






Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis

Lucy Platt¹ , Silvia Minozzi², Jennifer Reed³, Peter Vickerman⁴ , Holly Hagan³, Clare French⁴, Ashly Jordan³, Louisa Degenhardt⁵ , Vivian Hope⁶ , Sharon Hutchinson⁷, Lisa Maher⁸ , Norah Palmateer⁷ , Avril Taylor⁹, Julie Bruneau¹⁰ & Matthew Hickman⁴ 

Centre for Research on Drugs and Health Behaviour, Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London, UK,¹ Department of Epidemiology, Lazio Regional Health Service, Rome, Italy,² New York University, College of Nursing, New York, NY, USA,³ School of Social and Community Medicine, University of Bristol, Bristol, UK,⁴ National Drug and Alcohol Research Centre, University of New South Wales, Randwick, Australia,⁵ Public Health Institute, Liverpool John Moores University, Liverpool, UK,⁶ School of Health and Life Sciences, Glasgow Caledonian University, Glasgow and Health Protection Scotland, Glasgow, UK,⁷ Kirby Institute, University of New South Wales, Sydney, Sydney, Australia,⁸ School of Social Sciences, University of West of Scotland, Paisley, UK⁹ and Department of Family and Emergency Medicine, University of Montreal, Montreal, Canada¹⁰

ABSTRACT

Aims To estimate the effects of needle and syringe programmes (NSP) and opioid substitution therapy (OST), alone or in combination, for preventing acquisition of hepatitis C virus (HCV) in people who inject drugs (PWID). **Methods** Systematic review and meta-analysis. Bibliographic databases were searched for studies measuring concurrent exposure to current OST (within the last 6 months) and/or NSP and HCV incidence among PWID. High NSP coverage was defined as regular NSP attendance or $\geq 100\%$ coverage (receiving sufficient or greater number of needles and syringes per reported injecting frequency). Studies were assessed using the Cochrane risk of bias in non-randomized studies tool. Random-effects models were used in meta-analysis. **Results** We identified 28 studies ($n = 6279$) in North America (13), United Kingdom (five), Europe (four), Australia (five) and China (one). Studies were at moderate (two), serious (17) critical (seven) and non-assessable risk of bias (two). Current OST is associated with 50% [risk ratio (RR) = 0.50, 95% confidence interval (CI) = 0.40–0.63] reduction in HCV acquisition risk, consistent across region and with low heterogeneity ($I^2 = 0$, $P = 0.889$). Weaker evidence was found for high NSP coverage (RR = 0.79, 95% CI = 0.39–1.61) with high heterogeneity ($I^2 = 77\%$, $P = 0.002$). After stratifying by region, high NSP coverage in Europe was associated with a 56% reduction in HCV acquisition risk (RR = 0.44, 95% CI = 0.24–0.80) with low heterogeneity ($I^2 = 12.3\%$, $P = 0.337$), but not in North America (RR = 1.58, $I^2 = 89.5\%$, $P < 0.001$). Combined OST/NSP is associated with a 74% reduction in HCV acquisition risk (RR = 0.26, 95% CI = 0.07–0.89, $I^2 = 80\%$, $P = 0.007$). According to Grades of Recommendation Assessment, Development and Evaluation (GRADE) criteria, the evidence on OST and combined OST/NSP is low quality, while NSP is very low. **Conclusions** Opioid substitution therapy reduces risk of hepatitis C acquisition and is strengthened in combination with needle and syringe programmes (NSP). There is weaker evidence for the impact of needle syringe programmes alone, although stronger evidence that high coverage is associated with reduced risk in Europe.

Keywords Cochrane, harm reduction, hepatitis C, incidence, meta-analysis, needle and syringe programmes, opioid substitution therapy, review, substance use.

Correspondence to: Lucy Platt, Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, UK. E-mail: lucy.platt@lshtm.ac.uk

Submitted 11 May 2017; initial review completed 19 July 2017; final version accepted 21 August 2017

INTRODUCTION

Hepatitis C virus (HCV) is a major global public health concern, with approximately 114.9 (91.9–148.7) million

people having antibodies to HCV [1], 3–4 million people newly infected each year and 350 000 deaths occurring annually [2,3]. People who inject drugs (PWID) are the key at risk group in most high-income countries, and in

most countries more than half of PWID have been infected with HCV [4].

Evidence shows that injecting with needles and syringes used previously by someone else is the main risk factor for infection with HIV and HCV among PWID [5,6]. Additional risks for HCV acquisition in this population include sharing drug preparation containers, filters, rinse water and backloading (a method of sharing drugs by transferring them from the needle of one syringe into the barrel of another) [5,6]. The provision of sterile injecting equipment through needle and syringe programmes (NSP) and enrolment in opioid substitution treatment (OST) are among the primary interventions for reducing HCV and HIV transmission among PWID. NSPs provide sterile needles and syringes and other injecting equipment to PWID via fixed-sites, outreach, peer networks, vending machines and pharmacies. By maximizing the amount of sterile injecting equipment (including syringes, cookers, cottons) in circulation, the time infected equipment remains in circulation decreases and the proportion of unsafe injections or the need to share equipment to prepare drugs reduces [7]. OST is prescribed to dependent opioid users to diminish the use and effects of illicitly acquired opioids and reduce the frequency of injection and exposure to unsafe injecting practices [8]. The most commonly prescribed forms of OST are opiate agonist treatments—methadone maintenance therapy and buprenorphine maintenance treatment. NSPs and OST are often the first point of service contact for PWID and so they provide referrals and support to other social and welfare services.

There is good evidence that NSP and OST in combination reduce injecting risk behaviours and some evidence of an impact on HIV incidence. However, evidence for their impact on HCV incidence among PWID is limited [9–15]. Recent reviews have estimated a moderate effect of NSPs in reducing HIV transmission by 48% [95% confidence interval (CI) = 3–72%] and strong evidence for OST reducing HIV transmission by 54% (95% CI = 33–68%) [16,17]. Previous evidence syntheses for use of NSPs have focused primarily on HIV as the main outcome and, as a consequence, failed to include all the available evidence on HCV [8,11,13,18]. Another review that measured the effect of NSP use did not include a meta-analysis due to heterogeneity in the measurement of NSP exposure, and focused on evidence from North America, limiting the generalizability of findings to other settings, including Europe [19]. An analysis of pooled data examined the effect of NSP coverage on HCV incidence showed that high coverage of NSP ($\geq 100\%$ of injections with a sterile syringe) or receipt of OST either currently or within the past 6 months can each reduce HCV infection risk by 50% and in combination by 80%. The small number of incident HCV cases meant that the

efficacy estimate for 100% NSP among those not on OST was weak [20].

Evidence of the effect of NSP with and without OST on HCV incidence is inconclusive [11]. There is a need to strengthen this existing evidence base, including a more refined measure of coverage of NSP that accounts for frequency and the degree to which the NSP meets individuals' requirement for needles and syringes in order to inform interventions to reduce the burden of HCV. We undertook a Cochrane Systematic Review and meta-analysis of unpublished and published studies. Our primary objective was to assess the impact of NSPs with and without OST on the incidence of HCV infection among PWID. Our secondary objective involved estimating any differential effect of variables including duration of treatment, geographical setting, study setting (i.e. community, or treatment) and sample characteristics (such as age, sex, experience of prison, homelessness, use of stimulant injection). Full methods are reported in the Cochrane Review [21].

METHODS

Search

We carried out two separate systematic search strategies. The first identified studies examined directly the impact of OST or NSP in relation to HCV incidence. The second focused on identifying cohort studies that reported HCV incidence among PWID. These studies were examined to identify whether they reported the impact of OST or NSP in relation to HCV transmission in secondary analyses. Where no measure was reported, authors of studies were contacted and asked if OST or NSP exposures were measured, and if so to provide unpublished data. The full search terms are reported in the Cochrane Review [21]. Multiple databases were included up to March 2017 [Medline, PsycInfo, Embase, Cochrane Drug and Alcohol Group Specialized Register, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, Global Health, Cinahl (EBSCO Host), Web of Science], as well as conference abstracts of the International HIV/AIDS Society and the European Association for the Study of Liver conference and the International Symposium on Hepatitis Care in Substance Users. Grey literature was searched from European Monitoring Centre on Drugs and Drug Addiction and the European Centre for Disease Control.

Study selection

Two reviewers screened full text copies of relevant articles to determine whether they met eligibility criteria. There was no language restriction.

Data extraction and analysis

For the full data extraction form see the full Cochrane Review [21], which included study design and recruitment; sample characteristics; intervention; outcome measure and intervention effect. Data were double-extracted.

Eligibility criteria

We included all observational (prospective and retrospective cohorts, cross-sectional surveys and case-control studies) or experimental studies that: (a) measured exposure to either intervention against no intervention or a reduced exposure and reported HCV incidence as an outcome; and (b) reported a minimum of two seroconversions. We included studies that measured incidence of HCV in PWID via repeated testing, such as detection of HCV RNA-positive among HCV-negative participants. OST exposure was measured through self-report, defined as the use of prescribed methadone or buprenorphine within the last 6 months. High NSP coverage was defined as obtaining 100% of needles and syringes from a safe source, reporting obtaining $\geq 100\%$ of sterile needles and syringes per injecting frequency, regular attendance at least once per week at an NSP or obtaining most needles and syringes from an NSP during the last 6 months. We excluded studies measuring HCV incidence using self-reported data and those conducted in prison settings.

Risk of bias

We assessed the quality of included studies through the Cochrane risk of bias assessment tool for non-randomized studies of interventions [22]. This assesses studies according to seven domains: confounding; selection bias; measurement of interventions; departures from intervention; missing data; measurement of outcomes; and selection of reported results, to give an overall risk of bias classified into four categories of low to critical. We decided that minimum adjustment for confounding should include time since first injection or age and injecting frequency at baseline. We assessed the overall quality of the evidence for the primary outcome using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system [23]. We used funnel plots (plots of the effect estimate from each study against the sample size or effect standard error) to assess the potential for bias related to the size of the studies, which could indicate possible publication bias.

Summary measures and synthesis of results

We used a random-effects meta-analysis for the primary analyses, allowing for heterogeneity between and within studies. Effect estimates derived from studies adjusting for

confounders as well as those that did not (unadjusted estimates) were pooled in separate meta-analyses. We examined heterogeneity with the I^2 statistic and identified reasons for heterogeneity using univariable random-effects meta-regression to compare subgroups by geographical region of study; site of recruitment; proportion of female participants; main drug injected; type of NSP; frequency of injecting; and study design. We used sensitivity analyses to determine to what extent the overall intervention effect was changed by: the inclusion of studies at severe or unclear risk of bias; the inclusion of studies that did not adjust for confounders; exclusion of unpublished data sets; and excluding cross-sectional studies that measured intervention effect at baseline only.

RESULTS

The numbers of studies identified, reviewed and selected and the reasons for exclusion for both searches are shown in Fig. 1. We identified 21 published studies that directly included measures of the impact of exposure to either OST or NSP on HCV transmission [12,24–43]. In addition, we identified 11 eligible prospective studies that measured HCV incidence and contacted the authors of these papers [44–54]. Of these, unpublished data were obtained from cohort studies in Montreal (Canada) [Bruneau (unpublished)]; Baltimore (USA) [Mehta (unpublished)], San Francisco (USA) [Page (unpublished)], Sydney and Melbourne (Australia) [55] [Maher (unpublished)], London (UK) [Judd (unpublished)] and three cross-sectional surveys in Bristol, Birmingham and Leeds (UK) [Hope (unpublished)]. In total we included 1736 HCV incident infections and 6513.04 person-years of follow-up. Overall HCV incidence ranged between 5.9 and 42 cases per 100 person-years throughout the studies.

Description of studies

Table 1 summarizes the characteristics of the included studies undertaken in the United States ($n = 8$), UK ($n = 5$), Canada ($n = 5$), Australia ($n = 5$) and one study each in the Netherlands, France, Italy, Spain and China. Twenty-one of the included studies reported the impact of OST [12,24,25,30,31,34,36–38,40–43,55,56] [Bruneau (unpublished), Mehta (unpublished), Page (unpublished), Maher (unpublished), Judd (unpublished), Hope (unpublished)]. Seventeen studies reported the impact of NSP [12,26–29,32,33,35,39,41,43] [Bruneau (unpublished), Mehta (unpublished), Page (unpublished)]. Four studies assessed the impact of combined NSP with OST [12,29,32] [Bruneau (unpublished)]. There were no experimental studies. Sample size varied from 46 to 2788, with participants recruited through street outreach, respondent-driven sampling or service providers. Twenty-

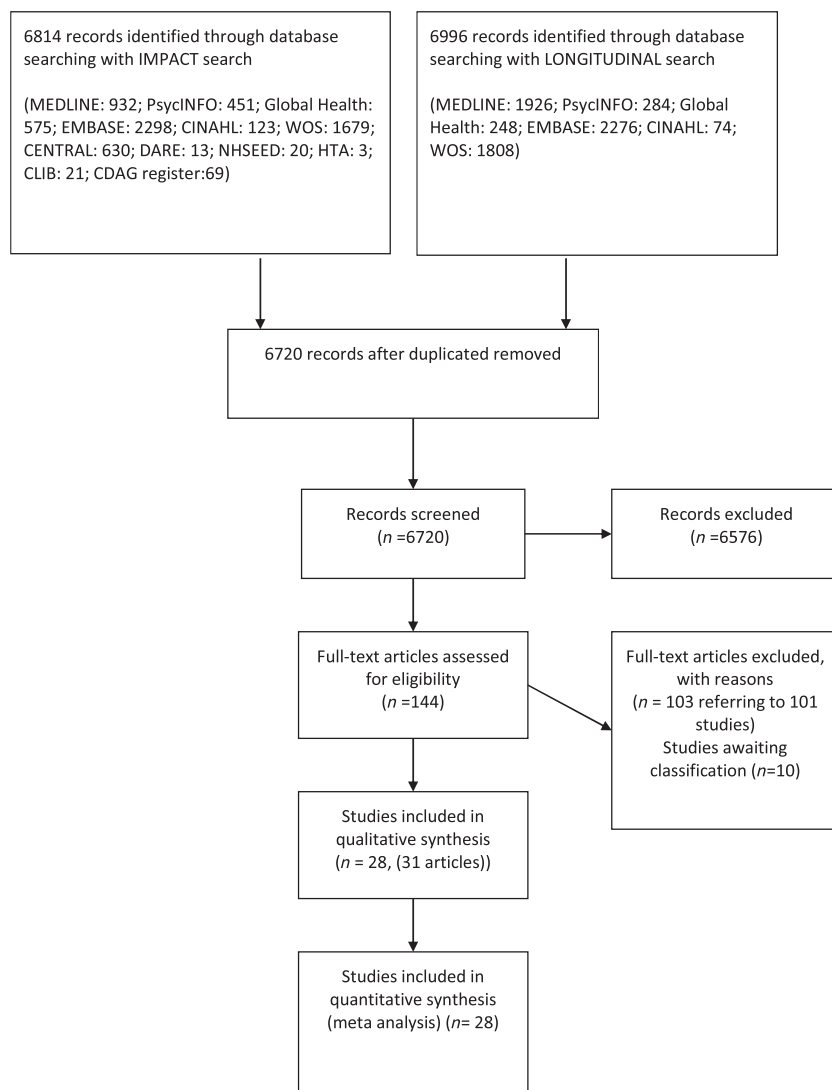


Figure 1 Flow-chart of included studies

five studies reported the sex of participants, of which 32% (range = 2.8–55.9%) was the mean proportion of women across the studies. Three were excluded from this analysis, as they published only unadjusted estimates of life-time use of OST versus never using OST [36,41,42].

Risk of bias

Risk of bias decisions are summarized in last column of Table 1 and in the Supporting information, Table S1. Only two studies were judged at moderate overall risk of bias [38,40], 17 studies were judged as serious overall risk of bias [24,26–33,37,39,41,43] [Bruneau (unpublished), Maher (unpublished)] and seven were at critical risk [25,34–36,42,55] [Judd (unpublished)]. For two studies [Mehta (unpublished), Page (unpublished)], we did not have enough information to make a judgement.

Current use of opioid substitution therapy

We pooled data from a total of 17 studies that measured current OST [12,24,25,30–32,34,37,38,40,41,43], including five unpublished estimates [55] [Bruneau (unpublished), Maher (unpublished), Judd (unpublished), Hope (unpublished)]. Twelve studies (6361 participants) presented adjusted measures, on which the primary analyses were focused [24,30,31,34,38,40,43,56] [Bruneau (unpublished), Mehta (unpublished), Maher (unpublished), Judd (unpublished)]. Random-effect meta-analysis of multivariable estimates showed that OST was associated with a 50% reduction in the risk of HCV infection [risk ratio (RR) = 0.50] with little heterogeneity between studies ($I^2 = 0$, $P = 0.889$).

This effect was maintained when the analysis was limited to exclude two studies judged to be at critical risk of bias [34] [Judd (unpublished)] and one study where

Table 1 Characteristics and risk of bias of included studies.

Author	Design	Sex	Age (years)	n	HCV/ 100 py	New HC/py	Interventions	Effect estimate	Confounders included in analysis	Risk of bias
Aitken, 2015 [55]	Cohort	31.7%	29.4 (median)	98	8.6	17/196	OST current use of OST in last month	HR 0.8 (0.3–2.0)	–	C
Australia Bruneau, 2015	Cohort	NA	37.4% < 30	285	17.3	102/589.35	OST current use of OST in last 6 months 3	HR 0.74 (0.47–1.16) AOR = 0.74 (0.47–1.16)	Years injecting, numbers of injection in past month	S
[Bruneau unpublished]							NSP (high; high NSP (>100% coverage)	HR 0.77 (0.5–1.19) AOR = 0.7 (0.45–1.09)	Years injecting, numbers of injection in past month	
Canada							Combined NSP/OST	HR 0.63 (0.37–1.07)	Years injecting, numbers of injection in past month	
							OST in last 6 months and high (> 100% coverage)	AOR = 0.59 (0.35–1.01)	Years injecting, numbers of injection in past month	
Craine, 2009 [24]	Cohort	29.0%	27.2 (mean)	286	5.9	17/287.33	OST current In OST at interview	HR 0.37 (0.17–0.8) AOR = 0.39 (0.18–0.86)	Years injecting, numbers of injection in past month	
Wales							OST other ^a (high dose ≥ 60 mg)	HR 1.15 (0.7–1.89)	Years injecting, numbers of injection in past month	
Crofts, 1997 [25]	Cohort*	41.9%	29.2 (mean)	73	22.2	13/85.4	OST other ^a (low dose < 60 mg)	AOR = 1.06 (0.64–1.77)	Region, homelessness, sharing equipment, sharing needles (all in last 12 months)	S
Australia							OST current	IRR 0.27 (0.095–0.77) AOR = 0.34 (0.12–0.99)	–	
							In OST at interview	IRR 1.8 (0.37–4.77)	–	
Hagan, 1995 [26]	Case– control	45.0%	24% < 25	46		20/NA	Continuous OST during follow-up	IRR 0.66 (0.55–0.79)	–	
USA							OST other ^a (interrupted use)	OR 0.12 (0.026–0.55) AOR = 0.14 (0.03–0.62)	Sex, age, ethnicity, and duration of injection	S
Hagan, 1999 [27]	Cohort	38.0%	19% < 25	187	20.8	26/209	NSP (low) ^a Ever used NSP	RR 1.42 (0.64–3.13) AOR = 1.31 (0.79–2.2)	Onset of injection < 1 year from baseline interview, sharing at baseline	S
USA							NSP (high) current regular NSP use			
							NSP (low) ^a			

(Continues)

Table 1. (Continued)

Author	Design	Sex	Age (years)	n	HCV/ 100 py	New HC/py	Interventions	Effect estimate	Confounders included in analysis	Risk of bias
Holtzman, 2009 [28] USA	Cohort	38.0%	28% < 21	1288	139/NA	NSP (low) ^a NSP use in the last 6 months	OR	1.72 (0.71–4.19) AOR = 2.59 (0.79–8.5)	Onset of injection < 1 year from baseline interview, sharing at baseline	S
Hope, 2011 [29] UK	Cross- sectional	23.0%	17% < 25	119	14/35	NSP alone (high); high NSP (≥ 100% coverage NSP/OST combined OST in last 6 months and high (> 100% coverage)	IRR	1.22 (0.86–1.74) AOR = 1.49 (0.96–2.29)	Duration of injection, shared needles/ paraphernalia; daily injecting; injecting with others	S
Hope, 2015 [Hope (unpublished)] UK	Cross- sectional	25.0%	27.4	919	30.3	NSP high NSP coverage (≥ 100% coverage) (low NSP, no OST) OST current and low (< 100% coverage)	IRR	0.11 (0.024–0.53) IRR 0.17 (0.12–1.54)	–	S
Judd, 2015 [Judd (unpublished)] UK	Cohort	29.0%	27.4	149	42	Use of OST in last 4 weeks Birmingham: Bristol: Leeds NSP high NSP coverage (≥ 100% coverage)	OR	1.55 (0.14–17.4) 0.24 (0.05–1.16) 1.31 (0.08–21.5)	–	C
					49/116.7	OST current Use of methadone in last 6 months	RR	0.99 (0.21–4.59) 0.73 (0.04–11.98) 0.55 (0.05–6.26) 0.47 (0.16–1.33) AOR = 0.49 (0.17–1.47)	Duration and frequency of injecting	C

(Continues)

Table 1. (Continued)

Author	Design	Sex	Age (years)	n	HCV/ 100 py	New HC/py	Interventions	Effect estimate	Confounders included in analysis	Risk of bias
Lucidarme, 2004 [30] France	Cohort	17.6%	26.9 (mean)	165	11	16/178.4	OST current No definition	RR 0.34 (0.11–0.99) AOR = 0.41 (0.12–1.4)	Sex, geographical region, condom use, daily injection of cocaine, duration of injecting, sharing paraphernalia (cotton, cup, water)	S
Maher, 2015 [Maher (unpublished)] Australia	Cohort	38.0%	24 (median)	368	24.9	53/212.86	OST current OST in last 6 months NSP (low) ^a	HR 0.43 (0.24–0.75) AOR = 0.46 (0.25–0.84) HR 1.86 (1.05–3.28) AOR = 0.15 (0.88–2.78)	Duration and frequency of injecting Duration and frequency of injecting	S
Mehra, 2015 [Mehra (unpublished)] USA	Cohort		34 (median)	324	17.8	27/166.5	OST current OST in last 6 months NSP (low) ^a	IRR 0.6 (0.14–2.51) AOR = 0.82 (0.19–3.54) IRR 1.38 (0.17–11.5) AOR = 0.76 (0.1–5.67)	Years injecting, daily injection, age (for whole cohort) Years injecting, daily injection, age (for whole cohort)	N/I
Nolan, 2014 [31] Canada	Cohort	30.4%	23–34	1004	6.32	184/2108.4	OST current MMT in last 6 months	OR 0.67 (0.45–0.99) AOR = 0.47 (0.29–0.76)	Unstable housing, cocaine, heroin or methamphetamine injection, cohort and year of recruitment, follow-up time	S
Page, 2015 [Page (unpublished)] USA	Cohort	21.7%	33.7 (mean)	552	25.1	171/681.3	NSP (low) ^a NSP use in the last 3 months	HR 2.82 (1.84–4.34) AOR = 2.62 (1.71–4.02)	Years injecting, age, sex, race, homeless, and recent jail	N/I
Palmaateer, 2014 [32]	Cross- sectional	27.5%	34 (mean)	2788	7.3	392/602.7	OST current; OST at time of survey; low NSP (< 200%)	OR 0.51 (0.29–0.9) AOR = 0.52 (0.23–1.18)	Survey year, homelessness or stimulant injection in last 6 months, time since onset of injecting	S

(Continues)

Table 1. (Continued)

Author	Design	Sex	Age (years)	n	HCV/ 100 py	New HC/py	Interventions	Effect estimate	Confounders included in analysis	Risk of bias
Scotland							NSP (high) high NSP (> 200%) coverage and not on OST; OST/NSP combined; high NSP (> 200%) coverage	OR 0.26 (0.08–0.88) AOR = 0.18 (0.04–0.87)	Survey year, homelessness in last 6 months, stimulant injection in last 6 months, time since onset of injecting	
							OST/NSP combined; high NSP (> 200%) coverage	OR 0.24 (0.1–0.6) AOR = 0.05 (0.01–0.18)	Survey year, homelessness in last 6 months, stimulant injection in last 6 months, time since onset of injecting	
							OST/NSP combined; low NSP (< 200%) coverage	OR 0.48(0.27–0.95) AOR = 0.59 (0.26–1.35)	Survey year, homelessness in last 6 months, stimulant injection in last 6 months, time since onset of injecting	
Patrick, 2001 [33] Canada	Cohort	30.3%	34 (median)	155	29.1	62/207.95	NSP (high) Attendance at least 1 per week at NSP in last 6 months	HR 3.69 (2.12–6.43) AOR = 2.56 (1.37–6.79)	Sex, injection of cocaine or speedballs, frequency of injection	S
Rezza, 1996 [34] Italy	Case– control	2.8%	21% > 28	106	28.6	21/73.4	OST current OST in last 6 months	OR AOR = 0.34 (0.10–1.11)	Female gender, age, duration of drug use, injection of cocaine	C
Ruan, 2007 [36] China	Cohort		44% < 28	86	33.0	47/258	OST other ^a Ever used OST	RR 0.5 (0.2–1.3)	–	C
Roy, 2007 [35] Canada	Cross- sectional	27.0%	31.8 (mean)	359	27.1	94/267	NSP (low) ^a Use of NSP in last 6 months	HR 3.02 (95% CI NA)	Age, injection experience, injection with used needle, drug most often injected, sex work, district of recruitment	C
Spittal, 2012 [37] Canada	Cohort	53.4%	23 (median)	148	11.6	45/338.6	OST current In OST at time of survey (yes/no)	HR 2.11 (0.83–5.37)	–	S
Thiede, 2000 [38]	Cohort	48.9%	5.4% < 25	80	8.75	7/80	OST current Continuous use during follow-up	OR 0.3 (0.01–3.6) AOR = 0.4 (0.0–4.2)	Injected at follow-up, pooled money to buy drugs, injected with used needles, backloading	M

(Continues)

Table 1. (Continued)

Author	Design	Sex	Age (years)	n	HCV/ 100 py	New HC/py	Interventions	Effect estimate	Confounders included in analysis	Risk of bias
USA							OST other ^a	OR 0.8 (0.01–3.6)	Injected at follow-up, pooled money to buy drugs, injected with used needles, backloading	
Thorpe, 2002 [39]	Cohort	39.7%	52% 18–22 years	353	10	29/327.2	Interrupted left treatment at least 1 during follow up NSP (low) ^a Use of NSP in last 6 months	AOR = 1.2 (0.2–7.3) HR 1.29 (0.6–2.79)	Receptively sharing syringes, sharing cookers, cotton filters, rinse water or backloading	S
Tsui, 2014 [40]	Cohort	31.9%	16% 15–18	552	25.1	145/680	OST current and other Opiate agonist therapy maintenance treatment in last 3 months; OST other ^a Opiate agonist detoxification in last 3 months	HR 0.31 (0.14–0.65) AOR = 0.39 (0.18–0.87)	Age, duration of injection drug use, sex, ethnicity, homelessness or incarceration in past 3 months	M
Vallejo, 2015 [41]	Cohort	27.3%	40% ≥ 25	137	39.8	42/105.4	OST other ^a Life-time use of OST	IRR 0.9 (0.5–1.6)	Age, duration of injection drug use, sex, ethnicity, homelessness or incarceration in past 3 months	S
Spain										
Van Den Berg, 2007 [12]	Cohort	33.0%	31.4 (median)	168	6.78	57/598.56	OST current; OST ≥ 60 mg methadone daily NSP alone; High NSP (100% coverage) Combined OST/NSP high NSP Combined OST/NSP low NSP	IRR 0.67 (0.39–1.13) IRR 0.62 (0.3–1.3)	Duration of injection, HIV status of steady partner Duration of injection, HIV status of steady partner	S
Netherlands							OST other ^a (high dose) OST other ^a (low dose) OST other ^a Ever used OST (yes/no)	RR 0.15 (0.05–6-0.4) AOR = 0.36 (0.13–1.03) RR 1.04 (0.53–2.05) AOR = 1.17 (0.59–2.31) RR 0.68 (0.39–1.13) RR 0.58 (0.3–1.15) OR 1.08 (0.37–3.17)		C
Van Beek, 1998 [42] Australia	Cohort*	55.9%	61.5% < 20	152	20.9	26/148.2				

(Continues)

Table 1. (Continued)

Author	Design	Sex	Age (years)	n	HCV/ 100 py	New HC/py	Interventions	Effect estimate	Confounders included in analysis	Risk of bias
White, 2014 [43] Australia	Cohort	25.0%	27 (median)	127	7.9	20/215.2	OST; OST last 6 months	HR Heroin users 0.65 (0.15– 2.94) AOR = 0.56 (0.12– 2.56) Amphetamine users 0.14 (0.04–0.51) AOR = 0.51(0.18–0.04)	Sex, ethnic background, age, daily or more frequent injecting, receptive syringe sharing and not receiving OST while reporting heroin or other opioids as the main drug injected	S
White, 2014 [43] Australia							NSP (low) ^a Accessed NSP in last 6 months;	HR 1.0 (0.36–2.86)	–	–

HR = hazard ratio; OR = odds ratio; AOR = adjusted odds ratio; RR = risk ratio; IRR = incident rate ratio; HCV = hepatitis C virus; OST = opioid substitution therapy; py = person-years; NSP = needle and syringe programme; NA = not available.
^aNot reported in the primary analysis. Risk of bias: C = critical; S = serious; M = moderate; L = low; N/I = no information, HCV incidence for cross-sectional surveys calculated as $I = [(365/T)/n] / [(N-n) + (365/T)/n]$, where I = Incidence, T = estimated mean duration of the HCV antibody-negative/RNA-positive 'window period' = 75 days, n = number of HCV incident infections (HCV antibody-negative and HCV RNA-positive) and N = number of susceptibles (HCV antibody-negative); NA = not available. *Signifies retrospective follow-up.

there was insufficient information to give an overall risk of bias assessment [Mehta (unpublished)] (RR = 0.51, $I^2 = 0\%$, $P = 0.68$). The intervention effect was unchanged when the analysis excluded two cross-sectional studies [34,56] that reported baseline measures of effect only (3367 participants, RR = 0.51, $I^2 = 0.0\%$, $P = 0.73$). The intervention effect strengthened when estimates from four unpublished data sources [Bruneau (unpublished), Mehta (unpublished), Maher (unpublished), Judd (unpublished)] were excluded (RR = 0.42, $I^2 = 0\%$, $P = 0.96$). The intervention effect weakened slightly, and heterogeneity increased if all unadjusted estimates were pooled from 16 studies (10 647 participants, RR = 0.57, $I^2 = 32.4$, $P = 0.09$ (Supporting information, Figs S1–S4).

We found no evidence that effectiveness varied by geographical region (Fig. 2) or study design. We did find evidence of differential impact in the proportion of female participants in the sample. With each 10% increase of female participants in sample, the effect of intervention exposure was reduced (ratio of RRs = 1.59) (Table 2).

High coverage of needle and syringe programmes

Five studies (3530 participants) reported adjusted measures of high NSP coverage compared to no or low NSP coverage and HCV incidence [27,29,33,56], including one unpublished data set [Bruneau (unpublished)]. Random-effect meta-analysis showed weak evidence of an effect of high coverage of NSP on the reduction in the risk of HCV infection (RR = 0.79) and high heterogeneity between studies ($I^2 = 77\%$, $P = 0.002$). Random-effects meta-analysis of seven studies (6455 participants) that presented unadjusted estimates show that the weak intervention effect was unchanged (RR = 0.77, $I^2 = 79\%$, $P = 0.000001$) (Fig. 3). Evidence of any intervention effect became weaker after excluding the unpublished data set [Bruneau (unpublished)] (RR = 0.77, $P < 0.001$). No NSP studies were rated critical on the risk of bias tool (Supporting information, Fig. S5).

High NSP coverage was associated with a 56% reduction in HCV acquisition risk (RR = 0.44) with low heterogeneity ($I^2 = 12.3\%$, $P = 0.337$) when pooling unadjusted estimates from Europe, but no effect for North America and high heterogeneity (RR = 1.58, $I^2 = 89.5\%$, $P = 0 < 0.001$) (Fig. 3). This pattern was maintained in the pooling of adjusted estimates, with a reduction in HCV acquisition associated with high NSP coverage in Europe (RR = 0.24) and low heterogeneity ($I^2 = 0$, $P = 0.66$), but not in North America (RR = 1.58), and high heterogeneity ($I^2 = 89.5$, $P < 0.001$) (Fig. 4). The meta-regression analysis also showed evidence of differential impact by region comparing North America with Europe (ratio of RRs = 3.73, $P = 0.06$) (Table 2). Univariable meta regression analysis also suggested some

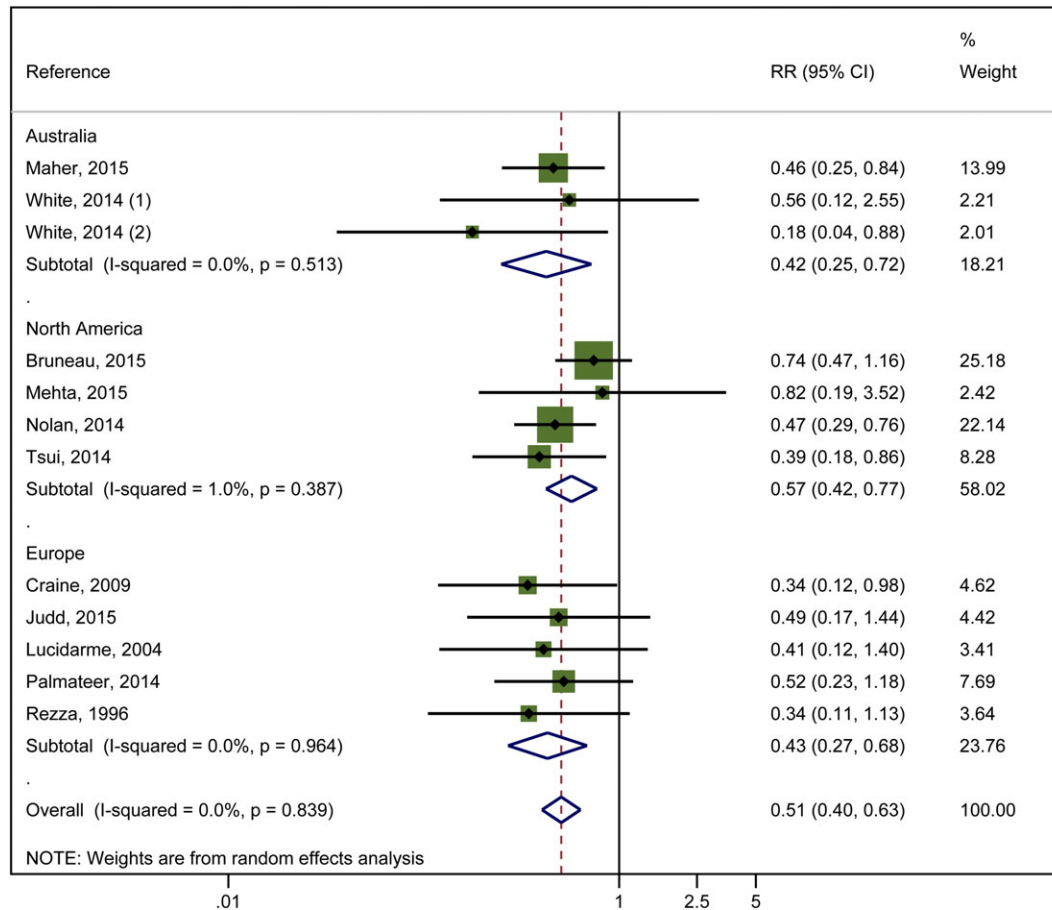


Figure 2 Impact of current use of opioid substitution therapy (OST) versus no OST on hepatitis C virus (HCV) incidence from studies adjusted for confounders and stratified by region. [Colour figure can be viewed at wileyonlinelibrary.com]

association between high coverage of NSP and study design (ratio of RRs = 3.5, P -value = 0.087 comparing cross-sectional with longitudinal study design); this was reduced when adjusted for geographical region (ratio of RRs = 1.7, P -value = 0.577). We found no evidence of differential impact by proportion of female participants in the sample, homelessness or experience of prison.

Combination interventions: OST and high/low NSP

Random-effects meta-analysis pooling adjusted measures from three studies [12,56] [Bruneau (unpublished)] (3241 participants) showed that combined use of OST and high coverage of NSP was associated with a 74% risk reduction in HCV acquisition (RR = 0.26, I^2 = 80% P = 0.007). This effect was maintained when pooling unadjusted measures from four studies (3356 participants, RR = 0.29, I^2 = 64.4% P = 0.038) (Fig. 5).

The effect of exposure to OST and low coverage of NSP from pooling adjusted measures from two studies (2956 participants) was weaker (RR = 0.87, I^2 = 36.0% P = 0.67). This effect remained unchanged when pooling unadjusted measures from three studies

(3071 participants) (RR = 0.76, I^2 = 29.6% P = 0.24) (Fig. 6).

Publication bias

A funnel plot of 13 estimates (12 studies) and Egger's bias coefficient (-0.87 , P = 0.106) suggested no evidence of publication bias in studies of current OST exposure. A funnel plot of five estimates (five studies) and Egger's bias coefficient (-1.65 , P = 0.54) suggested little evidence of publication bias in studies of high NSP coverage, although this analysis included only five studies and may be under-powered (Supporting information, Figs S6,S7).

Quality of evidence

Evidence for current use of OST is considered to be low quality because it was derived from observational studies with serious risk of bias. Evidence for combined use of OST and NSP was also considered to be low quality. Evidence for the effect of NSP was judged to be very low quality (because of the high heterogeneity and smaller

Table 2 Univariable meta-regression analysis for studies measuring impact of current use of opioid substitution therapy (OST) and high-coverage needle and syringe programmes (NSP) on hepatitis C virus (HCV) incidence.

Variable	Current use of OST						High coverage of NSP					
	Studies	Univariable rate ratio (95% CI)	Ratio of rate ratios 95% CI	P-value	Tau-squared	I ²	Studies	Univariable rate ratio (95% CI)	Ratio of rate ratios (95% CI)	P-value	Tau-squared	I ²
Geographical region												
Europe	8	0.51 (0.37–0.70)	1.0 (Ref)				5	0.44 (0.24–0.80)	1.0 (Ref)			
Australia	5	0.55 (0.28–1.11)	1.12 (0.52–2.41)									
North America	6	0.69 (0.44–1.08)	1.42 (0.73–2.78)	0.53	0.1032	33.7%	3	1.58 (0.57–4.42)	3.73 (0.95–14.7)	0.057	0.41	71.7%
Site of recruitment												
Service attenders	12	0.67 (0.49–0.92)	1.0 (ref)				3	0.67 (0.28–1.59)	1.0 (Ref)			
Community	7	0.49 (0.33–0.73)	0.73 (0.42–1.27)	0.256	0.06	32.3%	5	0.82 (0.29–2.32)	0.76 (0.12–4.88)	0.74	0.89	79.9%
Study design												
Cross-sectional	4	0.51 (0.31–0.85)	1.0				3	0.34 (0.16–0.75)	1.0 (Ref)			
Prospective cohort	15	0.58 (0.43–0.77)	1.12 (0.48–2.61)	0.784	0.1001	35.3%	4	1.26 (0.55–2.93)	3.53 (0.78–15.86)	0.087	0.478	74.5%
Females	17	1.59 (1.13–2.29)	1.59 (1.13–2.29)	0.01	0.04	13.8%	7	2.97 (0.38–23.1)	2.97 (0.38–23.1)	0.24	0.87	81.3%
Prison	11	1.057 (0.61–1.79)	1.057 (0.61–1.79)	0.821	0.4303	56.3%	3	NA	NA			
Homelessness	12	1.08 (0.83–1.40)	1.08 (0.83–1.40)	0.521	0.2327	39.8%	6	1.01 (0.38–2.67)	1.01 (0.38–2.67)	0.976	1.53	80.6%
Injection of stimulants	12	0.89 (0.65–1.22)	0.89 (0.65–1.22)	0.373	0.17	36.2%	7	1.08 (0.47–2.51)	1.08 (0.47–2.51)	0.827	1.15	80.4%
Daily injection	7	0.88 (0.64–1.22)	0.88 (0.64–1.22)	0.373	0.17	47.3%	5	3.66 (0.22–61.3)	3.66 (0.22–61.3)	0.239	1.15	

CI = confidence interval; NA = not available.

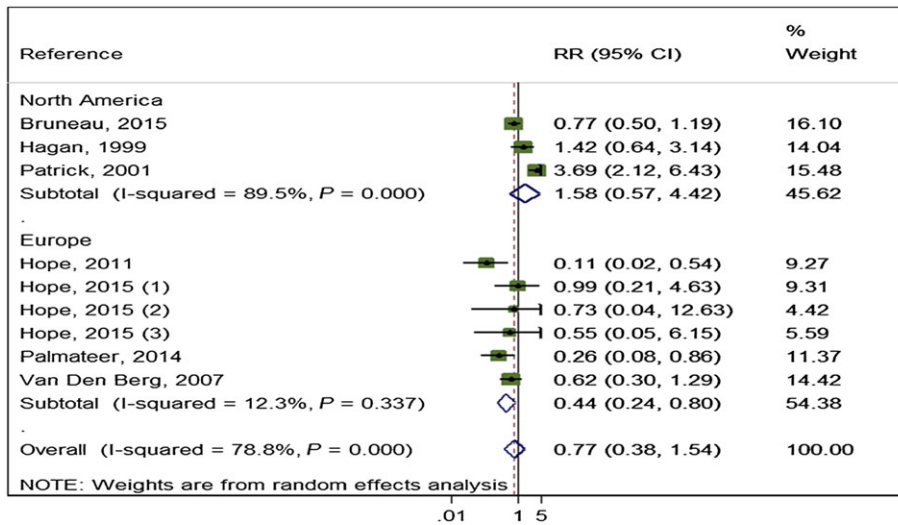


Figure 3 Impact of high-coverage needle and syringe programmes (NSP) versus no/low coverage on hepatitis C virus (HCV) incidence from pooling unadjusted measures by region. [Colour figure can be viewed at wileyonlinelibrary.com]

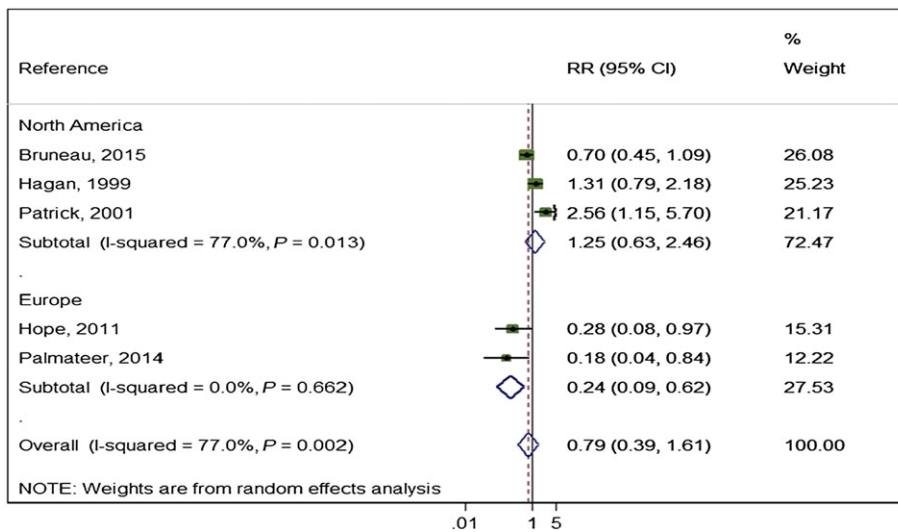


Figure 4 Impact of high-coverage needle and syringe programmes (NSP) versus no/low coverage on hepatitis C virus (HCV) incidence from studies adjusted for confounders and by region. [Colour figure can be viewed at wileyonlinelibrary.com]

effect size), according to the GRADE criteria [23]. These are reported in detail in the Cochrane Review [21].

DISCUSSION

Main findings

Opioid substitution treatment (OST) is associated consistently with an average 50% reduction in the risk of new HCV infections among PWID. The combined use of high-coverage NSP with OST is associated with an average reduction in risk of HCV infection by 74%. There is weaker evidence that high coverage of NSP is associated with a reduction in risk of new HCV infections globally. There were no trials identified in the review. The majority of the observational studies were assessed to be at severe or

critical risk of bias, and the strength of the evidence generated was low in the case of OST and very low for NSP [21].

Strengths and limitations

The two key limitations of the review are heterogeneity in measurement of exposure to NSPs and confounding. Consistent measures of NSP exposure through coverage of injections by clean needles and syringes were used throughout the European studies [12,29,32] [Hope (unpublished)], whereas the North American studies drew upon varied definitions of NSP use that focused on frequency of attendance at NSPs [27,33] [Bruneau (unpublished)]. The measure of 100% NSP coverage corresponds to the situation where a person reports that

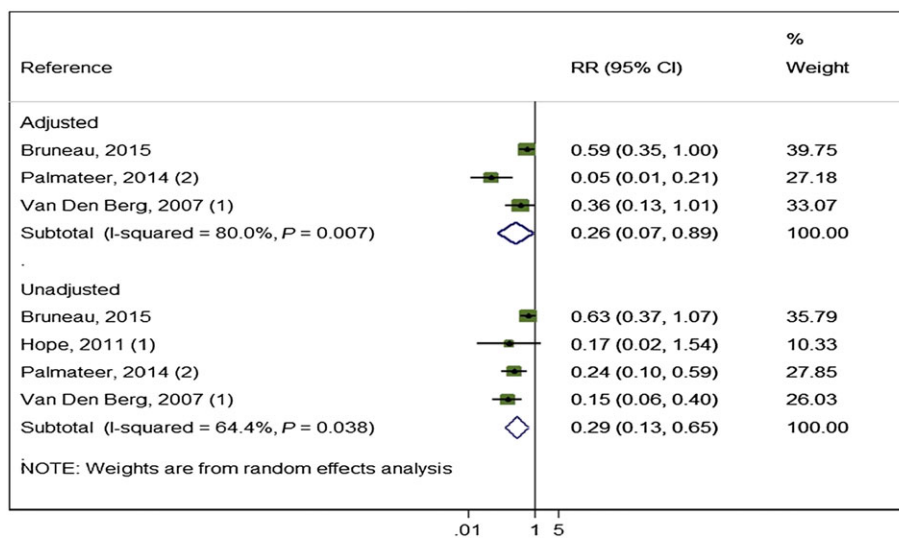


Figure 5 Impact of opioid substitution therapy (OST) combined with high-coverage needle and syringe programmes (NSP) from studies adjusting for confounders and all pooled estimates. [Colour figure can be viewed at wileyonlinelibrary.com]

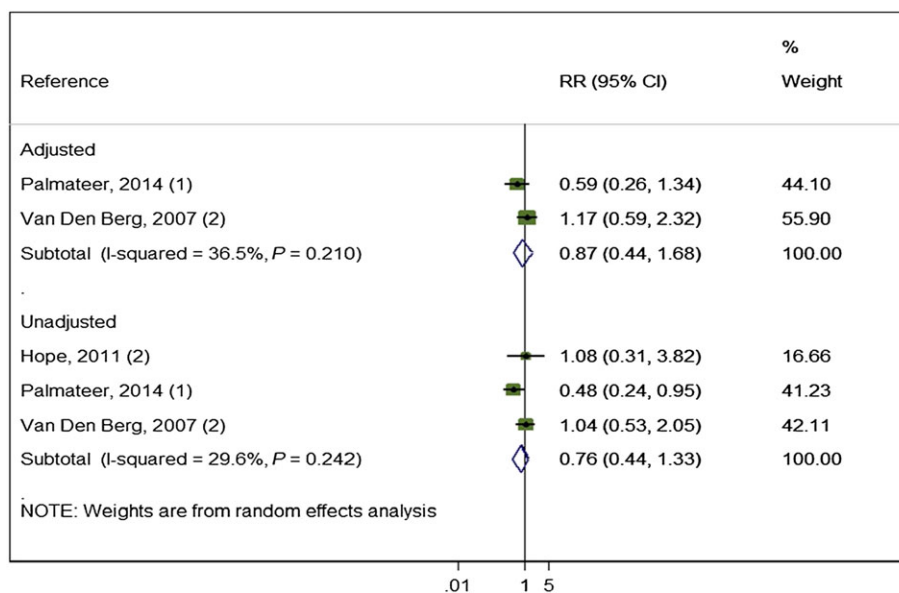


Figure 6 Impact of opioid substitution therapy (OST) combined with low-coverage needle and syringe programmes (NSP) from studies adjusting for confounders and all pooled estimates. [Colour figure can be viewed at wileyonlinelibrary.com]

they receive sufficient or a greater number of sterile syringes per reported injecting frequency, and is found in sites which allow PWID to collect a large number of syringes or attend very regularly, rather than in sites which adopt a more restricted form of exchange. It is also possible that the population exposed to 100% coverage are more compliant than the comparison group in terms of regular attendance and uptake of needles and syringes. However, we cannot assume that they necessarily use all needles and syringes obtained, as HCV transmission still occurs in this population. Inconsistencies in NSP measurement contributed to heterogeneity observed

among studies ($I^2 = 77%$, $P = 0.002$), while differences in study design, exposure measurement and patterns of injecting may have contributed to the lack of effect of NSPs on HCV transmission observed in North America. The European definition of coverage may include needles and syringes obtained from pharmacies, secondary distribution via friends or via outreach, whereas the North American definition is specific to fixed-site NSP use. In reality, PWID may obtain needles and syringes from multiple sources and, as a consequence, use NSPs less frequently for social support, HIV/HCV testing and counselling and other specialist advice. These additional

services are essential to prevent the spread of blood-borne viruses and reduce inequalities in health over time [57], but the immediate effect on HCV incidence may be difficult to assess where measurement of exposure does not capture uptake of sterile needles and syringes from other sources. Measurement of NSP use that focuses on needles and syringes without taking into account acquisition of other drug preparation equipment from NSPs may also have contributed to the lack of an association in some settings, particularly in the United States, where almost half of HCV seroconversions have been attributed to the shared use of cookers (spoons) and cottons [5]. It is also hypothesized that less frequent use of NSPs and lack of federal funding for NSPs in the United States has resulted in lower coverage among PWID overall, which may mask an intervention effect, although in cities where the studies took place coverage is not as low as for the United States overall [58,59]. The higher proportion of stimulant injectors in US studies also may contribute to lower impact. Meta-regression analysis suggested no differential impact between intervention effect and study design for current use of OST, but suggested that longitudinal studies of NSP found a lower effect than cross-sectional studies which were associated with European settings.

The control of confounders was limited and inconsistent across the studies. However, synthesized effect estimates for OST and combined effect of OST and high-coverage NSP were consistent throughout multiple studies and maintained between analyses that adjusted for confounders and those that did not, suggesting the variation did not affect the results. We cannot rule out the effect of residual confounding on NSP—especially for the lack of association between NSP use and HCV from studies in North America. For example, it has been shown that people who attend NSPs regularly in North America also report greater injecting risk behaviours and other social vulnerabilities (including sex work or homelessness), and that after adjustment for these factors any positive association between HCV or HIV transmission and NSP attendance is reduced [60,61].

An additional limitation is that the GRADE criteria used by Cochrane assess automatically evidence from observational studies as low quality [23]. The merits and limitations of using Cochrane Reviews and GRADE criteria in developing guidelines in the addictions field has been discussed recently [62], alongside a recognition for the need to separate out the quality of the evidence from the strength of the ensuing recommendation [63]. We agree that this is an important distinction to make when examining the effect of interventions where there is no experimental evidence, and it is not ethical to conduct randomized controlled trials. Observational studies can give misleading results, and in some notable examples have been shown to

be false when compared to evidence from randomized trials [64]. Nonetheless, consideration of other criteria for assessing quality of evidence may be needed—such as size of effect, consistency across sensitivity analyses, supporting evidence, and use of instrumental variables to test for confounding [23].

Other evidence

This is the first global quantitative systematic review of the effectiveness of OST and NSP on reducing HCV, building upon an earlier narrative review that OST and NSP reduce injecting risk and global reviews on HIV [14,16,17]. Our findings corroborate a pooled analysis, which suggested that receiving OST and high coverage of NSP can reduce HCV infection risk alone, but is greater in combination [20]. Our findings suggested a stronger effect of high NSP coverage in Europe, but no effect in North America. This corroborates findings from another review that found increased risk of seroconversion associated with NSP attendance that relied predominantly upon evidence from North America [19]. Meta-regression analysis suggested evidence of a differential impact of OST by the proportion of female participants in the sample, with the effectiveness of the intervention reduced by 59% with every 10% increase in female participants. This corroborates other evidence that women are at increased risk of acquiring hepatitis C compared to men and may have poorer access to OST, possibly as a result of services not taking into account gender-specific needs or being tailored towards men [65–67].

Implications

Given the low quality of evidence for NSP, there is an urgent need to improve transparency and consistency in reporting of observational studies in order to support future natural experiments and systematic reviews measuring the impact of the intensity of intervention coverage upon HCV and other outcomes. The development of improved and consistent measures of NSP coverage, along with more consistent reporting of the conduct of studies to measure exposure to NSPs and the assessment of confounders, are needed to strengthen the evidence on the impact of NSP.

It has been noted that the greatest benefits for people with mental health and addiction problems including PWID will be derived from providing better evidenced-based care in relation to medication, substitution therapies and abstinence programmes, as well as addressing underlying social problems arising from homelessness and criminalization [68]. This is particularly relevant in low- and middle-income countries, where resources may be more restricted [62]. There is a wealth of evidence from high-income settings of the beneficial effects of OST in

reducing injection-related harms, including HIV and bacterial infections, and improving access to services [11,17,19,20,69,70]. However, global coverage of OST remains very low, prohibited in the Russian Federation and often restricted by age or duration of dependency prior to treatment entry [71]. Our findings show the need to remove restrictions on the concurrent use of both NSP and OST to maximize reduction in HCV transmission. We had insufficient data to measure the impact of OST dosage on HCV acquisition risk, but two studies that stratified by dose showed that reduced risk was associated with high doses of methadone (≥ 60 mg), pointing to the importance of providing adequate dosages [12] [Bruneau (unpublished)]. Distribution of needles and syringes through NSPs needs to be maintained alongside provision of OST. NSP and OST services also need to develop gender-sensitive policies and practices to encourage women to use services addressing gender-specific injecting related risk and other health and social welfare needs. The potential role of the new era of highly curative short-course direct-acting antiviral therapies for HCV to reduce HCV transmission also needs to be considered [72], and within this the importance of ensuring equitable access of PWID to OST and NSPs that can facilitate HCV testing and treatment. In summary, our findings provide strong evidence that OST and in combination with high-coverage NSP should be expanded to prevent the transmission of HCV and reduce associated morbidity and mortality.

Declarations of interest

J.B., L.D., Hickman, Hutchinson and Vickerman are members of the Editorial board of *Addiction*. S.H. reports personal fees from Abbvie and Gilead outside the submitted work. A.T. reports grants from NHS National Services Scotland during the conduct of the study. L.M. and L.D. are supported by an Australian National Health and Medical Research Council Research Fellowship. H.H. is supported by a grant from the US NIH. L.D. has received investigator-initiated untied educational grants from Reckitt Benckiser, Indivior and Mundipharma. None of those funders had any role in the design, conduct, analysis, write-up or decision to publish their findings.

Acknowledgements

We would like to acknowledge the help of Shruti Mehta, Thomas Kerr, Meghan Morris and Ali Judd for providing us access to unpublished data and measures of association between the interventions and HCV risk acquisition that were used in the analysis. We thank Zuzana Mitrova for her support with the searches. We thank Julian Higgins for his advice on the use of the ACROBAT 'Risk of bias' assessment tool and statistical advice on the options for pooling different observational study designs.

References

- Gower E., Estes C., Blach S., Razavi-Shearer K., Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; **61**: S45–57.
- Mohd Hanafiah K., Groeger J., Flaxman A. D., Wiersma S. T. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatol (Balt)* 2013; **57**: 1333–42.
- Perz J. E., Armstrong G. L., Farrington L. A., Hutin Y. J., Bell B. P. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006; **45**: 529–38.
- Degenhardt L., Charlson F., Stanaway J., Larney S., Alexander L. T., Hickman M. *et al.* Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the global burden of disease study. *Lancet Infect Dis* 2013; **16**: 1385–98.
- Pouget E. R., Hagan H., Des Jarlais D. C. Meta-analysis of hepatitis C seroconversion in relation to shared syringes and drug preparation equipment. *Addiction* 2012; **107**: 1057–65.
- Strathdee S. A., Hallett T. B., Bobrova N., Rhodes T., Booth R., Abdool R. *et al.* HIV and risk environment for injecting drug users: the past, present, and future. *Lancet* 2010; **376**: 268–84.
- Kaplan E. H., Heimer R. A model-based estimate of HIV infectivity via needle sharing. *J Acquir Immune Defic Syndr* 1992; **5**: 1116–8.
- Tilson H., Aramrattana A., Bozzette S. A. *Preventing HIV Infection Among Injecting Drug Users in High-Risk Countries: an Assessment of the Evidence*. Washington, DC: Institute of Medicine; 2007.
- Gibson D. R., Flynn N. M., McCarthy J. J. Effectiveness of methadone treatment in reducing HIV risk behavior and HIV seroconversion among injecting drug users. *AIDS* 1999; **13**: 1807–18.
- Jones L., Pickering L., Sumnall H., McVeigh J., Bellis M. A. *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.
- 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; **105**: 844–59.
- 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; **102**: 1454–62.
- Gibson D. R., Flynn N. M., Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. *AIDS* 2001; **15**: 1329–41.
- Gowing L., Farrell M. F., Bornemann R., Sullivan L. E., Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev* 2011; Issue 8. Art. No.: CD004145. <https://doi.org/10.1002/14651858.CD004145.pub4>.
- MacArthur G. J., van Velzen E., Palmateer N., Kimber J., Pharris A., Hope V. *et al.* Interventions to prevent HIV and

- hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. *Int J Drug Policy* 2014; **25**: 34–52.
16. Aspinall E. J., Nambiar D., Goldberg D. J., Hickman M., Weir A., Van Velzen E. *et al.* Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis. *Int J Epidemiol* 2014; **43**: 235–48.
 17. MacArthur G. J., Minozzi S., Martin N., Vickerman P., Deren S., Bruneau J. *et al.* Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ* 2012; **345**: e5945.
 18. Wodak A., Cooney A. *Effectiveness of Sterile Needle and Syringe Programming in Reducing HIV/AIDS Among Injecting Drug Users*. Geneva: World Health Organization; 2004.
 19. Hagan H., Pouget E. R., Des Jarlais D. C. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *J Infect Dis* 2011; **204**: 74–83.
 20. Turner K. M., Hutchinson S., Vickerman P., Hope V., Craine N., Palmateer 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; **106**: 1978–88.
 21. Platt L., Minozzi S., Reed J., Vickerman P., Hagan H., French C. *et al.* Effectiveness of needle/syringe programmes and opiate substitution therapy in preventing HCV transmission among people who inject drugs. *Cochrane Database Syst Rev* 2016; <https://doi.org/10.1002/14651858.CD012021>.
 22. Sterne J. A., Hernán M. A., Reeves B. C., Savović J., Berkman N. D., Viswanathan M. *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.
 23. Atkins D., Best D., Briss P. A., Eccles M., Falck-Ytter Y., Flórrorpp S. *et al.* Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**: 1490.
 24. Craine N., Hickman M., Parry J. V., Smith J., Walker A. M., Russell D. *et al.* Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size. *Epidemiol Infect* 2009; **137**: 1255–65.
 25. Crofts N., Nigro L., Oman K., Stevenson E., Sherman J. Methadone maintenance and hepatitis C virus infection among injecting drug users. *Addiction* 1997; **92**: 999–1005.
 26. Hagan H., Des Jarlais D. C., Friedman S. R., Purchase D., Alter M. J. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health* 1995; **85**: 1531–7.
 27. Hagan H., McGough J. P., Thiede H., Weiss N. S., Hopkins S., Alexander E. R. Syringe exchange and risk of infection with hepatitis B and C viruses. *Am J Epidemiol* 1999; **149**: 203–13.
 28. Holtzman D., Barry V., Ouellet L. J., Des Jarlais D. C., Vlahov D., Golub E. T. *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; **49**: 68–73.
 29. Hope V. D., Hickman M., Nguui S. L., Jones S., Telfer M., Bizzarri M. *et al.* Measuring the incidence, prevalence and genetic relatedness of hepatitis C infections among a community recruited sample of injecting drug users, using dried blood spots. *J Viral Hepatitis* 2011; **18**: 262–70.
 30. Lucidarme D., Bruandet A., Ilef D., Harbonnier J., Jacob C., Decoster A. *et al.* Incidence and risk factors of HCV and HIV infections in a cohort of intravenous drug users in the north and east of France. *Epidemiol Infect* 2004; **132**: 699–708.
 31. Nolan S., Dias Lima V., Fairbairn N., Kerr T., Montaner J., Grebely J. *et al.* The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users. *Addiction* 2014; **109**: 2053–9.
 32. Palmateer N. E., Taylor A., Goldberg D. J., Munro A., Aitken C., Shepherd S. J. *et al.* Rapid decline in HCV incidence among people who inject drugs associated with national scale-up in coverage of a combination of harm reduction interventions. *PLOS ONE* 2014; **9**: e104515.
 33. Patrick D. M., Tyndall M. W., Cornelisse P. G. A., Li K., Sherlock C. H., Rekart M. L. *et al.* Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. *Can Med Assoc J* 2001; **165**: 889–95.
 34. Rezza G., Sagliocca L., Zaccarelli M., Nespoli M., Siconolfi M., Baldassarre C. Incidence rate and risk factors for HCV seroconversion among injecting drug users in an area with low HIV seroprevalence. *Scand J Infect Dis* 1996; **28**: 27–9.
 35. Roy E., Alary M., Morissette C., Leclerc P., Boudreau J.-F., Parent R. *et al.* High hepatitis C virus prevalence and incidence among Canadian intravenous drug users. *Int J STD AIDS* 2007; **18**: 23–7.
 36. Ruan Y., Qin G., Yin L., Chen K., Qian H.-Z., Hao C. *et al.* Incidence of HIV, hepatitis C and hepatitis B viruses among injection drug users in southwestern China: a 3-year follow-up study. *AIDS* 2007; **21**: S39–46.
 37. Spittal P. M., Pearce M. E., Chavoshi N., Christian W. M., Moniruzzaman A., Teegee M. *et al.* The Cedar Project: high incidence of HCV infections in a longitudinal study of young aboriginal people who use drugs in two Canadian cities. *BMC Public Health* 2012; **12**: 632.
 38. Thiede H., Hagan H., Murrill C. S. Methadone treatment and HIV and hepatitis B and C risk reduction among injectors in the Seattle area. *J Urban Health* 2000; **77**: 331–45.
 39. Thorpe L. E., Ouellet L. J., Hershov R., Bailey S. L., Williams I. T., Williamson J. *et al.* Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. *Am J Epidemiol* 2002; **155**: 645–53.
 40. Tsui J. I., Evans J. L., Lum P. J., Hahn J. A., Page K. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. *JAMA Intern Med* 2014; **174**: 1974–81.
 41. Vallejo E., Barrio G., Brugal M. T., Pulido J., Toro C., Sordo L. *et al.* High hepatitis C virus prevalence and incidence in a community cohort of young heroin injectors in a context of extensive harm reduction programmes. *J Epidemiol Community Health* 2015; **69**: 599–603.
 42. van Beek I., Dwyer R., Dore G. J., Luo K., Kaldor J. M. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. *BMJ* 1998; **317**: 433–7.
 43. White B., Dore G. J., Lloyd A. R., Rawlinson W. D., Maher L. Opioid substitution therapy protects against hepatitis C virus acquisition in people who inject drugs: the HITS-c study. *Med J Aust* 2014; **201**: 326–9.
 44. Page K., Hahn J. A., Evans J., Shiboski S., Lum P., Delwart E. *et al.* Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis* 2009; **200**: 1216–26.
 45. Roy E., Boudreau J.-F., Boivin J.-F. Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. *Drug Alcohol Depend* 2009; **102**: 158–61.

46. Sendi P, Hoffmann M., Bucher H. C., Erb P, Haller P, Gyr N. *et al. Drug Alcohol Depend* 2003; **69**: 183–8.
47. Shannon K., Kerr T., Marshall B., Li K., Zhang R., Strathdee S. A., *et al.* Survival sex work involvement as a primary risk factor for hepatitis C virus acquisition in drug-using youths in a Canadian setting. *Arch Pediatr Adolesc Med* 2010; **164**: 61–5.
48. Solomon S. S., Celentano D. D., Srikrishnan A. K., Vasudevan C. K., Murugavel K. G., Iqbal S. H. *et al.* Low incidences of human immunodeficiency virus and hepatitis C virus infection and declining risk behaviors in a cohort of injection drug users in Chennai, India. *Am J Epidemiol* 2010; **172**: 1259–67.
49. Stein M. D., Herman D. S., Anderson B. J. A trial to reduce hepatitis C seroincidence in drug users. *J Addict Dis* 2009; **28**: 389–98.
50. Stephens B. P., Tait J., Evans M., Dillon J. F. The natural history of the acquisition of HCV in chaotic PWID. *Hepatology (Balt)* 2013; **58**: 1103A.
51. Tsirogianni E., Kokkonis G., Tziokgas K., Tsekoura P., Stafilidou M., Sotiriadou K. *et al.* Incidence of new HCV infection or reinfection after successful anti-HCV therapy among people who inject drugs attending a substitution treatment programme in northern Greece. *Suchtmed Forsch Prax* 2013; **15**: 260.
52. Villano S. A., Vlahov D., Nelson K. E., Lyles C. M., Cohn S., Thomas D. L. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *J Clin Microbiol* 1997; **35**: 3274–7.
53. Widell A., Alanko M., Flamholz L., Jacobssen H., Molnegren V., Bjorkman P. Continued heavy transmission of HCV in a needle exchange program that is associated with minimal transmission of HIV. A nine year longitudinal cohort study. *J Hepatology* 2009; **50**: S161.
54. Yang J., Oviedo-Joekes E., Christian K. W. M., Li K., Louie M., Schechter M. *et al.* The cedar project: methadone maintenance treatment among young aboriginal people who use opioids in two Canadian cities. *Drug Alcohol Rev* 2011; **30**: 645–51.
55. Aitken C., Agius P. A., Higgs P. G., Stooze M. A., Bowden D. S., Dietze P. M. The effects of needle-sharing and opioid substitution therapy on incidence of hepatitis C virus infection and reinfection in people who inject drugs. *Epidemiol Infect* 2017; **145**: 796–801.
56. Palmateer N., Hutchinson S., McAllister G., Munro A., Cameron S., Goldberg D. *et al.* Risk of transmission associated with sharing drug injecting paraphernalia: analysis of recent hepatitis C virus (HCV) infection using cross-sectional survey data. *J Viral Hepatitis* 2014; **21**: 25–32.
57. Strathdee S. A., Patrick D. M., Currie S. L., Cornelisse P. G., Rekart M. L., Montaner J. S. *et al.* Needle exchange is not enough: lessons from the Vancouver injecting drug use study. *AIDS* 1997; **11**: F59–65.
58. 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; **99**: 1049–52.
59. Des Jarlais D. C., Nugent A., Solberg A., Feelemyer J., Mermin J., Holtzman D. Syringe service programs for persons who inject drugs in urban, suburban, and rural areas—United States, 2013. *Morb Mortal Wkly Rep* 2015; **64**: 1337–41.
60. Wood E., Lloyd-Smith E., Li K., Strathdee S. A., Small W., Tyndall M. W. *et al.* Frequent needle exchange use and HIV incidence in Vancouver, Canada. *Am J Med* 2007; **120**: 172–9.
61. Hagan H., McGough J. P., Thiede H., Hopkins S. G., Weiss N. S., Alexander E. R. Volunteer bias in nonrandomized evaluations of the efficacy of needle-exchange programs. *J Urban Health* 2000; **77**: 103–12.
62. Barbui C. Do Cochrane systematic reviews meet WHO needs? *Addiction* 2015; **110**: 899–900.
63. Davoli M., Amato L., Clark N., Farrell M., Hickman M., Hill S. *et al.* The role of Cochrane reviews in informing international guidelines: a case study of using the grading of recommendations, assessment, development and evaluation system to develop World Health Organization guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. *Addiction* 2015; **110**: 891–8.
64. Lawlor D. A., Davey Smith G., Ebrahim S. Commentary: The hormone replacement–coronary heart disease conundrum: is this the death of observational epidemiology? *Int J Epidemiol* 2004; **33**: 464–7.
65. Iversen J., Page K., Madden A., Maher L. HIV, HCV and health-related harms among women who inject drugs: implications for prevention and treatment. *J Acquir Immune Defic Syndr* 2015; **69**: S176–81.
66. Miller C. L., Wood E., Spittal P. M., Li K., Frankish J. C., Braitstein P. *et al.* The future face of coinfection: prevalence and incidence of HIV and hepatitis C virus coinfection among young injection drug users. *J Acquir Immune Defic Syndr* 2004; **36**: 743–9.
67. Tracy D., Hahn J. A., Fuller Lewis C., Evans J., Briceno A., Morris M. D. *et al.* Higher risk of incident hepatitis C virus among young women who inject drugs compared with young men in association with sexual relationships: a prospective analysis from the UFO study cohort. *BMJ Open* 2014; **4**: e004988.
68. Sederer L. I., Sharfstein S. S. Fixing the troubled mental health system. *JAMA* 2014; **312**: 1195–6.
69. Vickerman P., Martin N., Turner K., Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. *Addiction* 2012; **107**: 1984–95.
70. Vickerman P., Platt L., Jolley E., Rhodes T., Kazatchkine M. D., Latypov A. Controlling HIV among people who inject drugs in Eastern Europe and Central Asia: insights from modeling. *Int J Drug Policy* 2014; **25**: 1163–73.
71. Mathers B. M., Degenhardt L., Ali H., Wiessing L., Hickman M., Mattick R. P. *et al.* Reference Group to the UN on HIV and Injecting Drug Use. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet* 2010; **375**: 1014–28.
72. Martin N. K., Vickerman P., Foster G. R., Hutchinson S. J., Goldberg D. J., Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatology* 2011; **54**: 1137–44.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Risk of bias of included studies.

Figure S1 Impact of current use of opioid substitution therapy (OST) versus no OST on hepatitis C virus (HCV)

incidence from studies adjusting for confounders but excluding those judged to be at critical risk of bias.

Figure S2 Impact of current use of opioid substitution therapy (OST) versus no OST on hepatitis C virus (HCV) incidence from studies adjusting for confounders but excluding cross-sectional study designs.

Figure S3 Impact of current use of opioid substitution therapy (OST) versus no OST on hepatitis C virus (HCV) incidence from studies adjusting for confounders but excluding unpublished data sets.

Figure S4 Impact of current use of opioid substitution therapy (OST) versus no OST on hepatitis C virus (HCV) incidence from unadjusted studies.

Figure S5 Impact of high-coverage needle and syringe programmes (NSP) versus no or low coverage on hepatitis C virus (HCV) incidence from studies adjusting for confounders but excluding unpublished data sets.

Figure S6 Funnel plot of 12 studies included in meta-analysis of studies regarding the impact of opioid substitution therapy (OST) in relation to hepatitis C virus (HCV) incidence among people who inject drugs.

Figure S7 Funnel plot of 5 studies included in meta-analysis of studies regarding the impact of high-coverage needle and syringe programmes (NSP) in relation to hepatitis C virus (HCV) incidence among people who inject drugs.