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

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Abstract

Aims: A systematic review and meta-analysis were undertaken to estimate the effects of needle 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: Bibliographic databases were searched for studies measuring concurrent exposure to current OST (within last 6 months) and/or NSP and HCV incidence among PWID. High NSP coverage was defined as regular NSP attendance or ≥100% coverage (receiving sufficient or greater number of needles/syringes per reported injecting frequency). Studies were assessed using the Cochrane risk of bias in non-randomised studies tool. Random effects models were used in meta-analysis.

Results: We identified 28 studies (n=6279) in North America (13), UK (5), Europe (4), Australia (5), and China (1). Studies were at moderate (2), serious (17) critical (7) and non-assessable risk of bias (2). Current OST is associated with 50% (risk ratio (RR) 0.50 95% 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 76% reduction in HCV acquisition risk (RR=0.24 95% CI=0.07-0.89, I^2=80% p=0.007). According to 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 syringe programmes There was weaker evidence for the impact of needle syringe programmes alone, although stronger evidence that high coverage is associated with reduced risk in Europe.

Key words: Opioid substitution therapy, needle/syringe programmes, hepatitis C, incidence, substance use, Cochrane, meta-analysis, review, harm reduction

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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 over half of PWID have been infected with HCV.[4]

Evidence shows that injecting with needle/syringes previously used 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). {Pouget, 2012 #26}{Strathdee, 2010 #25} 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/syringes and other injecting equipment to PWID, via fixed-sites, outreach, peer networks, vending machines, and pharmacies. By maximising 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%).{Aspinall, 2014 #38;MacArthur, 2012 #39} Previous evidence syntheses for use of NSPs has focussed primarily on HIV as the main outcome and, as a consequence, failed to include all the available evidence on HCV. [11 8, 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 focussed on evidence from North America, limiting the generalisability 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 (≥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.{Palmateer, 2010 #37} 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/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), 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 that directly examined the impact of OST or NSP in relation to HCV incidence. The second focussed 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 Specialised 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

See the full Cochrane Review[21] for the full data extraction form 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 2 sero-conversions. 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 use of prescribed methadone or buprenorphine within the last 6 months. High NSP coverage was defined as obtaining 100% of needles/syringes from a safe source, reporting obtaining ≥100% of sterile needles/syringes per injecting frequency, regular attendance at least once per week at an NSP, or obtaining most needles/syringes from an NSP in 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 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 datasets; 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 figure 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 authors of these articles.[44-54] Of these, unpublished data were obtained from cohort studies in Montreal (Canada)[55]; Baltimore (USA)[56], San Francisco (USA),[57] Sydney and Melbourne (Australia)[58, 59], London (UK)[60] and three cross-sectional surveys in Bristol, Birmingham, Leeds.[61] 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 across the studies.

[Insert Figure 1]

Description of studies

Table 1 summarises the characteristics of the included studies undertaken in the USA (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, 55-62]Seventeen studies reported the impact of NSP. [12, 26-29, 32, 33, 35, 39, 41, 43 55-57, 59, 60] Four studies assessed the impact of combined NSP with OST.[12, 29, 32, 55] 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 five studies reported the sex of participants, of which the mean proportion of women across the studies was 32% (range 2.8-55.9%). Three were excluded from this analysis since they only published unadjusted estimates of lifetime use of OST versus never using OST.[36, 41, 42]

[Insert Table 1]

Risk of bias

Risk of bias decisions are summarised in last column of Table 1 and in the Web appendix (Table A). Only two studies were judged at moderate overall risk of bias,[38, 40] seventeen studies were judged as serious overall risk of bias,[24, 26-33, 37, 39, 41, 43, 55, 59] and seven were at critical risk.[25, 34-36, 42, 58, 60] For two studies,[56, 57] we did not have enough information to make a judgment.

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, 58-61] Twelve studies (6361 participants) presented adjusted measures, on which the primary analyses were focused.[24, 30, 31, 34, 38, 40, 43, 55, 56, 59, 60, 62] Random effect meta-analysis of multivariable estimates showed that OST was associated with a 50% reduction in the risk of HCV infection (Risk ratio=0.50) with little heterogeneity between studies (I^2=0, p=0.889).

[Insert Figure 2]

This effect was maintained when the analysis was limited to exclude two studies judged to be at critical risk of bias[34, 60] and one study where there was insufficient information to give an overall risk of bias assessment[56] (Risk ratio=0.51, I^2=0%, p=0.68,). The intervention effect was unchanged when the analysis excluded two cross-sectional studies[34, 62] that reported baseline measures of effect only (3367 participants Risk ratio=0.51, I^2=0.0%, p=0.73). The intervention effect strengthened when estimates from four unpublished data sources[55, 56, 59, 60] were excluded (Risk ratio=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 (10647 participants, Risk ratio=0.57, I^2=32.4, p=0.09 (Figures A-D, web appendix).

We found no evidence that effectiveness varied by geographical region (Figure 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 rate ratios=1.59) (Table 2).

High coverage of needle 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, 62] including one unpublished dataset.[55] Random effect meta-analysis showed weak evidence of an effect of high coverage of NSP on the reduction in the risk of HCV infection (Risk ratio= 0.79) and high heterogeneity between studies (I^2 =77%, p=0.002). Random effects meta-analysis of 7 studies (6455 participants) that presented unadjusted estimates show that the weak intervention effect was unchanged (Risk ratio= 0.77, I^2=79%, p=0.000001) (Figure 4). Evidence of any intervention effect became weaker after excluding the unpublished dataset[55] (Risk ratio=0.77, p<0.001). No NSP studies were rated critical on the risk of bias tool (Figure E Web appendix).

[Insert Figures 3 and 4]

High NSP coverage was associated with a 56% reduction in HCV acquisition risk (Risk ratio=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). (Figure 4) 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) (Figure 3). The meta-regression analysis also showed evidence of differential impact by region comparing North America with Europe (Ratio of rate ratios= 3.73, p=0.06) (Table 3). Univariable meta regression analysis also suggested some association between high coverage of NSP and study design (Ratio of rate ratios=3.5, p value=0.087 comparing cross-sectional with longitudinal study design), this was reduced when adjusted for geographical region (Ratio of rate ratios=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.

[Insert Table 2]

Combination interventions: OST and high/low NSP

Random effects meta-analysis pooling adjusted measures from three studies[12, 55, 62] (3241 participants) showed that combined use of OST and high coverage of NSP was associated with a 74% risk reduction in HCV acquisition (Risk ratio=0.26, I^2=80% p=0.007). This effect was maintained when pooling unadjusted measures from 4 studies (3356 participants, Risk ratio= 0.29, I^2=64.4% p=0.038) (Figure 6).

[Insert Figure 5]

The effect of exposure to OST and low coverage of NSP from pooling adjusted measures from two studies (2956 participants) was weaker (Risk ratio=0.87, I^2=36.0% p=0.67). This effect remained unchanged when pooling unadjusted measures from three studies (3071 participants) (Risk ratio=0.76, I^2=29.6% p=0.24) (Figure 6).

[Insert Figure 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 5 estimates (5 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 only included 5 studies and may be under powered. (Figures F and G in web appendix).

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 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 consistently associated 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/syringes were used across the European studies{Hope, 2011 #5}{Hope, 2015 #50}{Van Den Berg, 2007 #31}{Palmateer, 2014 #63}, whereas the North American studies drew on varied definitions of NSP use that focussed on frequency of attendance at NSPs.{Patrick, 2001 #9}{Hagan, 1999 #4}{Bruneau, 2015 #48} The measure of 100% NSP coverage corresponds to the situation where a person reports that 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 possible also that the population exposed to 100% coverage are more compliant than the comparison group in terms of regular attendance and uptake of needles/syringes. However, we cannot assume that they necessarily use all needles/syringes obtained since 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/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/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[63], but the immediate effect on HCV incidence may be difficult to assess where measurement of exposure doesn't capture uptake of sterile needles/syringes from other sources. Measurement of NSP use that focuses on needles/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 US where nearly half of HCV seroconversions have been attributed to the shared use of cookers (spoons) and cottons.[5] It is also hypothesised 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 US overall.[64 65] 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 did suggest 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, synthesised effect estimates for OST and combined effect of OST and high coverage NSP were consistent across 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.[66 67]

An additional limitation is that the GRADE criteria used by Cochrane automatically assesses 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 recently discussed[68] alongside a recognition for the need to separate out the quality of the evidence from the strength of the ensuing recommendation.[69] We agree 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

randomised controlled trials. Observational studies can give misleading results and in some notable examples have been shown to be false when compared to evidence from randomised trials.[70] 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 on an earlier narrative review that OST and NSP reduce injecting risk and global reviews on HIV. [14, 17]{Aspinall, 2014 #38} 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 on evidence predominantly 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.{Iversen, 2015 #69}{Miller, 2004 #70}{Tracy, 2014 #72}

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 on 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 criminalisation.{Sederer, 2014 #108} This is particularly relevant in low and middle-income countries where resources may be more restricted.[68] There is a wealth of evidence from high-income settings of the beneficial effects of OST in reducing injecting injection related harms, including HIV and bacterial infections, and improving access to services.[11, 17, 19, 20, 71, 72] 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.[73] Our findings show the need to remove restrictions on the concurrent use of both NSP and OST to maximise 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 (≥60mg) pointing to the importance of providing adequate dosages.{Van Den Berg, 2007 #31;Bruneau, 2015 #48} Distribution of needles/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,{Martin, 2011 #109} 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.

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Table 1: Characteristics and risk of bias of included studies

Author	Design	Sex	Age	N	HCV/ 100 py	New HC/py	Interventions		Effect estimate	Confounders included in analysis	Rick of bias
Aitken, 2015[58] Australia	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
Bruneau, 2015[55] Canada	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
							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	
							Combined NSP/OST OST in last 6 months & high (>100% coverage)	HR	0.63 (0.37-1.07) AOR=0.59 (0.35-1.01)	Years injecting, numbers of injection in past month	
							OST other^ (high dose ≥60 mg)	HR	0.37 (0.17-0.8) AOR=0.39 (0.18-0.86)	Years injecting, numbers of injection in past month	
							OST other^ (low dose <60 mg)	HR	1.15 (0.7-1.89) AOR=1.06 (0.64-1.77)	Years injecting, numbers of injection in past month	
Craine, 2009[24] Wales	Cohort	29.0 %	27.2 (mean)	286	5.9	17/287.33	**OST current** In OST at interview	IRR	0.27 (0.095-0.77) AOR=0.34 (0.12-0.99)	Region, homelessness, sharing equipment, sharing needles (all in last 12 months)	
Crofts, 1997[25] Australia	Cohort*	41.9 %	29.2 (mean)	73	22.2	13/85.4	**OST current** Continuous OST during follow up	IRR	1.8 (0.37-4.77)	-	S
							OST other^ (Interrupted use)	IRR	0.66 (0.55-0.79)	-	
Hagan, 1995[26] USA	Case-control	45.0 %	24% < 25	46		20/NA	**NSP (low)^** Ever used NSP	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] USA	Cohort	38.0 %	19% <25	187	20.8	26/209	**NSP (high)** current regular NSP use	RR	1.42 (0.64-3.13) AOR=1.31 (0.79-	Onset of injection < 1 year from baseline interview, sharing at baseline	S

Author	Design	Sex	Age	N	HCV/ 100 py	New HC/py	Interventions		Effect estimate	Confounders included in analysis	Rick of bias
									2.2)		
							NSP (low)^		1.72 (0.71-4.19) AOR=2.59 (0.79-8.5)	Onset of injection < 1 year from baseline interview, sharing at baseline	
Holtzman, 2009[28] USA	Cohort	38.0 %	28% <21	1288		139/NA	**NSP (low) ^** NSP use in the last 6 months	OR	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, 2011[29] UK	Cross-sectional	23.0 %	17% <25	119	40	14/35	**NSP alone (high)**; high NSP (≥100% coverage	IRR	0.11 (0.024-0.53)	-	S
							NSP/OST combined OST in last 6 months & high (>100% coverage)	IRR	0.17 (0.12-1.54)	-	
							NSP/OST combined OST in last 6 months & low (<100% coverage)	IRR	1.08 (0.31-3.82)	-	
Hope, 2015[61] UK	Cross-sectional	25.0 %		919	9.9	30.3	**OST current** Use of OST in last 4 weeks Birmingham: Bristol: Leeds	OR	 1.55 (0.14-17.4) 0.24 (0.05-1.16) 1.31 (0.08-21.5)	-	S
							NSP high NSP coverage (≥100% coverage) (Low NSP, no OST) Bristol: Leeds: Birmingham:	OR	 0.99 (0.21-4.59) 0.73 (0.04-11.98) 0.55 (0.05-6.26)	-	
Judd, 2015[60] UK	Cohort	29.0 %	27.4	149	42	49/116.7	**OST current** Use of methadone in last 6 months	RR	0.47 (0.16-1.33) AOR=0.49 (0.17-1.47)	Duration and frequency of injecting	C
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

Author	Design	Sex	Age	N	HCV/ 100 py	New HC/py	Interventions		Effect estimate	Confounders included in analysis	Rick of bias
Maher, 2015[59] Australia	Cohort	38.0 %	24 (median)	368	24.9	53/212.86	**OST current** OST in last 6 months	HR	0.43 (0.24-0.75) AOR=0.46 (0.25-0.84)	Duration and frequency of injecting	S
							NSP (low)^	HR	1.86 (1.05-3.28) AOR=0.15 (0.88-2.78)	Duration and frequency of injecting	
Mehta, 2015[56] USA	Cohort		34 (median)	324	17.8	27/166.5	**OST current** OST in last 6 months	IRR	0.6 (0.14-2.51) AOR=0.82 (0.19-3.54)	Years injecting, daily injection, age (for whole cohort)	N/I
							NSP (low)^	IRR	1.38 (0.17-11.5) aor=0.76 (0.1-5.67)	Years injecting, daily injection, age (for whole cohort)	
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)	Uunstable housing, cocaine, heroin or methamphetamine injection, cohort and year of recruitment, follow-up time	S
Page, 2015[57] USA	Cohort	21.7 %	33.7 (mean)	552	25.1	171/681.3	**NSP (low) ^** 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
Palmateer, 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
Scotland							**NSP (high)** high NSP (>200%) coverage and not on OST;	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

Author	Design	Sex	Age	N	HCV/ 100 py	New HC/py	Interventions		Effect estimate	Confounders included in analysis	Rick of bias
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^** 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) ^** Use of NSP in last 6 months	HR	3.02 (95% CI n/a)	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
USA							**OST other^** Interrupted left treatment at least 1 during follow up	OR	0.8 (0.01-3.6) AOR=1.2 (0.2-7.3)	Injected at follow-up, pooled money to buy drugs, injected with used needles, backloading	
Thorpe, 2002[39] USA	Cohort	39.7 %	52% 18-22 years	353	10	29/327.2	**NSP (low) ^** Use of NSP in last 6 months	HR	1.29 (0.6-2.79	Receptively sharing syringes, sharing cookers, cotton filters, rinse water or backloading	S
Tsui, 2014[40] USA	Cohort	31.9 %	16% 15-18	552	25.1	145/680	**OST current & other** Opiate agonist therapy maintenance treatment 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
							OST other ^Opiate agonist detoxification in last 3 months	HR	1.45 (0.8-2.69)	Age, duration of injection drug use, sex, ethnicity, homelessness or incarceration in past 3 months	
Vallejo, 2015[41] Spain	Cohort	27.3 %	40% ≥25	137	39.8	42/105.4	**OST other^** Lifetime use of OST	IRR	0.9 (0.5-1.6)	-	S
Van Den Berg, 2007[12]	Cohort	33.0 %	31.4 (median)	168	6.78	57/598.56	**OST current;** OST ≥60 mg methadone daily	IRR	0.67 (0.39-1.13)	-	S
Netherlands							**NSP alone;** High NSP (100% coverage)	IRR	0.62 (0.3-1.3)	-	

Author	Design	Sex	Age	N	HCV/ 100 py	New HC/py	Interventions		Effect estimate	Confounders included in analysis	Rick of bias
							Combined OST/NSP high NSP	RR	0.15 (0.05-6-0.4) AOR=0.36 (0.13-1.03)	Duration of injection, HIV status of steady partner	
							Combined OST/NSP low NSP	RR	1.04 (0.53-2.05) AOR=1.17 (0.59-2.31)	Duration of injection, HIV status of steady partner	
							OST other^ (high dose)	RR	0.68 (0.39-1.13)		
							OST other^ (Low dose)	RR	0.58 (0.3-1.15)		
Van Beek, 1998[42] Australia	Cohort*	55.9 %	61.5% <20	152	20.9	26/148.2	**OST other^** Ever used OST (yes/no)	OR	1.08 (0.37-3.17)		C
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)** ^ Accessed NSP in last 6 months;	HR	1.0 (0.36-2.86)	-	

HR=Hazard Ratio OR=Odds Ratio RR=Risk Ratio IRR=incident rate ratio ^Not reported in the primary analysis N/A=Not available 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)

Table 2: Univariable metagression analysis for studies measuring impact of current use of OST and high coverage NSP on HCV incidence

	Current use of OST						**High coverage of NSP**					
Variable	**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**
Geographic 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)**	0.01	0.04	13.8%	7		2.97(0.38-23.1)	0.24	0.87	81.3%
Prison	11		1.057 (0.61-1.79)	0.821	0.4303	56.3%	3		n/a			
Homelessness	12		1.08 (0.83-1.40)	0.521	0.2327	39.8%	6		1.01 (0.38-2.67)	0.976	1.53	80.6%
Injection of stimulants	12		0.89 (0.65-1.22)	0.373	0.17	36.2%	7		1.08 (0.47-2.51)	0.827	1.15	80.4%

Daily injection	7		0.88 (0.64-1.22)	0.373	0.17	47.3%	5		3.66 (0.22-61.3)	0.239	1.15	

Figure 1: Flow chart of included studies

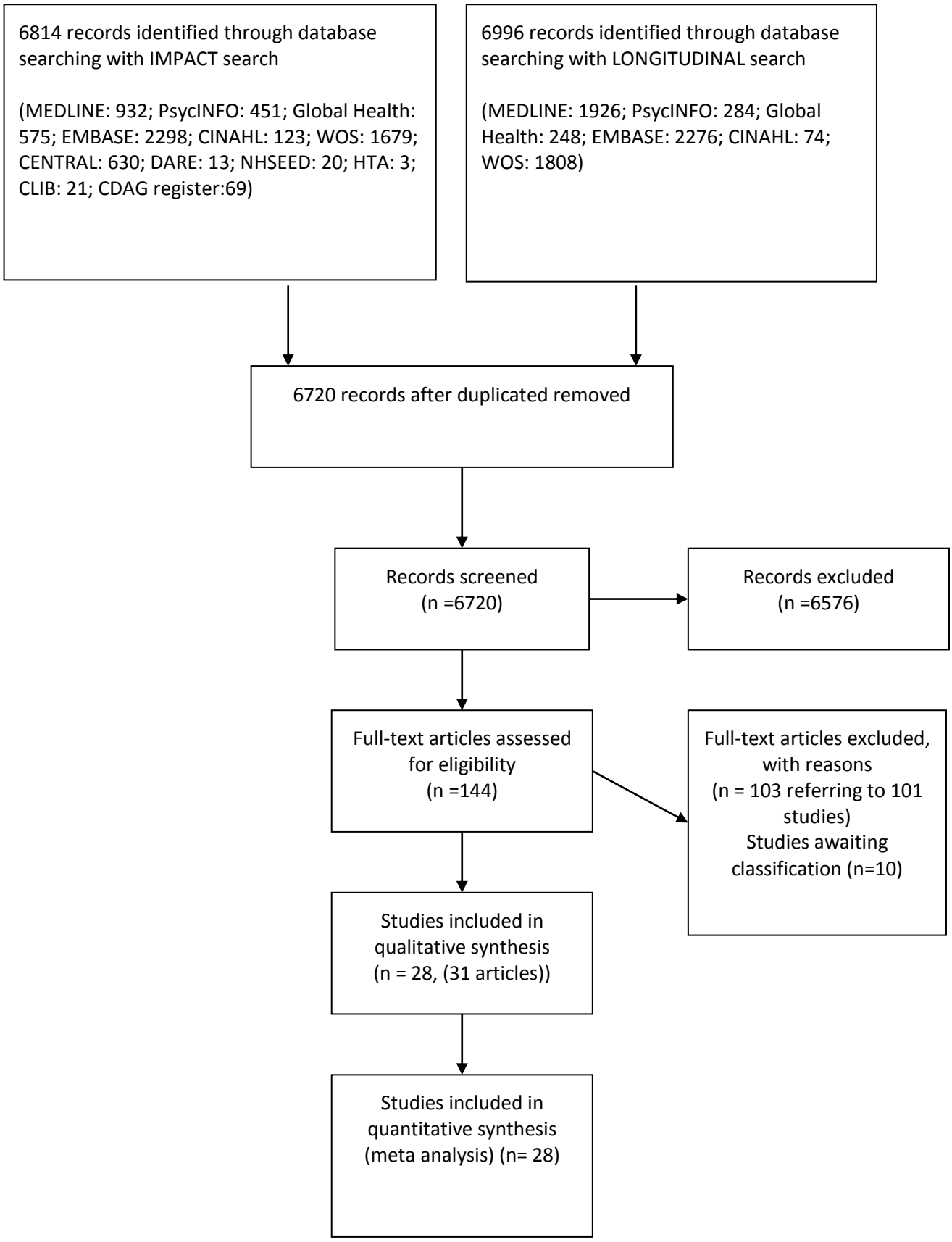


Figure 2: Impact of current use of OST versus no OST on HCV incidence from studies adjusted for confounders and stratified by region

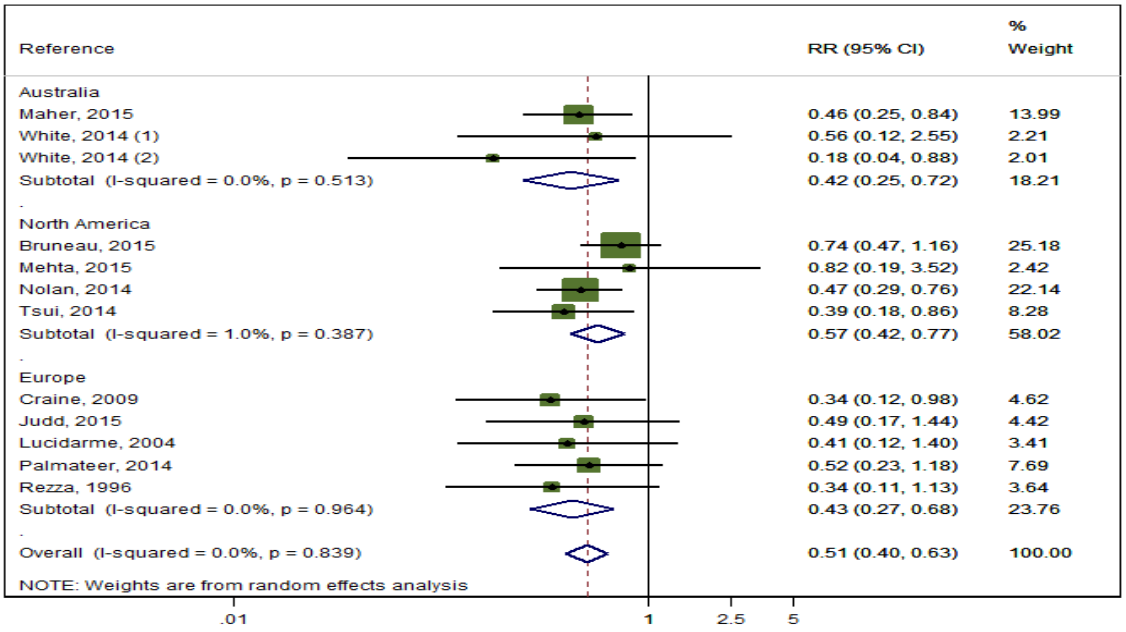


Figure 3: Impact of high coverage NSP versus no/low coverage on HCV incidence from studies adjusted for confounders and by region

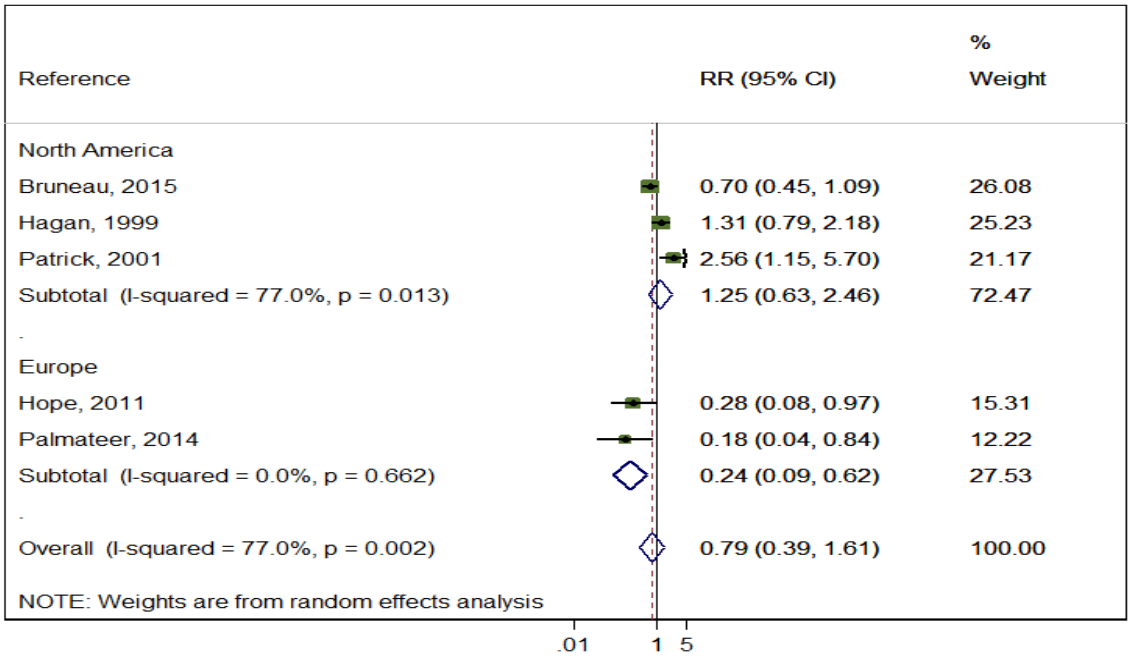


Figure 4 Impact of high coverage NSP versus no/low coverage on HCV incidence from pooling unadjusted measures by region

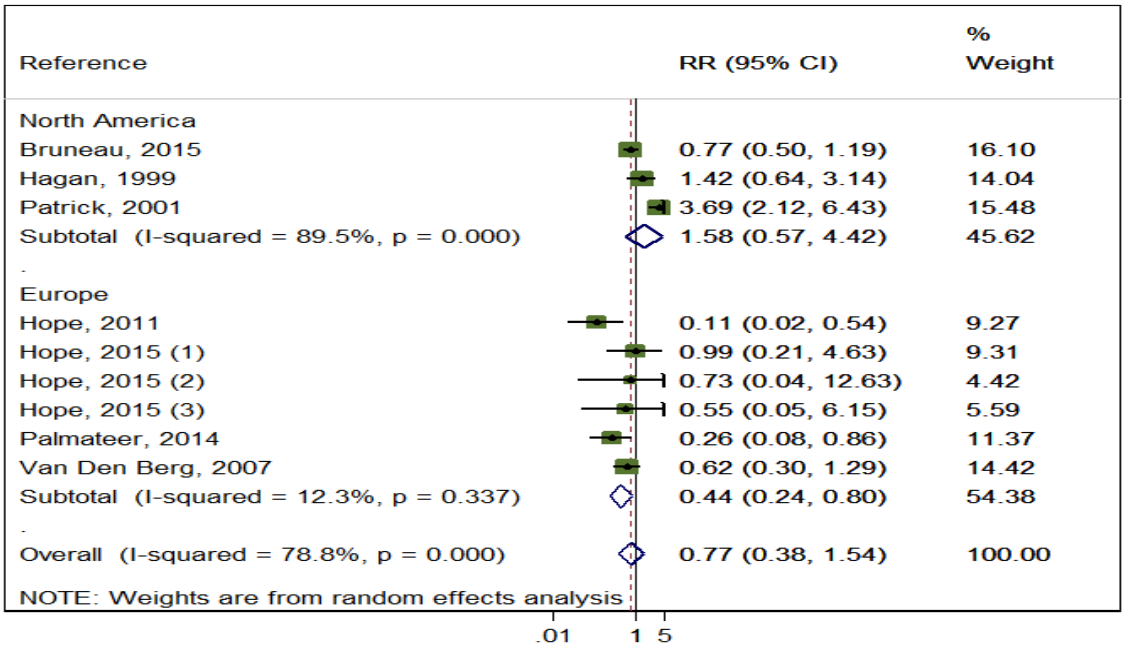


Figure 5: Impact of OST combined with high coverage NSP from studies adjusting for confounders and all pooled estimates

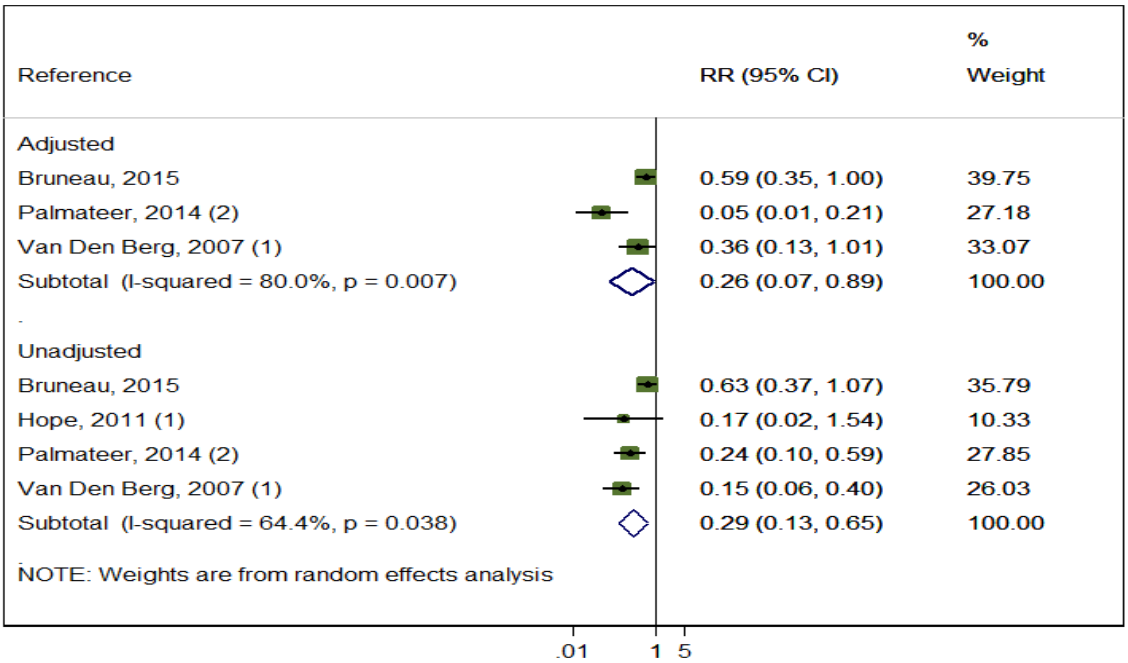
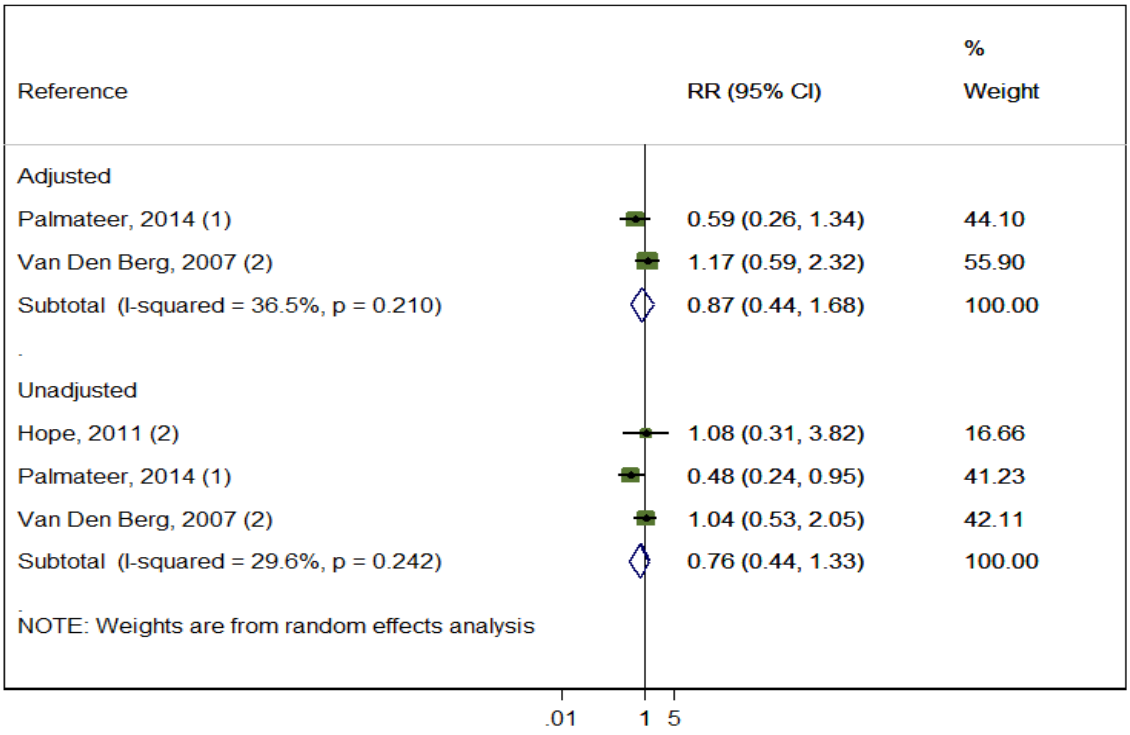


Figure 6: Impact of OST combined with low coverage NSP from studies adjusting for confounders and all pooled estimates



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