Addiction

REVIEW

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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

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ABSTRACT

Aims To review the evidence on the effectiveness of harm reduction interventions involving the provision of sterile injecting equipment in the prevention of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) transmission among injecting drug users (IDUs). The interventions assessed were needle and syringe programmes (NSP), alternative modes of needle/syringe provision (pharmacies, vending machines and outreach) and the provision of injecting equipment other than needles/syringes. **Methods** Systematic searches of the English language literature to March 2007 were undertaken to identify systematic, narrative or meta-analytical reviews (also known as a review of reviews) of the impact of interventions on HCV transmission, HIV transmission or injecting risk behaviour (IRB). Critical appraisal criteria classified the reviews as either high quality ('core') or supplementary: a framework based on the quality of reviews, the reviewers' conclusions and the designs/findings of the primary studies was used to derive evidence statements. **Results** Three core and two supplementary reviews of injecting equipment interventions were identified. According to the proposed framework, this study found (a) insufficient evidence to conclude that any of the interventions are effective in preventing HCV transmission; (b) tentative evidence to support the effectiveness of NSP in preventing HIV transmission; (c) sufficient evidence to support the effectiveness of NSP (and tentative evidence of an additional impact of pharmacy NSP) in reducing self-reported IRB; and (d) little to no evidence on vending machines, outreach or providing other injecting equipment in relation to any of the outcomes. **Conclusions** The evidence is weaker than given credit for in the literature. The lack of evidence for effectiveness of NSP *vis-à-vis* biological outcomes (HCV and HIV incidence/prevalence) reflects the limitations of studies that have been undertaken to investigate these associations. Particularly for HCV, low levels of IRB may be insufficient to reduce high levels of transmission. New studies are required to identify the intervention coverage necessary to achieve sustained changes in blood-borne virus transmission.

Keywords Hepatitis C, HIV, needle-exchange programmes, review.

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INTRODUCTION

There are an estimated 15.9 million injecting drug users (IDUs) world-wide [1]. These individuals are at high risk of contracting blood-borne viruses (BBVs), namely the hepatitis C virus (HCV) and the human immunodeficiency virus (HIV), due to risky injecting practices such as the sharing of needles/syringes. Among IDUs, HCV prevalence rates of more than 50% have been reported in 49 countries and HIV prevalence rates of more than 20% have been reported in 14 countries [1,2].

Needle and syringe programmes (NSP) are a critical component of harm reduction interventions to reduce transmission of BBVs among IDUs [3]. These programmes

usually consist of fixed-site specialist services, although alternative access is offered through, for example, pharmacies, vending machines and outreach [3]. Some programmes also distribute injecting equipment other than needles/syringes, which may include such items as cookers, filters and water ampoules, as these types of equipment may also present a risk of BBV transmission [4].

Many reviews on the effectiveness of interventions providing injecting equipment have been conducted to date, between them covering different types of service provision and a range of outcome measures. The goal of this study was to: (i) synthesize the available evidence of the effectiveness of interventions involving injecting equipment provision in reducing HCV and HIV transmission among IDUs; and (ii) to identify gaps and inconsistencies in the evidence base to highlight where future research is needed. The interventions considered were fixed-site specialist services, as well as alternative modes of needle/syringe provision (pharmacies, vending machines and outreach), and the provision of injecting equipment other than needles/syringes.

METHODS

We adopted a 'review of reviews' approach as proposed by the Health Development Agency (HDA) [5]: given the increasing number of reviews of effectiveness of public health interventions in the literature, the goal of a review of reviews is to bring together the evidence from reviews, rather than to undertake a systematic review of the primary literature in itself.

Inclusion and exclusion criteria

Systematic reviews, syntheses or meta-analyses looking at the effectiveness of injecting equipment interventions in relation to the prevention of HCV, HIV or self-reported injecting risk behaviour (IRB) among IDUs were considered for inclusion. The relevant interventions were: (i) fixed-site specialist needle and syringe programmes (referred to as NSPs henceforth); (ii) alternative access to sterile needles/syringes via pharmacies, vending machines or outreach; and (iii) the provision of sterile drug preparation equipment (other than needles/syringes). The outcomes of interest were HCV prevalence or incidence, HIV prevalence or incidence and self-reported IRB. IRB was considered to include the borrowing, lending or re-use of needles/syringes or other drug preparation equipment. Papers that considered only the sexual transmission of HCV or HIV were excluded, as were papers that did not report their literature review methods. The literature search was limited to English language reviews only.

Search strategy

The following electronic databases were searched: CINAHL, Cochrane Library, EMBASE, IBSS, MEDLINE and PsycINFO. The publications of key international agencies were also searched: the European Monitoring Centre on Drugs and Drug Addiction, the National Institute on Drug Abuse, the US Institute of Medicine, the United Nations Office on Drugs and Crime Prevention and the World Health Organization. All databases were searched from 1980 to March 2007, with the exception of CINAHL, which was searched from 1982 to March 2007. At the screening stage it became apparent that the relevant reviews from the 1980s and 1990s had been superseded by more recent reviews; consequently, the period was restricted to 2000 onwards.

Review selection

The identified abstracts were screened and evaluated by two reviewers to determine whether the paper met the inclusion criteria. If there was disagreement between the two reviewers regarding the relevance of an abstract the full paper was retrieved for further evaluation. The two reviewers screened the full papers independently to determine eligibility for inclusion; in the event of lack of concordance, a decision was reached by discussing the points of disagreement.

Critical appraisal

The selected reviews were appraised critically using a tool developed by the HDA, which considers the strength of the methods used to identify the relevant literature, the appraisal of the primary literature, the quality of methodological analysis (in the case of meta-analyses) and the appropriateness of the conclusions [5]. The papers were then categorized as one of the following: (i) to be included as data where the whole of the review is judged to be of high quality; (ii) to be included as data where only part of the review is judged to be of high quality; or (iii) to be included only as potential background or contextual material. Papers categorized as 1 or 2 were included as high-quality ('core') reviews and the remaining papers were retained as 'supplementary' reviews, not considered to be of sufficient quality to rely on the authors' conclusions but viewed as potentially providing complementary information on the effectiveness of the interventions. Meta-analyses were not necessarily assigned a higher score than other types of reviews; reviews had to satisfy the majority of the critical appraisal criteria in order to be classed as a core review.

Data extraction and synthesis

From each review, we extracted information on the reviewers' assessment of the evidence and the number,

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

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

[a]Modified from Ellis *et al.* 2003 [6].

design and findings of relevant primary studies. Information on primary studies was extracted from the reviews; in the case where reviews reported discrepant study findings, the primary studies were consulted.

The level of evidence in support of (or discounting) the effect of an intervention was classified as: 'sufficient'; 'tentative'; 'insufficient'; or 'no' evidence from reviews. These were derived using a framework (Table 1) based on the quality of the reviews, the reviewers' conclusions and the designs/findings of the primary studies included in the reviews [6]. In the absence of controlled trials, longitudinal cohort and case–control designs (involving incident cases) were considered to be more 'robust', whereas ecological, serial cross-sectional and cross-sectional designs were considered to be 'weaker'.

RESULTS

The literature search generated 1083 references after exclusion of duplicates (Fig. 1). Abstracts were reviewed and 976 were excluded, leaving 43 papers related to injecting equipment interventions to be screened. Full screening eliminated a further 25, leaving 18 for critical appraisal. Of the 18 papers, three were judged to be core reviews and the remainder were retained as supplementary reviews. Five (three core and two supplementary) were drawn upon for evidence (Table 2). A critical appraisal summary for the supplementary reviews not included in the evidence base is given in the Supporting Information, Appendix S1.

The findings of the reviews (and primary studies) are presented below (and in Table 3) for each intervention and outcome. Apropos the results of primary studies, a 'positive' finding refers to an observed reduction in the stated outcome (e.g. HCV prevalence) associated with the intervention, a 'negative' finding refers to an increase in the outcome associated with the intervention, and 'no association' refers to no statistically significant association between the outcome and intervention. Where a review reported a study finding as positive or negative, it was assumed that the result was statistically significant at the 5% level even if this was not stated explicitly; where a review reported 'no association', it was assumed that this indicated a non-statistically significant result.

Needle and syringe programmes (NSP)

Effects on HCV incidence/prevalence

Three core reviews [3,7,8] and one supplementary review [9] considered the impact of NSP on HCV incidence or prevalence. The core reviews focused primarily on HIV outcomes and therefore may not have identified all of the relevant HCV-related literature: Wodak &

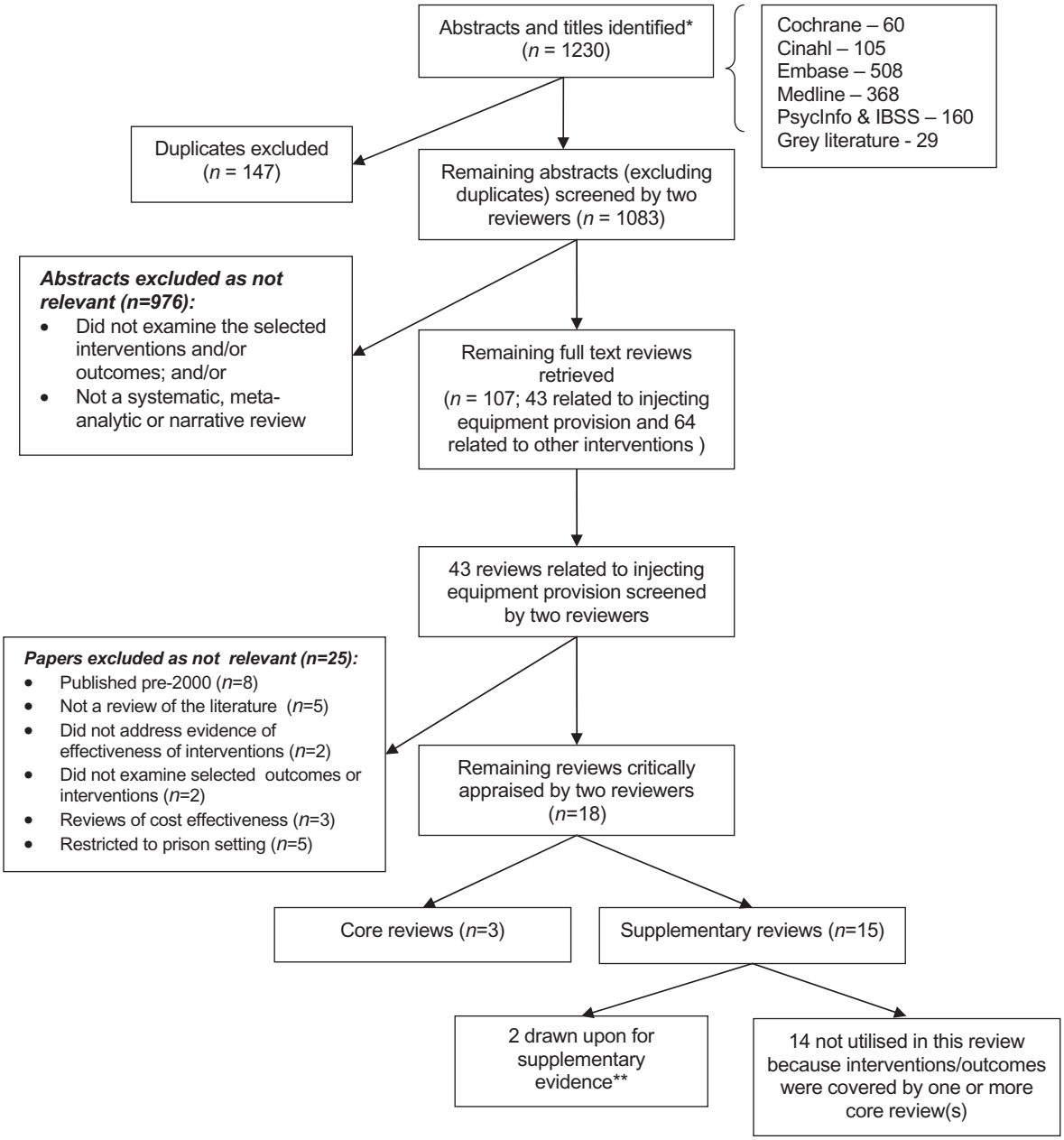

Figure 1 Papers identified in the review of reviews. *In addition to reviews of injecting equipment provision interventions, the initial search also included reviews of the following interventions: information, education, counselling and outreach; opiate substitution therapy; hepatitis C virus (HCV) testing and knowledge of HCV status; drug consumption rooms; treatment for HCV infection; promotion of non-injecting routes of administration; structural interventions; and bleach disinfection of needles/syringes. Only interventions involving the provision of injecting equipment are considered in this paper. **One review [93] was identified after the search was carried out

Cooney referred to only one HCV study [10], Tilson *et al.* identified six [10–15] and Gibson *et al.* included three [10,16,17]. None of these reviews examined HCV in any depth, and only Tilson *et al.* drew conclusions, stating there was moderate evidence that 'HIV prevention programs that include NSP' have less of an impact on HCV transmission than on HIV transmission.

The three core reviews covered seven primary studies between them and the supplementary review, which focused exclusively on HCV outcomes, included an additional nine relevant papers [18–26], although three of these present duplicate data [18–20] (Supporting Information, Appendix S2). There were seven primary studies with positive findings, but these mainly involved weaker designs. The stronger study designs (cohorts) showed mainly either no association or negative findings between NSP and HCV seroconversion. Given an absence of clear statements from the core reviews, and inconsistent

Table 2 Summary of reviews of injecting equipment interventions.

Author and date	*Title*	*Inclusion criteria/terms of reference*	*Dates covered*	*Interventions covered*	*Critical assessment*	*No. studies*[a]
Gibson *et al.* 2001 [8]	Effectiveness of syringe exchange programmes in reducing HIV risk behaviour and HIV seroconversion among IDUs	Published studies of the effectiveness of syringe exchange programmes in reducing HIV risk behaviour and HIV seroconversion among IDUs, regardless of design. Also included studies that examined effects of syringe exchange on HBV and HCV seroconversion	1989–end 1999	NSP	Core review	3 HCV 6 HIV 23 self-reported injecting risk behaviour
Islam & Conigrave 2007 [93]	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	To examine the available evidence for the effectiveness of syringe dispensing machines and mobile van or bus based NSPs in making services accessible to hard-to-reach and high-risk groups of IDUs.	Not specified	Vending machines	Supplementary review	1 self-reported injecting risk behaviour
Tilson *et al.* 2007 [3]	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Published and unpublished literature on the effectiveness of HIV prevention interventions (drug dependence treatment, sterile needle and syringe access and outreach and education programmes) for IDUs	1980–January 2006	NSP, pharmacy NSP, vending machines, provision of other injecting equipment	Core review	6 HCV 12 HIV 24 self-reported injecting risk behaviour
Wodak & Cooney 2004 [7]	Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users	To evaluate evidence on the effectiveness of sterile needle and syringe programming (including other injecting paraphernalia) for HIV prevention among IDUs in different contexts	1989–2002	NSP, pharmacy NSP, vending machines	Core review	1 HCV 10 HIV 28 self-reported injecting risk behaviour
Wright & Tompkins 2006 [9]	A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users	Intervention or observational studies describing a primary prevention intervention targeting injecting drug using populations with the outcome to reduce either the prevalence or incidence of hepatitis C infection	Up to end 2002	NSP	Supplementary review	9 HCV

[a]Number of primary studies in the review, listed by outcome. AIDS: acquired immune deficiency syndrome; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IDU: injecting drug user; NSP: needle and syringe programmes.

Table 3 Summary of evidence used in the derivation of evidence statements for each intervention: (a) needle and syringe programmes (NSP), (b) pharmacy NSP, (c) vending machines, (d) outreach NSP and (e) provision of other injecting equipment and each outcome [HCV (hepatitis C virus), HIV (human immunodeficiency virus) and self-reported injecting risk behaviour].

Outcome	*Gibson (2001)*	*Tilson (2007)*	*Wodak (2004)*	*Primary studies*[a]	*Evidence statement*
(a) Needle and syringe programmes (NSP)					
HCV	No statement of evidence	Tentative statement of evidence discounting the effects of NSP	No statement of evidence	Inconsistent evidence; 14 studies: 7 positive (1 CC, 1 EC, 2 SCS, 3 CS) 2 negative (2 COH) 5 no association (2 COH, 2 SCS, 1 CS)	Insufficient evidence to either support or discount the effectiveness of NSP
HIV	Clear statement of evidence in support of NSP, but conflicting with the primary studies reviewed	Tentative statement of evidence in support of NSP	Clear statement of evidence in support of NSP, but conflicting with the primary studies reviewed	Consistent evidence from multiple weaker studies; 16 studies: 10 positive (2 COH, 4 EC, 2 SCS, 2 CS) 2 negative (2 COH) 4 no association (2 COH, 2 CC)	Tentative evidence to support the effectiveness of NSP
Self-reported injecting risk behaviour	Clear statement of evidence in support of NSP based on consistent evidence from multiple robust studies	Clear statement of evidence in support of NSP	No statement of evidence	Consistent evidence from multiple robust studies; 43 studies: 39 positive (20 COH, 1 EC, 7 SCS, 11 CS) 1 negative (1 CS) 3 no association (1 COH, 2 CS)	Sufficient evidence to support the effectiveness of NSP
(b) Pharmacy NSP					
HCV					No evidence
HIV			Tentative statement of evidence in support of pharmacy NSP providing benefits in addition to dedicated NSP, but conflicting with the primary studies reviewed	Insufficient evidence from few studies with weak designs; 2 studies: 2 positive (1 SCS, 1 CS) 0 negative 0 no association	Insufficient evidence
Self-reported injecting risk behaviour		Tentative statement of evidence in support of pharmacy NSP, based on consistent evidence from a small number of weak studies	Tentative statement of evidence in support of pharmacy NSP providing benefits in addition to dedicated NSP, based on consistent evidence from multiple weaker studies	Consistent evidence from multiple weaker studies; 7 studies 7 positive (2 SCS and 5 CS) 0 negative 0 no association	Tentative evidence

(c) Needle/syringe vending machines				
HCV				No evidence
HIV	No statement of evidence	Statement of evidence in support of vending machines, but conflicting with the primary studies reviewed	Insufficient evidence; 1 study: 0 positive 0 negative 1 no association (1 CS)	Insufficient evidence
Self-reported injecting risk behaviour	Statement of insufficient evidence	Statement of evidence in support of vending machines, but conflicting with the primary studies reviewed	Insufficient evidence; 1 study: 1 positive (1 CS) 0 negative 0 no association	Insufficient evidence
(d) Outreach NSP				
HCV				No evidence
HIV				No evidence
Self-reported injecting risk behaviour				No evidence
(e) Provision of other injecting equipment				
HCV				No evidence
HIV				No evidence
Self-reported injecting risk behaviour	No statement of evidence		Inconsistent evidence from a small number of studies; 4 studies: 2 positive (1 COH, 1 CS) 0 negative 2 no association (2 COH)	Insufficient evidence

COH: cohort; CC: case–control; EC: ecological; SCS: serial cross-sectional; CS: cross-sectional. [a]Findings of primary studies were extracted from reviews. A positive finding refers to a reduction in the stated outcome associated with the intervention; a negative finding refers to an increase in the outcome associated with the intervention, and 'No association' refers to no change in the outcome, or a change that did not reach statistical significance, associated with the intervention. Where a review reported a study finding as positive or negative, it was assumed that the result was statistically significant even if this was not stated explicitly.

evidence from the primary studies identified by the reviews, we concluded that the level of evidence is insufficient (Table 3).

Effects on HIV incidence/prevalence

Three core reviews examined HIV prevalence/incidence, covering 16 primary studies between them. Tilson *et al.* identified four prospective cohort [12,27–29], two case–control [30,31], three ecological [15,32,33] and two serial cross-sectional studies [34,35]; others [36,37], that did not form part of their evidence base, were also included in their discussion. They highlighted the findings of two prospective cohort studies conducted in Montreal and Vancouver [27,28] that reported higher incidence of HIV seroconversion among NSP attenders, but acknowledged that a number of factors could have contributed to, or accounted for, these results including: high-risk individuals being more likely to use NSP (selection bias) and the availability of clean injecting equipment through sources other than NSP (dilution bias). They also made reference to four ecological studies demonstrating declining HIV prevalence/incidence in the context of NSP provision or expansion [15,32,33,36]. Tilson *et al.* concluded that 'the evidence of the effectiveness of [NSE] in reducing HIV prevalence is considered modest, based on the weakness of these study designs'.

Wodak & Cooney stated: 'there is compelling evidence that increasing the availability and utilization of sterile injecting equipment by IDU reduces HIV infection substantially'. This review, however, did not consider separately the effects of NSP on HIV transmission versus IRB: possibly, the evidence of effectiveness of NSP in reducing IRB had a bearing on conclusions drawn with respect to HIV. Of the 38 studies they reviewed, 10 were relevant to HIV [27–30,32,33,38–41]; five had positive findings [32,33,38–40], two had negative findings [27,28] and three did not find an association [29,30,41]. Four of the five positive findings were generated by studies with weaker designs [32,33,39,40].

Gibson *et al.* reviewed studies published up to 1999; all were covered in the later reviews discussed above. Particular consideration of potential bias was given for the studies with negative results, but not for those with protective findings. They concluded that there is 'substantial evidence that syringe exchange programs are effective in preventing [HIV risk behaviour and] HIV seroconversion among IDU'. However, as above, their conclusions were apparently inconsistent with the HIV studies reviewed: two cohort studies showed an increased risk of HIV infection associated with NSP [27,28], one (meta-analysis of cohort data from three studies) showed a protective effect of NSP [38] and three (one cohort and two case–control) showed no association [29–31].

Reflecting on the findings of the primary studies (Table 3; details in Supporting Information, Appendix S3), the most rigorous (cohort and case–control) provided conflicting evidence. The conclusions of Tilson *et al.* are consistent with the equivocal results from cohort and case–control studies. Furthermore, this review undertook the most rigorous evaluation of the primary studies and was the only review to consider HIV incidence/prevalence as a separate outcome. Thus, on the basis of a tentative statement from one core review, supported by consistent evidence from less robust primary studies, we concluded that there is tentative evidence to support the effectiveness of NSP in reducing HIV transmission.

Effects on self-reported injecting risk behaviour

Self-reported IRB has been studied more frequently than biological outcomes (HCV and HIV), and this is reflected in the numbers of primary studies (43 in total) identified by the three core reviews (Supporting Information, Appendix S4).

Tilson *et al.* identified 25 studies [11,35,41–63], 14 of which were longitudinal cohorts, and demonstrated reductions in self-reported needle sharing (lending or borrowing needles/syringes) [11,41–43,45,47,49,53,54,56,57,59,60,62]. They concluded that there was moderate evidence to show that 'multi-component HIV prevention programs that include needle and syringe exchange' are associated with a reduction in self-reported sharing of needles and syringes.

Wodak & Cooney identified 28 primary studies of IRB (needle/syringe borrowing, lending or re-use); among these, there were 24 positive [41–43,45,50,54–56,60,61,64–77], one negative [51], one indeterminate result [78] and two showing no association [48,79]. [Wodak & Cooney cited 29 studies, but one of these (Gibson, D. R. & Flynn, N. M. (2001) AIDS Research Institute, University of California, San Francisco), is not a primary research study.] The reviewers did not formulate any conclusions specifically regarding IRB.

The 23 studies [48,50,51,54–56,60,61,64–67,69–71,74–79] identified by Gibson *et al.* were covered by the other two core reviews, with the exception of Broadhead *et al.* [80] and Hagan *et al.* [81]. Both studies were suggestive of a protective effect of NSP: Broadhead *et al.* noted an increase in the reported re-use and sharing of syringes *after the closure* of an NSP. Hagan *et al.* observed a decline in the proportion borrowing used syringes among NSP attendees (pre- versus post-intervention comparison). The authors concluded that there is substantial evidence that NSPs are effective in preventing HIV risk behaviour among IDUs.

Table 3 lists the studies included within the three core reviews: of 43 studies, 39 were positive and 20 of these

were cohort studies. Thus, based on consistent evidence across multiple robust studies, as well as statements of evidence in support of an effect of NSP on self-reported IRB from two core reviews, we judged there to be sufficient evidence from these reviews to support the effectiveness of NSP in reducing self-reported IRB.

Pharmacy access

Effects on HCV incidence/prevalence

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

Effects on HIV incidence/prevalence

One core review examined the effectiveness of pharmacy access to needles/syringes in reducing HIV prevalence [7]: two relevant studies were identified (Supporting Information, Appendix S5). The first, a serial cross-sectional study conducted in the United Kingdom, observed declines in HIV prevalence among IDUs coinciding with a period of increased access to needles/syringes through pharmacies and NSP [82]. The second, a cross-sectional survey, found a lower HIV prevalence in diabetic IDUs, who had ready access to sterile syringes through pharmacies compared with non-diabetic IDUs [83]. They also referred to two studies as evidence of 'replication of findings': Des Jarlais *et al.* [36] found that pharmacy exchange was a common characteristic of cities that had maintained HIV prevalence rates of less than 5% over the previous 5 years, and De Jong *et al.* [84] observed a low HIV infection rate in Georgia, where syringes were readily available in pharmacies.

Wodak & Cooney 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 a core review, however, the evidence is based on a small number of primary studies with weak designs, and we therefore considered the evidence to be insufficient.

Effects on self-reported injecting risk behaviour

Tilson *et al.* and Wodak & Cooney examined seven studies of the effects of pharmacy access to needles/syringes on IRB (Supporting Information, Appendix S6). Tilson *et al.* identified two studies (both serial cross-sectional) that compared IRB before and after liberalization of the laws permitting syringe sale from pharmacies in New York and Connecticut [85,86]: both found that reports of syringe sharing among IDUs declined. The authors concluded: '. . . A few studies have examined the impact on drug-related HIV risk, and found suggestive evidence of a reduction'. Wodak & Cooney reported the results of a further five cross-sectional studies [83,87–90]: all findings were positive. Given consistent evidence from less robust studies identified within two core reviews, we concluded that the level of evidence is tentative.

Vending machines

Effects on HCV incidence/prevalence

We did not identify any reviews that examined the effects of vending machines on HCV transmission.

Effects on HIV incidence/prevalence

One core review [7] reported the results of a cross-sectional study of IDUs [91], which found that primary users of vending machines were less likely to be HIV positive, although this was not significant after adjustment. Although the 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', this was based on one study of vending machines with a weak design and we therefore concluded that there was insufficient evidence.

Effects on self-reported injecting risk behaviour

Tilson *et al.* and Wodak & Cooney both mentioned a cross-sectional pilot study of vending machines in a German prison [92], although their reporting of the study results differ. Wodak & Cooney reported that significant decreases in needle-sharing subsequent to the introduction of the programme were found, whereas Tilson *et al.* stated that this study showed that IDUs will use vending machines as a source of sterile needles/syringes. Other studies discussed by these reviews looked at the characteristics of vending machine users and the acceptability of machines. Tilson *et al.* concluded that there was insufficient evidence of the effectiveness of vending machines in reducing HIV risk; the conclusions of Wodak & Cooney are as above for HIV.

We identified a supplementary review published after our search was undertaken [93] that cited a paper summarizing experiences with vending machines in prison [94]: the reviewers stated that machines in Germany and Switzerland reduced syringe sharing significantly, although the study designs were not reported.

Given the above conflicting statements of evidence from the core reviews and only one primary study with a weak design and insufficient detail regarding a second paper, we concluded that there is insufficient evidence.

Outreach needle and syringe programmes

Effects on HCV incidence/prevalence, HIV incidence/prevalence and self-reported injecting risk behaviour

No reviews were identified that examined the effects of outreach needle/syringe provision in relation to any of the outcomes.

Provision of sterile drug preparation equipment (other than needles/syringes)

Effects on HCV incidence/prevalence and HIV incidence/prevalence

We did not identify any reviews that examined provision of drug preparation equipment in relation to HCV or HIV outcomes.

Effects on self-reported injecting risk behaviour

Tilson *et al.* identified four relevant studies (Supporting Information, Appendix S7): a cohort [53] and cross-sectional study [52] both found that the provision of drug preparation equipment was associated with declines in equipment sharing, whereas two other cohort studies [11,49] found no association between use of NSP (which presumably provided drug preparation equipment, although this was not stated explicitly) and reductions in equipment sharing. Given that there was no statement of evidence from this core review, and inconsistent evidence from a small number of studies, we concluded that the level of evidence is insufficient.

DISCUSSION

We found insufficient evidence from these reviews to conclude that NSP is effective in preventing HCV transmission among IDUs. The body of evidence was more robust in relation to HIV prevention (i.e. a larger number of studies and more with positive findings); however, we identified discrepancies between core reviews—in the studies they identified, their reports of study designs and findings and the conclusions they drew from their respective bodies of evidence—and we could only conclude that the evidence for the effectiveness of NSP in preventing HIV transmission is tentative. We also found that ecological studies have suggested more consistently a positive impact of NSP on HCV and HIV than individual-level observational studies. In contrast to the findings pertaining to biological outcomes (HCV and HIV), there was sufficient evidence to demonstrate that NSP is effective in reducing self-reported IRB. There was also tentative evidence to suggest that pharmacy provision, in addition to dedicated NSP, is effective in reducing such behaviour. With regard to the remaining interventions (vending machines, outreach NSP, provision of injecting equipment other than needles/syringes), we found no or insufficient evidence to either support or discount their effectiveness in relation to any of the outcomes.

Our findings highlight an absence of reviews that have been undertaken for many of the interventions we considered; for some (vending machines, outreach, provision of other injecting equipment), this probably reflects a lack of primary studies. For NSP and HCV no high-quality (core) reviews have addressed this association specifically, although at least 14 studies had been published to December 2002. *Vis-à-vis* NSP and HIV, at least 16 primary studies examined this association, but previous reviews [7,8] seem to have overstated the evidence in their assessment of these studies [95]. In general, we found that reviews gave more consideration to issues of bias and limitations in studies with negative findings than in studies with positive (protective) findings, and thus may have ascribed less importance to negative findings when synthesizing the evidence.

It is important, however, to emphasize that our conclusions of insufficient/tentative evidence do not equate to evidence for lack of effectiveness for these interventions: these findings may, in part, be attributable to limitations of the primary studies. One of the criticisms of studies investigating NSP effectiveness in preventing BBVs is that they do not measure accurately the coverage or intensity of the intervention delivered (i.e. the amount of injecting equipment distributed) [96]. Many of the NSPs studied had strict limits on the numbers of needles/syringes that could be distributed at any one visit and therefore were probably not providing adequate amounts for clients' needs. Thus, residual sharing, even among IDUs who access NSP regularly, is likely to occur. Modelling studies have predicted reductions in HIV and HCV as NSP coverage is increased or as IRB decreases [97,98]; however, the optimal level of coverage required to reduce HIV and HCV transmission is unknown and will depend on the local context, including the baseline prevalence of HCV/HIV, levels of IRB and injecting networks.

Further consideration of the limitations of the primary studies helps to explain our finding of a discrepancy between the results of ecological studies and individual-level studies (cohort and case–control). First, individual-level, non-randomized studies of IDUs are difficult to design and execute, and thus highly susceptible to bias. In cohort studies, for example, two groups, such as NSP attenders and non-attenders, are usually compared with respect to the outcome. This measurement of the exposure to the intervention has generally been limited because: (i) these groups are 'self-selecting' and thus may be inherently different with respect to characteristics, including injecting risk, that can influence the outcome [96]; and (ii) the distinction between exposed

and unexposed groups is inadequate (for example, unexposed individuals may have access to clean needles/syringes from other sources or exposed individuals may still be engaging in injecting risk despite high uptake of NSP), potentially diluting the effect size [8]. Ecological studies, by contrast, are more likely to report a positive association: because one cannot isolate the effects of a single intervention nor control for confounding factors in an ecological study, such studies may in fact be measuring the impact of several interventions and/or other factors. This is consistent with a recent study that found no independent effect of either NSP or methadone maintenance treatment, but that those participating in both services had a reduced incidence of HIV and HCV [99].

All the evidence for NSP effectiveness is based on observational study designs, i.e. exposure to NSP has not been randomized. Observational studies, as discussed above, are generally at risk of confounding and selection bias. However, it is difficult logistically and ethically to conduct a randomized trial for interventions such as NSP, which have face validity and have already been introduced widely [96]. It has been suggested that community randomized trials, comparing a basic package of services with an enhanced package, are a feasible alternative study design. These trials would randomize participants on a group basis, rather than an individual basis, thereby avoiding some of the biases associated with observational designs [3].

Another methodological issue is that the primary studies might not have been adequately powered to detect an impact of NSP. Few of the reviews addressed this issue in their reporting of the studies and therefore it was usually unclear whether equivocal findings were due to a lack of power or truly represented no association.

The reliance on self-reported risk behaviour is a problem for epidemiological studies examining the effectiveness of harm reduction interventions. Although it has been suggested that self-reported behaviour by heroin users and IDUs can be reliable [100,101], it is uncertain whether this applies to all behaviours. Limitations of self-reported injecting risk may explain our finding of greater strength of evidence for behavioural measures than for biological measures. First, differential reporting of risk behaviour between exposed and unexposed groups could bias measures of the effectiveness of NSP; for example, if IDUs exposed to NSP are more sensitized to the risks of sharing and more reluctant to report this behaviour than unexposed individuals. Secondly, some modelling studies [102] have suggested that the association between IRB and HIV/HCV transmission does not follow a dose–response relationship; rather, a reduction in injecting risk has to surpass a threshold level before changes in HIV/HCV transmission are observed. Consequently, a change in IRB may have no impact on HIV/HCV incidence, thereby limiting the usefulness of IRB as a proxy measure for the effectiveness of an intervention.

We acknowledge that we may have missed potentially relevant reviews by limiting our search to English language reviews and those published from 2000 onwards. To address the latter, we revisited and examined the eight excluded pre-2000 reviews for references relating to our interventions and outcomes of interest, and found only one published study that was missed by the reviews we reviewed [103]. This study was relating to HIV as an outcome and would not have changed our conclusion, as it was a positive finding from a weaker study design (serial cross-sectional).

A limitation of the review of reviews methodology is that we do not know whether gaps in the evidence might be filled by recent primary research. To address this, we undertook a search of the primary English language literature, which identified several recent cohort studies of NSP and HCV/HIV [99,104–106]. Although these studies generally presented improvements upon previous research in terms of larger sample sizes, careful adjustment for potential confounders and improved measurements of NSP use, none found an independent effect of NSP use on HCV or HIV seroconversion. Our conclusions are supported by a recent review undertaken for NICE [107].

Another limitation of our methodology is the reliance on the reviewers' identification of the relevant studies and their accounts of the designs and findings of the primary studies. In considering the primary evidence, we used the study design as a proxy for study quality; however, other factors—for example sample size and recruitment strategy—affect the integrity of a study's results. The likelihood of having missed primary studies is a possibility for HCV, which the core reviews did not set out to examine specifically: we attempted to compensate for this by including the studies identified by a supplementary review that focused on HCV as an outcome. With regard to HIV and injecting risk behaviour, three core reviews examined these outcomes as their primary objective and, given the large number of studies identified for each outcome and the large overlap between the studies identified by each review, we believe that we are likely to have captured the key primary studies for the years searched.

Countries face a challenge in reducing, or maintaining low, prevalence of BBVs among IDUs and good quality research is fundamental to formulating policy on the development of public health interventions. The findings of this review should not be used as a justification to close NSPs or hinder their introduction, given that the evidence remains strong regarding self-reported IRB and given that there is no evidence of negative consequences from the reviews examined here. We recommend a

step change in evaluations of harm reduction interventions so that future evaluations: (i) focus on biological outcomes rather than behavioural outcomes and are powered to detect changes in HCV incidence; (ii) consider complete packages of harm reduction interventions rather than single interventions; (iii) are randomized where possible (preferably at the community level); and (iv) compare additional interventions or increased coverage/intensity of interventions with current availability.

Declarations of interest

None.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Summary of critical appraisal of supplementary reviews not included in the evidence base.
Appendix S2 Summary of results of primary studies of the effectiveness of needle and syringe programmes (NSP) with respect to hepatitis C virus (HCV) prevalence/incidence outcomes, by study design and review.
Appendix S3 Summary of results of primary studies of the effectiveness of needle and syringe programmes (NSP) with respect to human immunodeficiency virus (HIV) prevalence/incidence outcomes, by study design and review.
Appendix S4 Summary of results of primary studies of the effectiveness of needle and syringe programmes (NSP) with respect to self-reported injecting risk behaviour outcomes, by study design and review.
Appendix S5 Results of primary studies of the effectiveness of pharmacy access to needle and syringes with respect to human immunodeficiency virus (HIV) prevalence/incidence outcomes by study design.
Appendix S6 Summary of results of primary studies of the effectiveness of pharmacy access to needle and syringes with respect to self-reported injecting risk behaviour outcomes, by study design and review.
Appendix S7 Summary of results of primary studies of the effectiveness of providing sterile drug preparation equipment with respect to self-reported injecting risk behaviour outcomes, by study design.

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