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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

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ABSTRACT

Aims To investigate whether opiate substitution therapy (OST) and needle and syringe programmes (NSP) can reduce hepatitis C virus (HCV) transmission among injecting drug users (IDUs). **Design** Meta-analysis and pooled analysis, with logistic regression allowing adjustment for gender, injecting duration, crack injecting and homelessness. **Setting** Six UK sites (Birmingham, Bristol, Glasgow, Leeds, London and Wales), community recruitment. **Participants** A total of 2986 IDUs surveyed during 2001–09. **Measurement** Questionnaire responses were used to define intervention categories for OST (on OST or not) and high NSP coverage (≥100% versus <100% needles per injection). The primary outcome was new HCV infection, measured as antibody seroconversion at follow-up or HCV antibody-negative/RNA-positive result in cross-sectional surveys. **Findings** Preliminary meta-analysis showed little evidence of heterogeneity between the studies on the effects of OST ($I^2 = 48\%$, $P = 0.09$) and NSP ($I^2 = 0\%$, $P = 0.75$), allowing data pooling. The analysis of both interventions included 919 subjects with 40 new HCV infections. Both receiving OST and high NSP coverage were associated with a reduction in new HCV infection [adjusted odds ratios (AORs) = 0.41, 95% confidence interval (CI): 0.21–0.82 and 0.48, 95% CI: 0.25–0.93, respectively]. Full harm reduction (on OST plus high NSP coverage) reduced the odds of new HCV infection by nearly 80% (AOR = 0.21, 95% CI: 0.08–0.52). Full harm reduction was associated with a reduction in self-reported needle sharing by 48% (AOR 0.52, 95% CI: 0.32–0.83) and mean injecting frequency by 20.8 injections per month (95% CI: −27.3 to −14.4). **Conclusions** There is good evidence that uptake of opiate substitution therapy and high coverage of needle and syringe programmes can substantially reduce the risk of hepatitis C virus transmission among injecting drug users. Research is now required on whether the scaling-up of intervention exposure can reduce and limit hepatitis C virus prevalence in this population.

Keywords HCV, methadone, needle and syringe programmes, opiate substitution treatment, primary prevention.

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INTRODUCTION

Hepatitis C virus (HCV) is a major cause of liver disease [1]. In the United Kingdom, there are approximately 200 000 cases of HCV and injecting drug use is the key exposure for more than 85% of all these infections and 95% of infections acquired in the United Kingdom [2–6]. Prevention of HCV infection among injecting drug users (IDUs) is critical to reduce HCV transmission and long-term morbidity [7–9]. The prevalence of HCV varies between and within countries: in several UK cities more than half the IDU population are infected with HCV [7,10,11]. Surveillance data also suggest that, after declining during the 1990s, HCV risk has been

increasing more recently among IDUs, especially among recent initiates [12,13].

Two important interventions for IDUs are opiate substitution therapy (OST) to reduce drug dependence and injecting frequency and the provision of clean injecting equipment through needle and syringe programmes (NSP) to reduce unsafe injecting (i.e. sharing used syringes). While there is good evidence that these interventions reduce self-reported injecting risk behaviour, there is little direct evidence of their impact on HCV incidence, leading to an assessment of the evidence of efficacy of these interventions as insufficient or, at best, weak [14,15]. In contrast, several studies show that OST reduces HIV transmission [16] and ecological studies also suggest that NSP is associated with reduced blood-borne virus transmission [17,18]. However, studies that have compared HIV or HCV incidence among IDUs by NSP exposure are inconsistent [14,19]. There is an order of magnitude difference in transmissibility and prevalence between HIV and HCV in IDUs, therefore levels of intervention coverage that prevent HIV may not necessarily prevent HCV infection among IDUs [20]. There have been few assessments of the independent and combined effects of interventions on HCV transmission [14,21,22]. One analysis of the Amsterdam cohort reported that the combination of OST and full NSP reduced HCV [and human immunodeficiency virus (HIV)] incidence by nearly two-thirds, but found no evidence of any independent intervention effects [23]. Through pooling data from six studies across the United Kingdom, our aim in this paper is to determine whether OST and NSP, singly or in combination, can reduce HCV transmission among IDUs.

METHODS

Data sources

Studies were included if they contained individual-level data on both intervention coverage (NSP and/or OST) and a measure of newly acquired HCV infection among IDUs surveyed in the community. To ensure comprehensive inclusion of appropriate studies, we consulted UK experts and conducted a review of electronic databases. Studies published prior to 2000 or conducted in prisons were excluded. We used the following search strategy: Web of Science, PubMed using the terms '(HCV OR hepatitis C virus) AND (incidence OR injecting risk behaviour) AND (injecting drug user OR IDU) AND (England OR Wales OR Scotland OR United Kingdom)'.

Six UK studies (Birmingham ($n = 310$), Bristol ($n = 299$) [22], Glasgow ($n = 947$) [24], Leeds ($n = 302$), London ($n = 428$) [25] and Wales ($n = 700$) [21]) fulfilled the inclusion criteria (Table 1). Three studies (Glasgow, London and Wales) recruited IDUs in the community (NSP, drug treatment or street settings) and the remaining three (Birmingham, Bristol and Leeds) recruited IDUs through respondent-driven sampling (RDS) [26]. Five of the studies recruited individuals who had injected drugs in the last 4 weeks, while the study in Glasgow included those who had ever injected drugs. The London study was also confined to recent initiates to injecting (i.e. aged less than 30 years or with fewer than 6 years injecting). The four cross-sectional studies (Birmingham, Bristol, Glasgow and Leeds) used a laboratory assay to identify recently acquired infection from dried blood spot samples [22], defined as individuals who tested HCV RNA-positive among those who tested HCV antibody-negative. The two cohort studies (London and Wales) identified incident infections as individuals who were HCV antibody-negative at baseline and were re-tested antibody-positive at 12-month follow-up [21,25], otherwise known as antibody seroconversion.

Outcomes

The primary outcome was new HCV infection (yes/no), based on the aforementioned definitions of recently acquired infection (for cross-sectional studies) and incident infection (for cohort studies). The secondary outcomes were based on the self-report of injecting risk behaviour, namely needle sharing in the last month (yes/no) and the number of injections in the last month (mean).

Interventions

We generated individual binary measures for OST and NSP coverage. In the cross-sectional studies, opiate substitution treatment (OST) was defined as current (yes/no), while in the cohort studies OST was defined as more than 6 months on OST in the last year (yes/no). In the United Kingdom, OST is primarily oral methadone [27]. For Glasgow, only information on oral methadone was used to generate this measure. NSP coverage was defined as the percentage of injections for which a sterile needle had been obtained from a NSP, and was calculated based on the average number of sterile needles obtained from NSP divided by the average number of injections, reported for a given time-period (last 4 weeks, with the exception of 6 months in the Glasgow study). Sterile needles either obtained from or provided to other IDUs were not included in this calculation. NSP coverage was then converted into a binary variable, where high NSP coverage referred to $\geq$100% needles per injection (i.e. one or more sterile needles were obtained from a NSP for each injection reported) [23,28]. For the London study, a comparable measure of NSP coverage could not be calculated.

Table 1 Study design, sample characteristics, risk behaviours, outcome measures and intervention coverage reported in each study.

	Bristol	*Leeds*	*Birmingham*	*Glasgow*[c]	*Wales*	*London*
Year	*2006*	*2008*	*2009*	*2008–09*	*2004–06*	*2001–02*
Study design and recruitment	Respondent-driven sampling			Cross-sectional, NSP	Cohort, NSP and other community settings	
Inclusion criteria	Injected last 4 weeks			Ever injected	Injected last 4 weeks	Injected last 4 weeks, and <30 years old or <6 years injecting
Test method	Dried blood spot (DBS) antibody test and RNA test				DBS antibody test	Oral fluid antibody test
Total participants (*n*)	299	302	310	947	Follow-up 406 (120 HCV-positive at baseline) from 700 total	Follow-up 282 (133/282 HCV-positive at baseline) from 428 total
HCV prevalence (%)	59% (177/299)	60% (182/302)	42% (130/310)	70% (651/928)	26% (184/700)	43% (180/422)
Male (%)	77%	76%	88%	72%	74%	68%
Age (mean)	32.2	32.6	33.5	34.9	30.1	27.7
Years injecting (mean)	11.7	12.0	9.8	11.6	8.9	3.9
Homeless last year (%)	58% (174/299)	52% (156/301)	62% (194/310)	32% (303/946)[c]	39% (158/404)	35% (93/263)
Inject crack last month (%)	63% (187/299)	80% (185/302)	56% (174/310)	3% (31/947)	22% (91/406)	
New HCV infection (definition)	HCV RNA-positive in those antibody-negative at baseline				HCV antibody-positive at follow-up in those antibody-negative at baseline	
New HCV infection (%)	14/115	2/120	2/180	6/270	17/286	49/149
Estimated HCV incidence[a]	40 per 100 py	7.6 per 100 py	5.2 per 100 py	10.0 per 100 py	5.6 per 100 py	42 per 100 py
Injections last month (mean)[b]	53.6	50.5	42.9	26.8	36.9 (follow-up)	84.2 (follow-up)
Shared needles last month (%)	28% (83/299)	7% (20/302)	3% (10/310)	6% (57/941)	9% (35/406)	12% (32/269)
Low NSP coverage: <100% (%)[c]	46% (137)	36% (108)	20% (63)	18% (172)	39% (126/325)	NA
High NSP coverage: ≥100%	53% (160)	63% (190)	78% (246)	43% (412)	54% (177)	
Non-current IDUs, on OST		0.3% (1)		35% (314)	7% (23)	
On OST (%)[d]	58% (172)	60% (180)	65% (203)	76% (723)	57% (231/403)[d]	26% (73)[d]
Not on OST	42%	40%	35%	24%	43%	74% (209)

[a]Hepatitis C virus (HCV) incidence calculated for cross-sectional studies 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 incident infections (HCV antibody-negative and HCV RNA-positive), and *N* = number of susceptibles (HCV antibody-negative). [b]Number of injections in last month = times inject per day [b]number of days injected in last month (except Glasgow which was calculated from mid-value of questionnaire ranges). [c]Low needle and syringe programme (NSP) coverage <100% also includes those who report injecting and did not report collecting any needles or missing data on needles obtained. [d]For London and Wales 'on opiate substitution therapy (OST)' if on OST for ≥6 months in last year. NSP: needle and syringe programmes; IDU: injecting drug user; py: person-years; NA: not applicable.

The binary variables for OST and NSP were then combined to form a measure of harm reduction coverage with four categories, as defined in Table 2.

Data analysis

Primary outcome: new HCV infection

Subjects included in the analysis. Of the total 2986 participants across the six UK studies, 1457 with an initial HCV antibody-negative test result were considered for inclusion in analysis of the primary outcome (Fig. 1). The analysis involved: (i) a meta-analysis of the (unadjusted) effect of OST on new HCV infection (confined to 1079 subjects, excluding a further 41 who reported no injections or OST during the at-risk period, and 337 who had missing HCV test results for either RNA or follow-up antibody); (ii) a meta-analysis of the (unadjusted) effect of high NSP coverage on new HCV infection [(confined to 922 subjects, excluding those indicated in (i), and a further 157 who had missing NSP data]; and (iii) a pooled analysis of the (unadjusted and adjusted) effects of OST and NSP on new HCV infection [confined to 919 subjects, excluding those indicated in (i) and (ii), and a further three who had missing covariate information].

Table 2 Definition of level of harm reduction according to NSP coverage and OST status.

		NSP coverage: needles per injection ≥100%	
Intervention status		*Yes*	*No*
Receiving OST	Yes	Full harm reduction[a]	Partial harm reduction
	No	Partial harm reduction	Minimal harm reduction

[a]Includes individuals who were on opiate substitution therapy (OST) but reported no injections in the last month (cross-sectional studies) or last year (cohort studies). NSP: needle and syringe programme.

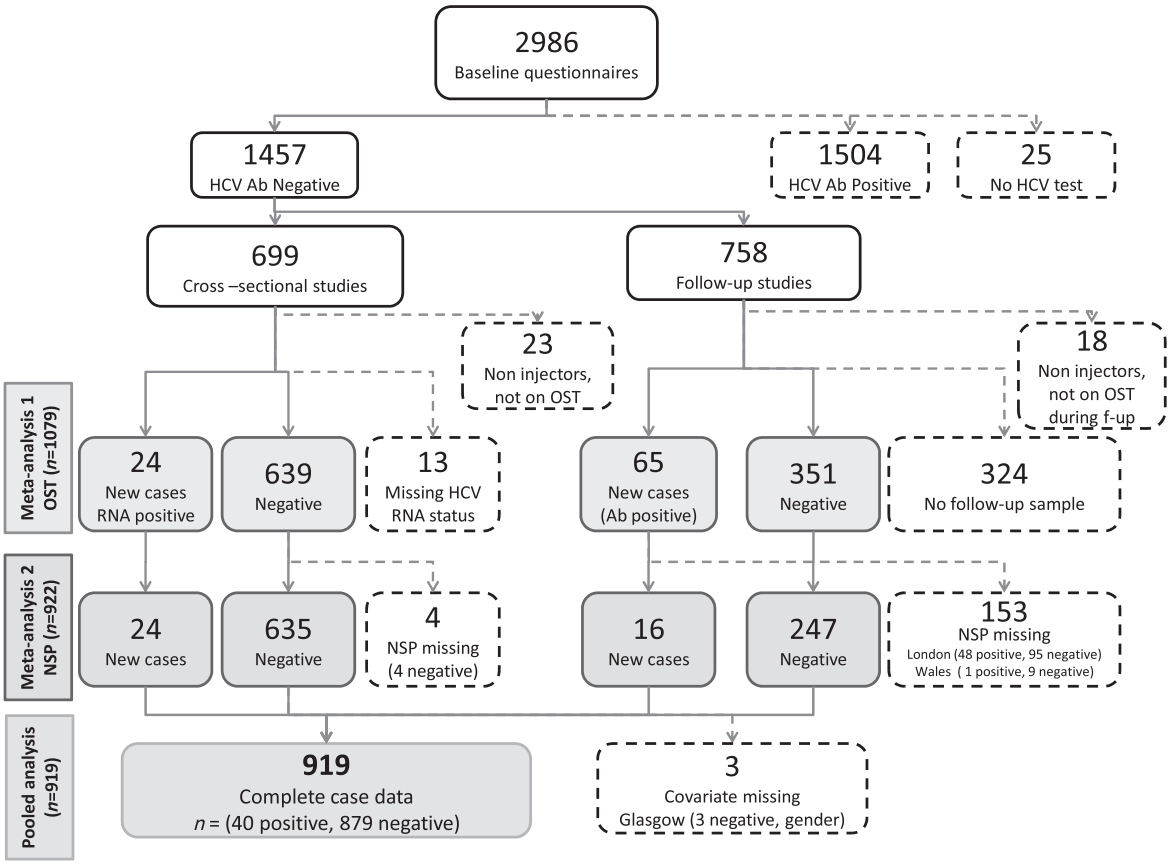

Figure 1 Hepatitis C virus (HCV) antibody (Ab) and RNA test results among individuals in the combined UK sample of injecting drug users; NSP: needle and syringe programmes; OST: opiate substitution therapy

Meta-analysis to test for study heterogeneity in the effects of OST and NSP on new HCV infection. Separate logistic regression models were used to estimate the study-specific associations of the (unadjusted) effects of OST and NSP on new HCV infection. Counts of new HCV infections were sparse, such that, for one study (Birmingham), there were no cases in one intervention group. In order to fit the regression model, we augmented the data as recommended by Wilson by adding one case and three controls to the intervention group with previously zero cases [29,30]. This gave a total of 1083 individuals included in meta-analysis 1 (OST) and 926 in meta-analysis 2 (NSP). The I^2 statistic (the proportion of variation in effect size that could be attributed to differences between the studies [31]) was calculated to assess between study heterogeneity in the effects of OST and NSP on new HCV infection.

Pooled analysis of the effects of OST and NSP on new HCV infection. There was no evidence of heterogeneity between the studies, so the data were pooled in subsequent analyses and the augmented data points removed ($n = 919$). Logistic regression was used to generate unadjusted and adjusted odds ratios (OR) of the risk of new HCV infection associated with each intervention measure: (i) OST (currently on versus not on) (ii) high NSP coverage (≥100% versus <100% needles per injection) and (iii) levels of harm reduction (OST and NSP) coverage (as defined in Table 2). Key confounders adjusted for in the analysis were gender [12], injecting duration [10,32], injecting crack [25] and homelessness [11,21].

Secondary outcomes: self-reported injecting risk behaviour

We further examined the risk of self-reported injecting risk behaviour: (i) the proportion needle sharing and (ii) the mean number of injections, both reported in the last month, according to levels of harm reduction (OST and NSP) coverage (as defined in Table 2), using logistic regression [for (i)] and linear regression [for (ii)]. A total of 2143 subjects with information on these self-reported injecting risk behaviours and reported OST and NSP status were included in this analysis (including HCV antibody-positive cases); subjects reporting no injections and no intervention exposure were excluded. Key confounders adjusted for in the analysis were as in the previous analysis (gender, injecting duration, injecting crack and homelessness).

All analyses were performed in STATA version 11 (StataCorp, 1984–2009) (STATA '.do' files are available on request from the corresponding author).

FINDINGS

Sample characteristics

The six studies included are summarized in Table 1. Approximately three-quarters of participants were male. The London study recruited recent initiates to injecting, thus the mean age (27.4 years) and injecting duration (3.8 years) are lower than in the other studies. The mean age in the other five studies ranged from 29.6 years (Wales) to 34.9 years (Glasgow) and the mean injecting duration ranged from 8.5 years (Wales) to 12.0 years (Leeds). The background prevalence of HCV was highest in Glasgow (70%) and lowest in Wales (26%). The estimated incidence was approximately five per 100 person-years in Birmingham, Leeds and Wales, 10 per 100 person-years in Glasgow and 40 per 100 person-years in Bristol and London. At baseline, more than half of IDUs (57%) reported exposure to OST and two-thirds (67%) of those currently injecting were classified as high coverage NSP, i.e. reported obtaining at least as many sterile needles as injections over the measurement period.

Meta-analysis to test for study heterogeneity in the effects of OST and NSP on new HCV infection

The meta-analyses indicated that both OST and high NSP coverage were associated with a reduction in the risk of new HCV infection (Fig. 2). There was no evidence of heterogeneity between the studies for the effects of either NSP ($I^2 = 0\%$ $P = 0.75$) or OST ($I^2 = 48\%$, $P = 0.09$), and therefore we pooled the data to allow adjustment for covariates.

Pooled analysis of the effects of OST and NSP on new HCV infection

The impact of OST and NSP coverage on new HCV infection are shown in Table 3 for the complete case data ($n = 919$). IDUs currently on OST had a 64% reduced odds of new HCV infection compared with those not on OST [(OR = 0.36, 95% confidence interval (CI): 0.19–0.70]. High NSP coverage (≥100% versus <100% needles per injection) almost halved the risk of new HCV infection (OR = 0.52, 95% CI: 0.28–0.99); those subjects who were on OST but reported no injections were excluded from this NSP analysis. Gender, homelessness and injecting crack cocaine were associated with a two- to threefold increase in risk of new HCV infection (Table 3), but did not alter the intervention effects. The adjusted OR (AOR) for OST was 0.41 (95% CI: 0.21–0.82) and for high NSP coverage the AOR was 0.48 (95% CI: 0.25–0.93). The complete case analysis excluded the London study, as it did not measure NSP coverage. The introduction of the London data set did not alter the

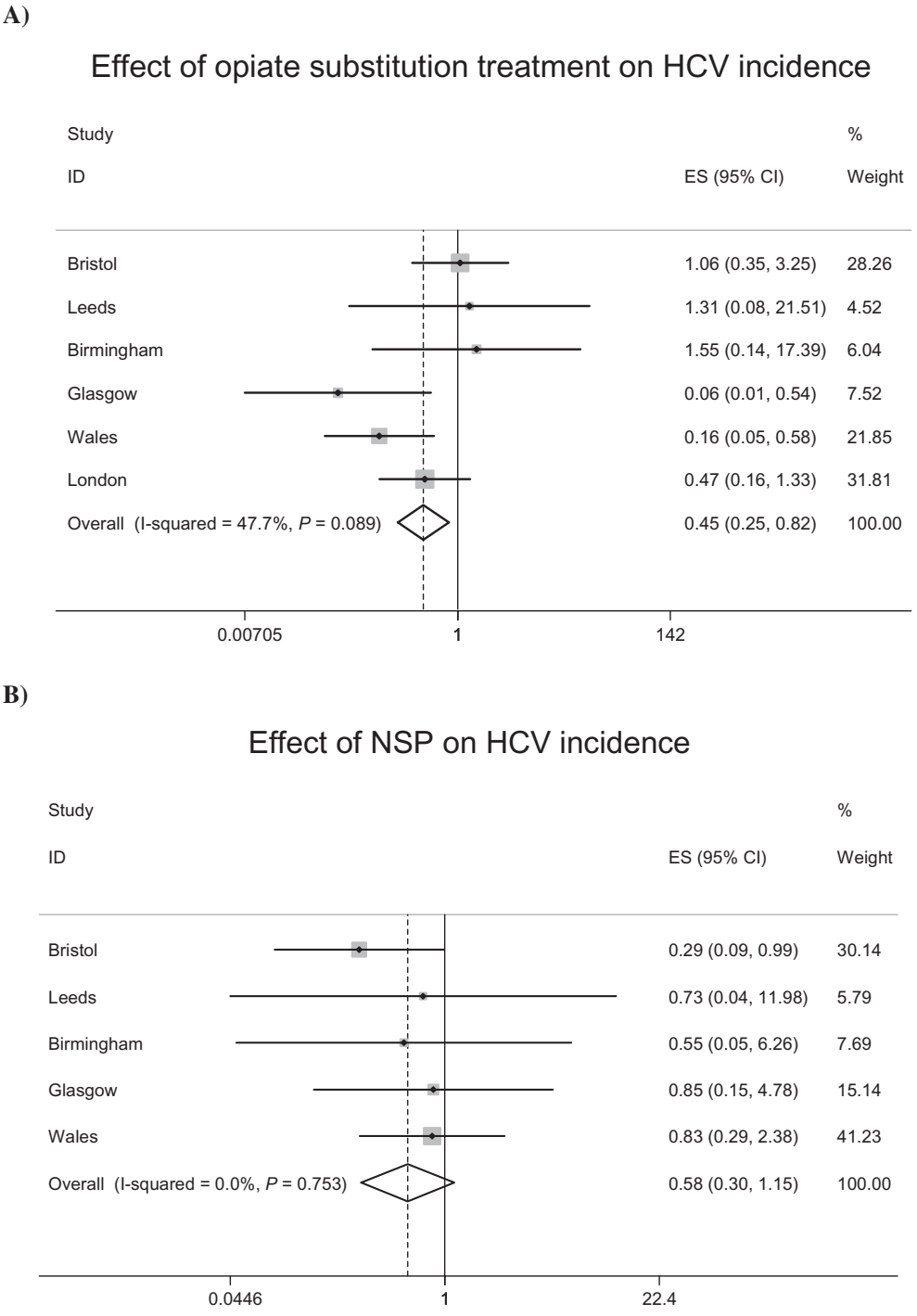

Figure 2 Meta-analysis of the effect of interventions on new hepatitis C virus (HCV) infection. (a) Opiate substitution therapy ($n = 1083$, 1079 + 4 added to Birmingham). (b) High needle and syringe programmes (NSP) coverage ($n = 926$, 922 + 4 added to Birmingham); CI: confidence interval; ES: effect size

findings, generating an effect estimate for OST on HCV transmission of 60% reduction ($n = 1076$, AOR 0.40, 95% CI: 0.21–0.79), which was consistent with the analysis shown in Table 3 (likelihood ratio test of interaction, $P = 0.66$).

In the combined analysis, the risk of new HCV infection was almost 80% lower among those on full harm reduction as defined in Table 2 (AOR = 0.21, 95% CI: 0.08–0.52) compared to those on minimal harm reduction. There was also weaker evidence for a reduction

Table 3 Relationship between intervention coverage and the outcome of new hepatitis C virus (HCV) infection, for the complete case data ($n = 919$).[a]

	New HCV infection								
				Unadjusted			*Adjusted*		
Intervention coverage	*No*	*Yes*	*%*	*OR*	*95% CI*	*P-value*	*OR*	*95% CI*	*P-value*
(a) OST									
On OST[b]	526	14	2.6%	0.36	0.19–0.70	0.003	0.41	0.21–0.82	0.01
Not on OST	353	26	6.9%	Ref.	–	–	Ref.	–	–
(b) NSP[c]									
≥100% coverage	539	21	3.8%	0.52	0.28–0.99	0.045	0.48	0.25–0.93	0.03
<100% coverage	254	19	7.0%	Ref.	–	–	Ref.	–	–
(c) Combined (NSP and OST)									
Full harm reduction: ≥100% coverage, on OST[b]	392	8	2.0%	0.19	0.08–0.47	<0.001	0.21	0.08–0.52	0.001
≥100% coverage, not on OST	233	13	5.3%	0.52	0.23–1.15	0.10	0.50	0.22–1.12	0.09
<100% coverage, on OST[c]	134	6	4.3%	0.41	0.15–1.12	0.08	0.48	0.17–1.33	0.16
Minimal harm reduction: <100% coverage, not on OST	120	13	9.8%	Ref.	–	–	Ref.	–	–
Covariates					Gender		2.1	1.04–4.34	0.039
					Injecting duration		1.0	0.44–2.07	0.906
					Crack injection		1.9	0.99–3.78	0.054
					Homelessness		2.9	1.41–5.97	0.004

[a]Logistic regression used to calculate unadjusted and adjusted odds ratio (OR) (adjusted for the following covariates: female gender; homeless in last year; injected crack in last month; duration injecting <2.5 years) with *P*-values and 95% confidence intervals (CI). [b]Includes or [c]excludes 86 cases [involving 0 new hepatitis C virus (HCV) infections] who were on opiate substitution therapy (OST) but reported no injections in the last month (cross-sectional studies) or last year (cohort studies). NSP: needle and syringe programme.

in the risk of new HCV infection for those on partial harm reduction (compared to minimal harm reduction), with an AOR of 0.50 (95% CI: 0.22–1.12) for those exposed to high NSP coverage but not on OST and an AOR of 0.48 (95% CI: 0.17–1.33) for those exposed to OST reporting injecting but not high NSP coverage.

Pooled analysis of the effects of OST and NSP on injecting risk behaviours

Overall (after exclusions for missing exposure data), 201 of 2143 (9.4%) individuals reported sharing needles in the last month; the mean number of injections was 34.5 in the last month. Participants exposed to minimal harm reduction (no OST < 100% NSP coverage) reported injecting on average 52.2 times, and 13% reported sharing needles in the last month (Table 4). For those in full harm reduction compared to minimal harm reduction, the risk of needle sharing was 48% (AOR 0.52, 95% CI: 0.32–0.83) and the mean injecting frequency was reduced by 20.8 injections per month (95% CI: −27.3 to −14.4). There was evidence of a smaller reduction (−13.4, 95% CI: −20.9 to −5.9) in injecting frequency in those on OST who are injecting but not exposed to high NSP coverage (partial harm reduction), but insufficient evidence for a reduction in reported sharing in those exposed to high coverage NSP but not on OST (AOR 0.73, 95% CI: 0.44–1.22). There was no evidence of any change in injecting frequency or reported sharing for those exposed to high coverage NSP and no OST or those exposed to OST but not high coverage NSP, respectively.

DISCUSSION

Using pooled data from the United Kingdom, we demonstrate that 'harm reduction' interventions (namely OST and high NSP coverage) can reduce HCV transmission among IDUs. To date, such evidence has been reviewed as insufficient [14,15] or assumed based on self-reported behaviour change or ecological studies [33]. In our analysis of UK data, after adjustment for important confounders (such as gender, homelessness and crack use), exposure to high NSP coverage and OST approximately halved the risk of HCV infection, and the combination of OST and NSP could reduce HCV incidence by up to 80%. The true effect of OST may be greater still, as several of the UK studies involved only current IDUs (i.e. those who had injected in the last 4 weeks) and thus we will have under-represented those who cease injecting during treatment in the analysis. In line with previous evidence, we show that OST and NSP, especially in combination, are associated with reductions in injecting risk [16,17,19].

Table 4 Relationship between intervention coverage [combination of needle and syringe programme (NSP) and opiate substitution therapy (OST)] and self-reported injecting risk behaviour outcomes of (i) needle sharing and (ii) mean number of injections in the last month, $n = 2143$ [all cases including hepatitis C virus (HCV) antibody-positive].

Intervention coverage	*(i) Needle sharing in last month (%)*	*Unadjusted OR*[a]	*95% CI*	*P value*	*Adjusted OR*[a]	*95% CI*	*P value*
Full harm reduction: ≥100% coverage, on OST[c]	71/1114 (6%)	0.47	0.29–0.75	0.001	0.52	0.32–0.83	0.007
≥100% coverage, not on OST	43/451 (10%)	0.73	0.44–1.20	0.216	0.73	0.44–1.22	0.229
<100% coverage, on OST[d]	59/357 (17%)	1.36	0.84–2.22	0.209	1.46	0.89–2.40	0.131
Minimal harm reduction: <100% coverage, not on OST	28/221 (13%)	Ref			Ref		
Covariates		Gender (female)			1.23	0.86–1.76	0.255
		Injecting duration			1.74	0.99–3.08	0.056
		Injecting crack			1.69	1.24–2.30	0.001
		Homeless in last year			1.83	1.34–2.51	<0.001
Intervention coverage	*(ii) Mean number of injections in last month (n)*	*Unadjusted Mean difference*[b]	*95% CI*	*P-value*	*Adjusted Mean Difference*[b]	*95% CI*	*P-value*
Full harm reduction: ≥100% coverage, on OST[c]	29.0 (1114)	−23.2	−29.9 to −16.6	<0.001	−20.8	−27.3 to −14.4	<0.001
≥100% coverage, not on OST	55.4 (451)	+3.2	−4.2 to 10.7	0.395	+4.1	−3.1 to 11.2	0.263
<100% coverage, on OST[d]	38.2 (357)	−14.0	−21.7 to −6.2	<0.001	−13.4	−20.9 to −5.9	<0.001
Minimal harm reduction: <100% coverage, not on OST	52.2 (221)	Ref			Ref		
Covariates		Gender			0.82	−3.7 to 5.3	0.720
		Injecting duration			10.2	4.2 to 16.3	0.001
		Injecting crack			24.0	19.8 to 28.3	<0.001
		Homeless in last year			7.2	3.2 to 11.1	<0.001

[a]Logistic regression used to calculate unadjusted and adjusted odds ratio (OR) (adjusted for the following covariates: female gender; homeless in last year; injected crack in last month; duration injecting <2.5 years) with *P*-values and 95% confidence intervals (CI). [b]Linear regression used to calculate unadjusted and adjusted mean difference (adjusted for the following covariates: female gender; homeless in last year; injected crack in last month; duration injecting <2.5 years) with *P*-values and 95% confidence intervals. [c]Includes or [d]excludes those who were on OST but reported no injections in the last month (cross-sectional studies) or last year (cohort studies).

Strengths and limitations

By pooling data across multiple studies we build upon and strengthen the evidence generated by the Amsterdam cohort, which failed to find any independent effects of OST and NSP [23]. Each individual UK study provided mainly equivocal findings, especially for NSP, as shown in Fig. 2, and without pooling may have simply corroborated the assessment that evidence of any intervention effect was insufficient [15].

Our key limitation is study power. The number of new HCV infections was too few to compute and synthesize separate effect estimates by study site, such as through a multi-level model. Instead, we used data augmentation to show that there was no evidence of heterogeneity in the intervention effects by site. This was important, as by pooling the data we could also adjust for factors that influence HCV incidence and may affect intervention effectiveness. In our pooled data, new HCV infection was significantly higher among women, crack injectors and homeless IDUs, but we found no evidence that the interventions effects (i.e. risk of HCV associated with NSP and OST) varied by these covariates. Interpretation of our findings still must be cautious, however, as again our power for testing an interaction was low, and there may be other confounders that influence the intervention effect. If heterogeneity had been found, which could occur in future if other studies from the United Kingdom and elsewhere are added, then we will have to use more complicated augmentation techniques [34].

Our measure of NSP coverage exposure may also be subject to biases which are difficult to quantify. The measure does not account for sterile needles obtained from other IDUs or given away/sold to other IDUs in the calculation of coverage. Each of these factors could alter the ratio of needles to injections (in opposing directions). The component measures of injecting frequency and needles obtained are subject to recall biases and whole number effects. Even if the numbers reported were accurate for a given month and imply sufficient needles for an individual's demand, this does not preclude specific instances of unsafe injecting. Conversely, some people who report less than 100% coverage under our measure may acquire sterile needles regularly from a friend and therefore inject safely. Finally, this measure does not take account of injecting frequency which may moderate the level of risk for a given coverage—as, for example, someone injecting once and obtaining one needle has the same NSP coverage as someone injecting 100 times and obtaining 100 needles. None the less, as the outcome (recent HCV infection) is objective and unknown to the participant at the time of measuring NSP exposure there is unlikely to be any systematic/differential bias in relation to the intervention effect. However, there is likely to be some non-differential misclassification bias which may dilute the intervention effect of NSP. In addition, with greater study power it would be important to consider whether there is a dose relationship between the risk of HCV infection and NSP coverage.

We combined UK cohort and cross-sectional studies that measured incident or recent HCV infection, in part because the former studies are more rare—but this does mean that the specific questions determining intervention coverage and exposure time varied. Our pooled analysis modelled the number of new HCV infections rather than an incidence rate which, although not ideal, as it potentially reduces power and loses information on follow-up time, is not a critical problem as the follow-up periods in the longitudinal studies were relatively short ($\leq$12 months). We are confident that we have not missed any UK studies that measure HCV incidence and intervention exposure. The study recruitment, characteristics of the sample and range of HCV prevalence and incidence are similar to those in other countries [10], suggesting that the findings may be generalizable to non-UK settings. For instance, HCV incidence ranging from five to 40 per 100 person-years is also found in the United States [10,35]. This heterogeneity in HCV risk may reflect selection biases or differences between the studies, as the studies recruited subjects with varying levels of injecting frequency, risk behaviours and intervention exposure and in areas with differing background HCV prevalence, and it is uncertain which incidence estimates (if any) are representative. More importantly, however, we show a positive intervention effect despite differences in risk (as the effect estimates remained after adjustment for covariates and there was no evidence of heterogeneity between the studies). If there is a selection bias, it is towards under-representing injectors that cease injecting during OST which may underestimate the intervention effect of OST and full harm reduction.

Implications

Evidence that OST and NSP are associated with lower injecting risk is readily available and strong. Unfortunately, changes in self-reported injecting risk behaviours are not always a good predictor or guarantee of a change in HCV incidence [36,37]. The problem we face in preventing HCV is that injecting is a chronic enduring condition (with mean injecting duration at least from 8 to 12 years and perhaps as long as 20) [33,38,39]; and that in sites with high background HCV prevalence, even very little injecting risk will still lead to persistently high endemic levels of HCV [40]. It is hardly surprising, therefore, that studies that simply measure exposure to NSP may generate equivocal findings in relation to HCV incidence [15]. We measured and assessed the impact

of high NSP coverage where individuals obtain a sufficient number of sterile needles for their injecting frequency. Under these conditions NSP, especially if combined with OST, was effective, and supports recommendations within the United Kingdom, Europe and globally on the need to expand NSP and OST to prevent HCV infection [7,15,41–44]. None the less, even with high coverage some injectors still became infected. We provide direct evidence that HCV transmission can be prevented, and it is likely that OST and NSP have averted many infections; however, given the high background HCV risk in some populations, the question remains on what levels of OST and NSP coverage (and behaviour change) are required to drive down HCV prevalence (and whether these are sustainable) [12,36,45].

Other meta-analyses have illustrated the high HCV risk among IDUs [10,46]. The evidence needs to be strengthened and extended in two ways. First, our findings need to be corroborated, and the number of studies or public health surveillance programmes that measure HCV incident infections and intervention exposure increased. In this way, surveillance will move from describing disease prevalence or burden to evaluating and monitoring intervention impact. Secondly, we need to address and monitor the population impact of different levels of intervention coverage; that is, to compare HCV incidence between IDU populations with different levels of intervention exposure and consider what combination of interventions, including HCV treatment, are most likely to make sustained and substantial reductions in HCV transmission in the population [5].

Declarations of interest

None.

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