. Effectiveness of a mobile medical van in providing screening services for STDs and HIV. Public Health Nurs. 2002 Sep-Oct; 19(5):345-53.

Lindenburg CEA, Lambers FAE, Urbanus AT, Schinkel J, Jansen PLM, Krol A, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. 2011 2011(1):23-31.

Rick Lines R, Jürgens R, Betteridge G, Stöver H, Laticevschi D, Joachim Nelles, editors. Prison needle exchange: Lessons from a comprehensive review of international evidence and experience. 2nd edition. Canadian HIV/AIDS Legal Network: Toronto: 2006.

Linssen L, de Jong W, Wolf J. Gebruiksruimten: Een systematisch overzicht van de voorziening en de effecten ervan. Utrecht: Trimbos-Instituut, ontwikkelcentrum Social Verslavingsbeleid; 2000.

Litwin AH, Harris KA, Jr., Nahvi S, Zamor PJ, Soloway IJ, Tenore PL, et al. Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. J Subst Abuse Treat. 2009 Jul; 37(1):32-40.

Ljungberg B, Christensson B, Tunving K, Andersson B, Landvall B, Lundberg M, et al. HIV prevention among injecting drug users: three years of experience from a syringe exchange program in Sweden. J Acquir Immune Defic Syndr. 1991; 4(9):890-5.

Longshore D, Bluthenthal RN, Stein MD. Needle exchange program attendance and injection risk in Providence, Rhode Island. AIDS Educ Prev. 2001 Feb; 13(1):78-90.

Lurie P, Drucker E. An opportunity lost: HIV infections associated with lack of a national needle-exchange programme in the USA. Lancet. 1997 Mar 1;349(9052):604-8.

Lurie P, Gorsky R, Jones TS, Shomphe L. An economic analysis of needle exchange and pharmacy-based programs to increase sterile syringe availability for injection drug users. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18 Suppl 1:S126-32.

MacDonald MA, Wodak AD, Dolan KA, van Beek I, Cunningham PH, Kaldor JM. Hepatitis C virus antibody prevalence among injecting drug users at selected needle and syringe programs in Australia, 1995-1997. Collaboration of Australian NSPs. Med J Aust. 2000 Jan 17;172(2):57-61.

MacDonald M, Law MG, Kaldor JM, Hales J, Dore GJ. Effectiveness of needle and syringe programmes for preventing HIV transmission. Int J Drug Policy. 2003; 14(5-6):353-7.

Malliori M, Sypsa V, Psichogiou M, Touloumi G, Skoutelis A, Tassopoulos N, et al. A survey of bloodborne viruses and associated risk behaviours in Greek prisons. Addiction. 1998 Feb; 93(2):243-51.

Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001 Sep 22; 358(9286):958-65.

Mansson AS, Moestrup T, Nordenfelt E, Widell A. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. Scand J Infect Dis. 2000; 32(3):253-8.

Medley A, Kennedy C, O'Reilly K, Sweat M. Effectiveness of peer education interventions for HIV prevention in developing countries: a systematic review and meta-analysis. AIDS Educ Prev. 2009 Jun; 21(3):181-206.

Meijer G, de Jong A, Koeter M, Bieleman B. Gebruik van de straat: Evaluatie gebruiksruimte binnenstad-Zuid Groningen. Groningen-Rotterdam: INTRAVAL2001.

Miller CL, Tyndall M, Spittal P, Li K, Palepu A, Schechter MT. Risk-taking behaviors among injecting drug users who obtain syringes from pharmacies, fixed sites, and mobile van needle exchanges. J Urban Health. 2002 Jun; 79(2):257-65.

Miller M, Mella I, Moi H, Eskild A. HIV and hepatitis C virus risk in new and longer-term injecting drug users in Oslo, Norway. J Acquir Immune Defic Syndr. 2003 Jul 1;33(3):373-9.

Minder Nejedly M, Bürki CM. Monitoring HIV risk behaviours in a street agency with injection room in Switzerland. Bern: Medizinische Fakultät der Universität Bern; 1996.

Monterroso ER, Hamburger ME, Vlahov D, Des Jarlais DC, Ouellet LJ, Altice FL, et al. Prevention of HIV infection in street-recruited injection drug users. The Collaborative Injection Drug User Study (CIDUS). J Acquir Immune Defic Syndr. 2000 Sep 1;25(1):63-70.

Morissette C, Cox J, De P, Tremblay C, Roy E, Allard R, et al. Minimal uptake of sterile drug preparation equipment in a predominantly cocaine injecting population: implications for HIV and hepatitis C prevention. Int J Drug Policy. 2007 May; 18(3):204-12.

Morrison DS, Gilchrist G, Ahmed S. Potential of specialist drug services to deliver hepatitis B vaccination. 2002 2002(4):321-3.

MSIC Evaluation Committee. Final report of the evaluation of the Sydney Medically Supervised Injecting Centre. Sydney: MSIC; 2003.

Nacopoulos AG, Lewtas AJ, Ousterhout MM. Syringe exchange programs: Impact on injection drug users and the role of the pharmacist from a U.S. perspective. J Am Pharm Assoc. 2010 Mar-Apr 1; 50(2):148-57.

Neaigus A, Zhao M, Gyarmathy VA, Cisek L, Friedman SR, Baxter RC. Greater drug injecting risk for HIV, HBV, and HCV infection in a city where syringe exchange and pharmacy syringe distribution are illegal. J Urban Health. 2008 May;85(3):309-22. Epub 2008 Mar 14.

Needle RH, Burrows D, Friedman SR, Dorabjee J, Touze G, Badrieva L, et al. Effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users. Int J Drug Policy. 2005; 16(SUPPL. 1):S45-S57.

Nelson KE, Vlahov D, Cohn S, Lindsay A, Solomon L, Anthony JC. Human immunodeficiency virus infection in diabetic intravenous drug users. Jama. 1991 Oct 23-30; 266(16):2259-61.

Obadia Y, Feroni I, Perrin V, Vlahov D, Moatti JP. Syringe vending machines for injection drug users: an experiment in Marseille, France. Am J Public Health. 1999 Dec; 89(12):1852-4.

Oliver K, Maynard H, Friedman SR, Des Jarlais DC. Behavioral and community impact of the Portland Syringe Exchange Program. In: National Research Council and Institute of Medicine, editors. Proceedings, workshop on needle exchange and bleach distribution programs. Washington, DC: National Academy Press; 1994. p35-46.

Ompad DC, Fuller CM, Vlahov D, Thomas D, Strathdee SA. Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland. Clin Infect Dis. 2002 Oct 1; 35(7):783-8.

Ouellet L, Huo D, Bailey SL. HIV risk practices among needle exchange users and nonusers in Chicago. J Acquir Immune Defic Syndr. 2004 Sep 1; 37(1):1187-96.

Palmateer N, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. Addiction. 2010 May; 105(5):844-59.

Palmateer NE, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of harm reduction interventions in preventing hepatitis C transmission among injecting drug users: a review of reviews. Glasgow: Health Protection Scotland; 2008.

Paone D, Des Jarlais DC, Caloir S, Friedmann P, Ness I, Friedman SR. New York syringe exchange: An overview. In: National Research Council and Institute of Medicine, editors. Proceedings, workshop on needle exchange and bleach distribution programs. Washington, DC: National Academy Press; 1994. p47-63.

Parsons J, Hickman M, Turnbull PJ, McSweeney T, Stimson GV, Judd A, et al. Over a decade of syringe exchange: results from 1997 UK survey. Addiction. 2002 Jul; 97(7):845-50.

Patrick DM, Strathdee SA, Archibald CP, Ofner M, Craib KJ, Cornelisse PG, et al. Determinants of HIV seroconversion in injection drug users during a period of rising prevalence in Vancouver. Int J STD AIDS. 1997 Jul; 8(7):437-45.

Patrick DM, Tyndall MW, Cornelisse PG, Li K, Sherlock CH, Rekart ML, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. CMAJ. 2001 Oct 2;165(7):889-95.

Peak A, Rana S, Maharjan SH, Jolley D, Crofts N. Declining risk for HIV among injecting drug users in Kathmandu, Nepal: the impact of a harm-reduction programme. AIDS. 1995 Sep;9(9):1067-70.

Pinkerton SD, Holtgrave DR, DiFranceisco W, Semaan S, Coyle SL, Johnson-Masotti AP. Cost-threshold analyses of the National AIDS Demonstration Research HIV prevention interventions. AIDS. 2000 Jun 16;14(9):1257-68.

Pinkerton SD, Kahn JG, Holtgrave DR. Cost-effectiveness of community-level approaches to HIV prevention: A review. Journal of Primary Prevention. 2002; 23(2):175-98.

Pollack HA. Cost-effectiveness of harm reduction in preventing hepatitis C among injection drug users. Med Decis Making. 2001 Sep-Oct; 21(5):357-67.

Poschadel S, Höger R, Schnitzler J, Schreckenberger D. Evaluation der Arbeit der Drogenkonsumräume in der Bundesrepublik Deutschland:Endbericht im Auftrag des Bundesministeriums für Gesundheit. 149). DBfGuSSSB, editor. Baden-Baden: Nomos-Verlags-Gesellschaft.; 2003.

Pouget ER, Deren S, Fuller CM, Blaney S, McMahon JM, Kang SY, et al. Receptive syringe sharing among injection drug users in Harlem and the Bronx during the New York State Expanded Syringe Access Demonstration Program. J Acquir Immune Defic Syndr. 2005 Aug 1; 39(4):471-7.

Power R, Nozhkina N. The value of process evaluation in sustaining HIV harm reduction in the Russian Federation. AIDS. 2002 Jan 25;16(2):303-4.

Prendergast ML, Urada D, Podus D. Meta-analysis of HIV risk-reduction interventions within drug abuse treatment programs, J Consult Clin Psychol. 2001 Jun;69(3):389-405.

Ramasamy P, Lintzeris N, Sutton Y, Taylor H, Day CA, Haber PS. The outcome of a rapid hepatitis B vaccination programme in a methadone treatment clinic. 2010 2010(2):329-34.

Reyes Fuentes VC. 15 Jahre Fixerraum Bern. Auswirkungen auf soziale und medizinische Aspekte bei Drogenabhängigen. Bern: University of Bern2003.

Rhodes T, Judd A, Mikhailova L, Sarang A, Khutorskoy M, Platt L, et al. Injecting equipment sharing among injecting drug users in Togliatti City, Russian Federation: maximizing the protective effects of syringe distribution. J Acquir Immune Defic Syndr. 2004 (a) Mar 1; 35(3):293-300.

Richard AJ, Mosier V, Atkinson JS. New syringe acquisition and multi-person use of syringes among illegal drug users. J Public Health Policy. 2002;23(3):324-43.

Riley ED, Safaeian M, Strathdee SA, Marx MA, Huettner S, Beilenson P, et al. Comparing new participants of a mobile versus a pharmacy-based needle exchange program. J Acquir Immune Defic Syndr. 2000 May 1; 24(1):57-61.

Ronco C, Spuhler G, Coda P, Schopfer R. Evaluation der Gassenzimmer I, II und III in Basel. Sozial- und Praventivmedizin. 1996; 41:S58-S68.

Sarang A, Rhodes T, Platt L. Access to syringes in three Russian cities: implications for syringe distribution and coverage. 2008:S25-36, 2008 Apr.

Sarkar K, Mitra S, Bal B, Chakraborty S, Bhattacharya SK. Rapid spread of hepatitis C and needle exchange programme in Kolkata, India. Lancet. 2003 Apr 12; 361(9365):1301-2.

Schechter MT, Strathdee SA, Cornelisse PG, Currie S, Patrick DM, Rekart ML, et al. Do needle exchange programmes increase the spread of HIV among injection drug users?: an investigation of the Vancouver outbreak. AIDS. 1999 Apr 16; 13(6):F45-51.

Schoenbaum EE, Hartel DM, Gourevitch MN. Needle exchange use among a cohort of injecting drug users. AIDS. 1996 Dec; 10(14):1729-34.

Sears C, Guydish JR, Weltzien EK, Lum PJ. Investigation of a secondary syringe exchange program for homeless young adult injection drug users in San Francisco, California, U.S.A. J Acquir Immune Defic Syndr. 2001 Jun 1;27(2):193-201.

Sears C, Weltzien E, Guydish J. A cohort study of syringe exchangers and nonexchangers in San Francisco. J Drug Issues. 2001 b, 31 (2):445-464.

Sergeyev B, Oparina T, Rumyantseva T, Volkanevskii V, Broadhead R, Heckathorn D, et al. HIV Prevention in Yaroslavl, Russia: A Peer-Driven Intervention and Needle Exchange. Journal of Drug Issues. 1999; 29(4):777-804.

Sharma M, Burrows D, Bluthenthal R. Coverage of HIV prevention programmes for injection drug users: Confusions, aspirations, definitions and ways forward. 2007 2007(2):92-8.

Singer M, Himmelgreen D, Weeks MR, Radda KE, Martinez R. Changing the environment of AIDS risk: findings on syringe exchange and pharmacy sales of syringes in Hartford, CT. Med Anthropol. 1997 Dec; 18(1):107-30.

Smyth BP, Keenan E, O'Connor JJ. Evaluation of the impact of Dublin's expanded harm reduction programme on prevalence of hepatitis C among short-term injecting drug users. J Epidemiol Community Health. 1999 Jul;53(7):434-5.

Somaini B, Wang J, Perozo M, Kuhn F, Meili D, Grob P, Flepp M. A continuing concern: HIV and hepatitis testing and prevalence among drug users in substitution programmes in Zurich, Switzerland. AIDS Care. 2000 Aug;12(4):449-60.

Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, et al. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. Health Technol Assess. 2002;6(31):1-122.

Stoltz JA, Wood E, Small W, Li K, Tyndall M, Montaner J, et al. Changes in injecting practices associated with the use of a medically supervised safer injection facility. J Public Health (Oxf). 2007 Mar; 29(1):35-9.

Stoove MA, Gifford SM, Dore GJ. The impact of injecting drug use status on hepatitis C-related referral and treatment. 2005 Jan 2005(1):81-6.

Stöver H, Nelles J. Ten years of experience with needle and syringe exchange programmes in European prisons. Int J Drug Policy. 2003;14(5-6): 437-444.

Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, et al. Needle exchange is not enough: lessons from the Vancouver injecting drug use study. AIDS. 1997 Jul; 11(8):F59-65.

Taylor A, Goldberg D, Hutchinson S, Cameron S, Gore SM, McMenamin J, et al. Prevalence of hepatitis C virus infection among injecting drug users in Glasgow 1990-1996: are current harm reduction strategies working? J Infect. 2000 Mar; 40(2):176-83.

Thiede H, Hagan H, Campbell JV, Strathdee SA, Bailey SL, Hudson SM, et al. Prevalence and correlates of indirect sharing practices among young adult injection drug users in five U.S. cities. Drug Alcohol Depend. 2007 Apr 25.

Thorpe LE, Ouellet LJ, Hershow R, Bailey SL, Williams IT, Williamson J, et al. Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. Am J Epidemiol. 2002 Apr 1; 155(7):645-53.

Tilson H, Aramrattana A, Bozzette S, Celentano D, Falco M, Hammett T, et al. Preventing HIV Infection among Injecting Drug Users in High Risk Countries: An Assessment of the Evidence. Washington DC: Institute of Medicine; 2007.

Tilson H, Aramrattana A, Bozzette SA, Celentano DD, Falco M, Hammett TM, et al. Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence. Washington: The National Academies Press; 2007.

Trubnikov MN, Khodakevich LN, Barkov DA, Blagovo DV. Sources of injecting equipment for drug users in Moscow, Russia. Int J Drug Policy. 2012 Sep;14(5-6):453-55.

Turner K, Hutchinson S, Vickerman P, Hope V, Craine N, Palmeteer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction. 2011 Nov;106(11):1978-88. doi: 10.1111/j.1360-0443.2011.03515.x. Epub 2011 Aug 24.

van Ameijden EJ, van den Hoek AR, Coutinho RA. Injecting risk behavior among drug users in Amsterdam, 1986 to 1992, and its relationship to AIDS prevention programs. Am J Public Health. 1994 Feb;84(2):275-81.

van Ameijden EJ, Van den Hoek JA, Mientjes GH, Coutinho RA. A longitudinal study on the incidence and transmission patterns of HIV, HBV and HCV infection among drug users in Amsterdam. Eur J Epidemiol. 1993 May;9(3):255-62.

van Ameijden EJ, van den Hoek JA, van Haastrecht HJ, Coutinho RA. The harm reduction approach and risk factors for human immunodeficiency virus (HIV) seroconversion in injecting drug users, Amsterdam. Am J Epidemiol. 1992 Jul 15; 136(2):236-43.

van de Laar TJ, Langendam MW, Bruisten SM, Welp EA, Verhaest I, van Ameijden EJ, et al. Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. J Med Virol. 2005 Dec; 77(4):509-18.

van Den Berg C, Smit C, Van Brussel G, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction. 2007 Sep; 102(9):1454-62.

van den Hoek JA, van Haastrecht HJ, Coutinho RA. Risk reduction among intravenous drug users in Amsterdam under the influence of AIDS. Am J Public Health. 1989 Oct;79(10):1355-7.

van der Poel A, Barendregt C, van de Mheen D. Drug Consumption Rooms in Rotterdam: An Explorative Description. European Addiction Research. 2003; 9:94-100.

Vazirian M, Nassirimanesh B, Zamani S, Ono-Kihara M, Kihara M, Ravari SM, et al. Needle and syringe sharing practices of injecting drug users participating in an outreach HIV prevention program in Tehran, Iran: A cross-sectional study. Harm Reduct J. 2005 Oct 7;2:19.

Vertefeuille J, Marx MA, Tun W, Huettner S, Strathdee SA, David Vlahov. Decline in self-reported high-risk injection-related behaviors among HIV-seropositive participants in the Baltimore needle exchange program. AIDS Behav. 2000;4(4): 381-388.

Vickerman P, Hickman M, Judd A. Modelling the impact on Hepatitis C transmission of reducing syringe sharing: London case study. Int J Epidemiol. 2007; 36:396-405.

Vidal-Trecan G, Coste J, Varescon-Pousson I, Christoforov B, Boissonnas A. HCV status knowledge and risk behaviours amongst intravenous drug users. Eur J Epidemiol. 2000 May; 16(5):439-45.

Vlahov D, Junge B, Brookmeyer R, Cohn S, Riley E, Armenian H, et al. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. J Acquir Immune Defic Syndr Hum Retrovirol. 1997 Dec 15; 16(5):400-6.

Voytek C, Sherman SG, Junge B. A matter of convenience: Factors influencing secondary syringe exchange in Baltimore, Maryland, USA. Int J Drug Policy. 2003;14(5-6):465-467.

Watters JK, Estilo MJ, Clark GL, Lorvick J. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. JAMA. 1994 Jan 12;271(2):115-20.

Wiebel WW, Jimenez A, Johnson W, Ouellet L, Jovanovic B, Lampinen T, et al. Risk behavior and HIV seroincidence among out-of-treatment injection drug users: a four-year prospective study. J Acquir Immune Defic Syndr Hum Retrovirol. 1996 Jul; 12(3):282-9.

Wiessing L, Likatavicius G, Klempova D, Hedrich D, Nardone A, Griffiths P. Associations between availability and coverage of HIV-prevention measures and subsequent incidence of diagnosed HIV infection among injection drug users. Am J Public Health. 2009 Jun; 99(6):1049-52.

Williams CT, Metzger DS. Race and distance effects on regular syringe exchange program use and injection risks: a geobehavioral analysis. 2010:Jun 2010.

Wodak A, Cooney A. Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users. Geneva: WHO2004.

Wood E. Summary of findings from the evaluation of a pilot medically supervised safer injecting facility. Canadian Medical Association Journal. 2006; 175(11):1399-404.

Wood E, Tyndall M, Stoltz J, Small W, Lloyd-Smith E, Zhang R, et al. Factors associated with syringe sharing among users of a medically supervised safer injecting facility. Am J Infect Dis. 2005;1(1):50-4.

Wood E, Kerr T, Spittal PM, Small W, Tyndall MW, O'Shaughnessy MV, et al. An external evaluation of a peer-run 'unsanctioned' syringe exchange program. J Urban Health. 2003 Sep;80(3):455-64.

Wood E, Tyndall MW, Spittal PM, Li K, Hogg RS, Montaner JS, et al. Factors associated with persistent high-risk syringe sharing in the presence of an established needle exchange programme. AIDS. 2002 Apr 12;16(6):941-3.

Wright NM, Campbell TL, Tompkins CN. Comparison of conventional and accelerated hepatitis B immunisation schedules for homeless drug users. Commun Dis Public Health. 2002 Dec;5(4):324-6.

Wright NM, Tompkins CN. A review of the evidence for the effectiveness of primary prevention interventions for Hepatitis C among injecting drug users. Harm Reduct J. 2006; 3:27.

Wu Z, Luo W, Sullivan SG, Rou K, Lin P, Liu W, et al. Evaluation of a needle social marketing strategy to control HIV among injecting drug users in China. AIDS. 2007 Dec;21 Suppl 8:S115-22.

Zanini B, Covolo L, Donato F, Lanzini A. Effectiveness and tolerability of combination treatment of chronic hepatitis C in illicit drug users: meta-analysis of prospective studies. Clin Ther. 2010 Dec; 32(13):2139-59.

Zurhold H, Kreuzfeld N, Degwitz P, Verthein U. Drogenkonsumräume: Gesundheitsförderung und Minderung öffentlicher Belastungen in europäischen Großstädten. Freiburg: Lambertus; 2001.

Appendix A-1. Search strategies original RoR

Note that access to the MEDLINE, Embase, and CINAHL databases was through OVID gateway. PsycInfo and IBSS were accessed through WebSPIRS 5. The Cochrane Library was accessed through Wiley InterScience.

Medline

Search Limits: Date range = 1980 to March Week 2 2007, Language = English

1. review.pt.
2. exp "review [publication type]"/
3. "consensus development conference [publication type]"/
4. exp "Meta-Analysis [Publication Type]"/
5. ((review$ or overview$) and (systematic or methodologic$ or quantitative$ or literature$)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. *Hepatitis C/pc
8. (hepatitis c or HCV).ti,ab.
9. *HIV Infections/pc
10. HIV.ti,ab.
11. transmission.ti,ab.
12. seroconver$.ti,ab.
13. risk behavio?r.ti,ab.
14. Risk Reduction Behavior/
15. Behavior Modification/
16. Needle Sharing/
17. Risk-taking/
18. 7 or (8 and 11) or (8 and 12) or 9 or (10 and 11) or (10 and 12) or 13 or 14 or 15 or 16 or 17
19. *Substance Abuse, Intravenous/
20. (substance$ or drug$).ti,ab.
21. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
22. (inject$ or intravenous).ti,ab.
23. 19 or (20 and 21) or (20 and 22)
24. Harm Reduction/
25. Intervention Studies/
26. Preventive Health Services/
27. Community Health Services/
28. Primary Prevention/
29. 24 or 25 or 26 or 27 or 28
30. (needle$ or syringe$).ti,ab.
31. exchange$.ti,ab.
32. Needle-Exchange Programs/
33. (30 and 31) or 32
34. outreach.ti,ab.
35. mobile.ti,ab.
36. backpack$.ti,ab.
37. (vending and machine$).ti,ab.
38. (30 and 34) or (30 and 35) or 36 or 37
39. (paraphernalia or equipment).ti,ab.
40. (distribu$ or provi$).ti,ab.
41. 39 and 40
42. *Methadone/
43. *Buprenorphine/

44. (substitution or maintenance).ti,ab.
45. 42 or 43 or 44 or "44".mp. [mp=title, subject heading word, abstract, instrumentation]
46. (bleach and disinfect$).ti,ab.
47. (needle and disinfect$).ti,ab.
48. 46 or 47
49. Health Education/
50. Patient Education/
51. Counselling/
52. Health Knowledge, Attitudes, Practice/
53. Health Promotion/
54. 49 or 50 or 51 or 52 or 53
55. outreach.ti,ab.
56. peer intervention.ti,ab.
57. peer education.ti,ab.
58. 55 or 56 or 57
59. HIV Infections/di
60. Hepatitis C/di
61. (HCV test$ or hepatitis c test$ or HIV test$).ti,ab.
62. Diagnostic Tests, Routine/
63. 59 or 60 or 61 or 62
64. ((HCV or hepatitis c) and treatment).ti,ab.
65. drug consumption rooms.ti,ab.
66. (safe$ inject$ and (site or facilit$)).ti,ab.
67. 65 or 66
68. (structural and intervention$).ti,ab.
69. (environment$ and intervention$).ti,ab.
70. 68 or 69
71. crack pipe$.ti,ab.
72. 29 or 33 or 38 or 41 or 45 or 48 or 54 or 58 or 63 or 64 or 67 or 70 or 71
73. 6 and 18 and 23 and 72

Embase

Search Limits: Date range = 1980 to 2007 Week 11, Language = English

1. review.pt
2. metaanalys$.ti,ab.
3. meta-analys$.ti,ab.
4. ((review$ or overview$) and (systematic or methodologic$ or quantitative$ or literature$)).ti,ab.
5. 1 or 2 or 3 or 4
6. *Hepatitis C/pc
7. (hepatitis c or HCV).ti,ab.
8. *Human Immunodeficiency Virus Infection/pc
9. HIV.ti,ab.
10. transmission.ti,ab.
11. seroconver$.ti,ab.
12. risk behavio?r.ti,ab.
13. ((needle$ or syringe$) and sharing).ti,ab.
14. Risk Reduction/
15. Behavior Modification/
16. High Risk Behavior/
17. 6 or (7 and 10) or (7 and 11) or 8 or (9 and 10) or (9 and 11) or 12 or 13 or 14 or 15 or 16

18. *Substance Abuse/
19. (substance$ or drug$).ti,ab.
20. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
21. (inject$ or intravenous).ti,ab.
22. 18 or (19 and 20) or (19 and 21)
23. Harm Reduction/
24. Intervention Study/
25. Preventive Health Service/
26. Primary Prevention/
27. Infection Prevention/
28. 23 or 24 or 25 or 26 or 27
29. (needle$ or syringe$).ti,ab.
30. exchange$.ti,ab.
31. 29 and 30
32. outreach.ti,ab.
33. mobile.ti,ab.
34. backpack$.ti,ab.
35. (vending and machine$).ti,ab.
36. (29 and 32) or (29 and 33) or 34 or 35
37. (paraphernalia or equipment).ti,ab.
38. (distribu$ or provi$).ti,ab.
39. 37 and 38
40. *Methadone/
41. *Buprenorphine/
42. substitution or maintenance.ti,ab.
43. 40 or 41 or 42
44. (bleach and disinfect$).ti,ab.
45. (needle and disinfect$).ti,ab.
46. 44 or 45
47. Health Education/
48. Patient Education/
49. Counselling/
50. Attitude to Health/
51. Health Promotion/
52. 47 or 48 or 49 50 or 51
53. outreach.ti,ab.
54. peer intervention.ti,ab.
55. peer education.ti,ab.
56. 53 or 54 or 55
57. Human Immunodeficiency Virus Infection/di
58. Hepatitis C/di
59. (HCV test$ or hepatitis c test$ or HIV test$).ti,ab.
60. Diagnostic Test/
61. 57 or 58 or 59 or 60
62. ((HCV or hepatitis c) and treatment).ti,ab.
63. drug consumption rooms.ti,ab.
64. (safe$ inject$ and (site or facility)).ti,ab.
65. 63 or 64
66. (structural and intervention).ti,ab.
67. (environment$ and intervention$).ti,ab.
68. 66 or 67

69. crack pipe.ti,ab.
70. 28 or 31 or 36 or 39 or 43 or 46 or 52 or 56 or 61 or 62 or 65 or 68 or 69
71. 5 and 17 and 22 and 70

CINAHL

Search Limits: Date range = 1982 to March Week 3 2007, Language = English

1. "Systematic Review"/
2. "Literature Review"/
3. 'Program Evaluation"/
4. "Meta analysis"/
5. ((review$ or overview$ or evaluation$) and (systematic or methodologic$ or quantitative$ or literature$)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. "Hepatitis C"/
8. (hepatitis c or HCV).ti,ab.
9. HIV Infections/
10. HIV.ti,ab.
11. transmission.ti,ab.
12. seroconver$.ti,ab.
13. Risk Taking Behavior/
14. risk behav$.ti,ab.
15. Health Behavior/
16. Needle Sharing/
17. 7 or (8 and 11) or (8 and 12) or 9 or (10 and 11) or (10 and 12) or 13 or 14 or 15 or 16
18. Substance Abuse, Intravenous/
19. Intravenous Drug Users/
20. (substance$ or drug$).ti,ab.
21. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
22. (inject$ or intravenous).ti,ab.
23. 18 or 19 or (20 and 21) or (20 and 22)
24. Harm Reduction/
25. Experimental Studies/
26. Preventive Healthcare/
27. Community Health Services/
28. 24 or 25 or 26 or 27
29. (needle$ or syringe$).ti,ab.
30. exchange$.ti,ab.
31. Needle Exchange Programs/
32. (29 and 30) or 31
33. outreach.ti,ab.
34. mobile.ti,ab.
35. backpack$.ti,ab.
36. (vending and machine$).ti,ab.
37. (29 and 33) or (29 and 34) or 35 or 36
38. (paraphernalia or equipment).ti,ab.
39. (distribut$ or provi$).ti,ab.
40. 38 and 39
41. Methadone/
42. BUPRENORPHINE/
43. (substitution or maintenance).ti,ab.

44. 41 or 42 or 43
45. (bleach and disinfect$).ti,ab.
46. (needle and disinfect$).ti,ab.
47. 45 or 46
48. Health Education/
49. Patient Education/
50. Health Promotion/
51. Counselling/
52. Attitude to Health/
53. 48 or 49 or 50 or 51 or 52
54. outreach.ti,ab.
55. peer intervention.ti,ab.
56. peer education.ti,ab.
57. 54 or 55 or 56
58. HIV Infections/di [Diagnosis]
59. Hepatitis C/di [Diagnosis]
60. (HCV test$ or hepatitis c test$ or HIV test$).ti,ab.
61. 58 or 59 or 60
62. ((HCV or hepatitis c) and treatment).ti,ab.
63. drug consumption room$.ti,ab.
64. (safe$ and inject$ and (site or facilit$)).ti,ab.
65. 63 or 64
66. (structural and intervention$).ti,ab.
67. (environment$ and intervention$).ti,ab.
68. 66 or 67
69. crack pipe$.ti,ab.
70. 28 or 32 or 37 or 40 or 44 or 47 or 53 or 57 or 61 or 62 or 65 or 68 or 69
71. 6 and 17 and 23 and 70

PsycInfo

Search Limits: Date range = 1980+, Publication type=unlimited, Language = English, Population = human, Age=unlimited, Target Audience=unlimited, Method =Literature Review, Supplement=unlimited.

1. Evidence Based Practice (DE)
2. Intervention (DE)
3. Program Evaluation (DE)
4. Meta analysis (ME)
5. 1 or 2 or 3 or 4
6. Intravenous Drug Usage (DE)
7. Drug abuse (DE)
8. Drug addiction (DE)
9. At risk populations (DE) **or** Developing countries (DE)
10. 6 or 7 or 8 [or 9] for EU review only
11. HIV ((KW)
12. Hepatitis C (KW)
13. Infectious Disorders (DE)
14. transmission (KW=)
15. seroconvert* (KW)
16. Needle Sharing (DE)
17. Risk Taking (DE)
18. Risk Management (DE)

19. Risk behavio?r (KW)
20. Treatment outcomes (DE)
21. Drug overdoses (DE)
22. Death and dying (DE)
23. Healthcare seeking behaviour (DE)
24. Healthcare utilization (DE)
25. Crime (DE)
26. Costs and cost analysis
27. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or [20 or 21 or 22 or 23 or 24 or 25 or 26] in square brackets for EU review only
28. AIDS Prevention (DE)
29. Harm reduction (DE)
30. Preventative Medicine (DE)
31. 28 or 29 or 30
32. Needle Exchange Programs (DE)
33. (needle* or syringe*) (KW)
34. exchange* (KW)
35. 32 or (33 and 34)
36. outreach (KW)
37. mobile (KW)
38. backpack* (KW)
39. (vending and machine*) (KW)
40. (32 and 36) or (32 and 37) or 38 or 39
41. (paraphernalia or equipment) (KW)
42. (distribu* or provi*) (KW)
43. 41 and 42
44. Methadone Maintenance (DE)
45. Buprenorphine (KW)
46. substitution or maintenance (KW)
47. 44 or 45 or 46
48. (bleach and disinfect*) (KW)
49. (needle and disinfect*) (KW)
50. 48 or 49
51. Naloxone (DE)
52. overdose prevention (KW)
53. (peer or take-home or prescription) (KW)
54. (51 and 53) or 52
55. Health Education (DE)
56. Health Promotion (DE)
57. Client Education (DE)
58. Counselling (DE)
59. Health Knowledge (DE)
60. 55 or 56 or 57 or 58 or 59
61. Outreach Programs (DE)
62. outreach (KW)
63. peer intervention (KW)
64. peer education (KW)
65. 61 or 62 or 63 or 64
66. HIV testing (DE)
67. (HCV test* or hepatitis c test* or HIV test*)(KW)
68. 66 or ((11 or 12) and 67)

69. ((HCV or hepatitis c) and treatment) (KW)
70. Safe* inject* and (site or facilit*) (KW)
71. Drug consumption rooms (KW)
72. 70 or 71
73. (structural and intervention) (KW=)
74. (environment* and intervention) (KW=)
75. 73 or 74
76. crack pipe(KW)
77. 31 or 35 or 40 or 43 or 47 or 50 or 54 or 60 or 65 or 68 or 69 or 72 or 75 or 76
78. 5 and 10 and 27 and 77

IBSS

Search Limits: Date range = 1980+, Publication type=unlimited, Language = English, Population = human, Age=unlimited, Target Audience=unlimited, Method = Review, Supplement=unlimited.

1. Intervention (DE)
2. Evaluation (DE)
3. Meta analysis TI or AB
4. Literature review (DE)
5. Systematic review TI or AB
6. 1 or 2 or 3 or 4 or 5
7. Drug-users (DE)
8. Drug-abuse (DE)
9. Inject* drug use* TI or AB
10. Drug-addiction (DE)
11. Developing countries (DE)
12. 7 or 8 or 9 or 10 or 11 or 12
13. HIV (DE)
14. Hepatitis (DE)
15. Hepatitis C TI or AB
16. transmission TI or AB
17. seroconvert* TI or AB
18. Risk (DE)
19. Needle Sharing TI or AB
20. Risk behavio?r TI or AB
21. Inject* frequency TI or AB
22. Inject* behavio?r TI or AB
23. Treatment outcomes TI or AB
24. Drug-overdose (DE)
25. Health seeking behaviour TI or AB
26. Healthcare utilization TI or AB
27. Access to healthcare (DE)
28. Crime or drug-related crime TI or AB
29. Cost benefit analysis (DE)
30. 13 or 14 or 15 or 16 or 17 or 18 or 20 or [21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29] in square brackets EU review only
31. Prevention (DE)
32. Harm reduction TI and AB
33. Public health (DE)
34. 31 or 32 or 33
35. needle and program* TI and AB

36. (needle* or syringe*) TI and AB
37. exchange* TI and AB
38. 35 or (36 and 37)
39. outreach TI and AB
40. mobile TI and AB
41. backpack* TI and AB
42. (vending and machine*) TI and AB
43. (38 and 39) or (38 and 40) or 41 or 42
44. (paraphernalia or equipment) TI and AB
45. (distribu* or provi*) TI and AB
46. 42 and 43
47. Methadone Maintenance TI and AB
48. Buprenorphine TI and AB
49. substitution or maintenance TI and AB
50. 47 or 48 or 49
51. (bleach and disinfect*) TI and AB
52. (needle and disinfect*) TI and AB
53. 51 or 52
54. Naloxone TI and AB
55. overdose prevention TI and AB
56. (peer or take-home or prescription) TI and AB
57. (54 and 56) or 55
58. Health Education TI or AB
59. Health Promotion (DE)
60. Counselling (DE)
61. Knowledge (DE)
62. 58 or 59 or 60 or 61
63. outreach TI and AB
64. peer intervention TI and AB
65. peer education TI and AB
66. 63 or 64 or 65
67. (HCV test* or hepatitis c test* or HIV test*) TI and AB
68. 67or ((13 or 14) and 68)
69. ((HCV or hepatitis c) and treatment) TI and AB
70. Safe* inject* and (site or facilit*) TI and AB
71. Drug consumption rooms TI and AB
72. 71 or 72
73. (structural and intervention) TI and AB
74. (environment* and intervention) TI and AB
75. 74 or 75
76. crack pipe TI and AB
77. 34 or 38 or 43 or 46 or 50 or 53 or 57 or 62 or 66 or 68 or 70 or 73 or 76
78. 6 and 12 and 30 and 77

Cochrane Library

Searched in: Cochrane Reviews, Other Reviews, Health Technology Assessments, Economic Evaluations

1. (HCV):ti,ab,kw or (hepatitis c):ti,ab,kw
2. (HIV):ti,ab,kw
3. (risk NEXT behav*):ti,ab,kw
4. (substance*):ti,ab,kw or (drug*):ti,ab,kw

5. (inject*):ti,ab,kw or (intravenous):ti,ab,kw
6. (#1 OR #2 OR #3)
7. (#4 AND #5)

Appendix A-2. Search terms updated RoR

Databases were searched with principally identical search terms as in the original RoR. Due to changed profiles of and access rights to databases however, some of the databases were searched through different portals compared to the original RoR:

- Cochrane Library, EMBASE, MEDLINE through OVID gateaway
- CINAHL, and PsycINFO through EBSCOhost
- IBSS through CSA IIllumina

The search terms used for searching OVID are listed below; search terms used for the EBSCO and CSA were derived directly from these search terms, with minor adaptations to fit the databases' syntax requirements.

Search terms used for searches through OVID:

1. review.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf]
2. exp "review"/
3. exp "consensus development conference"/
4. exp "meta-analysis"/
5. ((review$ or overview$) and (systematic or methodologic$ or quantitative$ or literature$)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language
8. limit 7 to yr="2007 -Current"
9. *Hepatitis C/pc
10. (hepatitis c or HCV).ti,ab.
11. *HIV Infections/pc
12. (HIV or human immunodeficiency virus).ti,ab.
13. transmission.ti,ab.
14. seroconver$.ti,ab.
15. risk behavio?r.ti,ab.
16. Risk Reduction Behavior/
17. Behavior Modification/
18. Needle Sharing/
19. Risk-taking/
20. 9 or (10 and 13) or (10 and 14) or 11 or (12 and 13) or (12 and 14) or 15 or 16 or 17 or 18 or 19
21. *Substance Abuse, Intravenous/
22. (substance$ or drug$).ti,ab.
23. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
24. (inject$ or intravenous).ti,ab.
25. 21 or (22 and 23) or (22 and 24)
26. Harm Reduction/
27. Intervention Studies/
28. Preventive Health Services/
29. Community Health Services/
30. Primary Prevention/
31. 26 or 27 or 28 or 29 or 30
32. (needle$ or syringe$).ti,ab.
33. (exchange$ or provi$ or distribu$).ti,ab.
34. Needle-Exchange Programs/
35. (32 and 33) or 34
36. outreach.ti,ab.
37. mobile.ti,ab.

38. backpack$.ti,ab.
39. (vending and machine$).ti,ab.
40. (32 and 36) or (32 and 37) or 38 or 39
41. (paraphernalia or equipment or foil).ti,ab.
42. (distribu$ or provi$).ti,ab.
43. 41 and 42
44. (bleach and disinfect$).ti,ab.
45. (needle and disinfect$).ti,ab.
46. 44 or 45
47. Health Education/
48. Patient Education/
49. Counselling/
50. Health Knowledge, Attitudes, Practice/
51. Health Promotion/
52. 47 or 48 or 49 or 50 or 51
53. outreach.ti,ab.
54. peer intervention.ti,ab.
55. peer education.ti,ab.
56. 53 or 54 or 55
57. HIV Infections/di
58. Hepatitis C/di
59. (HCV test$ or hepatitis c test$ or HIV test$ or human immunodeficiency virus test$).ti,ab.
60. Diagnostic Tests, Routine/
61. 57 or 58 or 59 or 60
62. ((HCV or hepatitis c) and treatment).ti,ab.
63. drug consumption rooms.ti,ab.
64. (safe$ inject$ and (site or facilit$)).ti,ab.
65. 63 or 64
66. (structural and intervention$).ti,ab.
67. (environment$ and intervention$).ti,ab.
68. 66 or 67
69. 31 or 35 or 40 or 43 or 46 or 52 or 56 or 61 or 62 or 65 or 68
70. 6 and 20 and 25 and 69
71. 7 and 8 and 70
72. remove duplicates from 71

Appendix B. Critical appraisal tool

Author(s):
Title:
Full bibliographic details (including ISSN/ISBN)

List the topic areas with which the review is concerned.

Is the paper best described as (tick as appropriate):
- Systematic review?
- Meta-analysis?
- Synthesis?
- Literature review?
- Other review (please specify)

Does it address (tick as appropriate)?
- Effectiveness (interventions and treatments)
- Causation
- Monitoring and surveillance trends
- Cost
- Inequalities
- Other (please specify)

Does the paper have a clearly focused aim or research question?	Yes	No	Unsure
Consider whether the following are discussed:			
• The population studied	Yes	No	Unsure
• The interventions given	Yes	No	Unsure
• The outcomes considered	Yes	No	Unsure
• Inequalities	Yes	No	Unsure

What measures of social difference do the authors use (e.g. class, occupation, socio-economic group, gender, ethnicity, age, residence, geography, disability)?

Do the reviewers try to identify all relevant English language studies?	Yes	No	Unsure
Do the reviewers consider non-English language primary sources?	Yes	No	Unsure
When reviewing articles consider whether details are given of:			
• Databases searched	Yes	No	Unsure
• Years searched	Yes	No	Unsure
• References followed up	Yes	No	Unsure
• Experts consulted	Yes	No	Unsure
• Grey literature searched	Yes	No	Unsure
• Search terms specified	Yes	No	Unsure
• Inclusion criteria described	Yes	No	Unsure
• Sensitivity and specificity	Yes	No	Unsure
• What materials were excluded	Yes	No	Unsure
• Whether the data extraction was performed in a systematic way (this is repeated further down)	Yes	No	Unsure
• Whether the criteria used to assess the quality of the primary studies were stated (this is repeated further down)	Yes	No	Unsure
Is the primary source used by the reviewers drawn from:			
• Peer-reviewed published materials	Yes	No	Unsure
• Non peer-reviewed published materials	Yes	No	Unsure
• Unpublished materials	Yes	No	Unsure
• Self-referential materials	Yes	No	Unsure
How are reviews rated?			
• Do the authors address the quality (rigour) of the included studies?	Yes	No	Unsure

Consider whether the following are used:

• A rating system	Yes	No	Unsure
• More than one assessor	Yes	No	Unsure

Do the authors acknowledge theoretical issues in:

• The materials they have reviewed?	Yes	No	Unsure
• Their own approach?	Yes	No	Unsure

Is the evidence categorised by reviewers?

If the evidence is calibrated, ranked or categorised, what measure/scale is used?

Have the results been combined?

If results have been combined was it reasonable to do so? Consider the following:

• Are the results of included studies clearly displayed?	Yes	No	Unsure
• Are the studies addressing similar research questions?	Yes	No	Unsure
• Are the studies sufficiently similar in design?	Yes	No	Unsure
• Are the results similar from study to study (test of heterogeneity)?	Yes	No	Unsure
• Are the reasons for any variation in the results discussed?	Yes	No	Unsure

Have the data been presented in a way which allows an independent assessment of the strength of the evidence to be made?	Yes	No	Unsure
Can statements made by the reviewers be tracked back to the primary sources precisely (by page number)?	Yes	No	Unsure
Are sufficient data from individual studies included to mediate between data and interpretation/conclusions?	Yes	No	Unsure
Does the paper cover all appropriate interventions and approaches for this field (within the aims of the study)?	Yes	No	Unsure

If no, what?

Issues of bias:

Does the review make clear what steps have been taken to deal with potential bias?	Yes	No	Unsure

If yes, what are these?

Have the authors taken care to avoid double counting of primary data?	Yes	No	Unsure
Do the authors refer to primary research studies in which they themselves have been involved?	Yes	No	Unsure
Do the authors have a vested interest in the direction of the evidence?	Yes	No	Unsure

If bias has not been overtly considered, or only partly considered, what are the potential biases which should have been acknowledged?

To what extent does the treatment of bias in the paper affect any conclusions in it about strengths of evidence?

What is the overall finding of the review? Consider:

- How the results are expressed (numeric – relative risks, etc.)?
- Whether the results could be due to chance (*p*-values and confidence intervals)?

Do the authors acknowledge any weaknesses in what they have written?

Relevance to developing and transitional populations

Can the results be applied/are the results generalisable to a developing/transitional country population group?	Yes	No	Unsure
• Are there cultural differences?	Yes	No	Unsure
• Are there differences in healthcare provision?	Yes	No	Unsure
• Is the paper focused on a particular target group (age, sex, population sub-group, etc.)?	Yes	No	Unsure

Can a judgement now be made of the review in the following four areas:

• The strengths of the evidence?	Yes	No	Unsure
• The weaknesses in the evidence?	Yes	No	Unsure
• The gaps in the evidence?	Yes	No	Unsure
• The currency in the evidence?	Yes	No	Unsure

Recommended category 1, 2, 3, or discard.

Additional comments:

Reviewer:
Date:

Adapted from Canning et al. (2004). Drug use prevention among young people: a RoR. Health Development Agency.

Appendix C. Study designs used to assess the effectiveness of harm reduction interventions

Table C-1. Main study designs used to assess the effectiveness of harm reduction interventions targeted at PWID

	Randomised controlled trial	Cohort (with non-randomised control group)	Cohort (pre vs. post-intervention comparison)	Case-control	Ecological	Serial cross-sectional	Cross-sectional
Type	Experimental	Observational					
Description	Researchers control which individuals are exposed to the intervention by random assignment. Individuals are then followed over time to see who develops the outcome of interest.	Individuals with and without the exposure of interest (i.e. exposed vs. not exposed to a harm reduction intervention) are followed over time and compared to see if they develop the outcome.	Compares the outcome of interest among a single group of individuals before and after (and sometimes during) the implementation of an intervention.	Individuals who have the condition of interest (cases) are identified and their past exposure to the intervention is compared with that of patients who do not have the condition (controls).	Measures the association between exposure and outcome variables at the population or community-level.	Measures the prevalence (or incidence) of the exposure and outcome at multiple points in time in comparable samples drawn from the same population.	Measures the prevalence of the exposure and outcome at one particular point in time.
Weight of evidence	Strongest	Stronger	Stronger	Stronger	Weaker	Weaker	Weaker
Example	Des Jarlais et al. (1992) enrolled non-injecting heroin users and randomly assigned them to receive the intervention (four group sessions) or the control condition of standard HIV prevention education materials. Subjects were followed-up to determine their incidence of injecting drug use.	Bruneau et al. (1997) followed users and non-users of NSP and compared HIV incidence between the two groups.	Vlahov et al. (1997) interviewed a sample of PWID who enrolled in an NSP at programme entry, 2 weeks, and six months later, and compared injecting risk behaviour between these times.	Hagan et al. (1995) compared prior use of syringe exchange between HCV-infected PWID (cases) and non-infected PWID (controls).	MacDonald et al. (2003) compared HIV prevalence over time in cities with and without NSP.	van Ameijden et al. (1992) compared injecting risk behaviour among different samples of PWID recruited (from the same sites) in successive years: 1986, 1987, 1988, 1989/90, and 1991/92.	Longshore et al. (2001) tested the correlation between the frequency of attendance at NSPs and injecting risk behaviour among a sample of PWID interviewed on a single occasion.
Establishes temporal sequence between exposure and outcome	Yes	Yes	Yes	Yes	Usually	Yes	No
Main limitations	Sometimes not feasible to undertake an RCT to evaluate harm reduction interventions	High probability of selection bias	Loss to follow-up; risk of confounding by changes over time in factors that may impact the outcome of interest	Information on the exposure is usually ascertained retrospectively, therefore there is a risk of inaccuracy and recall bias (if controls recall exposure differently from cases)	High risk of confounding by other factors	High risk of confounding by changes over time in factors that may impact the outcome of interest (e.g. diversity and coverage of interventions and changes in the drug market)	High risk of confounding by other factors; cannot know whether exposure precedes outcome
Strength of causal interpretations	Strongest – randomisation should theoretically eliminate selection bias	Potentially limited by systematic differences in the comparison groups	Limited by lack of a comparison group – other factors could be causing and/or contributing to the association	Potentially limited by sources of bias	Highly limited – other factors could be causing and/or contributing to the association	Highly limited – other factors could be causing and/or contributing to the association	Highly limited – due to lack of time dimension

Appendix D. Needle and syringe exchange programmes

Table D-1. Summary of reviews of NSP

Author and date	Title	Dates covered	Scope	Critical assessment	Number of studies[a]
Dolan and Niven, 2005	A review of HIV prevention among young PWID: a guide for researchers	Not specified	Young PWID	Supplementary review	3 injecting risk
Dolan et al., 2003a	Prison-based syringe exchange programmes: a review of international research and development	Up to Dec 2000	Prison NSP	Supplementary review	6 HCV/HIV 12 injecting risk
Gibson et al., 2001	Effectiveness of syringe exchange programs in reducing HIV risk behaviour and HIV seroconversion among PWID	Up to 1999	NSP	Core review	3 HCV 6 HIV 23 injecting risk
Stover and Nelles, 2003	Ten years of experience with needle and syringe exchange programmes in European prisons	Not specified	Prison NSP	Supplementary review	5 HCV/HIV 11 injecting risk
Tilson et al., 2007	Preventing HIV infection among PWID in high-risk countries: an assessment of the evidence	Up to Jan 2006	NSP (among other harm reduction interventions)	Core review	5 HCV 11 HIV 24 injecting risk
Wodak and Cooney, 2004	Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among PWID	Up to 2002	NSP (among other harm reduction interventions), prison NSP, cost studies	Core review	1 HCV 10 HIV 28 injecting risk
Wright and Tompkins, 2006	A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among PWID	Up to end 2002	NSP (among other harm reduction interventions), cost studies	Supplementary review	11 HCV
Nacopoulos et al., 2010	Syringe exchange programs: Impact on injection drug users and the role of the pharmacist from a US perspective	Up to 2010	NSP	Supplementary review	6 HCV/HIV 9 IRB
Hong and Li, 2009	HIV/AIDS behavioural interventions in China: a literature review and recommendation for future research	Up to April 2008	NSP (among other harm reduction interventions),	Supplementary review	2 HIV/HCV (1 in Chinese) 1 HCV

[a] *Listed by outcome*

Table D-2. Primary studies included within the core review papers (NSP)

	Core reviews		
	Tilson et al. (2007)	Wodak and Cooney (2004)	Gibson et al. (2001)
HCV studies			
Hagan and Thiede, 2000	✓		
Hagan et al., 1995	✓	✓	✓
Hagan et al., 1999			✓
Lamden et al., 1998			✓
Mansson et al., 2000	✓		
Sarkar et al., 2003	✓		
Taylor et al., 2000	✓		
Total	5	1	3
HIV studies			
Bruneau et al., 1997	✓	✓	✓
Coutinho, 2005	✓		
Des Jarlais et al., 1995	✓		
Des Jarlais et al., 1996		✓	✓
Des Jarlais et al., 2005a	✓		
Des Jarlais et al., 2005b	✓		
Hammett et al., 2006	✓		
Heimer et al., 1993		✓	
Hurley et al., 1997	✓	✓	
Ljungberg et al., 1991		✓	
MacDonald et al., 2003 (Health Outcomes International, 2002)	✓	✓	
Mansson et al., 2000	✓		
Monterroso et al., 2000		✓	
Patrick et al., 1997	✓	✓	✓

	Core reviews		
Schechter et al., 1999	✓	✓	✓
Strathdee et al., 1997	✓	✓	✓
van Ameijden et al., 1992	✓		✓
Total	13	10	6
Injecting risk behaviour studies			
Bluthenthal et al., 1998		✓	✓
Bluthenthal et al., 2000	✓	✓	
Broadhead et al., 1999			✓
Cox et al., 2000	✓	✓	
Des Jarlais et al., 1994		✓	✓
Des Jarlais et al., 2000b	✓		
Donoghoe et al., 1989		✓	✓
Donoghoe et al., 1992		✓	✓
Frischer and Elliott, 1993		✓	✓
Gibson et al., 2002	✓	✓	
Gleghorn et al., 1998		✓	
Guydish et al., 1995		✓	✓
Guydish et al., 1998		✓	✓
Hagan et al., 1993	✓		
Hagan et al., 1994			✓
Hagan and Thiede, 2000	✓		
Hammett et al., 2006	✓		
Hart et al., 1989	✓		
Hartgers et al., 1989		✓	✓
Hartgers et al., 1992	✓	✓	✓
Heimer et al., 1998		✓	
Huo et al., 2005	✓		
Keene et al., 1993	✓	✓	✓
Klee et al., 1991	✓	✓	✓
Klee and Morris, 1995		✓	✓
Longshore et al., 2001	✓		
Monterroso et al., 2000	✓	✓	
Oliver et al., 1994		✓	✓
Ouellet et al., 2004	✓		
Paone et al., 1994		✓	✓
Peak et al., 1995		✓	✓
Power et al., 2002		✓	
Schoenbaum et al., 1996	✓	✓	✓
Singer et al., 1997		✓	✓
van Ameijden et al., 1994	✓	✓	✓
van Ameijden and Coutinho, 1998	✓	✓	✓
van den Hoek et al., 1989	✓		
Vazirian et al., 2005	✓		
Vertefeuille et al., 2000	✓		
Vlahov et al., 1997	✓	✓	✓
Watters et al., 1994	✓	✓	✓
Wood et al., 2002	✓		
Wood et al., 2003	✓		
Total	**25**	**28**	**23**

Table D-3. Results of primary studies of the effectiveness of NSP with respect to HCV prevalence/incidence outcomes a

Author and year	Design	Finding	Results
Des Jarlais et al., 2005b	Ecological	Positive	From 1990 to 2001, a time period of large expansion of NSP in NYC, HCV prevalence declined significantly.
Goldberg et al. 1998/2001; Hutchinson et al. 2002	Serial cross-sectional	Positive	Significant declines in HCV prevalence were seen in Edinburgh and Glasgow between 1990 and 1997. No significant changes in prevalence were observed in the late 1990s in four health boards (with the exception of Glasgow and Lothian over 25 year olds).
Hagan et al., 1995	Case-control	Positive	Non-use of NSP was associated with a seven-fold greater risk of seroconversion (OR=7.3; 95% CI 1.6−32.8). Adjusted for sex, age, race, and duration of drug injection.
Hagan et al., 1999	Cohort	No association	Regular users had a RR of 1.31 (95% CI 0.8−2.2) relative to non-users; sporadic users had a RR of 2.59 (95% CI 0.8−8.5) relative to non-users. Adjusted for recent onset of injection and syringe sharing prior to enrolment.
Hagan and Thiede, 2000	Cohort	N/A	Reported injecting risk behaviour outcomes only.
Hernandez-Aguado et al., 2001	Serial cross-sectional	No change	No declines in HCV prevalence between 1990 and 1996 despite preventive measures in Spain.
Lamden et al., 1998	Cross-sectional	No association	Those who began injecting after 1986, when NSP was introduced in Liverpool, were just as likely to test HCV+ as those who had commenced prior to this (OR=0.8; 95% CI 0.4−1.5).
MacDonald et al., 2000	Serial cross-sectional	Positive	Prevalence declined significantly from 63% in 1995 to 51% in 1996 to 50% in 1997 among NSP attendees. Adjusted for duration of drug use.
Mansson et al., 2000	Cohort	Negative	HCV seroconversion correlated with frequent NSP use (OR 1.31; 95% CI 1.02−1.7). Adjusted for imprisonment, drug abstinence.
Patrick et al., 2001	Cohort	Negative	Frequent attendance at NSP associated with seroconversion (hazard ratio 2.56; 95% CI 1.37-4.79); adjusted for sex, cocaine use, and frequent injection. Frequent attendance was defined as at least once per week during the previous months.
Sarkar et al., 2003	Serial cross-sectional	Negative	HCV prevalence increased from 17% to 80% between 1996 and 2003, despite NSP.
Smyth et al., 1999	Cross-sectional	Positive	Those who had commenced injecting after Jan 1994 were significantly less likely to test HCV+ than those who had commenced injecting prior to this date. Adjusted for duration of injecting career and age.
Somaini et al., 2000	Cross-sectional	Positive	Protective effect in 'the order of 80% for those starting to PWID after 1991 as opposed to those starting before 1987.'
Taylor et al., 2000	Cross-sectional	Positive	Those who began injecting after the introduction of NSP (>1992) were less likely to test HCV+ than those who started before (<1998) (OR=0.4; 95% CI 0.2−0.6). Adjusted for variables including length of injecting career.
van Ameijden, 1993	Cohort (ecological)	No change	No significant reduction in incidence over the four year study period, despite NSPs being available in Amsterdam.
Wu et al., 2007	Serial cross-sectional	Positive	Among new injectors, the incidence of HCV was significantly lower in intervention communities (interventions included increased access to clean needle/syringes) than in control communities.
Holtzman, 2009	Pooling of data from two cohorts and one trial	No association	No significant associations between SEP participation and HCV infection rates. Authors attribute lack of positive result to dilution and selection bias.
Neaigus, 2008	Ecological study	Positive	Higher HCV prevalence among residents of a US city where NSP was illegal than in city where NSP was legal (OR=3.0, 95% CI 1.8−4.9).

[a] *Studies are those identified by the core reviews of Gibson et al. (2001), Tilson et al. (2007), Wodak and Cooney (2004) and the supplementary reviews of Wright and Tompkins (2006), Hong (2008) and Nacopoulos (2009); papers only published in these supplementary reviews are in Italic.*

Table D-4. Results of primary studies from core reviews of the effectiveness of needle and syringe exchange programmes with respect to HIV prevalence or incidence outcomes[a]

Author and year	Study design	Finding[b]	Results
*Bruneau et al., 1997	Cohort and nested case-control	Negative	The cohort study demonstrated a cumulative probability of HIV seroconversion of 33% for NSP users and 13% for nonusers (p<0.001); in the case-control study, consistent NSP use was associated with HIV seroconversion (OR = 10.5; 95% CI 2.7−41.0).
*Des Jarlais et al., 1995	Ecological	Positive	In five cities where HIV seroprevalence has remained <5% during the last 5 years, all had implemented harm reduction interventions including NSP.
Des Jarlais et al., 1996	Meta-analysis to combine HIV incidence data from 3 prospective cohort studies	Positive	Not using NSP was associated with a hazard ratio of 3.35 (95%CI 1.20−8.65) for incident HIV infection compared with using NSP, in a multivariate proportional hazards model.
*Des Jarlais et al., 2005a	Serial cross-sectional	Positive	HIV incidence declined from 3.55/100 person-years at risk (PYAR) from 1990 to 1992, to 2.63/100 PYAR from 1992 to 1995, to 1.05/100 PYAR from 1996 to 1998 and to 0.77/100 PYAR from 1999 to 2002 (p<0.001); there was a strong linear relationship between annual numbers of syringes exchanged and estimated HIV incidence.
Des Jarlais et al., 2005b	Ecological	Positive	From 1990 to 2001 HIV prevalence declined from 90 to 63% concurrent with large-scale expansion of NSP.
Hammett et al., 2006	Serial cross-sectional	Positive	HIV prevalence among PWID remained stable in China and declined in Vietnam, over the 24 months after implementation of an intervention (peer education and provision of clean needles).
Health Outcomes International., 2002	Ecological	Positive	See MacDonald et al., 2003
Heimer et al., 1993	Cross-sectional: random sample of syringes returned to an NSP	Positive	Within three months of implementing NSP, the percentage of syringes containing serum with HIV declined by one third.
*Hurley et al., 1997	Ecological	Positive	HIV seroprevalence increased 5-9% per year in 52 cities without NSP, and decreased by 5-8% per year in 29 cities with NSP.
Ljungberg et al., 1991	Cross-sectional	Positive	HIV seroprevalence among PWID in south Sweden was stable at ~1% in contrast with up to 60% in other Scandinavian sub-populations.
*MacDonald et al., 2003	Ecological	Positive	HIV prevalence declined by 18.6% per year in cities that introduced NSP compared with and 8.1% increase in cities without NSPs.
*Mansson et al., 2000	Prospective cohort	Positive	No new HIV infections during a median follow-up of 31 months of 515 NSP participants.
*Monterroso et al., 2000	Prospective cohort	No statistically significant association	Participation in NSPs associated with reduced risk of HIV incidence; finding was not statistically significant.
*Patrick et al., 1997	Case-control	No association	No association between frequency of NSP use and HIV seroconversion.
*Schechter et al., 1999	Prospective cohort	No association	No differences in HIV incidence between frequent NSP attendees and infrequent attendees
*Strathdee et al., 1997	Prospective cohort	Negative	Frequent NSP attendance was an independent predictor of HIV-positive serostatus.
van Ameijden et al., 1992	Case-control	No association	There was no evidence that obtaining new needles/syringes via the NSP was protective.

[a] *Modified from Wodak and Cooney (2004) and Tilson et al. (2007); Coutinho (2005) is excluded from this table because insufficient information regarding the study was provided by Tilson et al.*

[b] *Positive, negative, or equivocal refers to overall direction of association with HIV seroconversion*

** Studies marked by an asterisk were considered 'especially strong in terms of study design and relevance' by Tilson et al. (2007)*

Table D-5. Count of studies demonstrating positive, negative or no association between NSP and HIV prevalence / incidence by study design[†]

Study design	Author and year	Association
prospective cohort	*Bruneau et al., 1997[a]	Negative
	*Strathdee et al., 1997	Negative
	Des Jarlais et al., 1996	Positive
	*Mansson et al., 2000	Positive
	*Monterroso et al., 2000	No statistically significant association

Study design	Author and year	Association
	*Schechter et al., 1999	No association
case-control	*Patrick et al., 1997	No association
	van Ameijden et al., 1992	No association
ecological	*Des Jarlais et al., 1995	Positive
	*Des Jarlais et al., 2005[b]	Positive
	*Hurley et al., 1997	Positive
	*MacDonald et al., 2003[b]	Positive
serial cross-sectional	Des Jarlais et al., 2005[a]	Positive
	Hammett et al., 2006	Positive
cross-sectional	Ljungberg et al., 1991	Positive

[†] *The Heimer et al. (1993) study identified in Wodak and Cooney (2004) is excluded from this table as the outcome was not HCV incidence or prevalence among PWID, but rather the proportion of returned syringes containing HIV*

[a] *Bruneau et al. (1997) also conducted a nested case-control analysis, although this is not included in this table to avoid double counting of primary data*

[b] *Cited in Wodak and Cooney (2004) as Health Outcomes International (2002)*

* *Studies marked by an asterisk were considered 'especially strong in terms of study design and relevance' by Tilson et al. (2007)*

Table D-6. Results of primary studies from core reviews of the effectiveness of NSP with respect to injecting risk behaviour outcomes[a]

Author and year	Study design	Finding	Results
Bluthenthal et al., 1998	Cross-sectional	Positive	NSP use conferred a 40% protective effect on syringe sharing (OR=0.57, 95% CI 0.46-0.72).
*Bluthenthal et al., 2000	Prospective cohort	Positive	PWID who began using the syringe exchange were more likely to quit sharing syringes (AOR=2.68, 95% CI 1.35–5.33), as were those who continued using the syringe exchange programme (AOR=1.98, 95% CI 1.05–3.75)
Broadhead et al., 1999	Serial cross-sectional	Positive	Increased reuse, sharing of syringes after the closure of an NSP.
Cox et al., 2000	Prospective cohort	Positive	NSE users decreased needle and syringe sharing and frequency of drug use.
Des Jarlais et al., 1994	serial cross-sectional	Positive	Quarterly level of NSP use correlated negatively with proportion of PWID reporting borrowing and lending of syringes.
Des Jarlais et al., 2000b	Ecological	Positive	Three injection risk behaviours (any distributive needle sharing, any receptive needle sharing, any sharing at last injection) declined significantly over time (P<0.01). Participation in NSP increased between 1990 and 1997.
Donoghoe et al., 1989	Prospective cohort	Positive	Significant decline in syringe-sharing among NSP users in previous month compared with no change in control group.
Donoghoe et al., 1992	Cross-sectional	No association	NSP users and non-users equally likely to share used injection equipment.
Frischer and Elliott, 1993	Cross-sectional	Positive	NSP attendees were less likely than non-attendees to borrow used syringes.
*Gibson et al., 2002	Prospective cohort	Positive	In a multivariate analysis, the odds of HIV risk behaviour were decreased more than six-fold for PWID without other sources of syringes.
Gleghorn et al., 1998	Cross-sectional	Positive	PWID were most likely to have used a reliable source to obtain their most recent syringe in cities with an NSP (OR=5.3, 95% CI 3.3–8.5).
Guydish et al., 1995	Cross-sectional	Positive	Recent NSP users had fewer sharing partners and number of sharing partners was negatively correlated with number of NSP visits in past 30 days.
Guydish et al., 1998	Cross-sectional	Positive	Those who obtained a higher proportion of syringes from the NSP were less likely to report the sharing of syringes.
Hagan et al., 1993	Cross-sectional	Positive	The frequency of unsafe injection declined from 56 to 30 times a month.
Hagan et al., 1994	Prospective cohort	Positive	The proportion of respondents borrowing used syringes declined markedly (pre vs. post-comparison).
Hagan and Thiede, 2000	Prospective cohort	Positive	In univariate and multivariate analyses, NSP use was associated with a lower likelihood of injection with a used syringe. There was no association between NSP use and cooker or cotton sharing.
Hammett et al., 2006	Serial cross-sectional	Positive	Drug-related risk behaviours declined in frequency over the 24 months since the intervention.
*Hart et al., 1989	Prospective cohort	Positive	Self-reported rates of lending and borrowing used injecting equipment fell compared with rates before entry into the NSE and during the study.

Author and year	Study design	Finding	Results
Hartgers et al., 1989	Cross-sectional	Positive	NSP users were less likely to borrow than non-users in the previous month (10% compared with 23%) and also in previous two years (33% compared with 57%).
*Hartgers et al., 1992	Prospective cohort	No statistically significant association	Regular NSP users borrowed slightly less often than other users, although this was not statistically significant even after controlling for confounders.
Heimer et al., 1998	Retrospective cohort	Positive	Reported reuse of injection equipment declined by at least half in three of four cities.
Huo et al., 2005	Prospective cohort	Positive	The proportion of all sharing behaviour decreased significantly during follow-up. Participation in an NSP was associated with a one-third decrease in syringe and syringe-mediated sharing, but there was no association with sharing of cookers.
Keene et al., 1993	Cross-sectional	Positive	Only 9% of NSP attendees had recently shared syringes in 1990 compared with 41% of non-attendees.
Klee et al., 1991	Cross-sectional	Negative	Regular use of NSP was associated with the passing on of used syringes.
Klee and Morris, 1995	Cross-sectional	Indeterminate	Mixed patterns of NSP use and HIV risk behaviour in three studies.
Longshore et al., 2001	Cross-sectional	Positive	PWID who attended the NSP less frequently were more likely to report sharing needles and cookers.
*Monterroso et al., 2000	Prospective cohort	Positive	Not using previously used needles was significantly associated with use of NSPs in a multivariate model (OR=2.08).
Oliver et al., 1994	Prospective cohort	Positive	There was a substantial decline in sharing (20% to 7%), renting (9% to 3%) and borrowing of syringes.
*Ouellet et al., 2004	Prospective cohort	Positive	In a multivariate analysis, regular NSP users were significantly less likely to receptively share needles, lend used needles, reuse needles or share cookers, cottons or water.
Paone et al., 1994	Retrospective cohort	Positive	There was a decline in borrowing (29% to 12%), and renting or buying (22% to 6%) used syringes.
Peak et al., 1995	Serial cross-sectional	Positive	The median number of sharing partners declined from 2 to 1 and the median number of sharing occasions declined from 14 to 2 following NSP attendance.
Power et al., 2002	Cross-sectional	Positive	NSP attendees were significantly more likely to report using only their own needles, syringes, filters, and drug solution as compared with non-attendees.
*Schoenbaum et al., 1996	Prospective cohort	Positive	Exchange users were significantly less likely to share needles than non-users.
Singer et al., 1997	Serial cross-sectional	Positive	Respondents significantly reduced their 'reuse' of syringes following the introduction of NSP and legalisation of pharmacy sales.
van Ameijden et al., 1994	Serial cross-sectional	Positive	Borrowing of injection equipment declined from 51% to 20%; lending of injection equipment declined from 46% to 10% and reuse of needles/syringes declined from 63% to 39%.
van Ameijden and Coutinho, 1998	Prospective cohort	Positive	A large, initial reduction in borrowing, lending, and reusing needles occurred between 1986-1991. From 1991 to 1993 onwards there was no further reduction.
van den Hoek et al., 1989	Prospective cohort	Positive	Use of NSP increased over time. There was a decrease in sharing of used needles/syringes.
Vazirian et al., 2005	Cross-sectional	Positive	18.9% of those who received few needles/syringes from the NSP reported using a shared needle/syringe at their last injection, compared with no reports of sharing at the last injection among those who received more than seven syringes per week. There was no difference between the groups in the sharing of cookers.
*Vertefeuille et al., 2000	Prospective cohort	Positive	Enrolment in an NSP was associated with statistically significant declines in lending and borrowing used syringes.
*Vlahov et al., 1997	Prospective cohort	Positive	From baseline, two-week, and six-month follow-up visits, significant reductions were reported in using a previously used syringe, and lending a used syringe.
Watters et al., 1994	Serial cross-sectional	Positive	NSP use was a strong predictor of not sharing syringes (OR=0.71; 95% CI 0.59 to 0.87).
*Wood et al., 2002	Prospective cohort	Positive	Having difficulty gaining access to clean needles was independently associated with high-risk sharing. Acquiring needles exclusively from an NSP was negatively associated with sharing.
Wood et al., 2003	Prospective cohort	Positive	Use of the exchange was associated with safe syringe disposal.

[a] *Modified from Gibson et al., (2001), Wodak and Cooney (2004) and Tilson et al. (2007). Van Haastrecht et al. (1996) and Kaplan et al. (1991/1994/1995) are excluded from this table because they examined other outcomes (mortality, syringe return rates).*

** Studies marked by an asterisk were considered 'especially strong in terms of study design and relevance' by Tilson et al. (2007)*

Table D-7. Count of studies demonstrating positive, negative or null associations between NSP and injecting risk behaviour by study design

Study design	Author and year	Association
Cohort	*Bluthenthal et al., 2000	Positive
	Cox et al., 2000	Positive
	Donoghoe et al., 1989	Positive
	*Gibson et al., 2002	Positive
	Hagan et al., 1994	Positive
	Hagan and Thiede, 2000	Positive
	*Hart et al., 1989	Positive
	Heimer et al., 1998	Positive
	Huo et al., 2005	Positive
	*Monterroso et al., 2000	Positive
	Oliver et al., 1994	Positive
	*Ouellet et al., 2004	Positive
	Paone et al., 1994	Positive
	*Schoenbaum et al., 1996	Positive
	van Ameijden and Coutinho, 1998	Positive
	van den Hoek et al., 1989	Positive
	*Vertefeuille et al., 2000	Positive
	*Vlahov et al., 1997	Positive
	*Wood et al., 2002	Positive
	Wood et al., 2003	Positive
	Hartgers et al., 1992	No statistically significant association
Ecological	Des Jarlais et al., 2000b	Positive
Serial cross-sectional	Broadhead et al., 1999	Positive
	Des Jarlais et al., 1994	Positive
	Hammett et al., 2006	Positive
	Peak et al., 1995	Positive
	Singer et al., 1997	Positive
	van Ameijden et al., 1994	Positive
	Watters et al., 1994	Positive
Cross-sectional	Bluthenthal et al., 1998	Positive
	Frischer and Elliott, 1993	Positive
	Gleghorn et al., 1998	Positive
	Guydish and Clark, 1995	Positive
	Guydish et al., 1998	Positive
	Hagan et al., 1993	Positive
	*Hartgers et al., 1989	Positive
	Keene et al., 1993	Positive
	Longshore et al., 2001	Positive
	Power et al., 2002	Positive
	Vazirian et al., 2005	Positive
	Klee et al., 1991	Negative
	Donoghoe et al., 1992	No association
	Klee and Morris, 1995	Indeterminate

** Studies marked by an asterisk were considered 'especially strong in terms of study design and relevance' by Tilson et al. (2007)*

Appendix E. Alternative access to needles/syringes

Table E-1. Summary of reviews of alternative access to needles/syringes

Author and date	Title	Dates covered	Scope	Critical assessment	Number of studies
Islam and Conigrave, 2007	Assessing the role of syringe dispensing machines and mobile van outlets in reaching hard-to-reach and high-risk groups of injecting drug users (IDUs): a review	Not specified	Vending machines	Supplementary review	1 injecting risk
Tilson et al., 2007	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Up to Jan 2006	Pharmacy NSP, vending machines	Core review	5 HCV 11 HIV 24 injecting risk
Wodak and Cooney, 2004	Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users	Up to 2002	Pharmacy NSP, vending machines	Core review	1 HCV 10 HIV 29 injecting risk
Jones et al., 2010	Optimal provision of needle and syringe programmes for injecting drug users: A systematic review	Up to January 2008	Pharmacy NSP, fixed NSP, outreach NSP, vending machines; not prison based	Core review	2 HCV/HIV 9 Injecting risk
Islam, Wodak et al., 2008	The effectiveness and safety of syringe vending machines as a component of needle syringe programmes in community settings	Up to 2008	Community vending machines	Supplementary review	14 access to n/s and injecting risk behaviour

Table E-2. Results of primary studies included within the core review papers of the effectiveness of pharmacy access to needle and syringes with respect to HIV prevalence/incidence outcomes[a]

Author and year	Study design	Findings	Results
Hunter et al., 1995	Serial cross-sectional	Positive	There was a decrease in HIV prevalence among PWID from 12.8% in 1990 to 6.9% in 1993, coinciding with increased availability of syringes through pharmacies and NSP.
Nelson et al., 1991	Cross-sectional	Positive	A significantly lower proportion of diabetic PWID (9.8%), who had ready access to sterile needles/syringes through pharmacies, had HIV compared with non-diabetic PWID (24.3%) (p=0.03).
Singer et al., (1997)	Cross-sectional	Positive	'Significant' drop in HIV prevalence in PWID attending NSP in different settings including pharmacy.
Miller et al. (2002)	Cross-sectional	Positive	HIV prevalence lower among PWID using pharmacies than PWID who reported use of mobile vans or fixed site NSP to obtain sterile n/s.

[a] *Modified from Wodak and Cooney (2004) and Jones (2010).*

Table E-3. Results of primary studies included within the core review papers of the effectiveness of pharmacy access to needle and syringes with respect to injecting risk behaviour outcomes[a,b]

Author and year	Study design	Findings	Results
Calsyn et al., 1991	Cross-sectional	Positive	Subjects whose primary source of syringes was through pharmacy purchase shared equipment less frequently in the previous year (16.2%) than those with other primary sources (28.5%)
Gleghorn et al., 1995	Cross-sectional	Positive	PWID were less likely to use shooting galleries (adjusted odds ratio 0.33; 95% CI 01.4-0.75).
Groseclose et al., 1995	Serial cross-sectional	Positive	Compared behaviour before and after legalisation of syringe purchase and possession. Among PWID who reported ever sharing a syringe, syringe-sharing decreased after the new laws (52% before vs. 31% after; p = 0.02). Fewer PWID reported purchasing syringes on the street after the new laws (74% before vs. 28% after; p < 0.0001).
Ingold and Ingold, 1989	Cross-sectional	Positive	Liberalised syringe sales had an obvious effect on the behaviour of intravenous drug users: approximately half of them did not share syringes and purchased them at pharmacies, while the rest continued sharing syringes in a variety of ways. The authors concluded that the decision to make syringes freely available for sale was not, by itself, sufficient to cope with the syringe-sharing problem.

Author and year	Study design	Findings	Results
Nelson et al., 1991	Cross-sectional	Positive	Significantly more diabetic PWID (77%) reported using new equipment at least half the time as compared with non-diabetic PWID (64%) ($p<0.05$). Significantly more diabetic PWID (90%) reported not using equipment after someone else less than half the time compared with non-diabetic PWID (78%) ($p<0.01$). A lower proportion of diabetic PWID (37%) shared needles compared with non-diabetic PWID (48%) ($P<0.14$).
Pouget et al., 2005	Serial cross-sectional	Positive	Self-reports of receptive sharing fell from 13.4% in 2001 to 3.6% in 2003 following deregulation of the availability of syringes through pharmacies.
Richard et al., 2002	Cross-sectional	Positive	'New' syringe use was defined as always injecting with syringes that were obtained brand new from a pharmacy. Exclusive use of new syringes significantly decreased the odds that a respondent would report injecting after someone other than a sex partner (adjusted odds ratio 0.236, 95% CI 0.06−0.89).
Singer et al., (1997)	Cross-sectional	Positive	Injecting risk behaviour (using pre-used n/s) statistically significantly reduced as sterile n/s availability increased over time; NSP included pharmacy distribution. IRB lower among PWID using NSP and pharmacy-based NSP than among PWID not accessing either.
Bluthenthal et al., (2004)	Cross-sectional	Negative	PWID in cities with unlimited access through NSP were less likely to report syringe re-use than PWID in cities with limited N/S provision through pharmacies.
Fisher et al. (2003)	RCT	No difference	No difference over time between NSP or pharmacy sales on injection frequency.
Khoshnood et al. (2000)	Cross-sectional	No difference	There was no statistically significant difference in n/s sharing between PWID obtaining n/s from pharmacies or from NSP. PWID not using either service were statistically significant less likely to report needle sharing or re-use.
Obadia et al. (1999)	Cross-sectional	No difference	Compared sharing needles between PWID using pharmacies, NSP and vending machine to obtain n/s. No differences in sharing behaviour were found. Vending machine users were statistically significant less likely to have shared paraphernalia compared to users of other services.
Rhodes, Judd et al. (2004a)	Cross-sectional	Negative	PWID who obtained n/s from outreach worker or NSP compared to PWID who obtained n/s from pharmacies were less likely to share n/s.

[a] *Modified from Wodak and Cooney (2004), Tilson et al. (2007) and Jones (2010)*

[b] *In the Jones's review, injecting risk behaviour (sharing and re-use of n/s) and injecting frequency were included as outcome indicators.*

Appendix F. Provision of sterile drug preparation equipment

Table F-1. Summary of reviews of sterile drug preparation equipment provision

Author and date	Title	Dates covered	Scope	Critical assessment	Number of studies
Haydon and Fischer, 2005	Crack use as a public health problem in Canada: call for an evaluation of 'safer crack use kits'	Not specified	Non-injection drug use equipment	Supplementary review	None (in relation to the relevant outcomes)
Tilson et al., 2007	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Up to Jan 2006	Injection drug use equipment	Core review	5 HCV 11 HIV 24 injecting risk
Gillies et al., 2010	The provision of non-needle/syringe drug injecting paraphernalia in the primary prevention of HCV among injecting drug users: a systematic review	Up to Feb 2010	Injection drug use equipment (specified as drug cookers, filters and/or water)	Core review	1 HCV 0 HIV 13 Injecting risk behaviour

Table F-2. Results of primary studies from the core studies relating to the effectiveness of providing sterile drug preparation equipment with respect to HCV[a]

Author and year	Study design	Findings	Results
Morisette et al., 2007	Cross-sectional	Positive	Individuals reporting frequent use of sterile cookers and water (not filters), compared to PWID reporting infrequent use, were more likely to be self-reported HCV negative.

[a] *Modified from Gillies (2010)*

Table F-3. Results of primary studies from the core studies relating to the effectiveness of providing sterile drug preparation equipment with respect to injecting risk behaviour outcomes[a]

Author and year	Study design	Findings	Results
Hagan and Thiede, 2000	Prospective cohort	No association	There was no association between needle exchange use and cooker or cotton sharing.
Huo et al., 2005	Prospective cohort	No association	Participation in a needle exchange was associated with a one-third decrease in syringe and syringe-mediated sharing, but there was no association with cooker sharing.
Longshore et al., 2001	Cross-sectional	Positive	PWID who attended the needle exchange less frequently were more likely to report sharing cookers.
Ouellet et al., 2004	Prospective cohort	Positive	Regular needle exchange users were less likely to share cookers, cottons, and water, compared to those who did not use a needle exchange.
Huo et al., 2007	Cohort study	Positive	Reduced sharing of paraphernalia (i.e. risk behaviour) amongst attendants of NSP compared to non-users.
Sears et al,.2001(b)	Cohort study	Positive	Reduced sharing of paraphernalia (i.e. risk behaviour) amongst attendants of NSP compared to non-users.
Stolz et al, 2007	Cohort study	Positive	Increased use of clean water for injection amongst PWID frequently attending safer injection facilities compared to infrequent attendees.
Vlahov et al., 1997	Cohort study	Positive	Reduced proportion of PWID sharing paraphernalia after enrolment in NSP compared to pre-enrolment.
Bluthenthal et al., 1998	Serial cross-sectional studies	No association	Reduced temporal trend in sharing between participants in different study 'waves' however no statistically significant reduction in reported sharing behaviour at individual level.
Kipke et al., 1997	Cross-sectional	Positive	NSP users were less likely to report sharing of cookers, water and filters in preceding six months than non-NSP users.
Sears et al., 2001 (a)	Cross-sectional	No association	No association found between users of a new intervention peer-led NSP compared to users of existing NSPs.
Heimer et al., 2002	Cross-sectional	Positive	Reduced sharing of water between users of NSP compared to non-users, but no association found with use of cookers and filters.
Guydish et al., 1998	Cross-sectional	No association	PWID who shared rinse water reported significantly fewer n/s obtained through NSP compared to those not sharing.
Morisette et al., 2007	Cross-sectional	Positive	PWID who reported frequent use of sterile cookers, filters and water, were statistically significantly less likely to report sharing these paraphernalia in past six months.
Colon et al., 2009	Non-randomised intervention study (pilot)	Positive	Increased use of safer injection practices two weeks after completion of intervention to promote use of sterile injection materials.

[a] *Modified from Tilson et al. (2007) and Gillies (2010)*

Appendix G. Information, education and counselling and outreach

Table G-1. Summary of reviews of IEC and outreach

Author and date	Title	Dates covered	Scope	Critical assessment	Number of studies
Aggleton et al., 2005	HIV/AIDS and injecting drug use: Information, education and communication	Not specified	Cost studies	Supplementary review	Not specified
Copenhaver et al., 2006	Behavioural HIV risk reduction among people who inject drugs: Meta-analytic evidence of efficacy	Up to Mar 2004	IEC (RCTs only)	Core review	16 injecting risk behaviour
Coyle et al., 1998	Outreach-based HIV prevention for PWID: a review of published outcome data	Not specified	IEC, Outreach	Supplementary review	20 injecting risk
Dolan and Niven, 2005	A review of HIV prevention among young injecting drug users: a guide for researchers	Not specified	Young PWID	Supplementary review	2 injecting risk
Herbst et al., 2007	A systematic review and meta-analysis of behavioural interventions to reduce HIV risk behaviours of Hispanics in the United States and Puerto Rico	1988 to Dec 2005	IEC, Outreach (Latino populations only)	Core review	4 injecting risk
Jurgens, 2006	HIV/AIDS and HCV in prisons: a select annotated bibliography (part 2)	Mar to Nov 2005	IEC in prison	Supplementary review	None (in relation to relevant outcomes)
Lines et al., 2006	Prison needle exchange: lessons from a comprehensive review of international evidence and experience	Oct 2002 to Mar 2004	IEC in prison	Supplementary review	None (in relation to relevant outcomes)
Needle et al., 2005	Effectiveness of community-based outreach in preventing HIV/AIDS among PWID	Not specified	IEC, Outreach	Core review	2 HIV 5 injecting risk
Prendergast et al., 2001	Meta-analysis of HIV risk reduction interventions within drug abuse treatment programs	1985 to 1998	IEC	Core review	11 injecting risk
Tilson et al., 2007	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Up to Jan 2006	IEC, Outreach	Core review	1 HIV (referred to Clyle and Needle for injecting risk outcomes)
Medley et al., 2009	Effectiveness of peer education interventions for HIV prevention in developing countries: a systematic review and meta-analysis	Up to November 2006	Peer education in developing countries (inc 'upper-middle income countries')	Core review	4 HIV
Hong and Li, 2009	HIV/AIDS behavioural interventions in China: a literature review and recommendation for future research	Up to April 2008	HIV behavioural interventions (among other interventions like NSP and MMT)	Supplementary review	1 HIV/HCV 1 HIV knowledge 1 injecting risk behaviour

Table G-2. Primary studies included within the core review papers (IEC/outreach)

	Core reviews					
	Coyle et al., 1998	Herbst et al., 2007	Needle et al., 2005	Prendergast et al., 2001	Tilson et al., 2007*	Medley et al., 2009
HIV studies						
Wiebel et al., 1996			✓		✓	
Des Jarlais et al., 1998			✓			
Total			2		1	
Injecting risk behaviour studies						
Booth et al., 1991	✓					
Booth & Wiebel, 1992	✓					
Booth et al., 1993	✓					
Broadhead et al., 1998			✓			
Camacho et al., 1995	✓					
Castro and Tafoya-Barazza, 1997		✓				

	Core reviews					
Chaupette, 1992				✓		
Colon et al., 1992	✓					
Colon et al., 1993	✓	✓				
Colon et al., 1995	✓					
Cottler et al., 1998			✓			
Deren et al., 1995	✓					
Eldridge et al., 1997				✓		
Friedman et al., 1992	✓					
Gibson et al., 1999				✓		
Goldstein et al., 2002			✓			
Gordon, 1989				✓		
He et al., 1996	✓					
Kotranski et al., 1998	✓					
Kumar et al., 1998			✓			
Latkin, 1998			✓			
Malow et al., 1992				✓		
Malow et al., 1994				✓		
Neaigus et al., 1990	✓					
Robles et al., 1996	✓					
Robles et al., 2004		✓				
Schilling et al., 1991				✓		
Schilling et al., 2000		✓				
Siegal et al., 1995	✓					
Simpson et al., 1994	✓					
Sorensen et al., 1988				✓		
Sorensen et al., 1994				✓		
Stephens et al., 1991	✓					
Stevens et al., 1998	✓					
Sufian et al., 1991	✓					
Wechsberg et al., 1994	✓					
Weeks et al., 1996	✓					
Broadhead at al., 2006						✓
Hammett et al., 2006						✓
Li et al., 2001						✓
Sergeyev et al.,1999						✓
Total	**20**	**4**	**5**	**9**		**4**

** With respect to injecting risk behaviour outcomes, Tilson et al. cited the reviews Coyle et al. (1998) and Needle et al (2005) as their evidence.*

Appendix H. Knowledge of HCV status

Table H-1. Summary of reviews on knowledge of HCV status

Author and date	Title	Dates covered	Scope	Critical assessment	Number of studies
Stein et al. 2002	Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice	1996 to Jan 2002	Focus on relevance to UK setting	Core review	0 HCV 0 HIV 4 injecting risk 6 economic (review) 1 economic study

Table H-2. Results of primary studies on knowledge of HCV status with respect to injecting risk behaviour outcomes

Author and year	Study design	Finding	Results
Cook et al., 2001	Cross sectional N=341	No differences between self reported known HCV positive and HCV negative status	PWID who believed themselves to be HCV positive (by a previous test) did not differ significantly in their recent needle and syringe sharing or sharing of other equipment from those who believed themselves to be HCV negative (6% vs. 9%, p=0.592; 39% vs. 29%: p = 0.343).
Hagan et al., 2006*	Cross-sectional Multisite, USA N=3,004	Positive for known HCV negative status versus unknown serostatus No association for known HCV positive status	HCV-negative PWID aware of their sero-status were less likely than those unaware of their HCV sero-status to inject with a syringe used by another PWID (AOR 0.8, CI 0.6, 0.9) or to share drug filters (AOR 0.8, CI 0.6, 0.9). HCV positive PWID aware of their sero-status were no less likely than those unaware of their sero-status to report inject with a syringe used by another PWID (AOR 1.0, CI 0.7, 1.4) or pass on their syringes to others (AOR 0.9, CI 0.6, 1.3).
Kwiatkowski et al., 2002*	Cross-sectional Denver, USA N=197	Positive for known HCV positive status versus unknown status	PWID unaware of their HCV status (but who tested HCV positive) were significantly more likely than those who aware they were HCV positive to report recent sharing of needles (p<0.001) and paraphernalia (p<.05) and 'not always injecting safely' (p<0.05).
Malliori et al., 1998	Cross sectional Greece N=544 prisoners	No differences between known HCV positive and HCV negative status	39% of those who were aware of having had a previously positive HCV (or HBV) result reported sharing syringes in the previous month versus 37% of those who reported a negative previous test (not significant)
Miller et al., 2003*	Serial cross sectional surveys at NSPs Oslo, Norway 1992, N=288, 1994 N= 449, 1997 N= 523	No differences between known HCV positive and HCV negative status	No difference in syringe sharing practices between those who reported being HCV-infected and those who did not.
Ompad et al., 2002	Longitudinal Baltimore, USA N=106	No differences between knowledge of HCV positive versus HCV negative or unknown status	~50% of those who acquired knowledge of HCV positive status showed no change or an increase in indirect sharing and approximately one-third showed no change or an increase in backloading or needle sharing The comparisons between HCV positive and non-HCV positive or unknown groups were non-significant across all injecting risk behaviours.
Vidal-Trecan et al., 2000	Cross-sectional Paris, France N=592	Positive differences between known HCV negative status and unknown status Positive difference between HCV negative and HCV positive on use of new equipment	Unknown HCV status vs. HCV negative: No differences in lending (OR = 0.9, 95% CI, 0.6 to 1.5) or borrowing equipment (OR = 0.9, 95% CI, 0.6 to 1.5). HCV unknowns significantly less likely not to use new equipment (OR = 0.4, 95% CI, 0.3 to 0.6) and not to use clean equipment (OR = 1.9, 95% CI, 1.4 to 3.0) than HCV negatives. HCV positive vs. HCV negative: No differences in lending (OR = 1.4, 95% CI, 0.9 to 2.3) or borrowing equipment (OR = 1.2, 95% CI, 0.7 to 1.9). HCV positives significantly less likely not to use new equipment than HCV negatives (OR = 0.5, 95% CI, 0.3 to 0.8). No differences in not using clean equipment (OR = 1.4, 95% CI, 0.8 to 2.3).

** Primary study additional to those from core review*

Appendix I. Supervised injecting facilities

Table I-1. Summary of reviews on supervised injecting facilities

Author and date	Title	Dates covered	Outcomes/scope	Critical assessment	Number of studies[a]
Hedrich, 2004	European report on supervised injecting facilities	Up to end 2003	Process indicators and health outcomes	Supplementary review	1 HCV 1 HIV 13 injecting risk
Wood et al., 2006	Summary of findings from the evaluation of a pilot medically supervised safer injecting facility	2005–2006	Overview of Vancouver supervised injecting facility evaluation studies	Supplementary review	0 HCV 0 HIV 3 injecting risk
Kerr et al., 2007	The role of safer injection facilities in the response to HIV/AIDS among injection drug users	Up to 2007 (no dates specified in paper)	Health impacts of safer injection facilities	Supplementary review	0 HCV 0 HIV 13 injecting risk

[a] *Some studies look at more than one outcome.*

Table I-2. Results of primary studies of supervised injecting facilities with respect to HCV and HIV prevalence/ incidence from supplementary reviews

Author and year	Study design	Finding	Results
MSIC Evaluation 2003	Serial cross-sectional	No association	HCV incidence remained stable among PWID in the supervised injecting facility locality. There was a trend towards increased HCV prevalence among PWID but this was consistent with national trends among PWID.
MSIC Evaluation 2003	Ecological	No association	Trends in notifications of newly diagnosed HCV and HIV infections in the supervised inject facilities' locality were compared to control localities. No evidence of an increase or decrease in the incidence of notifications of HCV or HIV in the facilities locality was found to be attributable to the operation of the supervised injecting facility.

Table I-3. Results of primary studies of supervised injecting facilities with respect to injecting risk behaviour outcomes from supplementary reviews*

Author and year	Study design	Finding	Results
‡ Benninghoff et al., 2003	Serial cross sectional Geneva, Switzerland	Positive for passing on used syringes	No differences in reported syringe and other equipment sharing among supervised injecting facility clients in 2002 to that of PWID. PWID surveyed before the operation of the supervised injecting facility in 1996 and 2000 except supervised injecting facility clients were less likely to report passing a used syringe onto someone else.
Benninghoff & Dubois-Arber, 2002	Serial cross sectional Biel, Switzerland	Positive	Supervised injecting facility clients in 2002 reporting lower levels of syringe and other equipment sharing than PWID surveyed before the operation of the facility in 2000, but levels were still high.
‡ Jacob et al., 1999	Cross-sectional Hanover, Germany N=105	Positive	Use of the consumption room: 22% attributed positive changes in injecting hygiene and 36% less time spent in the open drug scene.
‡ Kerr et al., 2005	Prospective PWID cohort Vancouver, Canada N=431	Positive	After adjustment for relevant socio-demographic and drug-use characteristics supervised injecting facility use was with reduced syringe sharing (AOR 0.30, 0.11–0.82, p=0.02).
Linssen et al., 2001	Longditudinal Anhem, Netherlands N=19	Positive	Between baseline and four-to-six month follow-up clients reported increased knowledge about injecting hygiene and taking fewer health, which they attributed to the IEC provided at the supervised injecting facility.
‡ Meijer et al., 2001	Longditudinal Gronigen, Netherlands N=60	Positive	Between baseline and six month follow-up knowledge about injecting safety improved, an effect that increased with the length of time for which the clients had used the service.
‡ Nejedly & Bürki, 1996; Reyes-Fuentes, 2003; ‡ Ronco et al., 1996	Serial cross sectional Berne, Switzerland 1990, 1995, 2001	Positive	Decreasing levels of risk behaviour: Use of sterile equipment at their first injection (1990: 77%; 1995: 91% and 2001: 96%) and never accepting used injecting equipment (from 58% in 1990 to 75% in 1995).

Author and year	Study design	Finding	Results
MSIC Evaluation 2003	Serial cross-sectional	Trend toward positive	Supervised injecting facility clients were more likely than non clients to use sterile syringes for all injections and less likely to share syringes or other equipment but differences were not statistically significant. Almost half of supervised injecting facility clients reported their injecting practices had improved since using the facility, including less blood presence when injecting.
Poschadel et al., 2003	Cross sectional multi-site, Germany N=	Positive	~50% supervised injecting facility clients reported behavioural changes towards safer drug use which they attributed to the use of the supervised injecting facility. The majority of this group (83%) reported the systematic use of sterile syringes and other equipment.
Stolz et al., 2007	Prospective cohort Vancouver, Canada N=760	Positive	Consistent SIF use was associated with positive changes in injecting practices, including reuse syringes less often (AOR = 2.04, 95% CI = 1.38–3.01, *P* < 0.001), using clean water for injecting (AOR = 2.99, 95% CI = 2.13–4.18, *P* < 0.001), cooking or filtering drugs prior to injecting (AOR = 2.76, 95% CI = 1.84–4.15, *P* < 0.001), safer disposal of syringes (AOR = 2.13, 95% CI = 1.47–3.09, *P* < 0.001), easier finding a vein (AOR = 2.66, 95% CI = 1.83–3.86, *P* < 0.001) and injecting in a clean place (AOR = 2.85, 95% CI = 2.09–3.87, *P* < 0.001).
‡ Van der Poel et al., 2003	Cross sectional Rotterdam, Netherlands N=67	Positive	90% reported positive changes in their drug use-related risk behaviour since visiting supervised injecting facilities, in particular a decreased in drug use in public, improved hygiene, using less hurriedly and in a quieter environment.
‡ Wood et al., 2005	Prospective cohort Vancouver, Canada N=479	Positive	Exclusive supervised injecting facility use was inversely associated with syringe sharing (p=0.019). Ongoing injection-related HIV risk behaviour was reported among some SIF users, but rates of syringe sharing were substantially lower than observed previously in this community.
Zurhold et al., 2001	Cross sectional Hamburg, Germany N=616	Positive	~66% reported positive changes in injecting practices, including hygiene, taking more time, using in public less frequently, being more careful with their health. Frequent users reported greater levels of change than infrequent users.

** Primary studies from Hedrich and Wood reviews; the Kerr review did not provide sufficient information on included primary papers to be added. Primary papers marked with ‡ however were also included in the Kerr review (2007).*

Appendix J. Cost-effectiveness of NSP and provision of paraphernalia.

Table J-1. Summary of reviews of cost-effectiveness of NSP

Author and date	Title	Dates covered	Scope	Critical assessment	Number of studies[a]
De Wit and Bos, 2004	Cost-effectiveness of needle and syringe programmes: a review of the literature	Up to June 2002	Cost studies	Core review	1 HCV 7 HIV
Pinkerton et al., 2002	Cost-effectiveness of community-level approaches to HIV prevention: a review	Up to 1999	Cost studies	Core review	7 HIV
Wodak and Cooney, 2004	Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users	Up to 2002	Cost studies	Core review	1 HCV 10 HIV 28 injecting risk
Jones et al., 2008	A review of the effectiveness and cost-effectiveness of needle and syringe programmes for injecting drug users	1990 - 2008	Cost study	Core review	11 HIV 1 HCV 1 HIV/HCV

[a] *Studies are listed as HCV or HIV studies because the outcomes were the number of HIV/HCV averted infections; most studies used data on injecting risk behaviour from primary studies or empirical data to inform their models.*

Table J-2. NSP cost studies included within the core review papers

	Core reviews			
	De Wit and Bos (2004)	Pinkerton et al. (2002)	Wodak and Cooney (2004)	Jones et al. (2008)
HCV studies				
Health Outcomes International, 2002	✓			✓
Pollack, 2001				✓
Total	**1**			**2**
HIV studies				
Health Outcomes International, 2002	✓			✓
Gold et al., 1997	✓		✓	✓
Holtgrave et al., 1998	✓	✓	✓	✓
Jacobs et al., 1999*	✓		✓	✓
Kahn, 1992			✓	
Kahn, 1993		✓		
Kahn, 1998		✓	✓	
Kahn & DeCarlo, 1996			✓	
Kahn & Sanstad, 1997		✓	✓	
Kaplan, 1993/1995		✓		
Kumaranayake et al., 2000 (= draft publication of Kumaranayake et al., 2000)			✓	
Laufer, 2001	✓		✓	✓
Lurie and Drucker, 1997	✓		✓	✓
Lurie et al., 1998		✓	✓	
Pinkerton et al., 2000	✓			
Cabases & Sanchez, 2003				✓
Cohen et al., 2004				✓
Cohen et al., 2006				✓
Harris, 2006				✓
Kumaranayake et al., 2004 (= final publication of Kumaranayake et al., 2000)				✓
Vickerman et al., 2006				✓
Total	**7**	**6**	**11**	**11**

** Included in the Jones review as a 1998 publication ('working paper') of the same study.*

Table J-3. Results of primary studies of the cost-effectiveness of NSP in reducing HIV transmission[a]

Author and year	Study design	Type of NSP	Setting	Results
Health Outcomes International, 2002	Cost-effectiveness and cost-utility analyses (modelling of annual rate of change of seroprevalence)	Needle exchange	Australia	NSP is cost saving in all circumstances tested and is associated with gains in quality and quantity of life.
Gold et al., 1997	Cost-effectiveness analysis (decision analytical model)	Needle exchange from a mobile van	Canada	NSP is cost saving in all circumstances tested.
Holtgrave et al., 1998	Cost-effectiveness analysis (mathematical modelling in hypothetical cohort of 1 million PWID)	Pharmacy sales (75%), needle exchange programmes (25%)	US	Increasing access to sterile syringes with a one-year programme is cost saving.
Jacobs et al., 1999	Cost-effectiveness analysis (mathematical modelling using data from one intervention cohort)	Needle exchange	Canada	The NSP results in net savings and is therefore a dominant strategy in base case analysis, but not in all extreme value sensitivity analyses.
Kahn, 1992	Cost-effectiveness analysis	A variety of HIV prevention strategies including needle exchange	US	Cost per HIV infection prevented was lowest for needle exchange and counselling/education at about USD 4,000.
Kahn, 1993	Cost-effectiveness analysis (mathematical modelling using data from 12 epidemiological studies)	Needle exchange	US	Needle exchange would cost approximately USD 4,000 per HIV infection averted.
Kahn, 1998[b]	Cost-effectiveness analysis (mathematical modelling of data from four hypothetical needle exchanges)	Van-based needle exchange, storefront needle exchange, activist-run street-based needle exchange	US	The estimated cost per HIV infection averted ranged from USD 12,000 to 99,000.
Kahn and DeCarlo, 1995	Cost-effectiveness analysis	Not indicated	US	US $1 million in annual prevention spending over five years could prevent about 100 HIV infections in high-risk populations with HIV prevalence rates of 10 to 15%.
Kahn and Sanstad, 1997	Cost-effectiveness analysis (mathematical modelling using data from a behavioural study)	Needle exchange	US	The estimated cost per HIV infection averted was less than USD 3,000, suggesting that the NSP is cost-saving.
Kaplan, 1993; Kaplan, 1995	Cost-effectiveness analysis (modelling study using empirical data on average circulation time for needles from an NSP based in a mobile van)	Needle exchange from a mobile van	US	The programme was estimated to cost USD 93,000 per HIV infection averted, which is less than the cost of treating HIV disease, and thus cost-saving.
Kumarayanake et al., 2000	Cost-effectiveness analysis – draft report (final report in 2005, included below)	Harm reduction intervention strategy that included needle exchange	Belarus	The average cost per HIV infection averted was estimated at USD 68 less than the costs of treatment.
Laufer, 2001	Cost-effectiveness analysis (calculations of infections averted in seven NSP sites)	Needle exchange	US	NSP is cost-effective and cost-saving.
Lurie and Drucker, 1997	Cost-effectiveness analysis (modelling study in hypothetical cohort of PWID)	Needle exchange	US	NSP is cost saving (although programme costs were not studied).
Lurie et al., 1998	Threshold analysis (to determine the HIV incidence required for NSP to achieve cost neutrality)	Needle exchange, syringe sale, injection kit distribution, kit sale, pharmacy-based exchange	N/A	The estimated injection-related HIV incidence required for cost neutrality (i.e. for medical savings to equal programme costs) ranged from 0.3% to 2.1%.
Pinkerton et al., 2000	Cost-effectiveness and cost-utility analyses (mathematical modelling using data from eight different intervention cohorts)	A combination of interventions including needle exchange	US	NSP is most likely cost saving in all circumstances tested.
Cabases & Sanchez, 2003	Cost-effectiveness analysis comparing programmes costs to effectiveness measured as coverage (number of kits distributed divided by estimated number of injections by PWID in the population)	'anti-HIV kits' containing one sterile n/s, one condom, one paper towel and ampoule of distilled water.	Spain	Annual (incremental) costs of averting new HIV infection among PWID were lower than the cost of treating one infected person.

Author and year	Study design	Type of NSP	Setting	Results
Cohen et al., 2004	Cost-effectiveness study comparing CE of 26 HIV prevention programmes including needle exchange to costs of treatment of HIV	Needle exchange	US	ICER per averted HIV infection was USD 13,000 (adjusted to 12 months). Compared to HIV treatment, needle exchange was cost-effective when the HIV prevalence among PWID was high (above 20%).
Cohen et al., 2006	Cost-effectiveness study comparing CE of 6 HIV prevention programmes including needle exchange to costs of treatment of HIV among women only	Needle exchange	US	Cost per averted HIV infection was USD 9,000 (over three months).
Harris, 2006 (a)	Cost-effectiveness study assessing CE of a multi-site needle exchange programme.	Needle exchange	US	Extending the opening hours would be more cost-effective in reducing HIV. At optimal mode of functioning, estimated cost per HIV infection averted was USD 2,757.
Kumaranayake et al., 2004	Cost-effectiveness analysis final publication (see publication in year 2000, above).	Harm reduction intervention strategy that included needle exchange	Belarus	The average costs per HIV infection averted were estimated at USD 395 in a population with high HIV prevalence among PWID (74%). Sensitivity analysis showed that initial HIV prevalence had greatest effect on model outputs (i.e. increase in prevalence lead to higher CE ratio per averted HIV infection).
Vickerman et al, 2006	Cost-effectiveness analysis	Harm reduction intervention strategy that included needle exchange	Ukraine	Over one year, costs per HIV infection averted were estimated at USD 97. Sensitivity analysis showed that initial HIV prevalence and increase in transmission during initial phase of infection had greatest effect on CE ratio per averted HIV infection.

[a] *Modified from De Wit and Bos (2004), Pinkerton (2002), Wodak and Cooney (2004) and Jones (2008)*

[b] *Cited in Pinkerton (2002) as Kahn (1993)*

Appendix K. Two flowcharts relating to (A) the original RoR and (B) the updated RoR

Figure A. Flow chart of reviews retrieved in the original RoR (covering the period 2000–February 2007)

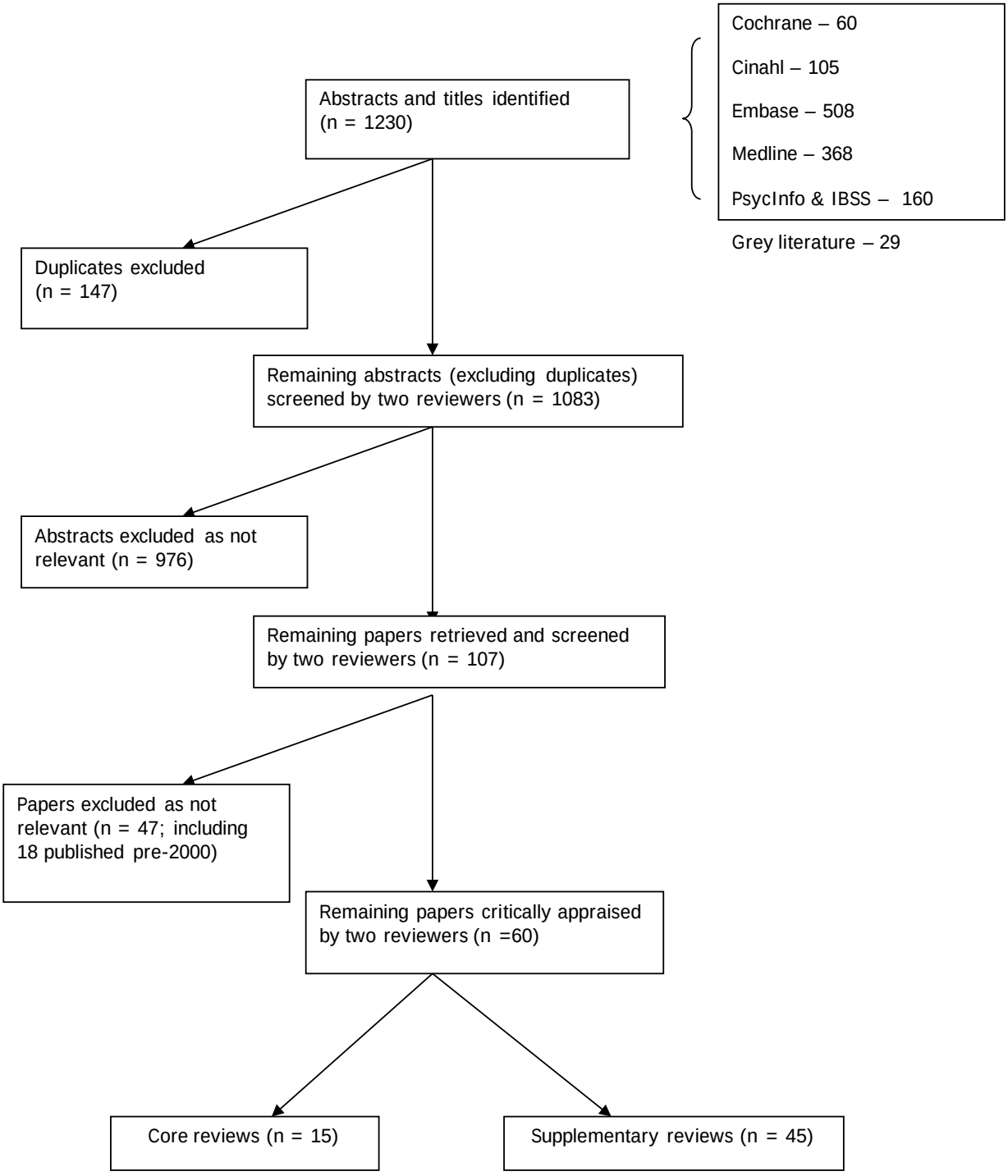
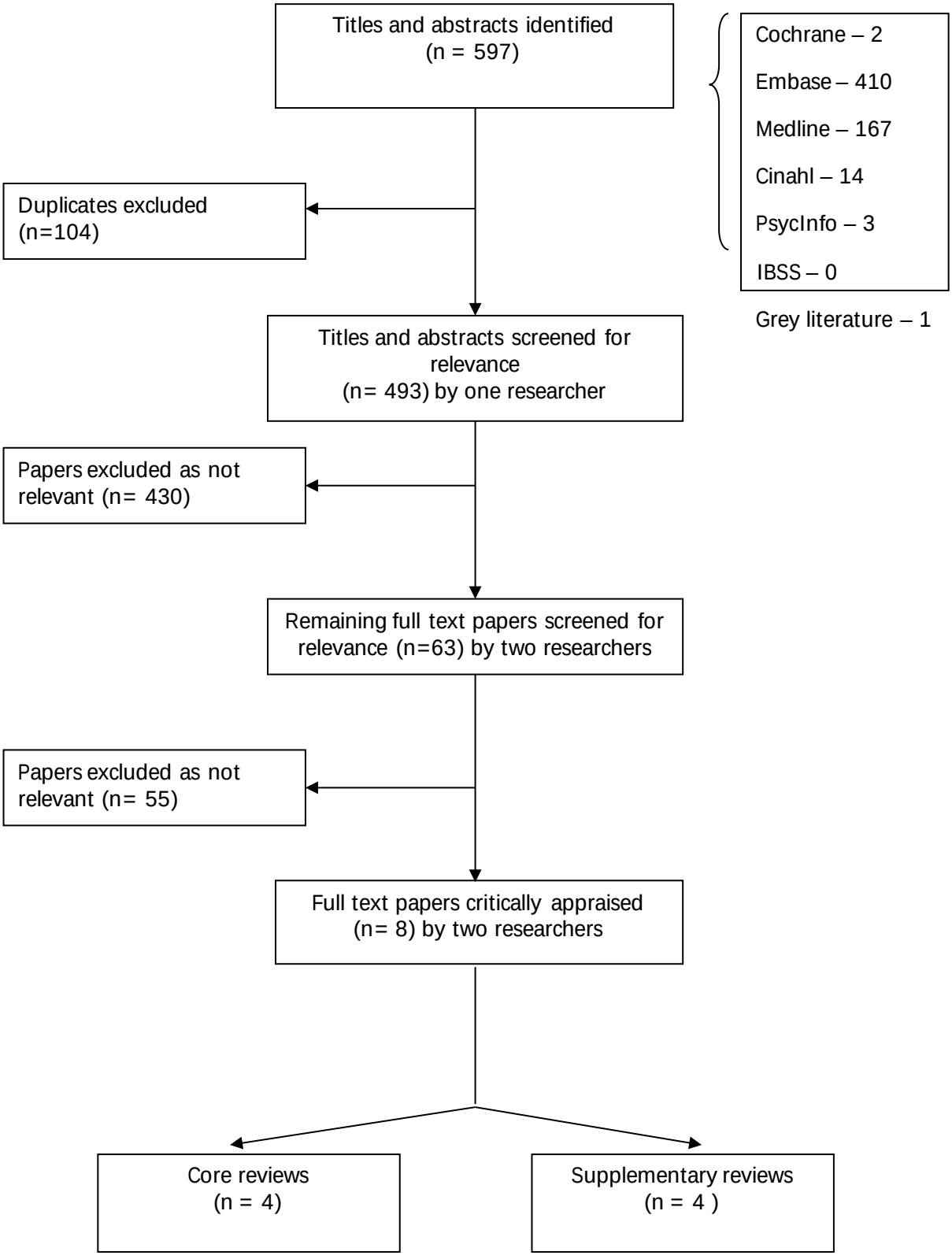


Figure B. Flow chart of reviews retrieved in the update of the RoR (covering the period March 2007–March 2011)



Appendix L. Search terms for the review of primary literature

Search terms topic 1 (NSP retention)

1. Needle Sharing/
2. *Substance Abuse, Intravenous/
3. (substance$ or drug$).ti,ab.
4. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
5. (inject$ or intravenous).ti,ab.
6. 1 or 2 or (3 and 4) or (3 and 5)
7. Harm Reduction/
8. Intervention Studies/
9. Preventive Health Services/
10. Community Health Services/
11. Primary Prevention/
12. 7 or 8 or 9 or 10 or 11
13. (needle$ or syringe$).ti,ab.
14. (exchange$ or provi$ or distribu$).ti,ab.
15. Needle-Exchange Programs/
16. (13 and 14) or 15
17. environment.ti,ab.
18. factor$.ti,ab.
19. facilititat$.ti,ab.
20. barrier$.ti,ab.
21. (17 or 18 or 19 or 20) and 16
22. 6 and 12 and 21
23. limit 22 to english language
24. limit 23 to yr="2000-Current"
25. remove duplicates from 24

Search terms topic 2 (service combinations)

1. *Hepatitis C/pc
2. (hepatitis c or HCV).ti,ab.
3. *HIV Infections/pc
4. (HIV or human immunodeficiency virus).ti,ab.
5. transmission.ti,ab.
6. seroconver$.ti,ab.
7. risk behavio?r.ti,ab.
8. Risk Reduction Behavior/
9. Behavior Modification/
10. Needle Sharing/
11. Risk-taking/
12. 1 or (2 and 5) or (2 and 6) or 3 or (4 and 5) or (4 and 6) or 7 or 8 or 9 or 10 or 11
13. *Substance Abuse, Intravenous/
14. (substance$ or drug$).ti,ab.
15. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
16. (inject$ or intravenous).ti,ab.
17. 13 or (14 and 15) or (14 and 16)

18. (needle$ or syringe$).ti,ab.
19. (exchange$ or provi$ or distribu$).ti,ab.
20. Needle-Exchange Programs/
21. (18 and 19) or 20
22. service$.ti,ab.
23. (mix or combination$ or model$ or deliver$).ti,ab.
24. (effective$ or reduc$).ti,ab.
25. 21 and 22 and 23
26. 12 and 17 and 24 and 25
27. limit 26 to english language
28. limit 27 to yr="2000-current"
29. remove duplicates from 28

Search terms topic 3 (coverage)

1. *Hepatitis C/pc
2. (hepatitis c or HCV).ti,ab.
3. *HIV Infections/pc
4. (HIV or human immunodeficiency virus).ti,ab.
5. transmission.ti,ab.
6. seroconver$.ti,ab.
7. risk behavio?r.ti,ab.
8. Risk Reduction Behavior/
9. Behavior Modification/
10. Needle Sharing/
11. Risk-taking/
12. 1 or (2 and 5) or (2 and 6) or 3 or (4 and 5) or (4 and 6) or 7 or 8 or 9 or 10 or 11
13. *Substance Abuse, Intravenous/
14. (substance$ or drug$).ti,ab.
15. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
16. (inject$ or intravenous).ti,ab.
17. 13 or (14 and 15) or (14 and 16)
18. Harm Reduction/
19. Intervention Studies/
20. Preventive Health Services/
21. Community Health Services/
22. Primary Prevention/
23. 18 or 19 or 20 or 21 or 22
24. (needle$ or syringe$).ti,ab.
25. (exchange$ or provi$ or distribu$).ti,ab.
26. Needle-Exchange Programs/
27. (24 and 25) or 26
28. service$.ti,ab.
29. (coverage or level$ or quantit$).ti,ab.
30. (effective$ or reduc$).ti,ab.
31. 27 and 28 and 29
32. 12 and 17 and 23 and 30 and 31
33. limit 32 to english language
34. limit 33 to yr="2000-current"
35. remove duplicates from 34

Search terms topic 4 (vaccination from NSP)

1. Needle Sharing/
2. *Substance Abuse, Intravenous/
3. (substance$ or drug$).ti,ab.
4. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
5. (inject$ or intravenous).ti,ab.
6. 1 or 2 or (3 and 4) or (3 and 5)
7. Harm Reduction/
8. Intervention Studies/
9. Preventive Health Services/
10. Community Health Services/
11. Primary Prevention/
12. 7 or 8 or 9 or 10 or 11
13. (needle$ or syringe$).ti,ab.
14. (exchange$ or provi$ or distribu$).ti,ab.
15. Needle-Exchange Programs/
16. (13 and 14) or 15
17. (vaccination$ or immunisation$).ti,ab.
18. (hepatitis B or HBV or (hepatitis A or HAV) or tetanus).ti,ab.
19. uptake.ti,ab.
20. complet$.ti,ab.
21. 17 and 18 and (19 or 20)
22. 6 and 12 and 16 and 21
23. limit 22 to english language
24. limit 23 to yr="1980-Current"
25. remove duplicates from 24

Search terms topic 5 (testing from NSP)

1. Needle Sharing/
2. *Substance Abuse, Intravenous/
3. (substance$ or drug$).ti,ab.
4. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
5. (inject$ or intravenous).ti,ab.
6. 1 or 2 or (3 and 4) or (3 and 5)
7. Harm Reduction/
8. Intervention Studies/
9. Preventive Health Services/
10. Community Health Services/
11. Primary Prevention/
12. 7 or 8 or 9 or 10 or 11
13. (needle$ or syringe$).ti,ab.
14. (exchange$ or provi$ or distribu$).ti,ab.
15. Needle-Exchange Programs/
16. (13 and 14) or 15
17. HIV infections/di
18. Hepatitis C/di
19. (HCV test$ or hepatitis C test$ or HIV test$ or human immunodeficiency virus test$).ti,ab.
20. diagnostic tests, routine/
21. 17 or 18 or 19 or 20

22. 6 and 12 and 16 and 21
23. limit 22 to english language
24. limit 23 to yr="2000-Current"
25. remove duplicates from 24

Search terms topic 6 (referral for treatment)

1. Needle Sharing/
2. *Substance Abuse, Intravenous/
3. (substance$ or drug$).ti,ab.
4. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
5. (inject$ or intravenous).ti,ab.
6. 1 or 2 or (3 and 4) or (3 and 5)
7. HIV infections/di
8. Hepatitis C/di
9. (HCV test$ or hepatitis C test$ or HIV test$ or human immunodeficiency virus test$).ti,ab.
10. diagnostic tests, routine/
11. refer$.ti,ab.
12. uptake.ti,ab.
13. ((HCV or hepatitis c) and treatment).ti,ab.
14. (7 or 8 or 9 or 10) and 11
15. 12 and 13
16. 6 and 14 and 15
17. limit 16 to english language
18. limit 17 to yr="2000-Current"
19. remove duplicates from 18

Search terms topic 7 (HCV treatment)

1. Needle Sharing/
2. *Substance Abuse, Intravenous/
3. (substance$ or drug$).ti,ab.
4. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
5. (inject$ or intravenous).ti,ab.
6. 1 or 2 or (3 and 4) or (3 and 5)
7. (outcome or respon$).ti,ab.
8. ("HCV treatment" or "hepatitis c treatment").ti,ab.
9. 7 and 8
10. 6 and 9
11. limit 10 to english language
12. limit 11 to yr="2000-Current"
13. remove duplicates from 12

Search terms topic 8 (IEC and skin infections)

1. Needle Sharing/
2. *Substance Abuse, Intravenous/
3. (substance$ or drug$).ti,ab.
4. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
5. (inject$ or intravenous).ti,ab.
6. 1 or 2 or (3 and 4) or (3 and 5)
7. health education/

8. patient education/
9. counselling/
10. health knowlegde, attitudes, practices/
11. health promotion/
12. 7 or 8 or 9 or 10 or 11
13. (bacterial and infection$).ti,ab.
14. 6 and 12 and 13
15. limit 14 to english language
16. limit 15 to yr="2000-Current"
17. remove duplicates from 16

Appendix M. Summary of evidence statements of updated RoR 2000–2011

The update of the RoR, adding reviews published from 2007 to 2011, resulted in evidence statements for evidence at review-level per intervention. These evidence statements are summarised and listed below; the interventions for which the evidence statements have been 'upgraded' as a result of the update were marked with an asterisk (*). Recently, more primary level evidence has become available which specifically indicates the benefits of offering (NSP and OST) services in combined programmes. Due to the fact that these papers were published very recently, they have not been included in published reviews; however a number of very relevant primary studies were included in the review of primary literature.

Effectiveness of NSP

At review level:

There is insufficient evidence to either support or discount the effectiveness of needle and syringe exchange programmes in reducing HCV transmission among PWID, although ecological investigations have demonstrated stable or declining HCV prevalence in the context of needle and syringe exchange programmes.

There is tentative evidence to support the effectiveness of needle and syringe exchange programmes in reducing HIV transmission among PWID.

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

Effectiveness of provision of non-needle and syringe drug injection equipment

At review-level:

* There is insufficient evidence to either support or discount the effectiveness of providing drug injecting equipment other than needles/syringes in reducing the transmission of HCV among PWID.

There is no evidence to either support or discount the effectiveness of providing drug injecting equipment other than needles/syringes in reducing the transmission of HIV among PWID.

* There is tentative evidence to support the effectiveness of providing drug injecting equipment other than needles/syringes in reducing injecting risk behaviour among PWID.

Effectiveness of different models of NSP: alternative access

At review-level, in relation to pharmacy access:

There is no evidence to either support or discount the effectiveness of pharmacy access to needles/syringes on reducing the transmission of HCV among PWID.

There is insufficient evidence to either support or discount the effectiveness of pharmacy access to needles/syringes in reducing HIV prevalence among PWID.

There is tentative evidence that pharmacy access is at least as effective as dedicated needle and syringe programmes in reducing self-reported injecting risk behaviour among PWID.

At review-level, in relation to vending machines:

There is no evidence to either support or discount the effectiveness of needle/syringe vending machines in reducing HCV transmission among PWID.

There is insufficient evidence to either support or discount the effectiveness of needle/syringe vending machines in reducing HIV transmission among PWID.

There is insufficient evidence to either support or discount the effectiveness of needle/syringe vending machines in reducing injecting risk behaviour among PWID.

At review-level, in relation to mobile vans as outreach needle and syringe programmes:

There is no evidence to either support or discount the effectiveness of outreach needle and syringe exchange programmes (mobile vans) in reducing the transmission of HCV among PWID.

* There is insufficient evidence to either support or discount the effectiveness of outreach needle and syringe exchange programmes (mobile vans) in reducing the transmission of HIV among PWID.

There is no evidence to either support or discount the effectiveness of outreach needle and syringe exchange programmes (mobile vans) in reducing injecting risk behaviour among PWID.

Effectiveness of provision of information, education and counselling and outreach

At review-level:

There is no evidence to either support or discount the effectiveness of information, education and counselling and/or outreach in reducing HCV transmission among PWID.

There is insufficient evidence to either support or discount the effectiveness of information, education and counselling and/or outreach in reducing HIV transmission among PWID.

There is tentative evidence to support the effectiveness of outreach, which includes information, education and counselling, in reducing injecting risk behaviour among PWID.

There is insufficient evidence to either support or discount the effectiveness of information, education and counselling in non-outreach settings in reducing injecting risk behaviour among PWID.

Effectiveness of diagnostic testing for HCV

At review-level:

There is no evidence to either support or discount the impact of gaining knowledge of HCV status on HCV incidence or prevalence.

There is insufficient evidence to either support or discount the impact of knowledge of HCV status on injecting risk behaviour.

Effectiveness of supervised injecting facilities

At review-level:

There is insufficient evidence to either support or discount the effectiveness of supervised injecting facilities with respect to HCV incidence.

There is insufficient evidence to either support or discount the effectiveness of supervised injecting facilities with respect to HIV incidence.

There is tentative evidence to support the effectiveness of supervised injecting facilities in reducing injecting risk behaviour and improving injecting hygiene, particularly for injections that take place on supervised injecting facility premises.

Cost-effectiveness of NSP and provision of drug injecting equipment

At review-level, in relation to cost-effectiveness of NSP:

There is insufficient evidence to either support or discount the cost-effectiveness of needle and syringe exchange programmes in preventing HCV transmission among PWID.

There is sufficient evidence to support the cost-effectiveness of needle and syringe exchange programmes in preventing HIV transmission among PWID, assuming a treatment effect of such programmes in reducing HIV transmission.

At review-level, in relation to cost-effectiveness of distribution of drug injecting equipment:

There is no evidence to either support or discount the cost-effectiveness of distribution of non-needle injecting equipment in preventing HCV transmission or HIV transmission.